MAX-PLANCK-INSTITUT FÜR KOHLENFORSCHUNG

technische universität dortmund

Asymmetrische Synthese und Diversifikation stannylierter Cyclopropane und deren Anwendung in der Totalsynthese von Naturstoffen

Dissertation

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Die vorliegende Arbeit entstand unter Anleitung von Prof. Dr. Alois Fürstner in der Zeit von Januar 2020 bis September 2024 am Max-Planck-Institut für Kohlenforschung in Mülheim an der Ruhr. Teile dieser Arbeit wurden bereits veröffentlicht:

F. P. Caló, A. Zimmer, G. Bistoni, A. Fürstner. From Serendipity to Rational Design: Heteroleptic Dirhodium Amidate Complexes for Diastereodivergent Asymmetric Cyclopropanation. *J. Am. Chem. Soc.* **2022**, *144* (16), 7465-7478.

A. Zimmer, A. Fürstner. Total Synthesis of the Humulene-Derived Sesquiterpenoid (−)-Integrifolian-1,5-dione. *ChemistryEurope* **2024**, e202400064.

Die Arbeiten erfolgten zum Teil in Zusammenarbeit mit Dr. Fabio Caló, Dr. Giovanni Bistoni und Sophia Engelhardt. Von diesen Mitarbeitern alleinverantwortlich erzielte Ergebnisse wurden als solche an entsprechender Stelle gekennzeichnet.

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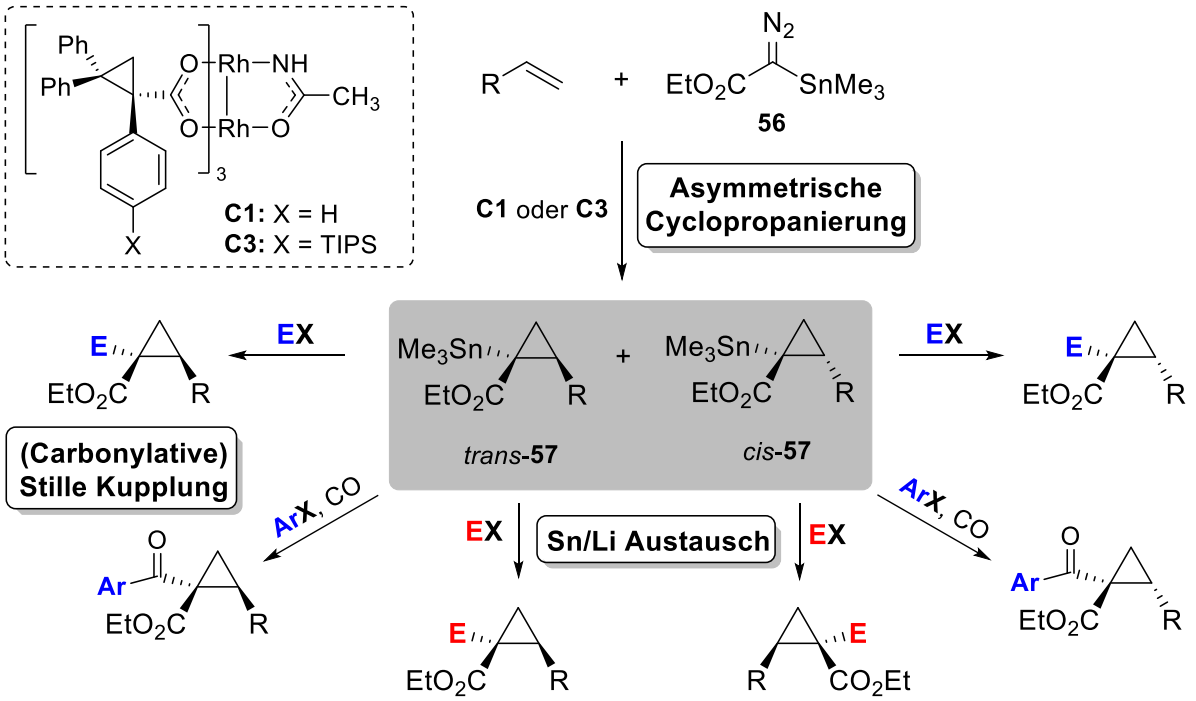
Inhalt

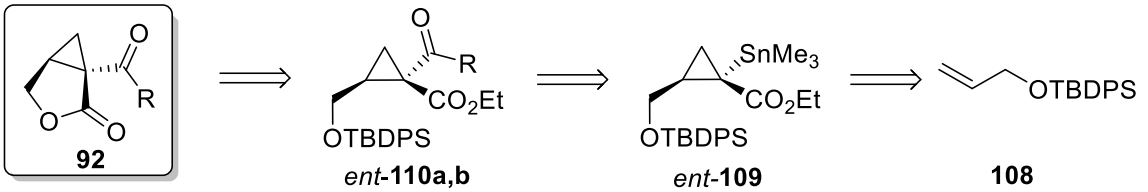
Cyclopropane sind nützliche Bausteine in der medizinischen Chemie sowie ein weit verbreitetes Strukturmotiv in (bioaktiven) Naturstoffen. Ihre asymmetrische Synthese kann mithilfe von Dirhodium Schaufelradkomplexen erreicht werden. Ein neuer heteroleptischer Dirhodium Katalysator **C1** für die enantioselektive Cyclopropanierung von Olefinen mit α-stannyliertem Diazo Ester **56** wurde in der Arbeitsgruppe entwickelt und basierend auf den Ergebnissen von DFT Berechnungen modifiziert um einen diastereoselektiven Abkömmling zu erhalten (**C3**). Anschließend konnten unter Einsatz dieses Katalysators zahlreiche optisch aktive, stannylierte Cyclopropane synthetisiert werden. Verschiedene Möglichkeiten der weitergehenden Diversifizierung wurden untersucht, darunter eine stereoretentive Stille Kupplung, welche die Einführung unterschiedlicher Elektrophile ermöglichte, sowie eine carbonylative Variante besagter Kupplung, durch die eine formale Acylierung erreicht wurde. Darüber hinaus wurde ein Zinn-Lithium-Austausch angewendet, welcher den Zugang zu weiterer struktureller Vielfalt der Cyclopropane eröffnete (Schema 1). Mithilfe der entwickelten Methodik lassen sich vielzählige, divers dekorierte und auf anderem Wege zum Teil schwer zugängliche, chirale Cyclopropane in optisch aktiver Form herstellen.



Schema 1. Konzeptionelle Übersicht der asymmetrischen Cyclopropanierung und anschließenden Diversifizierung.

Die entwickelte Methodik wurde anschließend in der Totalsynthese mehrerer Naturstoffe angewandt. Eine Zielstruktur umfasste die Familie der Salinilactone (**92**), welche aus *S. arenicola* isoliert wurde, eine Spezies von marinen Bakterien der Gattung *Salinispora*. Ihre Mitglieder verfügen über ein bizyklisches [3.1.0]-Lactongerüst mit variierender Acylseitenkette. Zwei der

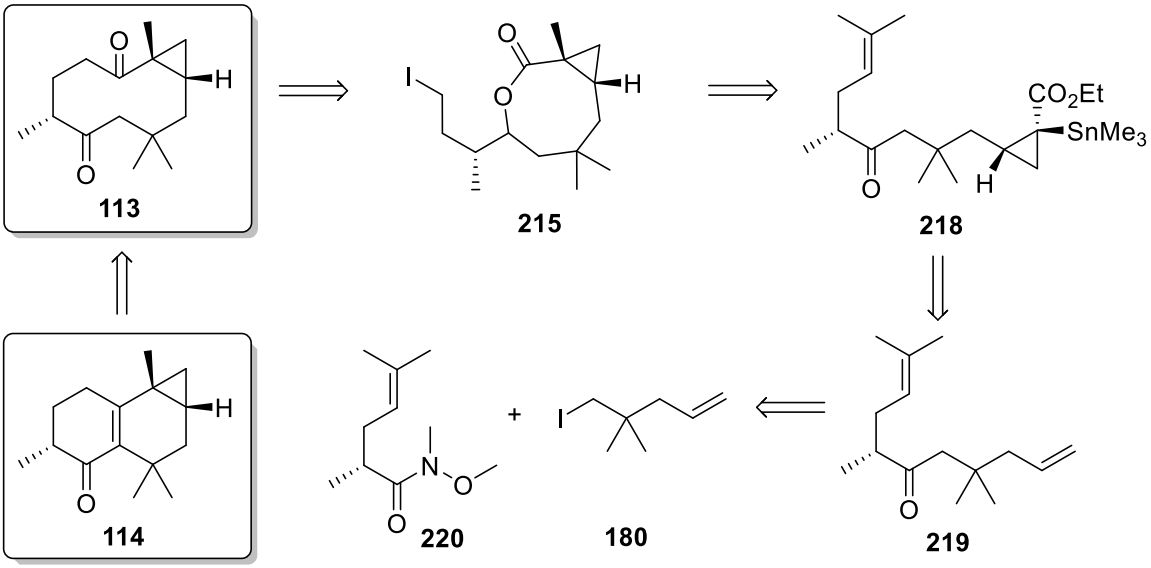
Mitglieder, Salinilacton B und C, wurden synthetisiert (Schema 2). Schlüsselschritte der Synthese umfassten die asymmetrische Cyclopropanierung eines geschützen allylischen Alkohols **108** gefolgt von Zinn-Lithium-Austausch zur Einführung der Acylseitenkette.



Salinilacton B (R = *n*Bu, **92a**)
Salinilacton C (R = CH_2*i*Bu, **92b**)

Schema 2. Retrosynthetische Analyse von Salinilactonen B und C.

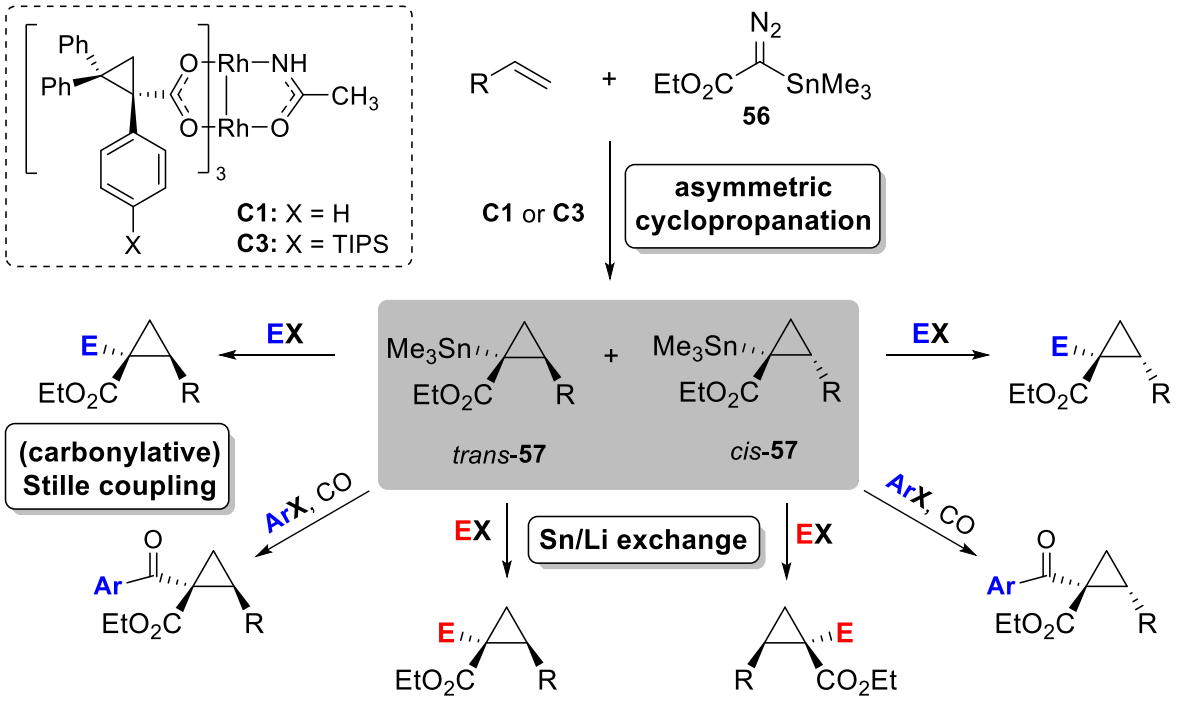
Eine weitere Zielstruktur war Integrifolian-1,5-dion (**113**), ein Naturstoff welcher aus *Lippia integrifolia* isoliert wurde, einem holzigen, in Agentinien beheimateten Busch. Die Struktur von Integrifolian-1,5-dion umfasst einen Cyclopropanring, welcher mit einem zehngliedrigen Kohlenstoffring verbunden ist, woraus sich ein Bicyclo[8.10]undecansystem ergibt. Die Synthese konnte über insgesamt 16 Schritte (14 Schritte in der längsten linearen Sequenz, Schema 3) erzielt werden, mit einer Gesamtausbeute von etwa 10 %. Ausgehend von einem Roche-Ester Derivat wurde ein fortgeschrittenes Olefinintermediat **219** hergestellt, welches mithilfe des Dirhodium Katalysators ***ent*-C3** asymmetrisch cyclopropaniert wurde (**218**). Anschließend wurde eine anspruchsvolle, stereoretentive Stille Kupplung mit Methyliodid als Elektrophil durchgeführt und so das 1,1,2-trisubstituierte Cyclopropanmotiv aufgebaut. Die Konstruktion des zehngliedrigen Rings erfolgte mithilfe einer Ringexpansionsstrategie. Schließlich wurde Integrifolian-1,5-dion erhalten, welches mittels drei weiterer Schritte in das nahe verwandte Lippifoli-1(6)-en-5-on (**114**) überführt werden konnte.



Schema 3. Retrosynthetische Analyse von Integrifolian-1,5-dion (113) und Lippifoli-1(6)-en-5-on (114).

Abstract

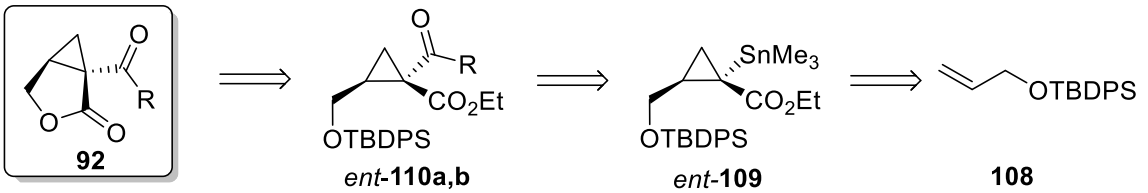
Cyclopropanes are useful building blocks in medicinal chemistry and a widespread structural motif in (bioactive) natural products. Their synthesis can be achieved in an asymmetric fashion by using dirhodium paddlewheel complexes as catalysts. A new heteroleptic dirhodium catalyst **C1** for the highly enantioselective cyclopropanation of olefins with α-stannylated diazo ester **56** was developed in the group and further modified in a DFT-guided process. The improved derivative **C3** delivered cyclopropanation products with high diastereoselectivity. Thus, a wide range of enantioenriched stannylated cyclopropanes was obtained. Different possibilities for further diversification were investigated, including a stereoretentive Stille coupling protocol, which allowed the introduction of various electrophiles, as well as a carbonylative version of said coupling, enabling formal acylation. Moreover, tin-lithium exchange was applied, providing access to a large structural diversity of cyclopropanes (Scheme 1). With the developed methodology, numerous differently functionalised chiral cyclopropanes can be prepared in optically active form, which would otherwise, in part, be difficult to obtain.



Scheme 1. Conceptional overview of the asymmetric cyclopropanation and the subsequent diversification.

The developed methodology was subsequently applied in the total synthesis of different natural products. One target structure was the family of salinilactones (**92**), which had been isolated from *S. arenicola*, a species of marine actynomycete bacteria of the genus *Salinispora*. Their members contain an unprecedented bicyclic [3.1.0]-lactone framework with a varying alkyl side chain. Two members of the family, namely salinilactones B and C, were synthesized with key steps of the

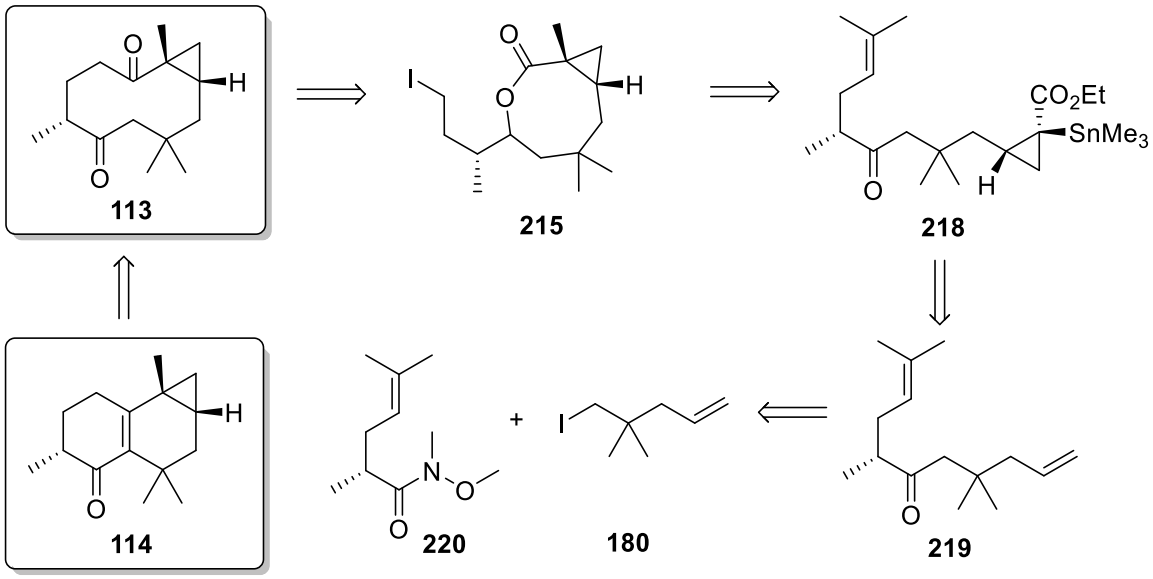
synthesis involving the asymmetric cyclopropanation of a protected allylic alcohol **108**, followed by tin-lithium exchange to introduce the acyl side chain (Scheme 2).



salinilactone B (R = *n*Bu, **92a**)
salinilactone C (R = CH_2*i*Bu, **92b**)

Scheme 2. Retrosynthetic analysis of salinilactones B and C.

Another target was integrifolian-1,5-dione (**113**), a natural product isolated from *Lippia integrifolia*, a woody shrub native to Argentina, whose structure contains a cyclopropane fused to a ten-membered ring, resulting in a bicyclo[8.1.0]undecan system. Its synthesis was achieved over 16 steps (14 steps longest linear sequence, Scheme 3) with approximately 10 % overall yield. The synthesis started from a Roche ester derivative, eventually leading up to the asymmetric cyclopropanation of an advanced intermediate olefin **219**. This was followed by a challenging stereoretentive Stille coupling using methyl iodide to construct the 1,1,2-trisubstituted cyclopropane motif. In order to successfully forge the ten-membered carbocycle, a ring expansion strategy was used. Proceeding from integrifolian-1,5-dione, the closely related lippifoli-1(6)-en-5-one (**114**) could be prepared as well over additional three steps.



Scheme 3. Retrosynthetic analysis of integrifolian-1,5-dione (113) and lippifoli-1(6)-en-5-one (114).

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Asymmetric Synthesis and Diversification of Stannylated Cyclopropanes and Their Application in the Total Synthesis of Natural Products

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1 Asymmetric Cyclopropanation and Downstream Diversification

1.1 Introduction

The cyclopropyl ring has been an intriguing structural motif for organic chemists ever since its first synthesis through the treatment of 1,3-dibromopropane with sodium reported in 1882 by August Freund[1]. The smallest member of the cycloalkanes comes with unique physical and chemical properties[2]. Unsubstituted cyclopropane possesses a fairly high ring strain of approximately 27 kcal/mol, largely owing to its profoundly decreased C-C bond angle of only 60° in addition to torsional strain[3]. As the result of the small bond angles, a unique bonding pattern arises as the orbitals are not able to align with the theoretical internuclear axis but are slightly bent outwards (Coulson-Moffitt model, Figure 1)[4]. This is only possible with an increased p-character of the bonding orbitals, leading to a hybridization close to sp^2. In fact, the chemical properties of a cyclopropyl ring more closely resemble those of C-C double bonds rather than cyclobutane[3b].

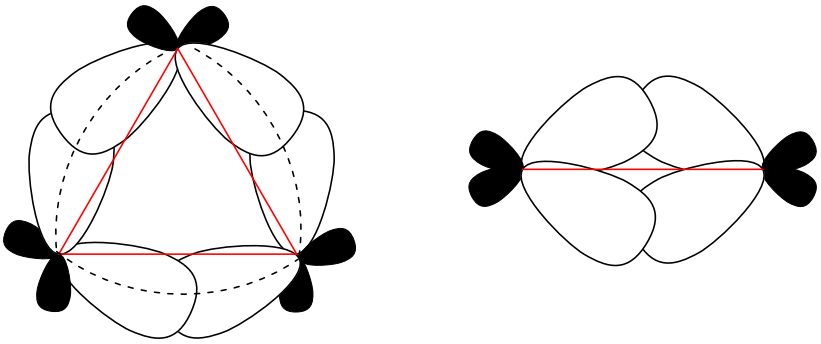


Figure 1. Valence bond model of cyclopropane (left) and ethylene (right).

A broad variety of cyclopropane-containing natural products have been isolated over the past decades and were subject to numerous total syntheses[5]. Some examples are shown below (Figure 2), which also exhibit promising biological properties. (+)-*trans*-Chrysanthemic acid is part of a family of natural insecticides[6] while coronatine exhibits phytotoxic activity[7]. Furthermore, ptaquiloside displays carcinogenicity[8] whereas curacin A was found to have antimitotic and antiproliferative effects[9]. An especially striking structure is that of U-106305, containing five contiguous cyclopropane rings which is a cholesteryl ester transferase protein inhibitor[10]. Beyond natural product chemistry, the cyclopropyl group has garnered increased interest by medicinal chemists, especially as a bioisoster for C-C double bonds (*vide supra*) due to its favourable influence on drug molecule properties. Increased metabolic stability, potency, bioavailability, brain permeability and aqueous solubility are only some of the diverse improvements that can be achieved by the incorporation of a cyclopropane moiety in a (potential) drug molecule[11]. Examples of drugs including one or more cyclopropyl units are milnacipran[12],

a serotonin-norepinephrine reuptake inhibitor (SNRI) and drospirenone[13], an orally administered contraceptive.

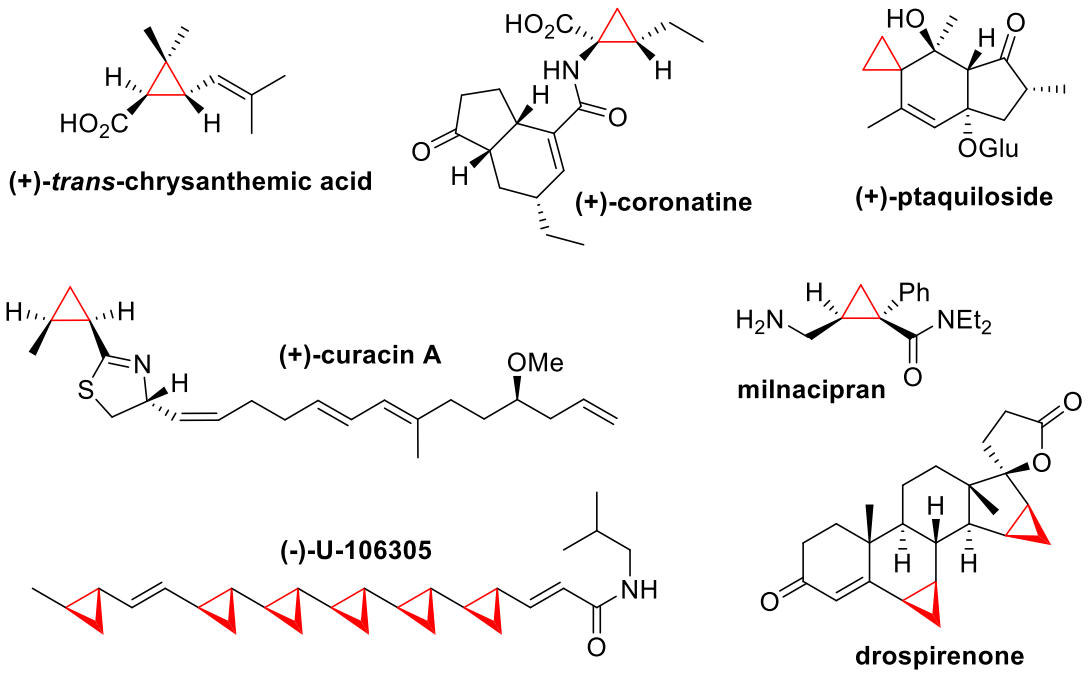


Figure 2. Overview of natural products and drug molecules containing one or more cyclopropyl units.

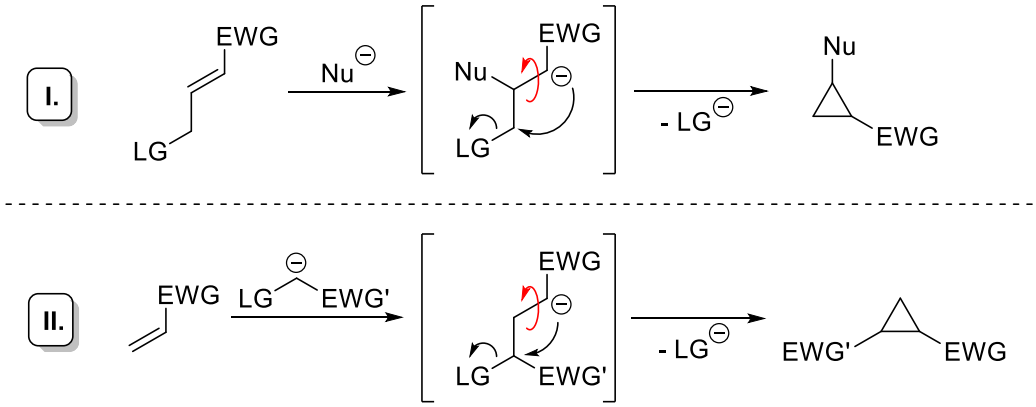
1.1.1 Asymmetric Synthesis of Cyclopropanes

Due to their intriguing properties (*vide supra*), the synthesis of cyclopropyl rings has been an ongoing endeavor for organic chemists. Generally, there are two main approaches to form a cyclopropane. One involves carbenes undergoing a formal [2+1] cycloaddition; the other is a 1,3-cyclization based on an entropically favoured, irreversible ring-closure. In particular, the development of methodologies for the formation of cyclopropanes in an asymmetric fashion remains highly desirable [14]. The main strategies to gain access to enantioenriched compounds that have been adopted for cyclopropanations include the use of enantioenriched starting materials, the introduction of a chiral auxiliary, or the application of a chiral catalyst. The latter is especially advantageous over the use of chiral auxiliaries as it does not add extra steps to the reaction sequence and produces overall less waste material, hence a better atom economy. Some of these approaches will be highlighted and discussed in the following sections.

1.1.1.1 Ring Closure Reactions

A well-established precedent for the 1,3-cyclization involves the conjugate addition of a nucleophile to an electron-deficient alkene, producing an intermediate that subsequently undergoes intramolecular ring closure[15]. In this so-called Michael-initiated ring closure (MIRC) either a nucleophile adds to an electrophilic substrate bearing a suitable leaving group, or the nucleophile itself contains the leaving group (mostly ylide species) and attacks the electron-

deficient olefin (Scheme 4). A prominent example for this type of reactivity is the Corey-Chaykovsky reaction of a sulfur ylide with an enone species[16]. With a few exceptions, the MIRC of acyclic olefins does not provide a stereospecific outcome due to the possible rotation around the intermediate single bond formed after nucleophilic attack. Only if the subsequent ring closure is faster than bond rotation, or if a configurationally stable tetrahedral intermediate is formed, is stereospecificity observed[14b]. Nevertheless, several asymmetric versions of the reaction have been reported, using chiral nucleophiles[17] or auxiliary-linked electrophiles[18] as well as organocatalytic methods[19].

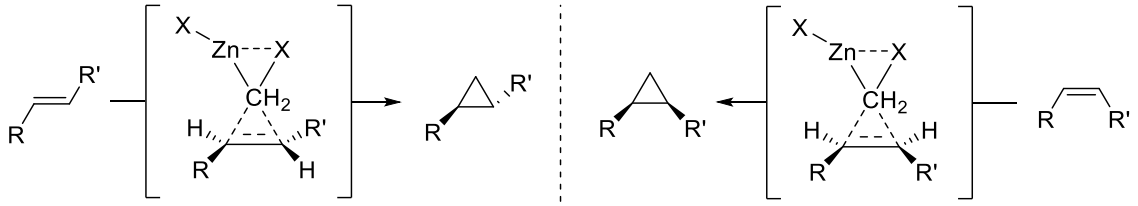


Scheme 4. Different possibilities for cyclopropanation *via* Michael-initiated ring closure (MIRC).

1.1.1.2 Carbene-based Cyclopropanations

Since carbenes are highly reactive species, for synthetic purposes they are usually generated *in situ*. Especially useful for cyclopropanations are (transition) metal carbenoids. Among the first to describe a cyclopropanation involving metal carbenoids were Simmons and Smith in the late 1950's, who treated alkenes with diiodomethane in the presence of activated zinc[20], in a procedure which is now well-known as the Simmons-Smith reaction. It quickly rose to popularity due to a broad substrate generality and functional group tolerance, stereospecificity with respect to the alkene geometry (most likely proceeding *via* a "butterfly-type" transition state[21], Scheme 5), as well as the *syn*-directing and rate-enhancing effect of proximal oxygen atoms[22]. Particularly the influence of oxygen atoms has been exploited for the development of asymmetric cyclopropanations involving allylic alcohols[23]. A variety of chiral auxiliaries has been reported which can be subdivided into general classes: allylic ethers, acetals, α,β-unsaturated carbonyl derivatives or enamines, and enol ethers. Carbohydrates have been successfully applied as auxiliaries providing high diastereoselectivities[24]. In case of acetal-derived auxiliaries, good results were achieved using tartaric acid[25] or threitol[26] derivatives. Although α,β-unsaturated esters and amides are rather uncommon substrates for this type of reaction, asymmetric reactions have been described using a bornane-derived auxiliary[27]. However, the addition of substoichiometric amounts of diethyl tartrate was necessary to obtain reasonable yields. Other

examples for chiral auxiliaries include oxazolidinones[28], (+)-camphor-derivatives[29] and boronic esters[30].



Scheme 5. Proposed transition states of Simmons-Smith cyclopropanation depending on olefin geometry.

The development of chiral ligands was investigated and the group of Charette made an important contribution in 1994 by introducing a bifunctional, amphoteric dioxaborolane ligand **1**[31] (Figure 3). This ligand has been successfully applied in the synthesis of different natural products including curacin A[32] and U-106305[33] (*vide supra*, Figure 2). Other examples of chiral ligands include BINOL[34]- and TADDOL[35]-derived phosphoric acids **2** and **3**. While the dioxaborolane ligand had to be applied in stoichiometric amounts, Charette could show that the BINOL[34a]- and TADDOL[36]-derived ligands provide promising enantiomeric ratios when used in substoichiometric quantities. Apart from that, to this day, there are still only a couple of catalytic methods for asymmetric Simmons-Smith cyclopropanations using substoichiometric amounts of catalyst. Examples include a chiral dipeptide (**4**) developed by the group of Shi[37] and an asymmetric aluminium-salen complex reported by Shitama and Katsuki[38].

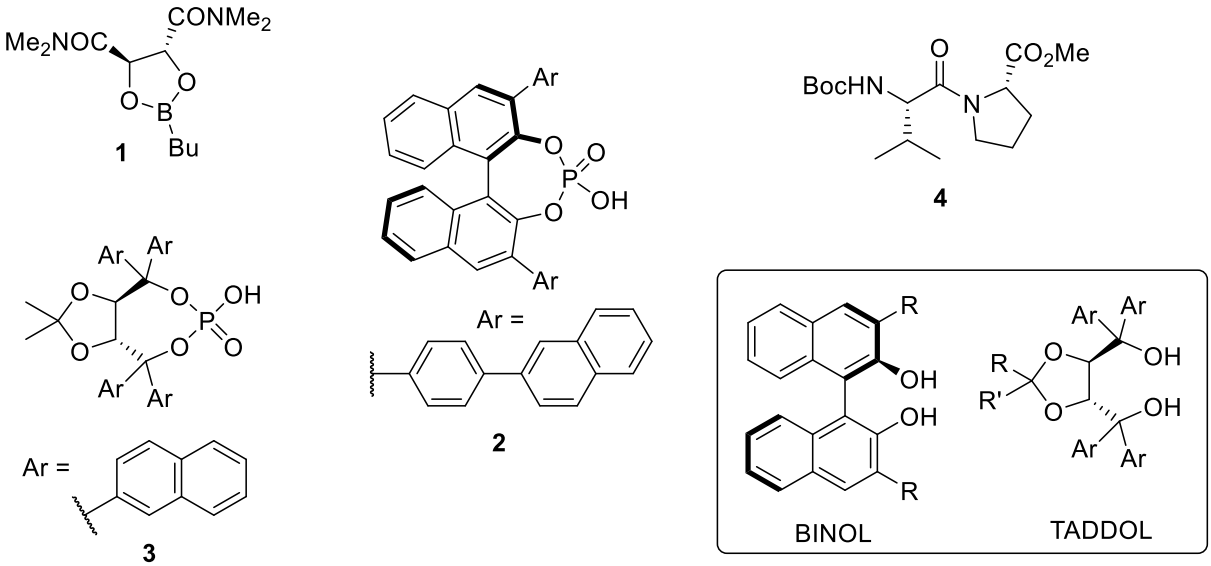
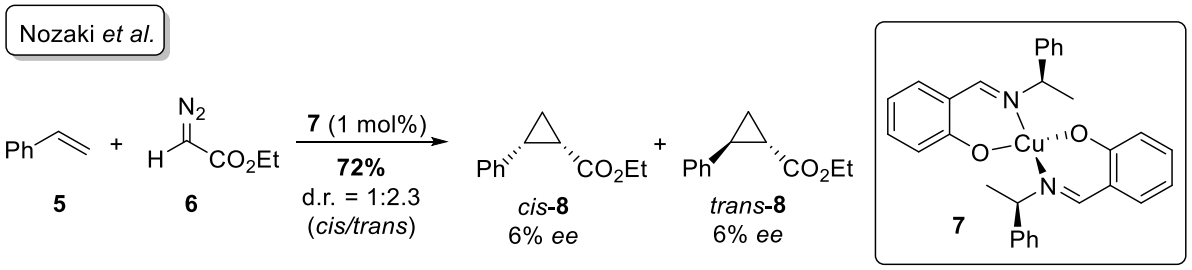


Figure 3. Chiral ligands for asymmetric Simmons-Smith cyclopropanations.

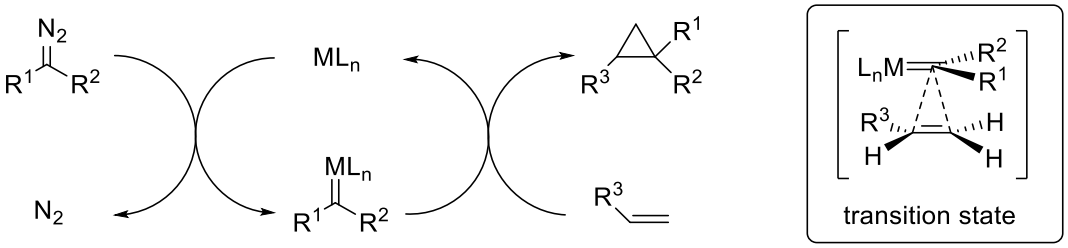
Beyond zinc, the use of transition metals as catalysts has risen to popularity since the report of Nozaki and coworkers in 1966 that a copper-carbenoid obtained through the decomposition of

diazoalkanes in presence of a chiral ligand promoted the asymmetric cyclopropanation of styrene[39] (Scheme 6).



Scheme 6. First example of asymmetric cyclopropanation using a transition metal catalyst.

A plethora of different transition metal catalysts has been developed over the past decades, the performance of each strongly depending on the nature of the diazo compound and whether an inter- or intramolecular reaction is carried out[14a]. Independent of the transition metal used, the widely accepted catalytic cycle proceeds *via* the formation of a metallocarbene complex after interaction of the catalyst with the diazo precursor and extrusion of nitrogen gas[14b, 40]. This is followed by a transfer of the carbene species onto the alkene (Scheme 7). The most successful and commonly applied transition metals for this transformation include copper[41], cobalt[42], ruthenium[43] and rhodium[44] of which the latter will be discussed more closely.



Scheme 7. Mechanism of the transition metal-catalyzed cyclopropanation *via* a metallocarbene species.

1.1.1.3 Dirhodium(II)-catalyzed Cyclopropanation

Dirhodium(II) paddlewheel complexes have emerged as highly successful catalysts for asymmetric cyclopropanations. They consist of a bimetallic core with a Rh-Rh single bond which is surrounded by four equatorial μ_2-ligands and two, generally labile, axial ligands[45] (Figure 4). In this form, the dirhodium(II) compounds are 18-electron complexes that become catalytically active if one of the axial ligands, most often a solvent molecule such as water or acetonitrile, dissociates, thereby generating an electron-deficient 16-electron complex[46]. The majority of dirhodium(II) catalysts are homoleptic, i.e. their four bridging ligands are chemically identical[47]. Typically, these ligands are either carboxylates, carboxamidates, or phosphonates, which all differently influence the electronic and steric properties of the overall catalyst and hence result in divergent reactivities and selectivities.

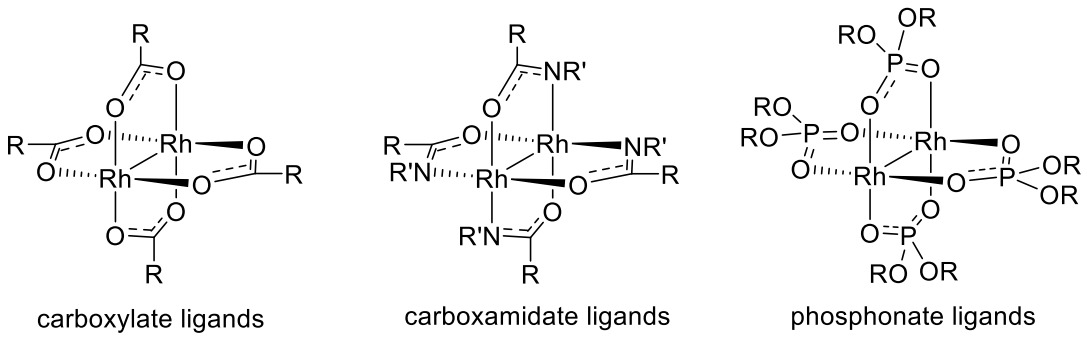


Figure 4. General structure of dirhodium paddlewheel complexes involving different types of ligands. Axially coordinating ligands omitted.

Dirhodium(II) phosphonates and carboxylates are comparatively electron-deficient making them kinetically very active, while the carboxamidate derivatives display a more electron-rich character, rendering them less catalytically active but more selective[44]. This observation is a result of the intrinsic electrophilicity of rhodium carbenes. Regarding their steric influence, the three-dimensional orientation of the ligands' blocking groups around the Rh-Rh core is crucial as it creates a chiral cavity around the axial coordination site and has thus been subject to extensive investigations. With respect to the Rh-Rh axis, the groups can either point up (α) or down (β), in principle resulting in four different orientation patterns[48] (Figure 5). Initially, it was proposed that only α,α,β,β- and α,β,α,β-arrangements would result in high enantioselectivities due to the presence of two equivalent catalyst faces[44]. However, Rh_2(*S*-PTTL)$_4$, a dirhodium paddlewheel complex developed by Hashimoto and coworkers[49], was shown to provide high enantioselectivities in cyclopropanation reactions and a model was proposed where the ligands' phthalimide groups adopt an α,α,α,α-orientation ("chiral crown") around one axial binding site while the *tert*-butyl-substituents block the access to the alternative binding site[50].

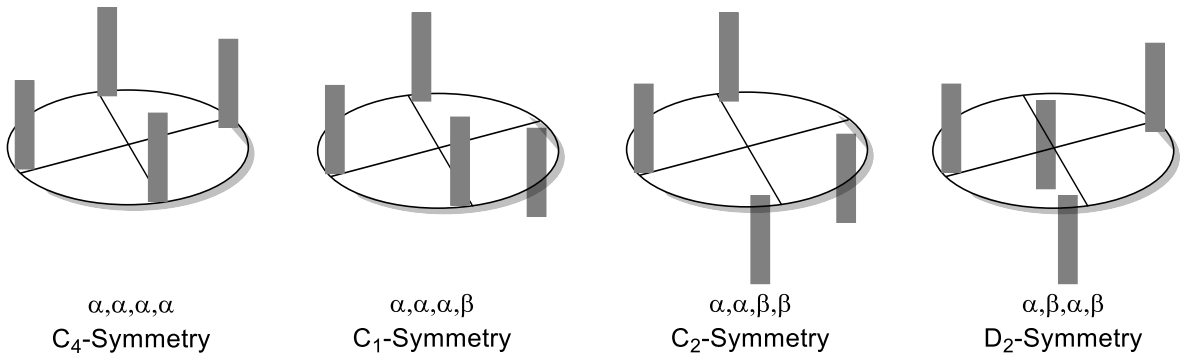
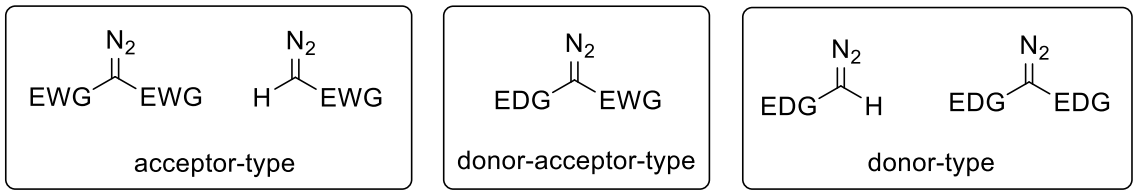


Figure 5. Possible orientations of ligands around the dirhodium axis.

At least in the solid state, this model could be confirmed *via* X-ray diffraction analysis of a carbene derivative of Rh_2(*S*-PTTL)$_4$[51]. Hence the original proposal regarding the ligands' orientation and the need for equivalent binding sites in the catalyst to achieve high levels of enantioselectivity possibly needs to be reconsidered. This is further underlined by certain examples of heteroleptic

dirhodium(II)-complexes that provided highly enantioselective cyclopropanations without possessing the supposedly required symmetry[52].

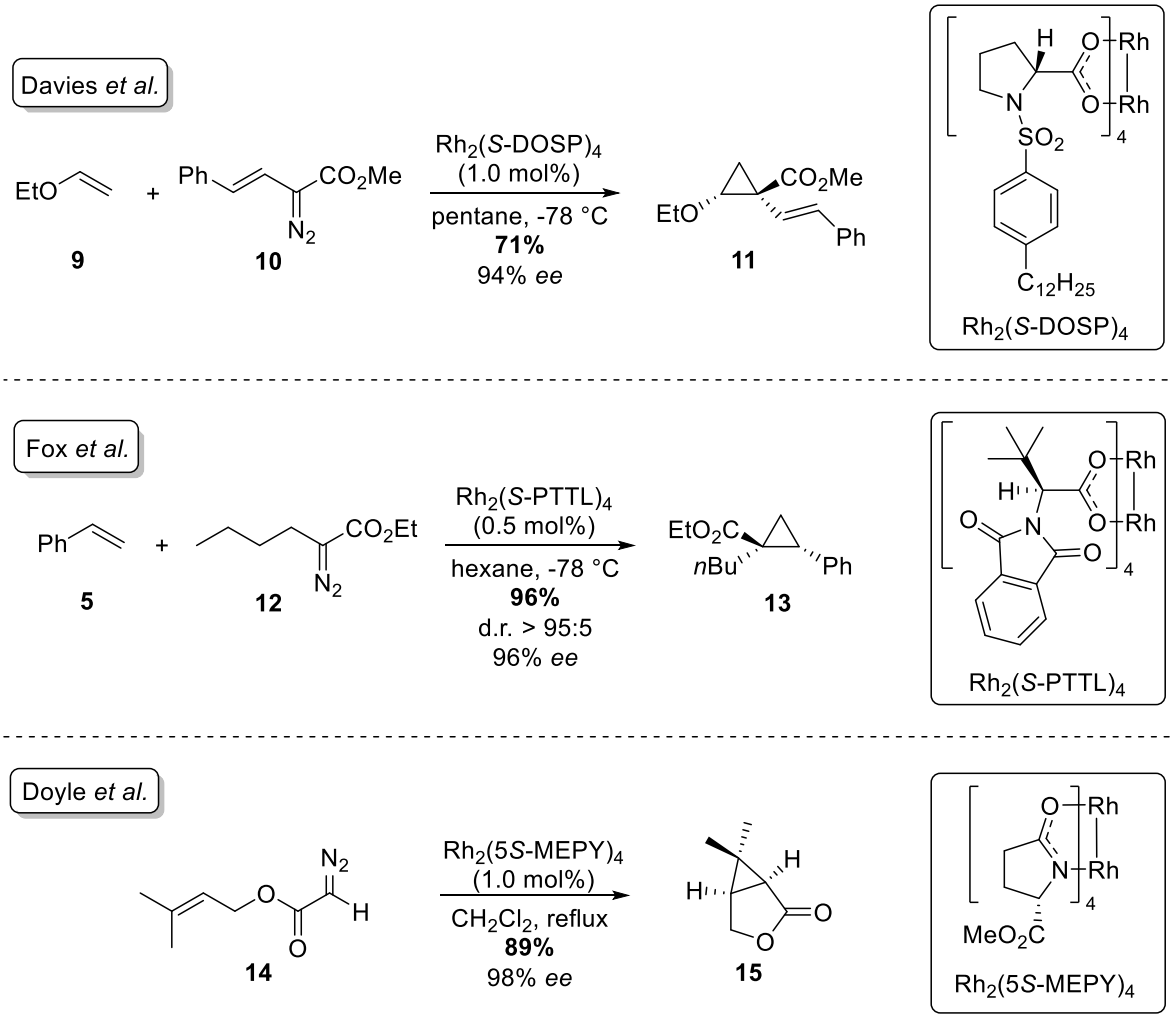
The nature of the diazo compound and thus the organic fragment of the resulting metal carbene is also of importance for the success of the cyclopropanation. Diazo compounds can be classified by the electronic properties of their substituents, being either electron-withdrawing, such as esters, nitriles, ketones, nitro groups or phosphonates, or electron-donating such as aryl, alkyl or alkenyl groups (Figure 6). In principle, all combinations of substituents are possible, from donor-donor- to acceptor-acceptor-type diazo compounds. They differ drastically in their applicability for dirhodium(II)-catalyzed cyclopropanations[14a]. By far the best results in terms of chemo- and diastereoselectivity have been observed when diazo compounds of the donor-acceptor-type were used with dirhodium(II)-catalysts[53]. The observed selectivity was investigated by means of a computational study where it was concluded that metal carbenes derived from donor-acceptor type diazo compounds have more stabilizing structural factors. Compared to acceptor-type carbene systems, this results in generally higher energy barriers for the cyclopropanation event and later transition states with increased charge build-up [54]. These factors lead to an increased selectivity between electronically different substrates. Furthermore, the proposed late transition state was argued to display less flexibility, thus increasing the influence of steric interactions during the approach of the alkene, which could explain the observed diastereoselectivity[55].



EWG = CO_2R, COR, CN, NO_2, SO_2R, $PO(OR)_2$, etc.
EDG = aryl, alkenyl, alkynyl, etc.

Figure 6. Categories of diazo compounds depending on the electronic properties of their substituents.

A successful example for dirhodium(II)-carboxylates is $Rh_2(DOSP)_4$, bearing proline-derived ligands which, among others, has been applied in the intermolecular asymmetric cyclopropanation of vinyl ethers[56], dienes[57] and alkynyldiazoacetates[58] (Scheme 8). Furthermore, the already mentioned $Rh_2(PTTL)_4$ was applied in the highly enantioselective cyclopropanation of alkyl diazoester **12**[50a]. Dirhodium(II)-carboxamidates, such as $Rh_2(MEPY)_4$, have on the other hand proven especially useful for intramolecular cyclopropanations, resulting in preferably small, ring-fused lactones or lactams[59].



Scheme 8. Application of chiral dirhodium paddlewheel complexes in inter- and intramolecular asymmetric cyclopropanations.

1.1.2 Functionalization of Cyclopropanes

Due to their intriguing physical and chemical properties (*vide supra*), cyclopropanes have been extensively used in organic synthesis[60]. Their inherent ring strain has been exploited as a driving force for reactions involving cleavage of the cyclopropane such as cycloadditions[61] or nucleophilic, electrophilic or redox-based ring fissions[60a, 60b, 62]. Also well-known are transformations such as the rearrangement of a vinylcyclopropane (VCP) into a cyclopentene, which was first described to occur upon pyrolysis of the respective starting materials[63] (Figure 7). Soon after its discovery, several other methods were developed to initiate the rearrangement under milder conditions, including photolysis[64] and transition metal catalysis[65]. The rearrangement can further be facilitated by the strategic placement of adequate substituents on the cyclopropyl ring[66]. A similar rearrangement can also take place with the respective carbonyl- or imine-substituted cyclopropanes, resulting in the formation of five-membered heterocycles in a transformation known as the Cloke-Wilson rearrangement[67]. Both versions of the

rearrangement have been successfully applied in the total synthesis of natural products such as aphidicolin[68], zizaene[69], mesembrine[70] and aspidospermine[71].

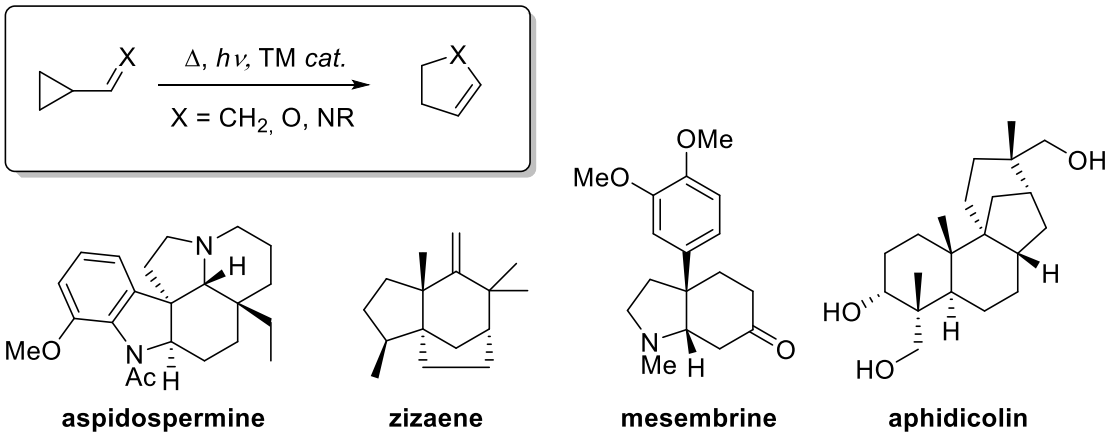


Figure 7. General depiction of vinylcyclopropane (VCP) rearrangement and examples of natural products that were synthesized involving the reaction.

During his studies on the VCP rearrangement, Vogel discovered the closely related divinylcyclopropane rearrangement which leads to the formation of cycloheptadienes[63b, 72] (Figure 8). While the *cis*-isomer readily underwent the Cope-type rearrangement, the *trans*-isomer required heating to 200 °C. The temperature could be decreased below 100 °C in the presence of hexafluoroacetylacetonatorhodium(I)[73]. Furthermore, photochemically induced *cis*/*trans*-isomerizations of divinylcyclopropane derivatives followed by rearrangement have been reported[74]. Similar to the VCP rearrangement, heteroatom variants including oxygen or nitrogen derivatives have been investigated as well[75]. The rearrangement constitutes a convenient method for the construction of fused bicyclic systems, especially in the synthesis of pseudoguaiane-type natural products[74b, 76]. Other natural products that have been synthesized incorporating the rearrangement include sinularene[77], colchicine[78] and schisanwilsonene A[79].

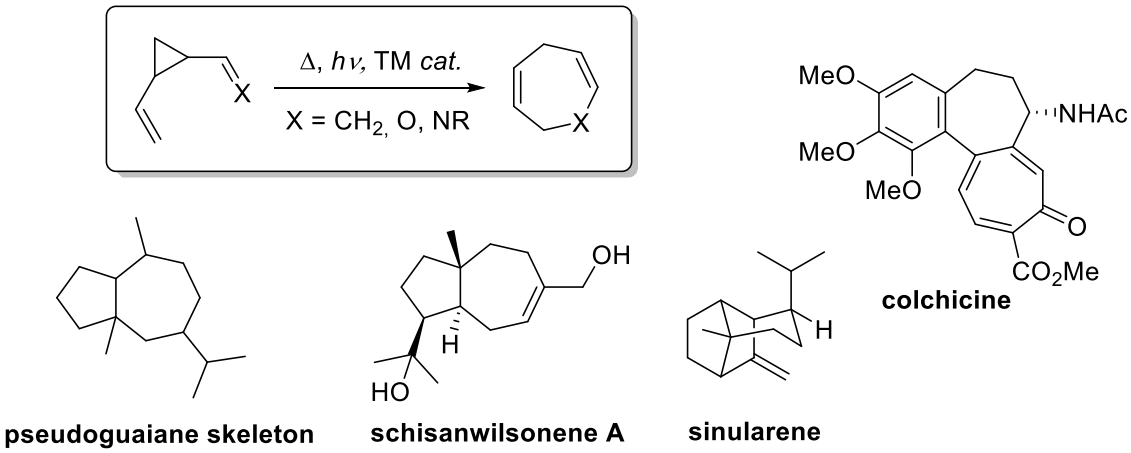
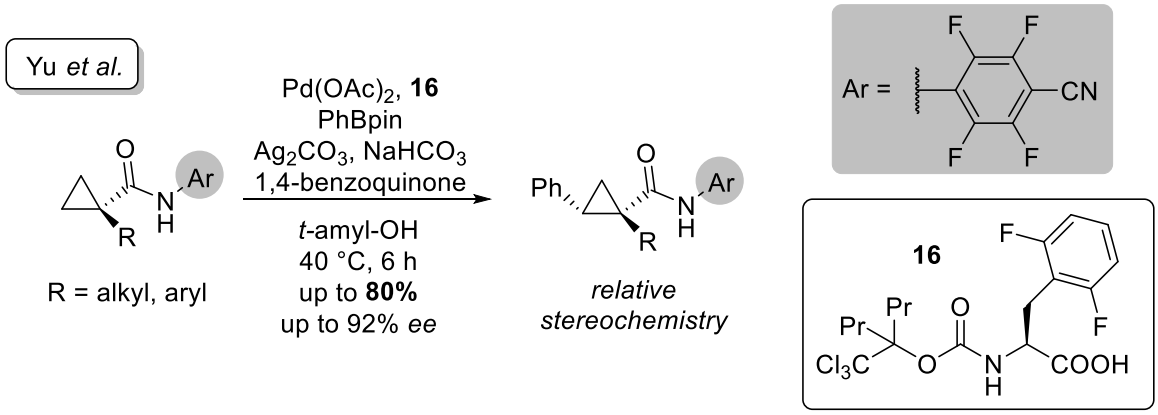


Figure 8. General depiction of divinylcyclopropane rearrangement and examples of natural products that were synthesized involving the reaction.

The unique bonding situation and sp²-like C-C-bond orbitals of the cyclopropyl motif have been taken advantage of for functionalizations that leave the three-membered ring intact. In particular, (transition-)metal catalyzed transformations have been developed[80]. The change in orbital hybridization leads to an increase in acidity of the C-H bonds in cyclopropane (pKa of ~46 compared to 51 in linear propane), making them more prone towards cleavage and facilitating C-H-functionalization. Hence, a variety of both inter-[81] and intramolecular[82] direct C-H-functionalizations of cyclopropanes have been reported in the literature. Notably, an additional electron-withdrawing or directing group is typically still required to ensure reactivity and selectivity. Most commonly used are (hetero)aryl amides such as, for example, aminoquinolione[83] or picolinamide[84]. After the first successful enantioselective catalytic cyclopropyl C-H activation by Yu and coworkers in 2011[85] (Scheme 9), several other enantioselective C-H-functionalizations have also been developed[86], often utilizing chiral amino acid-derived ligands[87]. In the majority of these cases, an arylation of the cyclopropane takes place and only few examples have been reported that involve other classes of coupling partners.



Scheme 9. Example for enantioselective cyclopropyl C-H activation.

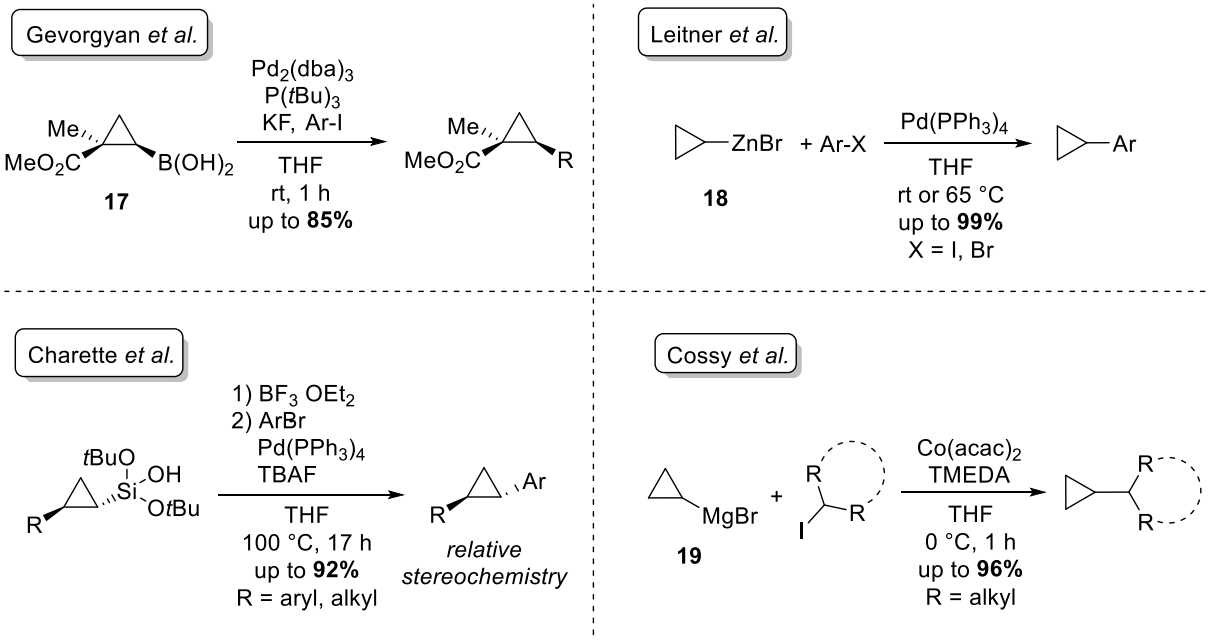
1.1.2.1 Metalated Cyclopropanes

Similar to a C-H bond, the atomic orbital on carbon participating in a carbon-metal bond will possess increased s-character in cyclopropane compared to its linear derivative[80a]. Thus, metalated cyclopropanes are promising nucleophiles for cross coupling reactions, as they will undergo transmetalation and reductive elimination faster than their non-cyclic alkylmetal counterparts. Moreover, they are unlikely to undergo β-hydride elimination because the theoretically resulting cyclopropene is thermodynamically highly unfavoured[80b],[1].

The first Suzuki-Miyaura coupling involving 1,2-*trans*-disubstituted cyclopropylboronic esters was reported in 1996[89] and since then it has found broad application in synthesis (Scheme 10).

[1] Conversely, although principally possible, the use of cyclopropanes as electrophiles is only rarely described in the literature[88]

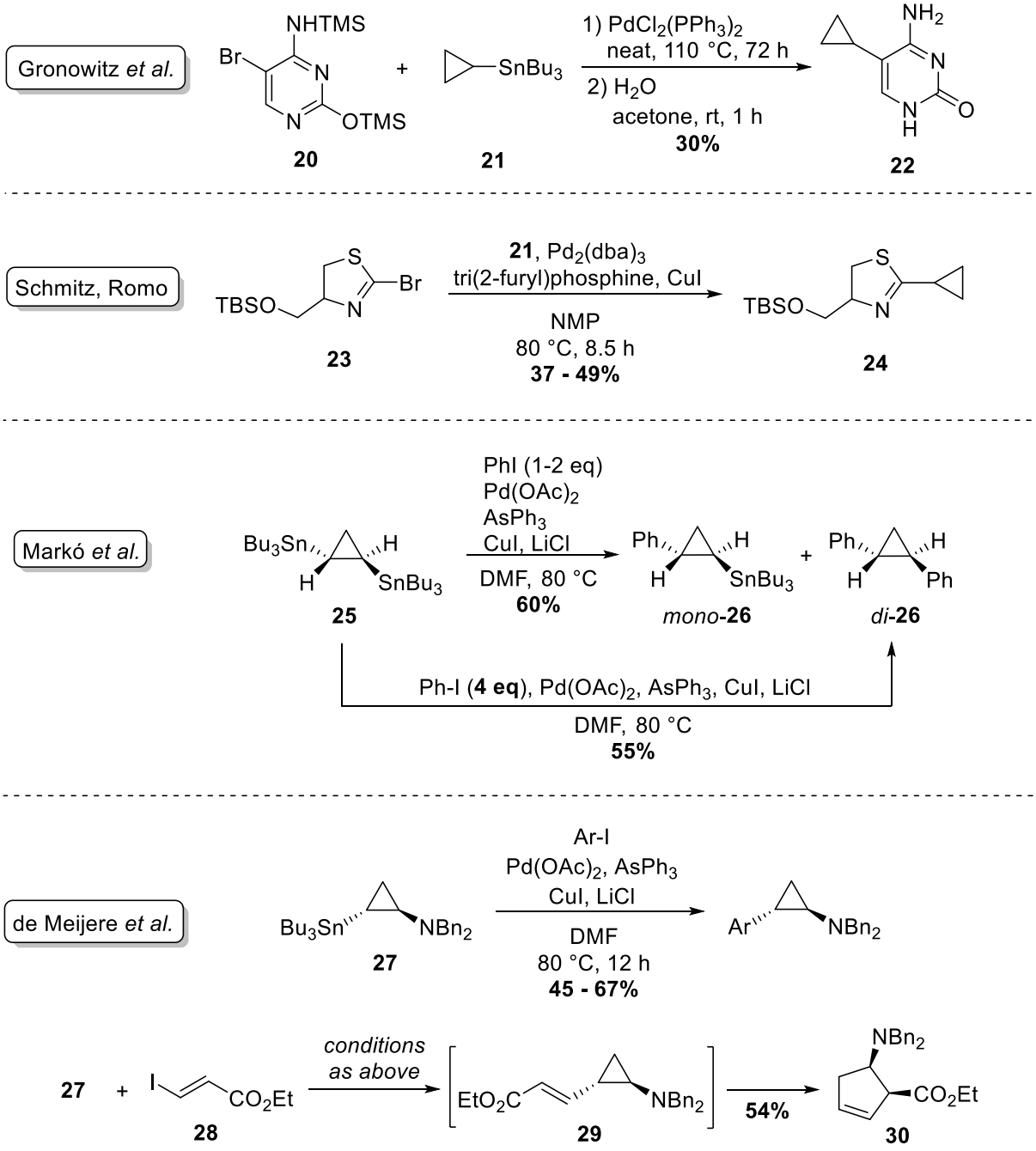
Beyond boronic esters[88b, 90], their typically more reactive boronic acid counterparts have been applied[91] as well as cyclopropyltrifluoroborates[92]. Notable examples include the successful coupling of a *cis*-substituted cyclopropylboronic acid **17**[93] and the application of tertiary cyclopropylboron nucleophiles[94]. Cyclopropylzinc halides (**18**) have been shown to participate in Negishi couplings[95], having recently been applied in an enantiodivergent relay coupling to generate enantioenriched cyclopropanes from racemic cyclopropylzinc reagents[96]. Kumada cross couplings involving cyclopropyl Grignard reagents (**19**) have exhibited a comparatively limited scope[97], mostly due to the lack of compatibility of Grignard reagents with many functional groups. Interestingly, only one cross coupling using silylcyclopropane nucleophiles has been reported thus far[98].



Scheme 10. Examples for cross couplings involving cyclopropyl nucleophiles: Suzuki (top left), Negishi (top right), Hiyama-Denmark (bottom left), Kumada (bottom right).

There are few reports of cyclopropylstannanes being applied in Stille cross couplings, most of which provide low to moderate yields (Scheme 11). Examples include the functionalization of brominated cytosine (**20**)[99] or thiazoline (**23**) derivatives[100] using monosubstituted tributylcyclopropylstannane **21**. In the latter case, the desired product is contaminated by an inseparable byproduct which the authors presume to be a pyrroline derivative, resulting from an iminocyclopropane rearrangement (*vide supra*). Cross couplings of 1,2-distannyl cyclopropane **25** with aryl iodide electrophiles have been carried out as well[101]. In order for the two-fold substitution to occur, an excess of four equivalents of phenyl iodide and increased catalyst loading was needed; otherwise a mixture of mono- and disubstituted cyclopropanes was obtained[101a]. The group of de Meijere cross-coupled *trans*-dibenzylamino-substituted cyclopropylstannane **27**

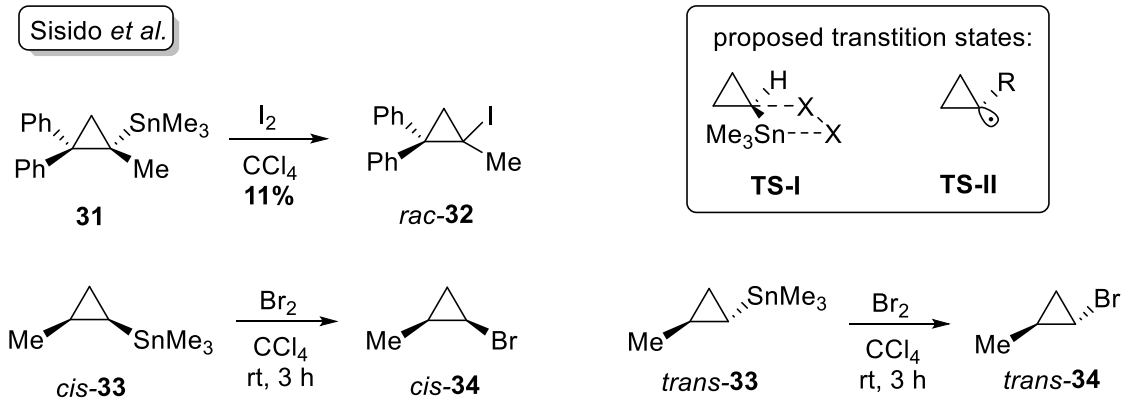
with aryl iodides. A VCP rearrangement was observed when they used iodoacrylate **28** as the electrophile, resulting in a five-membered carbocycle **30**[101b].



Scheme 11. Application of stannylated cyclopropanes in Stille cross couplings.

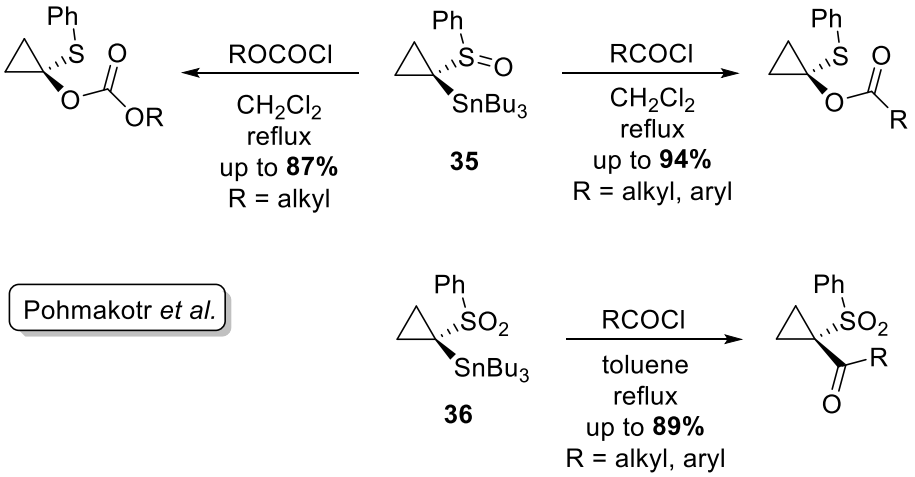
Despite their modest performance in Stille couplings, cyclopropylstannanes nevertheless constitute interesting building blocks due to their ability to undergo various other functionalizations[102]. Tin-halogen exchange has been investigated by the groups of Sisido[103] and Baekelmans[104] who observed a profound influence of the substitution pattern on the outcome of the reaction (Scheme 12). With geminally unsubstituted cyclopropylstannanes **33**, a retention of configuration in the obtained halogenated products **34** was detected[103c, 104] while in presence of

an additional geminal substituent (**31**) complete racemization occurred[103a, 103b]. This difference in the stereochemical outcome was proposed to be the result of two different mechanisms. One proceeds *via* an ionic pathway through a four-centered transition state (**TS-I**), leading to retention, while the other involves the formation of a tertiary radical species capable of epimerization (**TS-II**).



Scheme 12. Application of differently substituted cyclopropylstannanes in tin-halogen exchange.

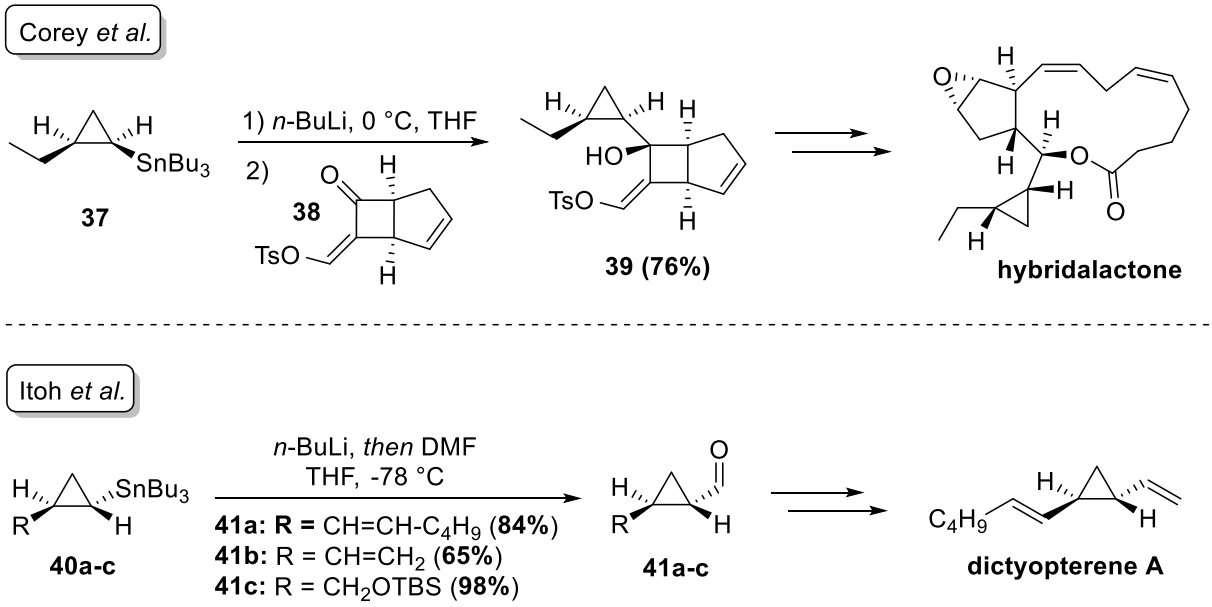
Another interesting transformation was described by the group of Pohmakotr, who discovered that the treatment of 1-phenylsulfinyl-1-tributylstannylcyclopropane **35** with acid chlorides or alkyl chloroformates resulted in a destannylative Pummerer rearrangement and the ultimate formation of acyloxy- or alkoxycarbonyloxy-derivatives[105] (Scheme 13). However, when the respective phenylsulfonyl derivative **36** was used, destannylative acylation occurred without rearrangement[106].



Scheme 13. Destannylative acylation and Pummerer rearrangement of cyclopropylstannanes.

At present, tin-lithium exchange is arguably the most widely applied transformation of cyclopropylstannanes. At temperatures below 0 °C the transformation is remarkably stereospecific, generally proceeding with retention of configuration[107]. Upon warming, epimerization of cyclopropyllithiums has been observed, especially if there are chelating

structural motifs present in the molecule[107a] or in the presence of α-functional groups able to stabilise a cyclopropyl anion such as bromo-[108], silyl-[109] or sulfur[110]-substituents. The lithiation proceeds most efficiently when THF is used as the solvent, while significantly slower transmetalation was observed in dimethoxyethane and none at all in diethyl ether or hexane[111]. In the majority of cases, *n*-butyllithium was applied as the lithiating reagent, although in case of *cis*-cyclopropylstannanes it was observed that methyllithium exhibited a superior performance[111]. Moreover, the tributyltin group is predominantly used, and it has been reported that treatment of respective trimethyltin derivatives with *n*-butyllithium resulted in tin-lithium exchange on the methyl fragment instead of the cyclopropyl group, replacing the methyl groups on the tin moiety by butyl groups[111-112]. After successful tin-lithium exchange, the intermediate cyclopropyllithium species can be trapped with various electrophiles including CO_2, formaldehyde, diphenyl disulfide, methyl iodide, TMSCl and DMF, among others[101a, 111, 113]. Accordingly, the methodology has been applied in total syntheses such as Corey's synthesis of hybridalactone[107c] or Itoh's synthesis of dictyopterene A[114] (Scheme 14).



Scheme 14. Application of tin-lithium exchange with cyclopropylstannanes in total syntheses of natural products.

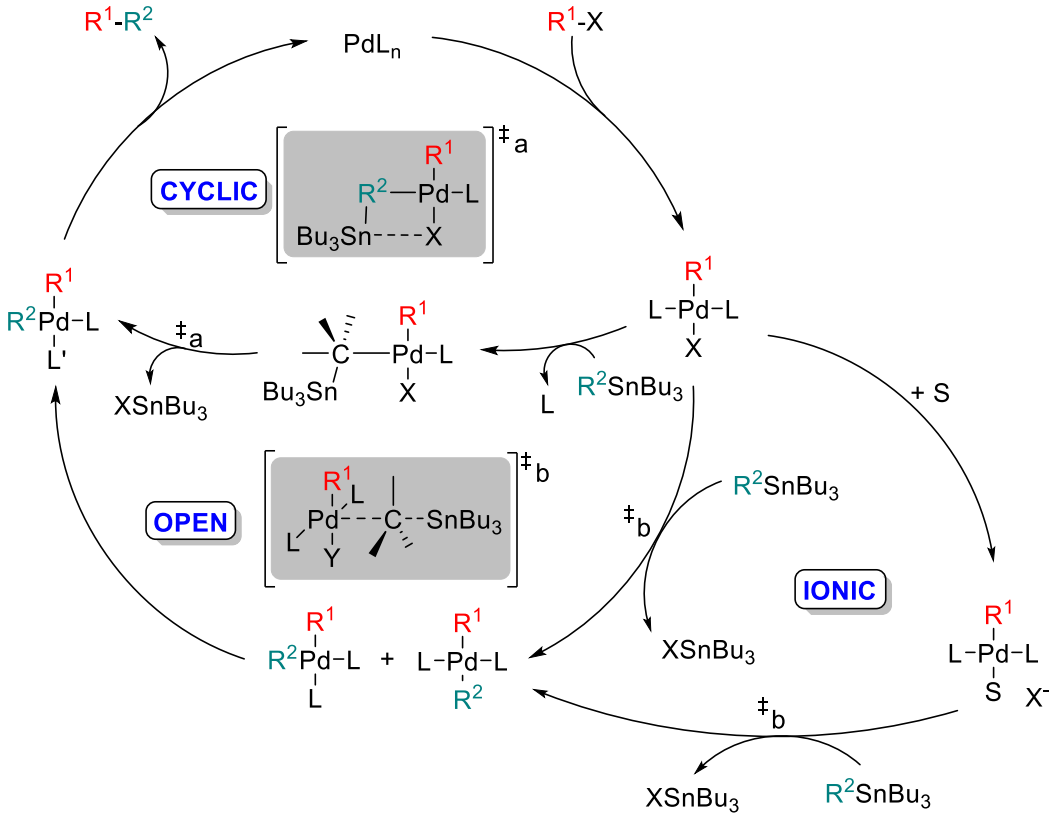
1.1.3 Stille-Migita Cross Coupling

The Stille coupling has been known for more than 40 years and continues to be a valuable tool for C-C bond formation in numerous synthetic applications due to its generally mild conditions without the need for an additional base and high functional group tolerance[115]. Although initially described by Eaborn[116] and Kosugi/Migita[117], the reaction bears Stille's name owing to his synthetic works and mechanistic studies on the topic[115d, 118]. Over the decades, some major improvements of the reaction have been achieved; such as the development of bulky phosphine ligands and the use of copper and fluoride salts as additives. The use of bulky phosphines offers

several advantages throughout the catalytic cycle[119]. During oxidative addition, their ability to form monoligated Pd(0) species causes increased reactivity due to vacant coordination sites and less ligand repulsions. If the phosphine ligand is also electron-rich in nature, it facilitates the oxidative addition step even more by creating a more reducing palladium species through electron donation. After oxidative addition, the resulting tricoordinated palladium species is more electrophilic compared to a tetracoordinated one and thereby the nucleophilic attack of the stannane, i.e. transmetalation, is more facile. The ligand also benefits the reductive elimination step due to very low barriers. The beneficial effect of copper(I) salts on the reaction rate ("copper effect") was first described by Liebeskind[120]. It was proposed that the copper ion functions as a ligand scavenger, enabling free coordination sites on palladium[121]. Furthermore, the *in situ* generation of an organocopper species *via* transmetalation from tin to copper potentially takes place, with the organocopper species in turn being more prone to undergo transmetalation to palladium[122].

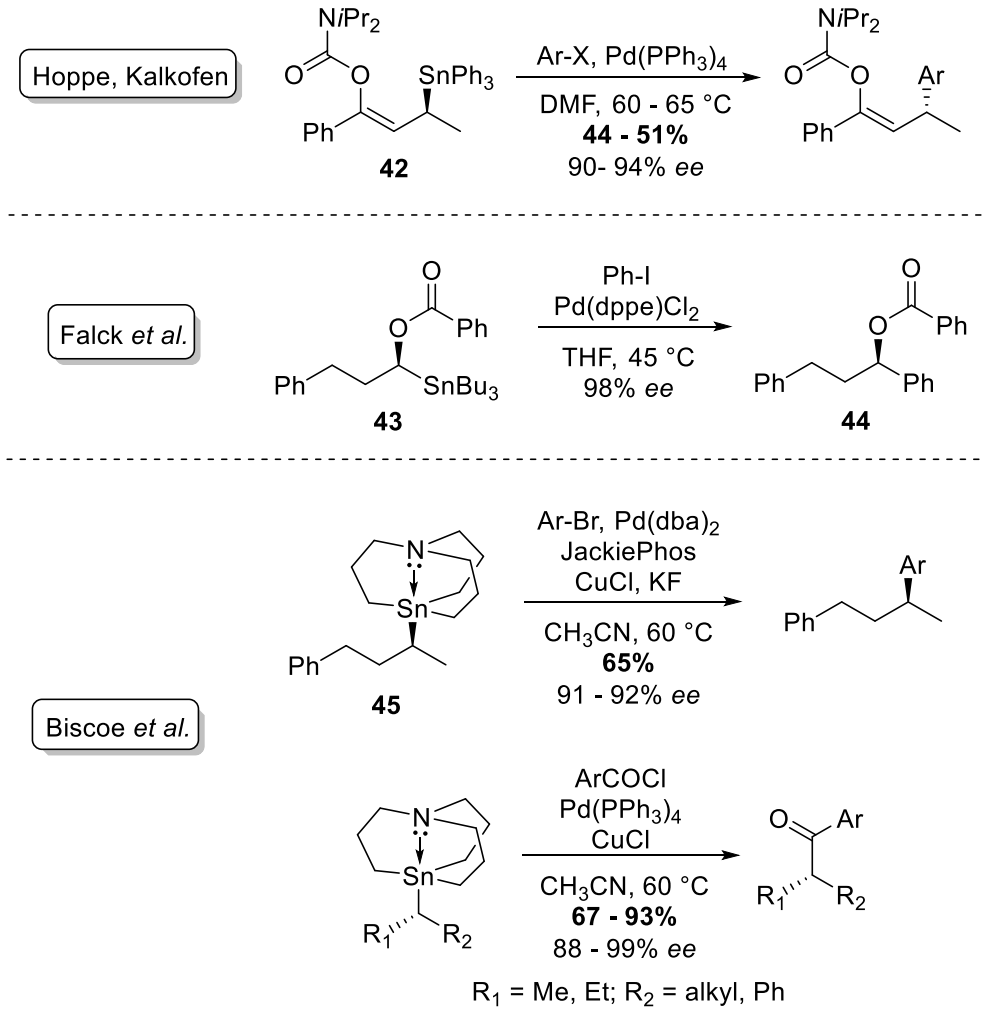
The addition of fluoride ions may enhance the Stille reaction in different ways. One hypothesis is the formation of a pentacoordinated and hence hypervalent anionic tin-ate species which is more reactive towards transmetalation to palladium[123]. It is also argued that fluoride ions function as a tin scavenger, forming less reactive or even insoluble R_3SnF species and thereby shifting the equilibrium of the transmetalation[124]. Fluoride ions might also promote the transmetalation step by coordinating to the palladium complex and making it more reactive towards the organotin nucleophile as well as enhancing reductive elimination[125]. A synergistic effect of combining both copper and fluoride sources has been reported, enabling the cross coupling of electronically unfavourable and sterically hindered substrates[124b, 126].

Stille originally proposed a four-step catalytic cycle, consisting of oxidative addition, transmetalation, isomerization and reductive elimination[115d]. Since then, a more detailed version of the catalytic cycle has emerged based on experimental observations and theoretical studies (Scheme 15). Of special interest when dealing with chiral stannanes is the mechanism of the transmetalation step which determines the stereochemical outcome in terms of inversion or retention of configuration at the chiral centre[119]. Three main pathways have been proposed for this step, cyclic, open or ionic, whereas the latter is a subcategory of the open pathway. The cyclic pathway is associated with retention of configuration; it is favoured for less polar, poorly coordinating solvents and requires a good bridging anionic ligand[127]. In contrast, the open or ionic pathway with inversion of configuration will be more likely if highly coordinating, polar solvents are used and in presence of poorly coordinating anionic ligands[128].



Scheme 15. Proposed catalytic cycle for Stille cross couplings.

An increasing amount of stereospecific Stille couplings has been reported in the literature over the past years[119]. In many cases, the activation of the secondary alkylstannane by additional α-functionalization or directing/coordinating groups is required for selective transmetalation[129]. Hoppe applied allylic stannane **42** with an additional alkenyl carbamate in the cross coupling with different aryl halides, consistently reporting > 90 % *ee* and complete inversion[130] (Scheme 16). Falck and coworkers coupled enantioenriched α-acyloxy-substituted secondary stannanes such as **43** with aryl and alkenyl iodides, reporting retention of configuration[131]. The first example involving unactivated secondary stannanes such as **45** was reported by Biscoe and coworkers, who increased the nucleophilicity of the stannane by applying azastannatranes[132]. The methodology was later extended towards acylation with slight modification of conditions[133]; in both cases retention of configuration was observed.



Scheme 16. Stereospecific Stille couplings of enantioenriched secondary alkylstanna(tra)nes.

1.2 Aim

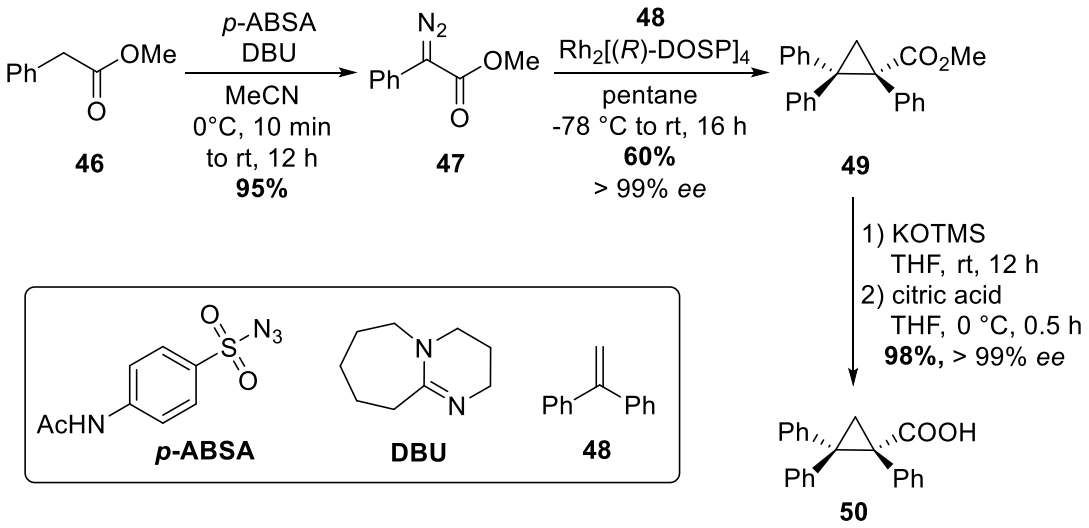
In preceeding studies, a heteroleptic dirhodium catalyst had been developed in our group that enabled the asymmetric cyclopropanation of olefins using an α-stannylated diazo ester[134]. The aim of this project was to further investigate the synthesis and downstream modification of the obtained enantioenriched cyclopropylstannanes. Focus should be put on stereospecific Stille couplings, ideally developing a methodology for the introduction of a variety of substituents and thus synthesizing a broad product library. In particular, compounds which would otherwise be incompatible with the given cyclopropanation conditions were of interest. Further transformations of the prospective Stille coupling products and other potential functionalizations of cyclopropylstannanes would be explored as well. This late stage diversification methodology would enable the access to various enantioenriched cyclopropanes by following the same general protocol without the need to optimize the reaction conditions for every single substrate.

1.3 Asymmetric Cyclopropanation

1.3.1 Synthesis of the 1st Generation Dirhodium Catalyst

Conceptualization of the dirhodium paddlewheel complex and its synthetis were conducted by Dr. Fabio Caló. Exploration of the cyclopropanation scope was conducted in cooperation with Dr. Fabio Caló[135].

The synthesis of the ligand **50** required for the desired dirhodium catalyst started from methyl phenylacetate **46**, which was converted into the respective diazo compound **47** upon treatment with *p*-ABSA under basic conditions[136] (Scheme 17). Cyclopropanation of **47** using Rh_2[(*R*)-DOSP]$_4$ as catalyst[137] afforded methyl ester **49**, which was converted into free carboxylic acid **50** by saponification with potassium trimethylsilanolate.

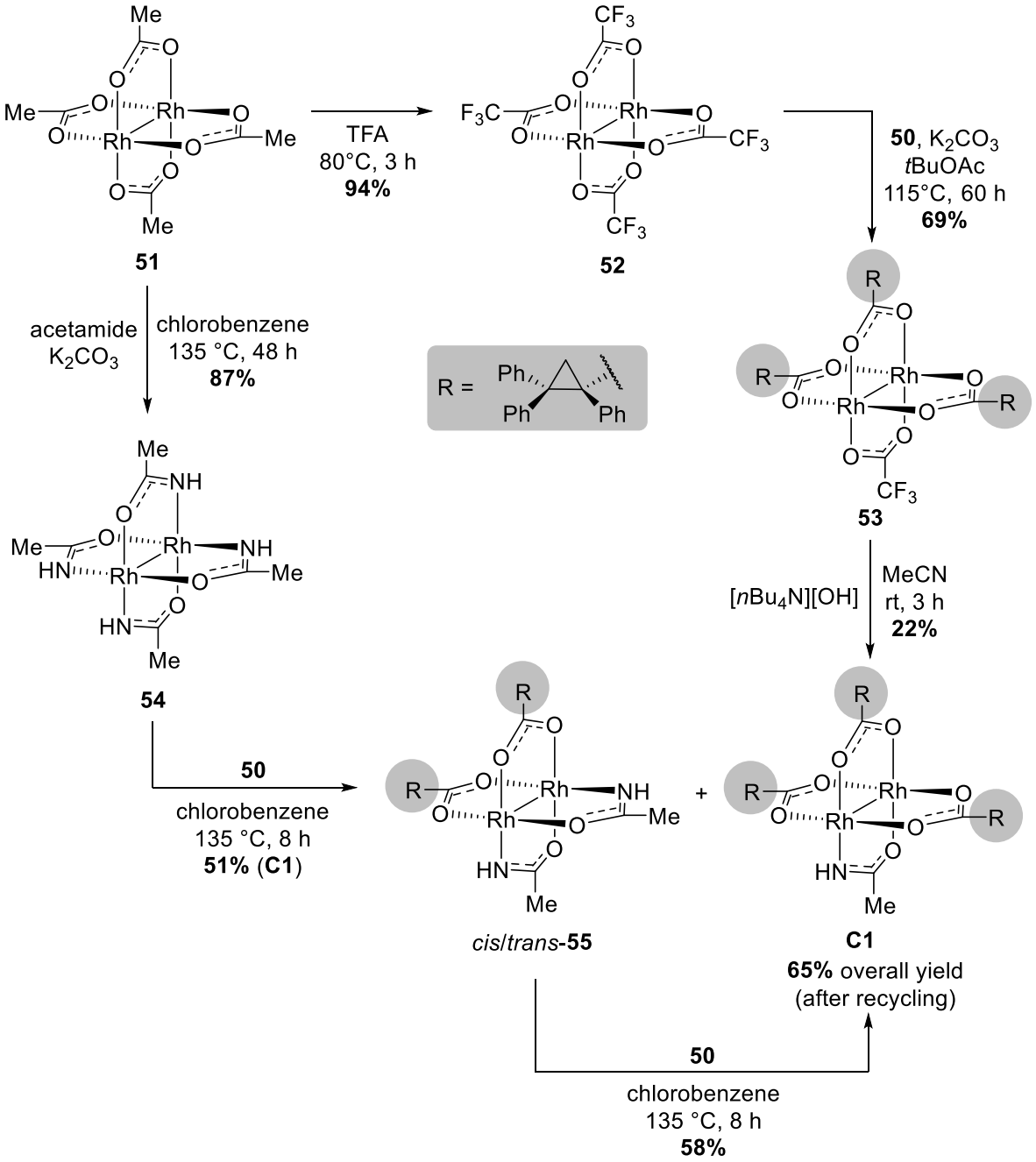


Scheme 17. Synthesis of ligand 50 for the dirhodium paddlewheel catalyst.

To introduce the ligand to the dirhodium scaffold, a procedure previously established in our goup was initially applied, which consisted of a three-fold ligand exchange on $Rh_2(TFA)_4$ (**52**)[134]. This compound can be synthesized by etching $Rh_2(OAc)_4$ (**51**) with trifluroacetic acid and is needed to facilitate the ligand exchange (Scheme 18). A modified Soxhlet apparatus was used when reacting $Rh_2(TFA)_4$ with ligand **50** in *tert*-butyl acetate at reflux temperature. The resulting heteroleptic rhodium complex **53** was then treated with tetrabutyl ammonium hydroxide in acetonitrile to install the acetamidate by replacing the last remaining trifluoroacetate ligand. The desired dirhodium acetamidate complex **C1** could be isolated by flash chromatography, albeit in poor yield of only 22 %.

Eventually, a more convenient and higher yielding route towards the desired heteroleptic dirhodium catalyst system was developed. Since the last step of the previous synthetic route was particularly problematic, strategic introduction of the acetamidate motif at an early stage was implemented. Therefore, $Rh_2(OAc)_4$ was converted into $Rh_2(acam)_4$ (**54**) by heating it to reflux in

chlorobenzene in the presence of acetamide using the modified Soxhlet apparatus (Scheme 18). Next, the three-fold ligand exchange was conducted with $Rh_2(acam)_4$ and ligand **50** in refluxing chlorobenzene which yielded the desired heteroleptic complex **C1** in 51 % yield. This could even be increased to 65 % overall yield, if the additionally obtained two-fold ligand exchange products ***cis-*** and ***trans*-55** were isolated and re-submitted to the reaction conditions.



Scheme 18. Synthesis of dirhodium catalyst C1 *via* $Rh_2(TFA)_4$ (top right) or $Rh_2(acam)_4$ (bottom left).

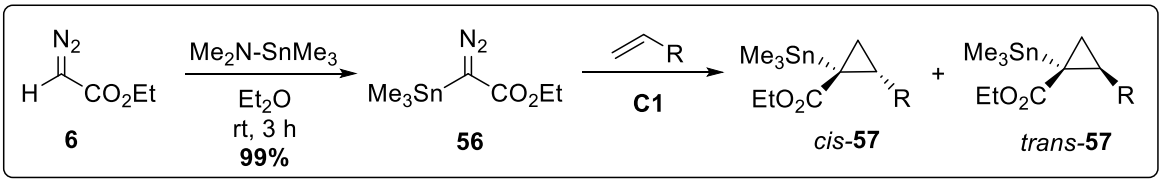
1.3.2 Scope of the 1st Generation Dirhodium Catalyst

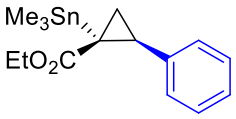
The dirhodium catalyst **C1** was applied in the cyclopropanation of various olefins in combination with α-stannylated ethyl diazoacetate **56**. This compound was prepared in almost quantitative

yield (> 90 %) from ethyl diazo acetate **6** and dimethylamino trimethyltin following the metal amide methodology[138] where the dimethylamine formed evaporates from the reaction mixture, driving the reaction to completion. Diazo stannane **56** is a light yellow, crystalline solid that is stable at room temperature. Under the conditions of the cyclopropanation reaction, dimerization of the diazo stannane **56** was observed as a significant undesired side reaction. It could be suppressed by dropwise addition of the solution of the diazo compound over a course of six hours to the mixture of catalyst and olefin by means of a syringe pump.

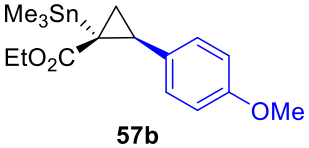
A broad variety of monosubstituted olefins underwent the cyclopropanation, including both electron-rich and -poor substrates (Scheme 19). The stannylated cyclopropanes **57** were obtained in medium to high yields and *ee*s. It is important to note that a loss of product in a range of 5 to 10 % could not be avoided during purification *via* flash chromatography, which became evident when comparing NMR yields and isolated yields. This was attributed to the mildly Brønsted acidic silica gel causing protodestannylation. While the enantioselectivity was excellent with the majority of substrates for both the *cis*- and the *trans*-isomers, the *cis*/*trans* diastereoselectivity remained rather low and appeared to depend mostly on the steric bulk of the olefinic substrate. The *cis*- and *trans*-isomers were not always fully seperable *via* flash chromatography, hence the diastereomeric ratio was determined *via* ^{1}H-NMR of the crude mixture and the yield is given for both isomers combined. The absolute configuration of the cyclopropanes was determined *via* X-ray diffraction analysis of the *para*-nitro phenyl and the phthalimide derivatives **57c** and **57g**. For the other substrates, the same absolute configuration was assumed by analogy. The relative stereochemistry was determined *via* NOESY NMR experiments.

Olefins with higher substitution patterns reacted less efficiently, most likely as a result of steric hindrance; indene was the only successful 1,2-substituted olefin (**57h**). In terms of 1,1 substitution, small carbocycles bearing an exomethylenic group could be cyclopropanated, resulting in spirocyclic compounds (**57m-o**). Furthermore, isobutene provided a dimethyl substituted cyclopropane **57l** in excellent yield and α-methyl styrene could also be cyclopropanated (**57d**). Beyond these examples, other 1,1-substituted olefins were no suitable substrates for the catalyst, for example when replacing the aforementioned methyl group with a CF_3 or TMS group. This lack of reactivity towards higher substituted olefins could however be taken advantage of when employing different dienes with which cyclopropanation exclusively occurred at the terminal double bond (**57i-k**).

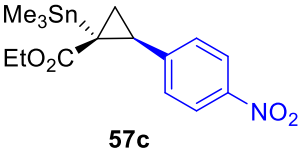




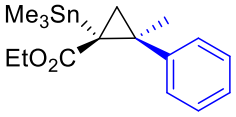
57a
78%, d.r. ≈ 1.4:1
97% *ee* (*cis*)
93% *ee* (*trans*)



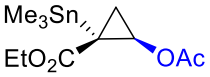
57b
76%, d.r. ≈ 1:1
97% *ee* (*cis*)
95% *ee* (*trans*)



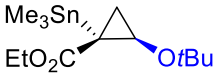
57c
61%, d.r. ≈ 1:1
82% *ee* (*cis*)
91% *ee* (*trans*)



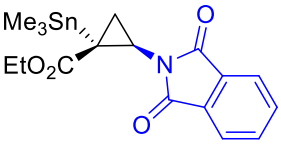
57d
51%, d.r. ≈ 1:1
96% *ee* (*cis*)
95% *ee* (*trans*)



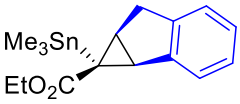
57e
59%, d.r. ≈ 2.8:1
84% *ee* (*cis*)
80% *ee* (*trans*)



57f
61%, d.r. ≈ 1.8:1
96% *ee* (*cis*)
98% *ee* (*trans*)



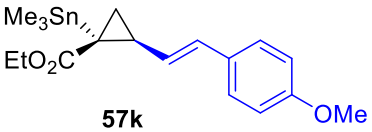
57g
54%, d.r. ≈ 1:5
96% *ee* (*trans*)



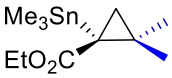
57h
75%, d.r. ≈ 1.1:1
93% *ee* (*cis*)
84% *ee* (*trans*)

57i
78%, d.r. ≈ 1:1
96% *ee* (*cis*)
95% *ee* (*trans*)

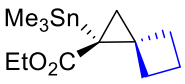
57j
55%, d.r. ≈ 2:1
94% *ee* (*cis*)
97% *ee* (*trans*)



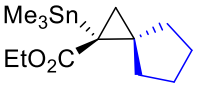
57k
72%, d.r. ≈ 2:1
97% *ee* (*cis*)
95% *ee* (*trans*)



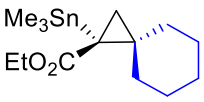
57l
99%, 97% *ee*



57m
74%, 94% *ee*



57n
73%, 94% *ee*



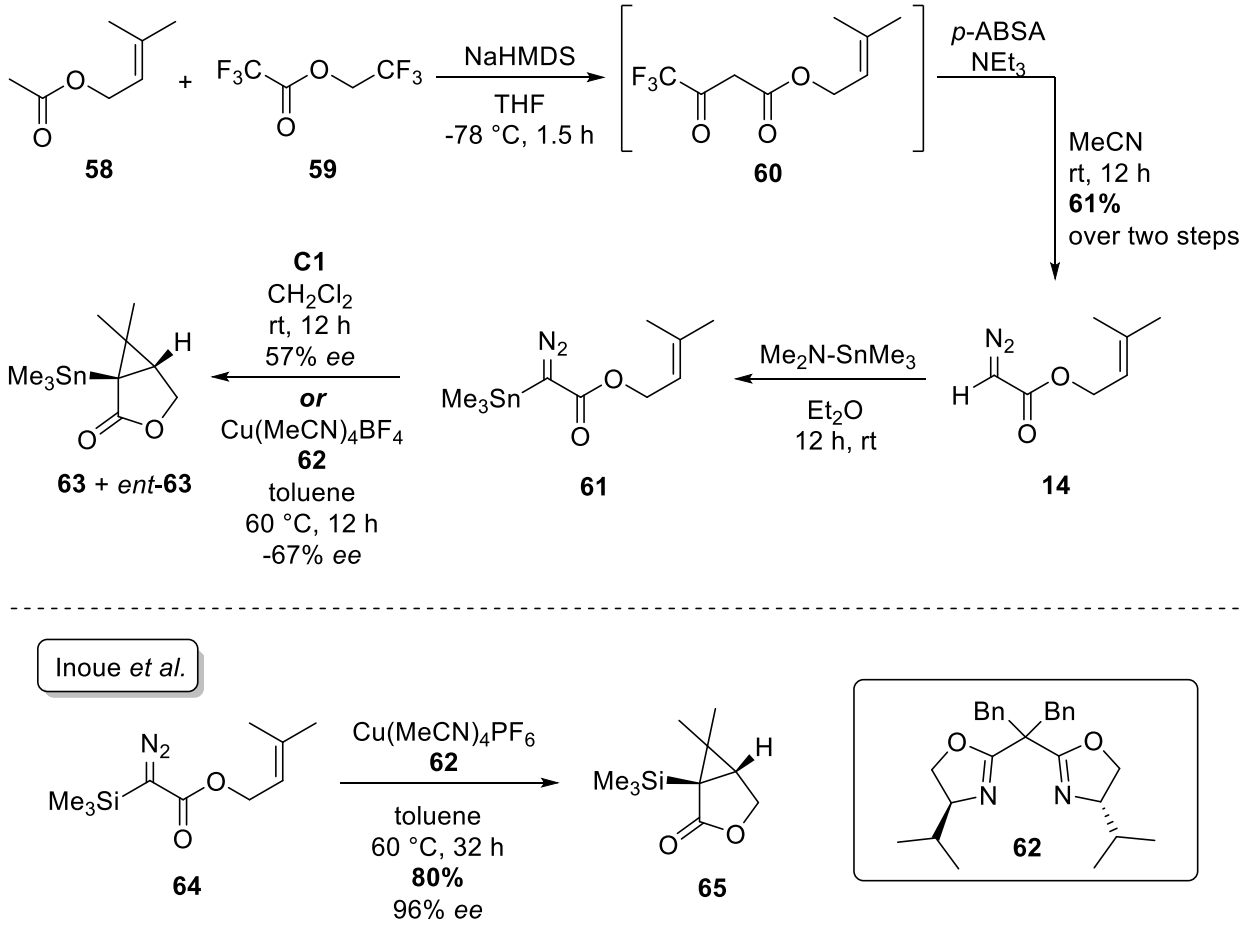
57o
47%, 97% *ee*

Scheme 19. Scope of asymmetric cyclopropanation using Rh_2(acam)((*R*)-TPCP)$_3$ (C1). Conditions: C1 (1 mol%), olefin (5.0 eq), CH_2Cl_2, rt, 6 h; d.r. given as *cis*/*trans*. Only *trans*-isomer depicted for clarity.

1.3.3 Intramolecular Cyclopropanation

We decided to explore whether the dirhodium catalyst **C1** could be used in intramolecular cyclopropanations, since so far only intermolecular reactions had been conducted. Accordingly, diazo ester **14** was synthesized as a precursor for the required stannane **61** using *p*-ABSA for a Regitz diazotransfer onto the intermediate diketone **60** followed by hydrolysis of the terminal ketone (Scheme 20). Stannylation was carried out following the same procedure as for diazo compound **56**; however, in this case purification was not possible *via* sublimation as the product

was not solid at room temperature. Distillation was attempted but resulted in decomposition of the product. Furthermore, the neat compound appeared to be unstable and was hence kept in solution at all times. For these reasons, no yields are reported for the respective reactions. Upon treatment of **61** with dirhodium catalyst **C1**, clean conversion towards the desired product **63** was observed, yet, only 57 % *ee* was achieved. The absolute configuration was not determined. The cyclopropanation was again attempted using copper catalysis with a chiral bisoxazoline ligand **62**. This catalytic system has been described by the group of Inoue for the intramolecular cyclopropanation of α-silylated diazo compounds such as **64**[139]. Similar to the previous reaction, clean conversion towards the desired product **63** was achieved, though only with a slightly higher *ee* of -67 %, indicating that in this reaction the opposite enantiomer was formed preferentially compared to what was obtained with the dirhodium catalyst.



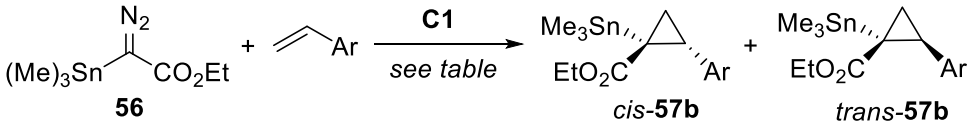
Scheme 20. Synthesis and dirhodium- or copper-catalyzed intramolecular cyclopropanation of stannylated allyl diazo ester 61.

1.3.4 Optimization of the Catalyst Loading

Since dirhodium paddlewheel complexes have been described to be reactive even at very low catalyst loadings[140], it was investigated whether this also applied to our heteroleptic dirhodium catalyst **C1**. The cyclopropanations were carried out with *p*-methoxystyrene as the model

substrate (Table 1). When lowering the catalyst loading to 0.05 mol% (entry 4) full conversion was still reached, and both yield and enantioselectivity remained consistently high compared to the standard catalyst loading of 1 mol% (entry 1). Further decreasing of the catalyst loading to 0.025 and 0.01 mol% resulted in significantly slower conversion and accordingly lower yield (entries 5 and 6). However, the *ee* remained high. With catalyst loadings even below 0.01 mol%, the reaction did not proceed and no conversion was observed after seven days (entry 7). Interestingly, when an additional 0.05 mol% of catalyst were added after this time, the reaction commenced and eventually product with high *ee* was formed, indicating that decomposition of starting material is not the main reason for the initial lack of conversion. A possible explanation might be that residual water from the solvent coordinates to the axial sites of the catalyst which results in an observable effect only at low catalyst loadings. However, the addition of molecular sieves to a reaction with 0.025 mol% of catalyst loading did not improve the outcome (entries 8 and 9). No influence of the catalyst loading on the diastereomeric ratio was observed.

Table 1. Optimization of catalyst loading for intermolecular cyclopropanation with C1.



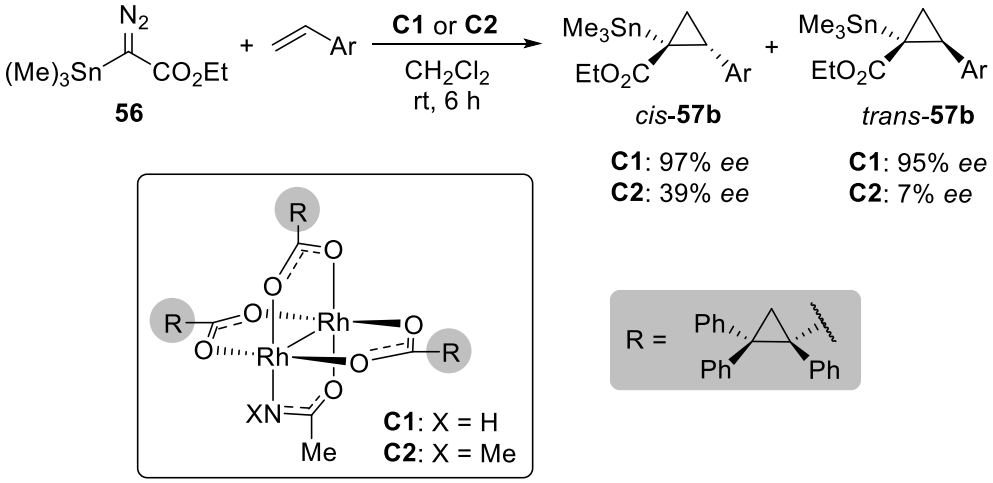
Entry	C1 [mol%]	Time	Yield[a] [%]	d.r.[b]	*ee* (*cis*)[c]	*ee* (*trans*)[c]	TON
1	1	12 h	51 (97)	1 : 1	97 %	95 %	96
2	0.5	12 h	74 (*quant.*)	1.1 : 1	97 %	95 %	204
3	0.1	12 h	67 (96)	0.97 : 1	98 %	95 %	953
4	**0.05**	**12 h**	**67 (*quant.*)**	**0.94 : 1**	**97 %**	**95 %**	**2015**
5	0.025	60 h	52 (68)	0.87 : 1	98 %	96 %	2800
6	0.01	72 h	60 (78)	1 : 1	98 %	95 %	7944
7	0.005	7 days	-[d]				
	+ 0.05	12 h	49 (55)	0.98 : 1	98 %	95 %	n.d.
8[e]	0.025	48	55	n.d.	n.d.	n.d.	n.d.
9[f]	0.025	14 days	28	n.d.	n.d.	n.d.	n.d.

All reactions conducted in CH_2Cl_2 and *p*-methoxystyrene (5.0 eq) at room temperature. [a] isolated yield (NMR yield). [b] determined from ^{1}H-NMR, given as *cis*/*trans*. [c] determined *via* chiral HPLC. [d] no conversion. [e] 4Å molecular sieves added. [f] 3Å molecular sieves added. Ar = *p*-MeO-C_6H_4. TON: turnover number (calculated from NMR yield). n.d.: not determined.

1.3.5 Development of the 2nd Generation Dirhodium Catalyst

DFT calculations were conducted by Dr. Giovanni Bistoni. Conceptualization of the dirhodium catalyst, its synthetis and the majority of the scope were realized by Dr. Fabio Caló[135].

It had been hypothesized that the high enantioselectivity of the dirhodium paddlewheel catalyst **C1** was to a great extent caused by the presence of an interligand hydrogen bonding between the acetamidate -NH group and the ester carbonyl of the reactive rhodium carbene. This hypothesis was reinforced by different control experiments involving derivatives of the parent dirhodium paddlewheel catalyst, in particular an *N*-methyl-capped version **C2**. Applying this catalyst in asymmetric cyclopropanation drastically decreased the *ee* (Scheme 21).



Scheme 21. Control experiments to investigate the influence of a proposed interligand hydrogen bond on the enantioselectivity of the cyclopropanation reaction. Ar = *p*-MeO-C$_6$H$_4$.

Despite its compelling enantioselectivity, the lack of diastereoselectivity of the catalyst constituted a major drawback. With the aim of gaining a better understanding of the transition states leading to the different diastereoisomers, DFT calculations were carried out for the attack of *p*-methoxystyrene towards the rhodium carbene (Figure 9). In accordance with experimental findings, the transition states leading to the 1*S*,2*R* and 1*S*,2*S* isomers (TS_C and TS_D) were roughly 2 kcal/mol higher in energy and hence these isomers were not observed in the product mixture. This increased energy barrier further supported the initial hypothesis of an interligand hydrogen bonding. For the olefin to attack the rhodium carbene *via* quadrant C or D, respectively, a massive distortion of the hydrogen bond would be required; thus, the transition states becomes energetically less favoured. On the other hand, the energy levels for the transition states towards the 1*R*,2*R* and 1*R*,2*S* isomers were very close and differed by only 0.7 kcal/mol which correlated with the experimentally determined low diastereomeric ratios.

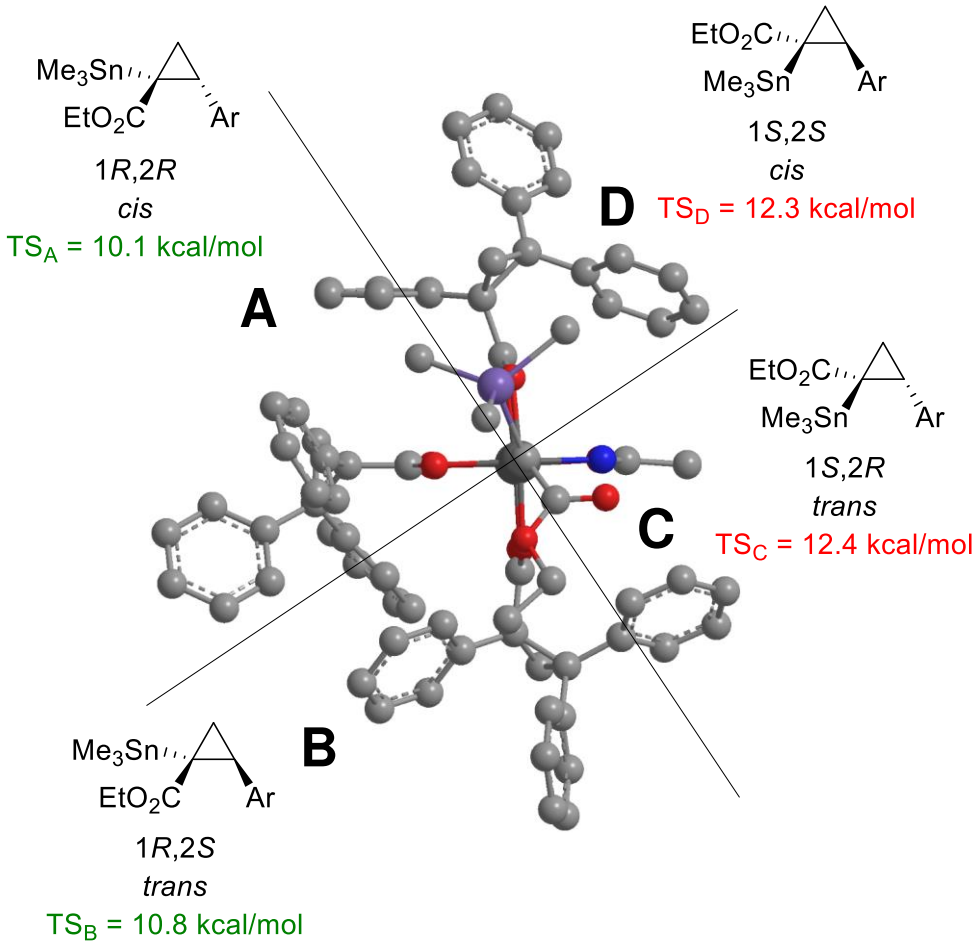


Figure 9. Computed structure of reactive dirhodium carbene complex of C1 and the transition state energies calculated for the four different possible trajectories of *p*-methoxystyrene. Ar = *p*-MeO-C_6H_4.

These insights prompted the conclusion to block one of the remaining two transition states (TS_A or TS_B) by chemically altering the ligand scaffold of the catalyst in order to achieve increased diastereoselectivity. A three-dimensional visualization of the rhodium carbene in form of a topographic sterical map based on the DFT calculations and a crystal structure of the catalyst **C1** suggested that a substituent in *para*-position of the ligand's α-phenyl ring might sterically block the trajectory A of the olefin and thus should reduce the formation of the 1*R*,2*R* isomer (Figure 10).

Various derivatives of the initial ligand **50** and the corresponding dirhodium catalysts were synthesized until eventually it was found that a TIPS-substituent in the described position induced the desired diastereoselectivity. The synthesis of the ligand followed a similar protocol as for the parent structure, starting from *para*-bromo substituted methyl phenylacetate **Br-46** (Scheme 22). Ligand exchange towards the desired dirhodium catalyst was carried out according to the improved synthetic method (*vide supra*), using $Rh_2(acam)_4$ as the precursor, resulting in dirhodium complex **C3** in 47 % yield.

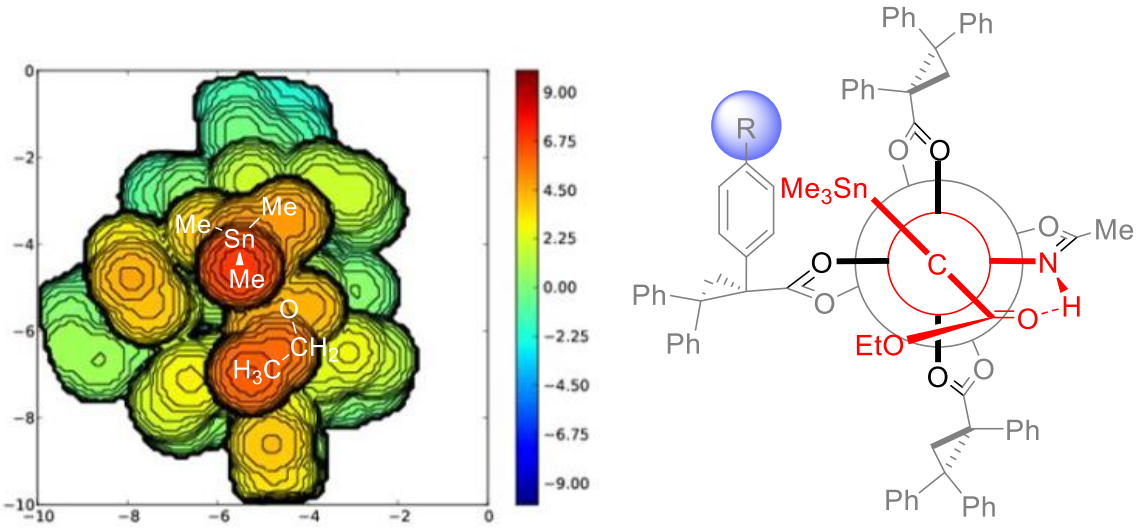
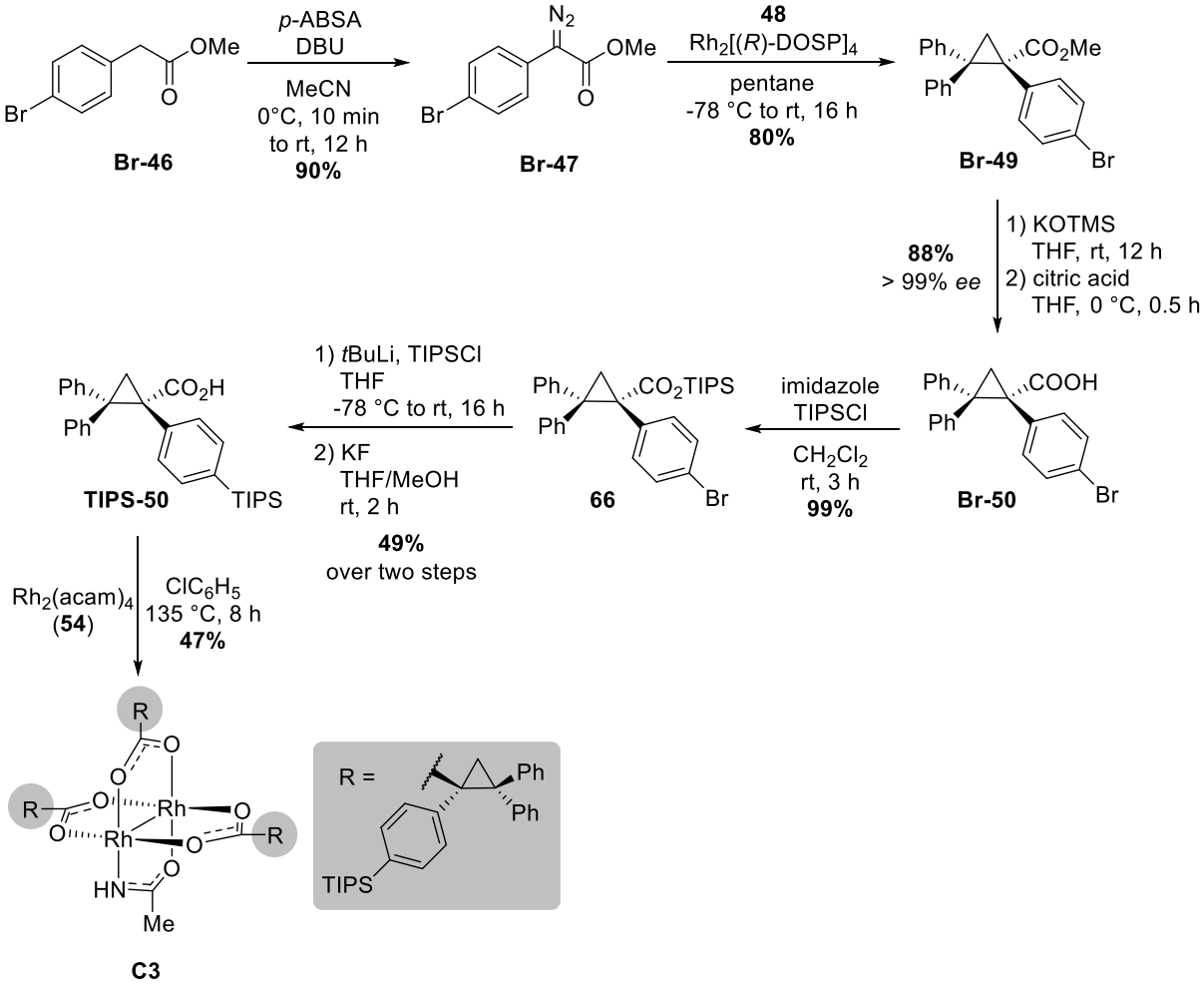


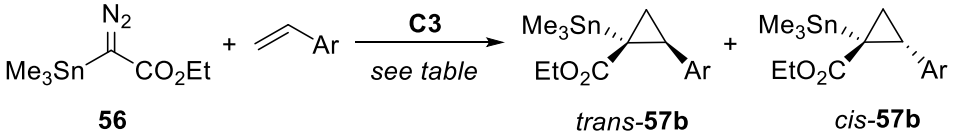
Figure 10. Topographic steric map of dirhodium carbene complex of C1 (left) and the derived ligand modification for a potentially *trans*-selective catalyst (right).



Scheme 22. Synthesis of 2nd generation dirhodium complex C3.

When carrying out the cyclopropanation of diazo compound **56** with *p*-methoxystyrene using the newly developed dirhodium catalyst **C3** under previous standard conditions, a d.r. of 16:1 in favour of the *trans*-isomer was observed (Table 2, entry 1). The diastereoselectivity could be increased even further by changing the solvent from dichloromethane to pentane and lowering the temperature to -20 °C. Similar to the parent catalyst, even at catalyst loadings as low as 0.05 mol% high yields, *ee*s and d.r.s were maintained. Additionally, it was no longer necessary to slowly add the diazo compound *via* syringe pump.

Table 2. Optimization of conditions for *trans*-selective cyclopropanation with C3.



56 *trans*-**57b** *cis*-**57b**

Entry	C3 [mol%]	Conditions	d.r.[a]	Yield[b] [%]	*ee* (*trans*)	*ee* (*cis*)
1	0.5	CH_2Cl_2, rt	16 : 1	62 (99)	97%	91%
2	0.5	CH_2Cl_2, -20 °C	14 : 1	n.d.	95%	n.d.
3	0.5	pentane, rt	16 : 1	(99)	97%	n.d.
4	0.5	pentane, -20 °C	22 : 1	(99)	96%	n.d.
5	0.05	pentane, -20 °C	21 : 1	69 (99)	97%	n.d.

All reactions were carried out with *p*-methoxystyrene (5.0 eq) and a reaction time of 6 h. [a] given as *trans*/*cis*, determined by ^{1}H-NMR of crude product. [b] isolated yield (NMR yield). n.d.: not determined. Ar = *p*-MeO-C_6H_4.

1.3.6 Scope of the 2nd Generation Dirhodium Catalyst

With the improved catalyst, the scope of cyclopropanation was re-evaluated. Substrates from the previous study were applied as well as several new olefins (Figure 11). Gratifyingly, a diversity of electronics, sterics and functional groups were tolerated and predominantly high yields, enantio- and diastereoselectivities were observed.

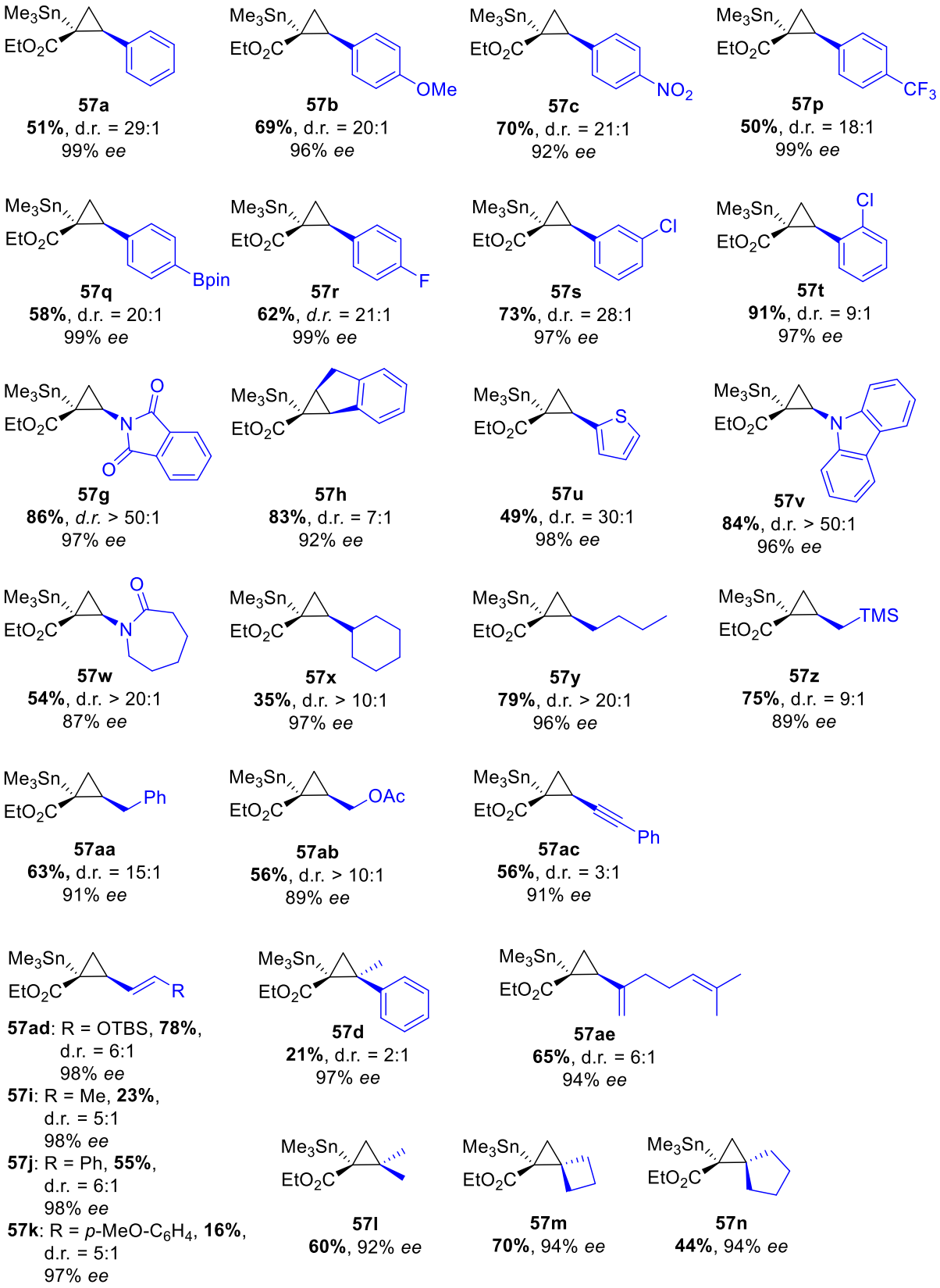


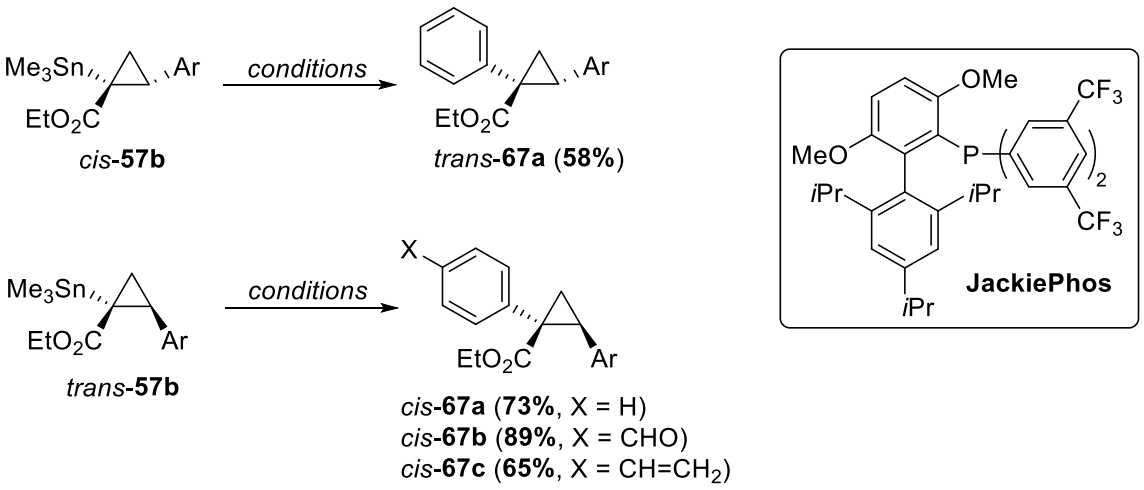
Figure 11. Scope of asymmetric cyclopropanation using dirhodium catalyst C3. Conditions: C3 (0.5 mol%), 56 (1.0 eq), olefin (5.0 eq), pentane, -20 °C, 6 h; *ee* given for *trans*-isomer, d.r. given as *trans*/*cis*.

1.4 Downstream Chemistry and Diversification

1.4.1 Stille Coupling

The investigation of the cross coupling reaction up to finding the initial hit conditions was carried out by Dr. Fabio Caló[135].

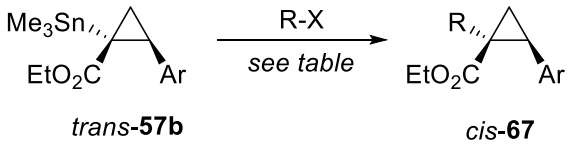
With the established methodology for the (diastereoselective) cyclopropanation of terminal olefins and the resulting generous pool of different optically active cyclopropylstannanes, further diversification *via* Stille-Migita cross coupling was explored. Various conditions using iodobenzene as a model electrophile had been tested, including Farina's $Pd(AsPh_3)_4$ catalyst[141], different copper additives to improve transmetalation[121-122] as well as the influence of tin scavengers, for example copper thiophene-2-carboxylate (CuTC) or a system developed by our group which combines CuTC with a phosphinate ($Ph_2PO_2NBu_4$)[142]. Other prominent tin scavengers are fluorides; cesium fluoride was investigated. Unfortunately, no satisfactory results had been observed in these experiments. Major problems were epimerization of the chiral centre and protodestannylation. Eventually, a hit had been found when conditions established by the group of Biscoe ($Pd(dba)_2$, JackiePhos, CuCl and KF in acetonitrile at 60 °C)[132] were applied to the system and the desired product was obtained with "stereoretention". When reducing the catalyst loading from 25 to 10 mol%, however, a distinct erosion of d.r. had been observed; this could be circumvented by changing the solvent to THF. With these modified conditions, it was possible to prepare a first small subset of cross coupled derivatives **67** (Scheme 23). Notably, although the reaction proceeds with retention of configuration at the stereocentre, the assignment changes from *cis* to *trans* and vice versa due to the changed priorities within the molecule according to CIP nomenclature.



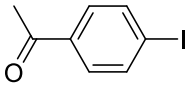
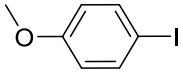
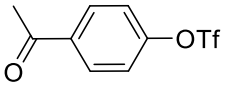
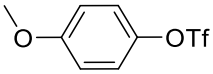
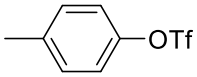
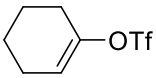
Scheme 23. Initial scope of stereoretentive Stille coupling with hit conditions: $Pd(dba)_2$ (0.1 eq), JackiePhos (0.2 eq), CuCl (2.0 eq), KF (2.0 eq), aryl iodide (2.0 eq), THF, 60 °C; d.r. of products >20:1 in favour of depicted isomer. Ar = *p*-MeO-C_6H_4.

Based on these findings it was of interest to explore the generality of the reaction with other electrophiles, especially those that would give products which would be challenging to access through direct cyclopropanation of an olefin with the respective diazo compound. To this end, a screening of electrophiles was conducted (Table 3).

Table 3. Further exploration of the scope of the Stille coupling with different electrophiles.



trans-**57b** *cis*-**67**

Entry	R-X	Time	Yield [%]
1		21 h[a]	63
2		16 h[a]	38
3		20 h	82
4		16 h	61
5		15 h	74
6		16 h[a]	51

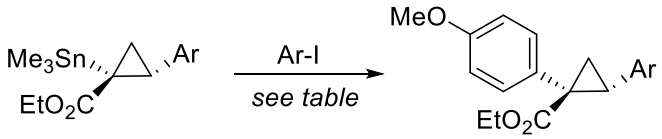
Reaction conditions: $Pd(dba)_2$ (0.1 eq), JackiePhos (0.2 eq), KF (2.0 eq), CuCl (2.0 eq), R-X (2.0 eq), THF, 60 °C. [a] no full conversion. Ar = *p*-MeO-C_6H_4.

The screening was started with 4-iodoacetophenone as a representative of electron-poor electrophiles; applying the previously established conditions led to a moderate yield of 63 %, albeit with incomplete conversion of the cyclopropylstannane ***trans*-57b** observed by GC-MS after stirring overnight (entry 1). A yield of only 38 % was observed when the more electron-rich *para*-methoxyphenyl iodide was used as the electrophile (entry 2). As an alternative to aryl iodides the corresponding triflates were tested in the cross coupling, based on the hypothesis that the triflate ion is less prone to coordinate to the intermediate palladium complex and thereby enhances the transmetalation step of the catalytic cycle. Interestingly, an increased yield of 82 and 61 % was obtained with the respective aryl triflates (entries 3 and 4). Other aryl and alkenyl triflates were employed (entries 5 and 6). As expected, the more electron-rich substrates resulted in lower yields compared to the more electron-poor ones. Based on GC-MS analyses, the major byproducts formed during the reaction were protodestannylated starting material and methylated

electrophile, which occurs if one of the methyl groups of the trimethyltin moiety is transferred instead of the cyclopropyl fragment.

As seen in Table 3, the conditions at hand delivered promising results with electron-poor electrophiles but there was still some room for improvement with more electron-rich coupling partners. It is common for such substrates to react less efficiently in cross couplings as they are less susceptible to oxidative addition. Due to the poor yield obtained with *para*-methoxyphenyl iodide in the previous screening, it was chosen as a model electrophile for optimization (Table 4). The ratio of ligand to palladium was increased from 2:1 to 4:1, resulting in a yield of 59 % of ***trans*-67d** (entry 1). The increased ligand to palladium ratio possibly facilitates the reductive elimination step. Changing the palladium source to $Pd(OAc)_2$ further raised the yield to 65 % but this was accompanied by circa 20 % of epimerization (entry 2). Going back to a Pd(0) source, $Pd_2(dba)_3$ eventually provided the best result with 70 % yield of cross coupling product (entry 3). Doubling of the catalyst loading did not further increase the yield (entry 4), nor did larger amounts of copper chloride or potassium fluoride (entries 5 and 6). Interestingly, leaving out the fluoride completely resulted in a heavily reduced conversion (entry 7). In all reactions, the major byproducts that could be determined by GC-MS analysis were protodestannylated starting material and methylated electrophile.

Table 4. Optimization of conditions for Stille coupling with *para*-methoxyphenyl iodide as model substrate for electron-rich electrophiles.



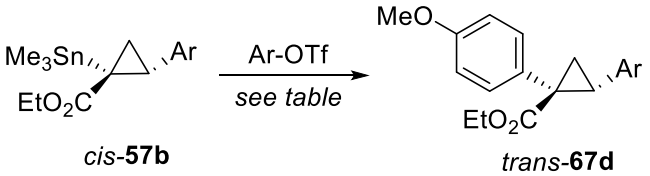
cis-**57b** *trans*-**67d**

Entry	Conditions (eq)	Yield [%]
1	$Pd(dba)_2$ (0.1), JackiePhos (**0.4**), KF (2.0), CuCl (2.0)	59
2	**$Pd(OAc)_2$** (0.1), JackiePhos (0.4), KF (2.0), CuCl (2.0)	65[a]
3	**$Pd_2(dba)_3$ (0.05), JackiePhos (0.4), KF (2.0), CuCl (2.0)**	**70**
4	$Pd_2(dba)_3$ **(0.1)**, JackiePhos (**0.8**), KF (2.0), CuCl (2.0)	70
5	$Pd_2(dba)_3$ (0.05), JackiePhos (0.4), KF (2.0), CuCl (**5.0**)	70
6	$Pd_2(dba)_3$ (0.05), JackiePhos (0.4), KF (**4.0**), CuCl (2.0)	65
7	$Pd_2(dba)_3$ (0.05), JackiePhos (0.4), CuCl (2.0)	n.d.[b]

All reactions were carried out with *p*-methoxyphenyl iodide (2.0 eq) in THF at 70 °C and stirred overnight if not mentioned otherwise. [a] approx. 20 % of epimerization observed in ^{1}H-NMR. [b] slow conversion, 48 h reaction time. n.d.: not determined. Ar = *p*-MeO-C_6H_4.

A similar optimization was conducted using *para*-methoxyphenyl triflate as a model substrate (Table 5). Based on the previous findings with iodide electrophiles, the palladium catalyst was switched for $Pd_2(dba)_3$ (entry 1). An increased amount of copper chloride decreased the yield (entry 2), on the other hand, reducing the amount of copper chloride did not improve the reaction outcome either (entry 3). Similar observations were made for potassium fluoride: neither increasing nor decreasing the KF loading improved the yield (entries 4 and 5). Copper chloride appeared to be crucial for the reaction, as when it was replaced by a combination of copper iodide and lithium chloride (entries 6 and 7), no conversion could be detected. Eventually, the yield was raised to 65 % when the amount of ligand was increased (entry 8), similar to what had been previously observed with aryl iodides.

Table 5. Optimization of conditions for Stille coupling with *para*-methoxyphenyl triflate.



cis-**57b** *trans*-**67d**

Entry	Conditions (eq)	Yield [%]
1	**$Pd_2(dba)_3$ (0.05),** JackiePhos (0.2), KF (2.0), CuCl (2.0)	56
2	$Pd_2(dba)_3$ (0.05), JackiePhos (0.2), KF (2.0), CuCl (**5.0**)	23
3	$Pd_2(dba)_3$ (0.05), JackiePhos (0.2), KF (2.0), CuCl (**1.0**)	47
4	$Pd_2(dba)_3$ (0.05), JackiePhos (0.2), KF (**4.0**), CuCl (2.0)	41
5	$Pd_2(dba)_3$ (0.05), JackiePhos (0.2), KF (**1.0**), CuCl (2.0)	41
6	$Pd_2(dba)_3$ (0.05), JackiePhos (0.2), KF (2.0), **CuI (1.0), LiCl (2.0)**	-[a]
7	$Pd_2(dba)_3$ (0.05), JackiePhos (0.2), KF (2.0), **CuI (2.0), LiCl (1.0)**	-[a]
8	**$Pd_2(dba)_3$ (0.05), JackiePhos (0.4), KF (2.0), CuCl (2.0)**	**65**

All reactions were carried out with *p*-methoxyphenyl triflate (2.0 eq) in THF at 70 °C and stirred overnight if not mentioned otherwise. [a] no conversion. n.d.: not determined. Ar = *p*-MeO-C_6H_4.

With the optimized conditions at hand, the scope of the Stille coupling was investigated (Figure 12). Starting with aryl electrophiles, the functional group tolerance and different substitution patterns were tested. Various different functional groups proved compatible such as ketones, ester, nitrile, nitro, methoxy or methyl groups. As expected, substituents in the *para*-position exhibited the fewest problems in terms of sterical hindrance of the substrates (**67d-j**). A *meta*-methoxy substituted aryl halide also coupled well with both *cis*- and *trans*-stannane (**67k**). Significant differences in reactivity of *cis*- and *trans*-stannanes could be observed when *ortho*-substituents were present in the aryl electrophiles (**67l-o**). While it is still possible to couple certain *ortho*-substituted substrates with the *trans*-stannane, the increased steric hindrance

about the aryl group pointing to the same side of the cyclopropyl ring as the trimethyltin group in the *cis*-stannane became apparent and only an aldehyde substituent was tolerated.

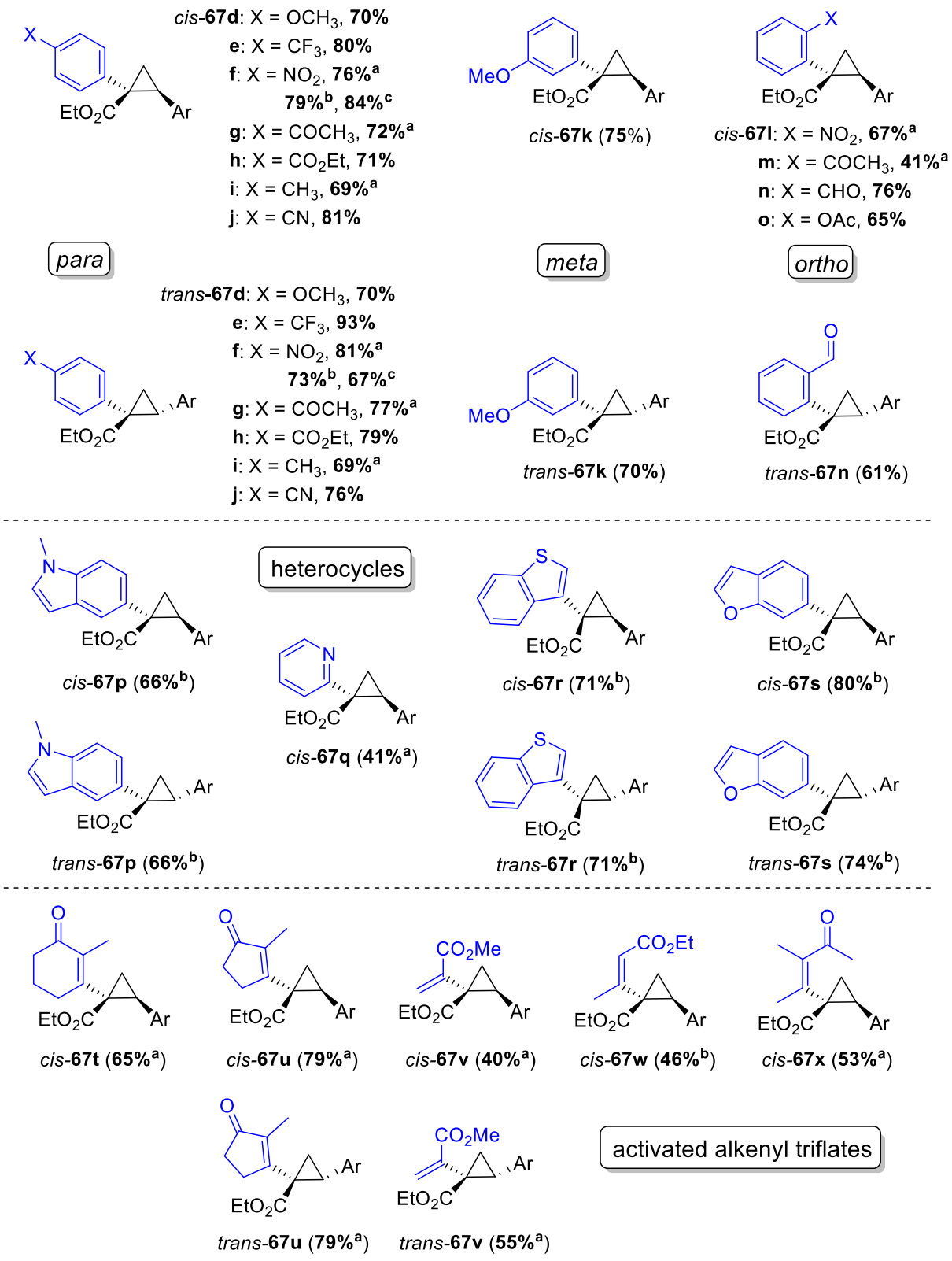


Figure 12. Scope of stereoretentive Stille coupling with stannane 57b under optimized conditions: $Pd_2(dba)_3$ (0.05 eq), JackiePhos (0.2 or 0.4 eq), CuCl (2.0 eq), KF (2.0 eq), R-I (2.0 eq), THF, 70 °C, 16 h. [a] R-OTf instead of R-I; [b] R-Br instead of R-I; [c] R-Cl instead of R-I. Ar = *p*-MeO-C_6H_4.

Furthermore, several heterocyclic compounds containing nitrogen, oxygen or sulfur could be introduced such as pyridine, indole, benzofurane or benzothiophene (**67p-s**). Pyridine is particularly interesting, as it could not be introduced with the developed dirhodium catalyst due to inactivation of the catalyst by coordination. Additionally, the methodology is not limited to aryl electrophiles and several activated alkenyl triflates could be successfully cross coupled (**67t-x**) potentially opening the way to further downstream modifications. Less successful substrates include unactivated alkenyl triflates or halides, aniline or phenol derivatives as well as more bulky *ortho*-substituted aryl halides.

So far, only variation of the electrophilic component of the reaction had been explored. Next, other enantioenriched cyclopropylstannanes were tested in the cross coupling, which were found to be equally suitable (Figure 13). The *gem*-dimethyl cyclopropane obtained from isobutene was subjected to cross couplings with different electrophiles, giving moderate to good yields while maintaining excellent *ee*s (**68a-d**) which further confirmed the stereoretentive pathway of the reaction. Furthermore, cyclopropylstannanes with different aryl substituents, including heterocycles, as well as those bearing an unactivated alkyl chain could successfully be applied in the cross coupling (**69a-e**).

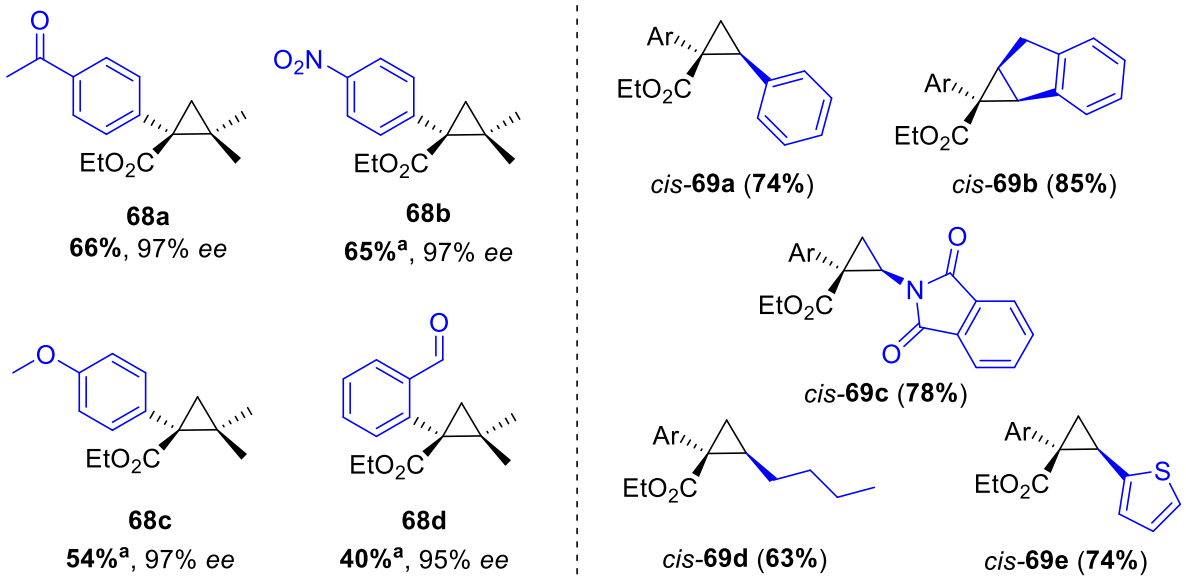
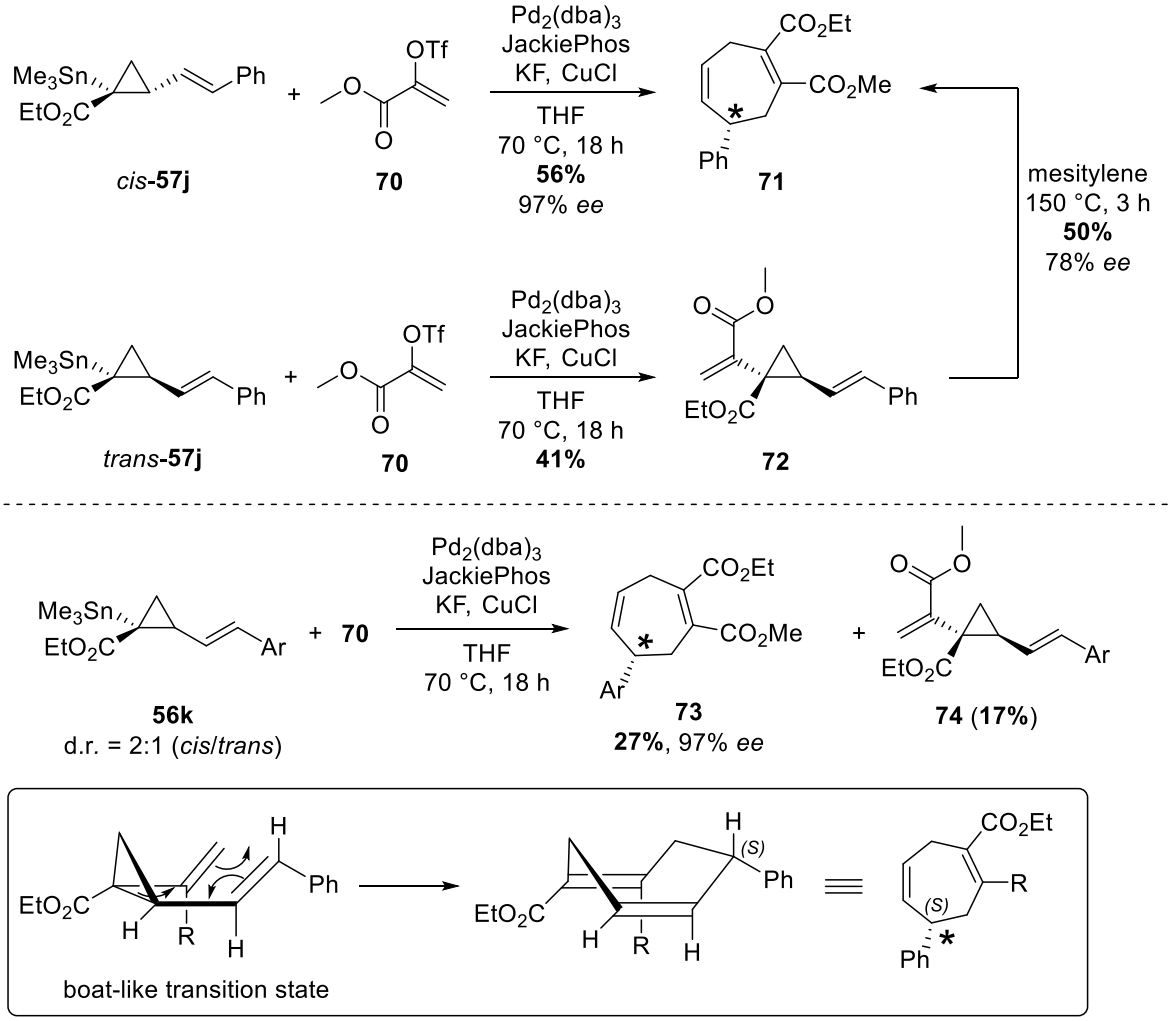


Figure 13. Scope of stereoretentive Stille coupling using different cyclopropylstannanes under optimized conditions: $Pd_2(dba)_3$ (0.05 eq), JackiePhos (0.2 or 0.4 eq), CuCl (2.0 eq), KF (2.0 eq), R-I (2.0 eq), THF, 70 °C, 16 h. [a] R-OTf instead of R-I. Ar = *p*-NO_2-C_6H_4.

1.4.2 Tandem Stille-Cope Reaction

An interesting tandem reaction was observed when a *cis*-cyclopropylstannane derived from a diene was used in combination with an alkenyl electrophile. The resulting dialkenylcyclopropane product immediately underwent a Cope-type rearrangement with opening of the cyclopropane to arrive at a seven-membered ring, which was obtained in high *ee* of 97 % (Scheme 24). Although

the absolute configuration of the newly formed stereocentre was not verified, it is likely of (*S*)-configuration based on the known configuration of the previous stereocentres, assuming that the rearrangement takes place in a concerted fashion *via* a boat-like transition state[143].



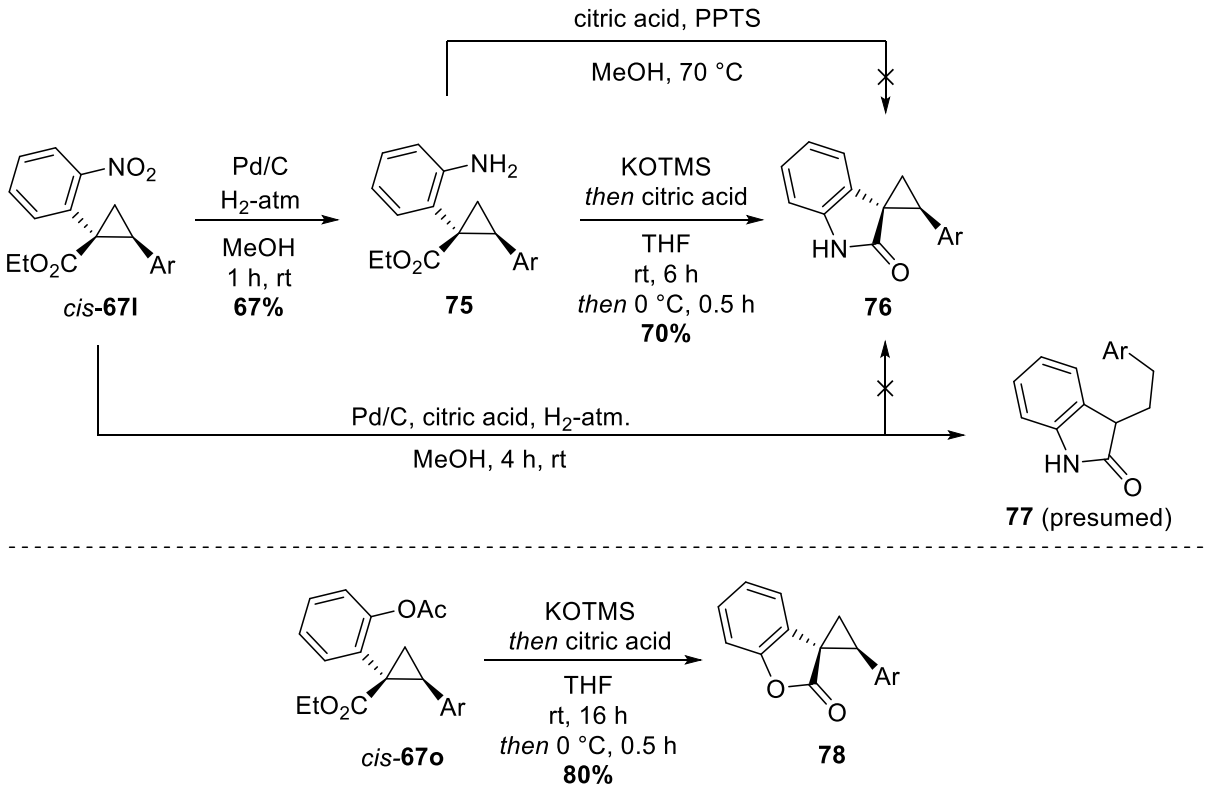
Scheme 24. Tandem Stille-Cope reaction *via* intermediary dialkenylcyclopropanes. Stereocentre indicated with asterisk was not determined and only derived from mechanistic model. Ar = *p*-MeO-C_6H_4.

When the same alkenyl triflate was applied in a cross coupling with the respective *trans*-stannane, only the expected cross coupling product **72** was obtained without rearrangement. Heating of the product to 150 °C in mesitylene eventually induced the rearrangement but with a yield of only 50 % and a decreased *ee* of 78 % of the same enantiomer. In order for the *trans*-isomer to undergo the rearrangement it has to isomerize to the *cis*-isomer, which was suggested to take place either *via* an intermediate diradical species[144] or through a one-center epimerization[145]. The fact that one isomer easily undergoes rearrangement and the other does not could be taken advantage of with substrates where the *cis*- and *trans*-isomer were not seperable. This was true for the *para*-methoxy derivative of the previously described stannane. Thus, a *cis*/*trans*-mixture of the stannane **56k** was submitted to the cross coupling conditions and the resulting products, one

being the seven-membered ring and the other the trisubstituted cyclopropane, could be separated *via* flash chromatography. Again, the rearranged product **73** maintained a high *ee* of 97 %.

1.4.3 Synthesis of Spirocycles

Another interesting downstream diversification was the potential formation of spirocyclic compounds such as lactams or lactones after cross coupling. Unfortunately, it was not possible to directly introduce *ortho*-amino or -hydroxyl substituted aryl rings *via* cross coupling. However, this problem could be solved by adding one step to the reaction sequence and starting either from the *ortho*-nitro (**67l**) or the *ortho*-acetate derivative (**67o**, Scheme 25). In order to access spirolactam **76**, the nitro group was first reduced to obtain aniline derivative **75**. This transformation was carried out using palladium on charcoal under one atmosphere of hydrogen. Initially, lactam formation was attempted *in situ* by adding citric acid to the mixture from the beginning[146]. However, in this case the desired product **76** was not obtained. Closer investigation of the NMR spectra suggested that the cyclopropane had been opened and reduced under the given conditions (**77**). The ring opening may have been caused either by the acidic conditions or in a palladium-catalysed fashion[147].



Scheme 25. Synthesis of spirocyclic compounds 76 and 78 using Stille coupling products with *ortho*-substituted aryl electrophiles.

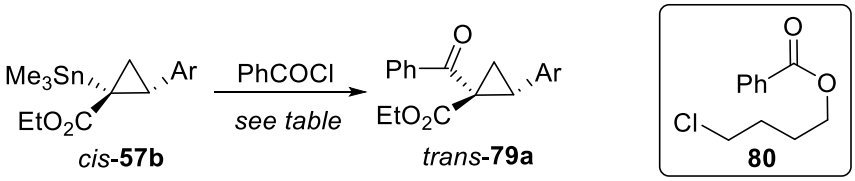
The procedure was then conducted in a stepwise manner, first isolating aniline derivative **75** and then treating it with citric acid and eventually PPTS. Still, the spirocyclic product was not obtained but a mixture of unidentified side products. Alternatively, **75** was submitted to basic conditions:

the convenient ester cleavage using potassium trimethylsilanolate, which had already been used for the catalyst ligand synthesis. Pleasingly, the spirolactam **76** was obtained in 70 % yield. Synthesis of the spirolactone **78** was more straightforward, as the lactone formation took place *in situ* during the saponification of the ethyl ester and the acetate protecting group of **67o**, which was again carried out with potassium silanolate. Spirolactone **78** was obtained in 80 % yield.

1.4.4 Carbonylative Stille Coupling

Another desirable functionalization of the optically active cyclopropylstannanes would be the introduction of acyl electrophiles which has been conducted by Biscoe *et al.* with their carbastannatrane system[133]. For the acylation, they describe a slightly modified protocol using $Pd(PPh_3)_4$ instead of $Pd(dba)_2$ and JackiePhos and omitting the potassium fluoride. Under these conditions, various enantioenriched secondary stannatranes could be coupled successfully with different acyl chlorides with net retention of configuration. Unfortunately, applying the same conditions to our cyclopropylstannane ***cis*-57b** did not provide positive results. Although the desired product ***trans*-79a** could be detected *via* GC-MS, it was accompanied by an unidentified side-product and a significant amount of protodestannylation (Table 6, entry 1).

Table 6. Attempts towards acylation of cyclopropylstannane *cis*-57b.



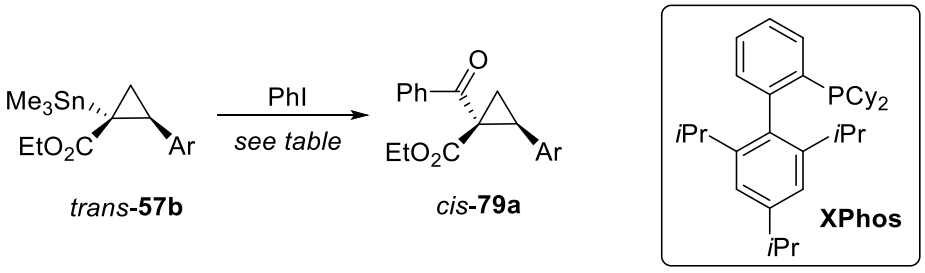
Entry	Conditions (eq)	Result
1	$Pd(PPh_3)_4$ (0.04), CuCl (2.0), MeCN, 80 °C, 4 days	***trans*-79a**, pds, unidentified side product
2	$Pd_2(dba)_3$ (0.05), JackiePhos (0.4), KF (2.0), CuCl (2.0), THF, 70 °C, 16 h[a]	***trans*-79a**, **80**, pds
3	$Pd_2(dba)_3$ (0.05), JackiePhos (0.4), KF (2.0), CuCl (2.0), MeCN, 70 °C, 16 h[a]	***trans*-79a**, ***trans*-67a**, pds
4	$Pd_2(dba)_3$ (0.05), JackiePhos (0.4), CuCl (2.0), MeCN, 70 °C, 4 days	***trans*-79a**, ***trans*-67a**, pds
5	$Pd_2(dba)_3$ (0.05), JackiePhos (0.4), CuCl (2.0), toluene, 110 °C, 16 h[a]	***trans*-79a**, pds

All reactions were carried out with benzoyl chloride (2.0 eq). [a] no full conversion. Ar = *p*-MeO-C_6H_4. pds: protodestannylation.

Hence, it was decided to test our established cross coupling conditions. Again, formation of the desired compound could be observed *via* GC-MS but the major species was a side product that most likely resulted from a reaction of benzoyl chloride with the solvent THF (**80**, entry 2). A similar reactivity has been described in the literature with $Pd(OAc)_2$[148]. Consequently, THF was no longer used as the solvent but replaced by acetonitrile (entry 3). After stirring overnight, the reaction mixture still mostly contained unreacted starting material ***cis*-57b**. Besides the desired product, protodestannylation was observed as well as non-carbonylated cross coupling product ***trans*-67a**. When potassium fluoride was left out and the reaction time was increased to four days the outcome did not improve (entry 4). Eventually, full conversion of the starting material was reached under these conditions, but mainly protodestannylation was obtained. In a last attempt, the solvent was changed to toluene and the temperature increased to 110 °C with the aim of accelerating the reaction (entry 5). Although compared to the previous experiments a higher conversion of starting material could be observed after stirring overnight, the reaction profile was not clean and again a significant amount of protodestannylation was observed. Even though the product ***trans*-79a** was formed in all the experiments according to GC-MS analysis, it was not possible to properly isolate it in any case.

An alternative approach to obtain formally acylated cyclopropanes was *via* carbonylative Stille coupling[149]. In a first experiment, the established cross coupling conditions were applied with the addition that CO was allowed to bubble through the solution for approximately half a minute before the flask was tightly closed and heated (Table 7, entry 1). After a reaction time of three days, there was still a significant amount of starting material ***trans*-57b** left in the mixture in addition to a considerable degree of protodestannylation. The catalyst was changed to 10 mol% of $Pd(PPh_3)_4$ and pleasingly, after stirring overnight, the desired product ***cis*-79a** could be isolated in 53 % yield (entry 2). Higher catalyst loadings of 15 mol% further increased the yield to 65 %, however there was no additional benefit when 25 mol% of $Pd(PPh_3)_4$ were used (entries 3 and 4). The ligand to palladium ratio was varied as well, but neither a decreased nor an increased ratio improved the outcome (entries 5 and 6). Other ligands were explored, such as triphenylarsine or tri(2-furyl)phosphine which are described to be "softer" ligands compared to triphenylphosphine. In both cases, product formation was accompanied by an increased amount of protodestannylation (entries 7 and 8). Additionally, XPhos was applied to investigate the effect of an electron-rich ligand (entry 9) which resulted in poor conversion and increased protodestannylation; less than 35 % of the desired product could be isolated. Notably, in none of the experiments was the cross coupling product **67a** observed without incorporation of CO.

Table 7. Carbonylative Stille coupling: Optimization of catalyst system.



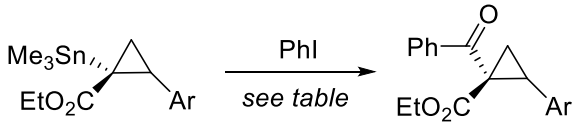
trans-**57b** *cis*-**79a**

Entry	Catalyst (eq)	Time	Yield [%]	Ratio SM : P[a]
1	$Pd_2(dba)_3$ (0.05), JackiePhos (0.4)	3 days	n.d.	49 : 51
2[b]	$Pd(PPh_3)_4$ (0.1)	22 h	53	13 : 87
3	**$Pd(PPh_3)_4$ (0.15)**	**25 h**	**65**	**11 : 89**
4	$Pd(PPh_3)_4$ (0.25)	2 days	65	5 : 95
5	$Pd_2(dba)_3$ (0.05), PPh_3 (0.2)	18 h	n.d.	32 : 68
6	$Pd(PPh_3)_4$ (0.1), PPh_3 (0.2)	2 days	59	8 : 92
7	$Pd(AsPh_3)_4$ (0.1)	3 days	41	16 : 84
8	$Pd_2(dba)_3$ (0.05), P(*o*-furyl)$_3$ (0.5)	3 days	47	11 : 89
9	$Pd_2(dba)_3$ (0.05), XPhos (0.4)	19 h	< 35	58 : 42

All reactions were carried out with iodobenzene (2.0 eq), KF (2.0 eq) and CuCl (2.0 eq) in THF at 70 °C under an atmosphere of CO. [a] determined *via* GC-MS. b ***cis*-57b** used. n.d.: not determined. Ar = *p*-MeO-C_6H_4.

Having identified a promising metal/ligand system, the influence of additives was explored (Table 8). When potassium fluoride was left out of the mixture, conversion drastically increased and the starting material **57b** was practically consumed overnight (entries 1 and 2). Yet, NMR analysis of the isolated product **79a** indicated epimerization of the quaternary stereocentre. Thus, we inferred that the additive must play a pivotal role in the reaction mechanism. Changing the amount of potassium fluoride added to the reaction did not have a significant impact. With more potassium fluoride the conversion was slightly decreased while protodestannylation increased (entries 3 and 4). It was further found that omitting copper chloride was unfavourable (entry 5) and no product formation was observed when it was replaced by copper iodide (entry 6). Similar to what had been found for potassium fluoride, changing the amount of copper chloride did not improve the yield (entries 7 to 9).

Table 8. Carbonylative Stille coupling: Investigation of additives.



57b **79a**

Entry	*cis-/trans*-57b	Additives (eq)	Time	Yield [%]	Ratio SM : P[a]
1	*cis*	CuCl (2.0)	22 h	71[b]	0 : 100
2	*trans*	CuCl (2.0)	22 h	59[b]	6 : 94
3	*trans*	CuCl (2.0), KF (**1.0**)	2 days	n.d.	21 : 79
4	*trans*	CuCl (2.0), KF (**4.0**)	2 days	53	25 : 75
5	*cis*	KF (2.0)	15 h	-	100 : 0
6	*cis*	**CuI** (2.0), KF (2.0)	15 h	-	100 : 0
7	*cis*	CuCl (**1.1**), KF (2.0)	3 days	n.d.	42 : 58
8	*trans*	CuCl (**1.1**), KF (2.0)	3 days	n.d.	64 : 36
9	*trans*	CuCl (**4.0**), KF (2.0)	3 days	41	n.d.

All reactions were carried out with iodobenzene (2.0 eq) and $Pd(PPh_3)_4$ (0.2 eq) in THF at 70 °C under an atmosphere of CO. [a] determined *via* GC-MS. [b] ^{1}H-NMR indicates complete epimerization. n.d.: not determined. Ar = *p*-MeO-C_6H_4.

With the optimized set of conditions for the carbonylative cross copling, it was time to explore the scope of the reaction (Figure 14). An acetophenone moiety could be introduced to both the *cis*- and the *trans*-stannane (**79b**). *meta*-Methoxyphenyl iodide was also successfully used with both isomers (**79c**). Attempting the cross coupling with an *ortho*-substituted aryl iodide was more challenging; the *trans*-stannane delivered the desired compound in moderate yield of 45 % (***cis*-79d**) while the *cis*-isomer of **57b** provided a complex mixture.

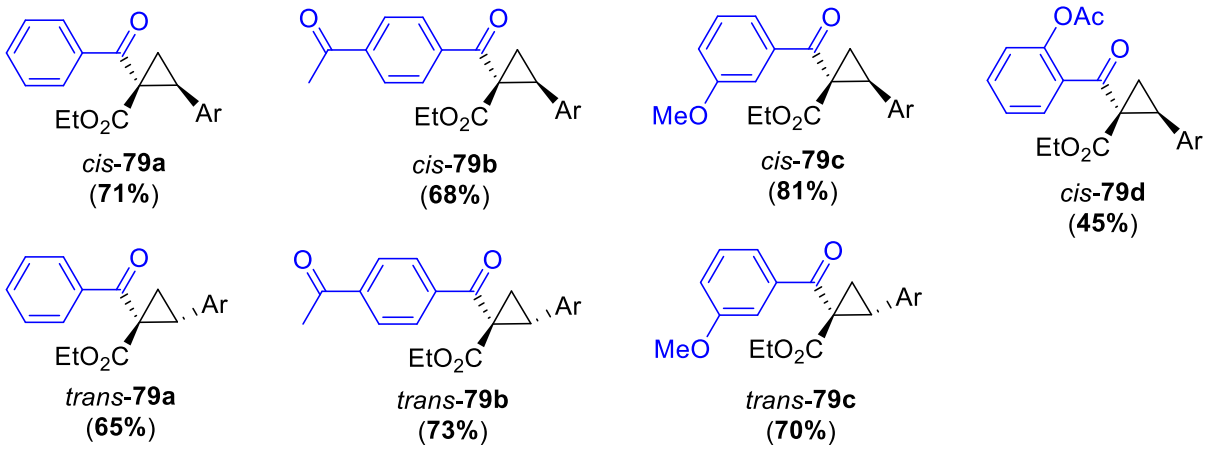


Figure 14. Scope of carbonylative Stille coupling under optimized conditions ($Pd(PPh_3)_4$ (0.15 eq), CuCl (2.0 eq), KF (2.0 eq), R-I (2.0 eq), CO, THF, 70 °C, 48 h). Ar = *p*-MeO-C_6H_4.

In this mixture, the product could be detected but also an inseperable, unidentified side product appeared to be present based on NMR analysis. A similar observation was made when *para*-nitro and *para*-cyano substituted aryl electrophiles were subjected to carbonylative cross coupling conditions. In the case of the cyano derivative, the compound that was isolated after the carbonylative cross coupling (**81b**) exhibited an unexpected shift in some proton and carbon signals in the NMR spectra. In particular, the cyclopropyl proton resonances could not be identified, indicating the absence of the cyclopropane ring (Figure 15). Additionally, the carbonyl signal around 200 ppm in ^{13}C-NMR was absent (Figure 16). The carbonylative cross coupling was also conducted with *para*-nitroaryl iodide as electrophile. Initially, the desired compound **79e** could be isolated and the aforementioned characteristic signals were in place. However, when the compound was re-analysed a couple of months later, the same changes in chemical shift were noticed that have been described for the *para*-cyano derivative.

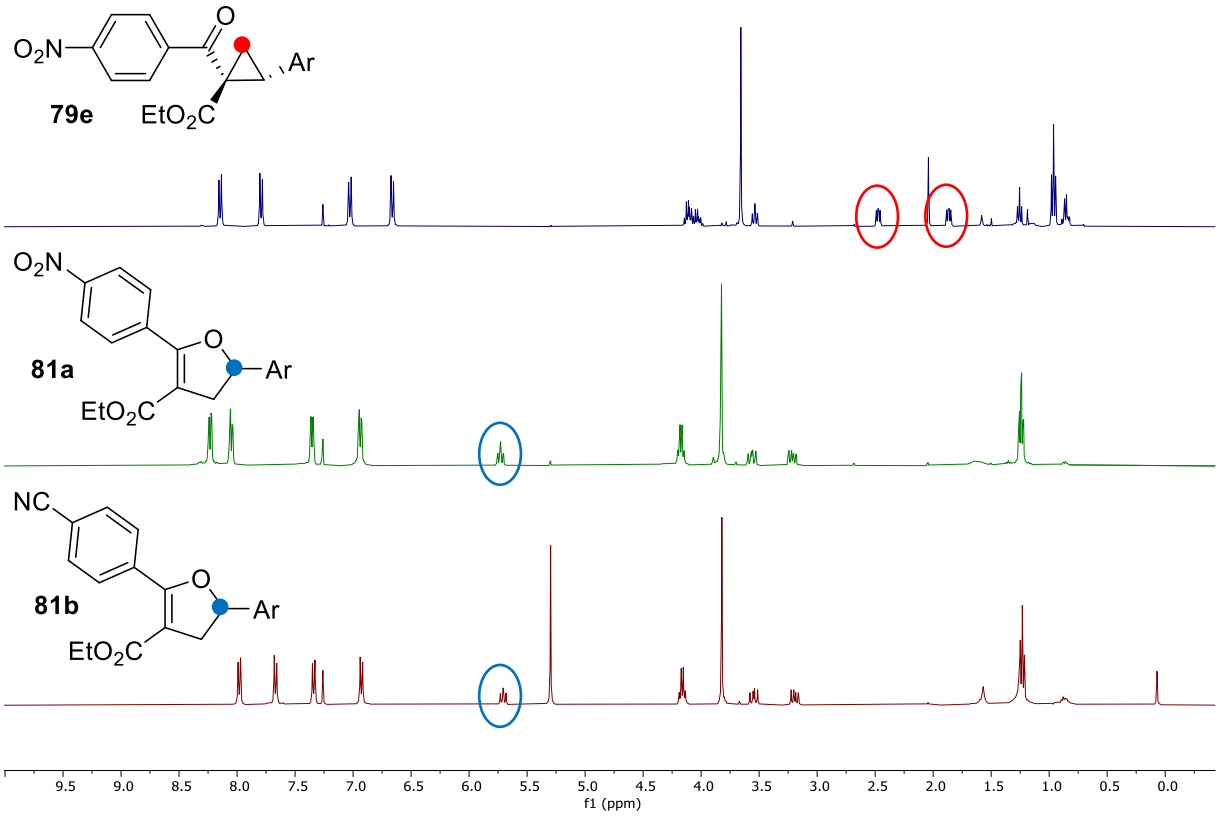


Figure 15. ^{1}H-NMR comparison of expected carbonylative coupling product (79e) and proposed rearrangement products (81a,b). Highlighted in red and blue are the indicative protons and their chemical shifts. Measured in $CDCl_3$ at 400 MHz. Ar = *p*-MeO-C_6H_4.

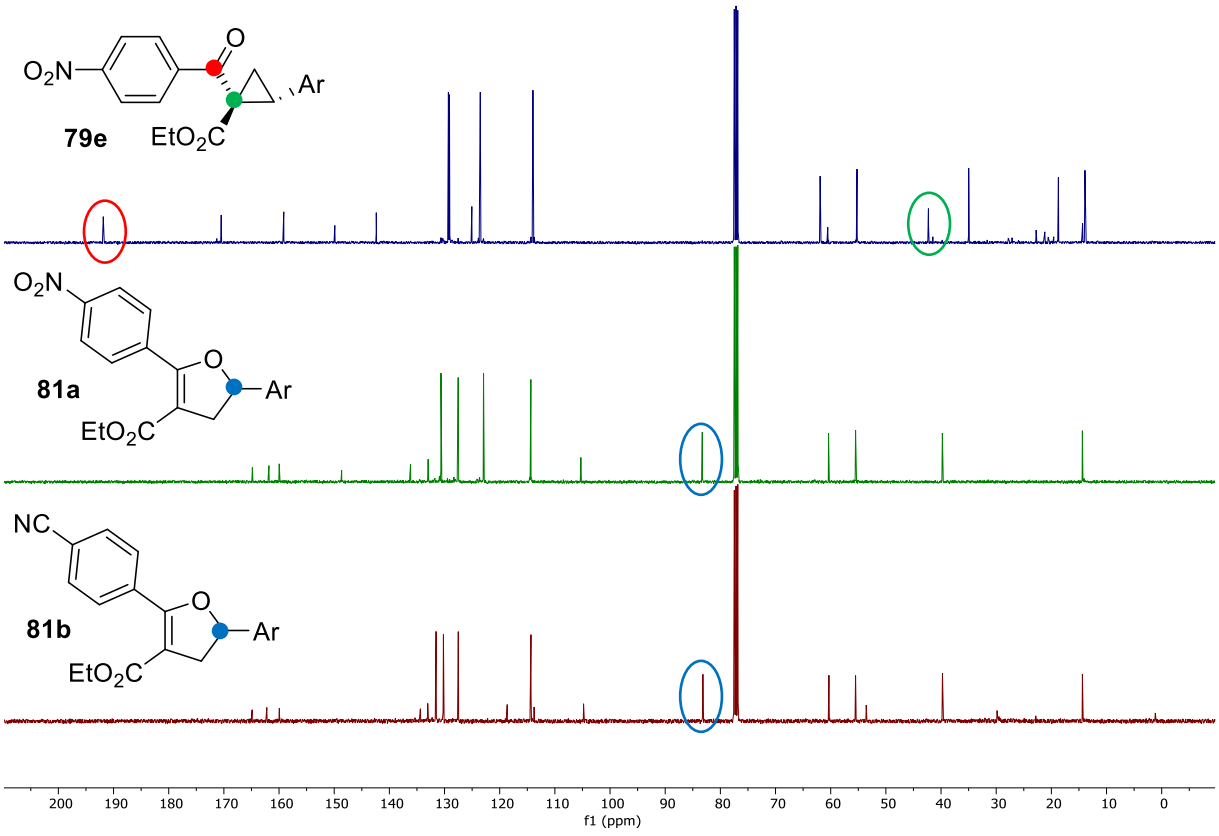
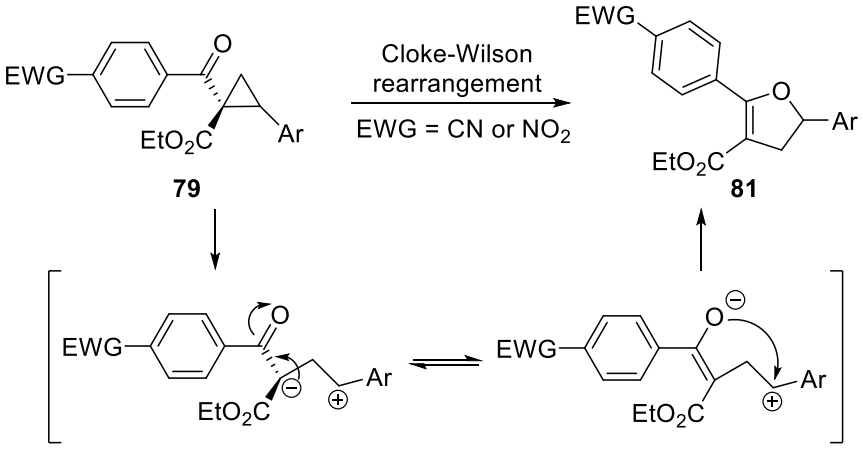


Figure 16. ^{13}C-NMR comparison of expected carbonylative coupling product (79e) and proposed rearrangement products (81a,b). Highlighted in red, green and blue are the indicative carbons and their chemical shifts. Measured in $CDCl_3$ at 101 MHz. Ar = *p*-MeO-C_6H_4.

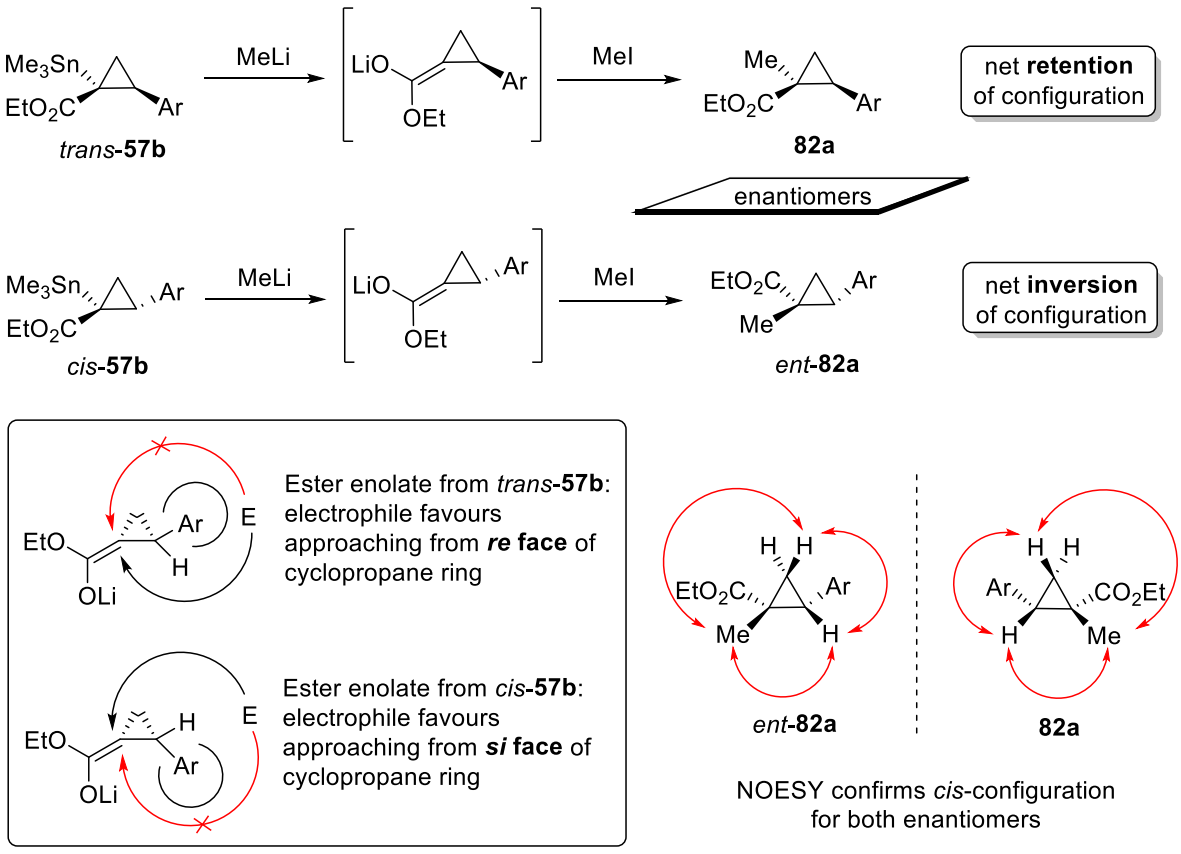
Based on these findings it was suggested that a Cloke-Wilson rearrangement towards **81a** had taken place after the cross coupling, which was probably more strongly accelerated through the presence of the nitrile substituent than a nitro group (Scheme 26). Generally, an electron-withdrawing substituent on the aryl ring makes the ketone more electron-deficient and stabilizes the transient ring-opened zwitterion, hence accelerating the rearrangement.



Scheme 26. Proposed mechanistic explanation for the observed Cloke-Wilson rearrangement. Ar = *p*-MeO-C_6H_4.

1.4.5 Tin-Lithium Exchange

Another potential route for diversification of the optically active cyclopropylstannanes envisaged a tin-lithium exchange. This approach was especially intriguing as it could enable the introduction of less activated electrophiles that would be difficult to install *via* Stille coupling. Thus, methyl iodide was chosen as a model electrophile that tends to be challenging in cross couplings. In the first experiment, cyclopropylstannane ***cis*-57b** was treated with methyllithium and the intermediate lithium ester enolate was trapped with methyl iodide; the corresponding methylated cyclopropane (***ent*-82**) could be isolated in 49 % yield (Table 9). It is important to note that the quaternary stereocentre is lost when the lithium enolate is formed; the diastereoselectivity of the alkylation of cyclopropylcarboxylates has been previously discussed in the literature[150]. Due to the steric hindrance by the aryl ring on the other side of the cyclopropane the approach of the electrophile occurs in a diastereoselective fashion, namely from the opposite side of the aryl ring substituent (Scheme 27). Hence, the final product is of *cis*-configuration, independent of the initial configuration of the employed stannane, which was confirmed *via* NOESY NMR.



Scheme 27. Overview and mechanistic analysis of tin-lithium exchange. Ar = *p*-MeO-C$_6$H$_4$.

This diastereoselective course results in the formation of antipodes of product depending on whether the *cis*- or the *trans*-isomer is used as the starting material of the reaction, which could be confirmed by chiral HPLC measurements (Figure 17) and is supported as well by the opposite sign of the specific rotation measured for both compounds. These observations further confirm

the initial postulate that the *cis*- and *trans*-isomers of the cyclopropanes vary in the stereocentre that is formed from the attack of the olefin during the cyclopropanation while the quaternary stereocentre resulting from carbene formation remains fixed.

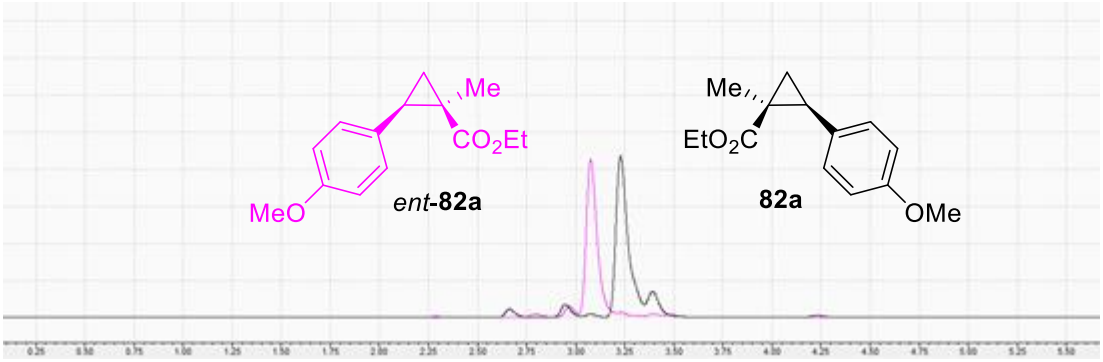
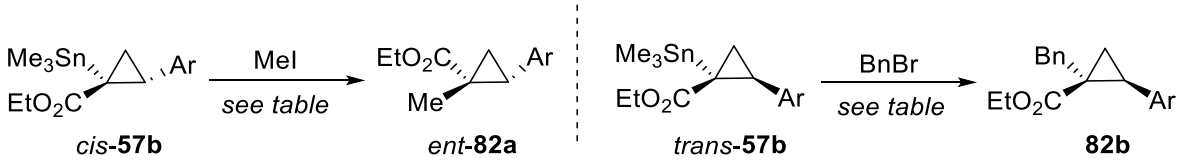


Figure 17. Overlay of chiral HPLC traces of 82a (black) and *ent*-82a (pink).

The reaction conditions of the tin-lithium exchange were further investigated (Table 9). Attempts to replace methyllithium with *n*-butyllithium or LiHMDS remained unsuccessful; besides some unidentified products, incomplete lithiation and protodestannylation were observed (entries 2 and 3). Decreasing the lithiation time proved beneficial to the reaction outcome (entries 4 to 7).

Table 9. Optimization of conditions for tin-lithium exchange.



Entry	[Li] (eq)	Electrophile (eq)	Lithiation time	Yield [%]
1	MeLi (6.0)	MeI (3.0)	30 min	49
2	***n*-BuLi (1.2)**	MeI (4.9)	15 min	n.d.
3	**LiHMDS (1.5)**	BnBr (1.6)	20 min	n.d.
4	MeLi (6.0)	MeI (6.0)	**1 h**	33
5	MeLi (1.2)	MeI (2.5)	**15 min**	59
6	MeLi (1.08)	BnBr (2.4)	**30 min**	37
7	MeLi (1.01)	BnBr (2.6)	**15 min**	49
8	MeLi (1.2)	**MeI (4.9)**	15 min	65
9[a]	MeLi (1.2)	MeI (2.5)	15 min	65
10	**MeLi (1.09)**	**MeI (2.5)**	**2 min**	**78**
11	**MeLi (1.08)**	**BnBr (2.4)**	**3 min**	**62**

All reactions were carried out in THF at -78 °C if not mentioned otherwise. [a] addition of MeLi at -90 °C. n.d.: not determined. Ar = *p*-MeO-C_6H_4.

Using a larger excess of methyl iodide or its addition at -90 °C instead of -78 °C did not significantly influence the yield (entries 8 and 9). A major improvement was achieved by drastically reducing the lithiation time to only a few minutes, which resulted in an increase in yield to 78 % with methyl iodide and 62 % when benzyl bromide was used (entries 10 and 11). These results suggest that the lithium ester enolate is probably not stable for prolonged times, even at cryogenic temperatures.

The scope of the reaction could be extended beyond methyl iodide and benzyl bromide (Figure 18). Allylation could be conducted (**82c**) and ketones such as acetone were also trapped by the ester enolate, resulting in a tertiary alcohol **82d**. Furthermore, the reaction posed an alternative to the previously unsuccessful acylation. Specifically, different aliphatic as well as (hetero)aromatic acid chlorides could be installed in place of the tin moiety (**82e-g**). An interesting observation was made when a trimethylsilyl halide was added. Other than expected, silylation did not occur at oxygen, which would have resulted in a silyl enol ester. Instead, a silicon-carbon bond was formed preferably, resulting in a TMS-substituted analogue of the stannane starting material (**82h**). All of the described examples provided moderate to good yields and cleanly delivered only one diastereoisomer.

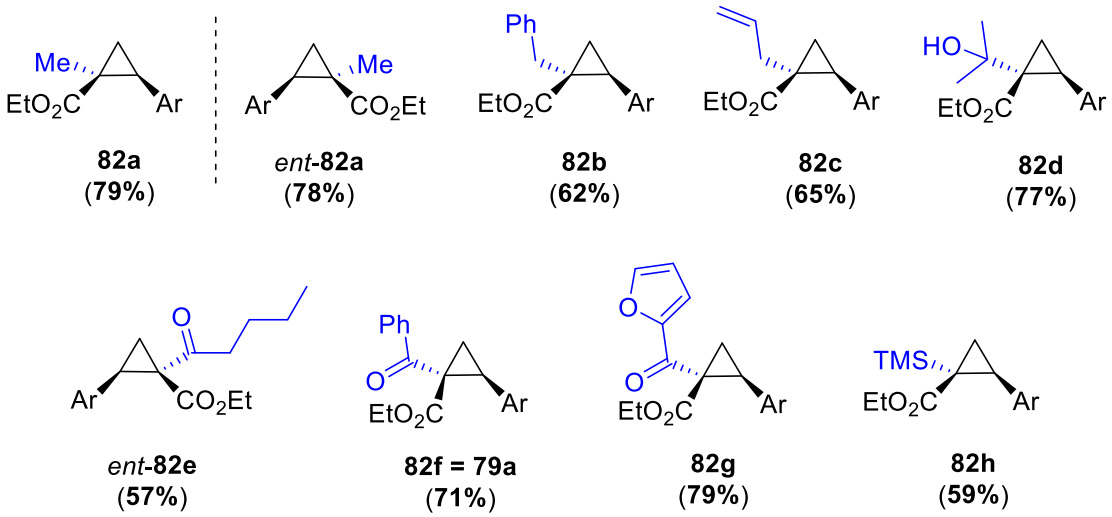
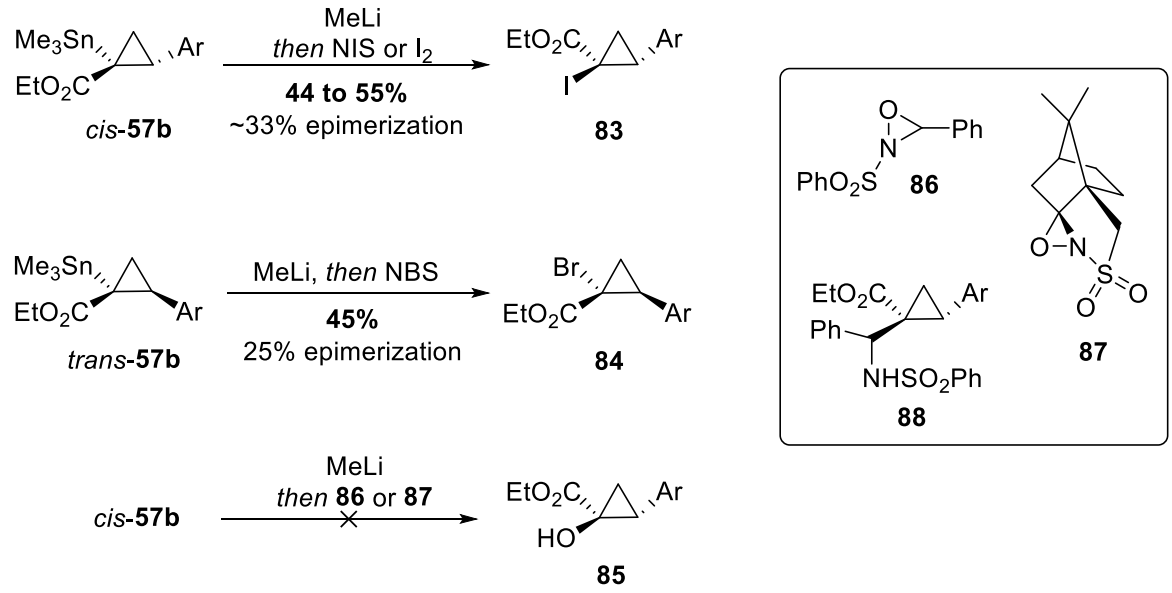


Figure 18. Scope of tin-lithium exchange under optimized conditions (MeLi (1.05 eq), R-X (>2.0 eq), THF, -78 °C to rt). Ar = *p*-MeO-C_6H_4.

1.4.6 Attempts Towards Heteroatom Substitution

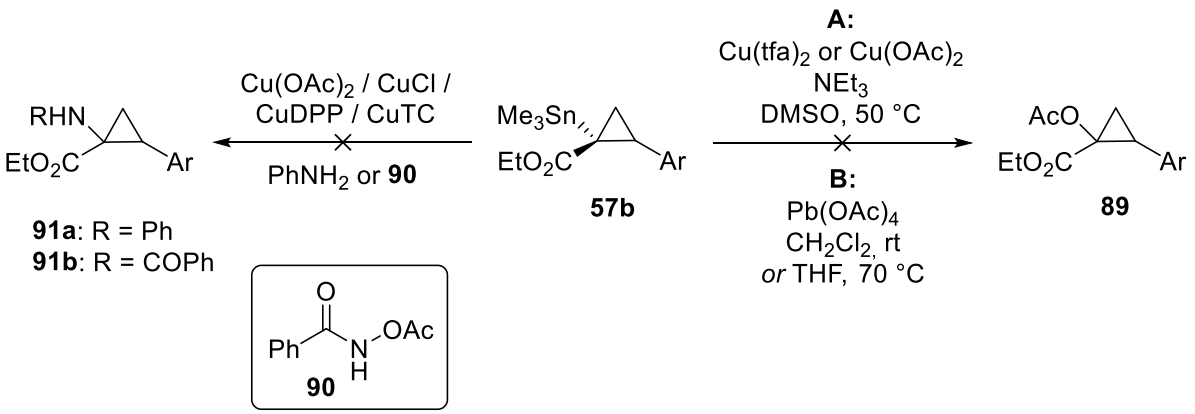
Several experiments were carried out with the aim of installing other heteroatoms (Scheme 28). A tin-lithium-halogen exchange was investigated using NBS, NIS or iodine. Although the desired products **83** and **84** could be isolated, albeit in only moderate yields of around 50 %, NMR analysis showed up to 33 % of epimerization. In this case, the electrophiles may have been small enough to overcome the steric hindrance of the aryl ring and approach the lithium enol ester from either side, resulting in the formation of two diastereoisomers. Moreover, a Rubottom-type oxidation of

the enolate was explored. Unfortunately, when Davis' oxaziridine **86** was employed, the newly formed compound was not the expected tertiary alcohol but rather resulted in incorporation of the oxaziridine moiety (**88**). When the camphorsulfonic acid-derived oxaziridine **87** was used, again no product was detected; only protodestannylation was observed.



Scheme 28. Attempts towards the introduction of iodide, bromide or oxygen substituents *via* lithiation. Ar = *p*-MeO-C$_6$H$_4$.

The introduction of oxygen substituents was investigated by means of Chan-Lam type conditions, involving a copper catalyst in combination with a base, usually carried out under air[151]. It is generally applied for the transformation of boronic acids into the respective C-O coupling products but the use of stannanes and siloxanes has been described as well. Unfortunately, no desired product **89** could be detected when the conditions were applied to our system (Scheme 29). A different approach was the oxidation with Pb(OAc)$_4$[152]; however, this also did not result in product formation. Finally, the introduction of nitrogen substituents was attempted, which can also be done by applying Chan-Lam conditions[153]. Different copper salts were tested under varying conditions but product **91** could not be isolated, although traces of it were detected *via* mass spectrometry.



Scheme 29. Attempts towards the introduction of oxygen or nitrogen substituents *via* copper catalysis. Ar = *p*-MeO-C_6H_4.

1.5 Conclusion

With the newly developed dirhodium catalyst **C3**, a broad scope of different asymmetric stannylated cyclopropanes could be prepared in a highly enantio- and diastereoselective fashion and in overall moderate to high yields. Subsequently, several downstream modifications were successfully achieved. Stereoretentive Stille cross coupling proved to be a useful methodology to introduce a variety of substituents and hence diversify the molecular scaffold. This method enabled even further transformations such as the synthesis of spirocyclic systems. A carbonylative version of the Stille coupling was also established, albeit with a somewhat limited scope. Furthermore, the tin-lithium exchange could be implemented as a suitable method for the diastereoselective introduction of various electrophiles like acid chlorides, which were unsuccessful under cross coupling conditions. Hence, this methodology enables the synthesis of otherwise difficultly accessible optically active cyclopropanes.

2 Application in Natural Product Synthesis

2.1 Introduction

When Wöhler synthesized urea for the first time in 1828 from silver isocyanate and ammonium chloride or alternatively from lead cyanate and ammonia[154], he most likely could not foresee the profound impact he made on the future of chemistry. Another milestone event was the synthesis of acetic acid by Kolbe in 1845[155], who was the first to use the term "synthesis" for the process of using certain chemical substances to assemble a new compound. Since then, the discipline of organic synthesis began to emerge and with it, the field of total synthesis was set in motion (Figure 19). Important early milestones include the syntheses of tropinone (Willstätter, 1901[156]; Robinson, 1917[157]) and haemin (H. Fischer, 1929)[158]. Tremendous contributions to the field were made by Robert B. Woodward in the mid-20th century who successfully synthesized a plethora of natural products of unprecedented complexity during his career, starting with quinine (1944)[159] and ending with erythromycin A (1981)[160]. His ability to generalize observations and translate them into useful theories was unparalleled and certainly inspired many chemists.

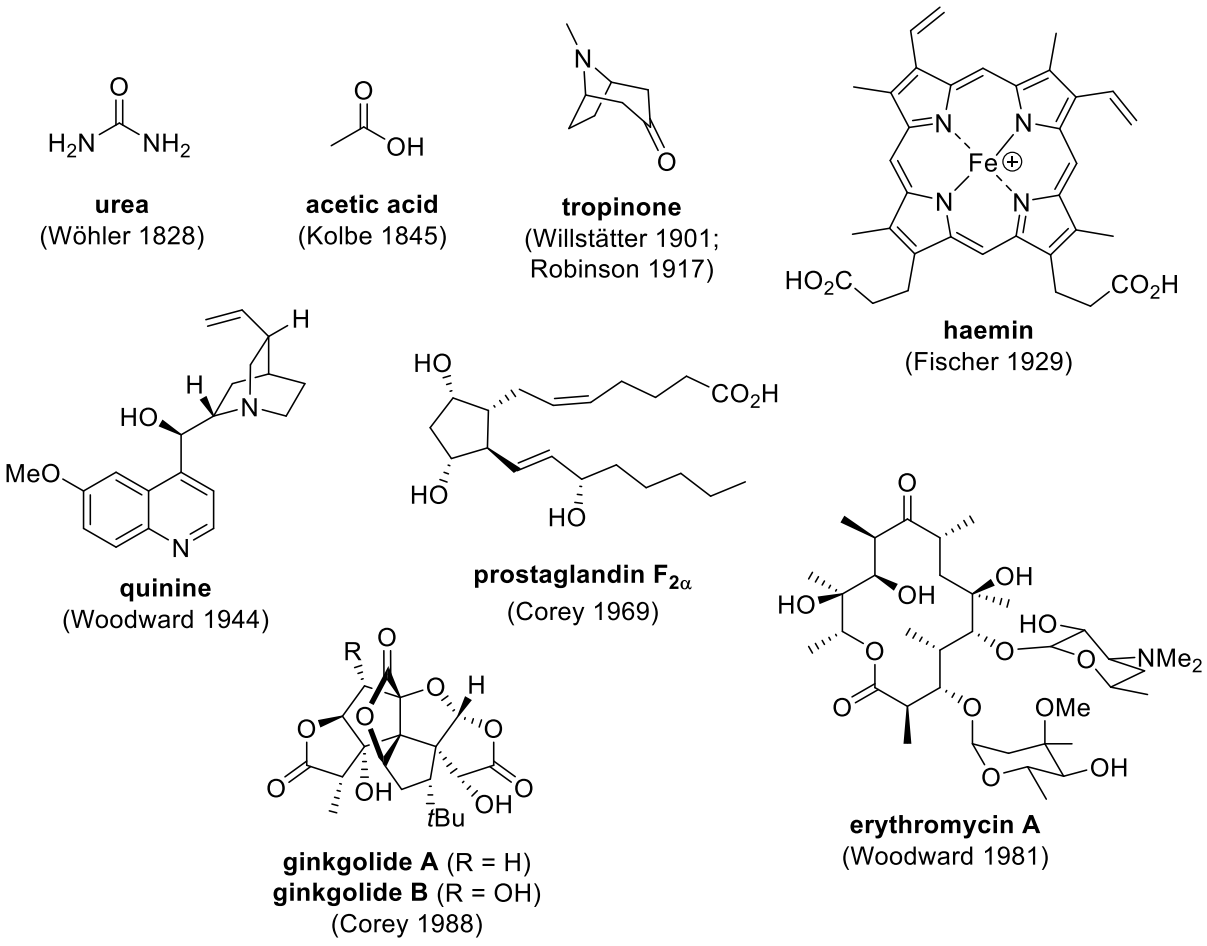


Figure 19. Selection of milestone natural products achieved by total synthesis.

In the second half of the 20th century, Corey further elevated the "art and science of total synthesis" by introducing a new systematic approach towards new target molecules, namely retrosynthetic analysis. This "logic of chemical synthesis"[161], together with the development of new synthetic methods along the way, became an integral part of the field and enabled the syntheses of more than 200 natural products in his laboratory, such as prostaglandin $F_{2\alpha}$ (1969)[162] or ginkgolide A[163] and B[164] (1988).

The importance of organic synthesis in general and total synthesis in particular was emphasized by the bestowal of Nobel Prizes on R. Willstätter (1915), H. Fischer (1929), R. Robinson (1947), R. B. Woodward (1965) and E. J. Corey (1990).

During the early endeavors, the main objective of total synthesis was to provide a proof of structure. Although this is still a valid purpose, with the advent of increasingly powerful analytical methods such as NMR spectroscopy or X-ray diffraction analysis, the motivation for total synthesis has evolved. An important factor certainly is the opportunity to discover new chemical reactivities and develop synthetic methods to master hitherto unsolved problems. Consequently, it has immensely contributed to society, especially medicine and biology, by providing a growing tool kit for the creation of new drug candidates or the investigation of genomics on a molecular level. To this day, total synthesis remains the ultimate test for the applicability of synthetic methodology and continues to be a driving force in the advancement of organic synthesis.

2.2 Aim

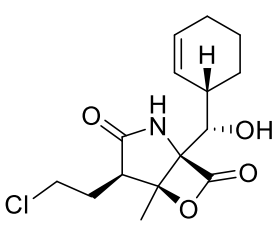
The aim of the project was to test and showcase the versatility of the previously developed methodology involving asymmetric cyclopropanation followed by downstream modification *via* Stille coupling or tin-lithium exchange. This was to be done by implementing the methodology in the total syntheses of different natural products, namely the salinilactones and integrifolian-1,5-dione.

2.3 Synthesis of Salinilactones

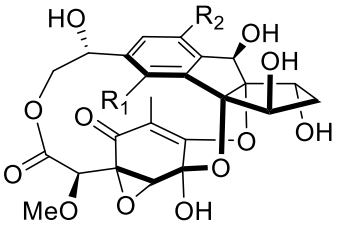
2.3.1 Introduction

A new genus of marine actinomycetes was first described in 1989[165]. It was given the name *Salinispora*, based on the observation that its growth heavily depends on the presence of sodium ions or seawater, and the taxon was formally described in 2005[166]. The genus includes three species, *S. tropica*, *S. arenicola* and *S. pacifica,* which have been isolated from tropical and subtropical regions all over the world[167]. Amongst a plethora of natural products that have been isolated from *Salinispora* strains[168], there are some that have raised particular interest amongst scientists due to their structural and biological features (Figure 20). Isolated from a strain of *S. tropica* in 2003 was salinosporamide A, which possesses an intriguing fused γ-lactam-β-lactone bicyclic ring system[169]. It displays potent *in vitro* cytotoxicity against various human cancer cell lines and a strong inhibition of 20S proteasome, which is a validated target for cancer chemotherapy[170]. Under the name marizomib it entered clinical trials soon after its first discovery[171]. In 2005, the first total syntheses of salinosporamide A were reported by the groups of Corey[172] and Danishefsky[173].

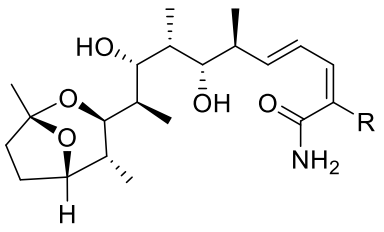
Another unique structural scaffold is present in sporolides A and B, halogenated macrocycles isolated from *S. tropica*[174]. While the sporolides displayed no biological activity in standard assays, an *in silico* target prediction revealed HIV-1 reverse transcriptase, among others, as a potential target with which they showed a maximum docking score. The findings could be further confirmed through an *in vitro* fluorescent assay where sporolide B exhibited good inhibitory activity against HIV-1 reverse transcriptase[175]. A total synthesis of sporolide B has been reported by the group of Nicolaou[176]. Further highlighting the structural variety of metabolites among *Salinispora* are the bicyclic polyketides saliniketals A and B, which have been isolated from a strain of *S. arenicola*[177]. These metabolites are potentially interesting for so-called chemoprevention of cancer, as they significantly inhibit ornithine decarboxylase induction, an important target in this field. Already shortly after their disclosure, total syntheses of saliniketals A and B were reported[178].



salinosporamide A



sporolide A (R_1 = Cl, R_2 = H)
sporolide B (R_1 = H, R_2 = Cl)



saliniketal A (R = H)
saliniketal B (R = OH)

Figure 20. Natural products that were isolated from *Salinispora* bacteria.

Salinilactones A-C, a family of natural products possessing an unprecedented [3.1.0]-lactone ring system, was uncovered upon analysis of volatiles emitted by *S. arenicola* in 2018[179] (Figure 21). Their structure was elucidated using various analytical methods including gas chromatography, mass spectrometry and DFT calculations and furthermore confirmed through chemical synthesis. In 2020, five more members, salinilactones D-H, were added to the family, all varying in the alkyl side chain of the molecule[180].

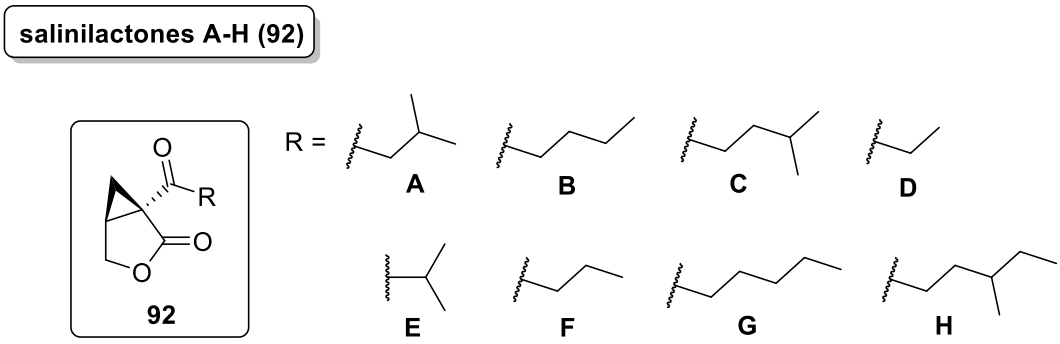
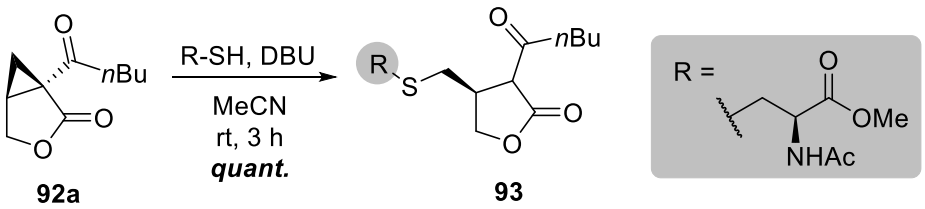


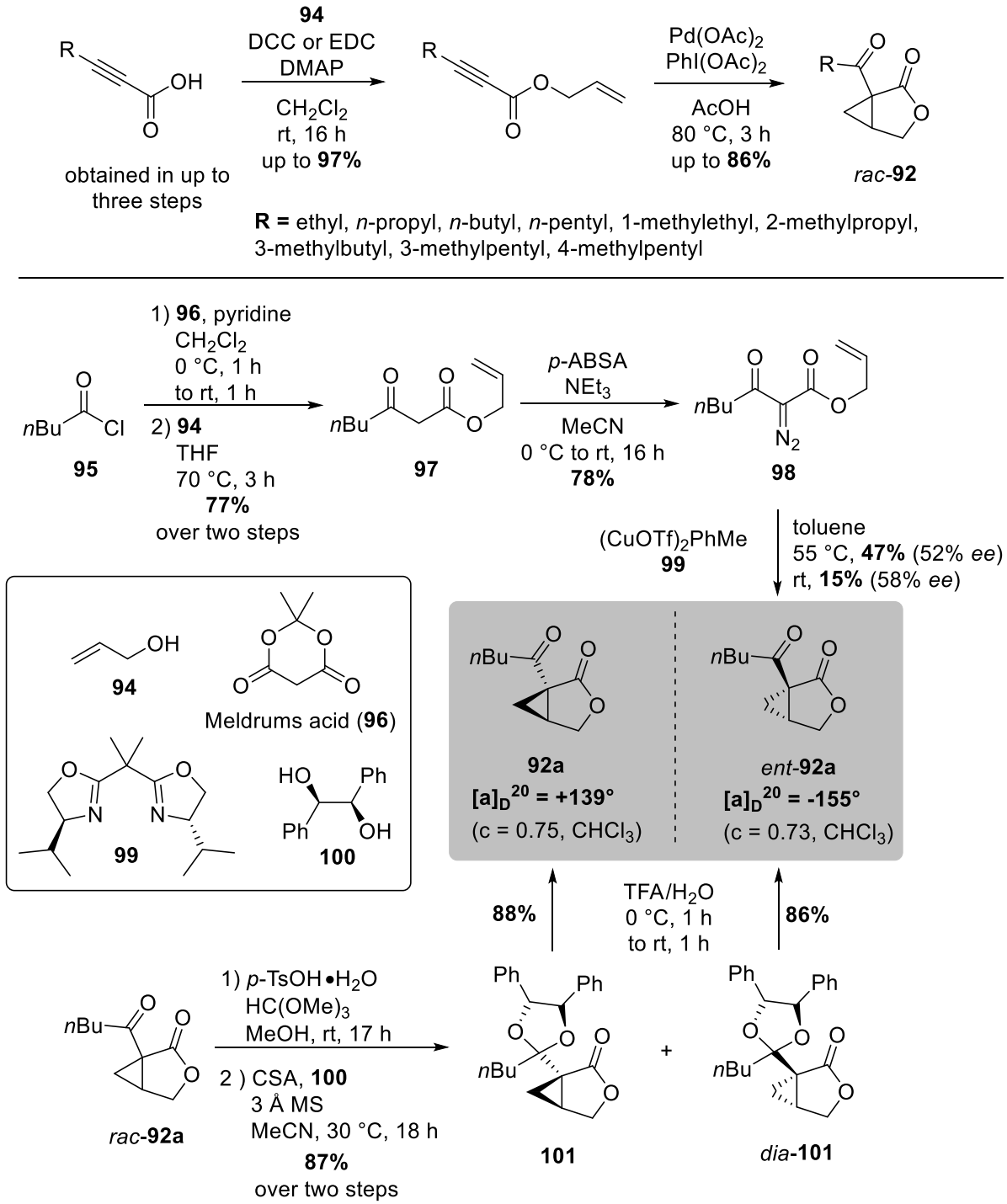
Figure 21. Members of the salinilactone family.

Biological studies of salinilactones A-C have shown growth inhibition of both a strain of *S. arenicola* as well as a Streptomyces strain. This self-inhibitory activity might imply that the molecules provide a signaling function amongst *Salinispora*[179]. Furthermore, in a toxicity assay with brine shrimp salinilactones A-C and G have shown significant activity, hinting towards substantial cytotoxicity of these compounds[180]. In a more recent study, the biological activity could further be specified and molecular targets were identified[181]. An activity-based protein profiling was carried out, revealing that protein disulfide-isomerases (PDIs) are inhibited by salinilactone B (**92a**) through covalent binding to the sulfur atom of cysteine side chains in the active site of the enzyme. Attack of the thiol likely occurs on the unsubstituted site of the cyclopropylring, as suggested by a model reaction (Scheme 30). Interestingly, the less abundant (1*S*,5*R*)-enantiomer of salinilactone B showed higher potency than the major (1*R*,5*S*)-enantiomer. Thioredoxin was disclosed as a secondary target, albeit slightly weaker inhibition efficacy compared to PDIs was observed.



Scheme 30. Model reaction to elucidate the enzyme binding of salinilactone B (92a).

The initial syntheses of salinilactones by the isolation team comprised four steps for the enantioenriched product and between three and five steps for the racemic material, depending on the availability of the starting material (Scheme 31).



Scheme 31. Racemic synthesis of salinilactones 92 (top) and asymmetric syntheses of salinilactone B (92a, bottom) as carried out by the isolation team.

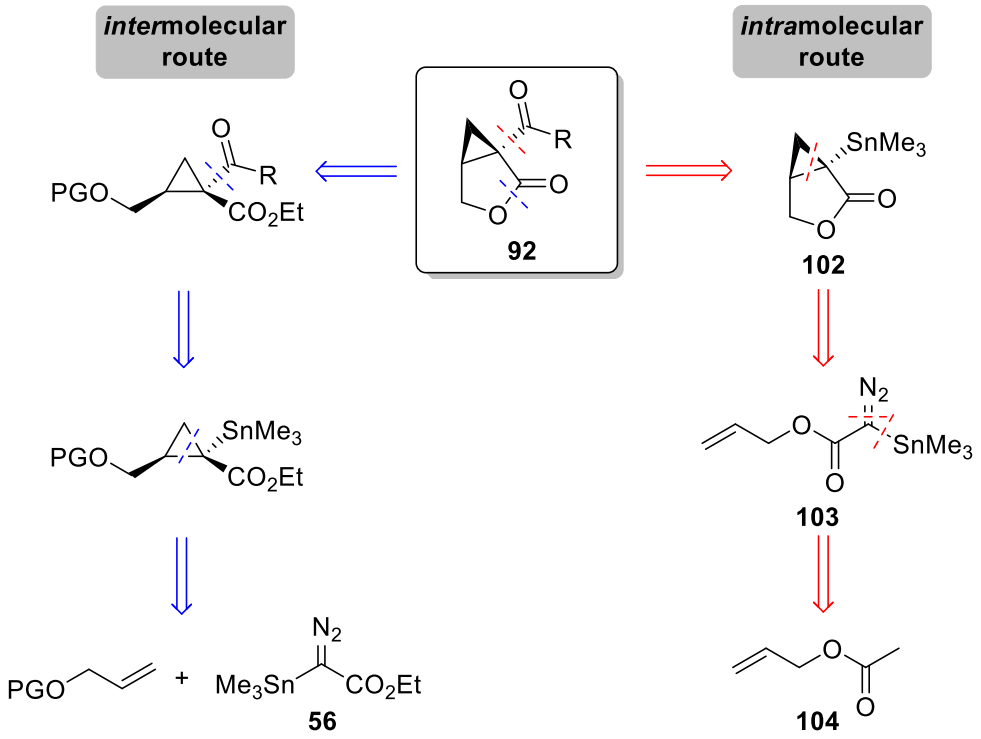
In both cases, the synthetic route had to be started from the beginning for every salinilactone derivative as the alkyl side chain was part of the initial starting material. The key step of the initial asymmetric synthesis was a copper-catalyzed intramolecular cyclopropanation of diazo

compound **98**[182] which yielded ***ent*-92a** with 52 % *ee*. Attempts to increase the *ee* by lowering the temperature was accompanied by a significant drop in yield with only minimally improved *ee* of 58 %. In order to obtain material of higher enantiopurity, the group eventually resorted to chiral resolution, using (*R*,*R*)-hydrobenzoin **100** as a chiral auxiliary[181].

2.3.2 Retrosynthetic Analysis

It was of interest to find out whether the salinilactones are a suitable target to showcase the versatility of the newly developed rhodium-catalyzed cyclopropanation and post-functionalization methodology. It would enable a more modular synthesis because the alkyl side chain could be introduced at a late stage of the synthesis. Additionally, it was anticipated that the rhodium-catalyzed cyclopropanation could provide higher enantioselectivity compared to the copper-catalyzed approach employed by the isolation team.

A main question of the retrosynthetic analysis was whether the key cyclopropanation should be carried out in an inter- or intramolecular fashion. For the intramolecular route (Scheme 32, red arrows), the acyl substituent would be introduced in the last step, after cyclopropanation of the allylic stannylated diazo ester **103**. Alternatively, regarding the intermolecular pathway (Scheme 32, blue arrows), formation of the lactone was envisioned as the final step, following the tin-lithium exchange to introduce the acyl substituent after intermolecular cyclopropanation employing an allylic alcohol and the established stannylated diazo ester **56**.

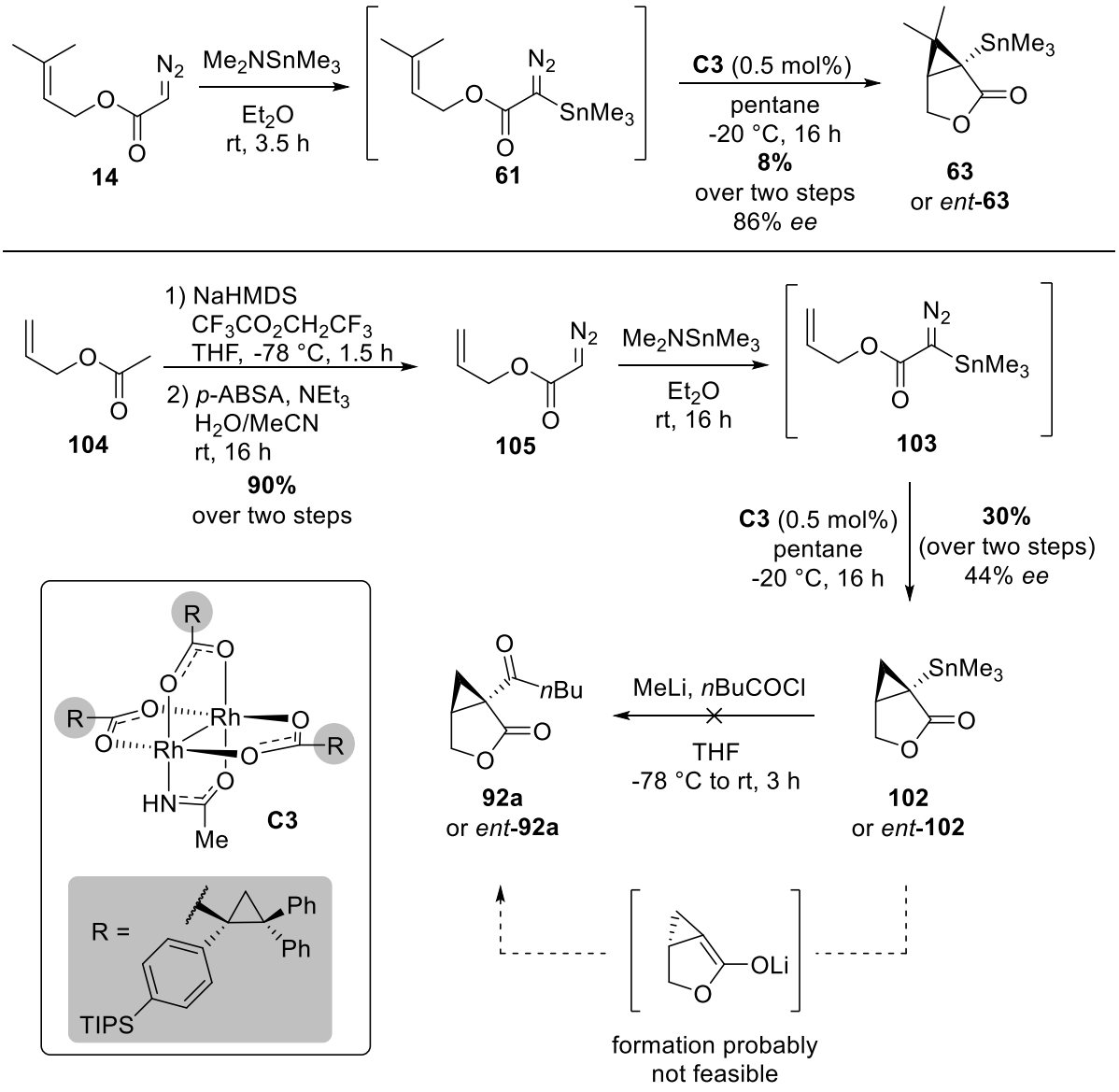


Scheme 32. Retrosynthetic analysis of salinilactones (92).

2.3.3 Forward Synthesis

2.3.3.1 Intramolecular Route

As described in section 1.3.3, the intramolecular cyclopropanation had been tested with the 1st generation dirhodium catalyst (**C1**), albeit with moderate success. However, due to the slightly shorter and more modular route in terms of late stage diversification and since the transformation had not yet been tried with the 2nd generation catalyst (**C3**), the intramolecular approach was investigated first (Scheme 33).



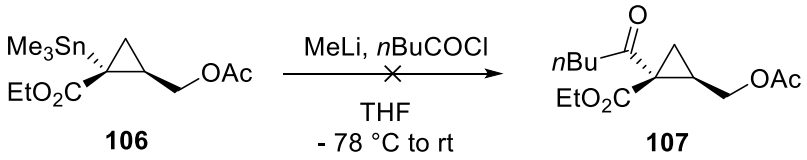
Scheme 33. Attempt towards synthesis of salinilactone B (92a) following the intramolecular approach.

From the previous project, a dimethyl-capped derivative **14** of the required substrate was still available as a model substrate. After stannylation of **14** with dimethylamino trimethyltin, the obtained intermediate **61** was submitted to cyclopropanation without prior purification. Even though the yield over two steps was poor, the *ee* of **63** was found to be a promising 86 % when

the 2nd generation dirhodium catalyst **C3** was used (absolute configuration was not determined). Encouraged by this result, the synthesis was attempted with the monosubstituted terminal olefin in place for the cyclopropanation. The respective diazo compound **105** was obtained from allyl acetate **104**, following a literature procedure[139]. Subsequent stannylation was carried out as described before, and the crude stannane **103** treated with 2nd generation dirhodium catalyst **C3**. The desired bicyclic lactone **102** could be isolated, however with only a moderate *ee* of 44 % in this case. Nevertheless, the subsequent modification *via* tin-lithium exchange was pursued with the material at hand, although without success. Probably the formation of the intermediate enolate at the bridgehead carbon atom was unfavoured according to Bredt's rule.

2.3.3.2 Intermolecular Route

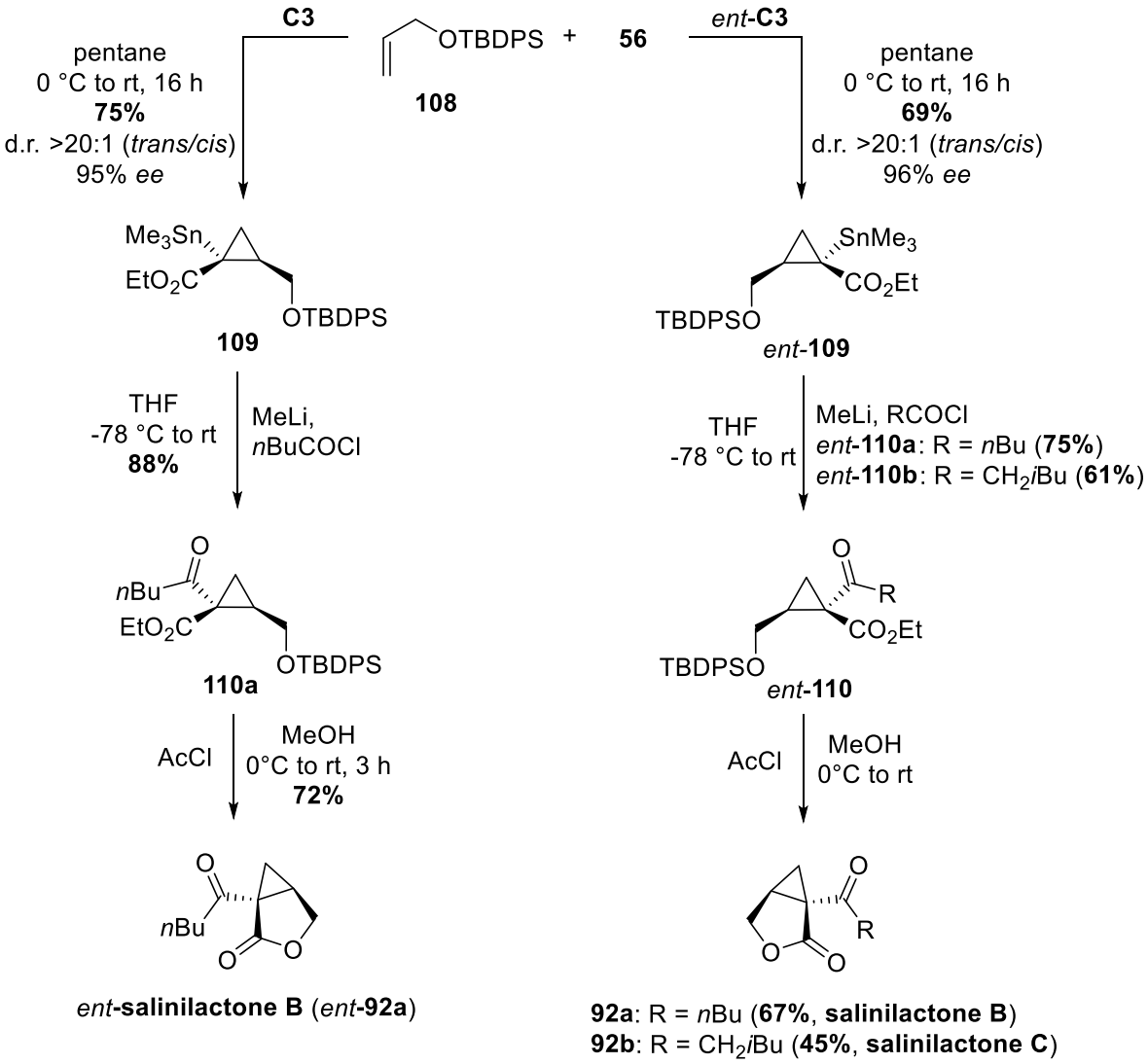
Consequently, the intermolecular route was pursued, starting from another building block that was available from the previous studies, namely stannylated cyclopropane **106** derived from allyl acetate. Unfortunately, it was not compatible with the lithiation conditions and no acylated cyclopropane **107** was obtained (Scheme 34). Since acetate protecting groups are generally not stable in presence of organolithium reagents, the outcome was not unexpected.



Scheme 34. Attempted tin-lithium exchange in presence of an acetate protecting group.

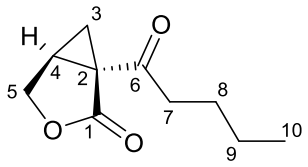
Thus, *tert*-butyldiphenylsilyl ether was chosen as a new protecting group for the allylic alcohol, which, besides being stable towards lithiation, would also significantly increase the mass of the molecule and therefore render it less volatile and easier to handle. Cyclopropanation of the TBDPS-protected allylic alcohol **108** was conducted with dirhodium catalyst **C3** and provided the desired compound **109** in 75 % yield and an *ee* of 95 % (Scheme 35). The diastereomeric ratio was greater than 20:1 in favour of the *trans*-isomer. The introduction of the acyl side chain *via* tin-lithium exchange proceeded smoothly, giving **110a** in 88 % yield without erosion of the stereocentre. When deprotection of the alcohol was first attempted with TBAF, the direct formation of the lactone ***ent*-92a** was observed. Isolation of the compound proved challenging due to coevaporation during removal of the solvent, THF. To circumvent this, the deprotection was performed with acetyl chloride in methanol, causing *in situ* formation of HCl. The workup and extraction were then conducted with CH_2Cl_2, which allowed for an easier removal of solvent at higher pressures and reduced the loss of product. In this way, *ent*-salinilactone B was obtained in 72 % yield.

Having established a route, the synthesis was repeated applying the (*S*)-enantiomer of the dirhodium catalyst (***ent*-C3**) in order to obtain the correct enantiomer of the natural product (Scheme 35). Cyclopropanation provided ***ent*-109** in similarly high yields and an *ee* of 96 %; the diastereomeric ratio was again greater than 20:1 in favour of the *trans*-isomer. Tin-lithium exchange was successfully applied to introduce two different acyl side chains. Deprotection and ensuing lactone formation provided salinilactones B and C in moderate to good yields. The analytical data were in good agreement with those reported in the literature[179] (Table 10 and Table 11).



Scheme 35. Synthesis of *ent*-salinilactone B (left) and salinilactones B and C (right).

Table 10. Comparison of NMR spectroscopic data of synthetic salinilactone B (92a) with the literature values[179].

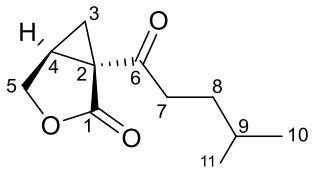


salinilactone B (92a):
$[a]_D^{20}$ (exp.) = +107.2° (c = 1.25, $CHCl_3$)
$[a]_D^{20}$ (Lit.) = +139° (c = 0.75, $CHCl_3$)

Atom No.	δ_{exp} ^{1}H [ppm][a]	δ_{Lit} ^{1}H [ppm][a]	δ_{exp} ^{13}C [ppm][b]	δ_{Lit} ^{13}C [ppm][c]
1	-		203.0	202.8
2	-		36.3	36.2
3	2.04 1.36	2.05 1.29 - 1.41	23.9	23.7
4	2.75	2.77	29.8	29.6
5	4.33 4.19	4.34 4.20	67.4	67.2
6	-		173.0	172.8
7	3.12 2.86	3.13 2.87	41.5	41.3
8	1.58	1.52 – 1.66	25.7	25.5
9	1.36	1.29 - 1.41	22.3	22.2
10	0.92	0.92	14.0	13.8

All spectra measured in $CDCl_3$. [a] 400 MHz. [b] 101 MHz. [c] 100 MHz.

Table 11. Comparison of NMR spectroscopic data of synthetic salinilactone C (92b) with the literature values[179].



salinilactone C (92b):
$[a]_D^{20}$ (exp.) = +95.3° (c = 1.0, $CHCl_3$)

Atom No.	δ_{exp} ^{1}H [ppm][a]	δ_{Lit} ^{1}H [ppm][a]	δ_{exp} ^{13}C [ppm][b]	δ_{Lit} ^{13}C [ppm][c]
1	-	-	203.2	203.0
2	-	-	36.3	36.1
3	2.05 1.38	2.05 1.39	24.0	23.8
4	2.75	2.76	29.8	29.6
5	4.33 4.19	4.34 4.20	67.4	67.2
6	-	-	172.9	172.8
7	3.13 2.87	3.13 2.82 – 2.93	39.9	39.7
8	1.50	1.43 – 1.65	32.4	32.2
9	1.59	1.43 – 1.65	27.8	27.6
10, 11	0.91	0.91	22.5, 22.6	22.3, 22.4

All spectra measured in $CDCl_3$. [a] 400 MHz. [b] 101 MHz. [c] 100 MHz.

2.3.4 Conclusion

Two different members of the salinilactone family were successfully obtained by the newly developed methodology of asymmetric cyclopropanation followed by downstream functionalization. The dirhodium catalyst **(*ent*-)C3** performed well with the olefinic substrate, providing very good diastereoselectivity and excellent enantioselectivity, thereby highlighting its general applicability. Concerning the downstream functionalization, a tin-lithium exchange was employed to install the acyl side chain, potentially enabling the facile synthesis of a library of non-natural derivatives for further biological studies.

2.4 Synthesis of Integrifolian-1,5-dione

2.4.1 Introduction

Plants of the genus *Lippia* belong to the Verbenaceae family, which includes around 200 species. One of them is *Lippia integrifolia*, commonly known by different names such as "incayuyo", "té del inca" or "poleo", a woody aromatic shrub that is native to central and northern Argentina[183]. Its aerial parts have been widely used in traditional medicine in form of infusions or decoctions for the treatment of dyspepsia, stomach aches, indigestions or flu, among other uses, as a sedative or soft diuretic[184]. Biological studies of essential oils of *L. integrifolia* have shown that they exhibit excellent repellent activity against *Triatoma infestans*[185], a common Chagas disease vector, and further insecticidal activity against beetles of the genus *Carpophilus* and *Oryzaephilus* which infest walnut trees[186]. Moreover, fungicidal activity of the essential oils has been reported against *Aspergillus* species[187], a fungus that causes deterioration of stored peanuts, and fungitoxicity against *Ascophaera apis*[188], causing a mycotic disease mainly in honeybees. Aqueous extracts of *L. integrifolia* were found to exhibit a strong *in vitro* antioxidative capacity and up to 40 % inhibition of the adhesion of *Helicobacter pylori* to stomach cells, rationalizing its traditional use for gastric inflammation[189]. Besides, significant choleretic activity and antispasmodic effects have also been observed[190]. Several other biological activities involving different parts of the plant have been reported[191]. Interestingly, the use of *L. integrifolia* as a seasoning has been included in the Argentine Food Code and it is an ingredient in some commercial beverages[192].

The chemical composition of the extracts of *L. integrifolia* has been extensively analysed[192-193] and besides various known compounds, such as limonene, camphor, spathulenol or α-humulene, some novel sesquiterpenoids with rare skeletons have been isolated (Figure 22). Several previously unknown compounds that are structurally based on the africane skeleton have been reported (**111**)[194]. It is noteworthy that this type of structural motif was first identified outside the plant kingdom in the form of africanene and africanol in soft corals[195]. The total syntheses of various africane-derived natural products have been reviewed[196]. Other compunds were identified to exhibit an asteriscane-type carbon skeleton (**112**)[194b, 194c]. Furthermore, a bicyclo[8.1.0]undecane system has been identified which was named integrifolian-1,5-dione (**113**), along with another novel sesquiterpene named lippifoli-1(6)-en-5-one (**114**) and derivatives thereof (**115**, **116**)[197]. Most likely, integrifolian-1,5-dione and its derivatives share a similar biogenetic pathway, originating from α-humulene (Scheme 36). It is proposed that α-humulene is epoxidised and then oxidized to deliver humulenedione, which was also isolated from *L. integrifolia*[198]. A comparable transformation involving epoxidation of α-humulene leading to bicyclohumulenone and africane-derivatives *via* transannular cyclization has been described[199] and would explain the occurrence of africane-type compounds in *L. integrifolia*.

Cyclopropanation of humulenedione would in turn lead to integrifolian-1,5-dione, from which lippifoli-1(6)-en-5-one and the aldol products can be derived[200].

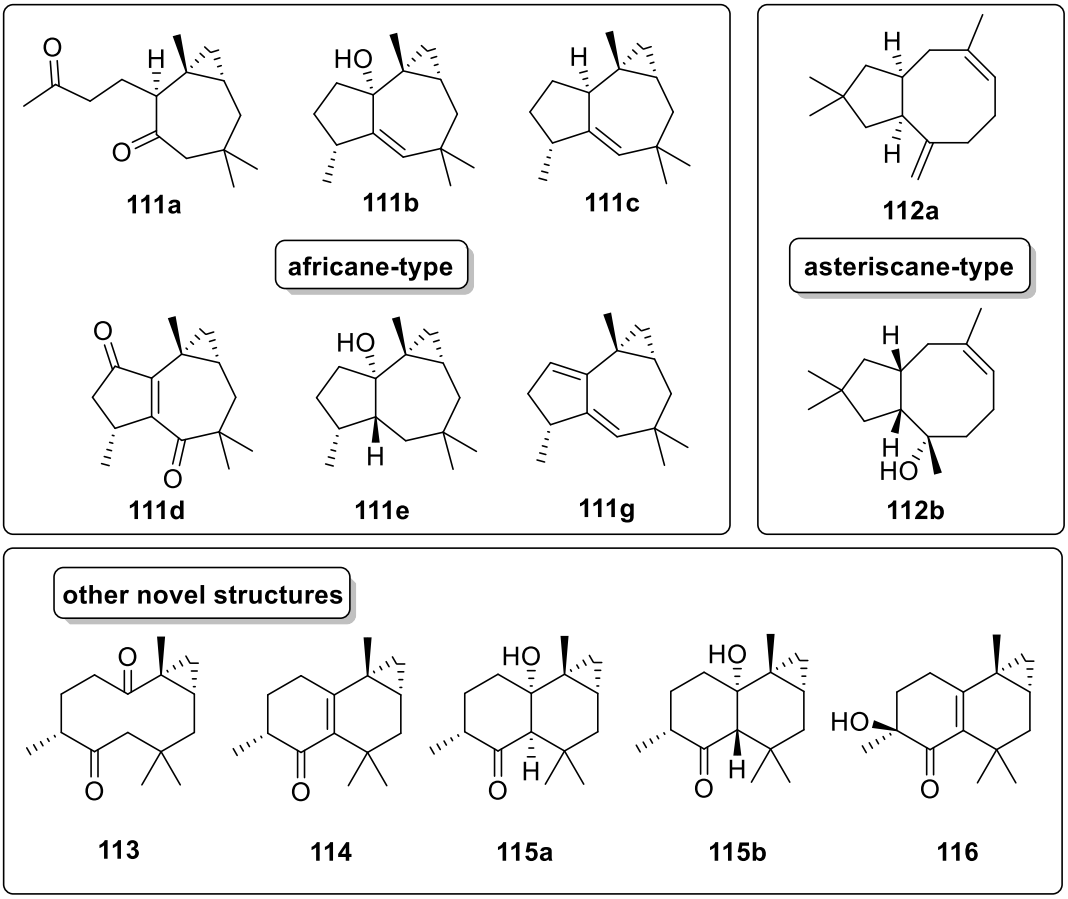
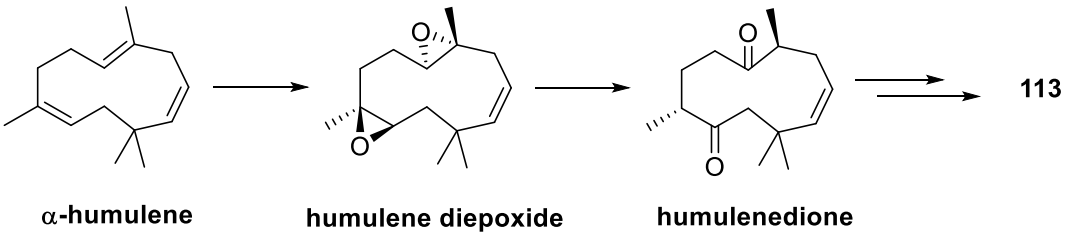


Figure 22. Natural products that were isolated from *Lippia integrifolia*.



Scheme 36. Proposed biosynthetic pathway of integrifolian-1,5-dione (113).

The structure of integrifolian-1,5-dione was first described in 1983. It was initially proposed that the cyclopropane ring was fused to the decane ring in a *trans* manner (**117**), in analogy to the already known structure of bicyclohumulenedione[201] (Figure 23). Almost ten years later, the structure was revised based on an X-ray diffraction analysis that clearly indicated the *cis*-fusion of the two carbocycles[197a]. In the same publication, a corrected structure for lippifoli-1(6)-en-5-one was reported as well, for which initially an africane-type skeleton had been suggested (**118**)[202]. A more detailed NMR spectroscopic analysis further supported the structures of **113** and **114**[203]. Although so far there are no studies reported about the bioactivity of either lippifoli-

1(6)-en-5-one or integrifolian-1,5-dione, one might expect them to exhibit pharmacological effects based on the previously described activity and biological effects of essential oils from *L. integrifolia*.

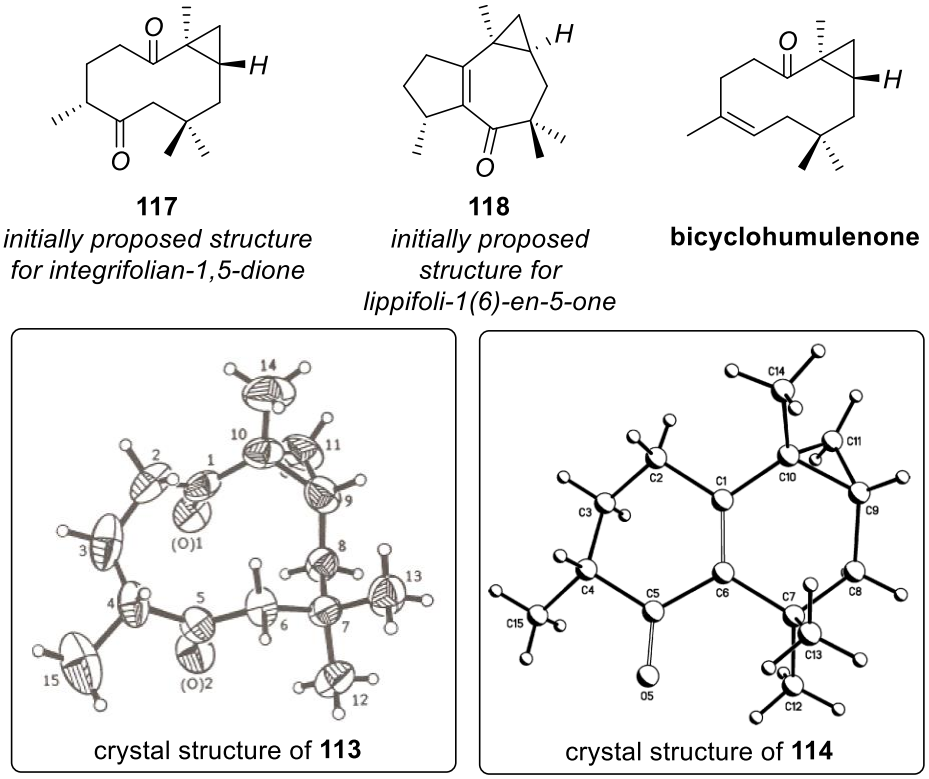


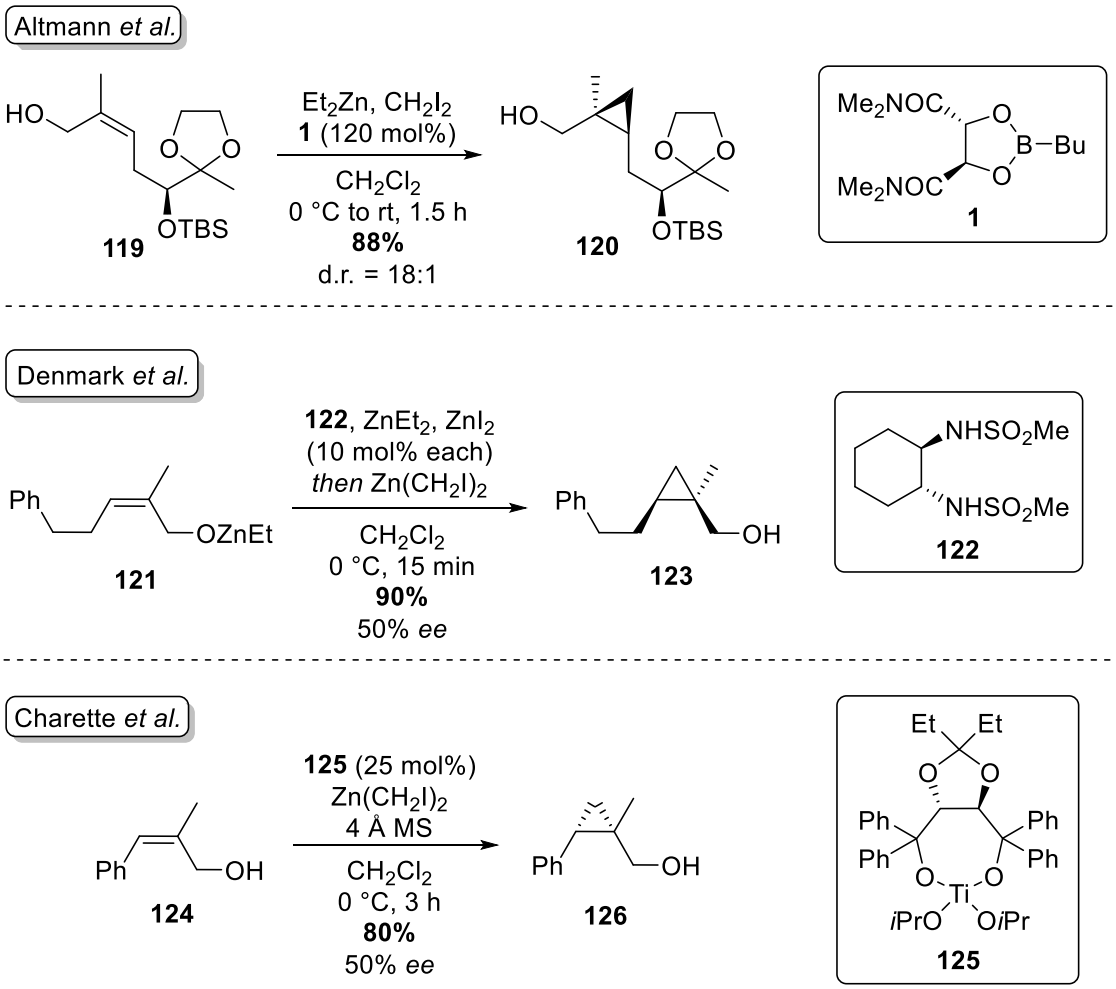
Figure 23. Initially proposed structures of integrifolian-1,5-dione and lippifoli-1(6)-en-5-one compared to bicyclohumulenone and the correct structures as verified by X-ray diffraction analysis.

2.4.2 Retrosynthetic Analysis

2.4.2.1 Asymmetric Synthesis of the 1,1,2-Trisubstituted Cyclopropane Motif

To this day, no total synthesis of integrifolian-1,5-dione has been reported despite the structure of the molecule being known for more than 30 years. It contains an intriguing 1,1,2-trisubstituted cyclopropane motif bearing an all-carbon quaternary stereocentre, which poses a synthetic challenge. In the literature there are only limited examples reporting the catalytic asymmetric synthesis of this type of scaffold, i.e. without the use of enantioenriched starting materials or chiral auxiliaries. As already discussed in section 1.1.1.2, approaches towards asymmetric Simmons-Smith cyclopropanations include Charrette's dioxaborolane ligand **1**, which has been applied in the asymmetric cyclopropanation towards similar structural motifs such as **120**[204] (Scheme 37). However, it requires stoichiometric or even higher amounts of the ligand with respect to the olefin. The use of a chiral disulfonamide **122** as catalyst was originally reported by Kobayashi and coworkers[205], but further modified by the group of Denmark who applied it to α,β-substituted allylic alcohols[206]. However, in the presence of an α-substituent, the enantioselectivity drops significantly, compared to only β-substituted allylic alcohols. Similar observations were made by

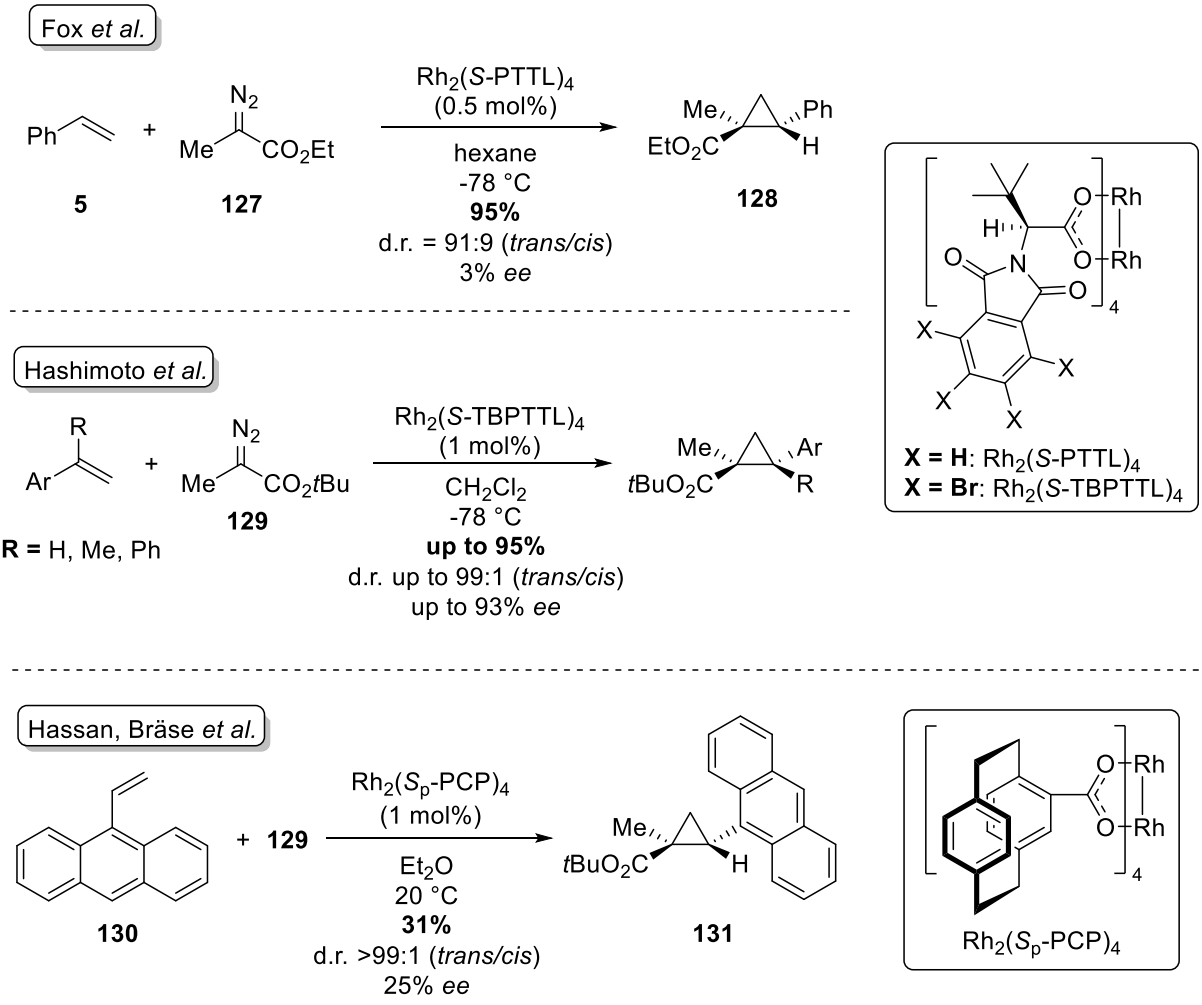
Charette when using his chiral titanium TADDOL complex **125**[36]: With a methyl group in the α-position of the allylic alcohol **124**, the *ee* of the product **126** was only 50 %.



Scheme 37. Asymmetric syntheses of 1,1,2-trisubstituted cyclopropanes bearing a methyl substituent *via* Simmons-Smith cyclopropanation.

Transition metal-catalyzed methods based on diazo decomposition would require an α-methylated diazo ester. Generally, α-alkylated diazo compounds have only rarely been applied in this context due to their propensity to undergo a β-hydride shift[207]. Still, some examples have been reported using chiral dirhodium paddlewheel complexes in combination with α-methylated diazo esters such as **127** or **129** (Scheme 38). The group of Fox only achieved 3 % *ee* of cyclopropane **128** with Rh_2(S-PTTL)$_4$ as catalyst[50a]. Hashimoto and coworkers were more successful with a slightly modified catalyst, Rh_2(S-TBPTTL)$_4$ and the *tert*-butyl ester of the diazo compound **129** instead of the ethyl ester **127**[208]. They could obtain up to 93 % *ee* and >99:1 d.r. in favour of the *trans*-isomer. However, their scope was limited to aromatic olefins, with one exception, and the *trans*-isomer does not represent the geometry needed in the case of integrifolian-1,5-dione. A conceptually novel dirhodium catalyst bearing planar chiral paracyclophane (PCP) ligand was introduced by Hassan and Bräse[209]. The catalyst provided the

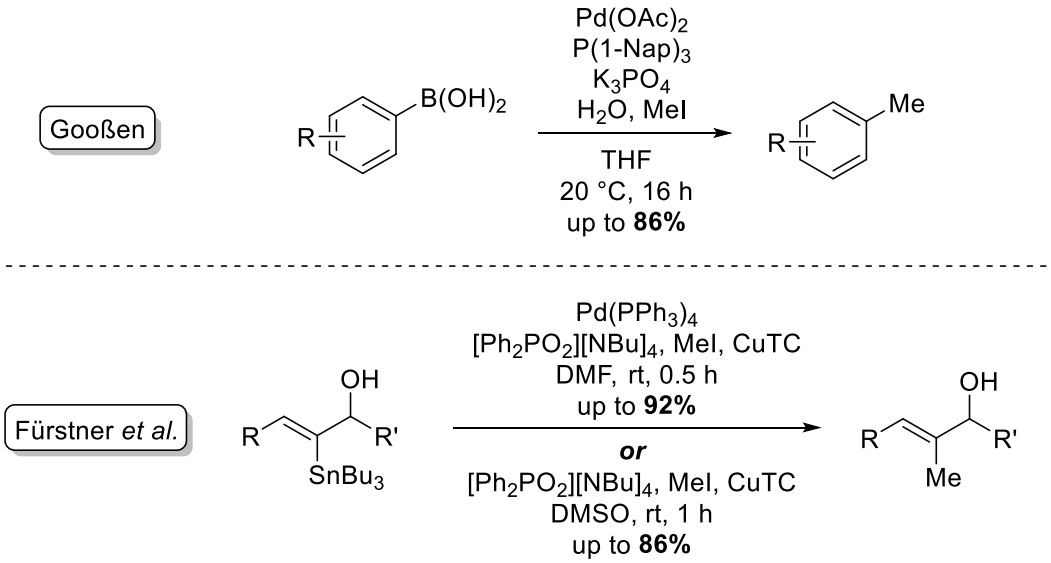
cyclopropanation products such as **131** in high diastereoselectivities but with *ee* values far below 50 %. Again, this example gave the *trans*-isomer which is not the desired motif with respect to the synthesis of integrifolian-1,5-dione.



Scheme 38. Asymmetric syntheses of 1,1,2-trisubstituted cyclopropanes bearing a methyl substituent using dirhodium paddlewheel complexes.

Accordingly, it was deemed a suitable target to further showcase the versatility of our methodology by synthesizing the stannylated cyclopropane using our *trans*-selective heteroleptic dirhodium catalyst (**C3**) followed by either tin-lithium exchange or Stille coupling. While it had already been shown that tin-lithium exchange does allow for the introduction of a methyl group (see section 1.4.5), attempting a Stille coupling involving methyl iodide as the electrophile would certainly pose a more daunting task, especially with the nucleophile comprising a tertiary alkyl group. Examples in the literature for these types of cross couplings are scarce, even with more well-behaved C(sp^2) coupling partners. The majoritiy of advances have been made in the field of radiochemistry with the aim of incorporating an ^{11}C-labeled methyl group[210]. In those protocols, the stannane is mostly used in a large excess, which is not suitable for our purposes. Gooßen reported a methodology for a Suzuki cross coupling of methyl iodide with aryl boronic acids as

the limiting reagent using tri-1-naphthylphosphine as a bulky ligand[211] (Scheme 39). Another Stille coupling procedure was developed by our group wherein the respective alkenylstannanes were treated with a combination of CuTC, $(Ph_2PO_2)NBu_4$ and (in some cases) $Pd(PPh_3)_4$, using a slight excess of methyl iodide[142]. Again, it is worth emphasizing that all of the aforementioned examples involve C(sp^2)-hybridized carbon nucleophiles.



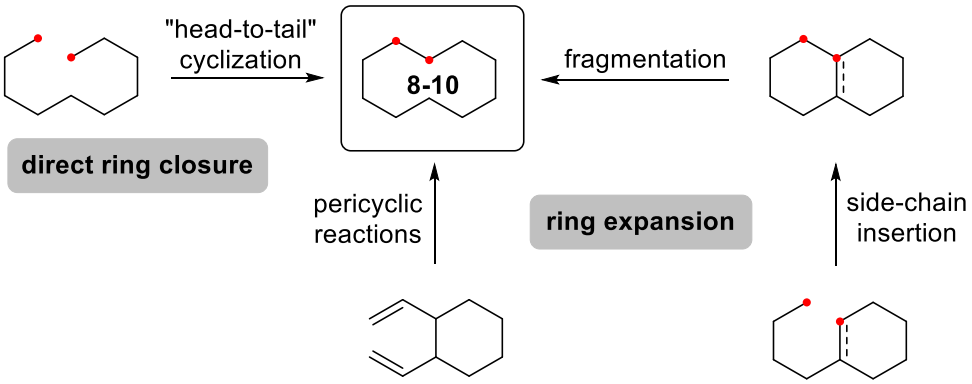
Scheme 39. Cross couplings with methyl iodide as the electrophile.

2.4.2.2 Synthesis of Medium-Sized Rings

Another synthetically challenging characteristic of the target molecule was the ten-membered carbocycle, owing to its theoretical ring strain of 12.2 kcal/mol[212]. This ring strain can be attributed to slightly distorted C-C bond angles expanded to 117°(Baeyer strain), forced eclipsed configurations and imperfect staggering (Pitzer strain) as well as transannular repulsions. In general, three major approaches towards the formation of medium-sized rings can be considered: one is the direct ring closure of an open chain system, another is ring contraction, and ring expansion is the final possibility (Scheme 40). The intramolecular ring closure or "head-to-tail" cyclization is not always a feasible option due to the aforementioned ring strain and competing intermolecular reactions[213]. Additionally, ring closure is accompanied by a loss of entropy which mandates an exergonic bond formation[214]. However, there are still successful methods to achieve this transformation, such as olefin metathesis[215] or free radical methods[216].

By far the most common approach towards medium-sized rings is *via* ring expansion where the difficult direct ring closure is avoided and instead smaller rings are enlarged[217]. One possibility is to utilize fragmentation, which can take place in a direct fashion by cleavage of the shortest bridge in a fused bicyclic system, for example *via* a Grob/Wharton-type reaction[218] or, in case of a double bond, by oxidative cleavage[219]. Another possibility is through the insertion of a side chain that is attached to a smaller ring and then cyclizes onto the ring followed by fragmentation.

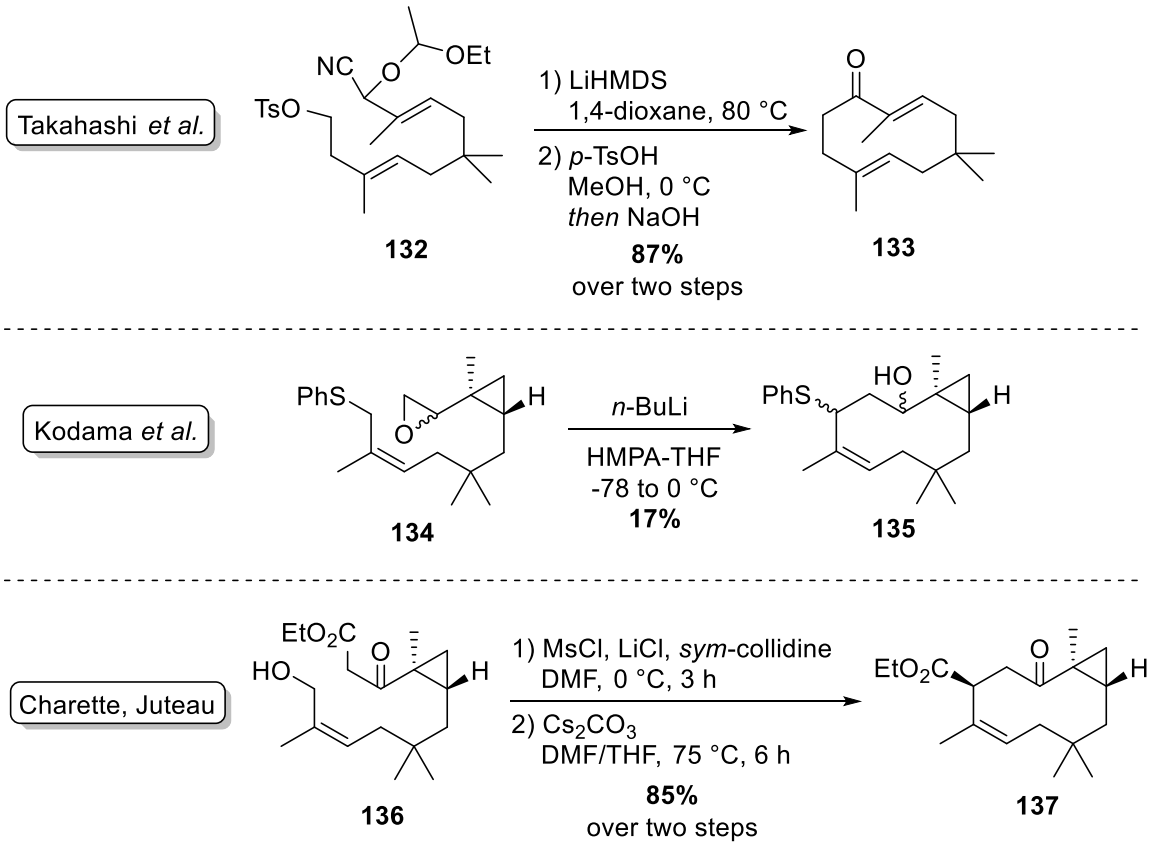
Cyclization of the side chain can be conducted with the help of reagents like samarium diiodide (Barbier-type reaction)[220] or tributyltin hydride (Dowd-Beckwith reaction)[221] in combination with suitable substrates. Another powerful tool for ring expansions are pericyclic reactions, most importantly [3,3]-sigmatropic rearrangements[222]. Many successful formations of medium-sized, including ten-membered rings, have been carried out *via* an oxy-Cope rearrangement[223].



Scheme 40. Overview of different approaches towards the synthesis of medium-sized rings.

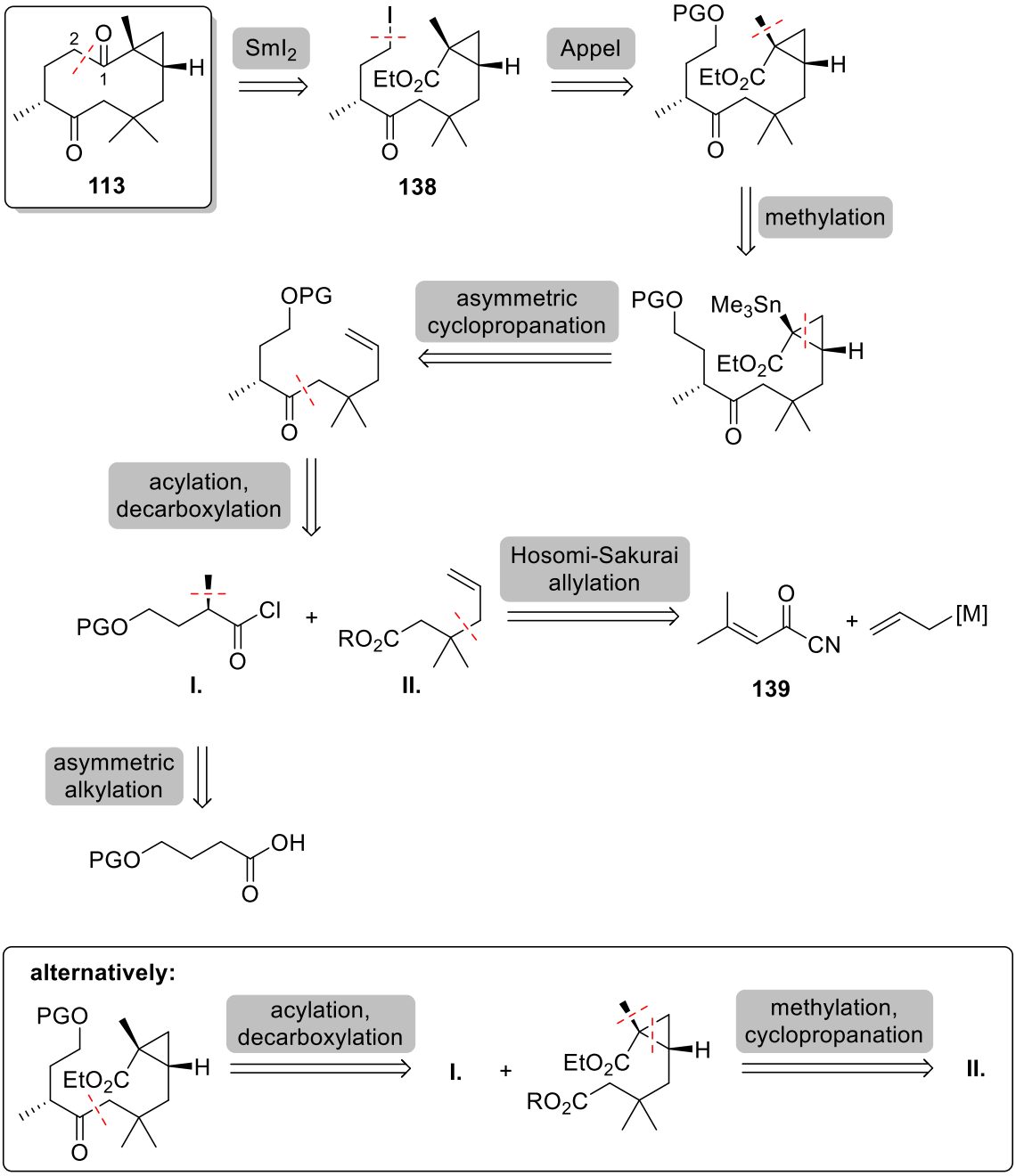
2.4.2.3 Retrosynthesis of Integrifolian-1,5-dione

Since there is no heteroatom-carbon bond in the ring of integrifolian-1,5-dione prone for cleavage, the best choice to disconnect the ring at a C-C bond is non-obvious. Although the direct formation of a ten-membered ring is not always favourable, it was decided to attempt this approach. This decision was encouraged by literature precedent of the synthesis of the rather similar bicyclohumulenone, where the ten-membered ring is closed in a direct manner from the respective open-chain molecule upon treatment with base[224] (Scheme 41). It was hypothesized that structural scaffolds such as the cyclopropyl group or the *gem*-dimethyl group would pre-organize the molecule in a way that facilitates ring closure. Furthermore, it was decided to attempt the ring closing reaction between C1 and C2 using samarium diiodide in an intramolecular Barbier reaction (Scheme 42); Molander and coworkers have shown that this kind of transformation is possible between an alkyl iodide and an ester[225]. The required ester would be introduced during the asymmetric cyclopropanation step due to the nature of the respective diazo compound **56** and it seemed reasonable to try and exploit this feature. The alkyl iodide **138** needed for this conversion was to be introduced *via* an Appel reaction and the respective precursor alcohol would be protected with a suitable protecting group.



Scheme 41. Literature examples for the synthesis of ten-membered carbocycles through direct ring closure of an open chain molecule.

The synthesis of the olefin required for the asymmetric cyclopropanation was planned *via* α-acylation of an ester, obtained through a Hosomi-Sakurai allylation, followed by Krapcho decarboxylation. Asymmetric introduction of the methyl group in α-position of the carbonyl function would be carried out *via* asymmetric alkylation using the well-known Evans auxiliary. It should be noted that some of the steps are potentially interchangeable in their order, especially with respect to the cyclopropanation. The advantage of an early introduction of the cyclopropane was that the expected excess amounts of olefin needed for the cyclopropanation could more easily be provided at an early stage of the synthesis. On the other hand, larger amounts of the valuable dirhodium catalyst and more of the toxic tin compounds would be needed, which could be circumvented by postponing this particular step to a later stage of the synthesis.



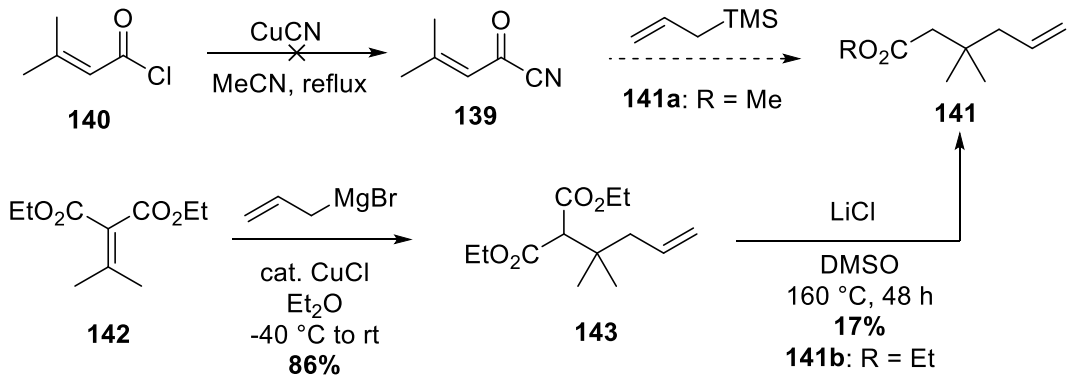
Scheme 42. Retrosynthetic analysis of integrifolian-1,5-dione (113).

2.4.3 Synthesis Attempt *via* Open Chain Cyclization

2.4.3.1 Synthesis of an Olefin Precursor and Cyclopropanation

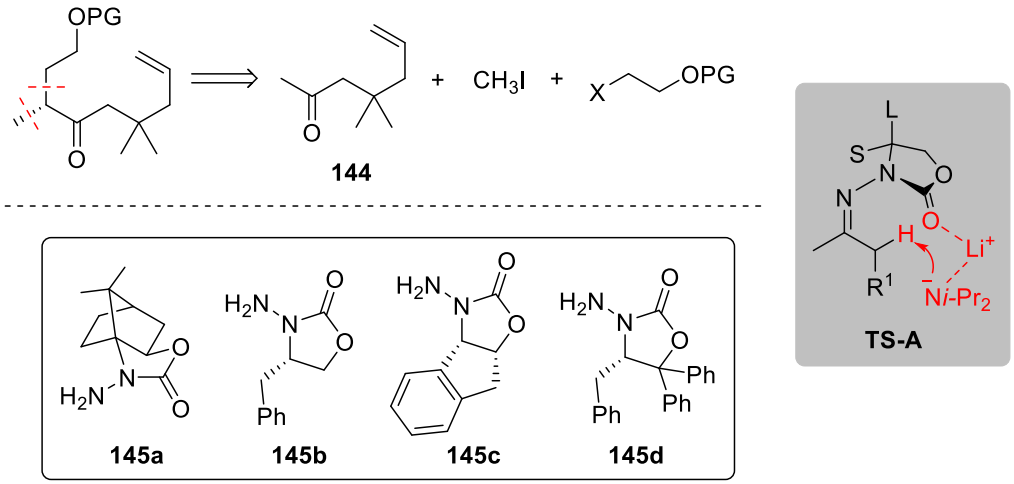
The synthesis commenced with the attempt to form carboxylic ester **141** containing a terminal olefin. The first attempt was *via* a literature-known cyanation reaction of the respective acid chloride **140** (Scheme 43)[226], which did not lead to the desired compound **139**. Alternatively, the ethyl ester derivative **141b** was prepared *via* a copper-catalyzed 1,4-addition of allylmagnesium bromide to diester **142**, followed by a Krapcho decarboxylation[227]. While the 1,4-addition gave a satisfactory yield of 86 %, the next step proceeded with only 17 % isolated yield of the desired

compound **141b** despite full conversion of the starting material **143**, due to compound loss for its high volatility.



Scheme 43. Synthesis of alkyl carboxylic ester 141 bearing a terminal olefin.

Therefore, an alternative route was explored with the carbon chain being disconnected on the alternative side of the carbonyl group (Scheme 44). Bond formation was envisioned *via* enolate chemistry, thereby avoiding the need for decarboxylation. Instead, an asymmetric alkylation approach was planned, in which the so-called *N*-amino cyclic carbamates (ACCs) would be utilized as auxiliaries. This type of auxiliary was introduced by the group of Coltart as a further advancement of Enders' SAMP/RAMP methodology[228].

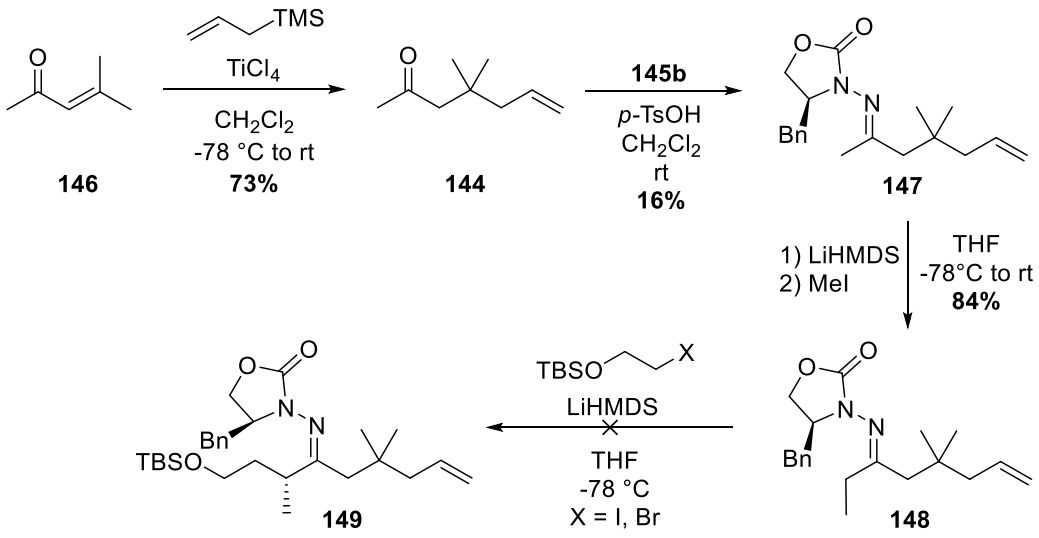


Scheme 44. Revised retrosynthetis of the terminal olefin *via* asymmetric alkylation and the proposed transition state TS-A of the auxiliary-bound hydrazone (S, L: small and large substituents); examples for ACC auxiliaries (145).

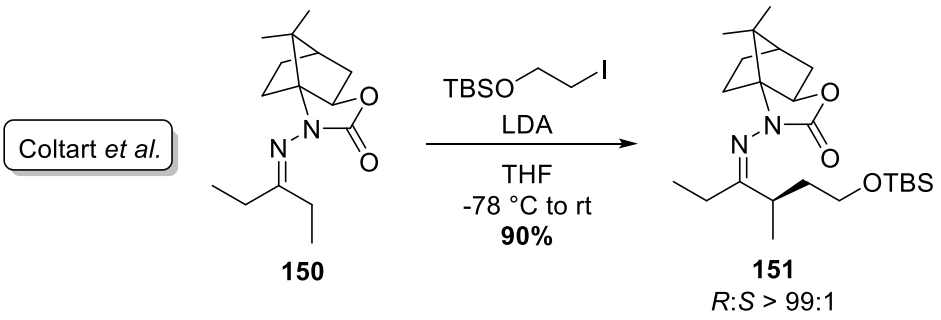
Both procedures rely on the intermediate transformation of the respective ketone into a hydrazone which can be stereoselectively alkylated at the α-position. Compared to the SAMP/RAMP methodology, using ACCs is advantageous as it does not require temperatures of -78 °C or below for deprotonation; temperatures up to 0 °C are tolerated. Moreover, the removal of the auxiliary is more convenient and does not chemically alter the auxiliary, which can

be recovered in high yields. For cleavage of the SAMP/RAMP auxiliaries, ozonolysis or quaternization followed by hydrolysis is needed, which both alters the auxiliary and limits its use to certain functional groups[228]. The applicability of ACCs has been shown in numerous cases[229].

The respective ketone **144** could be prepared in 73 % yield *via* a Hosomi-Sakurai allylation starting from enone **146** using $TiCl_4$ as Lewis acid and allyl trimethylsilane as nucleophile. Next, the asymmetric alkylation was tried using one of the ACC auxiliaries described above (Scheme 45). To test the methodology, the auxiliary **145b** was chosen due to its facile synthesis in one step from the respective oxazolidinone. The more selective analogue **145a**, for comparison, required a six-step synthesis starting from camphor sulfonic acid[229b]. Formation of the hydrazone **147** was successful, albeit low yielding, which might be due to impurities in the auxiliary. The subsequent initial alkylation using methyl iodide as the electrophile delivered the desired product **148**. Contrary to the literature precedent[229b] (Scheme 46), the second alkylation using a TBS-protected iodo- or bromoethanol were both unsuccessful and only unreacted starting material was reisolated. Presumably, the different auxiliary compared to the literature did not provide enough reactivity and/or the steric environment in the substrate at hand was unfavourable for the second alkylation.

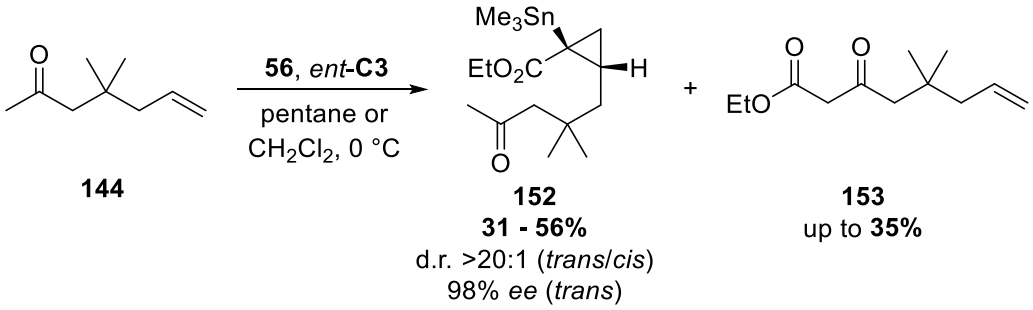


Scheme 45. Attempts at asymmetric alkylation of 144 using ACC auxiliary 145b.



Scheme 46. Asymmetric alkylation using portected iodoethanol and ACC auxiliary 145a.

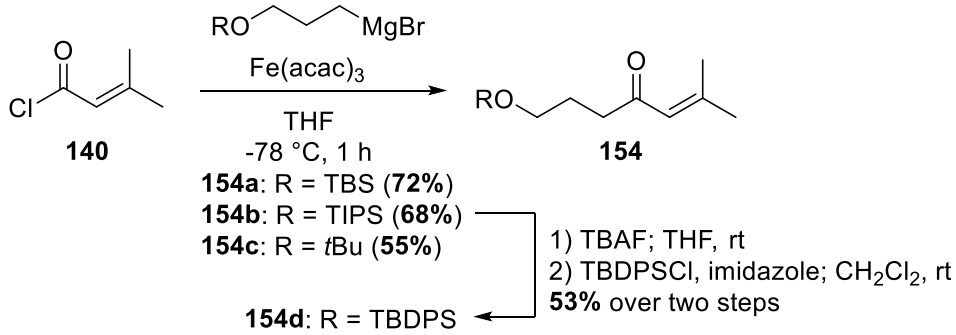
Notwithstanding these issues, olefin **144** was submitted to the cyclopropanation conditions to verify if the structural motif is tolerated by the catalyst. The desired cyclopropylstannane **152** was obtained with only 0.05 mol% of the 2nd generation dirhodium catalyst ***ent*-C3** and an excess of olefin **144** with diazo stannane **56** (Scheme 47). However, the yields remained low, reaching no more than 56 %. The outcome was similar in pentane and dichloromethane, suggesting that solubility was not an issue. Upon closer investigation, β-ketoester **153** could be identified as a side product of the reaction that formed to a significant extent (up to 35 %). This side product is likely the result of a nucleophilic attack of the enol tautomer of **144** on either the diazo stannane **56** itself or the intermediate carbene. Interestingly, the cyclopropanation product of this newly formed olefin **153** was not observed. Despite the low yield, the obtained cyclopropane **152** had a high *ee* (98 %) and d.r. (*trans*/*cis* >20:1 based on ^{1}H-NMR spectroscopy). The results were encouraging and we decided to prepare the proper substrate required for the route.



Scheme 47. Asymmetric cyclopropanation of olefin 144 with the 2nd generation dirhodium catalyst *ent*-C3.

Thus, the introduction of the alkyl chain was shifted to an earlier stage of the synthesis, prior to the Sakurai allylation event. At this point, we still planned to introduce the methyl group in α-position of the carbonyl by asymmetric alkylation employing the ACC auxiliary, based on the successful methylation of the previous substrate. Accordingly, linear bromopropanols bearing different hydroxy protecting groups were transformed into their respective Grignard reagents and then coupled to acid chloride **140** *via* an iron-catalyzed cross coupling[230]. This way, TBS-, TIPS- and *tert*-butyl-protected enones **154a-c** were obtained in moderate to good yields while the

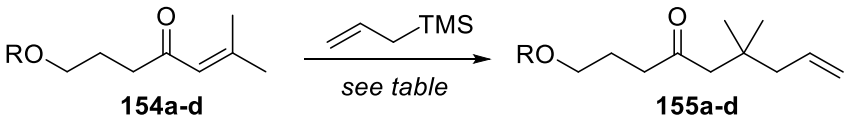
TBDPS-protected derivative **154d** was obtained by changing the protecting group of the former TIPS ether **154b** (Scheme 48).



Scheme 48. Synthesis of substrates 154 for Sakurai allylation *via* iron-catalyzed cross coupling.

When the enones were submitted to the Sakurai allylation procedure (Table 12), it was found that only the TBDPS-protected enone **154d** delivered the desired terminal olefin **155d** (entry 5). In case of the other protecting groups, no product formation was observed. GC-MS and TLC analyses indicate decomposition of the starting material, probably due to acid sensitivity of the silyl protecting groups. Changing the Lewis acid from $TiCl_4$ to BF_3•OEt_2 did not improve the outcome.

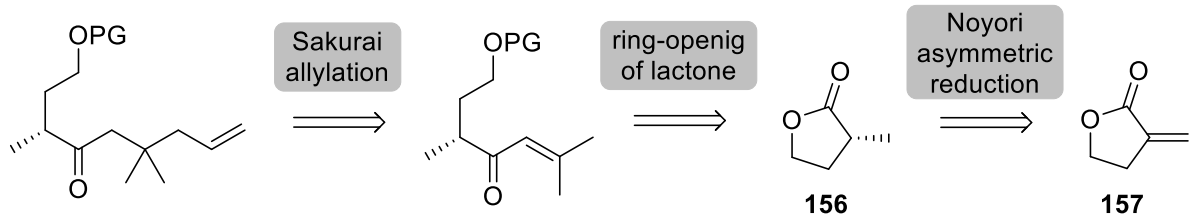
Table 12. Application of different substrates in the Sakurai allylation.



Entry[a]	R	Lewis acid (eq)	Conditions	Result
1	TBS (**a**)	$TiCl_4$ (1.1)	0 °C to rt, overnight	decomposition
2	TIPS (**b**)	$TiCl_4$ (1.05)	0 °C to rt, 1.5 h	decomposition
3	TIPS (**b**)	BF_3•OEt_2 (2.5)	0 °C to rt, overnight	decomposition
4	*t*Bu (**c**)	$TiCl_4$ (1.1)	rt, 1 h	decomposition
5	**TBDPS (d)**	**$TiCl_4$ (2.0)**	**rt, 1 h**	**65% yield**

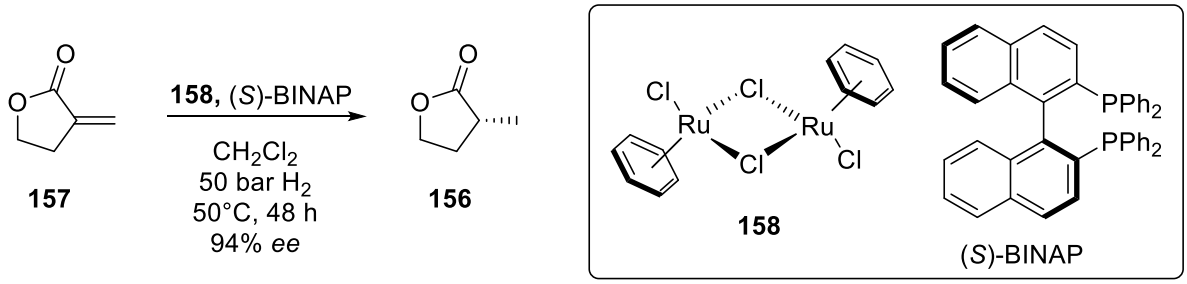
[a] All reactions were performed in CH_2Cl_2.

Based on the fact that the alkyl chain was to be introduced at an earlier stage of the synthesis and in order to avoid the use of auxiliaries, a new, more convenient synthetic route towards the required olefin was established. Starting from α-methylene-γ-lactone **157**, a literature-known, asymmetric Noyori hydrogenation can be performed using ruthenium catalyst **158** and a chiral BINAP ligand[231]. The resulting enantioenriched α-methyl-γ-lactone **156** would then further be transformed *via* ring opening to the desired species (Scheme 49).



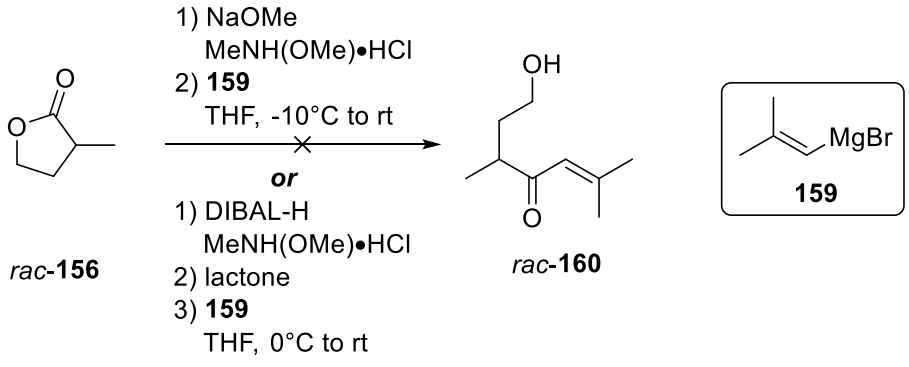
Scheme 49. Revised retrosynthetic analysis of the olefinic fragment.

The asymmetric reduction of lactone **157** proceeded with high enantioselectivity (94 % *ee*, Scheme 50). The yield was not determined because loss of the apparently volatile material was observed when evaporating the solvent during work-up. Due to the clean reaction profile and literature precedent, high yields of **156** were expected on scale after distillation.



Scheme 50. Asymmetric Noyori reduction of lactone 157.

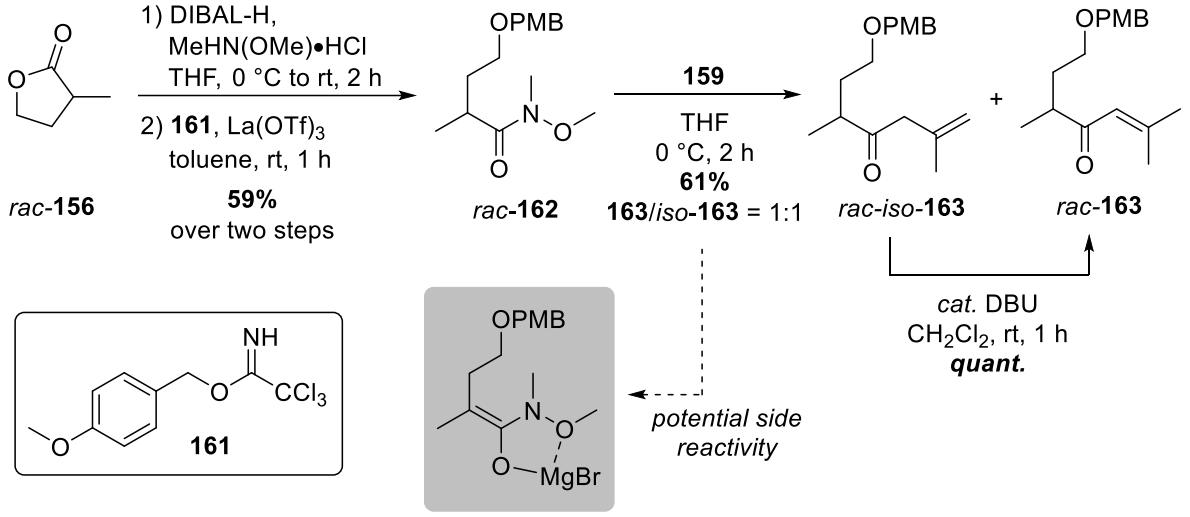
Racemic lactone **156** was used in the following experiments while optimizing and scouting the route. Initial attempts to transform the lactone ***rac*-156** into the Weinreb amide *in situ* and then directly react it with isobutenylmagnesium bromide **159** were unsuccessful[232]. Only trace amounts of an unknown product were obtained, which was not further analysed due to the overall poor outcome (Scheme 51).



Scheme 51. Attempted direct 1,2-addition of Grignard reagent 159 to lactone *rac*-156 *via in situ* formation of Weinreb amide species.

An alternative approach was to synthesize the Weinreb amide and then subject the crude product to protection conditions for the newly formed primary alcohol (Scheme 52). The choice of a suitable protecting group was carefully evaluated with respect to potential future reaction

conditions. Particularly, the Stille cross coupling was considered which posed an alternative reaction to replace the trimethyltin moiety by a methyl group, should the tin-lithium exchange not work. Although the TBDPS ether was shown to perform well in the Sakurai allylation (*vide supra*), it was feared that it might not be compatible with the prolonged exposure to potassium fluoride at elevated temperature which would be needed for the subsequent cross coupling. Therefore, the PMB protecting group was chosen because it was expected to be more stable under the given conditions.

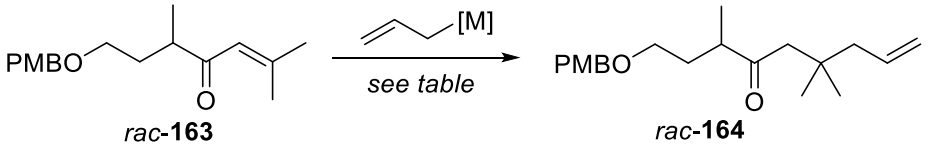


Scheme 52. Stepwise approach towards 1,2-addition of Grignard reagent 159 *via* isolation of PMB-protected Weinreb amide *rac*-162.

The PMB-protected Weinreb amide ***rac*-162** was prepared in a two-step telescoped process. It was then treated with isobutenylmagnesium bromide **159** and the resulting ketone **163** was obtained in a roughly 1:1 mixture of isomers containing either a conjugated or unconjugated C-C double bond. The undesired unconjugated double bond isomer could be transformed into the desired conjugated isomer by treatment with catalytic amounts of DBU. Unfortunately, even with an excess amount of Grignard reagent **159**, full conversion of ***rac*-162** was not achieved in the reaction.

The obtained enone ***rac*-163** was subjected to Sakurai allylation conditions using $TiCl_4$ as Lewis acid and allyl trimethylsilane as nucleophile (Table 13, entry 1). However, the desired product ***rac*-164** could not be detected, but only decomposition of the starting material was observed, possibly due to acid sensitivity of the PMB protecting group (entry 1). Similar observations were made when other Lewis acids or nucleophiles were applied, only traces of product could be detected at best (entries 2 to 4). Furthermore, 1,4-addition conditions were explored forming different copper species that were added to the enone, however again no conversion could be observed (entries 5 and 6).

Table 13. Attempts at Sakurai allylation of PMB-protected enone 163.

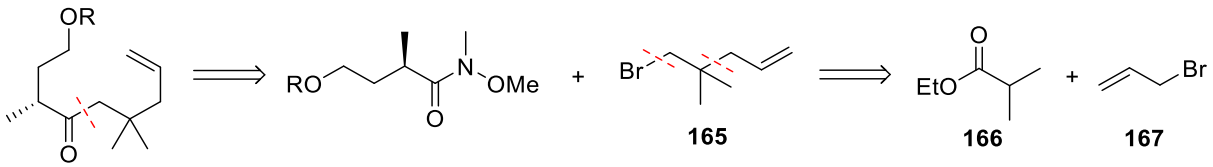


rac-**163** *rac*-**164**

Entry	Lewis Acid (eq)	[M]	Conditions	Result
1	$TiCl_4$ (1.1)	$SiMe_3$	CH_2Cl_2, -78 °C	decomposition
2	BF_3•OEt_3 (1.3)	$SnBu_3$	CH_2Cl_2, -78 °C to rt	decomposition
3	$SnCl_4$ (1.1)	$SiMe_3$	CH_2Cl_2, -78 °C to 0 °C to rt	no conversion
4	$TiCl_4$ (1.1)	$SnBu_3$	CH_2Cl_2, -78 °C	traces of product[a]
5	TMSCl (4.8)	CuMgBr[b]	THF, -78 °C to 0 °C to rt	no conversion
6	TMSCl (3.0)	(allyl)CuLi[c]	THF, -78 °C to rt	no conversion

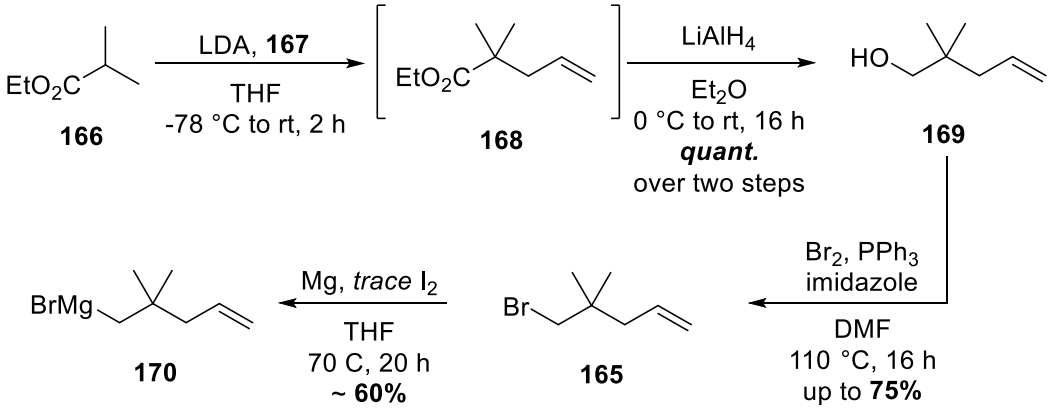
[a] detected *via* ^{1}H-NMR. [b] prepared *in situ* from LiCl, CuBr•dimethyl sulfide and allyl magnesium bromide.
[c] prepared *in situ* from LiCl, CuI and allyl tributyltin.

At this point, several issues had emerged that needed to be dealt with: insufficient conversion and double bond isomerization during the Grignard reaction as well as relatively unsuccessful Sakurai allylation. A potential solution to these problems was to introduce the terminal olefin as a 5C alkyl chain fragment in one step instead of the previous two-step approach, which would also be more convergent (Scheme 53). This required the synthesis of alkyl bromide **165**, which could then be converted into the desired Grignard reagent.



Scheme 53. Revised retrosynthetic analysis towards the introduction of a 5C alkyl side chain.

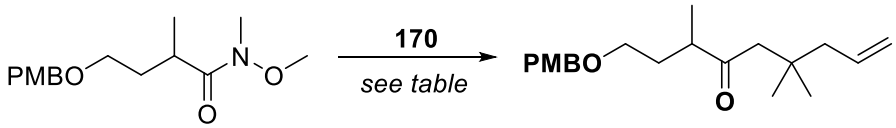
In a forward sense, the neopentylic alcohol **169** could be obtained in quantitative yield according to literature-known procedures[233]. Starting from ethyl ester **166** and allyl bromide, product **168** was formed by allylation and directly reduced by treatment with $LiAlH_4$. Careful evaporation of the solvent was required due to the volatility of alcohol **169**. Subsequent Appel reaction with triphenyl phosphine, imidazole and bromine in DMF at elevated temperature gave alkyl bromide **165** in good yields, which was then converted into the Grignard reagent **170** (Scheme 54). Formation of the Grignard reagent proceeded in yields of approximately 60 % (based on iodometric titration) despite the sterically demanding neopentylic scaffold.



Scheme 54. Synthesis of alkyl bromide 165 and formation of the respective Grignard reagent 170.

In the next step, the Grignard reagent **170** was added to the PMB-protected Weinreb amide ***rac*-162** (Table 14). When adding the Grignard reagent at 0 °C and then allowing the reaction mixture to slowly warm to room temperature, no conversion was observed, whereas heating the reaction mixture to reflux only led to decomposition of the starting material. Attempts to increase the reactivity of the Grignard reagent with additives (entries 3 and 4) also did not afford the desired product ***rac*-164**[234].

Table 14. Attempts towards 1,2-addition of Grignard reagent 170 to Weinreb amide *rac*-162.

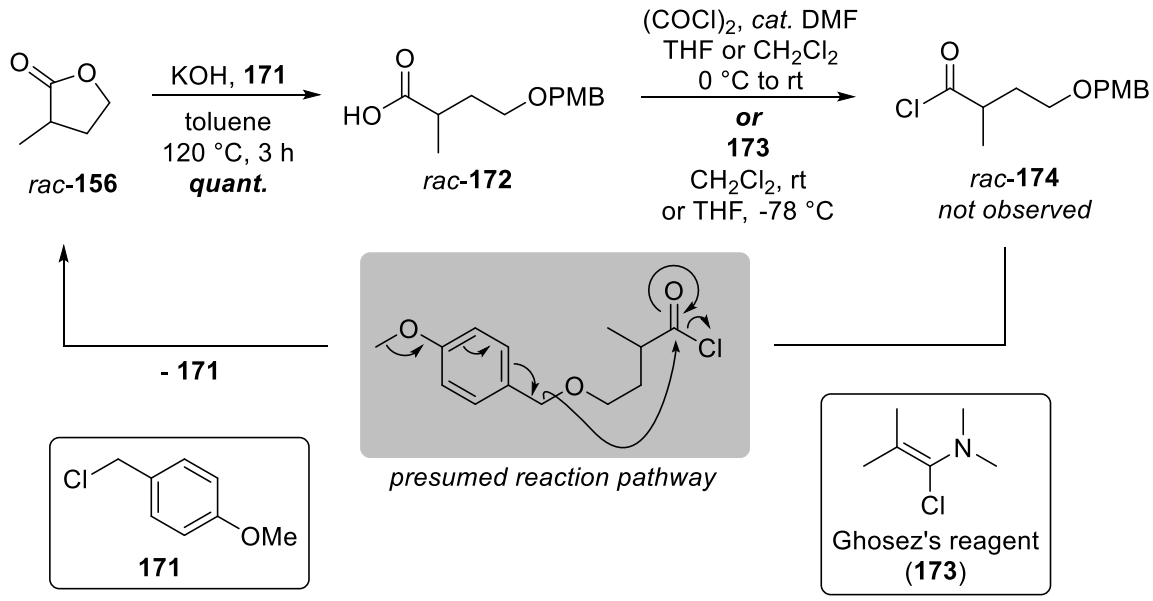


rac-162 *rac*-164

Entry	Conditions[a]	Additive	Result
1	0 °C to rt	-	no conversion
2	70 °C	-	decomposition
3	0 °C to rt	CuCl	no conversion
4	rt	dioxane	no conversion

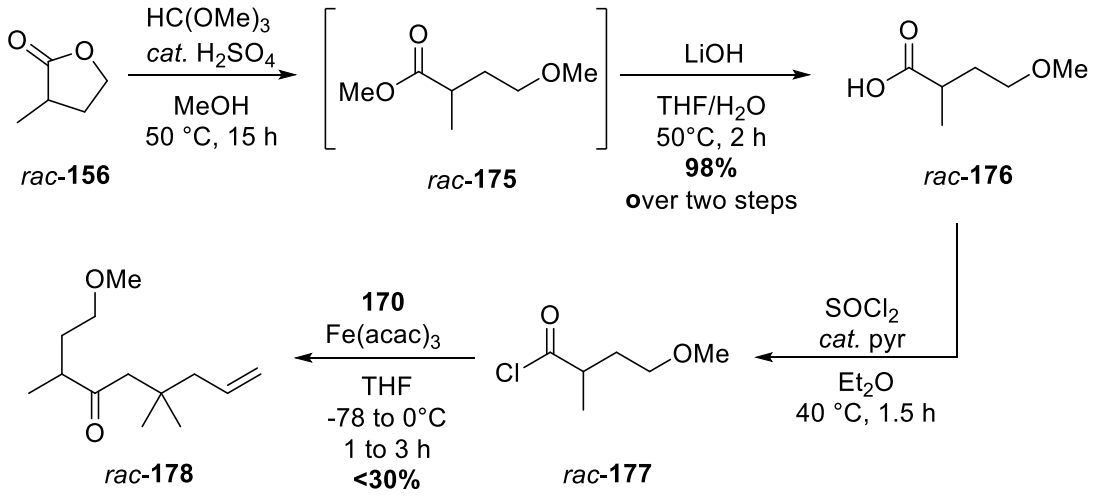
[a] All reactions were carried out in THF.

It was attempted to replace the Weinreb amide by an acid chloride to increase the reactivity (Scheme 55). Hence, the free carboxylic acid ***rac*-172** was synthesized from lactone ***rac*-156** and then subjected to treatment with either oxalyl chloride or Ghosez's reagent (**173**)[235]. In neither case was the desired acid chloride ***rac*-174** obtained; instead, the lactone ***rac*-156** was re-isolated. This closure presumably occurred due to an intramolecular attack of the ether oxygen. The released chloride in turn probably attacks the benzylic position of the PMB protecting group which regenerates chloride **171** once again.



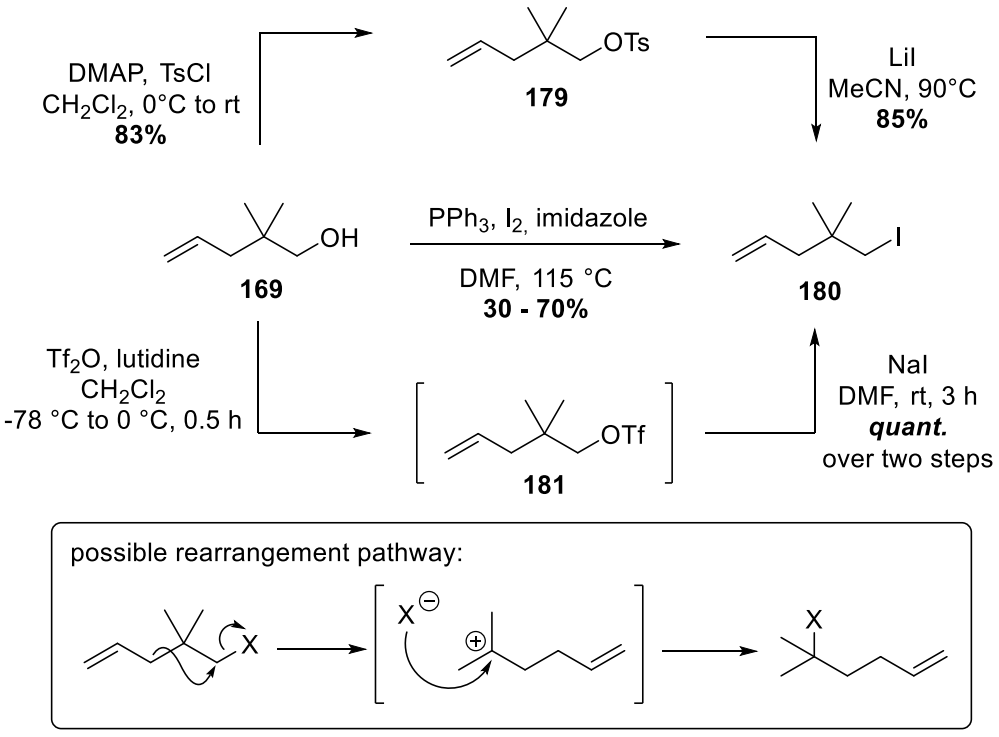
Scheme 55. Attempted synthesis of PMB-protected acid chloride *rac*-174 and proposed decomposition pathway.

To circumvent this problem, the PMB protecting group was exchanged for a methyl ether, which was considered to be more stable under the chlorination conditions. Thus, carboxylic acid ***rac*-176** was prepared by reacting lactone ***rac*-156** with trimethyl orthoformate in presence of catalytic amounts of sulfuric acid in methanol at elevated temperature and subsequent saponification of the methyl ester ***rac*-175** with lithium hydroxide (Scheme 56). Treatment of ***rac*-176** with thionyl chloride delivered the acid chloride ***rac*-177** which was used without further purification in the next step[236]. Addition of the Grignard reagent **170** was carried out following the same iron-catalyzed cross coupling protocol as depicted in Scheme 48[230]. Despite numerous experiments at different temperatures and with varying amounts of Grignard reagent, the desired ketone ***rac*-178** was not obtained in more than 30 % yield.



Scheme 56. Synthesis of Me-protected olefin intermediate *rac*-178 *via* acid chloride *rac*-177.

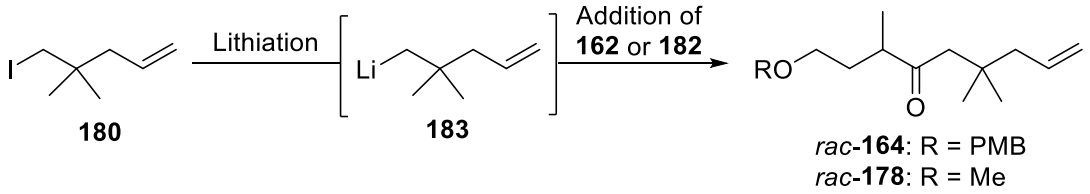
After unsuccessful attempts to increase the reactivity on the carbonyl group, substitution of the Grignard reagent for the more reactive organolithium compound was pursued. Apart from increasing the nucleophilicity, it was reasoned that the organolithium compound would be less likely to promote the formation of a chelated enolate. Preparation of the lithiated species was envisioned *via* lithium-halogen exchange of the corresponding alkyl iodide **180**. Accordingly, alcohol **169** was subjected to Appel conditions for iodination (Scheme 57). However, the yield of the reaction was varying strongly, contrary to similar literature-known procedures[233, 237]. The formation of an unidentified side product was indicated by NMR spectroscopy, possibly resulting from a rearrangement towards a *tert*-amyl system[238]. In an attempt to circumvent this problem, the alcohol was converted into a leaving group. In a Finkelstein reaction, the corresponding tosylate **179** was heated in the presence of lithium iodide in acetonitrile. In this way, the iodide **180** could be produced in a more realiable and higher yielding fashion. The yield was further improved when a triflate group was installed instead of the tosylate, bearing the advantage that no purification of the alkyl triflate **181** was needed after aqueous workup and that no heating was required during the subsequent Finkelstein reaction. The crude triflate was treated with sodium iodide in DMF at room temperature to afford the alkyl iodide **180** in overall high yields. Sometimes lower yields of alkyl iodide were observed, which was likely caused by the volatility of the compound leading to partial loss during evaporation of the solvent.



Scheme 57. Synthetic routes towards alkyl iodide 180 and proposed pathway for the presumably observed side product.

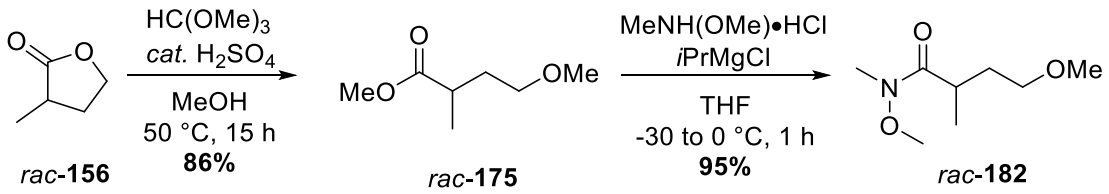
For the desired 1,2-addition, alkyl iodide **180** was lithiated by treatment with *tert*-butyllithium at cryogenic temperatures followed by addition of a solution of Weinreb amide ***rac*-162** (Table 15). In the initial experiment approximately 30 % of the product ***rac*-164** were obtained (entry 1). Optimization was attempted by reducing the amount of *tert*-butyllithium (entry 2), decreasing the lithiation time and replacing THF by pentane (entry 3). None of the experiments improved the outcome and the product was obtained in only 9 to 19 % yield. It was suspected that the PMB ether might not be stable enough under the given conditions and the methyl ether derivative ***rac*-182**, which can be obtained from lactone ***rac*-156** over two steps (Scheme 58), was again chosen as an alternative substrate. A first experiment provided 26 % of the product ***rac*-178** (entry 4). However, attempts to increase the yield by changing the amount of *tert*-butyllithium or varying the lithiation time remained unfruitful (entries 5 to 7).

Table 15. Lithiation of alkyl iodide 180 and 1,2-addition of the lithiated species to Weinreb amides.



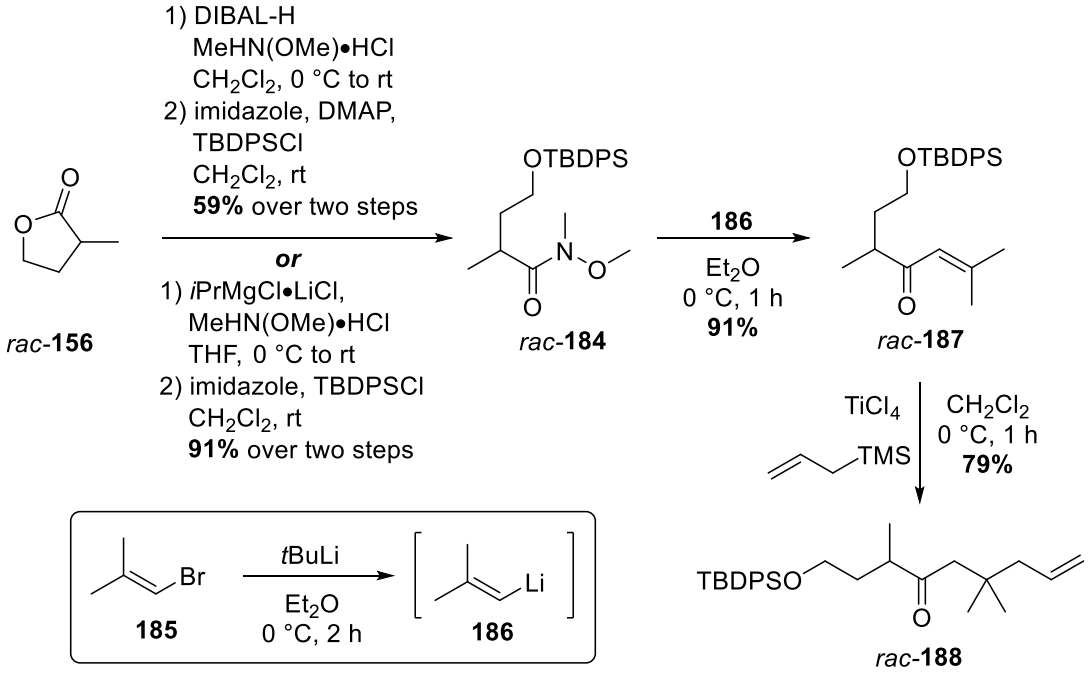
Entry	R	Conditions [a]		Yield
		Lithiation (eq)	Addition (eq)[b]	[%]
1	PMB	*t*BuLi (4.0), **180** (2.0), pentane, 1.5 h[c]	**162** (1.0), THF, 1 h	30
2	PMB	*t*BuLi (2.2), **180** (1.1), pentane, 0.5 h[c]	**162** (1.0), THF, 1 h	19
3	PMB	*t*BuLi (4.0), **180** (2.0), pentane, 0.5 h[c]	**162** (1.0), pentane, 1 h[d]	9
4	Me	*t*BuLi (2.0), **180** (1.0) Et_2O/pentane, 1.5 h[c]	**182** (1.0), Et_2O, 1.5 h	26
5	Me	*t*BuLi (4.0), **180** (2.0), Et_2O/pentane, 1 h[c]	**182** (1.0), Et_2O, 0.5 h	n.d.[e]
6	Me	*t*BuLi (2.0), **180** (1.0), Et_2O/pentane, 3 h[f]	**182** (1.5), Et_2O, 1 h	17
7	Me	*t*BuLi (2.0), **180** (1.0), Et_2O/pentane, 15 min[f]	**182** (1.0), Et_2O, 1.5 h	13

[a] All reactions were carried out at -78 °C. [b] Weinreb amide **162** or **182** was added in solution in the indicated solvent to the lithiated species **183**. [c] addition of *tert*-butyllithium to cooled solution of iodide **180**. [d] THF was added to the reaction after 45 min for better solubility. [e] Product was detected *via* GC-MS but contaminated with equal amount of presumably *t*Bu-substituted side product. [f] addition of iodide **180** to cooled solution of *tert*-butyllithium. n.d. = not determined.



Scheme 58. Synthesis of Me-protected Weinreb amide *rac*-182 from lactone *rac*-156.

These rather discouraging results regarding the addition of a 5C-alkyl chain fragment let us reconsider the two-step process involving the Sakurai allylation, despite the potential risk of the TBDPS ether being cleaved during the cross coupling at a later stage in the synthesis. Similar to the PMB-protected Weinreb amide ***rac*-162**, the synthesis commenced with the racemic lactone **156**. Following the same procedure using DIBAL-H, the product ***rac*-184** was obtained in 59 % yield over two steps. This result could be further optimized by employing isopropylmagnesium chloride-lithium chloride complex, achieving 91 % of the desired compound (Scheme 59).

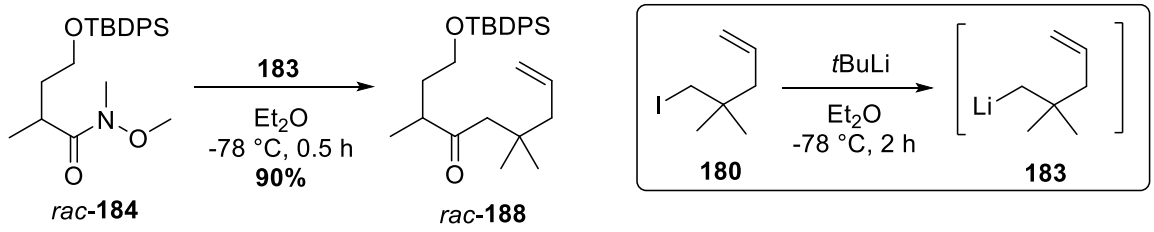


Scheme 59. Synthesis of TBDPS-protected olefin *rac*-188 in a two-step process including 1,2-addition of alkenyllithium 186 and Sakurai allylation.

With the complications when using isobutenylmagnesium bromide **159** in mind, the synthesis was continued employing the respective alkenyllithium species (**186**). The reaction was carried out according to a literature procedure, first adding alkenyl bromide **185** to a cooled solution of *tert*-butyllithium followed by a solution of Weinreb amide ***rac*-184** after two hours[239]. However, the yields were still deemed unsatisfactory, varying between 35 and 64 %. When the addition of substrates was reversed, i.e. the lithiated species being added to a cooled solution of the Weinreb amide, the outcome changed dramatically, giving ***rac*-187** in consistently high yields of up to 91 %.

In the subsequent Sakurai allylation, the conditions were slightly optimized by employing an excess of $TiCl_4$ at 0 °C instead of room temperature and the olefin ***rac*-188** was obtained in 79 % yield.

The successful 1,2-addition *via* lithiation of the alkenyl bromide following an inverted order of addition led us to reconsider the use of the previously failed 5C fragment. First, the *tert*-butyllithium was diluted in diethyl ether at -78 °C and the alkyl iodide **180** was added as a solution in pentane (Scheme 60). Stirring was continued for one to two hours while maintaining the temperature at -78 °C. Then, the lithiated species **183** was added to a cooled solution of the Weinreb amide ***rac*-184** resulting in full conversion after 30 minutes. The reaction was quenched at low temperature in order to avoid overaddition to give the desired product ***rac*-188** in up to 90 % yield. It was important to pay close attention to the amount of *tert*-butyllithium used in the reaction with respect to the alkyl iodide because unreacted *tert*-butyllithium was observed to add into the Weinreb amide in a competing reaction. The resulting side product was hardly separable from the desired product *via* flash chromatography.

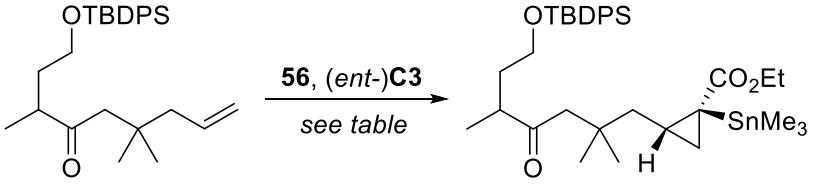


Scheme 60. Synthesis of TBDPS-protected olefin *rac*-188 *via* 1,2-addition of alkyllithium 183 to Weinreb amide *rac*-184.

With a good amount of terminal olefin ***rac*-188** at hand, it was time to test the first key reaction of the synthesis. The asymmetric cyclopropanation of ***rac*-188** was carried out using the previously developed *trans*-selective heteroleptic dirhodium paddlewheel complex ***ent*-C3** (Table 16). Initially, the reaction was conducted with 1 mol% of catalyst and an excess of five equivalents of olefin ***rac*-188** in pentane at 0 °C (entry 1). The obtained yield of **189** of 52 % and a diastereomeric ratio of 1:18 in favour of the *trans*-isomer appeared to be a promising start for further optimization. As with prior substrates, solubility in pentane had been an issue diminishing the yield. Therefore, the reaction was performed in CH_2Cl_2 (entry 2), but the yield did not increase. The excess amount of olefin could be lowered from five to two equivalents without a significant change in yield (entry 3). Increasing or decreasing the catalyst loading did not improve the outcome (entries 5 and 6). It was assumed that the attack of the olefin on the carbene is slow due to the steric hindrance caused by the neopentylic moiety and a significant amount of the carbene species decomposes before undergoing a productive reaction. A possible decomposition pathway could be *via* the attack of another molecule of the diazo compound on the carbene species.

Therefore it was decided to not add the diazo compound **56** in a single portion but to opt for a slow addition *via* syringe pump, as had been done with the 1st generation dirhodium paddlewheel catalyst **C1**. Additionally, the temperature was raised from 0 °C to room temperature. As dimerization of the diazo compound did not appear to be a major competing side reaction, it was decided to use the olefin ***rac*-188** as the limiting reagent and apply an excess of diazo stannane **56**. Furthermore, the olefin was arguably the more valuable material at this point of the synthesis. Eventually, cyclopropane **189** was obtained in a yield of 75 % (entry 7). With the optimized conditions, it was attempted to lower the catalyst loading, although to no avail (entry 8). On the other hand, increasing the catalyst loading did not increase the yield any further (entry 9).

Table 16. Optimization of asymmetric cyclopropanation of olefin *rac*-188 using 2nd generation dirhodium catalyst (*ent*-)C3.



rac-188 — **189**

relative stereochemistry shown

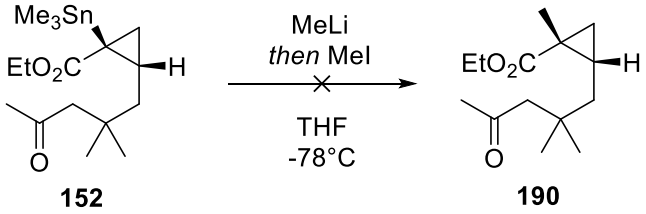
Entry	(*ent*-)C3 [mol%]	*rac*-188 [eq]	56 [eq]	T [°C]	Yield# [%]
1[a]	1	5	1	0	52
2[a,b]	1	5	1	0	45
3[a]	1	2	1	0	51
4[a]	1	1.2	1	0	38
5[a]	0.5	2	1	0	5
6[a]	2	2	1	0	53[c]
7[d]	**1**	**1**	**2.6**	**rt**	**75[e]**
8[d]	0.5	1	2.4	rt	n.r.[f]
9[d]	1.5	1	2.4	rt	71[g]

All reactions were carried out in pentane unless stated otherwise. # d.r. ~1:18 (*cis*/*trans*), determined by ^{1}H-NMR of crude product. [a] ***ent*-C3** used as catalyst. [b] CH_2Cl_2 used as solvent. [c] 85 % *brsm*. [d] **C3** used as catalyst. [e] addition of **56** *via* syringe pump over 10 h. [f] addition of **56** *via* syringe pump over 12 h. [g] addition of **56** *via* syringe pump over 8 h. n.r.: no reaction.

2.4.3.2 Introduction of the Methyl Group *via* Stille-Migita Coupling

The synthetic route continued with the next key step of the sequence, the stereoretentive introduction of the methyl group. Based on the synthesis of the salinilactones (section 2.3.3.2), the previously developed methodology for tin-lithium exchange was applied, using methyl iodide as an electrophile in this case. Unfortunately, the desired methylated product **190** could not be

detected (Scheme 61), probably due to the presence of the ketone that can either be attacked by methyllithium itself or degrade the reactive intermediate formed after tin-lithium exchange.

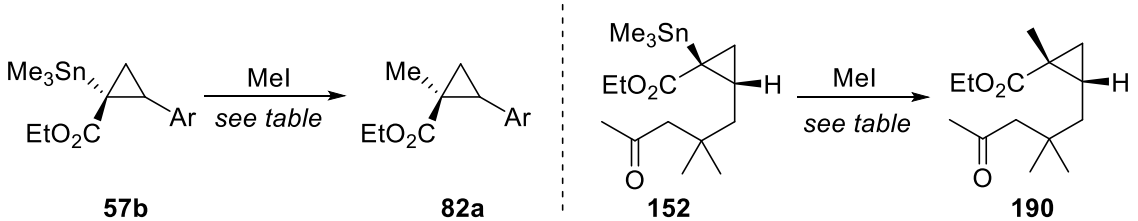


152 **190**

Scheme 61. Attempt towards introduction of the methyl group at the cyclopropane ring *via* tin-lithium exchange

As an alternative to the tin-lithium exchange, Stille cross coupling was explored to introduce the methyl group in presence of the carbonyl function despite a lack of literature precedent. The conditions were investigated using model substrate **57b** (Table 17). In this system, the desired product **82a** was formed without observable epimerization of the quaternary stereocentre, albeit with very slow conversion. Increasing the amount of copper chloride eventually yielded full conversion after 20 hours according to GC-MS analysis (entry 3). Subsequently, the cross coupling was tested with the cyclopropylstannane **152** which had failed in the tin-lithium exchange reaction. Even though the conversion remained slow, the desired product **190** was obtained, which was a promising result for the projected synthesis and for the generality of the methodology.

Table 17. Test reactions for the introduction of a methyl group *via* Stille cross coupling.



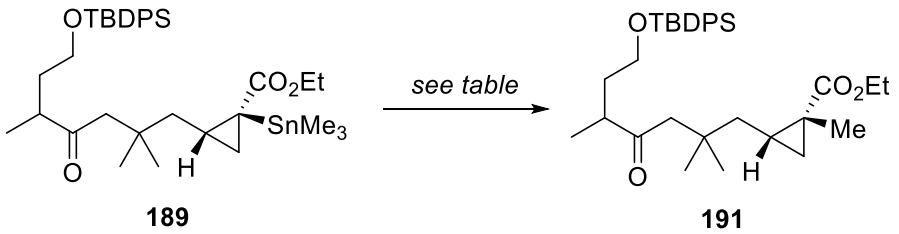
57b **82a** **152** **190**

Entry[a]	SM	KF [eq]	CuCl [eq]	Time	Conversion[b] [%]	Yield [%]
1[c]	**57b**	2	2	4 days	68	n.d.
2[c]	**57b**	5	2	2 days	67	n.d.
3[d]	**57b**	5	5	20 h	> 99	65
4	**152**	5	5	4 days	81	52[e,f]
5	**152**	2	5	4 days	86	71[f]
6	**152**	1	5	3 days	94	56

[a] All reactions were carried out in THF at 70 °C, using $Pd_2(dba)_3$ (0.05 eq), JackiePhos (0.4 eq) and excess methyl iodide. [b] determined by GC-MS. [c] ***cis*-57b** used. [d] ***trans*-57b** used. [e] increased amount of protodestannylation observed. [f] still contains minor impurities. n.d.: not determined. Ar = *p*-MeO-C_6H_4.

Next, cyclopropylstannane **189** was subjected to the Stille coupling (Table 18). Standard conditions and stirring overnight resulted in 54 % yield of **191** but no full conversion of the starting material **189** was achieved (entry 1). Increasing the amount of copper chloride and potassium fluoride neither improved yield nor conversion (entry 2).

Table 18. Optimization of conditions for the introduction of a methyl group *via* Stille coupling involving cyclopropylstannane 189.



189 **191**

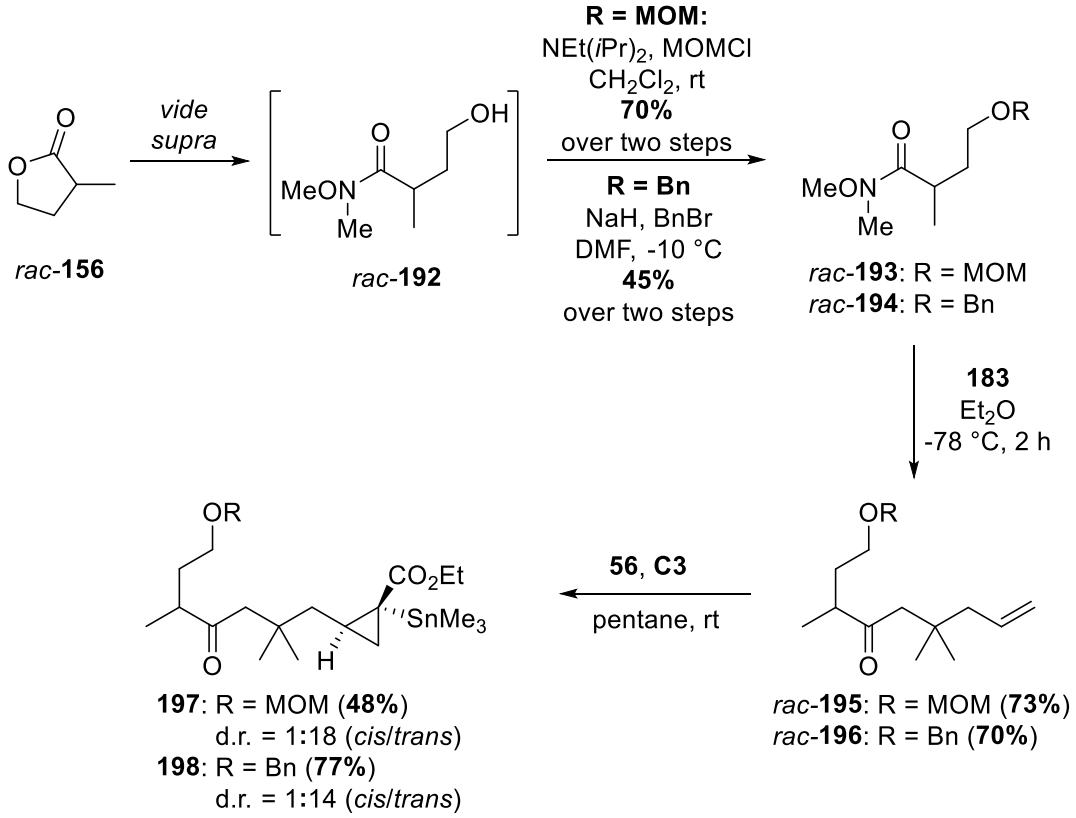
Entry[a]	Conditions (eq)	Time	Yield [%]
1	$Pd_2(dba)_3$ (0.05), JackiePhos (0.4), CuCl (2), KF (2), MeI (10)	16 h	54[b]
2	$Pd_2(dba)_3$ (0.05), JackiePhos (0.4), **CuCl (5)**, **KF (5)**, MeI (15)	18 h	39[b]
3	$Pd_2(dba)_3$ (0.05), JackiePhos (0.4), CuCl (2.3), **KF (2)**[c], MeI (15)	48 h	29[b]
4	$Pd_2(dba)_3$ (0.05), JackiePhos (0.4), CuCl (2), KF (2), MeI (22)	**72 h**	42[b]
5[d]	$Pd_2(dba)_3$ (0.05), **JackiePhos (0.6)**, CuCl (4), KF (4), MeI (63)	72 h	40[b]
6	$Pd_2(dba)_3$ (0.05), JackiePhos (0.4), CuCl (2.6), KF (2.7), MeI (> 200), **MeOTf** (3.5)	24 h	-
7	$Pd_2(dba)_3$ (0.05), JackiePhos (0.6), CuCl (2), KF (2), **MeOTf** (1.7)	3 h	-
8[d]	$Pd_2(dba)_3$ (0.05), JackiePhos (0.6), CuCl (2), KF (2), **LiI** (0.3), **$PO(OMe)_3$** (1.7)	16 h	traces[e]
9[d,f]	**JackiePhos-Pd-G3** (0.2), JackiePhos (0.6), CuCl (2.5), K_2CO_3 (0.5), MeI (37)	6 h	< 34[g]
10[d]	**JackiePhos-Pd-G4** (0.2), JackiePhos (0.6), CuCl (2.8), MeI (73)	20 h	< 38[g]

[a] Reactions were carried out at 70 °C in THF. [b] no full conversion. [c] KF only added after first 24 h. [d] diastereomer of **189** with opposite orientation of stereocentres applied. [e] mostly protodestannylation observed. [f] reaction conducted at 100 °C in μwave. [g] product contained major impurities.

When omitting the potassium fluoride, no conversion was observed after stirring overnight. Adding potassium fluoride to the reaction after 24 hours eventually resulted in 29 % yield (entry 3). Increasing the reaction time and the amount of ligand also yielded no significant improvement (entries 4 and 5). Next, the use of other methyl electrophiles was investigated. Use of methyl triflate led to decomposition of the material and an attempt to generate methyl iodide *in situ* from lithium iodide and trimethylphosphate only provided trace amounts of the desired compound but resulted mostly in protodestannylation (entries 6 to 8). Lastly, different

precatalysts were tried with the aim of avoiding the presence of dibenzylideneacetone (dba) which was suspected to interfere with the reaction. However, these efforts remained unsuccessful, both with regular heating and when conducted in the microwave at elevated temperatures (entries 9 and 10). The low overall yields were partially caused by incomplete conversion of **189**; however it is likely that decomposition occurred to a certain extent, especially with longer reaction times. In some cases, the removal of the protecting group could be observed *via* GC-MS analysis, which in turn might have led to further side reactions.

Based on these results, the protecting group strategy was changed by synthesizing the benzyl- and MOM-protected derivatives of cyclopropylstannane **189** as they were expected to be more stable under the cross coupling conditions. Starting again from the racemic lactone **156**, the respective Weinreb amides ***rac*-193** and ***rac*-194** were obtained (Scheme 62).

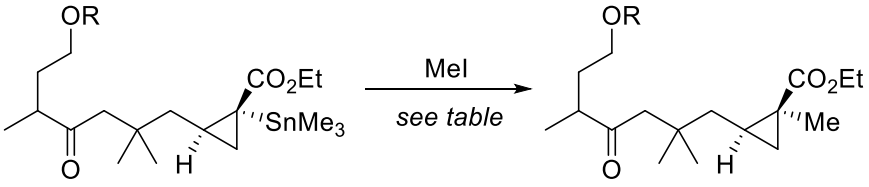


Scheme 62. Synthesis of MOM- and Bn-protected cyclopropylstannanes (197, 198)

The benzyl ether derivative ***rac*-194** was obtained in modest yield of 45 % and the formation of the starting material ***rac*-156** was observed, similar to what had been noticed during the attempted acid chloride formation of the PMB-protected derivative ***rac*-172**. Nevertheless, the synthesis was continued with the material at hand and both 1,2-addition *via* lithiation and the subsequent cyclopropanation proceeded without further complications.

Various conditions for the cross coupling were investigated with the newly obtained cyclopropylstannanes **197** and **198** (Table 19), mostly under microwave irradiation, with the aim to increase and accelerate conversion at higher temperatures. Unfortunately, none of the experiments delivered the desired product in good yield and neither the benzyl- nor the MOM-protected derivative appeared to be a suitable alternative to the TBDPS-protected cyclopropylstannane.

Table 19. Optimization of conditions for the introduction of a methyl group *via* Stille coupling involving cyclopropylstannanes 197 and 198.



197: R = MOM
198: R = Bn

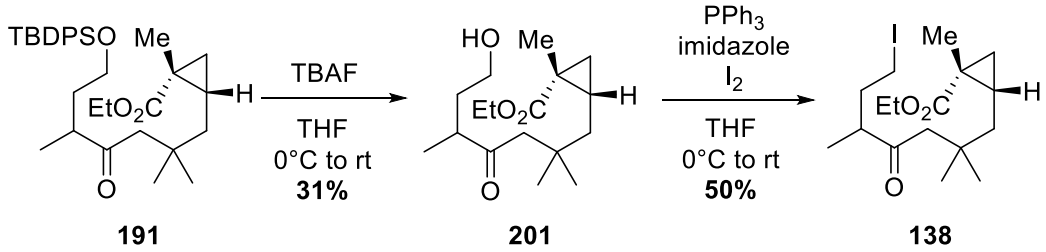
199: R = MOM
200: R = Bn

Entry[a]	R	Conditions (eq)	Time	Yield [%]
1	Bn	JackiePhos-Pd-G3 (0.2), CuCl (2.4), KF (2.2), K_2CO_3 (0.5)	20 h	32[b]
2	Bn	JackiePhos-Pd-G3 (0.2), **JackiePhos** (0.2), CuCl (2), KF (2), K_2CO_3 (0.5)	24 h	37[b]
3	Bn	JackiePhos-Pd-G3 (0.2), JackiePhos (**0.9**), CuCl (2), KF (2), K_2CO_3 (0.5)	20 h	46
4	Bn	JackiePhos-Pd-G3 (0.2), JackiePhos (0.6), CuCl (2), KF (3)	3 h	51
5[c]	Bn	JackiePhos-Pd-G3 (0.2), JackiePhos (0.6), CuCl (2), KF (2), K_2CO_3 (0.6)	72 h	37
6	Bn	JackiePhos-Pd-G3 (0.2), JackiePhos **(0.6)**[d], CuCl (2), KF (3)	40 h	< 51[e]
7	Bn	**JackiePhos-Pd-G4** (0.2), JackiePhos (0.6), CuCl (2), KF (3)	20 h	51[b]
8	Bn	JackiePhos-Pd-G4 (**0.1**), JackiePhos (**0.3**), CuCl (2), KF (2)	48 h	n.d.[e]
9	Bn	JackiePhos-Pd-G4 (0.2), JackiePhos (0.6), CuCl (2), KF (1)	**3 h**	37
10[c]	MOM	$Pd_2(dba)_3$ (0.05), JackiePhos (0.4), CuCl (2), KF (2)	4 d	traces[f]
11	MOM	JackiePhos-Pd-G4 (0.2), JackiePhos (0.6), CuCl (2), KF (3)	22 h	38

[a] Reactions were carried out in THF at 100 °C (μwave) and an excess of methyl iodide (> 25 eq). [b] no full conversion. [c] Reaction run at 70 °C in a pressure Schlenk flask. [d] additional JackiePhos (0.6 eq) added after 20 h. [e] contains significant amount of unidentified side product. [f] mostly still starting material **197**.

2.4.3.3 Attempts Towards Final Ring Closure

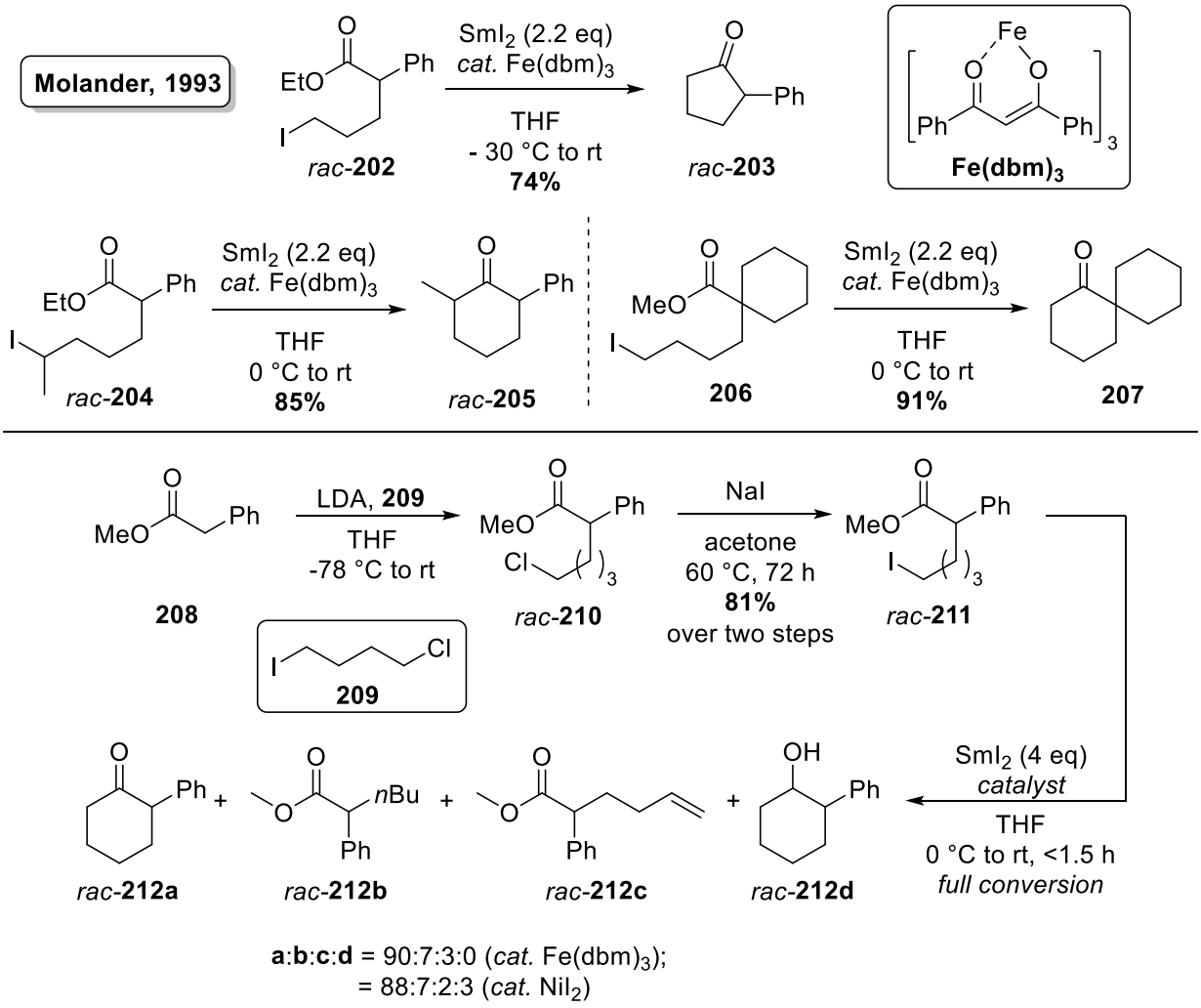
Despite the need for additional optimization in terms of the cross coupling, a sufficient amount of methylated cyclopropane **191** was obtained to continue with the synthesis. Deprotection of the TBDPS ether proceeded upon treatment with TBAF; at this stage, remaining impurities from the previous reaction could be removed (Scheme 63). The primary alcohol **201** was subjected to Appel conditions to afford alkyl iodide **138** as needed for the final ring closure.



Scheme 63. Synthesis of alkyl iodide 138 *via* deprotection and Appel reaction of 191 (unoptimized yields).

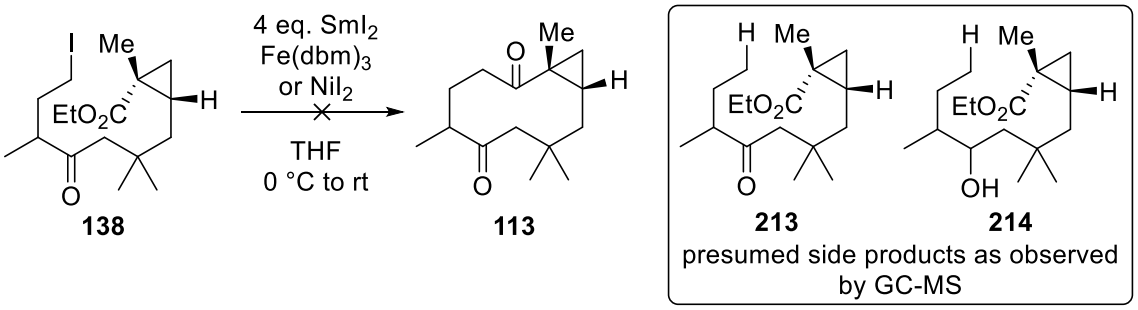
Before using alkyl iodide **138** in the intramolecular Barbier reaction, the reaction was conducted with a test substrate to optimize the conditions. The samarium diiodide needed for the reaction was freshly prepared from samarium metal and either diiodomethane or diiodoethane; the latter was washed with sodium thiosulfate prior to use to remove traces of iodine that can form over time. After stirring the mixture in THF at room temperature, a dark blue colour emerged indicating the successful formation of samarium diiodide. The concentration was determined *via* iodometric titration and the reagent could be stored under continued stirring and an excess amount of samarium metal for more than a month as recommended in the literature[240]. A test substrate ***rac*-211** resembling literature described compounds (**202**, **204**, **206**)[225] was prepared over two steps and then treated with the freshly prepared samarium diiodide (Scheme 64). With either $Fe(dbm)_3$ or nickel diiodide as a catalyst full conversion was achieved utilising four equivalents of samarium diiodide. The product distribution of **212** was analysed *via* GC-MS and the desired cyclohexanone **212a** was the major product constituting up to 90 % of the mixture. Minor components detected were the protodeiodination (**212b**) or elimination products (**212c**) as well as the overreduction product cyclohexanol **212d**.

Next, the ring closure was attempted with compound **138**, applying the aforementioned conditions. Initially, the iron catalyst $Fe(dbm)_3$ was tested and the reaction appeared to proceed with rather clean conversion and full consumption of the starting material. However, NMR and GC-MS analyses revealed a rather messy reaction profile; the desired product **113** could not be detected. Instead, protodeiodination (**213**) and ketone reduction (**214**) products were formed (Scheme 65).



Scheme 64. Literature examples of intramolecular Barbier reactions between an alkyl iodide and a carboxylic ester (top); synthesis of model substrate *rac*-211 and subsequent Barbier reaction (bottom).

The reaction was repeated once more with the iron complex and also with nickel diiodide but the outcome remained the same. Formation of the ten-membered ring from an open chain precursor is presumably too demanding.

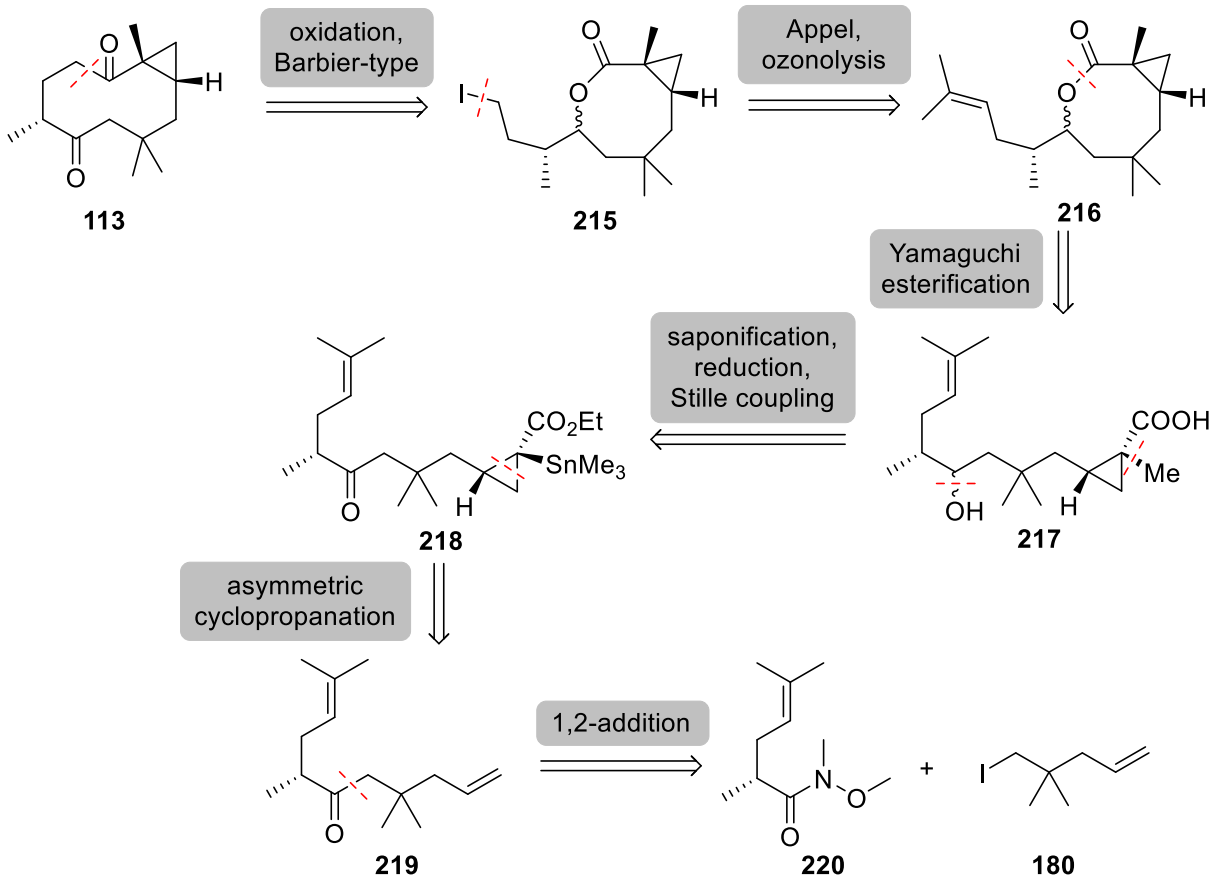


Scheme 65. Attempted intramolecular ring closure of open chain alkyl iodide 138 *via* Barbier reaction and presumed side products.

2.4.4 Synthesis *via* Ring Expansion Strategy

2.4.4.1 Revised Retrosynthetic Route

Up to this point, considerable issues had emerged that made it necessary to reconsider the synthetic strategy (Scheme 66). First and foremost, an alternative approach to achieve the final ring closure needed to be found. There is literature precedent of the attempted Barbier reaction being applied to lactone substrates, resulting in either bicyclic hemiacetals or ring-enlargement products forming up to nine-membered rings[225]. It was hypothesized that this ring expansion could be feasible for the formation of ten-membered rings as well. A lactone substrate such as **215** would form a six-membered transition state which is likely to be more favoured compared to the previous approach. Introduction of the alkyl iodide was still planned through an Appel reaction, however, the origin of the alcohol precursor had to be revised. During the Stille coupling, no satisfying result had been achieved with any of the protecting groups, even after various optimization attempts.



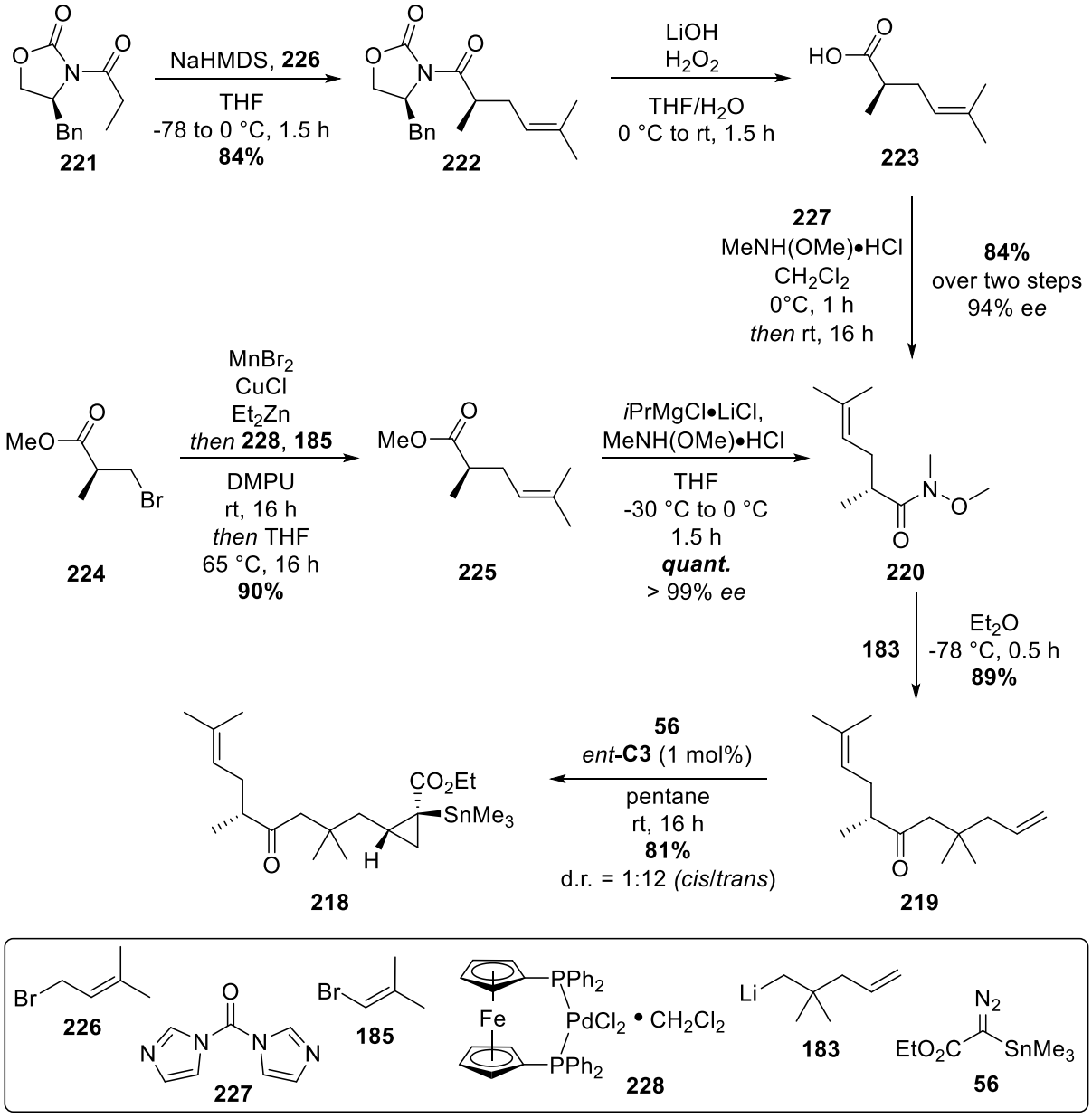
Scheme 66. Revised retrosynthetic route towards integrifolian-1,5-dione (113) following a ring expansion strategy.

For these reasons, it was decided to avoid the use of protecting groups altogether and switch to a functional group interconversion strategy. To this end, the alcohol should be introduced *via* ozonolytic cleavage of a dimethyl-capped alkene **216**. With this functionality being present from

an early stage of the synthesic route, the selectivity of the dirhodium catalyst (**C3**) for mono-substituted olefins could be highlighted during the cyclopropanation step. The lactone **216** would be formed *via* intramolecular Yamaguchi esterification of compound **217**, which in turn could be obtained from cyclopropanation product **218** in a sequence of Stille coupling, ketone reduction and ester saponification.

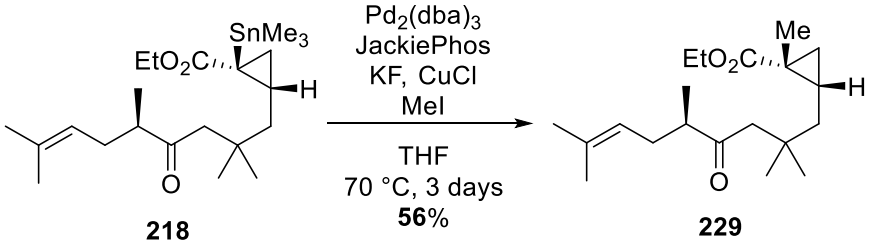
2.4.4.2 Synthesis of the New Olefin Fragment and Key Steps

In a forward sense, the synthesis initially commenced from Evans' auxiliary derivative **221** which was diastereoselectively prenylated, introducing the chiral centre in α-position to the carbonyl group (**222**, Scheme 67).



Scheme 67. Synthesis of cyclopropylstannane 218 starting from Evans' auxiliary 221 or Roche ester derivative 224.

The auxiliary was then cleaved and the resulting carboxylic acid **223** transformed into the Weinreb amide **220**. While these reactions were reasonably high yielding and the Weinreb amide was obtained with an *ee* of 94 %, a different, more atom economic approach was eventually chosen, avoiding the use of an auxiliary. We started with the Roche ester derivative **224**, which was subjected to modified Negishi conditions developed by the group of Knochel to obtain the homoallylic ester **225**[241]. In this reaction, the alkyl bromide **224** was first converted *in situ* into an organozinc species and subsequently treated with alkenyl bromide **185** and palladium catalyst **228**. The ester **225** was readily converted into the Weinreb amide **220** by treatment with isopropylmagnesium chloride-lithium chloride complex. Compared to the auxiliary-based approach, the latter route was one step shorter, provided higher yields while also giving an excellent *ee* of >99 %. The terminal olefin-bearing alkyl side chain was introduced by 1,2-addition of the previously described alkyllithium species **183**, derived from iodide **180**, to the Weinreb amide **220**, following the optimized lithiation protocol to access the olefin **219** in up to 89 % yield. Due to previous improvements of the cyclopropanation reaction, the desired product **218** was obtained in up to 81 % yield and with a d.r. of 12:1 in favour of the *trans*-isomer. The reaction was carried out using 1 mol% of dirhodium catalyst ***ent*-C3** in pentane at room temperature with slow addition of an excess amount of diazo stannane **56** to the reaction mixture *via* syringe pump.



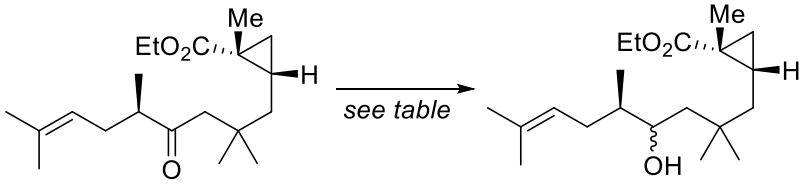
Scheme 68. Stille coupling of cyclopropylstannane 218 with methyl iodide.

With ample amounts of the cyclopropylstannane **218** at hand, the synthesis was continued with the stereoretentive Stille coupling (Scheme 68). The established conditions were employed and, similar to the previous substrates, the reaction initially suffered from slow conversion. It could eventually be pushed to near full conversion (> 95 % based on GC-MS analysis) by doubling the catalyst loading to 0.1 equivalents of $Pd_2(dba)_3$ and 0.8 equivalents of JackiePhos, as well as increasing the excess amount of copper chloride from five to ten equivalents. After three days of stirring at 70 °C, the desired compound **229** was isolated in 56 % yield.

2.4.4.3 Attempts to Improve the Diastereoselectivity of the 2° Alcohol Formation

After the successful cross coupling, the diastereoselective reduction of the ketone **229** was pursued (Table 20). While treatment with sodium borohydride provided the desired product (entry 1), it did so with poor diastereoselectivity, even upon addition of cerium trichloride (Luche conditions[242], entry 2).

Table 20. Optimization of carbonyl reduction of 229.



229 **230**

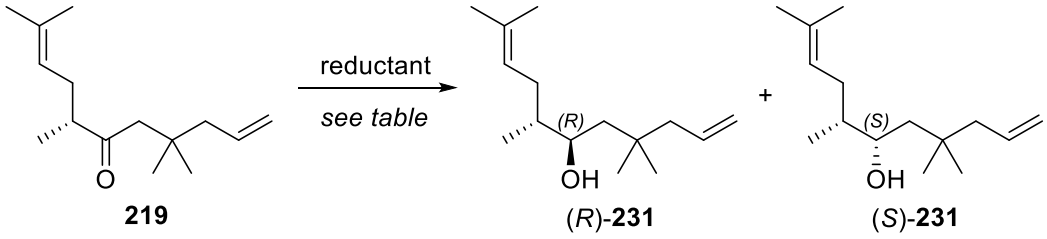
Entry	Conditions (eq)	d.r. of 230 (*R*:*S*)	Yield[#] [%]
1	$NaBH_4$ (2), EtOH, 0 °C to rt	1:1.7[a]	37
2	$NaBH_4$ (25), $CeCl_3$ (2), EtOH, -78 °C to rt[b]	1:2[c]	n.d.
3	*K*-Selectride (2), THF, -78 °C to rt	-	n.r.
4	*N*-Selectride (2), -55 °C to rt	-	n.r.
5	$LiAlH(OtBu)_3$ (6), THF, 0 °C	-	n.r.
6	(*S*)-2-Methyl-CBS-oxazaborolidine (0.4), catecholborane (10), CH_2Cl_2, -65 °C to rt	-	n.r.
7	$PhMe_2SiH$ (1.1), TBAF (0.05), DMPU, rt	-	n.r.
8	$NaBHEt_3$ (3), THF, 0 °C	1:2[a]	43
9	**$NaBHEt_3$ (1.5), THF, -78 °C**	**1:5[a]**	**89**

[#] combined yield of **(*S*)-** and **(*R*)-230**. [a] determined *via* ^{1}H-NMR. [b] no conversion at -78 °C. [c] determined *via* GC-MS. n.d.: not determined. n.r.: no reaction.

Even though the absolute configuration of the secondary alcohol **230** does not matter for the final natural product, it was still desirable to obtain a single diastereoisomer or at least a great excess of one so that the following steps do not have to be carried out separately with each diastereomer. Therefore, different bulky hydride reduction reagents were tested but the majority of them left the starting material untouched (entries 3 to 5). Additional attempts towards reduction employing a Corey-Bakshi-Shibata protocol or hydrosilanes remained unfruitful (entries 6 and 7). Eventually, the best result was obtained with sodium triethylborohydride at -78 °C obtaining 89 % yield with a d.r. of approximately 5:1 (entry 9). Mosher ester analysis of the major diastereomer revealed the absolute configuration of the secondary alcohol to be (*S*), which can be explained by the Felkin-Anh model.

The presence of an ethyl ester motif in compound **229** precluded the use of certain stronger reducing agents and therefore the reduction was also attempted at an earlier stage of the synthesis, prior to the cyclopropanation. While all of the applied reductants led to the formation of alcohol **231**, the diastereoselectivity remained poor (Table 21).

Table 21. Attempts to increase the diastereoselectivity of the carbonyl reduction.

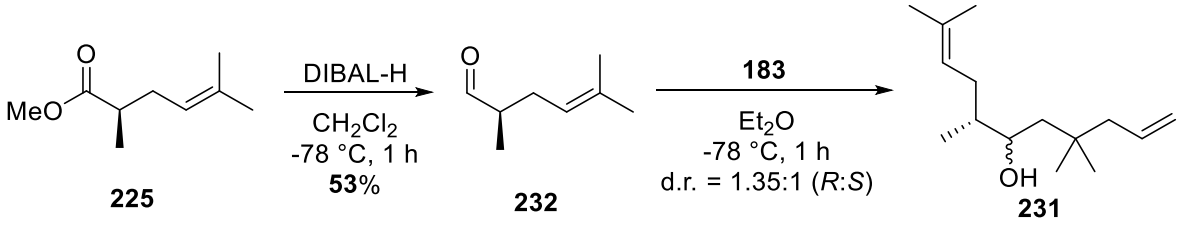


219 (*R*)-**231** (*S*)-**231**

Entry	Reductant[a]	d.r. of 231 (*R*:*S*)
1	*L*-Selectride[b]	1:1[c]
2	DIBAL-H	1:1[d]
3	$LiAlH(OtBu)_3$[b]	1:1.5
4	$LiBHEt_3$	1:1.75

[a] All reactions conducted with reductant (2.0 eq) in THF starting at -78 °C. [b] no reaction at -78 °C, warmed to 0 °C or rt. [c] determined *via* ^{1}H-NMR. [d] determined *via* GC-MS.

Another approach was to form the alcohol *via* 1,2-addition of alkyllithium **183** to aldehyde **232** instead of a reduction of the ketone (Scheme 69). It was hypothesized that the alkyllithium nucleophile would be sterically demanding enough to attack the aldehyde with higher selectivity according to a Felkin-Anh model. The required aldehyde **232** was prepared from methyl ester **225** in moderate yield, likely because of its volatility. Aldehyde **232** was then treated with the lithiated species **183** according to the optimized procedure. As expected, the minor diastereoisomer from ketone reduction **(*R*)-231** was now formed as the major component, yet the selectivity remained low.

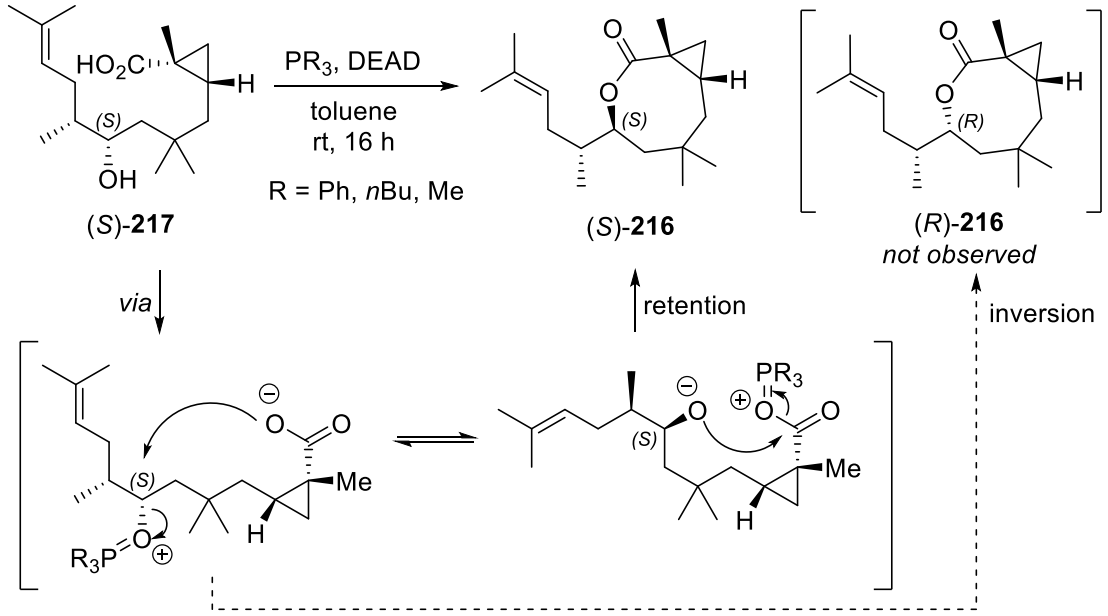


225 **232** **231**

Scheme 69. Synthesis of 2° alcohol 231 *via* 1,2-addition of alkyllithium species to aldehyde 232.

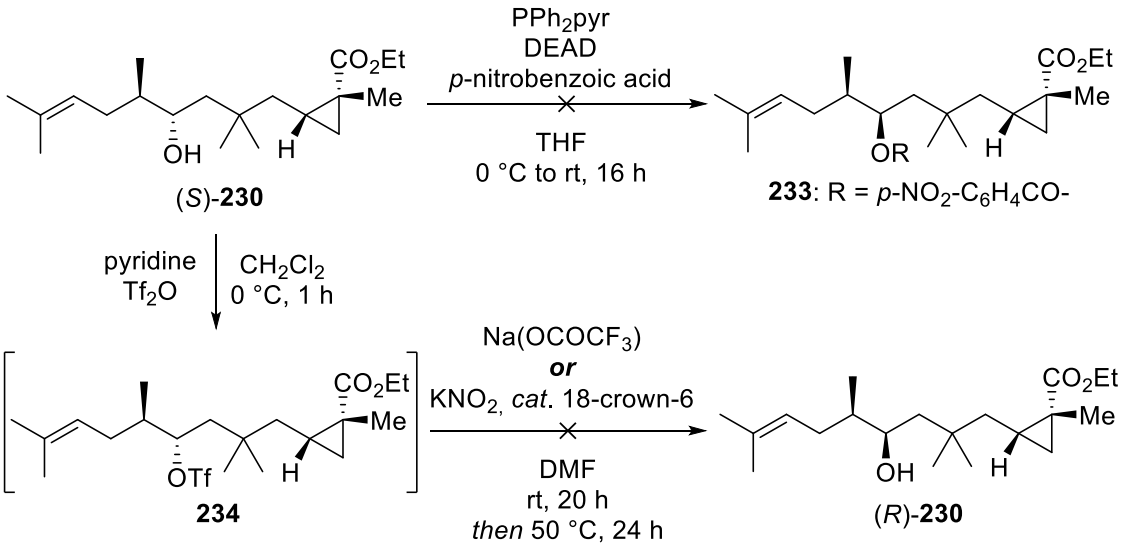
Since the two diastereomeric alcohols were partially separable *via* flash chromatography, we considered inversion of the stereochemistry of the minor isomer by the Mitsunobu protocol. After saponification of the ester **230** (*vide infra*), alcohol **(*S*)-217** was submitted to lactonization using either triphenyl, tri-*n*butyl or trimethyl phosphine in combination with diethyl azodicarboxylate (DEAD). After stirring of the mixture at room temperature in toluene overnight, the ring-closed product **216** was formed (Scheme 70). However, a comparison of the analytical data with the lactone **216** obtained under Yamaguchi conditions employing (*S*)-alcohol **217** (*vide infra*)

revealed that no inversion of the configuration had occurred. The lack of inversion was possibly the result of the phosphonium intermediate binding to the carboxylate rather than the alcohol oxygen due to its steric hindrance.



Scheme 70. Attempted inversion of 2° alcohol (*S*)-217 in an intramolecular fashion *via* Mitsunobu lactonization.

The Mitsunobu inversion was again attempted in an intermolecular format, using *para*-nitrobenzoic acid, which has been described in the literature to work well with sterically hindered secondary alcohols[243]. Yet, alcohol **(*S*)-230** failed to afford ester **233** and mostly unreacted starting material was recovered (Scheme 71).

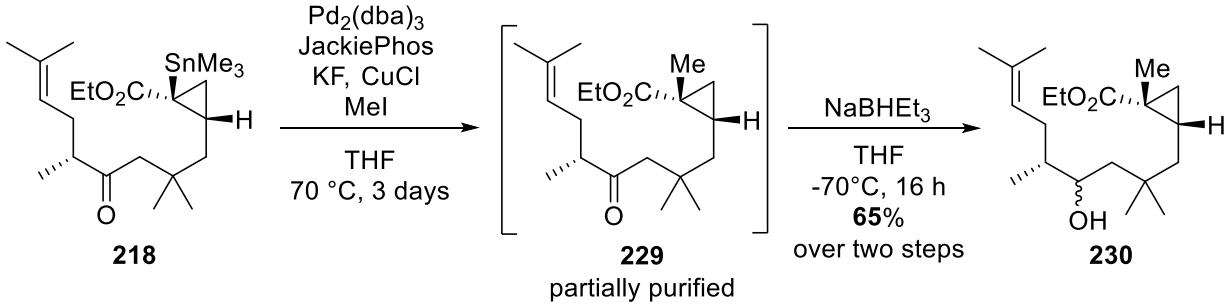


Scheme 71. Attempted inversion of 2° alcohol (*S*)-230 in an intermolecular fashion.

With the aim of increasing the reactivity, the triflate derivative **234** of the secondary alcohol was formed[244]. Unfortunately, neither treatment with KNO_2[245] nor sodium trifluoroacetate[246] led to any conversion into inverted alcohol **(*R*)-230.** Again, the steric hindrance of the secondary alcohol was presumably too high for the desired reactions to take place.

2.4.4.4 Synthesis of Lactone Derivatives

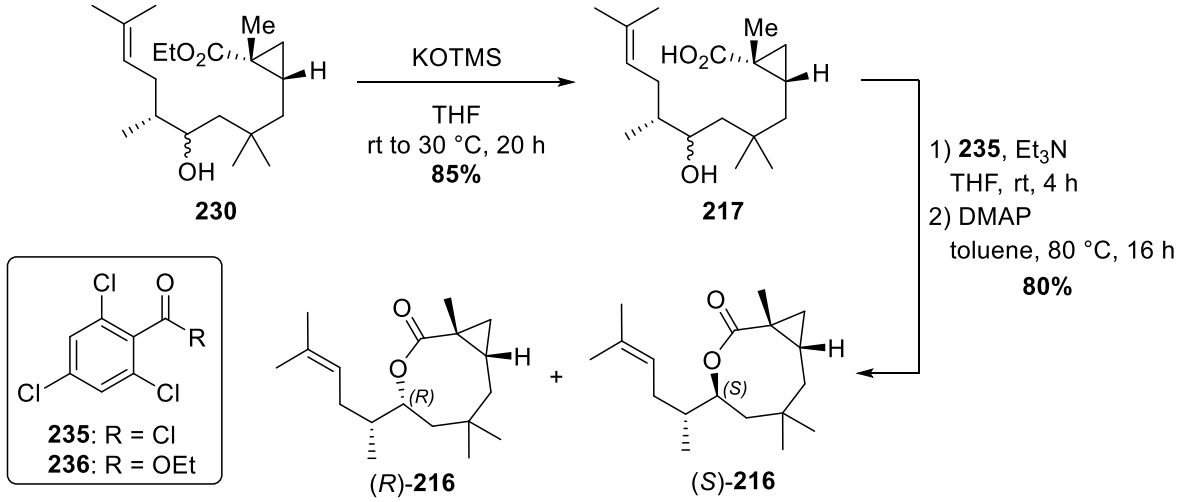
After the fruitless attempt to invert the secondary alcohol stereocentre of compound **230**, it was decided to proceed with the reduction using sodium triethylborohydride and continue the synthesis with both diastereoisomers. Material throughput after the cyclopropanation could be slightly increased by not fully purifying the cross coupling product **229**. The impurities were mainly the *cis*-isomer, trace amounts of unreacted starting material and protodestannylated compound, all of which were difficult to separate from the desired product *via* flash chromatography. To avoid the loss of product from overzealous purification, only a short chromatography was conducted, separating most of the impurities that originated from the ligand, catalyst and additives, and then directly subjecting the remaining mixture to the reduction conditions. Because the polarity changes drastically during the reduction, separation of the side products became more feasible at this stage. In this way, a 65 % overall yield of alcohol **230** could be achieved over two steps (Scheme 72).



Scheme 72. Optimized procedure for the synthesis of 2° alcohol 230 from cyclopropylstannane 218.

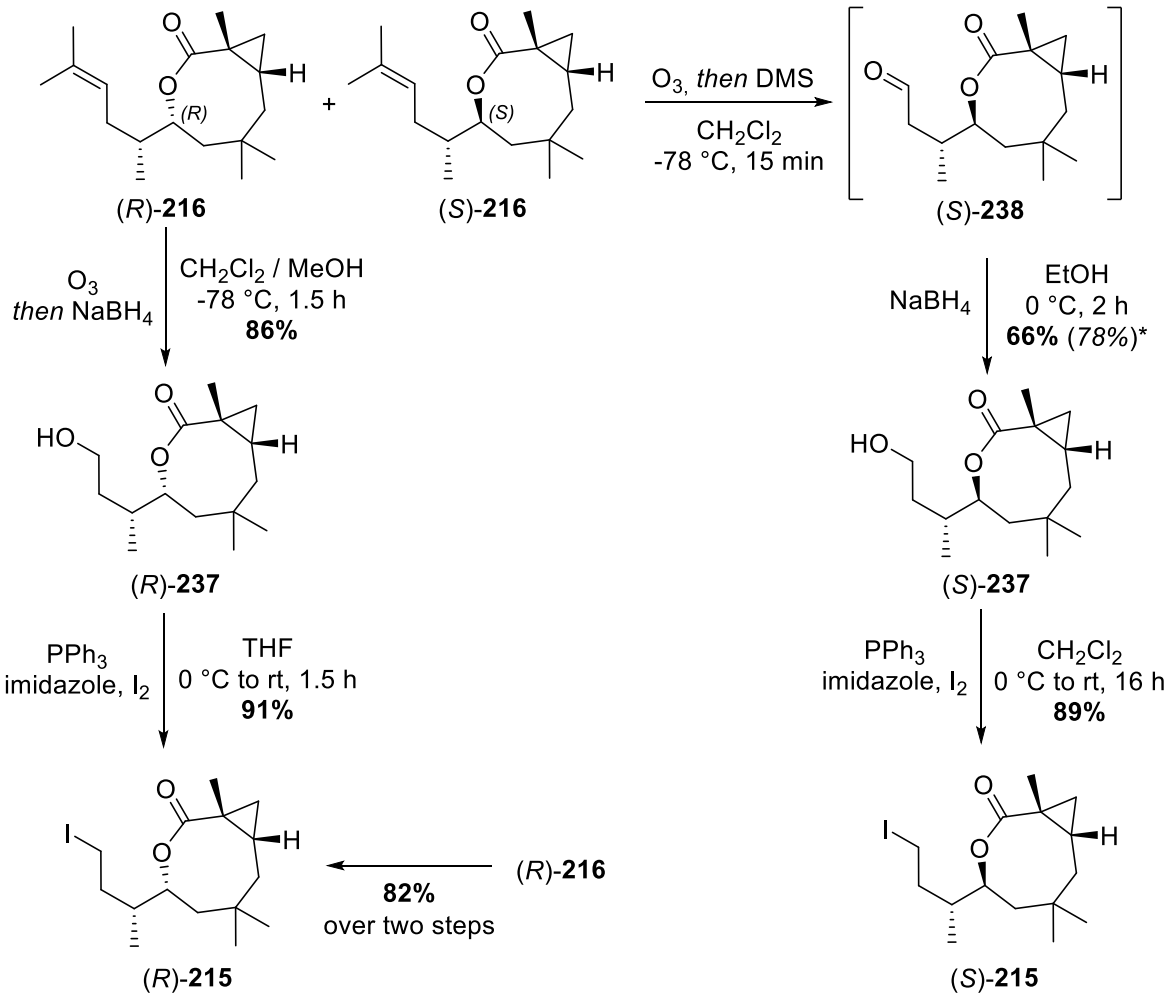
Next, the saponification of the ethyl ester was conducted using an excess of potassium trimethylsilanolate in THF at slightly elevated temperatures (Scheme 73). Subsequent lactonization of the resulting carboxylic acid **217** took place under Yamaguchi conditions. For analytical purposes, these steps were initially carried out with each diastereoisomer seperately. However, to continue the synthesis this is not necessary and the mixture of isomers formed by carbonyl reduction can be carried through to the lactones; the yields given refer to these experiments. Separation of the diastereoisomers *via* flash chromatography after the lactonization (**216**) was simple compared to prior stages as the R_f values of the two products differ significantly. From then on, the isomers were handled separately in each reaction (Scheme 74). It is important to note that in some cases, after Yamaguchi lactonization, a side product co-eluted during

chromatographic purification at the same R_f as the major isomer **(*S*)-216**, which turned out to be ethyl dichlorobenzoate **236**, derived from the respective acid chloride **235**.



Scheme 73. Saponification of ethyl ester 230 followed by Yamaguchi lactonization of 217.

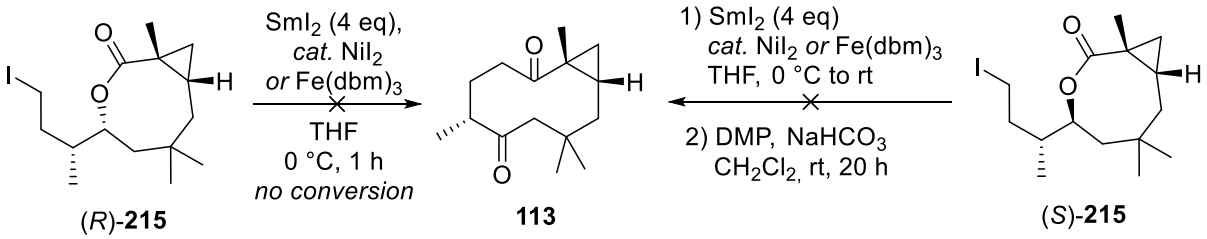
To introduce the primary alcohol on the side chain of the lactone, compound **216** was subjected to ozonolytic cleavage with subsequent reduction. Interestingly, in case of the (*R*)-isomer of **216**, it was possible to directly reduce the intermediate ozonide *in situ* by adding sodium borohydride, which gave the desired alcohol **(*R*)-237** in good yield. In contrast, for the major isomer **(*S*)-216** the addition of sodium borohydride to the ozonide led to decomposition. Accordingly, a detour *via* aldehyde **238** had to be taken, which was obtained by addition of dimethyl sulfide to the reaction mixture shortly after treatment with ozone. Following an aqueous work-up, the crude aldehyde was dissolved in ethanol and eventually reduced with sodium borohydride. In order to maintain adequate yields, it was important to pay close attention to the amount of reductant added to the mixture. Only a slight excess was necessary and larger amounts of sodium borohydride led to diminished yields. Fortunately, the presence of the previously described impurity **236** did not interfere with the ozonolysis and could be easily separated from the desired product **237** *via* flash chromatography after the reduction (yield of this experiment is given in brackets). The subsequent Appel reaction to convert the alcohols **237** into the respective primary iodides **215** proceeded smoothly with both isomers. For the minor (*R*)-isomer it was possible to directly apply the crude alcohol **(*R*)-237** after ozonolysis in the Appel reaction without prior purification, thus minimizing loss of valuable product during flash chromatography.



Scheme 74. Conversion of lactones 216 to their respective iodide derivatives 215 *via* ozonolysis and subsequent reductive quench followed by Appel reaction. * yield of experiment in presence of impurity from side product 236.

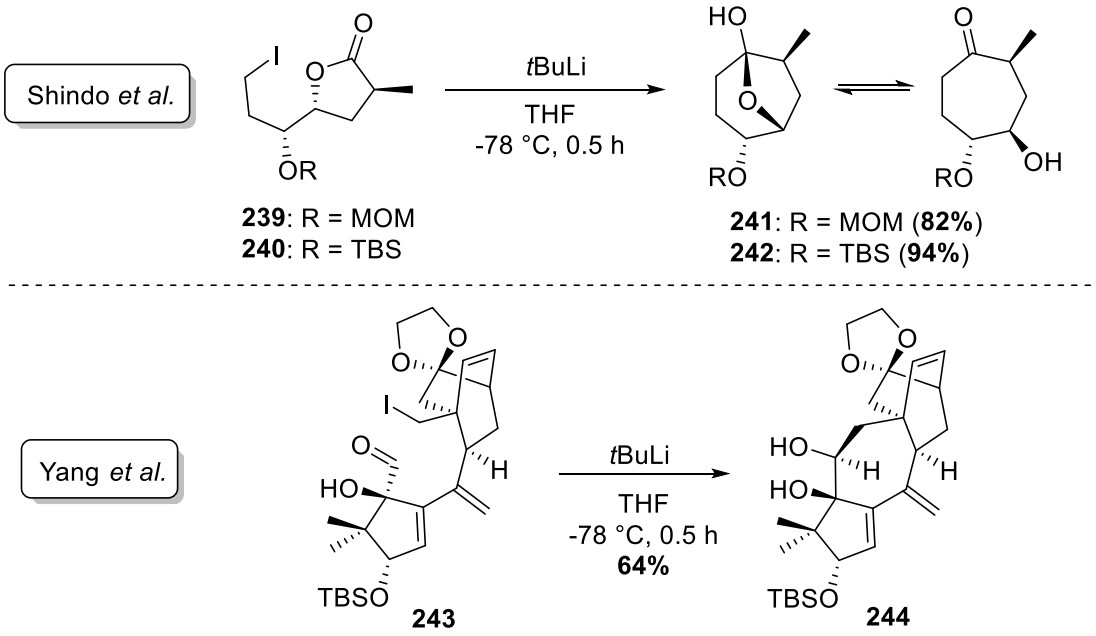
2.4.4.5 Endgame: Ring Closure

With the alkyl iodides **215** at hand, the ring closing reaction and oxidation to access the natural product integrifolian-1,5-dione (**113**) could be tested. As initially planned, samarium diiodide was first used to achieve the Barbier-type transformation. When the reaction was run at 0 °C, only very little conversion was observed and the starting material was mostly recovered (Scheme 75).



Scheme 75. Attempted synthesis of integrifolian-1,5-dione (113) from iodides 215 using samarium diiodide.

Nickel diiodide and $Fe(dbm)_3$ were tried as catalysts, but both provided similar unsuccessful outcomes. Allowing the reaction to warm to room temperature afforded a complex mixture. The desired natural product **113** could not be obtained by this approach.

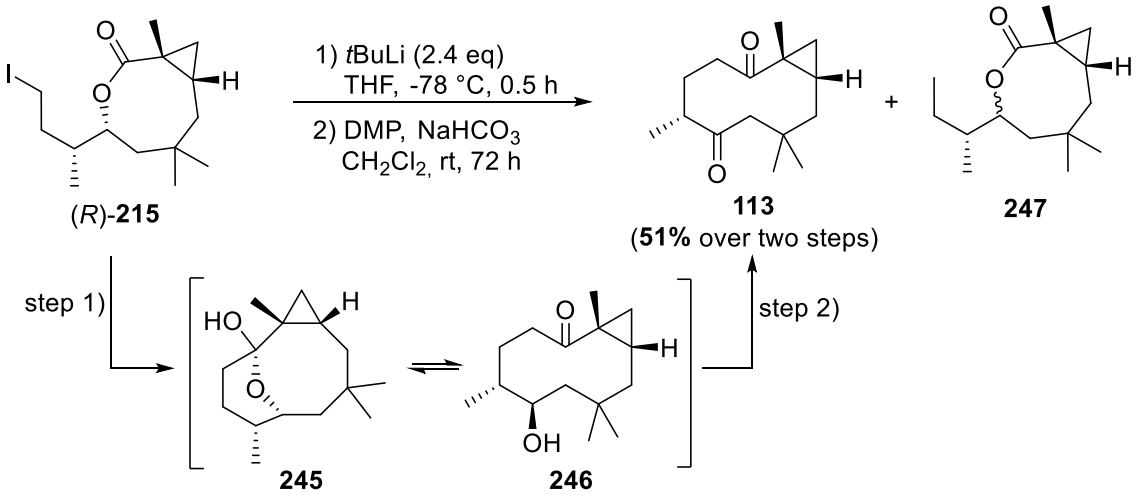


Scheme 76. Literature precedent for intramolecular ring closure between an alkyl iodide and a carbonyl group by treatment with *tert*-butyllithium.

Next, the use of *tert*-butyllithium was investigated based on literature precedent for similar transformations involving an intramolecular ring closure between an alkyl iodide and a carbonyl group (Scheme 76)[247]. In a first experiment, alkyl iodide **(*R*)-215** was treated with *tert*-butyllithium at -78 °C. The ^{13}C-NMR spectrum of the crude material suggested the presence of an acetal species **245**, indicated by a signal with a chemical shift of 100.5 ppm. The acetal is probably in equilibrium with the ring opened alcohol tautomer **246**; such an equilibrium has been described in the literature[247b]. This crude mixture was directly submitted to the oxidation conditions and the desired natural product **113** was obtained, accompanied by a protodeiodination side product **247** (Scheme 77).

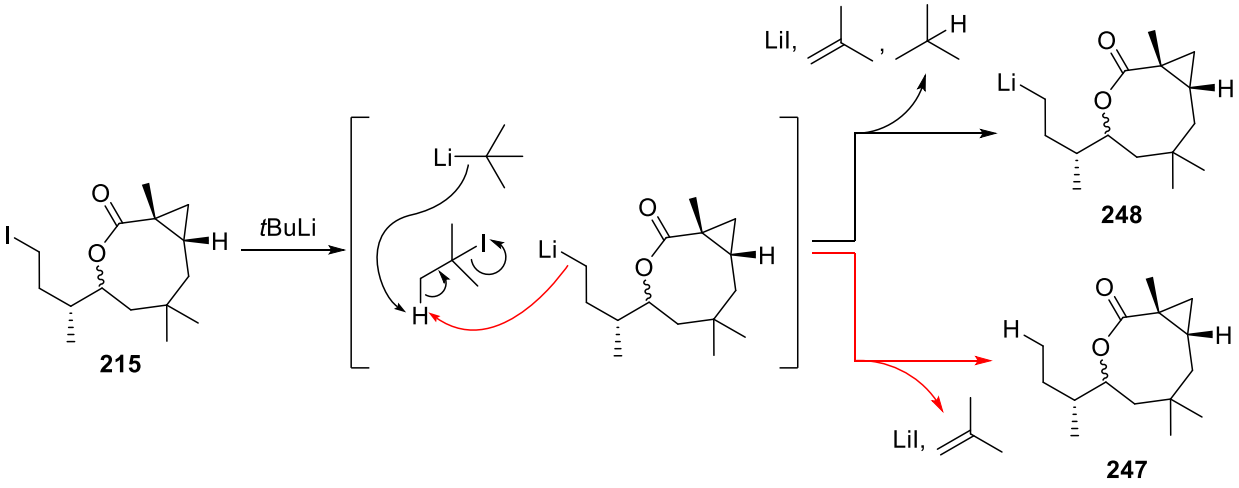
In order to reduce the degree of protodeiodination and hence increase the yield, the lithiation was conducted with an inverted order of addition, diluting the *tert*-butyllithium first in THF at -78 °C before adding the iodide **215** dropwise. It was suspected that the protodeiodination was the result of the lithiated species **248** reacting with the formed *tert*-butyliodide after the lithium-halogen exchange to form lithium iodide and isobutene along with the protodeiodination product **247** (Scheme 78). By having an excess of *tert*-butyllithium present in the reaction mixture from the beginning, it was anticipated that the *tert*-butyl iodide would more likely be quenched by the more reactive excess *tert*-butyllithium, leaving the desired lithiated species intact. Applying the

inverted order of addition reduced the degree of protodeiodination, albeit not completely, as judged by GC-MS analysis of the crude mixture.



Scheme 77. First experiment of the synthesis of integrifolian-1,5-dione 113 using *tert*-butyllithium to initiate ring closure.

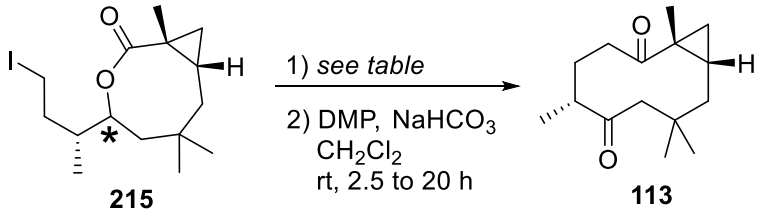
The yield was increased to 67 % with the (*R*)-isomer of **215** and up to 62 % when **(*S*)-215** was used (Table 22, entries 2 to 5). When the reaction was performed on slightly larger scale compared to the previous experiments, a drop in yield to 45 and 40 %, respectively, was noticed (entries 6 and 7). A change in solvent from THF to diethyl ether was tested, again on smaller scale, but did not lead to an improved outcome. While the yield remained moderate (58 %) for **(*R*)-215** (entry 8), it dropped to 45 % with **(*S*)-215**, where an increased amount of side product formation was observed *via* GC-MS analysis, including a species that possibly corresponded to a *tert*-butyl addition product (entry 9).



Scheme 78. Proposed pathways leaving the desired lithiated species 248 intact or resulting in the undesired protonated side product 247.

Since the desired transformation is an intramolecular process, the reaction concentration on larger scale was lowered (entries 10 and 11), but this did not improve the yield. The water content of the solvent was checked prior to the reaction to exclude this possible cause for protonation of the lithiated species (entry 11). As the used THF contained only 5 ppm of water, it was most likely not the reason for the comparably low yield.

Table 22. Optimization of reaction conditions for intramolecular ring closure of iodide 215.



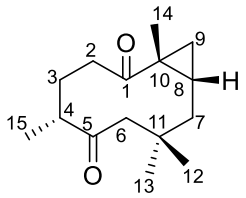
215 **113**

Entry	*(*R*)- or (*S*)-215	m (215) [mg]	c (215) [10^{-3} mol/L]	Conditions[a] (eq)	Yield [%][b]
1[c]	(*R*)	6	4.1	*t*BuLi (2.4), 0.5 h	51
2	(*S*)	3	4.1	*t*BuLi (4.1), 1 h	62
3	(*S*)	7	4.8	*t*BuLi (3.5), 1 h	57
4	(*R*)	3	4.1	*t*BuLi (4.1), 1 h	67
5	(*R*)	10	5.5	*t*BuLi (3.7), 2 h	67
6	(*R*)	31	12	*t*BuLi (4.0), 1 h	45
7	(*S*)	23	11	*t*BuLi (4.0), 1.5 h	40
8[d]	(*R*)	8	5.5	*t*BuLi (3.1), 2 h	58
9[d]	(*S*)	10	4.6	*t*BuLi (3.7), 5 h	45[e]
10	(*S*)	25	4.6	*t*BuLi (4.2), 2 h	46
11[f]	(*R*)	28	4.5	*t*BuLi (4.0), 1 h	46

[a] All reactions were carried out in THF at -78 °C, adding the iodide **215** to the cooled solution of *t*BuLi if not mentioned otherwise. [b] isolated yield of **113** after two steps. [c] initial experiment where *t*BuLi was added to solution of iodide **215**. [d] Et_2O used as solvent. [e] still contained impurities. [f] water content of solvent (THF) determined to be 5 ppm.

The analytical data of synthetic **113** was in good agreement with the literature reported values, meaning that the synthetic material was in fact identical to the isolated natural product[197a, 201, 203] (Table 23). However, several previously misassigned chemical shifts had to be corrected upon more thorough NMR analysis[203]. In the proton NMR spectrum, H13 and H14 were interchanged while in the carbon NMR spectrum the signal originally assigned to C3 corresponded to C8 and C3 was instead superimposed with C12. Additionally, the assignments for C10 and C11 needed to be interchanged.

Table 23. Comparison of NMR spectroscopic data of synthetic integrifolian-1,5-dione (113) with the reported literature values[201, 203].



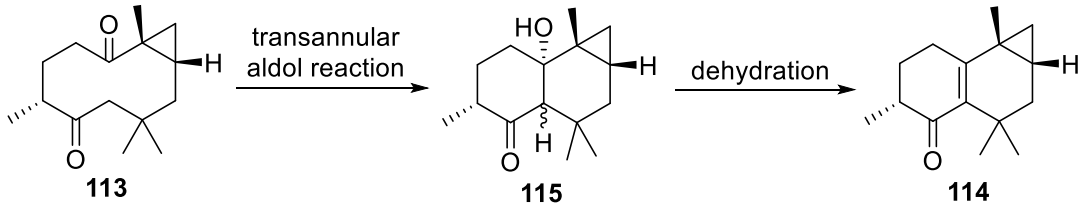
integrifolian-1,5-dione (113):
$[\alpha]_D^{20}$ (Lit.) = -29.1° (c = 9.6, $CHCl_3$)
$[\alpha]_D^{20}$ (exp.) = -24.9° (c = 1.0, $CHCl_3$)

Atom No.	δ_{exp} ^{1}H [ppm][a]	δ_{Lit} ^{1}H [ppm][b]	δ_{exp} ^{13}C [ppm][c]	δ_{Lit} ^{13}C [ppm][d]
1	-	-	207.8	207.4
2	2.29 3.14	2.29 3.15	38.6	38.6
3	2.25 1.61	2.25 1.61	29.7	29.7
4	2.36	2.35	46.9	46.8
5	-	-	212.9	212.5
6	2.02 2.51	2.02 2.51	52.7	52.7
7	1.43 1.53	1.43 1.53	35.1	35.2
8	1.08	1.08	30.4	30.4
9	0.64 1.34	0.65 1.34	20.3	20.3
10	-	-	31.7	31.7
11	-	-	32.3	32.3
12	0.92	0.92	29.6	29.7
13	1.18	1.18	28.9	28.9
14	1.46	1.46	21.5	21.5
15	0.99	0.98	17.2	17.2

All spectra were measured in $CDCl_3$. [a] 600 MHz. [b] 300 MHz. [c] 151 MHz. [d] 75.4 MHz.

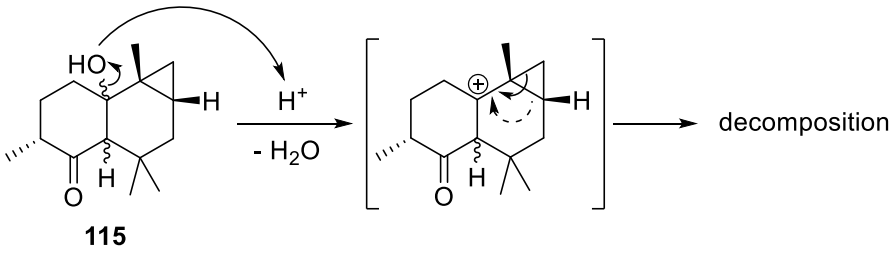
2.4.4.6 Transannular Aldol Reaction

With natural product integrifolian-1,5-dione in hand, the synthesis of further derivatives was pursued. Compound **115** was envisioned to be obtained through a transannular aldol reaction; subsequent dehydration thereof would lead to lippifoli-1(6)-en-5-one **114** (Scheme 79).



Scheme 79. Outline for the potential synthesis of lippifoli-1(6)-en-5-one (114) from integrifolian-1,5-dione (113).

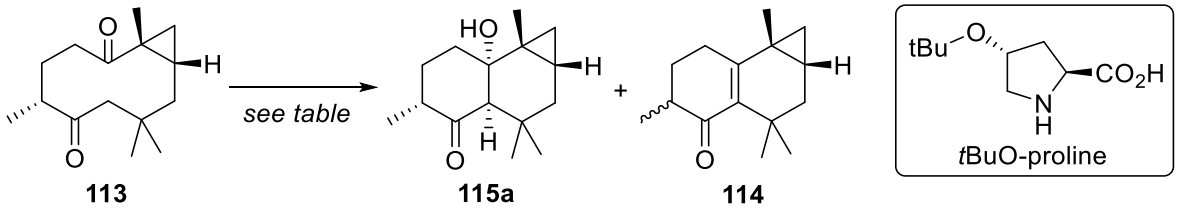
Various conditions were tested to achieve the transannular aldol addition (Table 24). Enamine catalysis, using either pyrrolidine[248] or a proline derivative[249] did not cause any conversion, despite prolonged reaction times and heating (entries 1 and 2). The sterically encumbered carbonyl in proximity to a *gem*-dimethyl motif likely failed to undergo enamine formation. An attempt to perform the transformation under acidic conditions was also not successful. When **113** was treated with trifluoroacetic acid at 0 °C [248, 250], no conversion was observed after stirring for over three hours (entry 3). Yet, if an excess amount of the acid was applied and the reaction was stirred at room temperature for a prolonged period of time, only the dehydration product **114** was observed besides noticeable decomposition (entry 4). A similar outcome was obtained with camphorsulfonic acid[251]; no conversion occurred at room temperature and heating led to formation of the dehydration product and partial decomposition (entry 5). Among other possible pathways, decomposition might have taken place through the formation of a carbocation next to the cyclopropane motif after aldol addition and subsequent elimination of the formed tertiary alcohol. The carbocation can then cause opening of the cyclopropane (Scheme 80).



Scheme 80. Possible pathway for the observed decomposition of 115 under acidic conditions.

Eventually, basic conditions were applied. An approach with basic alumina[251] as a heterogenous catalyst was not successful, with no conversion being observed (entry 6); addition of potassium hydroxide[252] on the other hand resulted in a rather messy reaction profile (entry 7). Gratifyingly, when the substrate was stirred with potassium carbonate in methanol at room temperature, an approximately 1:1 mixture of **115** and **114** was obtained (entry 8).

Table 24. Optimization of conditions for transannular aldol reaction of 113.



113 **115a** **114**

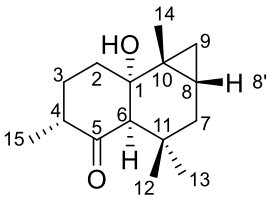
Entry	Catalyst (eq)	Conditions	Result
1	pyrrolidine (0.5)	CD_2Cl_2, rt (2 days) to 40 °C (5 h)	n.r.
2	*t*BuO-proline (0.2)	DMF-d7, rt (24 h) to 50 °C (5 h) to 70 °C (20 h)	n.r.
3	TFA (2)	CH_2Cl_2, 0 °C, 3.5 h	n.r.
4	TFA (excess)	CH_2Cl_2, rt, 5 days	**114**; **115** not observed
5	CSA (< 1)	toluene, rt (5 days) to 110 °C (20 h)	**114**; **115** not observed
6	Al_2O_3 (11)	CH_2Cl_2, rt, 24 h	n.r.
7	KOH (excess)	EtOH, rt, >5 days	messy, **114** detected; **115** not observed.
8	K_2CO_3 (4)	MeOH, rt, 5 days	**114** and **115** (1:1)
9	**Cs_2CO_3 (2x 2)**	**MeOH, rt, 2x 3 days**	**115a: 47% (56% *brsm*), 114: 20-25%[a]**

n.r.: no reaction. [a] mixture of epimers.

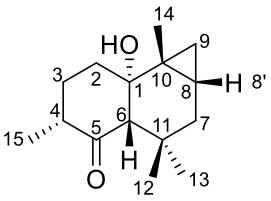
Only one diastereomer of the aldol addition product was formed with no indication of epimerization on the methyl group in α-position to the carbonyl function. The reaction could be further optimized by replacing potassium carbonate with cesium carbonate (entry 9), which reduced the amount of dehydration product formed during the reaction. The reaction was run over two cycles, isolating unreacted starting material after three days of stirring and resubmitting it to the reaction conditions. Thus, 46 % (56 % brsm) of the aldol addition product **115a** were obtained.

In contrast to integrifolian-1,5-dione, the analytical data of the isolated aldol reaction product **115a** was not consistent with the data reported in the literature[197b]. The observed chemical shifts in the NMR spectra were close to the reported values but the differences were too great to confirm the structure of either of the two proposed aldol addition products **115a** or **115b** (Table 25).

Table 25. Comparison of NMR spectroscopic data of synthetic 115a and the reported literature values for 115a and 115b[197b].



115a



115b

Atom No.	δ_{exp} ^{1}H (115a) [ppm][a]	δ_{Lit} ^{1}H (115a) [ppm][b]	δ_{Lit} ^{1}H (115b) [ppm][b]	δ_{exp} ^{13}C (115a) [ppm][c]	δ_{Lit} ^{13}C (115a) [ppm][d]	δ_{Lit} ^{13}C (115b) [ppm][d]
1	1.28	1.55	-	76.6	77.6	78.7
2	2.14 2.01	2.31 1.84	1.96 – 2.08	32.3	33.7	38.8
3	1.96 1.78	1.96 1.47	1.79 1.96 – 2.08	30.4	27.6	31.9
4	2.39	2.39	2.38	43.9	44.9	46.4
5	-	-	-	214.3	213.7	212.0
6	1.79	2.39	2.32	66.8	62.6	63.7
7	1.80 1.22	2.06 1.59	1.56 – 1.76	42.9	37.5	39.4
8	1.08	0.86	0.92	23.0	19.1	22.6
9	0.55 0.25	-0.09 0.46	1.00 0.24	20.7	20.9	15.7
10	-	-	-	26.8	23.7	24.7
11	-	-	-	34.6	30.9	30.6
12	1.13	1.11	1.28	26.2	31.7	25.5
13	0.76	1.00	0.94	29.9	28.6	34.0
14	1.11	1.09	1.14	22.1	22.3	24.4
15	1.05	1.00	1.01	14.9	14.8	14.4

All spectra were measured in $CDCl_3$. [a] 600 MHz. [b] 300 MHz. [c] 151 MHz. [d] 75.4 MHz.

A more detailed NMR spectroscopic analysis of the synthetic sample confirmed the proposed structure for **115a**. Consequently, this meant that the structure given by the isolation team was likely incorrect and did not correspond to what they had actually isolated. Some of the relevant NOEs that support the configuration of the synthesic compound are shown in Figure 24 (red arrows). Especially the "W"-type coupling (^{4}J) of 1.8 Hz between H6 and $H2_{eq}$ (indicated with pink

bonds) is characteristic. Most importantly, the proposed structure of product **115a** was confirmed by X-ray diffraction analysis (Figure 25), which implies an incorrect NMR assignment by the isolation team.

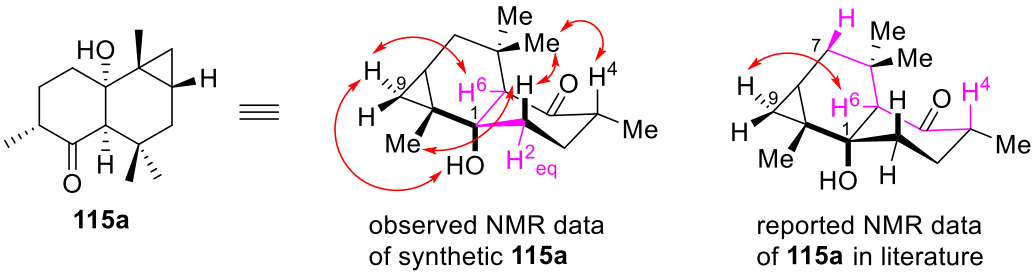


Figure 24. Detailed NMR spectroscopic analysis of synthetic 115a (left) compared with the literature-reported NMR data (right; red arrows: NOE correlations, pink bonds: observed *J*-couplings).

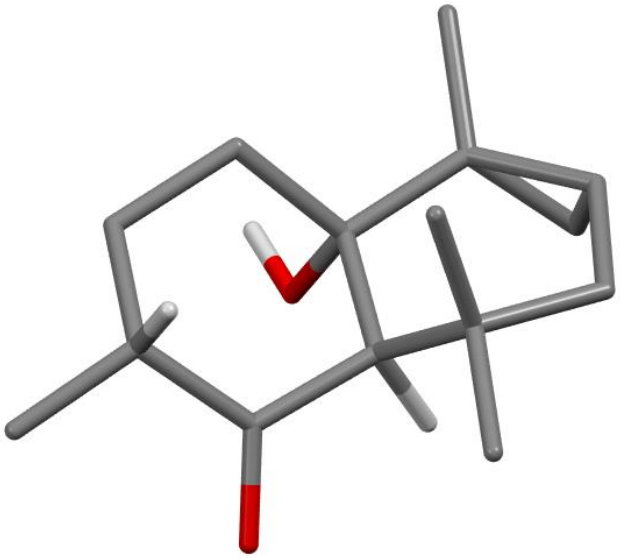


Figure 25. Crystal structure of synthetic 115a. Majority of the hydrogen atoms was omitted for clarity, except for OH and H6.

It was not possible to determine the actual structure of the natural product with certainty based on the NMR data provided by the isolation team due to some ambiguity in its interpretation. To begin with, they state a coupling between H4 and H6 with a magnitude of 1.0 Hz, which is not observed in our spectra and which they interpret as typical for cyclohexanones. If one were to interpret this as a W-type coupling, it might point towards a 4-*epi*-aldol product, with axial orientation of the methyl group at C4 (Figure 26). Still, in this case the characteristic W-type coupling between H6 and $H2_{eq}$ observed in our molecule should be expected, which is not reported for any of the compounds in the literature. The lack of this coupling could be explained if one

assumed a ring-flipped chair conformation of 4-*epi*-**115a**, resulting in equatorial orientation of the C4 methyl group. Notably, the coupling between H4 and H6 would then account for a $^4J_{H,H}$ diaxial coupling as it is also described in the cited literature[253].

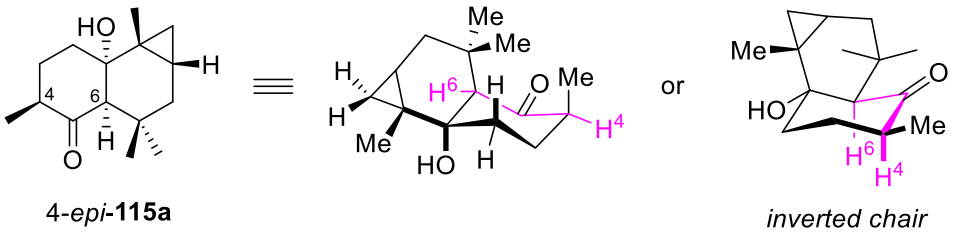


Figure 26. Suggestion for the actual structure of the isolated natural product bearing an inverted stereocentre at C4.

Interestingly, the isolation team also described this coupling for the *trans*-aldol product **115b** where there clearly is a diaxial correlation of H4 and H6, which would point towards H6 being axially oriented in the actual molecule. Simply changing the structure to the corresponding *trans*-decalin scaffold however seems unlikely as the literature-reported NMR data for the *trans*-aldol product, bearing a *trans*-decalin scaffold, shows significantly different values (see Table 25). Changing the orientation of the hydroxy group at C1 would result in a *cis*-aldol product again but of opposite orientation (1-*epi*-**115b**), which could explain the coupling between H6 and H7 ($^4J_{H,H}$ = 1.0 Hz) that is described in the literature but was not observed in our molecule (Figure 27).

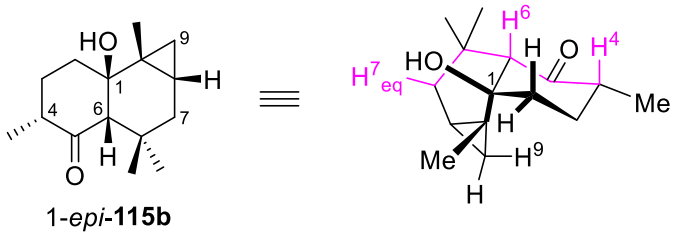


Figure 27. Suggestion for the actual structure of the isolated natural product with inverted stereochemistry at C1 and C6.

Another striking signal is the highly upfield shifted proton at the cyclopropyl ring at −0.09 ppm. Assuming this opposite *cis*-adol structure, the right hand part of the molecule most likely adopts a conformation in which the top of the cyclopropyl ring resides directly above the carbonyl group, which causes an anisotropic shielding. On the other hand, a deshielding of axially oriented protons compared to equatorial protons is a typical feature of cyclohexanones which can be seen for H4 and H6 in our NMR data (2.39 ppm versus 1.79 ppm). In the literature both H6 and H4 were reported with the same or very similar chemical shift for both the *cis*- and the *trans*-aldol isomer (2.39 and 2.38 ppm, respectively), hinting at both H4 and H6 being axially oriented. Furthermore, the characteristic W-type coupling between H6 and H2 that was observed in our molecule is not

described for any of the compounds in the literature, indicating that H6 is probably not equatorially oriented in the actual structure of the natural product.

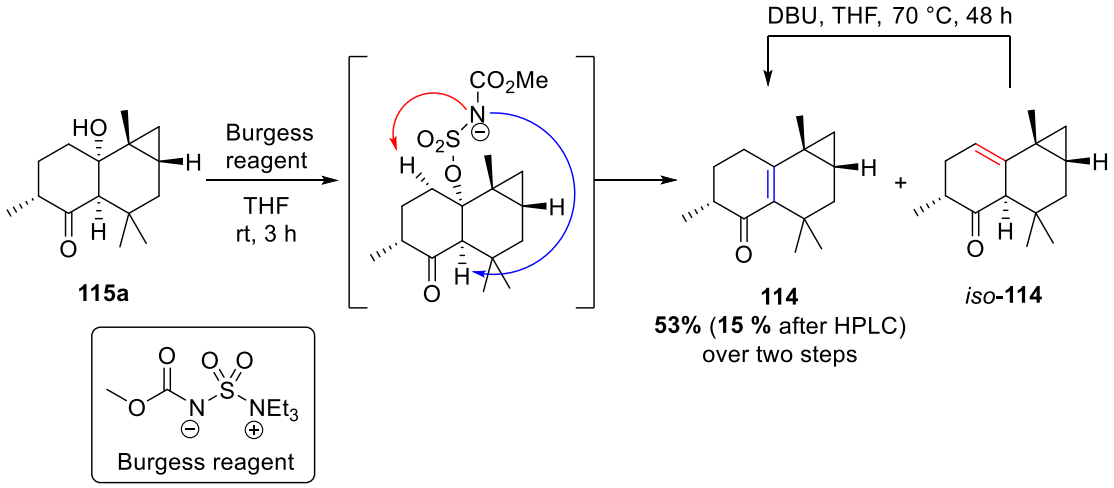
The structure of the actual natural product **115** cannot be determined with certainty for these reasons and due to a reported NOE correlation between H6 and H9, which would be highly unlikely in the case of structure 1-*epi*-**115b.** Besides, the assignment of H6 may not be correct to begin with. Both protons H6 and H4 are reported with the same chemical shift; however, H6 is claimed as a doublet, whereas in theory it should be a doublet of doublets, while H4 is reported as a multiplet. One of the H2 protons is also reported in a similar range, namely at 2.31 ppm; it may well be possible that either there was a misassignment of protons or that the observed NOE correlation originates from a different pair of protons than what was claimed.

All in all, based on the provided NMR data, the actual structure of the isolated compound cannot be assigned with certainty.

2.4.4.7 Synthesis of Lippifoli-1(6)-en-5-one

As previously mentioned, the dehydration product **114** was obtained in several of the aldol reactions, but only as a mixture of epimers at the C4 position which were inseparable *via* chromatography. In order to obtain pure, unepimerized lippifoli-1(6)-en-5-one (**114**), its synthesis was attempted in a stepwise manner from the isolated aldol addition product **115a**. Dehydration using Burgess reagent, which is specifically useful for *syn*-selective eliminations, proceeded cleanly. Unfortunately, two isomers were obtained in an approximately 1:3 ratio; the minor one being the desired natural product **114**, the major one most likely corresponding to the skipped enone *iso*-**114** originating from elimination of the proton on the opposite side of the alcohol (Scheme 81). Since it was not possible to separate the two isomers chromatographically, attempts were made to migrate the double bond into conjugation with the carbonyl group. This generally constitutes a rather straightforward transformation, as the conjugated enone is the thermodynamically favoured isomer and there are many sets of conditions to perform this transformation. However, in the present system there were some limitations in the choice of reagent. Transition metals and one-electron transfer processes were not feasible due to the risk of potentially opening the adjacent cyclopropane. For the same reason, any conditions that potentially resulted in the formation of a carbocation in α-position to the cyclopropane were avoided (*vide supra*). As this excluded Brønsted acids, a suitable base needed to be chosen to perform a base-promoted $E1_{cb}$ reaction. On the one hand, it needed to be small enough to be able to abstract the sterically hindered proton, on the other hand, the basicity had to be sufficiently mild to circumvent a possible epimerization of the carbonyl α-stereocentre. After unsuccessful attempts with neutral alumina, DMAP, quinuclidine or triethylamine, eventually an isomerization of the double bond could be observed with DBU at elevated temperatures. Only minor

epimerization of the α-carbonyl methyl group at C4 was observed. After purification and separation of the epimers by HPLC, lippifoli-1(6)-en-5-one **114** was successfully obtained. The comparably low yield, especially after HPLC separation, can, to a certain extent, be attributed to the volatility of the compound.



Scheme 81. Synthesis of lippifoli-1(6)-en-5-one 114 from 115a *via* Burgess dehydration and subsequent double bond isomerization.

The analytical data was in agreement with the literature[197a, 203] (Table 26). Notably, attempts to measure a specific rotation were unsuccessful, partially because of the small amount available (1 mg) but probably also because the reported value is very low ($[\alpha]_D^{20} = -0.12$, c = 0.85 in $CHCl_3$)[202]. The structure was confirmed based on comparison of the reported and experimental NMR data as well as characteristic NOE correlations (Figure 28).

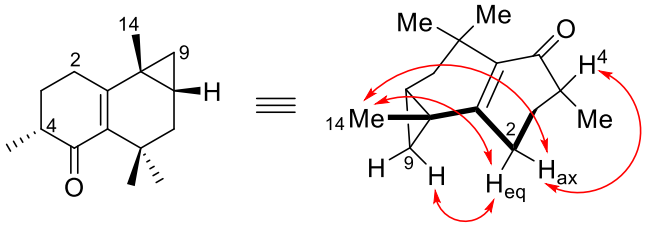
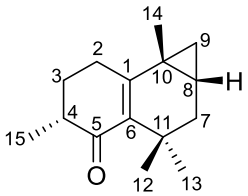
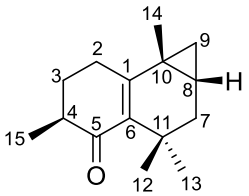


Figure 28. Structural analysis of synthetic 114 *via* NOESY NMR spectroscopy (NOE correlations indicated by red arrows).

Table 26. Comparison of NMR spectroscopic data of synthetic lippifoli-1(6)-en-5-one 114 with the reported literature values for 114 and 4-*epi*-114[197a, 203].



114



4-*epi*-114

Atom No.	δ_{exp} ^{1}H (1) [ppm][a]	δ_{Lit} ^{1}H (1) [ppm][b]	δ_{Lit} ^{1}H (2) [ppm][b]	δ_{exp} ^{13}C (1) [ppm][c]	δ_{Lit} ^{13}C (1) [ppm][d]	δ_{Lit} ^{13}C (2) [ppm][d]
1	-	-	-	160.3	160.2	158.4
2	2.45 2.34	2.45 2.33	2.64 2.27	28.8	28.7	26.5
3	1.50 1.97	1.50 1.96	2.02 1.66	30.3	30.2	30.7
4	2.19	2.18	2.38	42.6	42.4	41.8
5	-	-	-	201.5	201.4	202.6
6	-	-	-	140.2	140.0	140.3
7	1.86 1.14	1.85 1.24*	1.86 1.20*	43.6	43.5	43.5
8	1.09	1.1*	1.1*	19.2	19.1	19.5
9	0.27 0.83	0.27 0.83	0.31 0.84	26.4	26.3	26.8
10	-	-	-	20.6	20.4	19.8
11	-	-	-	33.7	33.5	33.7
12	1.17	1.18	1.20	29.0	27.5	28.2
13	1.19	1.17	1.14	27.6	28.9	28.6
14	1.19	1.18	1.22	23.0	22.8	23.2
15	1.12	1.11	1.08	16.8	16.7	15.3

All spectra were measured in $CDCl_3$. [a] 600 MHz. [b] 400 MHz, taken from ref [197a]. [c] 151 MHz. [d] 75.4 MHz, taken from ref [203]. *Literature[197a]: "obscured by intense methyl signals".

2.4.5 Conclusion

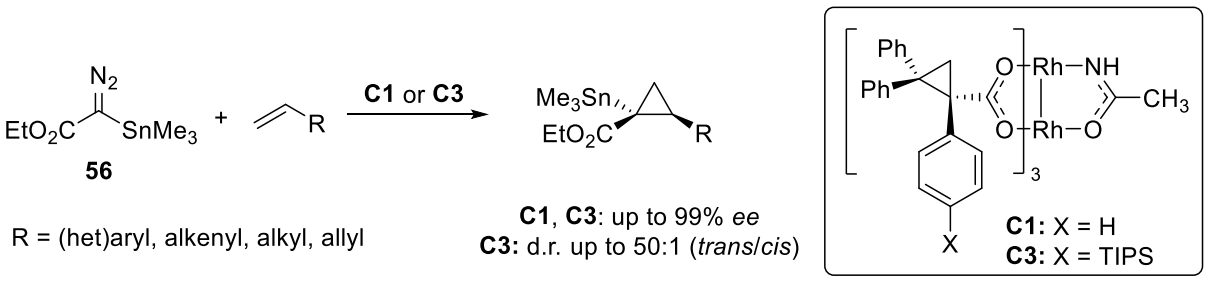
The natural product integrifolian-1,5-dione (**113**) was successfully prepared by a ring expansion strategy to form the ten-membered macrocycle. Furthermore, the *trans*-selective dirhodium catalyst ***ent*-C3** could once more be applied in a highly diastereoselective cyclopropanation, highlighting its distinct preference for terminal, monosubstituted olefins in presence of more

highly substituted alkenes. A hitherto unprecedented stereoretentive Stille cross coupling with methyl iodide as a challenging electrophile was successfully achieved. Using a transannular aldol reaction, another nominal natural product (**115a**) was obtained. However, this product was spectroscopically not in accord with the reported NMR data. With the structure of the synthesized compound unambiguously confirmed by NMR spectroscopy and X-ray diffraction analysis, the actual natural product structure remains elusive. Finally, through dehydration of the aldol reaction product, lippifoli-1(6)-en-5-one (**114**) was reached, another natural product of the integrifolian-1,5-dione family.

3 Summary

In this work, the synthesis and application of enantioenriched stannylated cyclopropanes has been investigated. Despite extensive research in the field of rhodium-catalyzed cyclopropanation, the enantioselective, intermolecular cyclopropanation of olefins involving α-stannylated diazoacetates had not previously been described outside of our group. It was desirable to close this gap and find a catalyst that could achieve this transformation, as the resulting optically active cyclopropylstannanes were deemed valuable potential building blocks for further modifications. This late-stage diversification approach would pose an advantage over established cyclopropanation methods, as it no longer requires a screening of different catalysts for each individually prepared diazo compound and could enable the synthesis of otherwise difficult to obtain enantioenriched cyclopropanes.

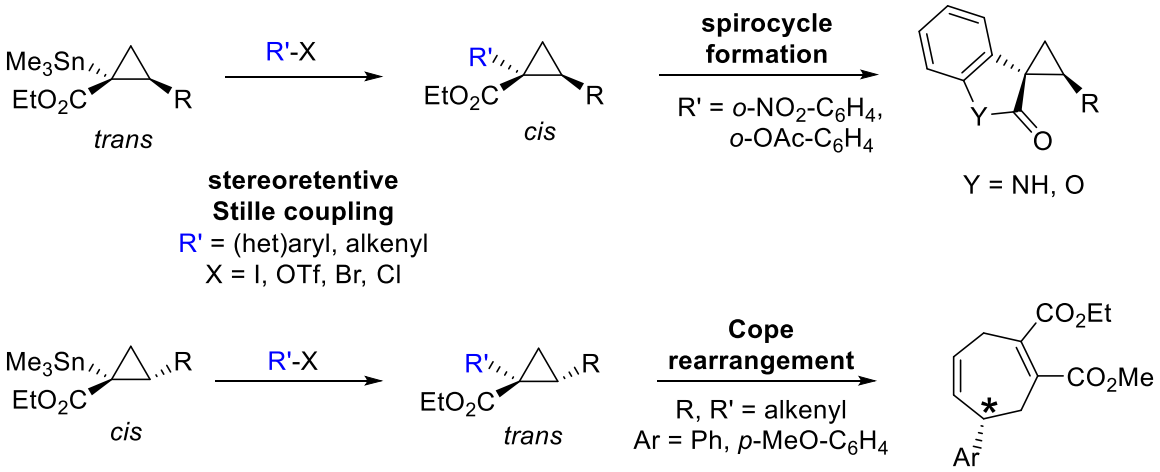
In this regard, a novel heteroleptic dirhodium catalyst was developed for the asymmetric synthesis of stannylated cyclopropanes (Scheme 82). A 1st generation catalyst **C1** provided high enantioselectivities even at low catalyst loadings of 0.05 mol%; a broad scope of olefinic substrates bearing various functional groups was successfully used. The catalyst could be further optimized with respect to diastereoselectivity in a process guided by DFT calculations. Thus, a 2nd generation of the catalyst (**C3**) was achieved, bearing an additional TIPS substituent on the ligands. The scope of the 1st generation catalyst could be reproduced and further expanded to a broad library of optically active cyclopropylstannanes with excellent diastereoselectivities of up to 50:1 (*trans*/*cis*) and up to 99 % *ee*.



Scheme 82. General overview of asymmetric cyclopropanation of olefins with diazo stannane 56 using 1st or 2nd generation dirhodium catalysts.

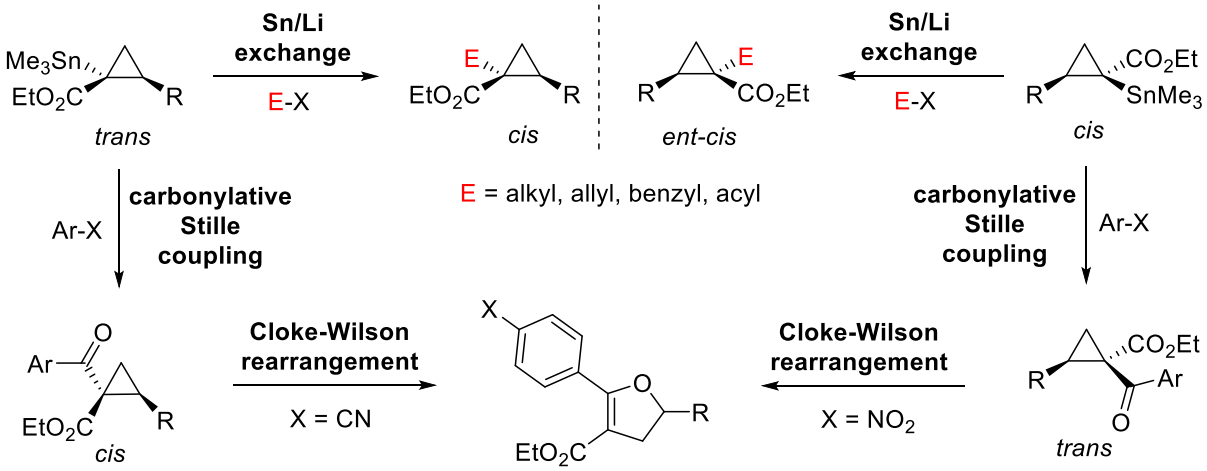
Investigating possible downstream modifications of the obtained enantioenriched cyclopropanes, a hitherto unprecedented Stille coupling of tertiary alkyl stannanes was achieved in a stereoretentive manner upon the formation of all-carbon quaternary stereocentres. The established protocol involved the use of $Pd_2(dba)_3$ and JackiePhos as ligand in combination with copper chloride and potassium fluoride as additives (Scheme 83). Various aryl and alkenyl electrophiles, including iodides, triflates, bromides and chloride, are amenable to the coupling

conditions enabling the synthesis of a diverse library of optically active cyclopropanes. A range of functional groups was tolerated, including certain heterocycles. Both *cis*-and *trans*-cyclopropylstannanes performed comparably well in the cross coupling, the only exception being more sterically hindered electrophiles such as *ortho*-substituted aryl halides. Some of the obtained cross coupling products could be further modified: Spirocyclic lactam and lactone derivatives were prepared and a tandem Stille-Cope reaction of *cis*-dialkenyl-substituted cyclopropanes yielded seven-membered rings.



Scheme 83. Overview of downstream diversification of cyclopropylstannanes *via* stereoretentive Stille coupling. *absolute configuration not determined, 97 % *ee.*

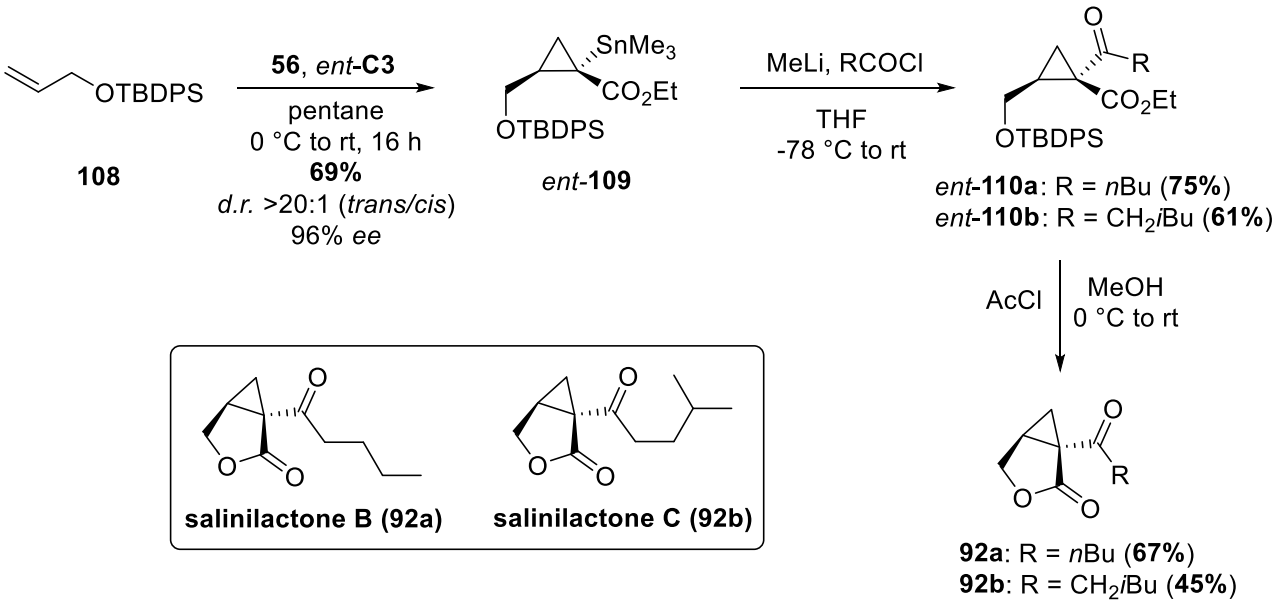
The stereoretentive Stille coupling was expanded to a carbonylative cross coupling by employing $Pd(PPh_3)_4$ instead of the $Pd_2(dba)_3$/JackiePhos catalyst system, resulting in formally acylated cyclopropanes. In some cases, a Cloke-Wilson rearrangement of the products was observed (Scheme 84).



Scheme 84. Further diversification of cyclopropylstannanes through tin-lithium exchange or carbonylative Stille coupling

Furthermore, tin-lithium exchange using methyllithium could successfully be carried out for the introduction of alternative substituents beyond what is feasible *via* (carbonylative) cross coupling. Despite the transient loss of one of the stereocentres during the reaction, the intermediate ester enolate can be trapped with several electrophiles in a diastereoselective fashion.

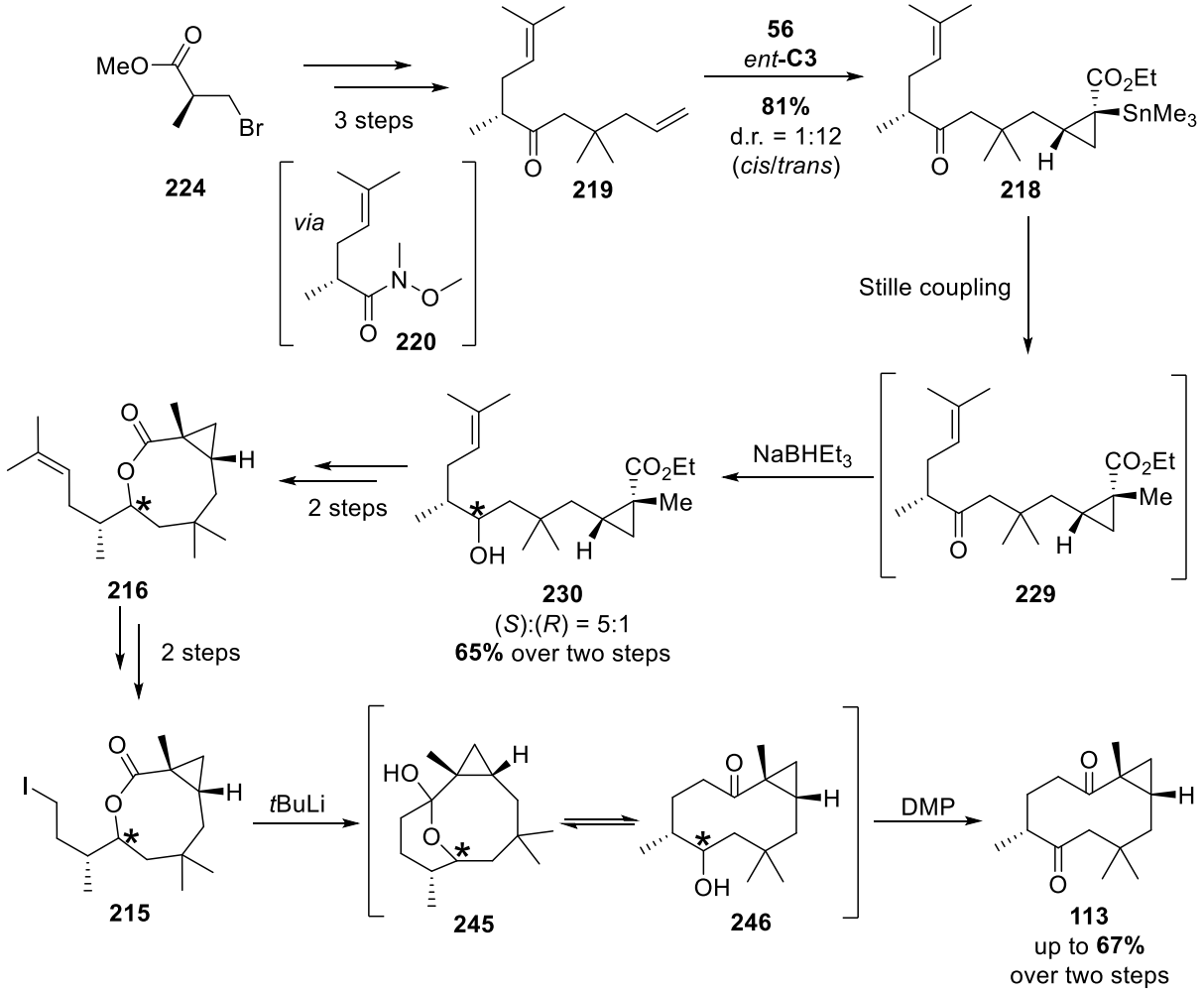
The methodology was successfully applied to the synthesis of different natural products. The first target was the family of salinilactones (**92**), isolated from *S. arenicola*, a species of marine actynomycete bacteria of the genus *Salinispora*. Eight congeners have been described so far which only deviate from one another in the alkyl side chain but all contain an unprecedented bicyclic [3.1.0]-lactone framework. Two members of the family, salinilactones B and C (**92a**, **92b**), were prepared over three steps in an overall yield of 36 and 19 %, respectively (Scheme 85). The asymmetric cyclopropanation of TBDPS-protected allylic alcohol **108** was carried out using dirhodium catalyst ***ent*-C3** to provide ***ent*-109** in high yield of 69 % with a d.r. of >20:1 (*trans*/*cis*) and outstanding enantioselectivity (96 % *ee*). For the introduction of the acyl side chain, the tin-lithium exchange protocol was utilized, which proceeded with excellent diastereoselectivity. With the synthesis of salinilactones, the advantage of our methodology to enable a late-stage diversification was highlighted as cyclopropylstannane ***ent*-109** represents a common intermediate towards all other members of the salinilactone family and potential non-natural derivatives.



Scheme 85. Synthetic route towards salinilactones B and C.

The second target was integrifolian-1,5-dione (**113**), a natural product isolated from *Lippia integrifolia*, a woody shrub native to Argentina. The structure contains a cyclopropane fused to a ten-membered ring, resulting in a bicyclo[8.1.0]undecane system. In the initial synthetic route, a

direct cyclization of an open chain structure to forge the ten-membered ring was attempted, but remained unsuccessful. A second approach was developed, following a ring expansion strategy (Scheme 86).

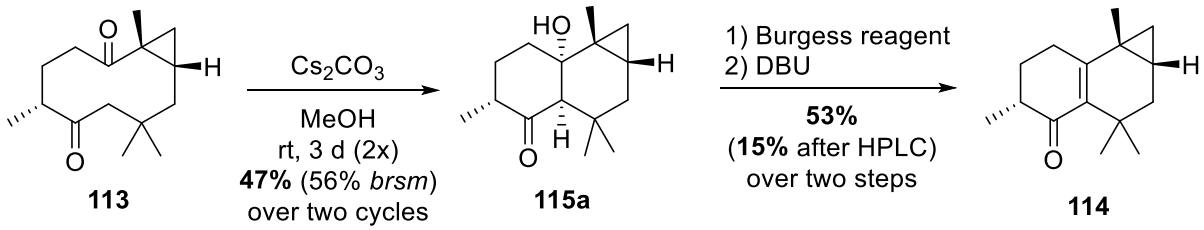


Scheme 86. Synthetic route towards integrifolian-1,5-dione 113. * (*S*)- and (*R*)-isomer were both carried forward in the synthesis.

Starting from the Roche ester derivative **224**, olefin **219** was prepared over three steps including Negishi coupling, formation of a Weinreb amide **220** and 1,2-addition of an alkyllithium derived from iodide **180**. The cyclopropanation was carried out using the 2nd generation dirhodium catalyst ***ent*-C3** and cyclopropane **218** was obtained in yields up to 81 % and a d.r. of 12:1 in favour of the desired *trans*-isomer. Subsequently, the challenging stereoretentive Stille coupling was successfully conducted using our previously established protocol, this time with methyl iodide as the electrophile. By delaying the purification of the cross coupling product until after the following ketone reduction, the removal of byproducts was facilitated and a yield of 65 % of **230** over two steps was achieved. Saponification and Yamaguchi esterification of the combined diastereoisomers led to lactones **216**, which could easily be separated at this stage *via* flash chromatography. Both isomers underwent functional group interconversion *via* ozonolysis

followed by a reductive quench and subsequent Appel reaction to obtain the alkyl iodides **215**. Upon treatment of iodides **215** with *tert*-butyllithium, a tricyclic hemiacetal **245** was formed in equilibrium with the respective bicyclic hydroxyketone tautomer **246**. Oxidation of this intermediate mixture with Dess-Martin periodinane resulted in the formation of integrifolian-1,5-dione (**113**) from both diastereoisomers in up to 67 % over the last two steps. In total, the route consisted of 16 steps (14 steps for the longest linear sequence) and afforded the natural product in approximately 10 % overall yield.

During the investigations towards the synthesis of lippifoli-1(6)-en-5-one (**114**), a transannular aldol reaction using cesium carbonate in methanol resulted in the formation of an addition product **115a**, which was allegedly another minor constituent of *L. integrifolia*. However, the spectroscopic data of the synthetic compound was not in accordance with the data reported in the literature. As our structure was unambiguously confirmed *via* X-ray diffraction analysis, the structure of the actual natural product must have been misassigned by the isolation team and remains elusive. A definite proposal for the actual structure could not be made based on the inconclusive NMR spectroscopic data reported in the literature. Eventually, dehydration of the aldol addition product using Burgess reagent followed by double bond isomerization with DBU resulted in the formation of lippifoli-1(6)-en-5-one (**114**, Scheme 87).



Scheme 87. Synthes of lippifoli-1(6)-en-5-one (114) from integrifolian-1,5-dione (113) over three steps.

Overall, a valuable tool for the diastereo- and enantioselective synthesis of cyclopropanes was established with the development of a new heteroleptic dirhodium complex followed by different protocols for various downstream modifications, including a stereoretentive Stille coupling of tertiary alkyl stannanes. A broad compound library was achieved involving otherwise difficult-to-prepare optically active cyclopropanes. The general applicability of the methodology was further highlighted by the successful total syntheses two different types of natural products: salinilactones B and C and integrifolian-1,5-dione.

4 Experimental Section

4.1 General Information

All reactions were conducted in flame-dried glassware under an argon atmosphere using anhydrous solvents, unless stated otherwise.

Purification of solvents was achieved by distillation over the indicated drying agents: THF, Et_2O (Mg/anthracene), CH_2Cl_2, DMPU (CaH_2), pentane, toluene (Na/K alloy), MeOH (Mg, stored over MS 3 Å). DMF, MeCN and Et_3N were dried by an adsorption solvent purification system based on molecular sieves.

For thin layer chromatography (TLC) pre-coated plates from Macherey-Nagel (POLYGRAM®SIL/UV254) were used. Visualization was carried out under UV-light (254 nm) and by staining with one of the following solutions: cerium ammonium molybdenate, basic $KMnO_4$. Flash chromatography was performed with Merck silica gel 60 (40 – 63 µm) with predistilled or HPLC grade solvents.

NMR spectra were recorded on Bruker AV 400, AVIII 600 or AVneo 600 spectrometres in the indicated solvents at 25 °C. Chemical shifts (δ) are given in ppm relative to TMS and coupling constants (J) in Hz. The (residual) solvent signals were used as references and the chemical shifts converted to the TMS scale ($CDCl_3$: δ_C = 77.2 ppm; residual $CHCl_3$: δ_H = 7.26 ppm; CD_2Cl_2: δ_C = 54.0 ppm; residual $CHDCl_2$: δ_H = 5.32 ppm; CD_3CN: δ_C = 1.3, 118.3 ppm; residual CD_2HCN: δ_H = 1.94 ppm). Multiplicities are indicated by the following abbreviations: s: singlet, d: doublet, t: triplet, q: quartet, p: pentet, h: hextet, hept: heptet, m: multiplet and combinations thereof. ^{13}C-NMR spectra were recorded with ^{1}H-decoupling and the chemical shift values are rounded to one decimal point. Signal assignments were accomplished *via* HSQC, HMBC, COSY, NOESY and other 2D experiments.

IR spectra were recorded on an Alpha Platinum ATR instrument (Bruker) and the wavenumbers ($\tilde{\nu}$) are given in cm^{-1}. Most weak and medium resonances were omitted.

MS (EI): Finnigan MAT 8200 (70 eV), ESI-MS: ESQ 3000 (Bruker); high resolution MS: Bruker APEX III FT-MS (7 T magnet) or MAT 95 (Finnigan); GC-MS: Shimadzu GCMS-QP2010 Ultra; GC: Agilent technologies 7890B with FID detector.

Optical rotations ($[\alpha]_D^{20}$) were measured with an A-Krüss Optronic Model P8000-t polarimeter at a wavelength of 589 nm.

Unless stated otherwise, all commercially available compounds (abcr, Acros, Sigma Aldrich, Alfa Aesar, FluoroChem, Strem Chemicals, TCI) were used as received.

4.2 Experimental Procedures

4.2.1 Synthesis of Dirhodium Catalysts

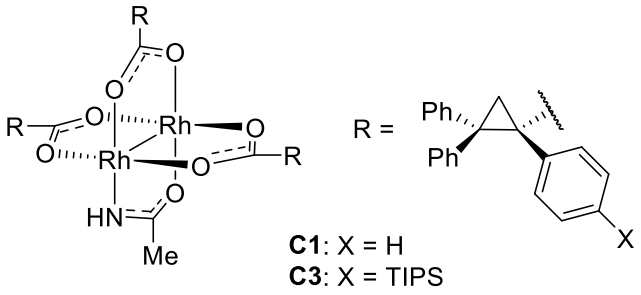
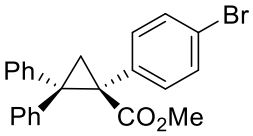
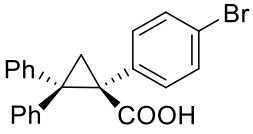


Figure 29. Compounds C1 and C3 were synthesised following literature protocols[134-135, 254].

Compound *ent*-Br-49: In a Schlenk flask, Rh_2-((*S*)-DOSP)$_4$ (25 mg, 0.013 mmol, 0.002 eq) and 1,1-diphenylethylene (3.0 mL, 17.0 mmol, 2.2 eq) were dissolved in pentane (150 mL) and the solution was cooled to -78°C. A solution of **Br-47** (2.0 g, 7.8 mmol, 1.0 eq) in pentane (10 mL) was added to the mixture in small portions over a course of 0.5 h. The mixture was warmed to room temperature and stirred overnight. The solvent was evaporated *in vacuo* and the crude product was purified *via* flash chromatography (SiO_2, hexanes/EtOAc 30:1 to 10:1). The obtained product was recrystallized from hexanes and the title compound was obtained as a white solid (2.0 g, 4.9 mmol, 63 %). $[\alpha]_D^{20}$ = 288.2° (c = 1.11, $CHCl_3$). **^{1}H-NMR** (400 MHz, $CDCl_3$): δ = 7.51 – 7.45 (m, 2H), 7.37 – 7.30 (m, 2H), 7.29 – 7.24 (m, 3H), 7.22 – 7.17 (m, 2H), 7.06 – 6.95 (m, 5H), 3.36 (s, 3H), 2.69 (d, *J* = 5.6 Hz, 1H), 2.40 (d, *J* = 5.7 Hz, 1H) ppm; **^{13}C{^{1}H}-NMR** (101 MHz, $CDCl_3$): δ = 171.1, 141.9, 139.4, 135.0, 133.7, 130.8, 130.0, 128.8, 128.5, 128.0, 127.2, 126.5, 121.3, 52.4, 44.8, 42.6, 22.9. **IR (ATR)**: $\tilde{\nu}$ [cm^{-1}] = 3024, 2947, 1720, 1489, 1447, 1432, 1304, 1214, 1140, 1074, 1009, 955, 871, 748, 694, 594, 531; **EI-MS**: *m/z* (%) = 406 (2), 347 (85), 295 (7), 268 (94), 191 (54), 165 (100), 126 (55); **HR-MS** (GC-EI): *m/z* calcd. for $[M]^+$: 406.0563, found: 406.0567.



Compound *ent*-Br-50: In a Schlenk tube, ***ent*-Br-49** (1.8 g, 4.4 mmol, 1.0 eq) was dissolved in THF (25 mL). A solution of KOTMS (5.0 g, 39.0 mmol, 8.8 eq) in THF (15 mL) was added and the mixture was stirred at room temperature overnight. Afterwards, it was cooled to 0°C and an aqueous solution of citric acid (2 M, 20 mL) was added. The mixture was kept stirring at 0°C for 0.5 h, then extracted with EtOAc (3x). The combined organic layers were washed with aq. HCl (2 M, 3x) and once with brine (30 mL), dried over $MgSO_4$, and the solvent was evaporated *in vacuo*. The title compound was obtained as a white solid without further purification (1.8 g, 4.5 mmol, quant., > 99.9 % *ee*). $[\alpha]_D^{20}$ = 221.6° (c = 1.03, $CHCl_3$); **^{1}H-NMR** (400 MHz, $CDCl_3$): δ = 7.46 (dd, *J* = 7.9 Hz, 1.6 Hz, 2H),



7.34 – 7.23 (m, 5H), 7.14 (d, *J* = 8.5 Hz, 2H), 7.04 – 6.93 (m, 5H), 2.58 (d, *J* = 5.6 Hz, 1H), 2.42 (d, *J* = 5.6 Hz, 1H) ppm; **^{13}C{^{1}H}-NMR** (101 MHz, $CDCl_3$): δ = 176.2, 141.4, 139.1, 134.5, 133.6, 130.8, 129.9, 128.7, 128.6, 128.0, 127.3, 126.7, 121.5, 46.0, 42.0, 23.4 ppm. **IR (ATR)**: $\tilde{\nu}$ [cm^{-1}] = 3024, 2854, 2620, 1686, 1489, 1411, 1302, 1238, 1074, 1011, 907, 864, 749, 693, 533; **ESI-MS**: *m/z* (%) = 785 (70, [2M-H]$^-$), 391 (49, [M-H]$^-$), 347 (100); **HR-MS** (ESI-neg): *m/z* calcd. for [M-H]$^-$: 391.03393, found: 391.03436.

The optical purity was determined by HPLC (Chiralcel OJ-3R, 4.6 mm i.D., methanol/water 85:15, 1.0 mL/min) **[t_R]** = 7.53 min (major), 9.64 min (minor).

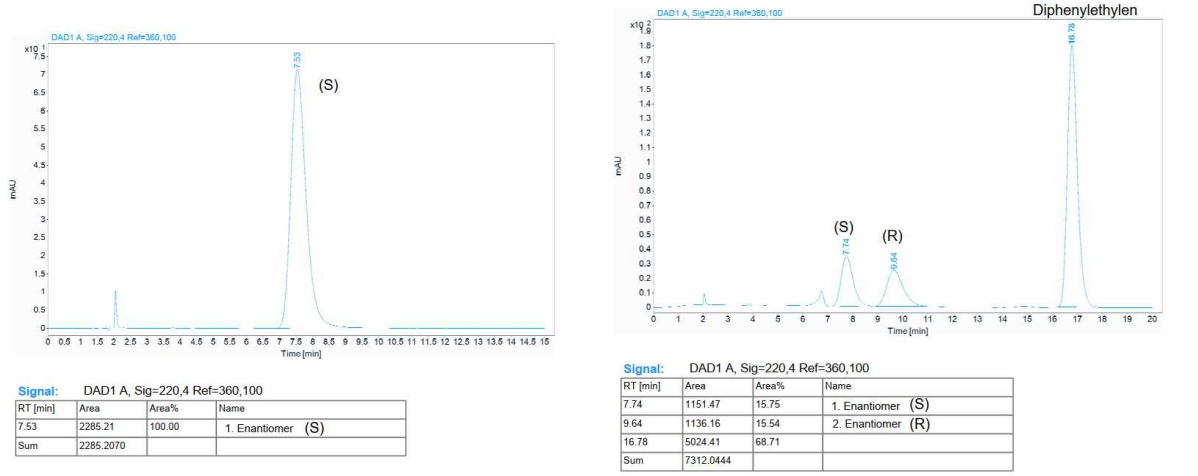
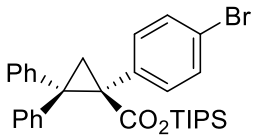


Figure 30. HPLC traces of enantioenriched *ent*-Br-50 (left) and racemic Br-50 (right).

Compound *ent*-66: In a Schlenk flask, ***ent*-Br-50** (1.57 g, 4.0 mmol, 1.0 eq) was dissolved in



CH_2Cl_2 (30 mL). A solution of imidazole (415 mg, 6.1 mmol 1.5 eq) in CH_2Cl_2 (10 mL) was added, followed by a dropwise addition of TIPSCl (1.2 mL, 5.61 mmol, 1.4 eq). The mixture was stirred at room temperature for 2 h. The reaction was quenched with water (20 mL), the layers were separated and the aqueous layer was extracted three times with MTBE. The combined organic layers were dried over $MgSO_4$ and the solvent was evaporated. The crude product was purified *via* flash chromatography (SiO_2, hexane/EtOAc 50:1) to obtain the title compound as a colourless, highly viscuous oil (2.07 g, 3.76 mmol, 94 %). $[\alpha]_D^{20}$ = 199.6° (c = 1.01, $CHCl_3$); **^{1}H-NMR** (400 MHz, $CDCl_3$): δ = 7.58 – 7.51 (m, 2H), 7.38 – 7.30 (m, 2H), 7.29 – 7.24 (m, 3H), 7.21 – 7.16 (m, 2H), 7.07 – 6.96 (m, 5H), 2.67 (d, *J* = 5.3 Hz, 1H), 2.42 (d, *J* = 5.3 Hz, 1H), 1.15 – 1.02 (m, 3H), 0.88 (dd, *J* = 10.4 Hz, 7.4 Hz, 18H) ppm; **^{13}C{^{1}H}-NMR** (101 MHz, $CDCl_3$): δ = 170.6, 141.7, 139.8, 136.2, 133.7, 130.7, 130.4, 128.8, 128.7, 127.9, 127.1, 126.4, 121.0, 45.2, 44.1, 24.0, 17.8, 17.7, 12.0 ppm. **IR (ATR)**: $\tilde{\nu}$ [cm^{-1}] = 3027, 2944, 2867, 1704, 1490, 1303, 1260, 1220, 1146, 1073, 1012, 883, 733, 694; **EI-MS**: *m/z* (%) = 550 (37, [M]), 507 (100), 426 (10), 376 (58), 348 (14), 295 (6), 268 (46),

252 (10), 191 (14), 165 (30), 115 (18); **HR-MS** (ESI-pos): *m/z* calcd. for $[M+Na]^+$: 571.16385, found: 571.16413.

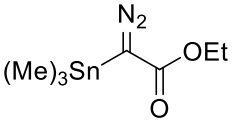
Compound *ent*-TIPS-50: In a Schlenk flask, ***ent*-66** (1.9 g, 3.46 mmol, 1.0 eq) was dissolved in THF (40 mL) and the solution was cooled to -78 °C. Then *tert*-butyllithium (1.7 M in pentane, 5.1 mL, 8.7 mmol, 1.5 eq) was added and the mixture was kept stirring at -78 °C for 15 min. Afterwards, TIPSCl (0.9 mL, 4.2 mmol, 1.2 eq) was added and the cooling bath was removed. The mixture was stirred at room temperature overnight. The reaction was quenched upon addition of a sat. aqueous solution of NH_4Cl. The aqueous layer was extracted three times with MTBE. The combined organic layers were washed once with brine, dried over $MgSO_4$ and the solvent was evaporated. The crude material was dissolved in THF (10 mL) and transferred into a round bottom flask. MeOH (40 mL) was added, followed by potassium fluoride (225 mg, 3.9 mmol, 1.1 eq) and the mixture was stirred at room temperature for 2 h. Then a sat. aqueous solution of NH_4Cl was added and the organic solvent was partially evaporated. The aqueous layer was then extracted with EtOAc (3x). The combined organic layers were washed once with brine, dried over $MgSO_4$, and the solvent was evaporated. The crude product was immobilized on Celite and purified *via* flash chromatography (SiO_2 hexane/EtOAc 10:1 to 3:1) to obtain the title compound as a light yellow solid (353 mg, 0.75 mmol, 22 %). $[\alpha]_D^{20}$ = 262.2° (c = 0.99, $CHCl_3$); **^{1}H-NMR** (400 MHz, $CDCl_3$): δ = 7.53 – 7.46 (m, 2H), 7.35 – 7.26 (m, 3H), 7.21 (d, *J* = 2.3 Hz, 4H), 6.92 – 6.81 (m, 5H), 2.59 (d, *J* = 5.6 Hz, 1H), 2.50 (d, *J* = 5.6 Hz, 1H), 1.29 (dq, *J* = 14.1 Hz, 7.4 Hz, 3H), 0.98 (dd, *J* = 7.5 Hz, 6.0 Hz, 18H) ppm; **^{13}C{^{1}H}-NMR** (101 MHz, $CDCl_3$): δ = 175.9, 141.5, 139.4, 135.5, 134.5, 133.4, 131.0, 130.2, 128.7, 128.6, 127.5, 127.2, 126.1, 45.7, 42.6, 23.3, 18.6, 18.6, 10.8 ppm. . **IR (ATR)**: $\tilde{\nu}$ [cm^{-1}] = 2942, 2864, 1689, 1450, 1251, 1014, 992, 882, 756, 702, 693, 678, 646; **EI-MS**: *m/z* (%) = 470 (23, [M]), 427 (100), 385 (37), 371 (23), 357 (58), 343 (27), 296 (30), 268 (14), 236 (19), 191 (27), 167 (23), 115 (17); **HR-MS** (ESI-neg): *m/z* calcd. for $[M-H]^-$: 469.25683, found: 469.25704.

Rh_2(acam)((*S*)-TIPS-TPCP)$_3$ (*ent*-C3): In a two neck flask equipped with a reflux condenser, $Rh_2(acam)_4$ (90 mg, 0.21 mmol, 1.0 eq) and ***ent*-TIPS-50** (295 mg, 0.63 mmol, 3.0 eq) were dissolved in chlorobenzene (30 mL). The solution was degassed for 15 min by bubbling argon through it. The mixture was then stirred at reflux temperature in an oil bath temperature of 140 °C for 8 h. After cooling to room temperature, the mixture was diluted with CH_2Cl_2 (10 mL) and washed with aq. NaOH (2 M, 3x), then with sat. aq. Na_2CO_3 and brine. The organic layer was then dried over $MgSO_4$ and the solvent evaporated. The crude product was immobilized on Celite and purified *via* flash chromatography

(SiO_2, toluene/MeCN 9:1 to 7:1 then hexane/EtOAc 5:1). The title compound was obtained as a green solid (115 mg, 0.067 mmol, 32 %). $[\alpha]_D^{20}$ = 159° (c = 0.1, $CHCl_3$); **^{1}H-NMR** (400 MHz, CD_3CN): δ = 7.41 – 6.64 (m, 57H), 3.73 (s, 1H), 2.36 (d, J = 5.3 Hz, 1H), 2.25 (d, J = 5.6 Hz, 1H), 2.02 (d, J = 5.1 Hz, 1H), 1.98 (d, J = 3.9 Hz, 1H), 1.80 (d, J = 5.6 Hz, 1H), 1.60 (d, J = 6.7 Hz, 4H), 1.47 – 1.23 (m, 15H), 1.13 – 0.91 (m, 73H) ppm; **^{13}C{^{1}H}-NMR** (101 MHz, CD_3CN): δ = 188.6, 186.1, 144.4, 144.0, 142.9, 142.8, 139.5, 139.2, 138.9, 135.0, 134.8, 134.6, 132.7, 132.5, 132.0, 131.5, 131.0, 130.6, 130.4, 130.1, 130.0, 128.8, 128.7, 128.3, 128.2, 128.0, 127.0, 126.8, 126.5, 126.4, 126.3, 126.1, 46.3, 44.2, 43.7, 25.1, 24.5, 23.6, 22.5, 19.0, 11.4; **IR (ATR)**: $\tilde{\nu}$ [cm^{-1}] = 3022, 2943, 2865, 1594, 1386, 882, 703; **ESI-MS**: *m/z* (%) = 1760 (38), 1696 (6, $[M+Na]^+$), 1690 (9, $[M+NH_4]^+$), 1672 (5, $[M]^+$), 506 (26), 474 (100), 441 (26), 409 (76); **HR-MS** (ESI-pos): *m/z* calcd. for $[M+Na]^+$: 1694.59836, found: 1694.59845.

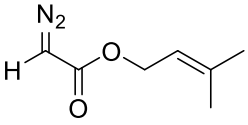
4.2.2 Synthesis of Stannylated Diazo Compounds

Ethyl 2-diazo-2-(trimethylstannyl)acetate (56): In a Schlenk flask, dimethylamino trimethyltin



(0.4 mL, 2.45 mmol) was diluted with diethyl ether (20 mL). Ethyl diazoacetate (6.4 M solution in CH_2Cl_2, 0.42 mL, 2.69 mmol) was then slowly added and the light yellow mixture was stirred at room temperature overnight. The diethyl ether was partly evaporated and the product was sublimed from the crude mixture at an oil bath temperature of 50°C with a Liebig condenser, which was cooled to -40°C. The sublimed yellow crystals were melted into a Schlenk flask and residues were rinsed from the condenser with diethyl ether (1 mL). The solvent was evaporated and the product further dried at high vacuum to give the title compound as yellow crystals (621 mg, 2.24 mmol, 91 %). **^{1}H-NMR** (400 MHz, CD_2Cl_2): δ = 4.12 (q, J = 7.1 Hz, 2H), 1.23 (t, J = 7.1 Hz, 3H), 0.38 (m, 9H) ppm; **^{13}C{^{1}H}-NMR** (101 MHz, CD_2Cl_2): δ = 61.1, 14.8, 1.3, -7.7 ppm; **^{119}Sn{^{1}H}-NMR** (149 MHz, CD_2Cl_2): δ = 25.5 ppm; **IR (ATR)**: $\tilde{\nu}$ [cm^{-1}] = 2984, 2911, 2871, 2321, 2109, 2067, 1665, 1464, 1444, 1395, 1365, 1350, 1272, 1169, 1112, 1044, 873, 772, 741, 556, 537, 508, 464, 416. The analytical data is consistent with the literature[138b].

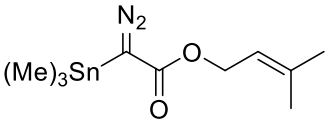
3-Methylbut-2-en-1-yl 2-diazoacetate (14): In a Schlenk flask, NaHMDS (2.37 g, 12.9 mmol)



was dissolved in THF (100 mL) and the solution cooled to -78°C. Then prenyl acetate (1.6 mL, 11.5 mmol) was added dropwise to the mixture. It was stirred at the same temperature for 40 min. 2,2,2-Trifluoroethyl trifluoroacetate (1.75 mL, 13.07 mmol) was added and the mixture was kept stirring at -78°C for 1 h. The cooling bath was removed and deionized water (3 mL) was added. After 10 min, acetonitrile (10 mL) was added, followed by a solution of *p*-ABSA, (2.76 g, 11.5 mmol) in acetonitrile (10 mL) and trimethylamine (6.4 mL, 45.9 mmol). The mixture was stirred at room

temperature overnight. It was concentrated, then diluted with diethyl ether (20 mL) and quenched with aq. NaOH (10 %, 30 mL). The aqueos layer was extracted with diethyl ether (3x). The combined organic layers were washed with brine, dried over Na_2SO_4, and the solvent was evaporated. The crude product was purified *via* flash chromatography (SiO_2, gradient of 0 to 10 % diethyl ether in hexane). The title compound was obtained as a yellow oil (1.09 g, 7.04 mmol, 61 %). **^{1}H-NMR** (400 MHz, $CDCl_3$): δ = 5.36 – 5.31 (m, 1H), 4.73 (s, 1H), 4.65 (d, J = 7.2 Hz, 2H), 1.75 (s, 3H), 1.71 (s, 3H) ppm; **^{13}C{^{1}H}-NMR** (101 MHz, $CDCl_3$): δ = 167.1, 139.5, 118.7, 61.8, 46.3, 25.9, 18.1 ppm; **IR (ATR)**: $\tilde{\nu}$ [cm^{-1}] = 3111, 2973, 2936, 2916, 2104, 1686, 1444, 1386, 1356, 1342, 1274, 1234, 1173, 1062, 1047, 996, 964, 915, 839, 780, 739, 637, 552, 460, 432; **GC-MS** [t_R] = 7.07 min, *m/z* (%) = 154 ([M], < 1), 125 (3), 111 (21), 81 (28), 69 (59), 53 (21), 41 (100). The analytical data is consistent with the literature[255].

3-Methylbut-2-en-1-yl 2-diazo-2-(trimethylstannyl)acetate (61): In a Schlenk flask, dimethylamino trimethyltin (0.1 mL, 0.61 mmol) was diluted with diethyl ether (5 mL). Compound **14** (100 mg, 0.65 mmol) was slowly added and the light yellow mixture was stirred at room temperature overnight. The solvent was then partially evaporated and the crude product was directly used in the following cyclopropanation (*vide infra*). **^{1}H-NMR** (400 MHz, CD_2Cl_2): δ = 5.34 – 5.29 (m, 1H), 4.56 (d, J = 7.2 Hz, 2H), 1.74 (s, 3H), 1.69 (s, 3H), 0.35 (s, 9H) ppm; **^{13}C{^{1}H}-NMR** (101 MHz, CD_2Cl_2): δ = 171.2, 139.1, 119.6, 62.0, 26.0, 18.3, 1.4, -7.7 ppm; **^{119}Sn{^{1}H}-NMR** (149 MHz, CD_2Cl_2): δ = 25.9 ppm; **IR (ATR)**: $\tilde{\nu}$ [cm^{-1}] = 3122, 2977, 2916, 2107, 1688, 1618, 1543, 1444, 1388, 1357, 1237, 1178, 1047, 1001, 916, 840, 776, 741, 545, 514, 461, 433; **GC-MS** [t_R] = 11.70 min, *m/z* (%) = 275 (43), 231 (27), 165 (100), 135 (37), 81 (60), 41 (53).



4.2.3 Cyclopropanation Reactions

Representative procedure for cyclopropanations with Rh_2(acam)((*R*)-TPCP)$_3$ (C1):

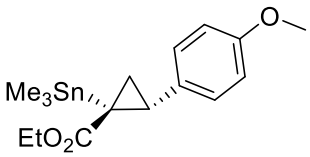
Compound 57b. In a Schlenk flask, complex **C1** (0.001 M in CH_2Cl_2, 0.74 mL, 0.74 µmol) was freed from solvent through heating under reduced pressure and dissolved in CH_2Cl_2 (25 mL). Then *p*-methoxy styrene (1.0 mL, 7.43 mmol) was added. A solution of diazo stannane **56** (411 mg, 1.48 mmol) in CH_2Cl_2 (4 mL) was slowly added to the mixture over a course of 6 h *via* a syringe pump and the mixture was kept stirring at room temperature for 12 h. The solvent was removed and the crude product was purified *via* flash chromatography (SiO_2, hexane/EtOAc 50:1 to 4:1). The title compound was obtained as a mixture of two diastereomers (*cis*/*trans* = 1:1, ^{1}H-NMR) as a colourless oil (444 mg, 78 % combined yield).

Representative procedure for cyclopropanations with Rh_2(acam)((*R*)-TIPS-TPCP)$_3$ (C3):

Compound 57b: In a cooling Schlenk flask, complex **C3** (4 mg, 2.39 µmol) was dissolved in pentane (8 mL). *p*-Methoxy styrene (0.35 mL, 2.63 mmol) was added and the mixture was cooled to – 20 °C. A solution of diazo stannane **56** (146 mg, 0.53 mmol) in pentane (4 mL) was added to the reaction mixture within 1 min and it was kept stirring at – 20 °C until full consumption of the diazo compound was observed by TLC. After warming to room temperature, the solvent was evaporated and the crude product was purified *via* flash chromatography (SiO_2, hexane/EtOAc 50:1 to 5:1). The title compound was obtained as a mixture of two diastereomers (*cis*/*trans* < 1:20, ^{1}H-NMR) as a colourless oil (166 mg, 82 %).

The racemic samples used as a reference to determine the enantiomeric excess were synthesized analogously using achiral $Rh_2(esp)_2$ as catalyst. The relative stereochemistry was assigned *via* ^{1}H,^{1}H-NOESY spectra.

***cis*-(57b):** colourless oil (with **C1**: 243 mg, 43 %, 99 % *ee*). $[\alpha]_D^{20}$ = 54.1° (c = 0.92, $CHCl_3$);



^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.16 – 7.11 (m, 2H), 6.82 – 6.77 (m, 2H), 4.13 (qd, *J* = 7.2 Hz, 4.0 Hz, 2H), 3.78 (s, 3H), 2.72 – 2.62 (m, 1H), 1.77 – 1.66 (m, 1H), 1.29 – 1.26 (m, 4H), -0.17 (s, 9H) ppm; **^{13}C{^{1}H}-NMR** (101 MHz, $CDCl_3$): δ = 137.3, 158.6, 132.1, 130.7, 113.7, 61.0, 55.4, 30.3, 21.2, 16.7, 14.4, -8.4 ppm; **^{119}Sn{^{1}H}-NMR** (149 MHz, $CDCl_3$): δ = 3.8 ppm; **IR (ATR)**: $\tilde{\nu}$ [cm^{-1}] = 3067, 3035, 2981, 2934, 2909, 2836, 1707, 1611, 1579, 1514, 1463, 1442, 1370, 1301, 1226, 1171, 1127, 1111, 1082, 1033, 968, 950, 893, 834, 806, 767, 722, 677, 560, 529, 513; **ESI-MS**: *m/z* (%) = 791 (31, $[2M+Na]^+$), 407 (100, $[M+Na]^+$), 369 (24), 323 (33), 293 (12); **HR-MS** (ESI-pos): *m/z* calcd. for $[M+Na]^+$: 407.06396, found: 407.06399.

The optical purity was determined by HPLC (Chiralpak IG-3, 3 µm, 4.6 mm i.D., *n*-heptane/isopropanol 98:2, 1 mL/min, 20 min) **[t_R]** = 3.3 min (major), 3.8 min (minor).

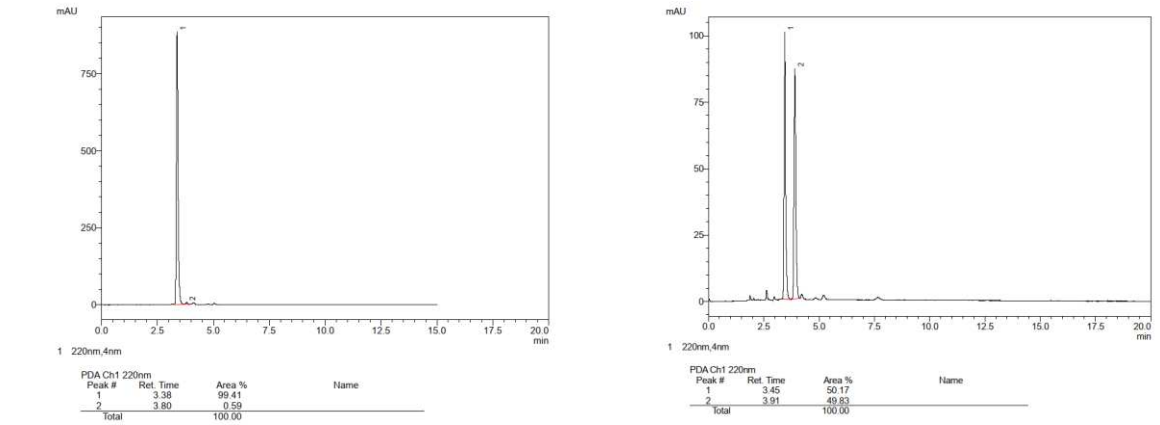
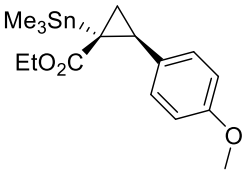


Figure 31. HPLC traces of enantioenriched *cis*-57b (left) and racemic *cis*-57b (right).

***trans*-(57b):** colourless oil (with **C1:** 201 mg, 35 %, 96 % *ee*; with **C3:** 166 mg, 82 %, 98 % *ee*).



$[\alpha]_D^{20}$ = −95.1° (c = 1.27, $CHCl_3$). **^{1}H-NMR** (400 MHz, $CDCl_3$): δ = 7.14 – 7.07 (m, 2H), 6.81 – 6.74 (m, 2H), 3.86 – 3.70 (m, 5H), 2.43 – 2.23 (m, 1H), 1.96 – 1.84 (m, 1H), 1.24 – 1.08 (m, 1H), 0.94 (t, *J* = 7.1 Hz, 3H), 0.19 (s, 9H) ppm; **^{13}C{^{1}H}-NMR** (101 MHz, $CDCl_3$): δ = 174.0, 158.3, 129.9, 129.7, 113.4, 60.4, 55.3, 27.9, 21.8, 14.3, 14.0, -9.6 ppm; **^{119}Sn{^{1}H}-NMR** (149 MHz, $CDCl_3$): δ = 23.0 ppm; **IR (ATR)**: $\tilde{\nu}$ [cm^{-1}] = 3059, 3033, 2979, 2908, 2835, 1711, 1689, 1612, 1583, 1513, 1462, 1443, 1388, 1364, 1282, 1246, 1206, 1177, 1165, 1113, 1080, 1035, 976, 836, 766, 731, 679, 562, 530, 512; **ESI-MS**: *m/z* (%) = 791 (29, $[2M+Na]^+$), 423 (5, $[M+K]^+$), 407 (100, $[M+Na]^+$), 369 (24), 323 (29), 293 (15); **HR-MS** (ESI-pos): *m/z* calcd. for $[M+Na]^+$: 407.06396, found: 407.06391.

The optical purity was determined by HPLC (Chiralpak IG-3, 3 µm, 4.6 mm i.D., *n*-heptane/isopropanol 98:2, 1 mL/min, 20 min) **[t_R]** = 5.0 min (major), 7.8 min (minor).

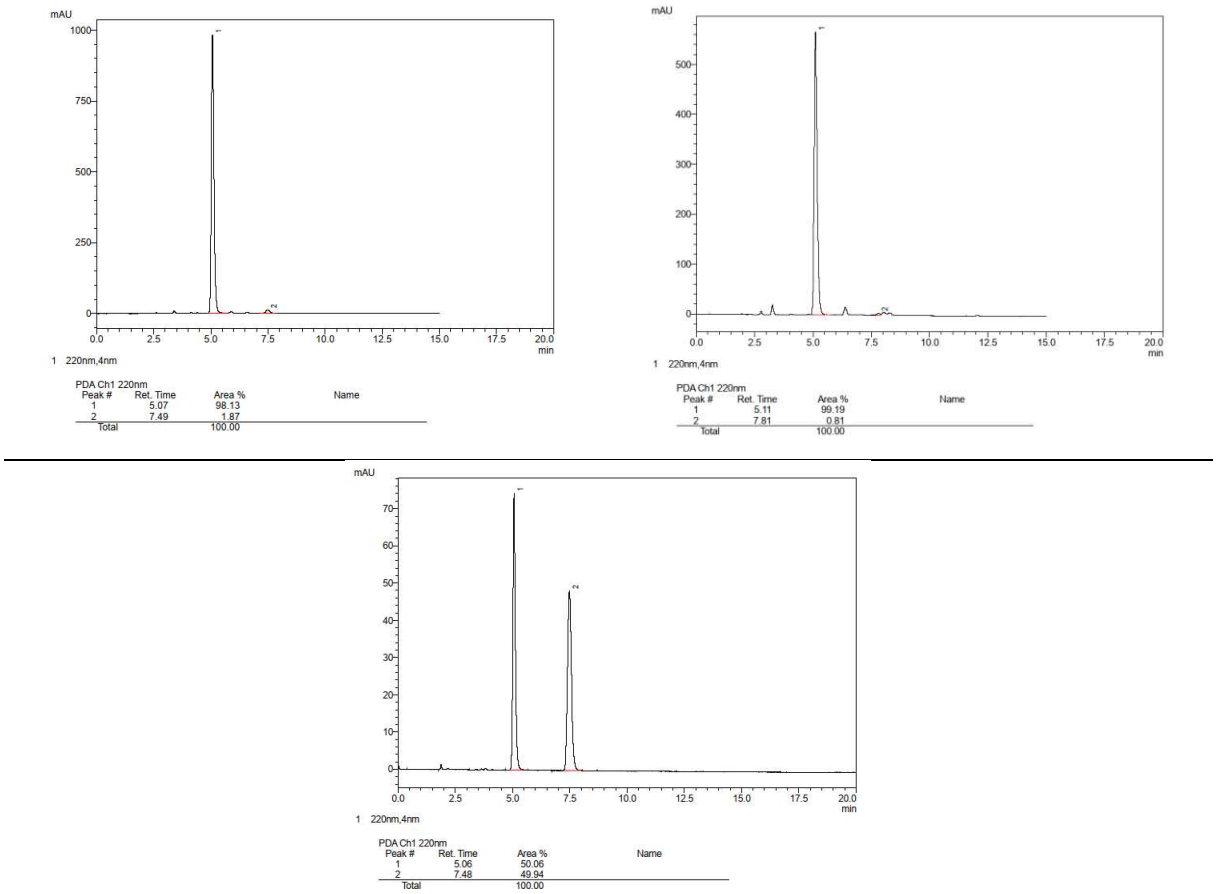
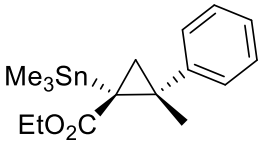


Figure 32. HPLC traces of enantioenriched *trans*-57b from C1 (top left), from C3 (top right), and racemic *trans*-57b (bottom).

The following compounds were prepared analogously to **57b**. Analytical data of compounds that were solely synthesized by Dr. Fabio Caló are reported in the literature[134, 254].

Compound 57d: Prepared according to the representative procedure for cyclopropanations using complex **C1** (73 mg, 51 % combined yield, *cis*/*trans* = 1:1, ^{1}H-NMR) or **C3** (28 mg, 21 % combined yield, *cis*/*trans* = 1:2, ^{1}H-NMR). Partial separation of the diastereomers for analytical purposes could be achieved *via* flash chromatography (fine silica, hexane/EtOAc 100:1).



***cis*-(57d):** colourless liquid (with **C1**: 96 % *ee*; with **C3**: 83 % *ee*). $[\alpha]_D^{20}$ = 2.6° (c = 1.0, $CHCl_3$); **^{1}H-NMR** (400 MHz, $CDCl_3$): δ = 7.30 – 7.21 (m, 4H), 7.19 – 7.14 (m, 1H), 4.21 – 4.05 (m, 2H), 1.50 (d, J = 4.7 Hz, 1H), 1.38 (s, 3H), 1.33 (d, J = 4.7 Hz, 1H), 1.27 (t, J = 7.1 Hz, 3H), -0.25 (s, 9H) ppm; **^{13}C{^{1}H}-NMR** (101 MHz, $CDCl_3$): δ = 175.4, 146.0, 128.8, 128.5, 126.8, 60.7, 32.5, 28.6, 23.7, 20.5, 14.8, -8.7 ppm; **^{119}Sn{^{1}H}-NMR** (149 MHz, $CDCl_3$): δ = 12.1 ppm; **IR (ATR)**: $\tilde{\nu}$ [cm^{-1}] = 3059, 3026, 2980, 2924, 2872, 1711, 1602, 1496, 1446, 1381, 1365, 1341, 1215, 1197, 1114, 1098, 1067, 1021, 879, 862, 765, 702, 529, 513; **EI-MS**: *m/z* (%) = 353 (76), 307 (96), 292 (18), 277 (38), 249 (3), 195 (3),

165 (100), 157 (38), 141 (35), 129 (96), 115 (52), 91(23), 77 (20), 65 (6), 51 (9); **HR-MS** (ESI-pos): *m/z* calcd. for $[M+Na]^+$: 391.06898 , found: 391.06932.

The optical purity was determined by HPLC (Chiralcel OJ-3R, 150 mm, 4.6 mm i.D., methanol/water 70 % to 90 %, 1.0 mL/min) **[t_R]** = 8.78 min (major), 10.67 min (minor).

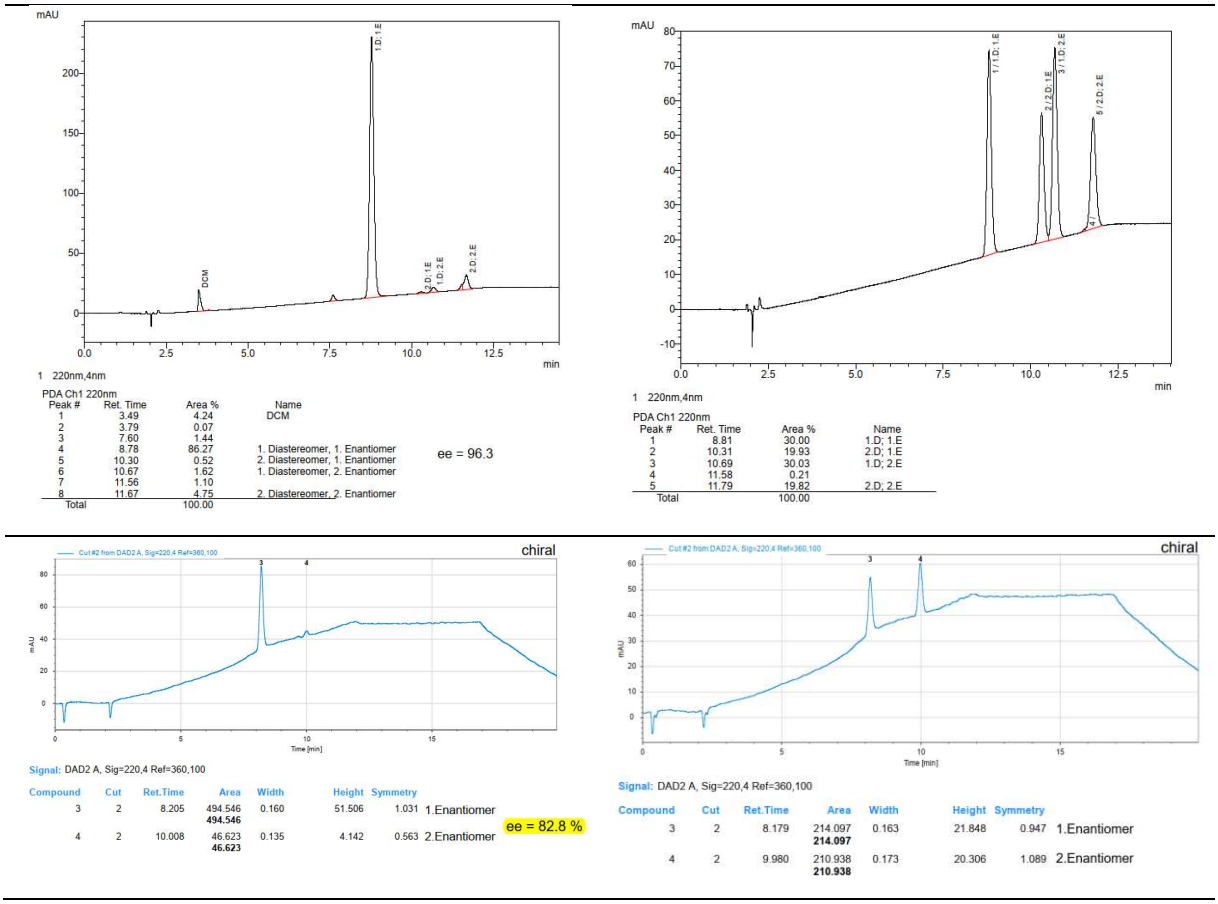
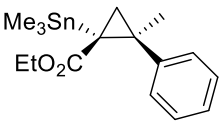


Figure 33. HPLC traces of enantioenriched *cis*-57d from C1 (top left) and from C3 (bottom left), of racemic diastereomeric mixture of *cis*-57d and *trans*-57d (top right) and racemic *cis*-57d (bottom right).

***trans*-(57d):** colourless liquid (with **C1**: 95 % *ee*; with **C3**: 97 % *ee*). $[\alpha]_D^{20}$ = −20.8° (c = 0.99, $CHCl_3$); **^{1}H-NMR** (600 MHz, $CDCl_3$): δ = 7.31 – 7.22 (m, 4H), 7.18 – 7.13 (m, 1H), 3.69 (qq, $J_{H,H}$ = 10.8 Hz, 7.1 Hz, 2H), 2.06 (d, J = 4.7 Hz, 1H), 1.49 (s, 3H), 1.00 (d, J = 4.7 Hz, 1H), 0.93 (t, J = 7.1 Hz, 3H), 0.26 (s, 9H) ppm; **^{13}C{^{1}H}-NMR** (101 MHz, $CDCl_3$): δ = 174.3, 143.2, 128.7, 128.1, 126.5, 60.4, 33.7, 29.1, 28.4, 21.0, 14.2, -7.6 ppm; **^{119}Sn{^{1}H}-NMR** (149 MHz, $CDCl_3$): δ = 7.8 ppm; **IR (ATR)**: $\tilde{\nu}$ [cm^{-1}] = 3059, 3026, 2978, 2924, 2871, 1716, 1687, 1602, 1496, 1445, 1377, 1365, 1289, 1272, 1206, 1193, 1114, 1091, 1066, 1025, 864, 764, 699, 553, 528, 511; **EI-MS**: *m/z* (%) = 353 (64), 307 (68), 277 (28), 249 (3), 203 (3), 165 (100), 149 (68), 141 (29). 135 (45), 129 (86), 115 (48), 91 (18), 77 (19), 51 (8); **HR-MS** (ESI-pos): *m/z* calcd. for $[M+Na]^+$: 391.06898, found: 391.06915.



The optical purity was determined by HPLC (Chiralcel OJ-3R, 150 mm, 4.6 mm i.D., methanol/water 70 % to 90 %, 1.0 mL/min) **[t_R]** = 10.31 min (major), 11.79 min (minor).

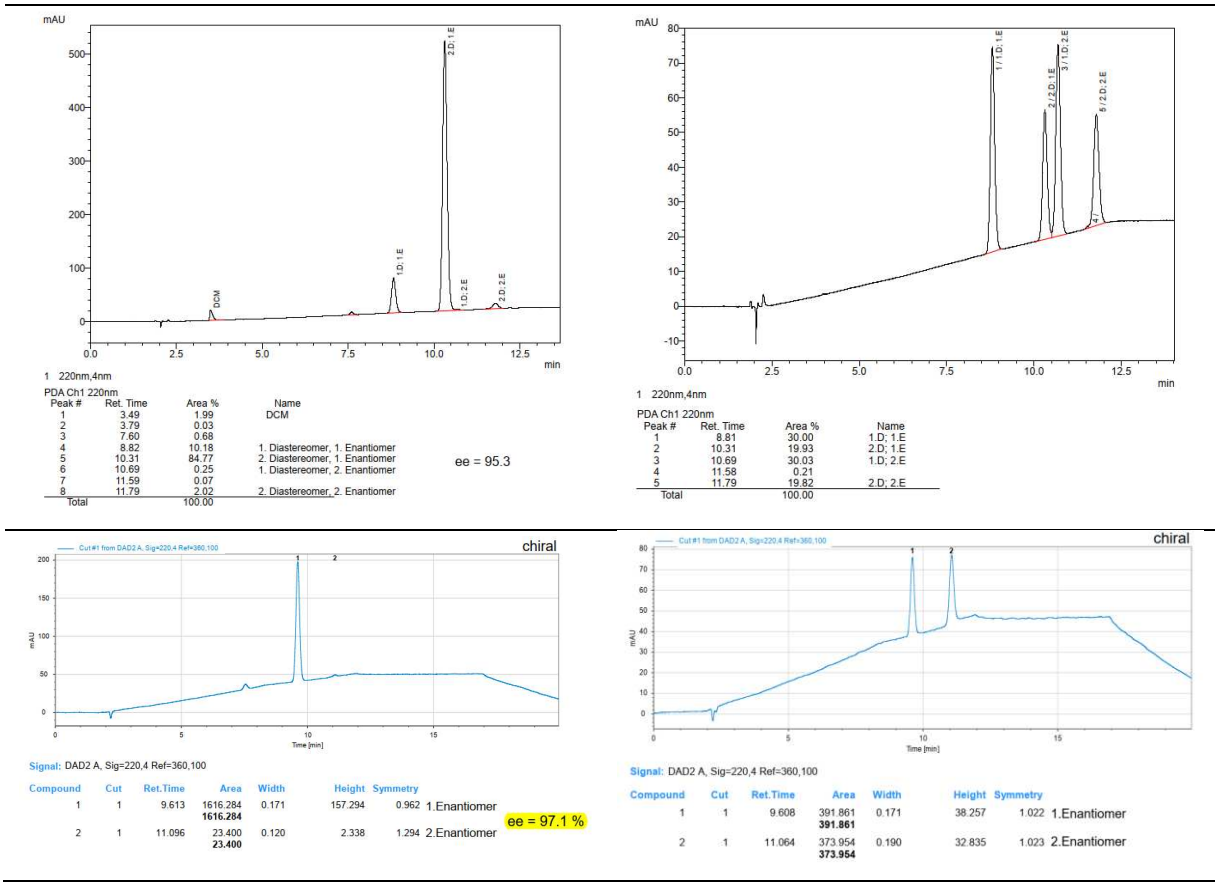


Figure 34. HPLC traces of enantioenriched *trans*-57d from C1 (top left) and from C3 (bottom left), of racemic diastereomeric mixture of *cis*-57d and *trans*-57d (top right) and racemic *trans*-57d (bottom right).

Compound 57i: Prepared according to the representative procedure for cyclopropanations using complex **C1** (152 mg, 78 % combined yield, *cis*/*trans* = 1:1, ^{1}H-NMR) or **C3** (25 mg, 23 % combined yield, *cis*/*trans* = 1:5, ^{1}H-NMR). No clean separation of diastereomers possible, assignment of NMR signals was accomplished based on different integrative ratio due to slight excess of one isomer in both experiments.

***cis*-(57i) and *trans*-(57i):** colourless liquid. **IR (ATR)**: $\tilde{\nu}$ [cm^{-1}] = 2981, 2916, 1710, 1447, 1366, 1276, 1234, 1208, 1188, 1169, 1116, 1047, 1025, 959, 840, 766, 527, 511; **EI-MS**: *m/z* (%) = 303 (70), 275 (19), 257 (32), 227 (67), 195 (12), 165 (100), 150 (68), 135 (40), 91 (9), 79 (24); **HR-MS** (GC-CI): *m/z* calcd. for [M+H]$^+$: 319.07145, found: 319.07101.

***cis*-(57i):** (with **C1**: 96 % *ee*; with **C3**: 98 % *ee*). **^{1}H-NMR** (400 MHz, $CDCl_3$): δ = 5.68 – 5.56 (m, 1H + *trans*-isomer), 5.14 (ddd, *J* = 15.1 Hz, 7.6 Hz, 1.6 Hz, 1H), 4.16 – 4.00 (m, 2H + *trans*-isomer), 2.01 – 1.92 (m, 1H), 1.65 (dd, *J* = 6.6 Hz, 1.6 Hz, 3H + *trans*-isomer), 1.60 (dd, *J* = 8.6 Hz, 4.1 Hz, 1H), 1.25 – 1.20 (m, 3H + *trans*-isomer), 0.90 (dd,

J = 6.1 Hz, 4.1 Hz, 1H), 0.13 (s, 9H + *trans*-isomer) ppm; **^{13}C{^{1}H}98-NMR** (101 MHz, $CDCl_3$): δ = 177.0, 131.3, 127.7, 60.9, 29.4, 20.2, 18.0, 17.9, 16.6, 14.4, -7.8 ppm; **^{119}Sn{^{1}H}-NMR** (149 MHz, $CDCl_3$): δ = 4.5 ppm.

The optical purity was determined by HPLC (Chiralpak AS-3R, 150 mm, 4.6 mm i.D, acetonitrile/water 45:55, 1.0 mL/min) **[t_R]** = 18.10 min (major), 19.60 min (minor).

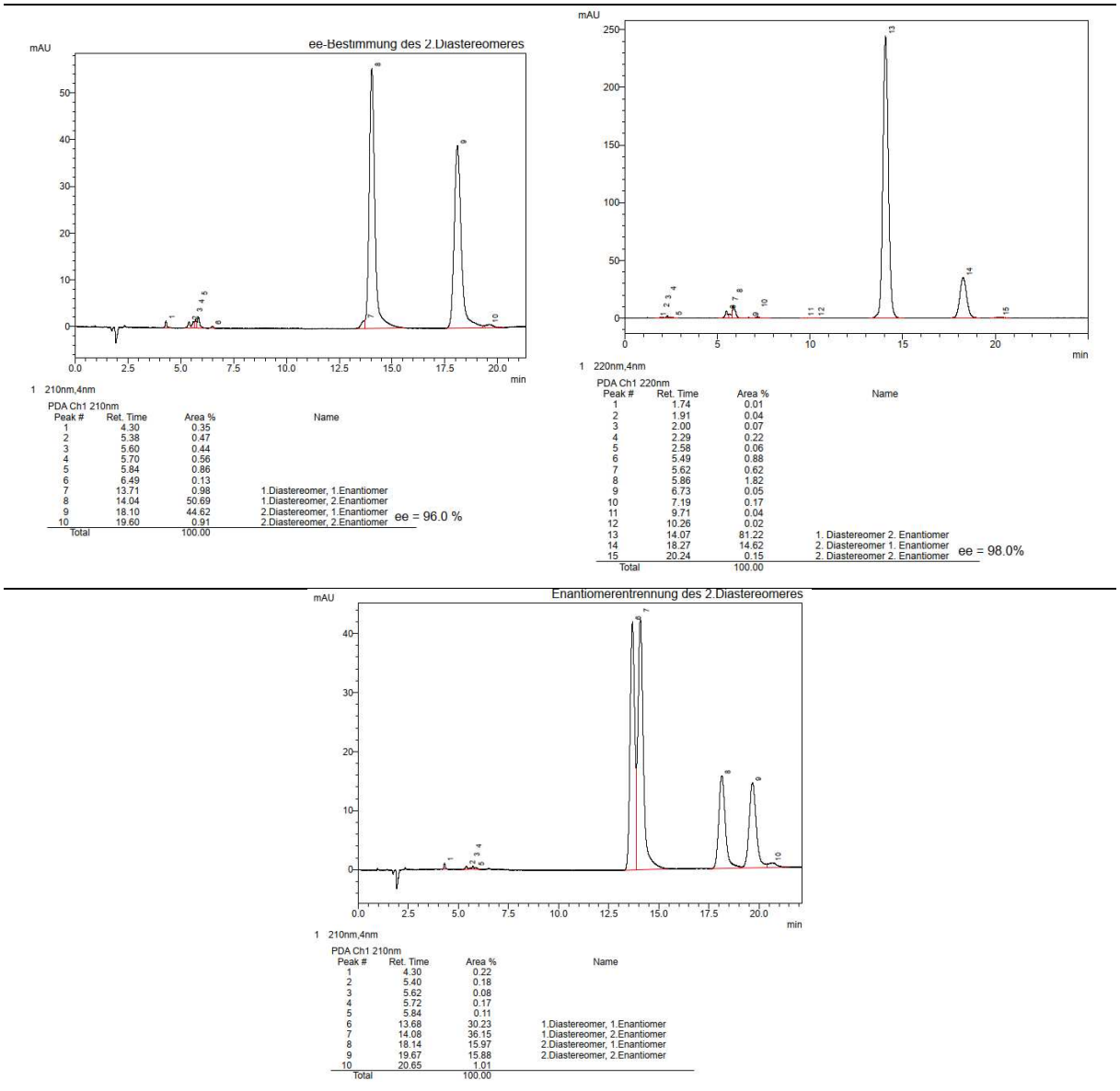
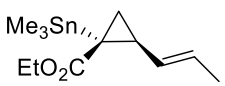


Figure 35. HPLC traces of enantioenriched *cis*- and *trans*-57i from C1 (top left) and from C3 (top right), and of racemic diastereomeric mixture of *cis*-and *trans*-57i (bottom).

***trans*-(57i):** (with **C1**: 95 % *ee*; with **C3**: 98 % *ee*). **^{1}H-NMR** (400 MHz, $CDCl_3$): δ = 5.68 – 5.56 (m,



1H), 5.22 (ddd, *J* = 15.2 Hz, 9.0 Hz, 1.7 Hz, 1H), 4.16 – 4.01 (m, 2H + *cis*-isomer), 1.74 (ddd, *J* = 9.1 Hz, 7.5 Hz, 5.8 Hz, 1H), 1.65 (dd, *J* = 6.5 Hz, 1.6 Hz, 3H + *cis*-isomer), 1.42 (dd, *J* = 5.8 Hz, 4.6 Hz, 1H), 1.22 (t, *J* = 7.1 Hz, 3H + *cis*-isomer), 1.00 (dd, *J* = 7.6 Hz, 4.7 Hz, 1H), 0.11 (s, 9H + *cis*-isomer) ppm; **^{13}C{^{1}H}-NMR** (101 MHz, $CDCl_3$): δ = 175.0,

129.4, 126.6, 60.7, 27.0, 19.3, 18.1, 16.6, 14.6, -9.6 ppm; **^{119}Sn{^{1}H}-NMR** (149 MHz, $CDCl_3$): δ = 21.8 ppm.

The optical purity was determined by HPLC (Chiralpak IC-3, 150 mm, 4.6 mm, i.D., acetonitrile/water 60:40, 1.0 mL/min) **[t_R]** = 4.96 min (major), 5.45 min (minor).

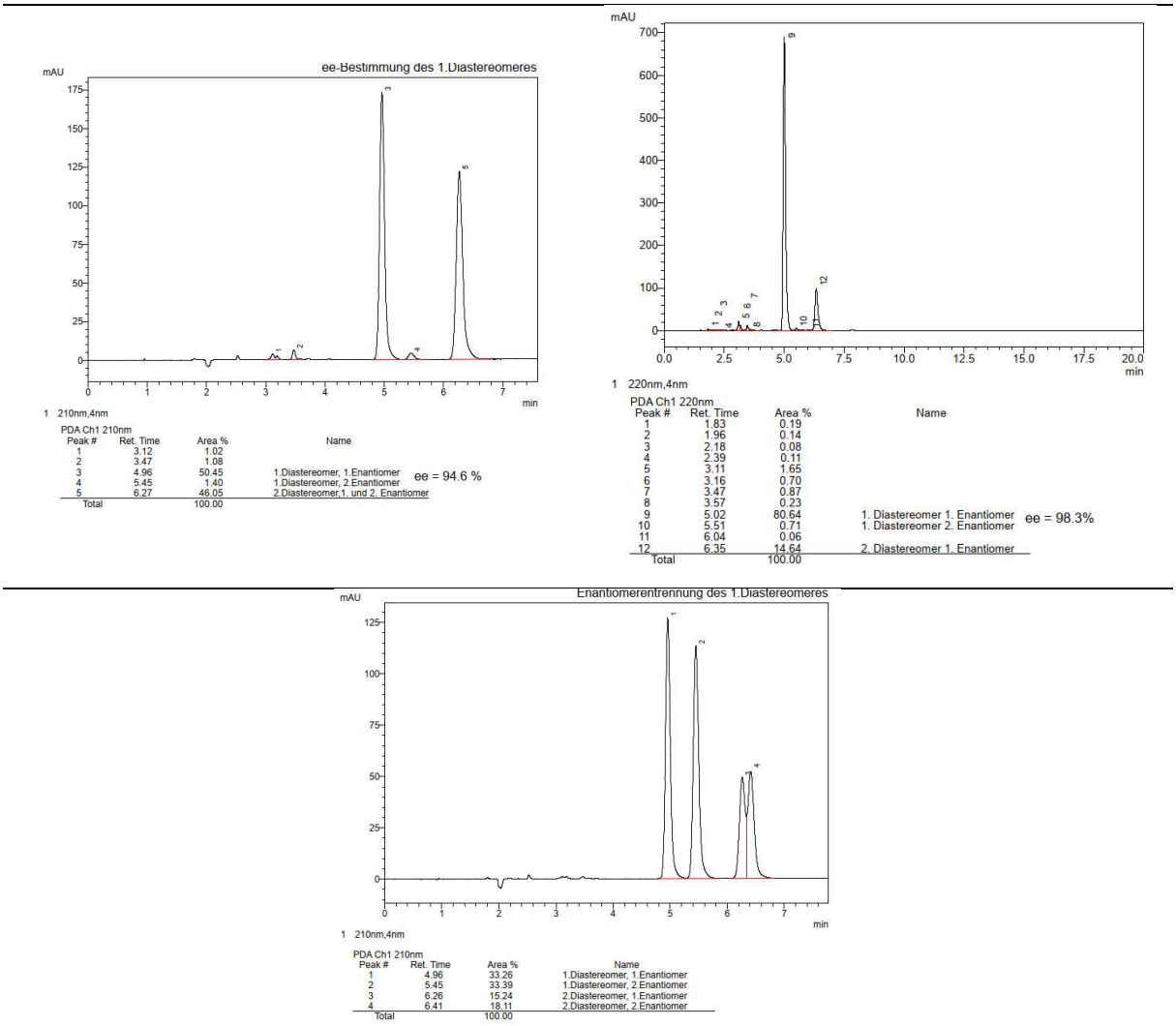


Figure 36. HPLC traces of enantioenriched *cis*- and *trans*-57i from C1 (top left) and from C3 (top right), and of racemic diastereomeric mixture of *cis*-and *trans*-57i (bottom).

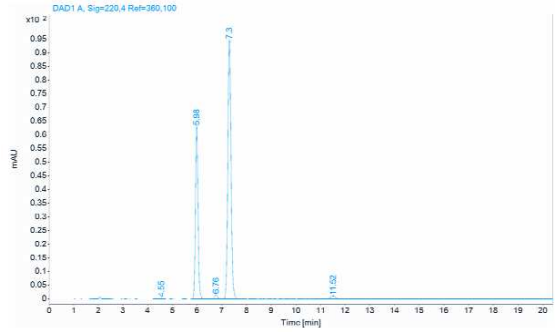
Compound 57j: Prepared according to the representative procedure for cyclopropanations using complex **C1** (72 mg, 55 % combined yield, *cis*/*trans* = 2:1, ^{1}H-NMR) or **C3** (49 mg, 55 % combined yield, *cis*/*trans* = 1:6, ^{1}H-NMR). Partial separation of the diastereomers for analytical purposes could be achieved *via* flash chromatography (fine silica, hexane/EtOAc 50:1).

***cis*-(57j):** colourless liquid (with **C1**: 94 % *ee*; with **C3**: 97 % *ee*). **$[\alpha]_D^{20}$** = 185.8° (c = 1.01, $CHCl_3$);

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.32 – 7.27 (m, 4H), 7.24 – 7.18 (m, 1H), 6.55 (d, J = 15.0 Hz, 1H), 5.85 (dd, J = 15.7 Hz, 8.4 Hz, 1H), 4.20 – 4.02 (m, 2H), 2.26 – 2.13 (m, 1H), 1.83 – 1.71 (m, 1H), 1.26 (t, J = 7.2 Hz, 3H), 1.15 – 0.99 (m, 1H), 0.18 (s,

9H) ppm; **^{13}C{^{1}H}-NMR** (101 MHz, $CDCl_3$): δ = 176.7, 137.2, 131.8, 130.6, 128.8, 127.4, 125.9, 61.1, 30.1, 21.0, 18.7, 14.4, -7.7 ppm; **^{119}Sn{^{1}H}-NMR** (149 MHz, $CDCl_3$): δ = 5.3 ppm; **IR (ATR)**: $\tilde{\nu}$ [cm^{-1}] = 3060, 3026, 2981, 2909, 1706, 1493, 1448, 1367, 1262, 1233, 1215, 1195, 1123, 1050, 1022, 957, 885, 853, 827, 767, 751, 692, 527, 512; **ESI-MS**: *m/z* (%) = 783 (21, $[2M+Na]^+$), 403 (100, $[M+Na]^+$), 365 (69), 319 (17), 239 (7); **HR-MS** (ESI-pos): *m/z* calcd. for $[M+Na]^+$: 403.06905, found: 403.06906.

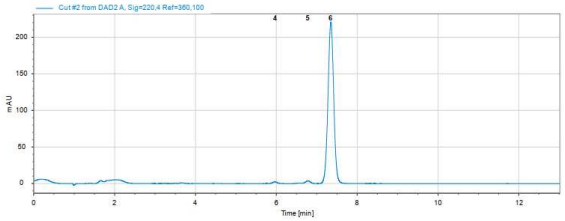
The optical purity was determined by HPLC (Chiralcel OD-3R, 150 mm, 4.6 mm i.D., acetonitrile/water 70:30, 1.0 mL/min) **[t_R]** = 6.76 min (minor), 7.30 min (major).



Signal: DAD1 A, Sig=220,4 Ref=360,100

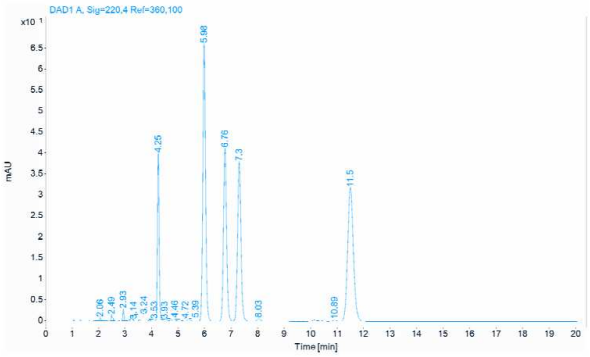
RT [min]	Area	Area%	Name
4.55	2.06	0.16	
5.98	454.93	34.35	1. Diastereomer 1. Enantiomer
6.76	12.04	0.91	2. Diastereomer 1. Enantiomer
7.30	840.82	63.49	2. Diastereomer 2. Enantiomer
11.52	14.57	1.10	1. Diastereomer 2. Enantiomer
Sum	1324.4210		

= 97.2 % ee
= 93.8 % ee



Signal: DAD2 A, Sig=220,4 Ref=360,100

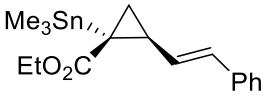
Compound	Cut	Ret.Time	Area	Width	Height	Symmetry
4	2	5.965	20.257 **20.257**	0.122	2.570	0.986
5	2	6.783	34.082 **34.082**	0.141	3.726	1.048
6	2	7.349	2168.980 **2168.980**	0.163	221.139	0.970



5.98	477.63	25.86	1. Diastereomer 1. Enantiomer
6.76	335.06	18.14	2. Diastereomer 1. Enantiomer
7.30	336.01	18.19	2. Diastereomer 2. Enantiomer
8.03	5.83	0.32	1. Diastereomer 2. Enantiomer

Figure 37. HPLC traces of enantioenriched *cis*- and *trans*-57j from C1 (top left) and *cis*-57j from C3 (top right), and of racemic diastereomeric mixture of *cis*-57j and *trans*-57j (bottom).

***trans*-(57j):** colourless liquid (with **C1**: 97 % *ee*; with **C3**: 98 % *ee*). $[\alpha]_D^{20}$ = −126.1° (c = 0.7, $CHCl_3$); **^{1}H-NMR** (400 MHz, $CDCl_3$): δ = 7.34 – 7.23 (m, 4H), 7.20 – 7.14 (m, 1H), 6.56 (d, *J* = 15.8 Hz, 1H), 6.05 (dd, *J* = 15.7 Hz, 9.4 Hz, 1H), 4.18 – 4.00 (m, 2H), 1.98 – 1.92 (m, 1H), 1.69 – 1.57 (m, 1H), 1.22 (t, *J* = 7.2 Hz, 3H), 1.17 (dd, *J* = 7.5 Hz, 4.7 Hz, 1H), 0.16 (s, 9H) ppm; **^{13}C{^{1}H}-NMR** (101 MHz, $CDCl_3$): δ = 174.8, 137.6, 130.8, 129.3, 128.6, 127.0, 130



126.0, 60.9, 28.0, 20.2, 17.7, 14.6, -9.5 ppm; **^{119}Sn{^{1}H}-NMR** (149 MHz, $CDCl_3$): δ = 22.4 ppm; **IR (ATR)**: $\tilde{\nu}$ [cm^{-1}] = 3025, 2983, 2917, 1709, 1492, 1448, 1365, 1276, 1215, 1177, 1115, 1027, 960, 908, 761, 692, 531, 512; **ESI-MS**: *m/z* (%) = 783 (13, $[2M+Na]^+$), 588 (3), 403 (100, $[M+Na]^+$), 381 (11, $[M+H]^+$), 365 (35), 319 (23); **HR-MS** (ESI-pos): *m/z* calcd. for $[M+Na]^+$: 403.06905, found: 403.06919.

The optical purity was determined by HPLC (Chiralcel OD-3R, 150 mm, 4.6 mm i.D., acetonitrile/water 70:30, 1.0 mL/min) **[t_R]** = 5.98 min (major), 11.52 min (minor).

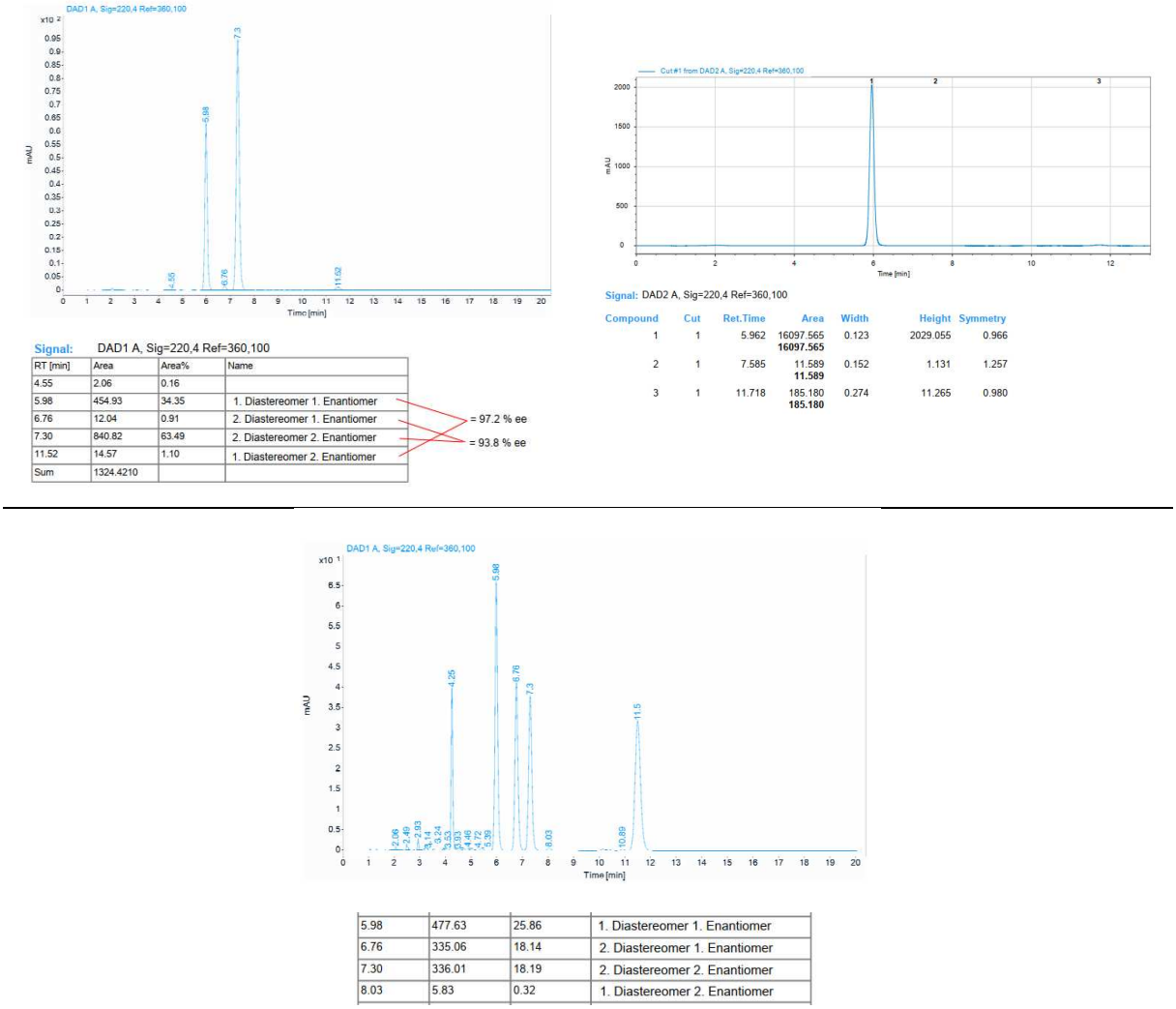
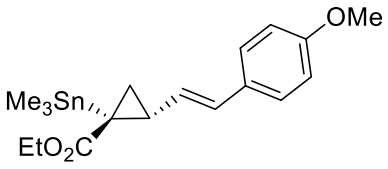


Figure 38. HPLC traces of enantioenriched *cis*- and *trans*-57j from C1 (top left) and *trans*-57j from C3 (top right), and of racemic diastereomeric mixture of *cis*-57j and *trans*-57j (bottom).

Compound 57k: Prepared according to the representative procedure for cyclopropanations using complex **C1** (160 mg, 72 % combined yield, *cis*/*trans* = 2:1, ^{1}H-NMR) or **C3** (26 mg, 16 % combined yield, *cis*/*trans* = 1:5, ^{1}H-NMR). No clean separation of diastereomers possible, assignment of NMR signals was accomplished based on different integrative ratio due to slight excess of one isomer in both experiments.

***cis*-(57k) and *trans*-(57k):** colourless liquid. **IR (ATR)**: $\tilde{\nu}$ [cm^{-1}] = 2981, 2908, 2836, 1705, 1607, 1677, 1510, 1464, 1442, 1365, 1300, 1241, 1173, 1109, 1033, 957, 822, 803, 763, 527, 511; **EI-MS**: *m/z* (%) = 410 (4, [M]), 395 (46), 319 (7), 245 (12), 199 (96), 171 (100), 151 (25), 128 (32), 115 (13), 84 (27), 49 (34); **HR-MS** (ESI-pos): *m/z* calcd. for [M+Na]$^+$: 433.07954, found: 433.07961.

***cis*-(57k):** (with **C1**: 97 % *ee*; with **C3**: 94 % *ee*). **^{1}H-NMR** (400 MHz, $CDCl_3$): δ = 7.22 – 7.20 (m, 2H), 6.86 – 6.82 (m, 2H), 6.49 (d, J = 15.6 Hz, 1H), 5.71 (dd, J = 15.7 Hz, 8.2 Hz, 1H), 4.17 – 4.02 (m, 2H + *trans*-isomer), 3.80 (s, 3H), 2.17 (tdd, J = 8.4 Hz, 6.0 Hz, 0.9 Hz, 1H), 1.80 – 1.69 (m, 1H), 1.25 (t, J = 7.2 Hz, 3H), 1.05 (dd, J = 6.0 Hz, 4.2 Hz, 1H), 0.16 (s, 9H + *trans*-isomer) ppm; **^{13}C{^{1}H}-NMR** (101 MHz, $CDCl_3$): δ = 176.8, 159.1, 131.2, 130.2, 130.1, 128.3, 127.1, 114.2, 61.0, 55.4, 30.1, 21.0, 18.6, 14.4, -7.7 ppm; **^{119}Sn{^{1}H}-NMR** (149 MHz, $CDCl_3$): δ = 4.9 ppm.



The optical purity was determined by HPLC (Chiralcel OJ-3R, 150 mm, 4.6 mm i.D., acetonitrile/water 55:45, 1.0 mL/min) **[t_R]** = 18.22 min (minor), 20.01 min (major).

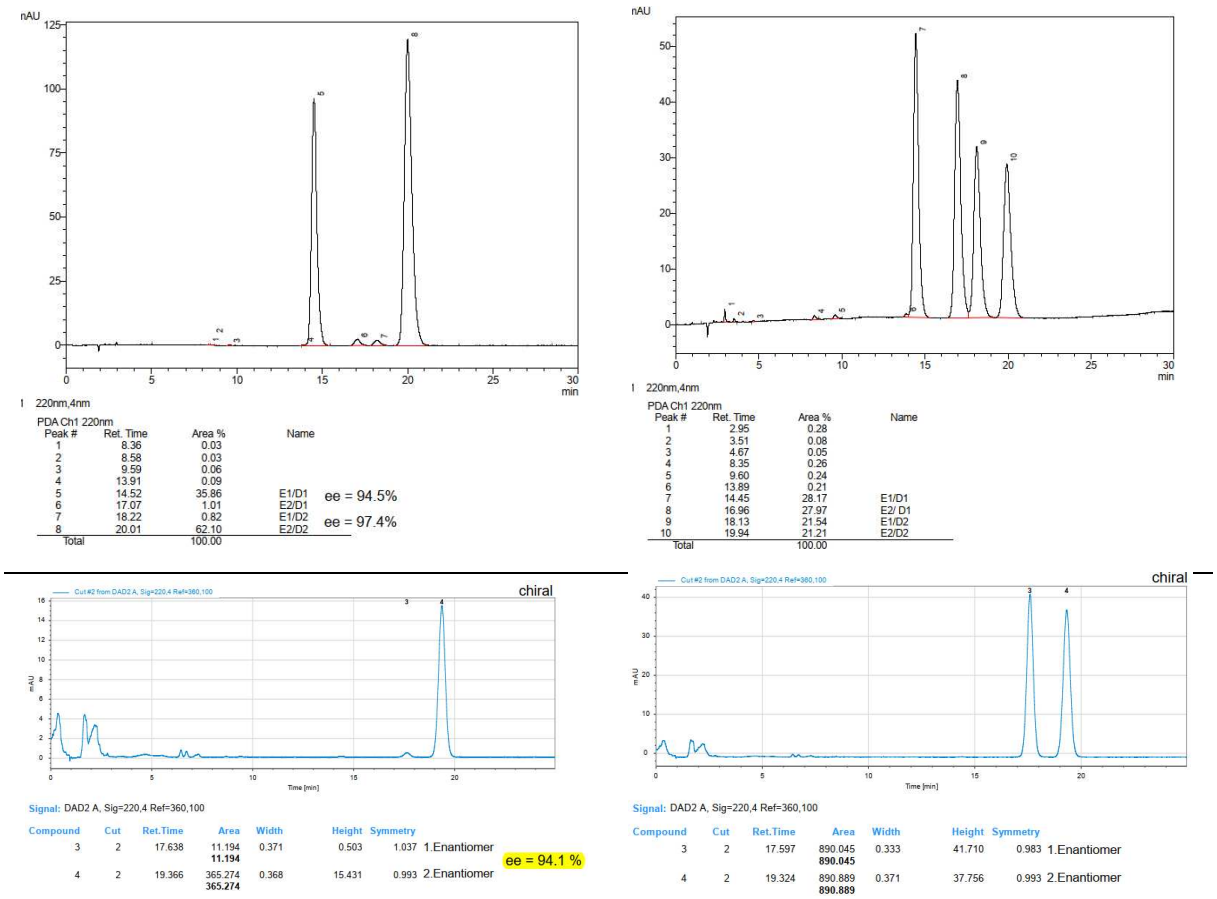
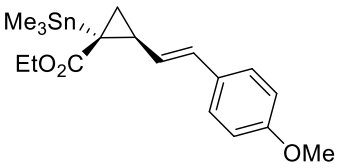


Figure 39. HPLC traces of enantioenriched *cis*- and *trans*-57k from C1 (top left) and *cis*-57k from C3 (bottom left), of racemic diastereomeric mixture of *cis*-57k and *trans*-57k (top right) and of racemic *cis*-57k (bottom right).

***trans*-(57k):** (with **C1**: 95 % *ee*; with **C3**: 97 % *ee*). **^{1}H-NMR** (400 MHz, $CDCl_3$): δ = 7.24 (d, J = 8.7 Hz, 2H), 6.81 (d, J = 8.9 Hz, 2H), 6.50 (d, J = 15.7 Hz, 1H), 5.90 (dd, J = 15.7 Hz, 9.4 Hz, 1H), 4.18 – 4.00 (m, 2H + *cis*-isomer), 3.79 (s, 3H), 1.93 (ddd, J = 9.4 Hz, 7.6 Hz, 5.7 Hz, 1H), 1.60 (dd, J = 4.0 Hz, 1.8 Hz, 1H), 1.21 (t, J = 7.1 Hz, 3H), 1.15 (dd, J = 7.5 Hz, 4.7 Hz, 1H), 0.15 (s, 9H + *cis*-isomer) ppm; **^{13}C{^{1}H}-NMR** (101 MHz, $CDCl_3$): δ = 174.9, 158.8, 131.2, 130.5, 130.2, 127.1, 114.0, 60.8, 55.4, 28.0, 20.1, 17.6, 14.6, -9.5 ppm; **^{119}Sn{^{1}H}-NMR** (149 MHz, $CDCl_3$): δ = 22.0 ppm.



The optical purity was determined by HPLC (Chiralcel OJ-3R, 150 mm, 4.6 mm i.D., acetonitrile/water 55:45, 1.0 mL/min) **[t_R]** = 15.52 min (major), 17.07 min (minor).

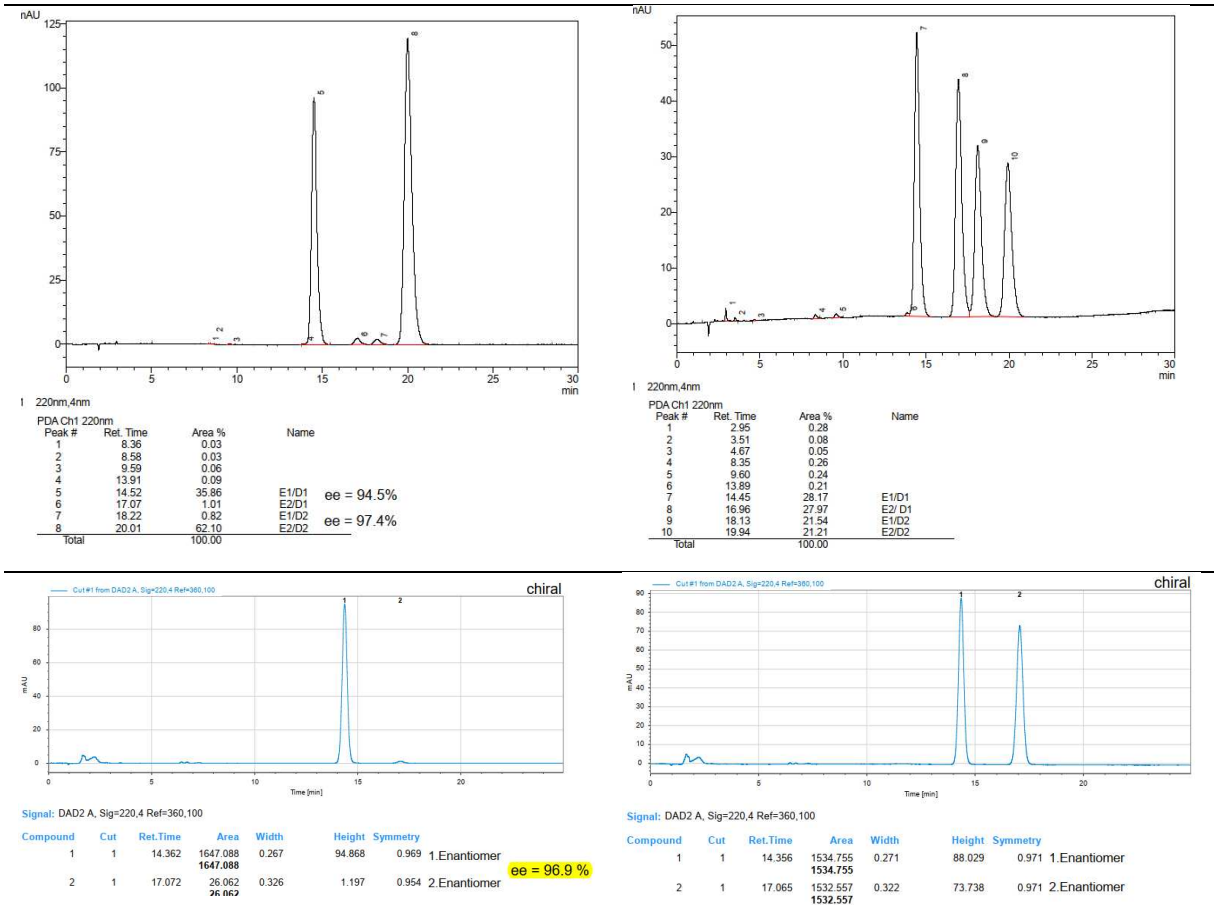
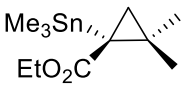


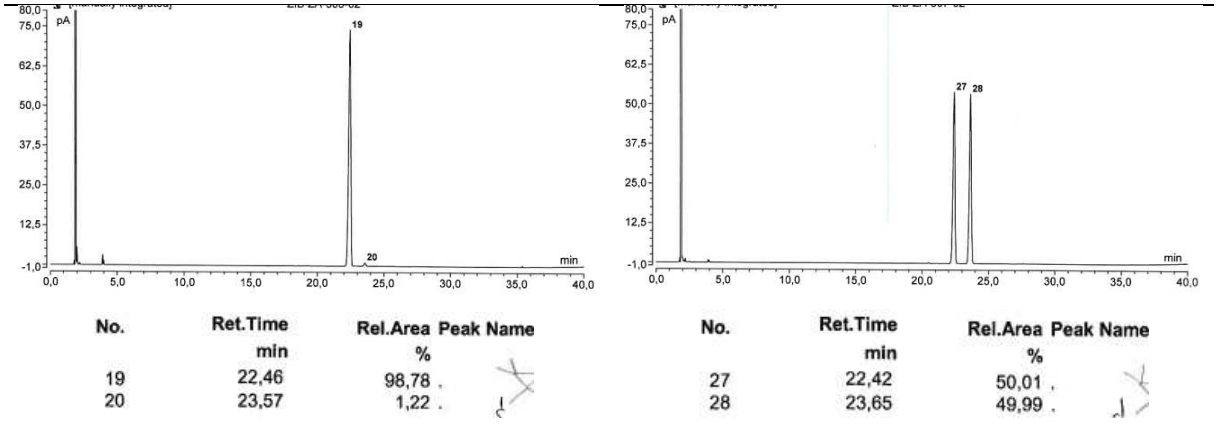
Figure 40. HPLC traces of enantioenriched *cis*- and *trans*-57k from C1 (top left) and *trans*-57k from C3 (bottom left), of racemic diastereomeric mixture of *cis*-57k and *trans*-57k (top right) and of racemic *trans*-57k (bottom right).

Compound 57l: Prepared according to the representative procedure for cyclopropanations using complex **C1**. Colourless oil (194 mg, 68 %, 98 % *ee*). **$[\alpha]_D^{20}$** = −11.1° (c = 1.01, $CHCl_3$); **^{1}H-NMR** (400 MHz, $CDCl_3$): δ = 4.07 (qd, J = 7.2 Hz, 2.2 Hz, 2H), 1.23 (td, J = 7.2 Hz, 2.2 Hz, 4H), 1.16 (d, J = 2.0 Hz, 3H), 1.10 (d, J = 2.2 Hz, 3H), 0.76 – 0.61 (m, 1H), 0.16 (d, J = 2.3 Hz, 9H) ppm; **^{13}C{^{1}H}-NMR** (101 MHz, $CDCl_3$): δ = 175.8, 60.4, 27.5, 27.1, 23.7, 22.9, 22.1,



14.7, -7.9 ppm; **^{119}Sn-NMR** (149 MHz, $CDCl_3$): δ = 11.3 ppm; **IR (ATR)**: $\tilde{\nu}$ [cm^{-1}] = 2980, 2947, 2920, 2872, 1712, 1460, 1445, 1387, 1375, 1364, 1331, 1267, 1238, 1211, 1197, 1091, 1028, 967, 857, 766, 528, 512; **EI-MS**: *m/z* (%) = 291 (58), 245 (100), 217 (68), 189 (18), 165 (62), 150 (43), 135 (41), 95 (8), 67 (13); **HR-MS** (GC-CI): *m/z* calcd. for $[M-H]^-$: 305.0558, found: 305.05547. The analytical data is consistent with the literature[256]

The optical purity was determined by chiral GC (BGB-176/BGB-15, 30 m, carrier gas H_2, 0.6 bar, temperature gradient 220/100 °C) **[t_R]** = 22.46 min (major), 23.57 min (minor).

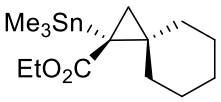


No.	Ret.Time min	Rel.Area %	Peak Name
19	22,46	98,78	
20	23,57	1,22	

No.	Ret.Time min	Rel.Area %	Peak Name
27	22,42	50,01	
28	23,65	49,99	

Figure 41. GC traces of enantioenriched 57l from C1 (left) and racemic 57l (right).

Compound 57o: Prepared according to the representative procedure for cyclopropanations



using complex **C1**. Colourless oil (43 mg, 47 %, 97 % *ee*). $[\alpha]_D^{20}$ = −4.8° (c = 1.0, $CHCl_3$); **^{1}H-NMR** (400 MHz, $CDCl_3$): δ = 4.17 – 4.01 (m, 2H), 1.65 – 1.55 (m, 4H), 1.51 – 1.38 (m, 3H), 1.38 – 1.30 (m, 1H), 1.28 – 1.21 (m, 4H), 1.17 (d, *J* = 4.3 Hz, 1H), 1.15 – 1.08 (m, 1H), 0.64 (d, *J* = 4.3 Hz, 1H), 0.15 (s, 9H) ppm; **^{13}C{^{1}H}-NMR** (101 MHz, $CDCl_3$): δ = 175.6, 60.4, 37.6, 32.3, 30.9, 27.7, 26.2, 26.0, 25.9, 21.1, 14.7, -7.8 ppm; **^{119}Sn-NMR** (149 MHz, $CDCl_3$): δ = 10.3 ppm; **IR (ATR)**: $\tilde{\nu}$ [cm^{-1}] = 2981, 2925, 2852, 1710, 1445, 1380, 1324, 1259, 1234, 1181, 1117, 1101, 1081, 1045, 960, 882, 851, 767, 528; **EI-MS**: *m/z* (%) = 331 (29), 285 (38), 257 (27), 165 (100), 151 (46), 135 (99), 121 (15), 107 (20), 91 (17), 79 (28); **HR-MS** (ESI-pos): *m/z* calcd. for $[M+Na]^+$: 369.0847, found: 369.08514.

The optical purity was determined by chiral GC (Hydrodex-gamma-TBDAc-CD, 25 m, carrier gas H_2, 0.6 bar, temperature gradient 220/90 °C) **[t_R]** = 128.89 min (minor), 133.05 min (major).

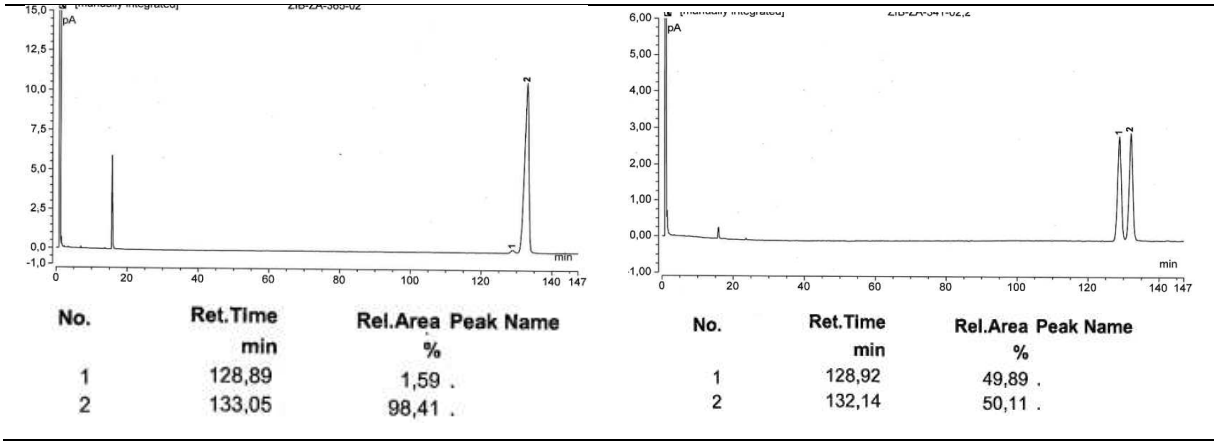
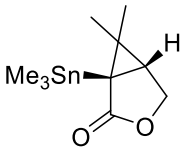


Figure 42. GC traces of enantioenriched 57o from C1 (left) and racemic 57o (right).

Compound 63 (or *ent*-63): From complex **C1**: The compound was prepared according to the representative procedure for cyclopropanations using diazo stannane **61**. From complex **C3**: In a cooling Schlenk flask, diazo compound **14** (75 mg, 0.49 mmol) was dissolved in Et_2O (5 mL). Then dimethylamino trimethyltin (0.08 mL, 0.49 mmol) was added and the mixture was stirred at room temperature for 4 h. The solvent was carefully evaporated under vacuum, the remaining crude material was dissolved pentane (5 mL) and cooled to – 20°C. Complex **C3** (4 mg, 2.3 µmol) was added and the mixture was stirred at - 20°C overnight. The reaction mixture was warmed to room temperature and the solvent was evaporated. The crude product was purified *via* flash chromatography to afford the title compound as a colourless oil (11 mg, 0.038 mmol, 8 %, with **C1**: 57 % *ee*, with **C3**: 86 % *ee*).



or enantiomer

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 4.30 (dd, J = 9.7 Hz, 5.4 Hz, 1H), 4.22 – 4.15 (m, 1H), 1.94 – 1.82 (m, 1H), 1.18 (s, 3H), 1.14 (s, 3H), 0.23 (s, 9H) ppm; **^{13}C{^{1}H}-NMR** (101 MHz, $CDCl_3$): δ = 179.3, 34.5, 29.1, 26.7, 26.5, 16.2, -8.1 ppm; **^{119}Sn-NMR** (149 MHz, $CDCl_3$): δ = 2.4 ppm; **IR (ATR)**: $\tilde{\nu}$ [cm^{-1}] = 2974, 2952, 2900, 1736, 1483, 1452, 1377, 1357, 1279, 1263, 1236, 1213, 1171, 1094, 1056, 1041, 1003, 989, 978, 942, 926, 896, 837, 814, 769, 718, 656, 633, 529, 513; **EI-MS**: *m/z* (%) = 275 (58), 257 (4), 231 (29), 201 (5), 165 (100), 150 (18), 135 (42), 108 (8), 97 (3), 81 (33), 67 (6), 53 (11), 41 (21); **HR-MS** (GC-CI): *m/z* calcd. for $[M+H]^+$: 291.0401, found: 291.0404.

Alternatively, compound **63** was synthesized according to the following procedure: In a Schlenk flask, $Cu(MeCN)_4BF_4$ (6.5 mg, 0.02 mmol, 0.17 eq) and BOX ligand **62** (13 mg, 0.03 mmol, 0.26 eq) were dissolved in toluene (15 mL) and the mixture was stirred at room temperature for 1 h. Diazo stannane **61** (38 mg, 0.12 mmol, 1.0 eq) was added as a solution in toluene (2 mL). The mixture was heated to 60°C and kept stirring overnight. The reaction was quenched with aq. ammonia solution (25 %, 3 mL). The aqueous layer was extracted with Et_2O (3x) and the combined organic layers were washed with brine and dried over Na_2SO_4. The solvent was removed *in vacuo* and the crude product was purified *via* flash chromatography (SiO_2, hexane/EtOAc 50:1). The title

compound was obtained as a colourless liquid (yield not determined, −67 % *ee*). Analytical data *vide supra*.

The optical purity was determined by chiral GC (G-TA 0.25/df, 30 m, carrier gas H_2, 0.6 bar, temperature gradient 220/140 °C) **[t_R]** = 9.74 min (major), 10.79 min (minor).

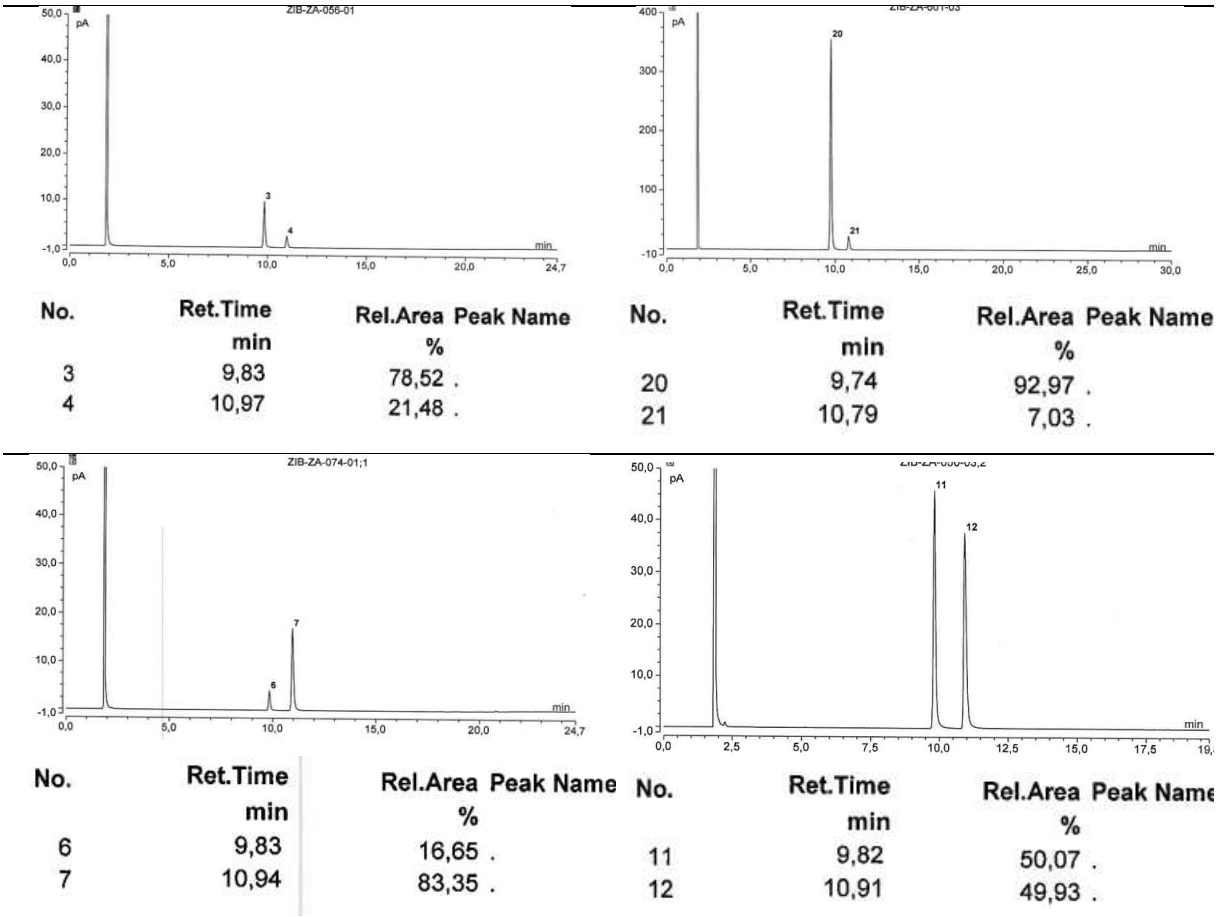
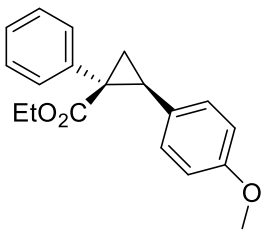


Figure 43. GC traces of enantioenriched 63 from C1 (top left), from C3 (top right), from copper catalysis (bottom left) and of racemic 63 (bottom right).

4.2.4 Stille Cross Coupling Reactions

***cis*-(67a):** In a 10 mL glass vial, $Pd(dba)_2$ (5 mg, 0.009 mmol), JackiePhos (13 mg, 0.016 mmol), KF (9 mg, 0.15 mmol) and CuCl (16 mg, 0.16 mmol) were mixed and the vial closed with a septum cap. It was evaucated and flushed with Argon over three cycles before THF (1 mL) was added. In a Schlenk flask, ***trans*-57b** (32 mg, 0.084 mmol) and iodobenzene (18 µL, 0.16 mmol) were dissolved in THF (1 mL). This solution was added to the catalyst solution *via* a syringe and the mixture was stirred at 60°C. Upon full conversion, the mixture was cooled to room temperature. It was diluted with MTBE (2 mL) and filtered over Celite. The crude product was submitted to flash chromatography (SiO_2, hexane/EtOAc 50:1) to obtain the title compound



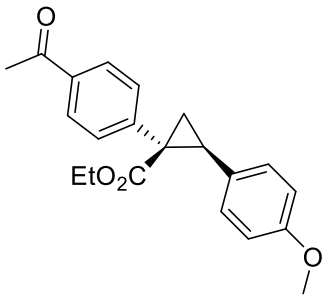
as a yellow oil (19 mg, 0.064 mmol, 77 %). $[\alpha]_D^{20}$ = −140.5° (c = 0.95, $CHCl_3$); **^{1}H-NMR** (400 MHz, $CDCl_3$): δ = 7.49 – 7.43 (m, 2H), 7.35 – 7.29 (m, 2H), 7.28 – 7.21 (m, 3H), 6.85 – 6.79 (m, 2H), 3.87 – 3.72 (m, 4H), 3.72 – 3.64 (m, 1H), 2.77 (t, *J* = 8.2 Hz, 1H), 2.26 (dd, *J* = 7.4 Hz, 5.1 Hz, 1H), 1.54 (dd, *J* = 9.1 Hz, 5.0 Hz, 1H), 0.81 (t, *J* = 7.1 Hz, 3H) ppm; **^{13}C{^{1}H}-NMR** (101 MHz, $CDCl_3$): δ = 170.8, 158.6, 140.6, 130.4, 130.3, 128.4, 127.3, 113.6, 60.8, 55.4, 38.1, 32.5, 18.2, 14.0 ppm; **IR (film, ATR)**: $\tilde{\nu}$ [cm^{-1}] = 3084, 3060, 3028, 2980, 2957, 2934, 2908, 2836, 1719, 1653, 1612, 1515, 1497, 1463, 1447, 1368, 1302, 1280, 1246, 1211, 1180, 1159, 1101, 1078, 1062, 1033, 980, 837, 807, 768, 744, 699, 555; **GC-MS** (GC-EI): *m/z* (%) = 296 (86, [M]), 250 (76), 223 (100), 207 (34), 178 (46), 165 (45), 145 (34), 115 (72), 91 (32), 77 (30); **HR-MS** (ESI-pos): *m/z* calcd. for [M+H]$^+$: 297.14852, found: 297.14827. Analytical data is consistent with the literature[134].

***trans*-(67a):** Prepared analogously to ***cis*-67a** from ***cis*-57b** (33 mg, 0.086 mmol) and iodobenzene (18 µL, 0.16 mmol). Colourless crystals (10 mg, 0.034 mmol, 43 %). $[\alpha]_D^{20}$ = 21.5° (c = 0.98, $CHCl_3$); **^{1}H-NMR** (400 MHz, $CDCl_3$): δ = 7.20 – 7.08 (m, 3H), 7.08 – 6.96 (m, 2H), 6.73 – 6.64 (m, 2H), 6.64 – 6.56 (m, 2H), 4.21 – 4.04 (m, 2H), 3.69 (s, 3H), 3.05 (dd, *J* = 9.4 Hz, 7.3 Hz, 1H), 2.10 (dd, *J* = 9.4 Hz, 4.8 Hz, 1H), 1.84 – 1.75 (m, 1H), 1.17 (t, *J* = 7.1 Hz, 3H) ppm; **^{13}C{^{1}H}-NMR** (101 MHz, $CDCl_3$): δ = 174.0, 158.2, 135.2, 132.1, 129.1, 128.6, 127.7, 127.0, 113.3, 61.3, 55.3, 37.4, 32.6, 20.4, 14.3 ppm; **IR (film, ATR)**: $\tilde{\nu}$ [cm^{-1}] = 3087, 3059, 3029, 2979, 2958, 2933, 2908, 2836, 1711, 1613, 1579, 1516, 1497, 1463, 1446, 1417, 1372, 1333, 1301, 1249, 1211, 1173, 1118, 1093, 1057, 1030, 975, 831, 809, 764, 734, 700, 579, 541; **GC-MS** (GC-EI): *m/z* (%) = 296 (85, [M]), 267 (13), 250 (78), 223 (100), 207 (37), 178 (56), 165 (54), 145 (42), 115 (100), 91 (48), 77 (47); **HR-MS** (GC-EI): *m/z* calcd. for [M]: 296.1407, found: 296.14079. Analytical data is consistent with the literature[134].

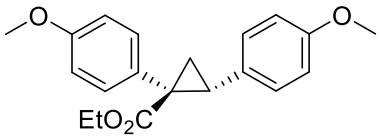
Representative procedure for stereoretentive Stille couplings: *trans*-(67g): In a pressure Schlenk flask, $Pd_2(dba)_3$ (3 mg, 3 µmol), JackiePhos (11 mg, 0.013 mmol), CuCl (13 mg, 0.13 mmol) and KF (9 mg, 0.15 mmol) were mixed and suspended in THF (2 mL). In another Schlenk flask, ***cis*-57b** (25 mg, 0.065 mmol) and 4-acetyl phenyl triflate (25 µL, 0.13 mmol) were dissolved in THF (1 mL). This solution was added to the catalyst solution *via* syringe and the mixture was stirred at 70°C. Upon full consumption of the starting material ***cis*-57b**, the mixture was diluted with MTBE, filtered and the solvent evaporated. The crude product was immobilized on Celite and purified *via* flash chromatography (SiO_2, hexane/MTBE 8:1 to 5:1) to afford the title compound as light yellow oil (17 mg, 0.05 mmol, 77 %). $[\alpha]_D^{20}$ = 5.1° (c = 1.00, $CHCl_3$); **^{1}H-NMR** (400 MHz, $CDCl_3$): δ = 7.75 – 7.69 (m, 2H), 7.16 – 7.09 (m, 2H), 6.73 – 6.67 (m, 2H), 6.63 – 6.56 (m, 2H), 4.21 – 4.04 (m, 2H), 3.69 (s, 3H), 3.10 (dd, *J* = 9.4 Hz,

7.3 Hz, 1H), 2.53 (s, 3H), 2.14 (dd, *J* = 9.4 Hz, 5.0 Hz, 1H), 1.84 (dd, *J* = 7.3 Hz, 5.0 Hz, 1H), 1.17 (t, *J* = 7.1 Hz, 3H) ppm; **^{13}C{^{1}H}-NMR** (101 MHz, $CDCl_3$): *δ* = 198.1, 173.2, 158.4, 140.9, 135.7, 132.3, 129.1, 127.9, 127.8, 113.5, 61.5, 55.2, 37.2, 32.9, 26.7, 20.1, 14.3 ppm; **IR (film, ATR)**: $\tilde{\nu}$ [cm^{-1}] = 2981, 2936, 2909, 2837, 1713, 1682, 1608, 1516, 1442, 1405, 1359, 1301, 1249, 1211, 1173, 1117, 1083, 1031, 978, 959, 837, 747, 612; **EI-MS**: *m/z* (%) = 338 (95, [M]), 309 (20), 292 (30), 265 (38), 221 (50), 178 (26), 165 (22), 121 (18), 91 (12); **HR-MS** (ESI-pos): *m/z* calcd. for $[M+Na]^+$: 361.14103, found: 361.14113.

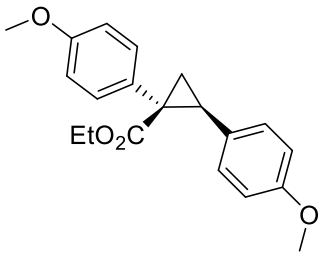
***cis*-(67g):** Prepared according to the representative procedure for Stille couplings from ***trans*-57b** (25 mg, 0.065 mmol) and 4-acetyl phenyl triflate (25 µL, 0.13 mmol) to afford the title compound as a light yellow oil (16 mg, 0.047 mmol, 72 %). $[\alpha]_D^{20}$ = −216.5° (c = 1.01, $CHCl_3$); **^{1}H-NMR** (400 MHz, $CDCl_3$): *δ* = 7.99 – 7.91 (m, 2H), 7.63 – 7.52 (m, 2H), 7.30 – 7.22 (m, 2H), 6.89 – 6.81 (m, 2H), 3.89 – 3.66 (m, 5H), 2.81 (dd, *J* = 9.0 Hz, 7.5 Hz, 1H), 2.61 (s, 3H), 2.34 (dd, *J* = 7.5 Hz, 5.2 Hz, 1H), 1.62 – 1.56 (m, 1H), 0.84 (t, *J* = 7.1 Hz, 3H) ppm; **^{13}C{^{1}H}-NMR** (101 MHz, $CDCl_3$): *δ* = 197.9, 170.1, 158.8, 145.9, 136.1, 130.4, 130.3, 128.5, 128.1, 113.6, 61.1, 55.4, 37.9, 32.8, 26.8, 18.5, 14.0 ppm; **IR (film, ATR)**: $\tilde{\nu}$ [cm^{-1}] = 2980, 2935, 2837, 1719, 1682, 1607, 1443, 1404, 1359, 1302, 1265, 1246, 1212, 1180, 1103, 1057, 1032, 958, 836, 600, 558; **EI-MS**: *m/z* (%) = 338 (78, [M]), 309 (17), 292 (25), 265 (32), 249 (65), 221 (43), 178 (22), 121 (16), 77 (11), 43 (100); **HR-MS** (ESI-pos): *m/z* calcd. for $[M+Na]^+$: 361.14103, found: 361.14107.



***trans*-(67d):** Prepared according to the representative procedure for Stille couplings from ***cis*-57b** (20 mg, 0.052 mmol) and *p*-iodoanisol (26 mg, 0.11 mmol) using 0.4 eq. of JackiePhos to afford the title compound as a yellow oil (12 mg, 0.037 mmol, 70 %). $[\alpha]_D^{20}$ = −12.8° (c = 0.996, $CHCl_3$). **^{1}H-NMR** (400 MHz, $CDCl_3$): *δ* = 6.96 – 6.90 (m, 2H), 6.72 – 6.64 (m, 4H), 6.64 – 6.58 (m, 2H), 4.22 – 4.04 (m, 2H), 3.73 (s, 3H), 3.71 (s, 3H), 3.00 (dd, *J* = 9.5 Hz, 7.2 Hz, 1H), 2.09 (dd, *J* = 9.4 Hz, 4.8 Hz, 1H), 1.73 (dd, *J* = 7.2 Hz, 4.8 Hz, 1H), 1.20 – 1.14 (m, 3H) ppm; **^{13}C{^{1}H}-NMR** (101 MHz, $CDCl_3$): *δ* = 174.3, 158.5, 158.2, 133.1, 129.2, 128.8, 127.8, 113.3, 113.2, 61.3, 55.3, 55.2, 36.6, 32.6, 20.6, 14.3 ppm; **IR (film, ATR)**: $\tilde{\nu}$ [cm^{-1}] = 2958, 2907, 2836, 1710, 1612, 1515, 1463, 1373, 1296, 1246, 1211, 1175, 1117, 1033, 977, 835, 756, 551; **ESI-MS**: *m/z* (%) = 675 (43, $[2M+Na]^+$), 509 (6, $[3M+Ca]^{2+}$), 425 (5), 349 (100, $[M+Na]^+$), 327 (29, $[M+H]^+$); **HR-MS** (ESI-pos): *m/z* calcd. for $[M+Na]^+$: 349.14103, found: 349.14077.

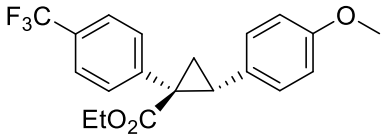


***cis*-(67d):** Prepared according to the representative procedure for Stille couplings from ***trans*-**



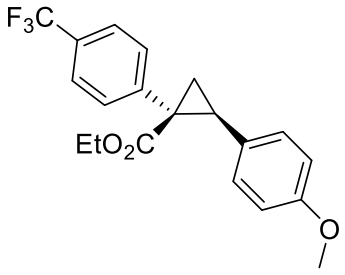
57b (25 mg, 0.065 mmol) and *p*-iodoanisol (32 mg, 0.14 mmol) using 0.4 eq. of JackiePhos to afford the title compound as a yellow solid (15 mg, 0.046 mmol, 70 %). $[\alpha]_D^{20}$ = −193.1° (c = 0.99, $CHCl_3$). **^{1}H-NMR** (600 MHz, $CDCl_3$): δ = 7.44 – 7.40 (m, 2H), 7.29 – 7.26 (m, 2H), 6.91 – 6.87 (m, 2H), 6.86 – 6.83 (m, 2H), 3.86 – 3.80 (m, 4H), 3.80 (s, 3H), 3.73 – 3.67 (m, 1H), 2.77 – 2.72 (m, 1H), 2.26 (dd, *J* = 7.4 Hz, 5.0 Hz, 1H), 1.54 (dd, *J* = 9.0 Hz, 5.0 Hz, 1H), 0.83 (t, *J* = 7.1 Hz, 3H) ppm; **^{13}C{^{1}H}-NMR** (101 MHz, $CDCl_3$): δ = 171.1, 158.8, 158.6, 132.8, 131.5, 130.3, 128.9, 113.8, 113.6, 60.8, 55.4, 55.4, 37.4, 32.8, 18.2, 14.0 ppm; **IR (film, ATR)**: $\tilde{\nu}$ [cm^{-1}] = 2957, 2915, 2836, 1717, 1612, 1512, 1463, 1442, 1292, 1244, 1211, 1174, 1101, 1032, 833, 808, 554; **ESI-MS**: *m/z* (%) = 675 (20, $[2M+Na]^+$), 509 (1, $[3M+Ca]^{2+}$), 425 (6), 365 (4, $[M+K]^+$), 349 (100, $[M+Na]^+$), 327 (18, $[M+H]^+$); **HR-MS** (ESI-pos): *m/z* calcd. for $[M+Na]^+$: 349.14103, found: 349.14078.

***trans*-(67e):** Prepared according to the representative procedure for Stille couplings from ***cis*-**



57b (25 mg, 0.065 mmol) and 1-iodo-4-(trifluoromethyl)benzene (27 mg, 0.1 mmol) to afford the title compound as a yellow oil (22 mg, 0.06 mmol, 93 %). $[\alpha]_D^{20}$ = 3.3° (c = 0.99, $CHCl_3$). **^{1}H-NMR** (400 MHz, $CDCl_3$): δ = 7.38 (d, *J* = 7.9 Hz, 2H), 7.16 – 7.11 (m, 2H), 6.71 – 6.66 (m, 2H), 6.64 – 6.58 (m, 2H), 4.21 – 4.04 (m, 2H), 3.70 (s, 3H), 3.09 (dd, *J* = 9.4 Hz, 7.3 Hz, 1H), 2.15 (dd, *J* = 9.4 Hz, 5.0 Hz, 1H), 1.82 (dd, *J* = 7.4 Hz, 5.1 Hz, 1H), 1.18 – 1.16 (m, 3H) ppm; **^{13}C{^{1}H}-NMR** (101 MHz, $CDCl_3$): δ = 189.1, 173.2, 158.4, 139.5, 132.4, 129.2 (q, $J_{C,F}$ = 290 Hz), 129.1, 127.8, 124.7, 113.5, 61.6, 55.3, 37.1, 32.8, 20.1, 14.3 ppm; **IR (film, ATR)**: $\tilde{\nu}$ [cm^{-1}] = 2982, 2938, 2838, 1716, 1617, 1517, 1449, 1410, 1373, 1324, 1251, 1211, 1164, 1122, 1067, 1020, 980, 840, 762, 609; **EI-MS**: *m/z* (%) = 364 (98, [M]), 318 (54), 291 (100), 233 (29), 183 (50), 145 (38), 121 (48), 77 (49), 29 (33); **HR-MS** (ESI-pos): *m/z* calcd. for $[M+Na]^+$: 387.11785, found: 387.11811.

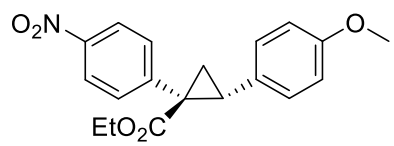
***cis*-(67e):** Prepared according to the representative procedure for Stille couplings from ***trans*-**



57b (25 mg, 0.065 mmol) and 1-iodo-4-(trifluoromethyl)benzene (25 mg, 0.09 mmol) to afford the title compound as a yellow oil (19 mg, 0.052 mmol, 80 %). $[\alpha]_D^{20}$ = −116.0° (c = 1.0, $CHCl_3$). **^{1}H-NMR** (500 MHz, $CDCl_3$): δ = 7.61 (s, 4H), 7.28 (d, *J* = 8.6 Hz, 2H), 6.89 – 6.84 (m, 2H), 3.90 – 3.79 (m, 4H), 3.79 – 3.70 (m, 1H), 2.80 (dd, *J* = 9.0 Hz, 7.5 Hz, 1H), 2.35 (dd, *J* = 7.4 Hz, 5.2 Hz, 1H), 1.60 (dd, *J* = 9.1 Hz, 5.2 Hz, 1H), 0.85 (t, *J* = 7.1 Hz, 3H) ppm; **^{13}C{^{1}H}-NMR** (101 MHz, $CDCl_3$): δ = 170.1, 158.8, 144.5, 130.7, 130.3, 128.8 (q, $J_{C,F}$ = 58 Hz), 128.1, 125.4, 113.7, 61.1, 55.4, 37.8, 32.8, 18.3,

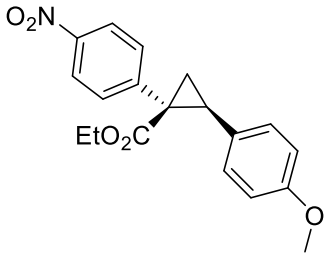
14.0 ppm; **IR (film, ATR)**: $\tilde{\nu}$ [cm^{-1}] = 2983, 2907, 2838, 1720, 1616, 1515, 1444, 1410, 1368, 1325, 1281, 1248, 1213, 1163, 1123, 1072, 1034, 1019, 982, 837, 807, 606; **EI-MS**: *m/z* (%) = 364 (100, [M]), 335 (40), 318 (54), 291 (88), 233 (26), 183 (36), 121 (30), 77 (26), 29 (13); **HR-MS** (ESI-pos): *m/z* calcd. for [M+Na]$^+$: 387.11785, found: 387.11813.

***trans*-(67f):** Prepared according to the representative procedure for Stille couplings from ***cis*-57b**



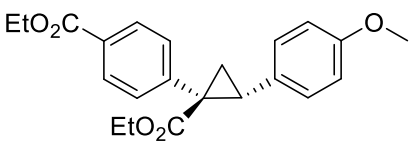
(25 mg, 0.065 mmol) and 4-nitrophenyl triflate (35 mg, 0.13 mmol) to afford the title compound as a light yellow oil (18 mg, 0.053 mmol, 81 %). $[\alpha]_D^{20}$ = 21.9° (c = 1.01, $CHCl_3$);**^{1}H-NMR** (400 MHz, $CDCl_3$): δ = 8.02 – 7.94 (m, 2H), 7.23 – 7.15 (m, 2H), 6.74 – 6.67 (m, 2H), 6.65 – 6.56 (m, 2H), 4.14 (qq, *J* = 10.8 Hz, 7.1 Hz, 2H), 3.69 (s, 3H), 3.14 (dd, *J* = 9.4 Hz, 7.3 Hz, 1H), 2.19 (dd, *J* = 9.4 Hz, 5.2 Hz, 1H), 1.88 (dd, *J* = 7.4 Hz, 5.2 Hz, 1H), 1.17 (t, *J* = 6.6 Hz, 3H) ppm; **^{13}C{^{1}H}-NMR** (101 MHz, $CDCl_3$): δ = 172.5, 158.6, 146.9, 143.2, 132.9, 129.1, 127.2, 123.0, 113.7, 61.8, 55.3, 37.0, 33.1, 20.0, 14.2 ppm; **IR (film, ATR)**: $\tilde{\nu}$ [cm^{-1}] = 2981, 2908, 2837, 1714, 1602, 1516, 1463, 1442, 1347, 1300, 1249, 1173, 1031, 856, 736, 701, 583; **GC-MS** (GC-EI): *m/z* (%) = 341 (91, [M]), 312 (66), 295 (82), 268 (100), 251 (24), 221 (59), 178 (89), 165 (47), 121 (34), 91 (27), 77 (27); **HR-MS** (GC-EI): *m/z* calcd. for [M]: 341.12577, found: 341.12594.

***cis*-(67f):** Prepared according to the representative procedure for Stille couplings from ***trans*-57b**



(25 mg, 0.065 mmol) and 4-nitrophenyl triflate (36 mg, 0.13 mmol) to afford the title compound as a light yellow oil (17 mg, 0.05 mmol, 76 %). $[\alpha]_D^{20}$ = −200.5° (c = 1.0, $CHCl_3$); **^{1}H-NMR** (600 MHz, $CDCl_3$): δ = 8.25 – 8.19 (m, 2H), 7.68 – 7.62 (m, 2H), 7.29 – 7.24 (m, 2H), 6.89 – 6.84 (m, 2H), 3.85 (dq, *J* = 10.8 Hz, 7.1 Hz, 1H), 3.80 (s, 3H), 3.74 (dq, *J* = 10.9 Hz, 7.1 Hz, 1H), 2.82 (ddt, *J* = 9.2 Hz, 7.6 Hz, 0.9 Hz, 1H), 2.39 (dd, *J* = 7.5 Hz, 5.3 Hz, 1H), 1.64 (dd, *J* = 9.2 Hz, 5.3 Hz, 1H), 0.85 (t, *J* = 7.1 Hz, 4H) ppm; **^{13}C{^{1}H}-NMR** (101 MHz, $CDCl_3$): δ = 169.5, 158.9, 147.9, 147.1, 131.1, 130.3, 127.6, 123.7, 113.7, 61.3, 55.4, 37.7, 33.2, 27.1, 18.6, 13.9 ppm; **IR (film, ATR)**: $\tilde{\nu}$ [cm^{-1}] = 2982, 2906, 2837, 1718, 1601, 1515, 1463, 1443, 1348, 1305, 1247, 1213, 1181, 1102, 1032, 837, 699, 558; **GC-MS** (GC-EI): *m/z* (%) = 341 (88, [M]), 312 (68), 295 (87), 284 (54), 268 (100), 221 (56), 178 (86), 121 (34), 91 (27), 77 (28); **HR-MS** (GC-EI): *m/z* calcd. for [M]: 341.12577, found: 341.12594.

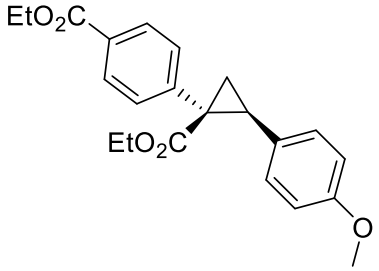
***trans*-(67h):** Prepared according to the representative procedure for Stille couplings from ***cis*-**



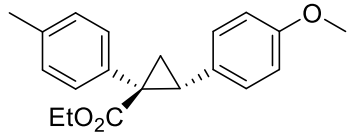
57b (25 mg, 0.065 mmol) and ethyl 4-iodobenzoate (33 mg, 0.12 mmol) to afford the title compound as a brown oil (19 mg, 0.052 mmol, 79 %). $[\alpha]_D^{20}$ = 11.1° (c = 0.51, $CHCl_3$). **^{1}H-NMR** (400 MHz, $CDCl_3$): δ = 7.83 – 7.77 (m, 2H), 7.13 – 7.05 (m, 2H), 6.73 – 6.65 (m, 2H), 6.62 – 6.55 (m, 2H), 4.32 (q, *J* = 7.1 Hz, 2H), 4.18 – 4.06 (m, 3H), 3.69 (s, 3H), 3.09 (dd, *J* = 9.4 Hz, 7.3 Hz, 1H), 2.13

(dd, *J* = 9.4 Hz, 5.0 Hz, 1H), 1.83 (dd, *J* = 7.3 Hz, 5.0 Hz, 1H), 1.36 (t, *J* = 7.1 Hz, 3H), 1.16 (t, *J* = 7.1 Hz, 3H) ppm; **^{13}C{^{1}H}-NMR** (101 MHz, $CDCl_3$): *δ* = 173.3, 166.7, 158.3, 140.5, 132.0, 129.1, 129.1, 129.0, 127.9, 113.5, 61.5, 61.0, 55.2, 37.2, 32.9, 20.1, 14.4, 14.2 ppm; **IR (film, ATR)**: $\tilde{\nu}$ [cm^{-1}] = 2980, 2936, 2906, 2837, 1710, 1612, 1515, 1463, 1444, 1368, 1272, 1248, 1211, 1174, 1102, 1022, 978, 831, 707, 552; **EI-MS**: *m/z* (%) = 368 (100, [M]), 322 (47), 295 (56), 249 (58), 221 (51), 178 (33), 121 (27), 91 (12); **HR-MS** (ESI-pos): *m/z* calcd. for [M+H]$^+$: 369.16965, found: 369.16985.

***cis*-(67h):** Prepared according to the representative procedure for Stille couplings from ***trans*-57b** (25 mg, 0.065 mmol) and ethyl 4-iodobenzoate (33 mg, 0.12 mmol) to afford the title compound as a yellow oil (17 mg, 0.046 mmol, 71 %). $[\alpha]_D^{20}$ = −193.8° (c = 1.0, $CHCl_3$). **^{1}H-NMR** (400 MHz, $CDCl_3$): *δ* = 8.09 – 7.95 (m, 2H), 7.59 – 7.47 (m, 2H), 7.28 – 7.26 (m, 2H), 6.90 – 6.79 (m, 2H), 4.38 (q, *J* = 7.1 Hz, 2H), 3.88 – 3.65 (m, 5H), 2.85 – 2.76 (m, 1H), 2.33 (dd, *J* = 7.5 Hz, 5.1 Hz, 1H), 1.62 – 1.56 (m, 1H), 1.40 (t, *J* = 7.1 Hz, 3H), 0.84 (t, *J* = 7.1 Hz, 3H) ppm; **^{13}C{^{1}H}-NMR** (101 MHz, $CDCl_3$): *δ* = 170.1, 166.5, 158.7, 145.6, 130.3, 130.2, 129.7, 129.5, 128.2, 113.6, 61.1, 61.0, 55.4, 38.0, 32.8, 18.4, 14.5, 14.0 ppm; **IR (film, ATR)**: $\tilde{\nu}$ [cm^{-1}] = 2981, 2937, 2905, 2836, 1714, 1611, 1515, 1463, 1444, 1367, 1273, 1247, 1212, 1179, 1102, 1061, 1021, 837, 706, 557; **ESI-MS**: *m/z* (%) = 759 (55, [2M+Na]$^+$), 572 (6, [2M+Ca]$^{2+}$), 391 (100, [M+Na]$^+$), 369 (92, [M+H]$^+$), 323 (10); **HR-MS** (ESI-pos): *m/z* calcd. for [M+Na]$^+$: 391.15159, found: 391.15134.



***trans*-(67i):** Prepared according to the representative procedure for Stille couplings from ***cis*-57b** (25 mg, 0.065 mmol) and *p*-tolyl triflate (25 µL, 0.14 mmol) to afford the title compound as a yellow oil (14 mg, 0.045 mmol, 69 %). $[\alpha]_D^{20}$ = 20.2° (c = 0.99, $CHCl_3$); **^{1}H-NMR** (400 MHz, $CDCl_3$): *δ* = 6.97 – 6.87 (m, 4H), 6.74 – 6.66 (m, 2H), 6.65 – 6.55 (m, 2H), 4.21 – 4.03 (m, 2H), 3.70 (s, 3H), 3.02 (dd, *J* = 9.4 Hz, 7.3 Hz, 1H), 2.24 (s, 3H), 2.08 (dd, *J* = 9.4 Hz, 4.8 Hz, 1H), 1.76 (dd, *J* = 7.3 Hz, 4.8 Hz, 1H), 1.18 (t, *J* = 7.1 Hz, 3H) ppm; **^{13}C{^{1}H}-NMR** (101 MHz, $CDCl_3$): *δ* = 174.2, 158.1, 136.5, 132.0, 131.9, 129.2, 128.8, 128.5, 113.3, 61.3, 55.3, 37.0, 32.6, 21.3, 20.5, 14.3 ppm; **IR (film, ATR)**: $\tilde{\nu}$ [cm^{-1}] = 2979, 2934, 2836, 1710, 1614, 1515, 1449, 1301, 1247, 1213, 1174, 1158, 1116, 1096, 1078, 1032, 977, 766, 699, 607; **GC-MS** (GC-EI): *m/z* (%) = 310 (78, [M]), 281 (14), 263 (69), 237 (100), 221 (32), 205 (9), 189 (29), 178 (35), 165 (34), 145 (51), 129 (40), 115 (26), 91 (26), 77 (20); **HR-MS** (GC-CI): *m/z* calcd. for [M]: 310.15635, found: 310.15659.



***cis*-(67i):** Prepared according to the representative procedure for Stille couplings from ***trans*-57b** (25 mg, 0.065 mmol) and *p*-tolyl triflate (25 µL, 0.14 mmol) to afford the title compound as a yellow oil (14 mg, 0.045 mmol, 69 %). $[\alpha]_D^{20}$ = −190.2° (c = 0.99, $CHCl_3$). **^{1}H-NMR** (400 MHz, $CDCl_3$): δ = 7.41 – 7.37 (m, 2H), 7.30 – 7.25 (m, 2H), 7.20 – 7.15 (m, 2H), 6.87 – 6.82 (m, 2H), 3.89 – 3.76 (m, 4H), 3.75 – 3.66 (m, 1H), 2.77 (dd, *J* = 9.0 Hz, 7.4 Hz, 1H), 2.36 (s, 3H), 2.27 (dd, *J* = 7.4 Hz, 5.0 Hz, 1H), 1.58 – 1.50 (m, 1H), 0.84 (t, *J* = 7.1 Hz, 3H) ppm; **^{13}C{^{1}H}-NMR** (101 MHz, $CDCl_3$): δ = 171.0, 158.6, 137.7, 137.0, 130.3, 130.2, 129.1, 128.9, 113.5, 60.8, 55.4, 37.8, 32.6, 21.3, 18.2, 14.0 ppm; **IR (film, ATR)**: $\tilde{\nu}$ [cm^{-1}] = 2980, 2933, 2836, 1719, 1655, 1613, 1514, 1447, 1367, 1301, 1246, 1211, 1177, 1100, 1061, 1033, 981, 837, 768, 699, 549; **GC-MS** (GC-EI): *m/z* (%) = 310 (76), 281 (14), 237 (100), 221 (30), 178 (34), 165 (34), 145 (50), 137 (19), 129 (40), 115 (26), 91 (25), 77 (20); **HR-MS** (GC-CI): *m/z* calcd. for [M]: 310.15635, found: 310.15652.

***trans*-(67j):** Prepared according to the representative procedure for Stille couplings from ***cis*-57b** (25 mg, 0.065 mmol) and 4-iodobenzonitrile (30 mg, 0.13 mmol) using 0.4 eq. of JackiePhos to afford the title compound as a yellow oil (16 mg, 0.05 mmol, 76 %). $[\alpha]_D^{20}$ = −1.7° (c = 1.01, $CHCl_3$). **^{1}H-NMR** (400 MHz, $CDCl_3$): δ = 7.47 – 7.35 (m, 2H), 7.17 – 7.07 (m, 2H), 6.71 – 6.65 (m, 2H), 6.65 – 6.56 (m, 2H), 4.18 – 4.08 (m, 2H), 3.70 (s, 3H), 3.11 (dd, *J* = 9.4 Hz, 7.3 Hz, 1H), 2.15 (dd, *J* = 9.4 Hz, 5.1 Hz, 1H), 1.83 (dd, *J* = 7.4 Hz, 5.2 Hz, 1H), 1.17 (t, *J* = 7.1 Hz, 3H) ppm; **^{13}C{^{1}H}-NMR** (101 MHz, $CDCl_3$): δ = 172.7, 158.5, 141.0, 132.8, 131.6, 129.0, 127.4, 119.0, 113.6, 110.8, 61.7, 55.3, 37.2, 33.0, 19.8, 14.2 ppm; **IR (film, ATR)**: $\tilde{\nu}$ [cm^{-1}] = 2981, 2935, 2837, 2228, 1714, 1611, 1516, 1463, 1442, 1373, 1302, 1250, 1211, 1176, 1031, 839, 594, 564; **ESI-MS**: *m/z* (%) = 813 (27), 665 (100, [2M+Na]$^+$), 461 (53), 344 (51, [M+Na]$^+$), 323 (98), 301 (44), 276 (29); **HR-MS** (ESI-pos): *m/z* calcd. for [M+Na]$^+$: 344.12571, found: 344.12543.

***cis*-(67j):** Prepared according to the representative procedure for Stille couplings from ***trans*-57b** (25 mg, 0.065 mmol) and 4-iodobenzonitrile (30 mg, 0.13 mmol) using 0.4 eq. of JackiePhos to afford the title compound as a brown solid (17 mg, 0.053 mmol, 81 %). $[\alpha]_D^{20}$ = −215.8° (c = 1.0, $CHCl_3$). **^{1}H-NMR** (400 MHz, $CDCl_3$): δ = 7.71 – 7.62 (m, 2H), 7.62 – 7.55 (m, 2H), 7.29 – 7.20 (m, 2H), 6.88 – 6.81 (m, 2H), 3.89 – 3.66 (m, 5H), 2.79 (dd, *J* = 9.2 Hz, 7.5 Hz, 1H), 2.36 (dd, *J* = 7.5 Hz, 5.3 Hz, 1H), 1.60 (dd, *J* = 9.3 Hz, 5.4 Hz, 1H), 0.85 (t, *J* = 7.1 Hz, 3H) ppm; **^{13}C{^{1}H}-NMR** (101 MHz, $CDCl_3$): δ = 169.7, 158.9, 145.8, 132.2, 131.1, 130.3, 127.7, 118.9, 113.7, 111.2, 61.2, 55.4, 37.9, 33.0, 18.4, 14.0 ppm; **IR (film, ATR)**: $\tilde{\nu}$ [cm^{-1}] = 2980, 2935, 2837, 2228, 1718, 1609, 1514, 1463, 1443, 1368, 1301,

1280, 1246, 1212, 1178, 1159, 1102, 1061, 1031, 836, 807, 570; **EI-MS**: *m/z* (%) = 321 (91, [M]), 292 (55), 275 (62), 248 (100), 232 (33), 203 (46), 140 (59), 121 (47), 77 (35), 51 (17); **HR-MS** (ESI-pos): *m/z* calcd. for [M-Na]$^+$: 344.12571, found: 344.12595.

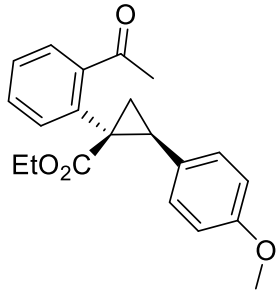
***trans*-(67k):** Prepared according to the representative procedure for Stille couplings from ***cis*-57b** (25 mg, 0.065 mmol) and 1-iodo-3-methoxybenzene (18 µL, 0.15 mmol) to afford the title compound as a brown oil (15 mg, 0.046 mmol, 70 %). $[\alpha]_D^{20}$ = 38.4° (c = 0.51, $CHCl_3$). **^{1}H-NMR** (400 MHz, $CDCl_3$): δ = 7.04 (t, *J* =7.9 Hz, 1H), 6.77 – 6.58 (m, 6H), 6.56 (dd, *J* = 2.6 Hz, 1.6 Hz, 1H), 4.22 – 4.04 (m, 2H), 3.70 (s, 3H), 3.63 (s, 3H), 3.04 (dd, *J* = 9.4 Hz, 7.3 Hz, 1H), 2.09 (dd, *J* = 9.4 Hz, 4.8 Hz, 1H), 1.78 (dd, *J* = 7.3 Hz, 4.9 Hz, 1H), 1.18 (t, *J* = 7.1 Hz, 3H) ppm; **^{13}C{^{1}H}-NMR** (101 MHz, $CDCl_3$): δ = 173.9, 158.9, 158.3, 136.7, 129.1, 128.6, 128.6, 124.6, 117.7, 113.3, 112.8, 61.3, 55.3, 55.2, 37.4, 32.6, 20.5, 14.3 ppm; **IR (film, ATR)**: $\tilde{\nu}$ [cm^{-1}] = 2958, 2836, 1711, 1610, 1583, 1516, 1493, 1452, 1370, 1337, 1250, 1208, 1176, 1156, 1118, 1037, 839, 700; **GC-MS** (GC-EI): *m/z* (%) = 326 (4, [M]), 280(100), 251 (39), 237 (35), 221 (13), 165 (12), 145 (26), 115 (7); **HR-MS** (GC-CI): *m/z* calcd. for [M+H]$^+$: 327.15909, found: 327.15902.

***cis*-(67k):** Prepared according to the representative procedure for Stille couplings from ***trans*-57b** (25 mg, 0.065 mmol) and 1-iodo-3-methoxybenzene (17 µL, 0.14 mmol) to afford the title compound as a brown oil (16 mg, 0.049 mmol, 75 %). $[\alpha]_D^{20}$ = −159.6° (c = 0.99, $CHCl_3$). **^{1}H-NMR** (400 MHz, $CDCl_3$): δ = 7.31 – 7.23 (m, 3H), 7.09 (dt, *J* = 7.7 Hz, 1.3 Hz, 1H), 7.04 (dd, *J* = 2.6 Hz, 1.6 Hz, 1H), 6.86 – 6.82 (m, 3H), 3.90 – 3.67 (m, 8H), 2.81 (dd, *J* = 9.0 Hz, 7.4 Hz, 1H), 2.28 (dd, *J* = 7.4 Hz, 5.0 Hz, 1H), 1.56 (dd, *J* = 9.0 Hz, 5.0 Hz, 1H), 0.85 (t, *J* = 7.1 Hz, 3H) ppm; **^{13}C{^{1}H}-NMR** (101 MHz, $CDCl_3$): δ = 170.7, 159.5, 158.6, 142.1, 130.3, 129.3, 128.7, 122.6, 116.2, 113.6, 112.5, 60.9, 55.4, 38.2, 32.5, 18.3, 14.0 ppm; **IR (film, ATR)**: $\tilde{\nu}$ [cm^{-1}] = 2958, 2936, 2836, 1718, 1609, 1582, 1514, 1489, 1463, 1367, 1303, 1285, 1245, 1227, 1178, 1155, 1102, 1036, 833, 781, 698, 560; **ESI-MS**: *m/z* (%) = 675 (26, [2M+Na]$^+$), 349 (100, [M+Na]$^+$), 327 (42, [M+H]$^+$), 281 (31); **HR-MS** (ESI-pos): *m/z* calcd. for [M+Na]$^+$: 349.14103, found: 349.14081.

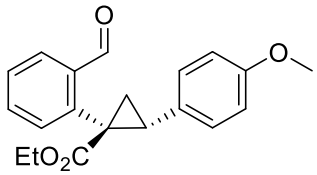
***cis*-(67l):** Prepared according to the representative procedure for Stille couplings from ***trans*-57b** (25 mg, 0.065 mmol) and 2-nitrophenyl triflate (36 mg, 0.13 mmol) to afford the title compound as a brown oil (15 mg, 0.044 mmol, 67 %). $[\alpha]_D^{20}$ = −326.7° (c = 1.01, $CHCl_3$). **^{1}H-NMR** (400 MHz, $CDCl_3$): δ = 7.97 (dd, *J* = 8.2 Hz, 1.4 Hz, 1H), 7.77 (dd, *J* = 7.8 Hz, 1.5 Hz, 1H), 7.65 (td, *J* = 7.6 Hz, 1.4 Hz, 1H), 7.48 (ddd, *J* = 8.1 Hz, 7.4 Hz, 1.4 Hz, 1H), 7.36 – 7.29 (m, 2H), 6.89 – 6.82 (m, 2H), 3.91 – 3.73 (m, 5H), 2.95 – 2.87 (m, 1H), 2.38 (dd, *J* = 7.8 Hz, 5.4 Hz, 1H), 1.40

(dd, *J* = 9.4 Hz, 5.4 Hz, 1H), 0.87 (t, *J* = 7.1 Hz, 3H) ppm; **^{13}C{^{1}H}-NMR** (101 MHz, $CDCl_3$): δ = 169.6, 158.8, 150.3, 135.9, 134.0, 133.1, 130.6, 128.6, 127.8, 124.7, 61.1, 55.4, 35.9, 33.9, 27.1, 18.7, 13.9 ppm; **IR (film, ATR)**: $\tilde{\nu}$ [cm^{-1}] = 2980, 2936, 2838, 1719, 1610, 1524, 1516, 1441, 1349, 1303, 1279, 1247, 1213, 1181, 1121, 1032, 838, 787, 743, 556; **ESI-MS**: *m/z* (%) = 705 (26, $[2M+Na]^+$), 531 (9, $[3M+Ca]^{2+}$), 380 (5, $[M+K]^+$), 364 (100, $[M+Na]^+$), 342 (25, $[M+H]^+$), 252 (17); **HR-MS** (ESI-pos): *m/z* calcd. for $[M+Na]^+$: 364.11554, found: 364.11548.

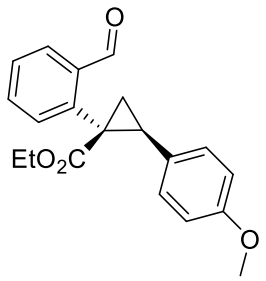
***cis*-(67m):** Prepared according to the representative procedure for Stille couplings from ***trans*-57b** (25 mg, 0.065 mmol) and 2-acetylphenyl triflate (35 mg, 0.13 mmol) to afford the title compound as a light yellow oil (9 mg, 0.027 mmol, 41 %). $[\alpha]_D^{20}$ = −219.8° (c = 0.9, $CHCl_3$). **^{1}H-NMR** (400 MHz, $CDCl_3$): δ = 7.71 (ddd, *J* = 13.8 Hz, 7.7 Hz, 1.3 Hz, 2H), 7.54 (td, *J* = 7.5 Hz, 1.4 Hz, 1H), 7.40 (td, *J* = 7.6 Hz, 1.3 Hz, 1H), 7.35 – 7.29 (m, 2H), 6.88 – 6.81 (m, 2H), 3.89 – 3.70 (m, 5H), 2.95 – 2.85 (m, 1H), 2.59 (s, 3H), 2.35 (dd, *J* = 7.6 Hz, 5.1 Hz, 1H), 1.23 (dd, *J* = 9.2 Hz, 5.1 Hz, 1H), 0.84 (t, *J* = 7.1 Hz, 3H) ppm; **^{13}C{^{1}H}-NMR** (101 MHz, $CDCl_3$): δ = 200.9, 170.7, 158.6, 140.5, 139.5, 133.4, 131.6, 130.5, 129.0, 128.8, 127.5, 113.5, 60.6, 55.4, 37.4, 34.1, 29.4, 19.6, 14.0 ppm; **IR (film, ATR)**: $\tilde{\nu}$ [cm^{-1}] = 2978, 2933, 2837, 1719, 1688, 1612, 1515, 1444, 1357, 1303, 1247, 1212, 1180, 1160, 1119, 1032, 838, 761, 601, 558; **ESI-MS**: *m/z* (%) = 699 (24, $[2M+Na]^+$), 527 (5, $[3M+Ca]^{2+}$), 377 (4, $[M+K]^+$), 361 (100, $[M+Na]^+$), 358 (8, $[2M+Ca]^{2+}$), 339 (7, $[M+H]^+$), 293 (4); **HR-MS** (ESI-pos): *m/z* calcd. for $[M+Na]^+$: 361.14103, found: 361.14096.



***trans*-(67n):** Prepared according to the representative procedure for Stille couplings from ***cis*-57b** (25 mg, 0.065 mmol) and 2-iodobenzaldehyde (32 mg, 0.14 mmol) using 0.4 eq. of JackiePhos to afford the title compound as a yellow oil (13 mg, 0.04 mmol, 61 %). $[\alpha]_D^{20}$ = 37.8° (c = 1.0, $CHCl_3$); **^{1}H-NMR** (400 MHz, $CDCl_3$): δ = 9.81 (s, 1H), 7.61 (d, *J* = 6.5 Hz, 1H), 7.52 (s, 2H), 7.38 – 7.29 (m, 1H), 6.56 (q, *J* = 8.9 Hz, 4H), 4.18 (dq, *J* = 10.8 Hz, 7.1 Hz, 1H), 4.05 (dq, *J* = 10.8 Hz, 7.1 Hz, 1H), 3.66 (s, 3H), 3.18 (dd, *J* = 9.5 Hz, 7.4 Hz, 1H), 2.24 (dd, *J* = 9.4 Hz, 5.2 Hz, 1H), 1.92 (s, 1H), 1.12 (t, *J* = 7.1 Hz, 3H) ppm; **^{13}C{^{1}H}-NMR** (101 MHz, $CDCl_3$): δ = 191.1, 173.0, 158.5, 137.5, 136.2, 133.5, 132.2, 123.0, 128.9, 127.9, 127.4, 113.4, 61.7, 55.2, 33.5, 14.2 ppm; **IR (film, ATR)**: $\tilde{\nu}$ [cm^{-1}] = 2932, 2838, 1714, 1696, 1599, 1516, 1453, 1302, 1250, 1174, 1119, 1033, 978, 830, 751; **GC-MS** (GC-EI): *m/z* (%) = 324 (1, [M]), 278 (59), 261 (13), 250 (32), 234 (22), 221 (10), 207 (22), 190 (62), 178 (29), 162 (23), 134 (100), 121 (41), 91 (20), 77 (18); **HR-MS** (ESI-pos): *m/z* calcd. for $[M+Na]^+$: 347.12538, found: 347.1256.

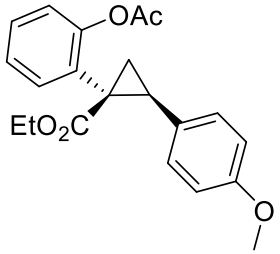


***cis*-(67n):** Prepared according to the representative procedure for Stille couplings from ***trans*-**



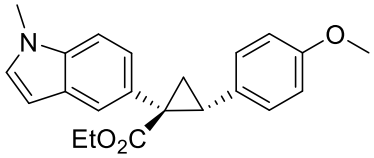
57b (25 mg, 0.065 mmol) and 2-iodobenzaldehyde (31 mg, 0.13 mmol) using 0.4 eq. of JackiePhos to afford the title compound as brown oil (16 mg, 0.049 mmol, 76 %). $[\alpha]_D^{20}$ = −167.3° (c = 1.0, $CHCl_3$); **^{1}H-NMR** (400 MHz, $CDCl_3$): δ = 10.54 (s, 1H), 7.96 – 7.91 (m, 1H), 7.66 – 7.57 (m, 2H), 7.50 – 7.44 (m, 1H), 7.33 – 7.27 (m, 2H), 6.91 – 6.84 (m, 2H), 3.91 – 3.69 (m, 5H), 2.91 (t, *J* = 8.5 Hz, 1H), 2.50 (dd, *J* = 7.7 Hz, 5.2 Hz, 1H), 1.61 (dd, *J* = 9.2 Hz, 5.2 Hz, 1H), 0.85 (t, *J* = 7.1 Hz, 3H) ppm; **^{13}C{^{1}H}-NMR** (101 MHz, $CDCl_3$): δ = 192.2, 169.9, 158.9, 142.9, 135.8, 134.0, 131.8, 130.3, 129.5, 128.2, 127.5, 113.7, 61.3, 55.4, 36.0, 33.7, 19.5, 14.0 ppm; **IR (film, ATR)**: $\tilde{\nu}$ [cm^{-1}] = 2980, 2935, 2837, 2760, 1694, 1598, 1515, 1444, 1368, 1308, 1278, 1248, 1211, 1181, 1119, 1033, 835, 753, 557; **GC-MS** (GC-EI): *m/z* (%) = 324 (1, [M]), 261 (12), 250 (28), 234 (20), 221 (9), 207 (21), 190 (58), 178 (28), 162 (22), 152 (9), 134 (100), 121 (38), 105 (8), 91 (20), 77 (17); **HR-MS** (ESI-pos): *m/z* calcd. for $[M+Na]^+$: 347.12538, found: 347.12543.

***cis*-(67o):** Prepared according to the representative procedure for Stille couplings from ***trans*-**



57b (25 mg, 0.065 mmol) and 2-iodophenyl acetate (36 mg, 0.14 mmol) using 0.4 eq. of JackiePhos to afford the title compound as a light brown oil (15 mg, 0.042 mmol, 65 %). $[\alpha]_D^{20}$ = −117.9° (c = 1.0, $CHCl_3$). **^{1}H-NMR** (400 MHz, $CDCl_3$): δ = 7.53 (dd, *J* = 7.6 Hz, 1.6 Hz, 1H), 7.34 (td, *J* = 7.7 Hz, 1.8 Hz, 1H), 7.31 – 7.28 (m, 2H), 7.27 – 7.24 (m, 1H), 7.11 (dd, *J* = 7.9 Hz, 1.3 Hz, 1H), 6.84 (d, *J* = 8.7 Hz, 2H), 3.89 – 3.70 (m, 5H), 2.89 (t, *J* = 8.4 Hz, 1H), 2.31 – 2.24 (m, 4H), 1.40 (dd, *J* = 9.2 Hz, 5.0 Hz, 1H), 0.86 (t, *J* = 7.1 Hz, 3H) ppm; **^{13}C{^{1}H}-NMR** (101 MHz, $CDCl_3$): δ = 170.0, 169.3, 158.7, 150.6, 132.8, 131.1, 130.4, 128.6, 128.2, 126.1, 122.9, 113.5, 61.0, 55.4, 34.3, 31.4, 21.2, 18.4, 14.0 ppm; **IR (film, ATR)**: $\tilde{\nu}$ [cm^{-1}] = 2981, 2935, 2837, 1766, 1722, 1612, 1515, 1491, 1450, 1368, 1310, 1280, 1247, 1212, 1188, 1115, 1036, 916, 838, 759, 558; **ESI-MS**: *m/z* (%) = 731 (4, $[2M+Na]^+$), 393 (28, $[M+K]^+$), 377 (100, $[M+Na]^+$), 372 (15, $[M+NH_4]^+$), 355 (8, $[M+H]^+$); **HR-MS** (ESI-pos): *m/z* calcd. for $[M+Na]^+$: 377.13594, found: 377.13616.

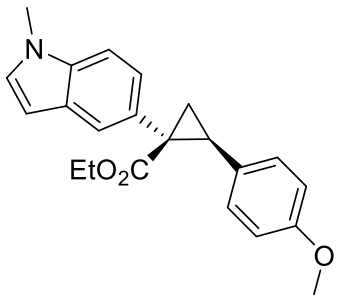
***trans*-(67p):** Prepared according to the representative procedure for Stille couplings from ***cis*-**



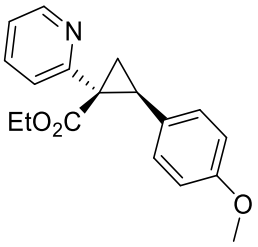
57b (20 mg, 0.052 mmol) and 5-bromo-1-methyl-1*H*-indole (23 mg, 0.11 mmol) using 0.4 eq. of JackiePhos to afford the title compound as a yellow oil (12 mg, 0.034 mmol, 66 %). $[\alpha]_D^{20}$ = −44.9° (c = 0.996, $CHCl_3$). **^{1}H-NMR** (400 MHz, $CDCl_3$): δ = 7.40 (d, *J* = 1.9 Hz, 1H), 7.03 (d, *J* = 8.5 Hz, 1H), 6.97 (d, *J* = 3.2 Hz, 1H), 6.83 – 6.77 (m, 1H), 6.70 (d, *J* = 8.7 Hz, 2H), 6.56 (d, *J* = 8.7 Hz, 2H), 6.37 (d, *J* = 3.2 Hz, 1H), 4.20 – 4.03 (m, 2H), 3.71 (s, 3H), 3.66 (s, 3H), 3.05 (dd, *J* = 9.5 Hz, 7.2 Hz, 1H), 2.14 (dd, *J* = 9.4 Hz, 4.7 Hz, 1H), 1.85 (dd, *J* = 7.2 Hz, 4.7 Hz, 1H), 1.16 (t,

J = 7.1 Hz, 3H) ppm; **^{13}C{^{1}H}-NMR** (101 MHz, $CDCl_3$): δ = 174.9, 158.0, 135.9, 129.2, 128.7, 128.1, 126.3, 125.9, 124.1, 113.2, 108.5, 101.0, 61.2, 55.2, 37.7, 33.0, 32.7, 21.3, 14.4 ppm; **IR (film, ATR)**: $\tilde{\nu}$ [cm^{-1}] = 2932, 2836, 1707, 1612, 1515, 1494, 1443, 1367, 1281, 1246, 1214, 1177, 1151, 1116, 1031, 980, 831, 721; **EI-MS**: *m/z* (%) = 349 (18, [M]), 320 (11), 303 (100), 276 (44), 260 (38), 231 (11), 217 (15), 189 (16), 168 (43), 156 (30), 145 (42), 130 (24), 115 (45), 77 (8); **HR-MS** (GC-EI): *m/z* calcd. for [M]: 349.16724, found: 349.16701.

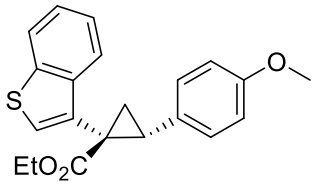
***cis*-(67p):** Prepared according to the representative procedure for Stille couplings from ***trans*-57b** (20 mg, 0.052 mmol) and 5-bromo-1-methyl-1*H*-indole (23 mg, 0.11 mmol) using 0.4 eq. of JackiePhos to afford the title compound as a light yellow solid (12 mg, 0.034 mmol, 66 %). $[\alpha]_D^{20}$ = −208.3° (c = 1.0, $CHCl_3$). **^{1}H-NMR** (400 MHz, $CDCl_3$): δ = 7.75 (s, 1H), 7.41 (d, *J* = 8.4 Hz, 1H), 7.32 (t, *J* = 9.6 Hz, 3H), 7.07 (d, *J* = 3.2 Hz, 1H), 6.87 (d, *J* = 8.7 Hz, 2H), 6.49 (d, *J* = 3.2 Hz, 1H), 3.90 – 3.77 (m, 7H), 3.75 – 3.64 (m, 1H), 2.87 (t, *J* = 8.1 Hz, 1H), 2.35 – 2.27 (m, 1H), 1.66 – 1.59 (m, 1H), 0.86 – 0.80 (m, 3H) ppm; **^{13}C{^{1}H}-NMR** (101 MHz, $CDCl_3$): δ = 171.6, 158.5, 136.0, 131.7, 130.3, 129.4, 129.3, 128.4, 124.5, 122.4, 113.5, 109.0, 101.1, 60.7, 55.4, 38.4, 33.0, 32.8, 18.5, 14.1 ppm; **IR (film, ATR)**: $\tilde{\nu}$ [cm^{-1}] = 2935, 2835, 1715, 1611, 1514, 1493, 1443, 1365, 1335, 1302, 1286, 1245, 1212, 1176, 1150, 1108, 1032, 837, 806, 760, 722; **EI-MS**: *m/z* (%) = 349 (19, [M]), 303 (100), 276 (50), 260 (41), 217 (15), 189 (17), 168 (49), 145 (45), 115 (48), 77 (8); **HR-MS** (GC-EI): *m/z* calcd. for [M]: 349.16724, found: 349.16703.



***cis*-(67q):** Prepared according to the representative procedure for Stille couplings from ***trans*-57b** (25 mg, 0.065 mmol) and pyridin-2-yl triflate (30 mg, 0.13 mmol) to afford the title compound as a colourless oil (8 mg, 0.027 mmol, 41 %). $[\alpha]_D^{20}$ = −210.2° (c = 0.8, $CHCl_3$); **^{1}H-NMR** (400 MHz, $CDCl_3$): δ = 8.54 (ddd, *J* = 4.9 Hz, 1.9 Hz, 1.0 Hz, 1H), 7.64 (td, *J* = 7.7 Hz, 1.9 Hz, 1H), 7.56 (dt, *J* = 8.0 Hz, 1.1 Hz, 1H), 7.24 (d, *J* = 8.2 Hz, 2H), 7.15 (ddd, *J* = 7.4 Hz, 4.8 Hz, 1.2 Hz, 1H), 6.85 – 6.78 (m, 2H), 3.88 (dq, *J* = 10.7 Hz, 7.1 Hz, 1H), 3.78 (s, 4H), 3.34 (t, *J* = 8.3 Hz, 1H), 2.35 (dd, *J* = 7.6 Hz, 4.9 Hz, 1H), 1.76 (dd, *J* = 9.1 Hz, 4.8 Hz, 1H), 0.87 (t, *J* = 7.1 Hz, 3H) ppm; **^{13}C{^{1}H}-NMR** (101 MHz, $CDCl_3$): δ = 170.2, 158.7, 158.5, 149.1, 136.2, 130.3, 128.6, 123.8, 121.7, 113.5, 60.9, 55.4, 39.5, 33.3, 20.2, 14.0 ppm; **IR (film, ATR)**: $\tilde{\nu}$ [cm^{-1}] = 3061, 2980, 2933, 2836, 1721, 1612, 1589, 1569, 1515, 1471, 1434, 1370, 1328, 1278, 1247, 1211, 1180, 1112, 1075, 1033, 838, 808, 778, 747, 559; **GC-MS** (GC-EI): *m/z* (%) = 297 (29, [M]), 251 (15), 223 (50), 208 (100), 180 (48), 152 (8), 112 (5), 90 (7), 78 (9); **HR-MS** (GC-CI): *m/z* calcd. for [M]: 297.13594, found: 297.13595.

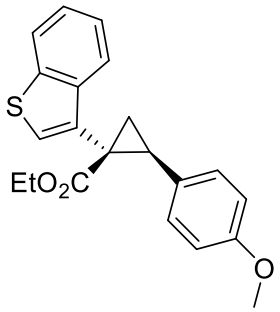


***trans*-(67r):** Prepared according to the representative procedure for Stille couplings from ***cis*-**



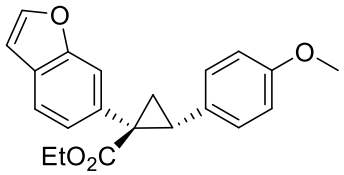
57b (20 mg, 0.052 mmol) and 3-bromobenzo[*b*]thiophene (23 mg, 0.11 mmol) using 0.4 eq. of JackiePhos to afford the title compound as brown oil (13 mg, 0.037 mmol, 71 %). $[\alpha]_D^{20}$ = 39.6° (c = 1.0, $CHCl_3$). **^{1}H-NMR** (400 MHz, $CDCl_3$): δ = 7.73 – 7.69 (m, 1H), 7.59 (dd, *J* = 6.5Hz, 2.8 Hz, 1H), 7.25 – 7.19 (m, 2H), 6.88 (s, 1H), 6.80 (d, *J* = 8.9 Hz, 2H), 6.55 (d, *J* = 8.7 Hz, 2H), 4.19 – 4.03 (m, 2H), 3.65 (s, 3H), 3.21 (dd, *J* = 9.5 Hz, 7.4 Hz, 1H), 2.21 (dd, *J* = 9.4 Hz, 4.8 Hz, 1H), 1.85 (dd, *J* = 7.4 Hz, 4.8 Hz, 1H), 1.09 (t, *J* = 7.1 Hz, 3H) ppm; **^{13}C{^{1}H}-NMR** (101 MHz, $CDCl_3$): δ = 173.5, 158.4, 139.7, 130.7, 130.7, 129.1, 128.3, 127.1, 124.1, 123.7, 122.8, 122.6, 113.2, 61.4, 55.2, 32.3, 31.3, 20.8, 14.3 ppm; **IR (film, ATR)**: $\tilde{\nu}$ [cm^{-1}] = 2979, 2906, 2836, 1710, 1612, 1515, 1461, 1431, 1368, 1279, 1246, 1206, 1176, 1143, 1096, 1031, 963, 833, 765, 731; **EI-MS**: *m/z* (%) = 352 (22, [M]), 306 (100), 279 (47), 263 (28), 234 (30), 215 (65), 202 (24), 189 (59), 171 (52), 159 (23), 145 (50), 115 (39), 91 (14), 77 (12); **HR-MS** (GC-EI): *m/z* calcd. for [M]: 352.11277, found: 352.11292.

***cis*-(67r):** Prepared according to the representative procedure for Stille couplings from ***trans*-**



57b (20 mg, 0.052 mmol) and 3-bromobenzo[*b*]thiophene (24 mg, 0.11 mmol) using 0.4 eq. of JackiePhos to afford the title compound as a brown oil (13 mg, 0.037 mmol, 71 %). $[\alpha]_D^{20}$ = −137.6° (c = 1.0, $CHCl_3$). **^{1}H-NMR** (400 MHz, $CDCl_3$): δ = 7.97 – 7.92 (m, 1H), 7.90 – 7.84 (m, 1H), 7.46 – 7.39 (m, 3H), 7.38 – 7.35 (m, 2H), 6.92 – 6.86 (m, 2H), 3.93 – 3.79 (m, 4H), 3.77 – 3.69 (m, 1H), 2.89 (t, *J* = 8.3 Hz, 1H), 2.44 – 2.38 (m, 1H), 1.59 (dd, *J* = 9.1 Hz, 4.9 Hz, 1H), 0.83 (t, *J* = 7.2 Hz, 3H) ppm; **^{13}C{^{1}H}-NMR** (101 MHz, $CDCl_3$): δ = 170.2, 158.7, 140.4, 139.3, 136.1, 130.4, 128.2, 125.5, 124.6, 124.2, 123.0, 122.9, 113.7, 61.0, 55.4, 32.3, 32.1, 18.6, 14.0 ppm; **IR (film, ATR)**: $\tilde{\nu}$ [cm^{-1}] = 3060, 2958, 2932, 2835, 1718, 1611, 1514, 1460, 1367, 1299, 1279, 1246, 1206, 1177, 1142, 1096, 1062, 1035, 831, 808, 764, 734, 699, 558, 527; **EI-MS**: *m/z* (%) = 352 (95, [M]), 306 (100), 279 (68), 215 (31), 171 (18), 77 (7); **HR-MS** (ESI-pos): *m/z* calcd. for [M+H]$^+$: 353.12059, found: 353.12109.

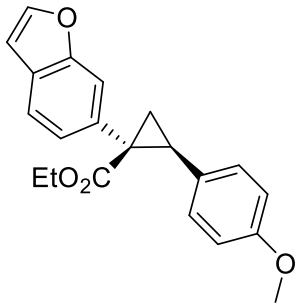
***trans*-(67s):** Prepared according to the representative procedure for Stille couplings from ***cis*-**



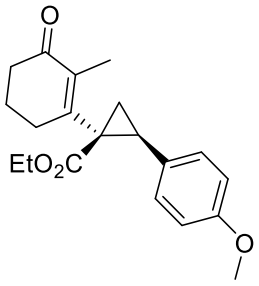
57b (20 mg, 0.052 mmol) and 6-bromobenzofuran (15 µL, 0.12 mmol) using 0.4 eq. of JackiePhos to afford the title compound as a yellow oil (13 mg, 0.039 mmol, 74 %). $[\alpha]_D^{20}$ = −31.0° (c = 1.0, $CHCl_3$). **^{1}H-NMR** (400 MHz, $CDCl_3$): δ = 7.54 (d, *J* = 2.3 Hz, 1H), 7.32 (d, *J* = 8.0 Hz, 1H), 7.23 (s, 1H), 6.93 – 6.86 (m, 1H), 6.71 (d, *J* = 8.7 Hz, 2H), 6.66 (d, *J* = 2.4 Hz, 1H), 6.57 (d, *J* = 8.7 Hz, 2H), 4.21 – 4.04 (m, 2H), 3.67 (s, 3H), 3.13 – 3.04 (m, 1H), 2.20 – 2.11 (m, 1H), 1.86 (dd, *J* = 7.4 Hz, 4.8 Hz, 1H), 1.17 (t, *J* = 7.1 Hz, 3H) ppm; **^{13}C{^{1}H}-NMR** (101 MHz, $CDCl_3$): δ =

174.0, 158.2, 154.7, 145.1, 131.8, 129.1, 128.5, 127.2, 126.3, 120.2, 114.8, 113.4, 106.6, 61.4, 55.2, 37.6, 32.9, 20.8, 14.3 ppm; **IR (film, ATR)**: $\tilde{\nu}$ [cm^{-1}] = 2980, 2935, 2907, 2836, 1711, 1612, 1516, 1427, 1372, 1303, 1249, 1208, 1177, 1152, 1117, 1029, 982, 832, 769, 736, 665, 642; **EI-MS**: *m/z* (%) = 336 (100, [M]), 307 (10), 290 (86), 263 (72), 247 (9), 219 (4), 189 (12), 155 (15), 121 (13), 91 (3); **HR-MS** (ESI-pos): *m/z* calcd. for [M+H]$^+$: 337.14343, found: 337.14381.

***cis*-(67s):** Prepared according to the representative procedure for Stille couplings from ***trans*-57b** (20 mg, 0.052 mmol) and 6-bromobenzofuran (15 µL, 0.12 mmol) using 0.4 eq. of JackiePhos to afford the title compound as a yellow oil (14 mg, 0.042 mmol, 80 %). $[\alpha]_D^{20}$ = −199.0° (c = 0.99, $CHCl_3$). **^{1}H-NMR** (400 MHz, $CDCl_3$): δ = 7.68 – 7.61 (m, 2H), 7.57 (d, *J* = 8.0 Hz, 1H), 7.41 (dd, *J* = 8.0 Hz, 1.6 Hz, 1H), 7.31 (d, *J* = 8.6 Hz, 2H), 6.87 (d, *J* = 8.7 Hz, 2H), 6.77 (d, *J* = 2.4 Hz, 1H), 3.92 – 3.77 (m, 4H), 3.75 – 3.67 (m, 1H), 2.90 – 2.81 (m, 1H), 2.38 – 2.29 (m, 1H), 1.63 (dd, *J* = 9.1 Hz, 5.0 Hz, 1H), 0.84 (t, *J* = 7.1 Hz, 3H) ppm; **^{13}C{^{1}H}-NMR** (101 MHz, $CDCl_3$): δ = 170.9, 158.6, 154.9, 145.5, 137.3, 130.3, 128.7, 126.7, 125.5, 120.8, 113.6, 113.3, 106.6, 60.9, 55.4, 38.3, 33.0, 18.5, 14.0 ppm; **IR (film, ATR)**: $\tilde{\nu}$ [cm^{-1}] = 2980, 2933, 2836, 1717, 1612, 1514, 1443, 1367, 1298, 1245, 1208, 1181, 1152, 1116, 1028, 930, 873, 836, 769, 735, 699, 652, 588; **EI-MS**: *m/z* (%) = 336 (100, [M]), 290 (85), 263 (73), 219 (5), 189 (18), 155 (16), 121 (14), 91 (5); **HR-MS** (GC-EI): *m/z* calcd. for [M]: 336.13561, found: 336.13573.



***cis*-(67t):** Prepared according to the representative procedure for Stille couplings from ***trans*-57b** (25 mg, 0.065 mmol) and 2-methyl-3-oxocyclohex-1-en-1-yl triflate (36 mg, 0.14 mmol) to afford the title compound as a colourless oil (14 mg, 0.043 mmol, 65 %). $[\alpha]_D^{20}$ = −101.2° (c = 0.99, $CHCl_3$). **^{1}H-NMR** (400 MHz, $CDCl_3$): δ = 7.23 – 7.17 (m, 2H), 6.86 – 6.79 (m, 2H), 3.90 – 3.72 (m, 5H), 2.81 – 2.69 (m, 1H), 2.63 (dd, *J* = 9.2 Hz, 7.7 Hz, 1H), 2.59 – 2.32 (m, 3H), 2.28 (dd, *J* = 7.7 Hz, 5.1 Hz, 1H), 2.08 – 1.99 (m, 2H), 1.88 (t, *J* = 1.9 Hz, 3H), 1.38 (dd, *J* = 9.3 Hz, 5.1 Hz, 1H), 0.93 (t, *J* = 7.1 Hz, 3H) ppm; **^{13}C{^{1}H}-NMR** (101 MHz, $CDCl_3$): δ = 200.1, 169.4, 158.7, 154.7, 135.8, 130.1, 127.7, 113.6, 61.0, 55.4, 37.9, 32.6, 31.6, 22.9, 20.2, 14.1, 12.2 ppm; **IR (film, ATR)**: $\tilde{\nu}$ [cm^{-1}] = 2935, 2869, 2836, 1722, 1666, 1613, 1515, 1443, 1383, 1352, 1295, 1246, 1209, 1178, 1157, 1116, 1037, 838, 808, 555; **ESI-MS**: *m/z* (%) = 679 (25, [2M+Na]$^+$), 512 (4, [3M+Ca]$^{2+}$), 351 (100, [M+Na]$^+$), 348 (15, [2M+Ca]$^{2+}$), 329 (49, [M+H]$^+$), 311 (8), 283 (12); **HR-MS** (ESI-pos): *m/z* calcd. for [M+Na]$^+$: 351.15668, found: 351.15677.



***trans*-(67u):** Prepared according to the representative procedure for Stille couplings from ***cis*-57b** (20 mg, 0.052 mmol) and 2-methyl-3-oxocyclopent-1-en-1-yl triflate (25 mg, 0.1 mmol) to afford the title compound as a yellow oil (13 mg, 0.041 mmol, 79 %). $[\alpha]_D^{20}$ = 104.8° (c = 1.0, $CHCl_3$). **^{1}H-NMR** (400 MHz, $CDCl_3$): δ = 6.94 – 6.84 (m, 2H), 6.80 – 6.66 (m, 2H), 4.26 – 4.08 (m, 2H), 3.75 (s, 3H), 3.09 (dd, *J* = 9.5 Hz, 7.5 Hz, 1H), 2.40 – 2.28 (m, 1H), 2.21 (ddd, *J* = 18.9 Hz, 7.1 Hz, 2.2 Hz, 1H), 2.11 – 2.01 (m, 2H), 1.90 – 1.81 (m, 1H), 1.74 (dd, *J* = 7.5 Hz, 5.2 Hz, 1H), 1.64 (t, *J* = 2.1 Hz, 3H), 1.24 (t, *J* = 7.2 Hz, 3H) ppm; **^{13}C{^{1}H}-NMR** (101 MHz, $CDCl_3$): δ = 210.6, 171.5, 165.7, 158.9, 142.6, 128.5, 127.5, 113.9, 61.7, 55.3, 34.5, 33.2, 32.9, 29.9, 20.1, 14.3, 9.4 ppm; **IR (film, ATR)**: $\tilde{\nu}$ [cm^{-1}] = 2980, 2922, 2838, 1699, 1644, 1612, 1516, 1443, 1388, 1372, 1301, 1252, 1208, 1175, 1156, 1119, 1065, 1032, 965, 838; **ESI-MS**: *m/z* (%) = 651 (16, $[2M+Na]^+$), 337 (100, $[M+Na]^+$), 315 (50, $[M+H]^+$); **HR-MS** (ESI-pos): *m/z* calcd. for $[M+Na]^+$: 337.14103, found: 337.14107.

***cis*-(67u):** Prepared according to the representative procedure for Stille couplings from ***trans*-57b** (20 mg, 0.052 mmol) and 2-methyl-3-oxocyclopent-1-en-1-yl triflate (25 mg, 0.1 mmol) to afford the title compound as a light yellow oil (13 mg, 0.041 mmol, 79 %). $[\alpha]_D^{20}$ = −184.8° (c = 1.0, $CHCl_3$). **^{1}H-NMR** (400 MHz, $CDCl_3$): δ = 7.24 – 7.17 (m, 2H), 6.87 – 6.80 (m, 2H), 3.93 – 3.74 (m, 5H), 2.85 – 2.68 (m, 2H), 2.65 – 2.54 (m, 1H), 2.46 (ddd, *J* = 6.1 Hz, 4.1 Hz, 3.1 Hz, 2H), 2.31 (dd, *J* = 7.7 Hz, 5.2 Hz, 1H), 1.83 (d, *J* = 4.2 Hz, 3H), 1.47 – 1.41 (m, 1H), 0.91 (t, *J* = 7.2 Hz, 3H) ppm; **^{13}C{^{1}H}-NMR** (101 MHz, $CDCl_3$): δ = 210.4, 168.8, 168.5, 158.9, 140.3, 130.3, 127.5, 113.7, 61.2, 55.4, 34.4, 34.1, 31.8, 29.5, 18.6, 14.1, 9.2 ppm; **IR (film, ATR)**: $\tilde{\nu}$ [cm^{-1}] = 2979, 2923, 2837, 1698, 1645, 1612, 1515, 1443, 1387, 1368, 1340, 1296, 1245, 1205, 1177, 1154, 1121, 1064, 1034, 833, 560, 549; **ESI-MS**: *m/z* (%) = 651 (19, $[2M+Na]^+$), 337 (100, $[M+Na]^+$), 315 (48, $[M+H]^+$); **HR-MS** (ESI-pos): *m/z* calcd. for $[M+Na]^+$: 337.14103, found: 337.14103.

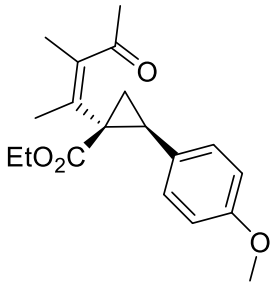
***trans*-(67v):** Prepared according to the representative procedure for Stille couplings from ***cis*-57b** (25 mg, 0.065 mmol) and methyl 2-(((trifluoromethyl)sulfonyl)oxy)acrylate (35 mg, 0.15 mmol) to afford the title compound as a colourless oil (11 mg, 0.036 mmol, 55 %). $[\alpha]_D^{20}$ = 91.6° (c = 1.0, $CHCl_3$). **^{1}H-NMR** (400 MHz, $CDCl_3$): δ = 7.01 – 6.94 (m, 2H), 6.76 – 6.70 (m, 2H), 6.25 (d, *J* = 1.2 Hz, 1H), 5.53 (d, *J* = 1.2 Hz, 1H), 4.23 (dq, *J* = 10.8 Hz, 7.1 Hz, 1H), 4.13 – 4.03 (m, 1H), 3.75 (s, 3H), 3.54 (s, 3H), 3.16 (dd, *J* = 9.2 Hz, 7.4 Hz, 1H), 1.77 (dd, *J* = 9.2 Hz, 5.2 Hz, 1H), 1.67 (dd, *J* = 7.4 Hz, 5.2 Hz, 1H), 1.21 (t, *J* = 7.1 Hz, 3H) ppm; **^{13}C{^{1}H}-NMR** (101 MHz, $CDCl_3$): δ = 173.0, 166.5, 158.6, 136.0, 129.9, 129.1, 127.2, 113.3, 61.3, 55.3, 51.7, 34.5, 31.7, 18.8, 14.3 ppm;

IR (film, ATR): $\tilde{\nu}$ [cm^{-1}] = 2964, 2908, 2838, 1719, 1612, 1516, 1438, 1369, 1337, 1249, 1205, 1175, 1154, 1120, 1030, 835, 814, 742, 531; **ESI-MS**: *m/z* (%) = 631 (14, [2M+Na]$^+$), 327 (100, [M+Na]$^+$), 305 (4, [M+H]$^+$); **HR-MS** (ESI-pos): *m/z* calcd. for [M+Na]$^+$: 327.12029, found: 327.1203.

***cis*-(67v):** Prepared according to the representative procedure for Stille couplings from ***trans*-57b** (25 mg, 0.065 mmol) and methyl 2-(((trifluoromethyl)sulfonyl)oxy)acrylate (36 mg, 0.15 mmol) to afford the title compound as a light yellow oil (8 mg, 0.026 mmol, 40 %). $[\alpha]_D^{20}$ = −101.1° (c = 0.99, $CHCl_3$). **^{1}H-NMR** (400 MHz, $CDCl_3$): δ = 7.32 – 7.27 (m, 2H), 6.85 – 6.79 (m, 2H), 6.35 (d, *J* = 1.0 Hz, 1H), 5.78 (d, *J* = 0.9 Hz, 1H), 3.87 – 3.81 (m, 4H), 3.80 – 3.75 (m, 4H), 2.73 – 2.67 (m, 1H), 2.14 (dd, *J* = 7.8 Hz, 5.0 Hz, 1H), 1.42 (dd, *J* = 9.2 Hz, 5.0 Hz, 1H), 0.90 (t, *J* = 7.1 Hz, 3H) ppm; **^{13}C{^{1}H}-NMR** (101 MHz, $CDCl_3$): δ = 170.1, 167.2, 158.6, 140.6, 130.5, 128.4, 126.7, 113.5, 60.8, 55.4, 52.2, 34.3, 32.6, 19.0, 14.0 ppm; **IR (film, ATR)**: $\tilde{\nu}$ [cm^{-1}] = 2982, 2954, 2838, 1724, 1612, 1515, 1439, 1367, 1302, 1246, 1212, 1176, 1157, 1120, 1091, 1034, 838, 811, 683, 561; **ESI-MS**: *m/z* (%) = 631 (9, [2M+Na]$^+$), 476 (2, [3M+Ca]$^{2+}$), 327 (100, [M+Na]$^+$), 324 (9, [2M+Ca]$^{2+}$), 305 (9, [M+H]$^+$), 259 (10); **HR-MS** (ESI-pos): *m/z* calcd. for [M+Na]$^+$: 327.12029, found: 327.12024.

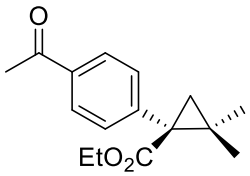
***cis*-(67w):** Prepared according to the representative procedure for Stille couplings from ***trans*-57b** (25 mg, 0.065 mmol) and ethyl 3-(((trifluoromethyl)sulfonyl)oxy)but-2-enoate (36 mg, 0.14 mmol) to afford the title compound as a colourless oil (10 mg, 0.03 mmol, 46 %). $[\alpha]_D^{20}$ = −45.3° (c = 1.0, $CHCl_3$). **^{1}H-NMR** (400 MHz, $CDCl_3$): δ = 7.23 – 7.16 (m, 2H), 6.84 – 6.76 (m, 2H), 5.91 (d, *J* = 1.4 Hz, 1H), 4.16 (qd, *J* = 7.2, 4.3 Hz, 2H), 3.89 – 3.71 (m, 5H), 2.60 (dd, *J* = 9.1 Hz, 8.0 Hz, 1H), 2.29 (dd, *J* = 7.9 Hz, 5.3 Hz, 1H), 2.20 (d, *J* = 1.4 Hz, 3H), 1.34 – 1.22 (m, 5H), 0.90 (t, *J* = 7.1 Hz, 3H) ppm; **^{13}C{^{1}H}-NMR** (101 MHz, $CDCl_3$): δ = 169.7, 165.6, 158.6, 154.0, 130.4, 128.5, 121.7, 113.5, 60.6, 60.2, 55.4, 36.2, 32.7, 25.2, 21.4, 14.4, 14.0 ppm; **IR (film, ATR)**: $\tilde{\nu}$ [cm^{-1}] = 2980, 2934, 2837, 1714, 1643, 1614, 1515, 1443, 1367, 1298, 1246, 1213, 1175, 1148, 1115, 1036, 837, 589; **ESI-MS**: *m/z* (%) = 687 (41, [2M+Na]$^+$), 518 (11, [3M+Ca]$^{2+}$), 371 (5, [M+K]$^+$), 355 (100, [M+Na]$^+$), 333 (63, [M+H]$^+$), 287 (29); **HR-MS** (ESI-pos): *m/z* calcd. for [M+Na]$^+$: 355.15159, found: 355.15161.

***cis*-(67x):** Prepared according to the representative procedure for Stille couplings from ***trans*-**



57b (25 mg, 0.065 mmol) and 3-methyl-4-oxopent-2-en-2-yl triflate (36 mg, 0.15 mmol) to afford the title compound as a light yellow oil (11 mg, 0.035 mmol, 53 %). $[\alpha]_D^{20}$ = −9.9° (c = 0.99, $CHCl_3$). **^{1}H-NMR** (400 MHz, $CDCl_3$): δ = 7.20 – 7.13 (m, 2H), 6.83 – 6.75 (m, 2H), 3.92 – 3.68 (m, 5H), 2.46 (dd, *J* = 9.2 Hz, 7.8 Hz, 1H), 2.28 (s, 3H), 2.14 (dd, *J* = 7.7 Hz, 5.1 Hz, 1H), 2.09 (d, *J* = 1.2 Hz, 3H), 1.86 (d, *J* = 1.1 Hz, 3H), 1.19 (dd, *J* = 9.3 Hz, 5.1 Hz, 1H), 0.91 (t, *J* = 7.1 Hz, 3H) ppm; **^{13}C{^{1}H}-NMR** (101 MHz, $CDCl_3$): δ = 205.8, 170.6, 158.6, 137.4, 137.1, 130.2, 128.4, 113.5, 60.6, 55.4, 38.3, 33.3, 30.1, 21.5, 20.5, 16.3, 14.1 ppm; **IR (film, ATR)**: $\tilde{\nu}$ [cm^{-1}] = 2980, 2934, 2837, 1716, 1689, 1612, 1515, 1443, 1354, 1299, 1247, 1211, 1179, 1138, 1096, 1034, 838, 808, 557; **GC-MS** (GC-EI): *m/z* (%) = 316 (1, [M]), 260 (4), 245 (9), 227 (45), 199 (90), 185 (17), 169 (9), 141 (12), 134 (100), 119 (16), 91 (15), 77 (9); **HR-MS** (GC-EI): *m/z* calcd. for [M]: 316.16691, found: 316.16697.

Compound 68a: Prepared according to the representative procedure for Stille couplings from **57l**



(25 mg, 0.082 mmol) and 1-(4-iodophenyl)ethan-1-one (41 mg, 0.17 mmol) to afford the title compound as a colourless oil (14 mg, 0.054 mmol, 66 %, 97 % *ee*). $[\alpha]_D^{20}$ = −70.4° (c = 1.0, $CHCl_3$). **^{1}H-NMR** (400 MHz, $CDCl_3$): δ = 7.92 – 7.86 (m, 2H), 7.48 – 7.42 (m, 2H), 4.18 – 3.97 (m, 2H), 2.59 (s, 3H), 1.75 (d, *J* = 4.9 Hz, 1H), 1.30 (s, 3H), 1.21 – 1.12 (m, 4H), 0.82 (s, 3H) ppm; **^{13}C{^{1}H}-NMR** (101 MHz, $CDCl_3$): δ = 198.1, 171.5, 143.8, 135.8, 131.7, 128.0, 61.2, 39.9, 26.8, 26.7, 25.7, 24.3, 21.1, 14.4 ppm; **IR (film, ATR)**: $\tilde{\nu}$ [cm^{-1}] = 2979, 2952, 2874, 1717, 1683, 1606, 1565, 1442, 1406, 1359, 1308, 1267, 1225, 1182, 1106, 1079, 1056, 1018, 958, 862, 601; **EI-MS**: *m/z* (%) = 260 (52, [M]), 232 (12), 214 (42), 199 (39), 171 (25), 157 (16), 143 (100), 128 (49), 115 (16), 102 (8), 59 (9), 43 (20); **HR-MS** (GC-EI): *m/z* calcd. for [M]: 260.1407, found: 260.14121.

The optical purity was determined by **GC** (BGB-176/BGB-15, 30 m, H_2 carrier gas, 0.6 bar, temperature gradient 220/165) **[t_R]** = 32.9 min (major), 33.5 min (minor).

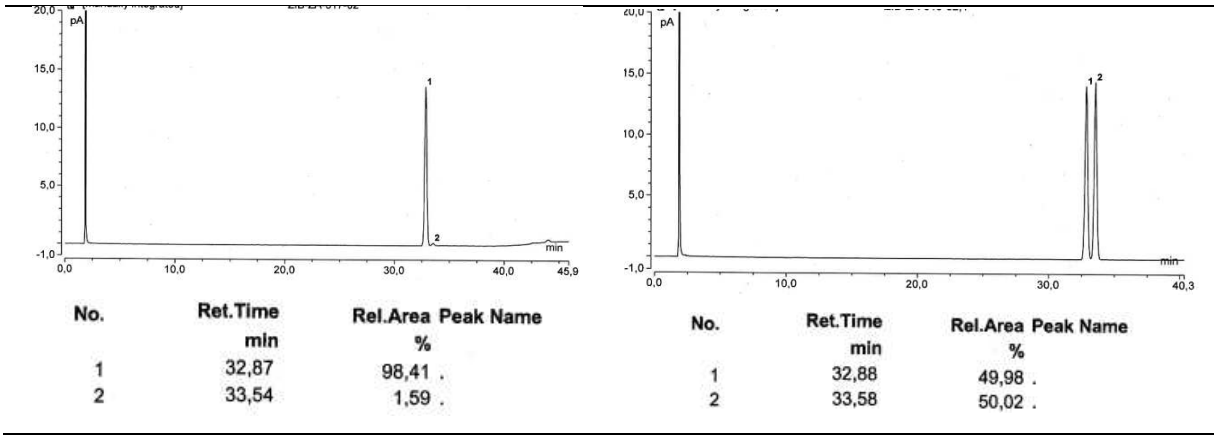
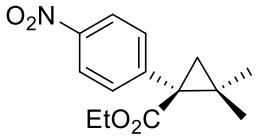


Figure 44. GC traces of enantioenriched 68a (left) and of racemic 68a (right).

Compound 68b: Prepared according to the representative procedure for Stille couplings from



57l (25 mg, 0.082 mmol) and 4-nitrophenyl triflate (46 mg, 0.17 mmol) to afford the title compound as a colourless oil (14 mg, 0.053 mmol, 65 %, 97 % *ee*). $[\alpha]_D^{20}$ = −40.0° (c = 1.0, $CHCl_3$). **^{1}H-NMR** (400 MHz, $CDCl_3$): δ = 8.19 – 8.13 (m, 2H), 7.56 – 7.49 (m, 2H), 4.20 – 3.99 (m, 2H), 1.82 (d, J = 5.1 Hz, 1H), 1.32 (s, 3H), 1.22 – 1.13 (m, 4H), 0.83 (s, 3H) ppm; **^{13}C{^{1}H}-NMR** (101 MHz, $CDCl_3$): δ = 170.9, 147.0, 145.9, 132.3, 123.1, 61.4, 39.7, 27.3, 26.0, 24.4, 21.0, 14.3 ppm; **IR (film, ATR)**: $\tilde{\nu}$ [cm^{-1}] = 2956, 2873, 1718, 1600, 1518, 1462, 1347, 1309, 1279, 1223, 1176, 1108, 1058, 1016, 974, 881, 858, 805, 744, 703, 527; **EI-MS**: *m/z* (%) = 263 (43, [M]), 235 (55), 217 (85), 202 (55), 188 (16), 172 (35), 142 (66), 129 (100), 115 (31), 102 (18), 59 (17); **HR-MS** (GC-EI): *m/z* calcd. for [M]: 263.11521, found: 263.1155.

The optical purity was determined by chiral GC (Hydrodex-gamma-TBDc-CD, 25 m, H_2 carrier gas, 0.6 bar, temperature gradient 220/160) **[t_R]** = 28.8 min (minor), 30.0 min (major).

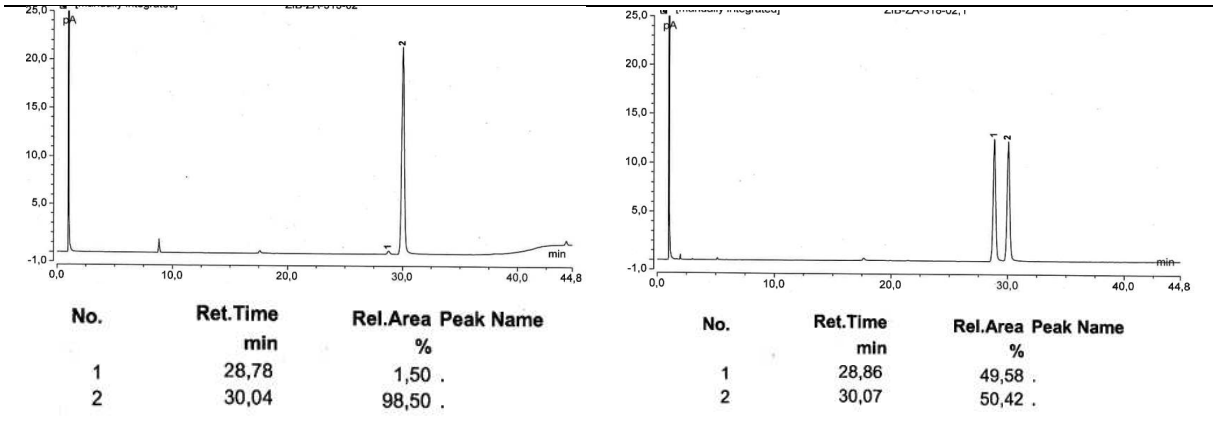
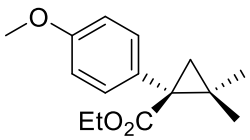


Figure 45. GC traces of enantioenriched 68b (left) and of racemic 68b (right).

Compound 68c: Prepared according to the representative procedure for Stille couplings from **57l**



(25 mg, 0.082 mmol) and 4-methoxyphenyl triflate (30 µL, 0.17 mmol) using 0.4 eq. of JackiePhos to afford the title compound as a colourless oil (11 mg, 0.044 mmol, 54 %, 97 % *ee*). $[\alpha]_D^{20}$ = −86.1° (c = 0.8, $CHCl_3$); **^{1}H-NMR** (400 MHz, $CDCl_3$): δ = 7.31 – 7.26 (m, 2H), 6.85 – 6.79 (m, 2H), 4.12 (dt, *J* = 10.8 Hz, 7.1 Hz, 1H), 4.02 (dq, *J* = 10.8 Hz, 7.1 Hz, 1H), 3.80 (s, 3H), 1.64 (d, *J* = 4.7 Hz, 1H), 1.26 (s, 3H), 1.19 (t, *J* = 7.1 Hz, 3H), 1.05 (d, *J* = 4.8 Hz, 1H), 0.84 (s, 3H) ppm; **^{13}C{^{1}H}-NMR** (101 MHz, $CDCl_3$): δ = 172.6, 158.6, 132.4, 130.4, 113.3, 60.9, 55.3, 39.2, 25.9, 25.4, 24.1, 21.4, 14.4 ppm; **IR (film, ATR)**: $\tilde{\nu}$ [cm^{-1}] = 2979, 2934, 2837, 1718, 1610, 1513, 1463, 1442, 1377, 1310, 1292, 1246, 1226, 1176, 1103, 1063, 1033, 833, 589, 551; **EI-MS**: *m/z* (%) = 248 (36, [M]), 219 (28), 202 (22), 173 (77), 159 (86), 144 (28), 133 (100), 115 (30), 91 (16), 77 (14); **HR-MS** (GC-EI): *m/z* calcd. for [M]: 248.1407, found: 248.14084.

The optical purity was determined by **GC** (BGB-176/BGB-15, 30 m, H_2 carrier gas, 0.6 bar, temperature gradient 220/140) **[t_R]** = 40.6 (major), 41.8 min (minor).

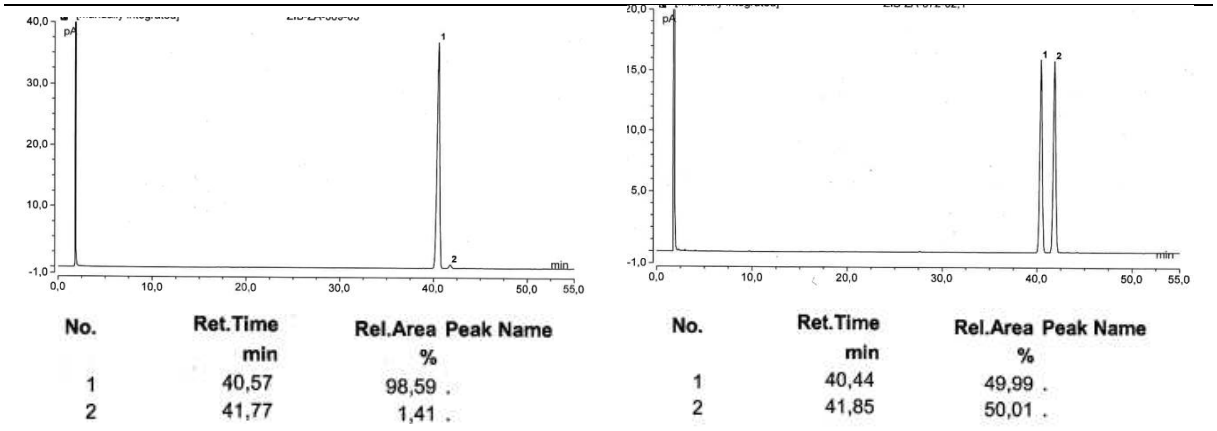
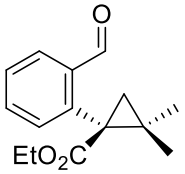


Figure 46. GC traces of enantioenriched 68c (left) and of racemic 68d (right).

Compound 68d: Prepared according to the representative procedure for Stille Couplings from



57l (25 mg, 0.082 mmol) and 2-formylphenyl triflate (43 mg, 0.17 mmol) using 0.3 eq. of JackiePhos to afford the title compound as a light yellow oil (8 mg, 0.032 mmol, 40 %, 95 % *ee*). $[\alpha]_D^{20}$ = −63.3° (c = 0.8, $CHCl_3$). **^{1}H-NMR** (400 MHz, $CDCl_3$): δ = 10.16 (s, 1H), 7.99 (d, *J* = 8.1 Hz, 1H), 7.52 (td, *J* = 7.5 Hz, 1.6 Hz, 1H), 7.40 (t, *J* = 7.5 Hz, 1H), 7.31 (d, *J* = 7.6 Hz, 1H), 4.20 – 4.08 (m, 1H), 3.99 (dq, *J* = 10.8 Hz, 7.1 Hz, 1H), 1.95 (d, *J* = 4.8 Hz, 1H), 1.37 (s, 3H), 1.26 (d, *J* = 7.1 Hz, 1H), 1.12 (t, *J* = 7.1 Hz, 3H), 0.82 (s, 3H) ppm; **^{13}C{^{1}H}-NMR** (101 MHz, $CDCl_3$): δ = 192.3, 171.4, 141.1, 137.0 133.8, 131.4, 127.9, 127.8, 61.6, 37.3, 28.5, 26.5, 24.7, 20.0, 14.2 ppm; **IR (film, ATR)**: $\tilde{\nu}$ [cm^{-1}] = 2955, 2931, 2872, 1718, 1695, 1599, 1448, 1393, 1307, 1220, 1193, 1162, 1107, 1065, 1022, 972, 860, 827, 754, 685, 655,

634, 538; **ESI-MS**: *m/z* (%) = 515 (15, $[2M+Na]^+$), 285 (9), 269 (100, $[M+Na]^+$), 247 (18, $[M+H]^+$), 229 (10), 201 (12); **HR-MS** (ESI-pos): *m/z* calcd. for $[M+Na]^+$: 269.11481, found: 269.11477.

The optical purity was determined by **GC** (BGB-176/BGB-15, 30 m, H_2 carrier gas, 0.6 bar, temperature gradient 220/140) **[t_R]** = 43.6 (major), 44.2 min (minor).

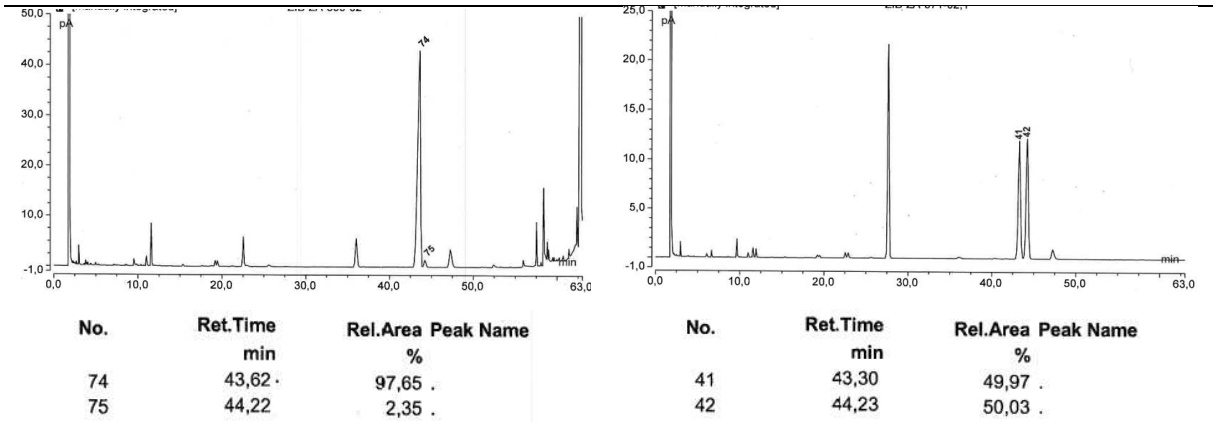


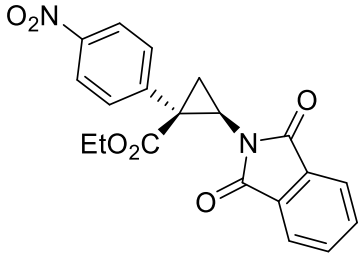
Figure 47. GC traces of enantioenriched 68d (left) and of racemic 68d (right).

***cis*-(69a):** Prepared according to the representative procedure for Stille couplings from ***trans*-57a** (20 mg, 0.057 mmol) and 1-iodo-4-nitrobenzene (28 mg, 0.11 mmol) using 0.4 eq. of JackiePhos to afford the title compound as an orange oil (13 mg, 0.042 mmol, 74 %). $[\alpha]_D^{20}$ = −193.8° (c = 1.0, $CHCl_3$). **^{1}H-NMR** (400 MHz, $CDCl_3$): δ = 8.23 (d, *J* = 8.7 Hz, 2H), 7.67 (d, *J* = 8.7 Hz, 2H), 7.39 – 7.30 (m, 4H), 7.29 – 7.23 (m, 1H), 3.88 – 3.78 (m, 1H), 3.77 – 3.66 (m, 1H), 2.88 (t, *J* = 8.4 Hz, 1H), 2.45 (dd, *J* = 7.6 Hz, 5.3 Hz, 1H), 1.67 (dd, *J* = 9.3 Hz, 5.3 Hz, 1H), 0.80 (t, *J* = 7.1 Hz, 3H) ppm; **^{13}C{^{1}H}-NMR** (101 MHz, $CDCl_3$): δ = 169.5, 147.8, 147.2, 135.7, 131.2, 129.2, 128.3, 127.3, 123.7, 61.3, 37.7, 33.7, 18.4, 13.8 ppm; **IR (film, ATR)**: $\tilde{\nu}$ [cm^{-1}] = 2981, 1717, 1600, 1518, 1497, 1451, 1347, 1310, 1279, 1211, 1175, 1105, 1026, 980, 855, 801, 769, 729, 697, 537; **EI-MS**: *m/z* (%) = 311 (4, [M]), 283 (3), 265(43), 238 (31), 218 (32), 192 (100), 165 (29), 115 (17), 107 (17), 79 (27); **HR-MS** (GC-EI): *m/z* calcd. for $[M]^+$: 311.11521 , found: 311.1153.

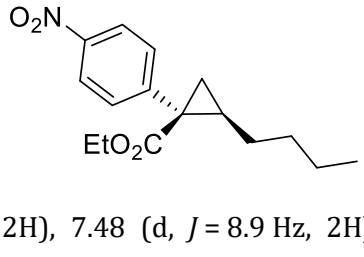
***cis*-(69b):** Prepared according to the representative procedure for Stille couplings from ***trans*-57h** (20 mg, 0.055 mmol) and 1-iodo-4-nitrobenzene (27 mg, 0.11 mmol) using 0.4 eq. of JackiePhos to afford the title compound as a yellow oil (15 mg, 0.046 mmol, 85 %). $[\alpha]_D^{20}$ = −184.1° (c = 1.01, $CHCl_3$). **^{1}H-NMR** (400 MHz, $CDCl_3$): δ = 8.19 (d, *J* = 8.9 Hz, 2H), 7.51 (d, *J* = 8.9 Hz, 2H), 7.45 – 7.40 (m, 1H), 7.20 – 7.15 (m, 3H), 3.82 – 3.65 (m, 2H), 3.54 (d, *J* = 17.5 Hz, 1H), 3.35 (dd, *J* = 17.5 Hz, 6.7 Hz, 1H), 3.18 (dd, *J* = 6.4 Hz, 1.5 Hz, 1H), 2.44 (t, *J* = 6.3 Hz, 1H), 0.75 (t, *J* = 7.1 Hz, 3H) ppm; **^{13}C{^{1}H}-NMR** (101 MHz, $CDCl_3$): δ = 168.0, 147.4, 146.9, 142.5, 141.2,

128.3, 127.1, 126.8, 125.5, 125.1, 123.9, 61.1, 41.3, 39.4, 34.1, 32.1, 13.7 ppm; **IR (film, ATR)**: $\tilde{\nu}$ [cm^{-1}] = 2979, 1722, 1597, 1516, 1476, 1462, 1345, 1279, 1250, 1175, 1149, 1112, 1067, 1032, 978, 856, 747, 724, 694; **EI-MS**: *m/z* (%) = 323 (3, [M]), 277 (13), 250 (28), 233 (3), 219 (11), 203 (100), 191 (15), 165 (6), 150 (3), 128 (3), 115 (18); **HR-MS** (GC-EI): *m/z* calcd. for [M]$^+$: 323.11521, found: 323.11542.

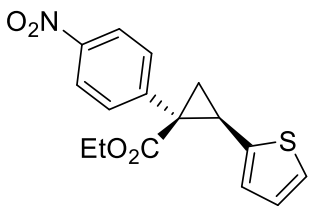
***cis*-(69c):** Prepared according to the representative procedure for Stille couplings from ***trans*-57g** (20 mg, 0.047 mmol) and 1-iodo-4-nitrobenzene (24 mg, 0.10 mmol) using 0.4 eq. of JackiePhos to afford the title compound as an orange oil (14 mg, 0.037 mmol, 78 %). $[\alpha]_D^{20}$ = −238.1° (c = 0.99, $CHCl_3$). **^{1}H-NMR** (400 MHz, $CDCl_3$): δ = 8.28 – 8.20 (m, 2H), 7.92 – 7.82 (m, 4H), 7.75 (dd, *J* = 5.4 Hz, 3.0 Hz, 2H), 4.01 – 3.83 (m, 2H), 3.19 (dd, *J* = 8.3 Hz, 6.1 Hz, 1H), 2.73 (t, *J* = 6.3 Hz, 1H), 2.09 – 2.00 (m, 1H), 0.95 (t, *J* = 7.1 Hz, 3H) ppm; **^{13}C{^{1}H}-NMR** (101 MHz, $CDCl_3$): δ = 169.4, 168.6, 147.6, 145.3, 134.5, 132.1, 131.8, 123.7, 123.6, 62.0, 36.0, 34.5, 20.3, 13.9 ppm; **IR (film, ATR)**: $\tilde{\nu}$ [cm^{-1}] = 2982, 2929, 1781, 1715, 1602, 1520, 1467, 1400, 1349, 1308, 1282, 1209, 1186, 1149, 1086, 1015, 860, 750, 720, 700, 530; **EI-MS**: *m/z* (%) = 380 (2, [M]), 334 (100), 306 (49), 204 (6), 104 (20), 76 (17); **HR-MS** (ESI-pos): *m/z* calcd. for [M+Na]$^+$: 403.09006, found: 403.08951.



***cis*-(69d):** Prepared according to the representative procedure for Stille couplings from ***trans*-57y** (20 mg, 0.06 mmol) and 1-iodo-4-nitrobenzene (32 mg, 0.13 mmol) using 0.4 eq. of JackiePhos to afford the title compound as a light yellow oil (11 mg, 0.038 mmol, 63 %). $[\alpha]_D^{20}$ = −83.5° (c = 0.94, $CHCl_3$). **^{1}H-NMR** (400 MHz, $CDCl_3$): δ = 8.15 (d, *J* = 8.9 Hz, 2H), 7.48 (d, *J* = 8.9 Hz, 2H), 4.20 – 4.00 (m, 2H), 1.70 – 1.60 (m, 3H), 1.57 – 1.35 (m, 5H), 1.33 – 1.28 (m, 1H), 1.16 (t, *J* = 7.1 Hz, 3H), 0.93 (t, *J* = 7.2 Hz, 3H) ppm; **^{13}C{^{1}H}-NMR** (101 MHz, $CDCl_3$): δ = 171.3, 148.9, 146.9, 131.2, 123.5, 61.4, 34.5, 31.9, 30.4, 27.4, 22.6, 21.0, 14.3, 14.2 ppm; **IR (film, ATR)**: $\tilde{\nu}$ [cm^{-1}] = 2958, 2929, 2861, 1720, 1601, 1520, 1464, 1446, 1349, 1309, 1280, 1184, 1141, 1103, 1057, 1015, 889, 856, 747, 699, 537; **EI-MS**: *m/z* (%) = 291 (23, [M]), 222 (43), 209 (20), 194 (81), 176 (42), 163 (25), 148 (100), 128 (51), 115 (52), 102 (19), 91 (11), 69 (10); **HR-MS** (GC-EI): *m/z* calcd. for [M]$^+$: 291.14651, found: 291.14685.

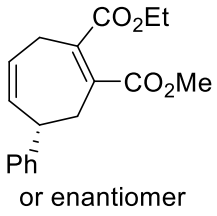


***cis*-(69e):** Prepared according to the representative procedure for Stille couplings from ***trans*-57u** (20 mg, 0.056 mmol) and 1-iodo-4-nitrobenzene (28 mg, 0.11 mmol) using 0.4 eq. of JackiePhos to afford the title compound as a yellow oil (13 mg, 0.041 mmol, 74 %). $[\alpha]_D^{20}$ = −158.3° (c = 1.0, $CHCl_3$). **^{1}H-NMR** (400 MHz, $CDCl_3$): δ = 8.22 (d, *J* = 8.9 Hz, 2H), 7.63 (d, *J* = 8.9 Hz, 2H), 7.22 – 7.16 (m, 1H), 6.95 (d, *J* = 3.7 Hz, 2H), 3.93 (dq, *J* = 10.8 Hz, 7.2 Hz, 1H), 3.83



(dq, *J* = 10.8 Hz, 7.1 Hz, 1H), 2.88 (dd, *J* = 9.1 Hz, 7.2 Hz, 1H), 2.43 (dd, *J* = 7.2 Hz, 5.3 Hz, 1H), 1.76 (dd, *J* = 9.3 Hz, 5.3 Hz, 1H), 0.93 (t, *J* = 7.2 Hz, 3H) ppm; **^{13}C{^{1}H}-NMR** (101 MHz, $CDCl_3$): δ = 168.9, 147.3, 147.0, 139.2, 131.2, 126.9, 126.7, 125.0, 123.7, 61.6, 38.6, 27.9, 20.2, 13.9 ppm; **IR (film, ATR)**: $\tilde{\nu}$ [cm^{-1}] = 2981, 1721, 1601, 1519, 1463, 1444, 1348, 1306, 1280, 1238, 1184, 1104, 1054, 1016, 855, 746, 698, 532; **EI-MS**: *m/z* (%) = 317 (41, [M]), 288 (39), 271 (50), 244 (45), 224 (23), 197 (100), 165 (61), 152 (31), 113 (25), 97 (21); **HR-MS** (GC-EI): *m/z* calcd. for [M]: 317.07163, found: 317.07167.

Compound 71 or *ent*-71: Prepared according to the representative procedure for Stille couplings



from ***cis*-57j** (25 mg, 0.065 mmol) and methyl 2-(((trifluoromethyl)sulfonyl)oxy)acrylate (35 mg, 0.15 mmol) to afford the title compound as a yellow oil (11 mg, 0.037 mmol, 56 %, 97 % *ee*). $[\alpha]_D^{20}$ = −33.9° (c = 0.99, $CHCl_3$). **^{1}H-NMR** (400 MHz, $CDCl_3$): δ = 7.37 – 7.28 (m, 2H), 7.28 – 7.17 (m, 3H), 5.84 – 5.74 (m, 1H), 5.66 (d, *J* = 11.4 Hz, 1H), 4.23 (q, *J* = 7.2 Hz, 2H), 3.70 – 3.66 (m, 4H), 3.36 (d, *J* = 18.4 Hz, 1H), 3.17 (dd, *J* = 18.0 Hz, 6.8 Hz, 1H), 3.01 (dd, *J* = 14.0 Hz, 10.8 Hz, 1H), 2.77 (dd, *J* = 13.9 Hz, 3.4 Hz, 1H), 1.31 (t, *J* = 7.2 Hz, 3H) ppm; **^{13}C{^{1}H}-NMR** (101 MHz, $CDCl_3$): δ = 168.7, 168.1, 144.5, 140.4, 137.4, 134.2, 128.7, 127.8, 126.8, 124.4, 61.5, 52.2, 42.2, 36.2, 27.9, 14.2 ppm; **IR (film, ATR)**: $\tilde{\nu}$ [cm^{-1}] = 3024, 2982, 2952, 2872, 1714, 1647, 1452, 1434, 1368, 1262, 1194, 1143, 1094, 1068, 1038, 900, 862, 811, 759, 701; **EI-MS**: *m/z* (%) = 268 (12), 254 (28), 239 (14), 222 (90), 211 (14), 194 (71), 167 (100), 152 (43), 115 (14), 91 (7); **HR-MS** (GC-CI): *m/z* calcd. for $[M+H]^+$: 301.14344, found: 301.14328.

The optical purity was determined by **HPLC** (Chiralcel OJ-3R, 150 mm, 4.6 mm i.D., acetonitrile/water 65:35, 1.0 mL/min) **[t_R]** = 4.10 (major), 6.09 min (minor).

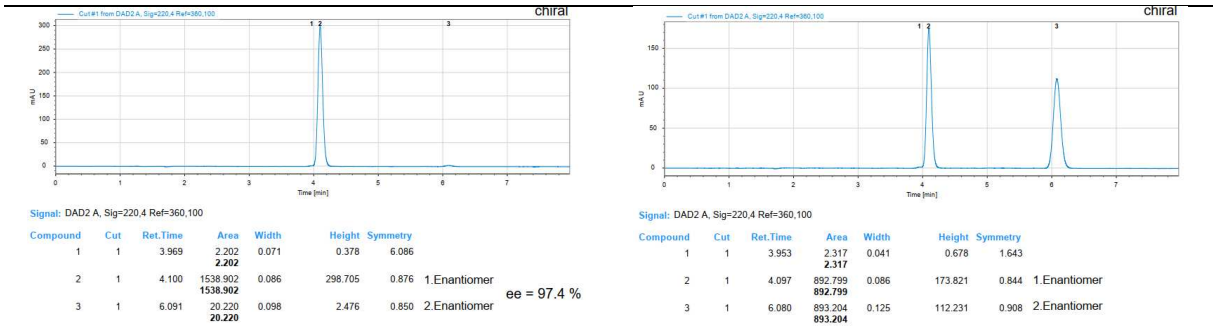
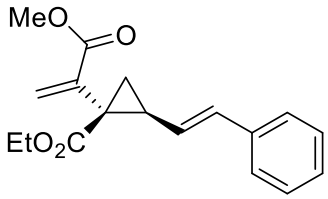


Figure 48. HPLC traces of enantioenriched 71 (left) and of racemic 71 (right).

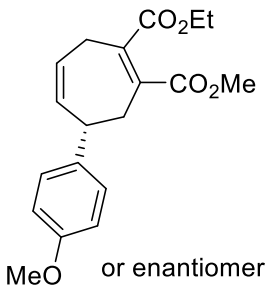
Compound 72: Prepared according to the representative procedure from ***trans*-57j** (25 mg, 0.065 mmol) and methyl 2-(((trifluoromethyl)sulfonyl)oxy)acrylate (36 mg, 0.15 mmol) to afford the title compound as a yellow oil (8 mg, 0.027 mmol, 41 %). $[\alpha]_D^{20}$ = −147.6° (c = 0.8, $CHCl_3$). **^{1}H-NMR** (400 MHz, $CDCl_3$): δ = 7.35 (dd, *J* = 8.4 Hz, 1.4 Hz, 2H), 7.28 (dd,



J = 8.3 Hz, 6.8 Hz, 2H), 7.23 – 7.17 (m, 1H), 6.64 (d, *J* = 15.8 Hz, 1H), 6.36 – 6.27 (m, 2H), 5.69 (d, *J* = 0.9 Hz, 1H), 4.20 – 4.03 (m, 2H), 3.78 (s, 3H), 2.32 – 2.22 (m, 1H), 1.90 (dd, *J* = 7.4 Hz, 4.9 Hz, 1H), 1.38 (dd, *J* = 9.0 Hz, 4.9 Hz, 1H), 1.19 (t, *J* = 3.5 Hz, 3H) ppm; **^{13}C{^{1}H}-NMR** (101 MHz, $CDCl_3$): δ = 170.9, 167.1, 140.1, 137.4, 132.5, 128.7, 127.3, 126.7, 126.4, 126.2, 61.3, 52.2, 34.1, 32.3, 22.3, 14.3 ppm; **IR (film, ATR)**: $\tilde{\nu}$ [cm^{-1}] = 2982, 2952, 2850, 1723, 1635, 1437, 1367, 1299, 1258, 1215, 1178, 1118, 1026, 964, 815, 763, 742, 693; **ESI-MS**: *m/z* (%) = 623 (41, $[2M+Na]^+$), 470 (22), 323 (100, $[M+Na]^+$), 301 (12, $[M+H]^+$), 269 (13), 255 (24); **HR-MS** (ESI-pos): *m/z* calcd. for $[M+Na]^+$: 323.12538, found: 323.12557.

Compounds 73 and 74: Prepared according to the representative procedure for Stille couplings from a diastereomeric mixture of ***cis*-** and ***trans*-57k** (50 mg, 0.12 mmol, *cis*/*trans* = 2:1) and methyl 2-(((trifluoromethyl)sulfonyl)oxy)acrylate (60 mg, 0.26 mmol) to afford the title compounds (18 mg, 0.054 mmol, 45 %, combined yield).

Compound 73 or *ent*-73: colourless oil (11 mg, 0.033 mmol, 27 %, 97 % *ee*). $[\alpha]_D^{20}$ = −53.3° (c = 1.0, $CHCl_3$). **^{1}H-NMR** (400 MHz, $CDCl_3$): δ = 7.19 – 7.13 (m, 2H), 6.88 – 6.80 (m, 2H), 5.79 5.73 (m, 1H), 5.63 (dd, *J* = 11.5 Hz, 1.1 Hz, 1H), 4.23 (q, *J* = 7.2 Hz, 2H), 3.79 (s, 3H), 3.67 (m, 4H), 3.33 (dt, *J* = 18.0 Hz, 4.8 Hz, 1H), 3.15 (dd, *J* = 17.9 Hz, 6.0 Hz, 1H), 2.97 (dd, *J* = 13.9 Hz, 10.9 Hz, 1H), 2.74 (dd, *J* = 13.9 Hz, 2.2 Hz, 1H), 1.30 (t, *J* = 7.2 Hz, 3H) ppm; **^{13}C{^{1}H}-NMR** (101 MHz, $CDCl_3$): δ = 168.7, 168.1, 158.5, 140.3, 137.5, 136.7, 134.5, 128.8, 124.1, 114.0, 61.5, 55.4, 52.2, 41.4, 36.4, 27.8, 14.2 ppm; **IR (film, ATR)**: $\tilde{\nu}$ [cm^{-1}] = 2983, 2952, 2837, 1717, 1647, 1610, 1511, 1456, 1435, 1368, 1250, 1177, 1092, 1069, 1035, 829; **ESI-MS**: *m/z* (%) = 683 (13, $[2M+Na]^+$), 353 (100, $[M+Na]^+$), 331 (35, $[M+H]^+$), 285 (13); **HR-MS** (ESI-pos): *m/z* calcd. for $[M+Na]^+$: 353.13594, found: 353.13576.



The optical purity was determined by **HPLC** (Chiralpak IJ-3, 150 mm, 4.6 mm i.D., acetonitrile/water 60:40, 1.0 mL/min) **[t_R]** = 4.57 (major), 5.22 min (minor).

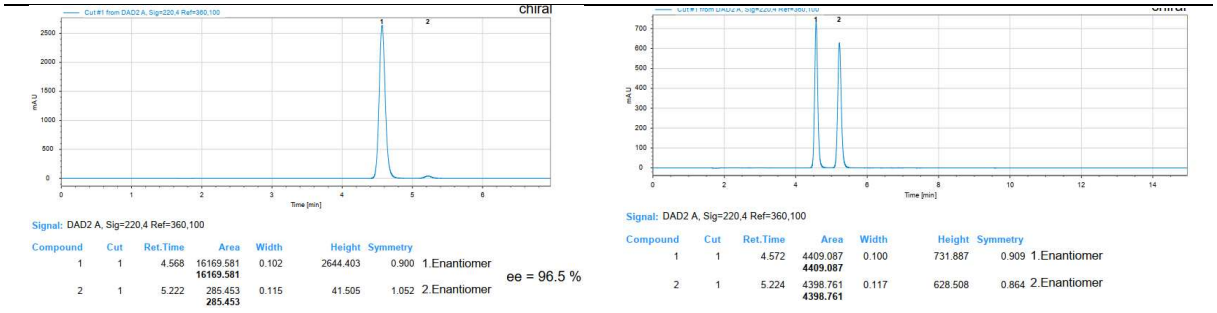
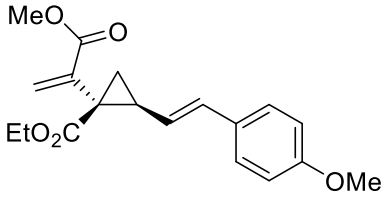


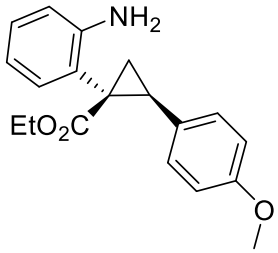
Figure 49. HPLC traces of enantioenriched 73 (left) and of racemic 73 (right).

Compound 74: light yellow oil (7 mg, 0.021 mmol, 17 %). $[\alpha]_D^{20}$ = −120.9° (c = 0.7, $CHCl_3$).



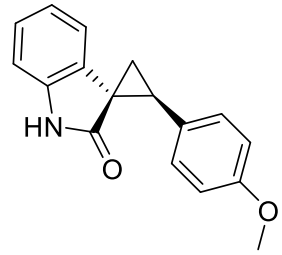
^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.32 – 7.26 (m, 2H), 6.86 – 6.79 (m, 2H), 6.58 (d, *J* = 15.8 Hz, 1H), 6.31 (d, *J* = 1.0 Hz, 1H), 6.15 (dd, *J* = 15.8 Hz, 9.0 Hz, 1H), 5.68 (d, *J* = 1.0 Hz, 1H), 4.19 – 4.02 (m, 2H), 3.80 (s, 3H), 3.78 (s, 3H), 2.32 – 2.19 (m, 1H), 1.87 (dd, *J* = 7.4 Hz, 4.9 Hz, 1H), 1.41 – 1.32 (m, 1H), 1.18 (t, *J* = 7.2 Hz, 3H) ppm; **^{13}C{^{1}H}-NMR** (101 MHz, $CDCl_3$): δ = 171.0, 167.1, 159.1, 140.2, 131.9, 130.3, 127.3, 126.3, 124.3, 114.1, 61.2, 55.4, 52.2, 34.1, 32.4, 22.2, 14.3 ppm; **IR (film, ATR)**: $\tilde{\nu}$ [cm^{-1}] = 3033, 2982, 2955, 2838, 1723, 1635, 1607, 1511, 1463, 1438, 1366, 1298, 1247, 1215, 1176, 1120, 1032, 965, 825; **ESI-MS**: *m/z* (%) = 683 (32, [2M+Na]$^+$), 515 (20), 353 (100, [M+Na]$^+$), 331 (12, [M+H]$^+$), 285 (18); **HR-MS** (ESI-pos): *m/z* calcd. for [M+Na]$^+$: 353.13594, found: 353.13617.

Compound 75: In a flame-dried Schlenk flask, ***cis*-67l** (18 mg, 0.053 mmol, 1.0 eq) was dissolved



in MeOH (1 mL). Then palladium on charcoal (10 wt%, 6 mg, 0.005 mmol, 0.1 eq) was added and the mixture was purged with hydrogen for 2 min. The mixture was stirred under a hydrogen atmosphere at room temperature for 1 h. Upon full conversion of starting material ***cis*-67l**, the mixture was diluted with CH_2Cl_2, filtered through a plug of Celite and the solvent was evaporated *in vacuo*. The crude product was immobilized on Celite and purified *via* flash chromatography (SiO_2, hexane/EtOAc 5:1) to afford the title compound as a slightly yellow oil (11 mg, 0.035 mmol, 67 %). $[\alpha]_D^{20}$ = −244.0° (c = 0.99, $CHCl_3$). **^{1}H-NMR** (400 MHz, $CDCl_3$): δ = 7.32 (t, *J* = 8.4 Hz, 3H), 7.12 (td, *J* = 7.6 Hz, 1.6 Hz, 1H), 6.85 (d, *J* = 8.7 Hz, 2H), 6.81 – 6.70 (m, 2H), 4.07 (s, 2H), 3.93 – 3.83 (m, 1H), 3.80 (s, 3H), 3.76 – 3.68 (m, 1H), 2.77 (t, *J* = 8.2 Hz, 1H), 2.35 (dd, *J* = 7.4 Hz, 4.9 Hz, 1H), 1.55 – 1.47 (m, 1H), 0.86 (t, *J* = 7.2 Hz, 3H) ppm; **^{13}C{^{1}H}-NMR** (101 MHz, $CDCl_3$): δ = 170.7, 158.6, 146.9, 131.5, 130.1, 128.7, 128.4, 125.1, 118.4, 116.0, 113.6, 61.0, 55.4, 35.6, 32.2, 18.1, 14.1 ppm; **IR (film, ATR)**: $\tilde{\nu}$ [cm^{-1}] = 3455, 3374, 3062, 2980, 2934, 2905, 2836, 1714, 1614, 1581, 1515, 1498, 1456, 1368, 1303, 1246, 1210, 1180, 1101, 1034, 980, 838, 808, 750, 524; **EI-MS**: *m/z* (%) = 311 (15, [M]), 265 (100), 248 (73), 236 (80), 222 (38), 204 (33), 193 (15), 165 (14), 145 (16), 130 (47), 121 (32), 91 (16), 77 (14); **HR-MS** (GC-EI): *m/z* calcd. for [M]: 311.15159, found: 311.15163.

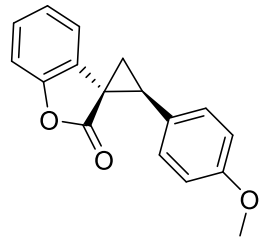
Compound 76: In a Schlenk flask, compound **75** (10 mg, 0.032 mmol) was dissolved in THF



(4 mL). Then TMSOK (41 mg, 0.32 mmol) was added and the mixture was stirred at room temperature for 6 h. The mixture was cooled to 0°C and an aqueous solution of citric acid (2 M, 10 mL) was added. After stirring for 0.5 h, the aqueous layer was extracted with EtOAc (3x), the combined organic layers were washed once with brine, dried over

$MgSO_4$, and the solvent was evaporated *in vacuo*. The crude product was immobilized on Celite and purified *via* flash chromatography (SiO_2, hexane/EtOAc 2:1 to 1:1) to obtain the title compound as a white solid (6 mg, 0.023 mmol, 70 %). $[\alpha]_D^{20}$ = −271.9° (c = 0.6, $CHCl_3$). **^{1}H-NMR** (400 MHz, $CDCl_3$): δ = 7.75 (s, 1H), 7.25 – 7.18 (m, 3H), 7.05 (t, *J* = 7.5 Hz, 1H), 6.94 (d, *J* = 7.5 Hz, 1H), 6.88 – 6.82 (m, 3H), 3.78 (s, 3H), 3.11 (t, *J* = 8.8 Hz, 1H), 2.36 (dd, *J* = 8.6 Hz, 4.9 Hz, 1H), 2.08 (dd, *J* = 9.0 Hz, 4.9 Hz, 1H) ppm; **^{13}C{^{1}H}-NMR** (101 MHz, $CDCl_3$): δ = 175.6, 158.9, 140.5, 131.6, 130.5, 126.8, 126.4, 122.0, 118.5, 113.5, 109.5, 55.3, 38.6, 34.2, 22.8 ppm; **IR (film, ATR)**: $\tilde{\nu}$ [cm^{-1}] = 3222, 2960, 2924, 2852, 1710, 1677, 1621, 1517, 1470, 1456, 1350, 1306, 1252, 1213, 1174, 1029, 988, 835, 750, 701, 649, 556, 521; **EI-MS**: *m/z* (%) = 265 (100, [M]), 250 (25), 222 (6), 204 (7), 178 (4), 165 (3), 133 (15), 102 (3), 89(4), 77 (4); **HR-MS** (ESI-pos): *m/z* calcd. for $[M+H]^+$: 266.11755, found: 266.11788.

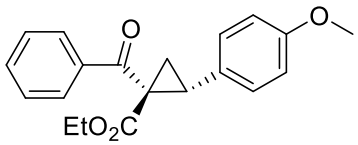
Compound 78: Prepared analogously to compound **76** from ***cis*-67o** (15 mg, 0.042 mmol) to afford the title compound as a light brown oil (9 mg, 0.034 mmol, 80 %).



$[\alpha]_D^{20}$ = −170.8° (c = 0.9, $CHCl_3$). **^{1}H-NMR** (400 MHz, $CDCl_3$): δ = 7.30 – 7.20 (m, 4H), 6.97 – 6.89 (m, 2H), 6.84 (d, *J* = 8.9 Hz, 2H), 3.81 (s, 3H), 2.69 (t, *J* = 8.4 Hz, 1H), 2.31 (dd, *J* = 7.8 Hz, 5.5 Hz, 1H), 1.73 (dd, *J* = 9.0 Hz, 5.4 Hz, 1H) ppm; **^{13}C{^{1}H}-NMR** (101 MHz, $CDCl_3$): δ = 176.6, 158.8, 156.1, 130.8, 130.1, 129.6, 127.4, 126.6, 120.9, 117.6, 113.9, 55.5, 34.3, 34.2, 17.9 ppm; **IR (film, ATR)**: $\tilde{\nu}$ [cm^{-1}] = 3010, 2926, 2853, 1686, 1611, 1541, 1454, 1415, 1289, 1245, 1177, 1115, 1034, 981, 946, 834, 806, 753, 627, 559, 534; **ESI-MS**: *m/z* (%) = 289 (3, $[M+Na]^+$), 267 (22, $[M+H]^+$); **HR-MS** (ESI-pos): *m/z* calcd. for $[M+Na]^+$: 289.08351, found: 289.08357.

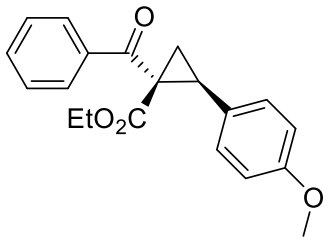
4.2.5 Carbonylative Stille Coupling Reactions

Representative procedure for carbonylative Stille couplings: *trans*-(79a): In a pressure Schlenk flask, $Pd(PPh_3)_4$ (9 mg, 0.008 mmol), CuCl (10 mg, 0.1 mmol) and KF (6 mg, 0.1 mmol) were mixed and dissolved in THF (2 mL). In another Schlenk flask, ***cis*-57b** (20 mg, 0.052 mmol) and iodobenzene (15 µL, 0.13 mmol) were dissolved in THF (1 mL). This solution was added to the catalyst solution *via* syringe and CO was bubbled through the solution for 20 seconds. The mixture was stirred at 70°C. Upon completion (monitored by GC-MS), the mixture was diluted with EtOAc, filtered, and the solvent evaporated. The crude product was immobilized on Celite and purified *via* flash chromatography (SiO_2, hexane/EtOAc 11:1 to 9:1) to afford the title compound as a light yellow oil (11 mg, 0.034 mmol, 65 %). $[\alpha]_D^{20}$ = 217.4° (c = 0.99, $CHCl_3$). **^{1}H-NMR** (400 MHz, $CDCl_3$): δ = 7.68 (d, *J* = 7.0 Hz, 2H), 7.40 (t, *J* = 7.4 Hz, 1H), 7.29 (t, *J* = 7.7 Hz, 2H), 7.04 (d, *J* = 8.9 Hz, 2H), 6.65 (d, *J* = 8.7 Hz, 2H), 4.11 (dq, *J* = 10.6 Hz, 7.1 Hz, 1H), 3.98 (dq,

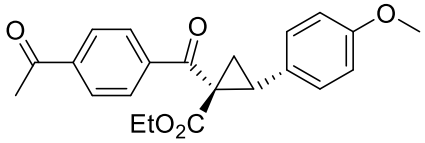


J = 10.8 Hz, 7.2 Hz, 1H), 3.65 (s, 3H), 3.49 (t, *J* = 8.7 Hz, 1H), 2.42 (dd, *J* = 8.1 Hz, 5.1 Hz, 1H), 1.75 (dd, *J* = 9.3 Hz, 5.1 Hz, 1H), 0.92 (t, *J* = 7.2 Hz, 3H) ppm; **^{13}C{^{1}H}-NMR** (101 MHz, $CDCl_3$): δ = 193.1, 171.3, 158.8, 137.7, 132.6, 129.2, 128.5, 128.2, 125.9, 113.8, 61.6, 55.2, 42.0, 33.8, 18.6, 13.8 ppm; **IR (film, ATR)**: $\tilde{\nu}$ [cm^{-1}] = 2981, 2932, 2838, 1721, 1677, 1612, 1582, 1516, 1448, 1373, 1324, 1304, 1268, 1251, 1220, 1176, 1149, 1119, 1031, 1008, 835, 692, 665, 539; **EI-MS**: *m/z* (%) = 324 (14, [M]), 278 (50), 216 (5), 200 (29), 165 (4), 145 (13), 105 (100), 77 (27); **HR-MS** (ESI-pos): *m/z* calcd. for [M+H]$^{+}$: 325.14344, found: 325.14351.

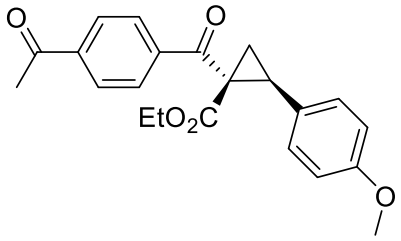
***cis*-(79a):** Prepared according to the representative procedure for carbonylative Stille couplings from ***trans*-57b** (20 mg, 0.052 mmol) and iodobenzene (11 µL, 0.10 mmol) to afford the title compound as a white solid (12 mg, 0.037 mmol, 71 %). $[\alpha]_D^{20}$ = −183.2° (c = 1.0, $CHCl_3$). **^{1}H-NMR** (400 MHz, $CDCl_3$): δ = 7.90 (d, *J* = 7.0 Hz, 2H), 7.54 (t, *J* = 7.4 Hz, 1H), 7.44 (t, *J* = 7.6 Hz, 2H), 7.23 (d, *J* = 8.7 Hz, 2H), 6.83 (d, *J* = 8.7 Hz, 2H), 3.78 (s, 3H), 3.72 (qd, *J* = 7.1 Hz, 4.8 Hz, 2H), 3.52 (t, *J* = 8.6 Hz, 1H), 2.40 (dd, *J* = 8.1 Hz, 4.8 Hz, 1H), 1.66 (dd, *J* = 9.1 Hz, 4.8 Hz, 1H), 0.70 (t, *J* = 7.1 Hz, 3H) ppm; **^{13}C{^{1}H}-NMR** (101 MHz, $CDCl_3$): δ = 195.3, 168.6, 158.9, 137.6, 132.9, 130.3, 128.6, 128.3, 126.9, 113.6, 61.2, 55.4, 42.5, 30.4, 20.4, 13.7 ppm; **IR (film, ATR)**: $\tilde{\nu}$ [cm^{-1}] = 3011, 2965, 2841, 1723, 1673, 1612, 1516, 1448, 1370, 1306, 1276, 1249, 1216, 1176, 1145, 1117, 1093, 837, 794, 716, 659, 554; **EI-MS**: *m/z* (%) = 324 (13, [M]), 278 (63), 250 (3), 200 (25), 165 (5), 145 (11), 105 (100), 77(31); **HR-MS** (GC-EI): *m/z* calcd. for [M]: 324.13561, found: 324.13573. The analytical data is consistent with the literature[257].



***trans*-(79b):** Prepared according to the representative procedure for carbonylative Stille couplings from ***cis*-57b** (20 mg, 0.052 mmol) and 1-(4-iodophenyl)ethan-1-one (27 mg, 0.11 mmol) to afford the title compound as a light yellow oil (14 mg, 0.038 mmol, 73 %). $[\alpha]_D^{20}$ = 194.2° (c = 0.99, $CHCl_3$). **^{1}H-NMR** (400 MHz, $CDCl_3$): δ = 7.87 (d, *J* = 8.6 Hz, 2H), 7.74 (d, *J* = 8.6 Hz, 2H), 7.03 (d, *J* = 8.7 Hz, 2H), 6.65 (d, *J* = 8.9 Hz, 2H), 4.15 – 3.96 (m, 2H), 3.65 (s, 3H), 3.52 (t, *J* = 8.7 Hz, 1H), 2.58 (s, 3H), 2.45 (dd, *J* = 8.1 Hz, 5.1 Hz, 1H), 1.81 (dd, *J* = 9.3 Hz, 5.2 Hz, 1H), 0.93 (t, *J* = 7.2 Hz, 3H) ppm; **^{13}C{^{1}H}-NMR** (101 MHz, $CDCl_3$): δ = 197.6, 192.7, 170.9, 159.0, 141.0, 139.7, 129.2, 128.6, 128.2, 125.5, 113.9, 61.8, 55.2, 42.2, 34.4, 26.9, 18.6, 13.9 ppm; **IR (film, ATR)**: $\tilde{\nu}$ [cm^{-1}] = 2933, 2838, 1722, 1680, 1611, 1515, 1442, 1404, 1370, 1303, 1248, 1176, 1149, 1118, 1087, 1030, 959, 829, 764, 542; **EI-MS**: *m/z* (%) = 366 (28, [M]), 320 (87), 277 (14), 249 (2), 200 (23), 147 (100), 91 (12); **HR-MS** (GC-EI): *m/z* calcd. for [M]: 366.14618, found: 366.14626.

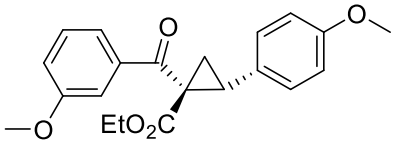


***cis*-(79b):** Prepared according to the representative procedure for carbonylative Stille couplings



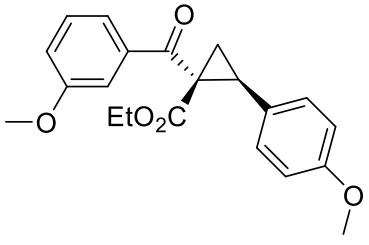
from ***trans*-57b** (20 mg, 0.052 mmol) and 1-(4-iodophenyl)ethan-1-one (26 mg, 0.11 mmol) to afford the title compound as a colourless solid (13 mg, 0.035 mmol, 68 %). $[\alpha]_D^{20}$ = −114.7° (c = 1.0, $CHCl_3$). **^{1}H-NMR** (400 MHz, $CDCl_3$): δ = 8.04 – 7.99 (m, 2H), 7.97 – 7.92 (m, 2H), 7.25 – 7.18 (m, 2H), 6.86 – 6.79 (m, 2H), 3.78 (s, 3H), 3.76 – 3.63 (m, 2H), 3.54 (t, *J* = 8.7 Hz, 1H), 2.64 (s, 3H), 2.44 (dd, *J* = 8.2 Hz, 4.8 Hz, 1H), 1.72 (dd, *J* = 9.2 Hz, 4.8 Hz, 1H), 0.69 (t, *J* = 7.2 Hz, 3H) ppm; **^{13}C{^{1}H}-NMR** (101 MHz, $CDCl_3$): δ = 197.6, 195.1, 168.3, 159.0, 141.3, 140.0, 130.3, 128.5, 128.3, 126.5, 113.7, 61.4, 55.4, 42.7, 31.0, 27.0, 21.0, 13.7 ppm; **IR (film, ATR)**: $\tilde{\nu}$ [cm^{-1}] = 2979, 2934, 2837, 1731, 1684, 1612, 1516, 1441, 1404, 1369, 1306, 1250, 1177, 1147, 1091, 1034, 996, 838, 765, 544; **EI-MS**: *m/z* (%) = 366 (23, [M]), 320 (92), 277 (15), 249 (2), 219 (7), 200 (24), 147 (100), 91 (13), 77 (7); **HR-MS** (GC-EI): *m/z* calcd. for [M]: 366.14618, found: 366.14648.

***trans*-(79c):** Prepared according to the representative procedure for carbonylative Stille couplings from ***cis*-57b** (20 mg, 0.052 mmol) and 1-iodo-3-methoxybenzene (15 µL, 0.13 mmol) to afford the title compound as a yellow oil (13 mg, 0.037 mmol, 70 %).



$[\alpha]_D^{20}$ = 209.7° (c = 0.49, $CHCl_3$). **^{1}H-NMR** (400 MHz, $CDCl_3$): δ = 7.29 – 7.25 (m, 1H), 7.23 – 7.17 (m, 2H), 7.07 – 7.02 (m, 2H), 6.95 (ddd, *J* = 8.0 Hz, 2.7 Hz, 1.1 Hz, 1H), 6.69 – 6.62 (m, 2H), 4.12 (dq, *J* = 10.8 Hz, 7.2 Hz, 1H), 3.99 (dq, *J* = 10.9 Hz, 7.2 Hz, 1H), 3.77 (s, 3H), 3.67 (s, 3H), 3.52 – 3.45 (m, 1H), 2.41 (dd, *J* = 8.1 Hz, 4.9 Hz, 1H), 1.75 (dd, *J* = 9.3 Hz, 4.9 Hz, 1H), 0.95 (t, *J* = 7.2 Hz, 3H) ppm; **^{13}C{^{1}H}-NMR** (101 MHz, $CDCl_3$): δ = 193.0, 171.3, 159.5, 158.8, 139.1, 129.2, 129.2, 126.0, 121.3, 119.3, 113.8, 112.5, 61.6, 55.5, 55.2, 42.2, 33.8, 18.6, 13.9 ppm; **IR (film, ATR)**: $\tilde{\nu}$ [cm^{-1}] = 2959, 2837, 1721, 1678, 1598, 1516, 1487, 1463, 1373, 1319, 1253, 1211, 1175, 1144, 1119, 1094, 1026, 836, 793, 685, 540; **ESI-MS**: *m/z* (%) = 731 (36, $[2M+Na]^+$), 393 (21, $[M+K]^+$), 377 (100, $[M+Na]^+$), 355 (45, $[M+H]^+$); **HR-MS** (ESI-pos): *m/z* calcd. for $[M+Na]^+$: 377.13594, found: 377.13613.

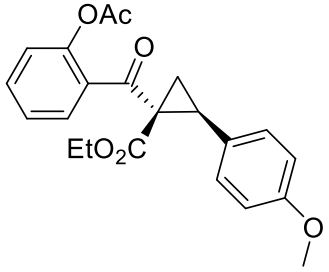
***cis*-(79c):** Prepared according to the representative procedure for carbonylative Stille couplings



from ***trans*-57b** (20 mg, 0.052 mmol) and 1-iodo-3-methoxybenzene (15 µL, 0.13 mmol) to afford the title compound as a yellow oil (15 mg, 0.042 mmol, 81 %). $[\alpha]_D^{20}$ = −6.8° (c = 1.01, $CHCl_3$). **^{1}H-NMR** (400 MHz, $CDCl_3$): δ = 7.48 (d, *J* = 7.7 Hz, 1H), 7.45 – 7.41 (m, 1H), 7.34 (t, *J* = 7.9 Hz, 1H), 7.23 (d, *J* = 8.9 Hz, 2H), 7.08 (dd, *J* = 7.7 Hz, 2.1 Hz, 1H), 6.82 (d, *J* = 8.7 Hz, 2H), 3.85 (s, 3H), 3.79 – 3.66 (m, 5H), 3.51 (t, *J* = 8.6 Hz, 1H), 2.39 (dd, *J* = 8.0 Hz, 4.8 Hz, 1H), 1.65 (dd, *J* = 9.1 Hz, 4.8 Hz, 1H), 0.72 (t, *J* = 7.1 Hz, 3H) ppm; **^{13}C{^{1}H}-NMR** (101 MHz, $CDCl_3$): δ = 195.1, 168.6, 159.9, 158.9, 138.9, 130.3, 129.6,

126.9, 120.9, 119.5, 113.6, 112.5, 61.3, 55.6, 55.4, 42.6, 30.3, 20.4, 13.7 ppm; **IR (film, ATR)**: $\tilde{\nu}$ [cm^{-1}] = 2936, 2836, 1686, 1600, 1580, 1514, 1490, 1463, 1398, 1375, 1247, 1216, 1176, 1088, 1035, 832, 763, 700, 543; **ESI-MS**: *m/z* (%) = 747 (17, [2M+K]$^+$), 731 (100, [2M+Na]$^+$), 726 (11, [2M+NH$_4$]$^+$), 655 (21), 393 (17, [M+K]$^+$), 377 (56, [M+Na]$^+$), 355 (52, [M+H]$^+$); **HR-MS** (ESI-pos): *m/z* calcd. for [M+H]$^+$: 355.154, found: 355.15405.

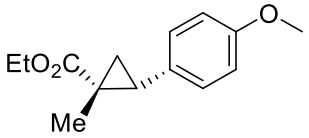
***cis*-(79d):** Prepared according to the representative procedure for carbonylative Stille couplings



from ***trans*-57b** (20 mg, 0.052 mmol) and 2-iodophenyl acetate (27 mg, 0.10 mmol) to afford the title compound as a light yellow oil (9 mg, 0.024 mmol, 45 %). $[\alpha]_D^{20}$ = −23.9° (c = 0.45, $CHCl_3$). **^{1}H-NMR** (400 MHz, $CDCl_3$): δ = 7.73 (dd, *J* = 7.8 Hz, 1.7 Hz, 1H), 7.53 – 7.45 (m, 1H), 7.30 (td, *J* = 7.5 Hz, 1.2 Hz, 1H), 7.19 (d, *J* = 8.2 Hz, 2H), 7.14 (dd, *J* = 8.1 Hz, 1.1 Hz, 1H), 6.80 (d, *J* = 8.9 Hz, 2H), 3.77 (s, 3H), 3.71 – 3.58 (m, 3H), 2.39 (dd, *J* = 8.2 Hz, 4.4 Hz, 1H), 2.34 (s, 3H), 1.77 (dd, *J* = 9.2 Hz, 4.4 Hz, 1H), 0.66 (t, *J* = 7.2 Hz, 3H) ppm; **^{13}C{^{1}H}-NMR** (101 MHz, $CDCl_3$): δ = 195.3, 169.3, 168.0, 159.0, 148.4, 132.6, 132.2, 130.4, 129.8, 126.7, 126.0, 123.1, 113.6, 61.2, 55.4, 44.5, 33.5, 22.6, 21.3, 13.5 ppm; **IR (film, ATR)**: $\tilde{\nu}$ [cm^{-1}] = 2981, 2936, 2838, 1768, 1731, 1685, 1645, 1604, 1515, 1484, 1448, 1370, 1341, 1296, 1248, 1187, 1112, 1083, 1032, 911, 834, 760, 542; **ESI-MS**: *m/z* (%) = 803 (10, [2M+K]$^+$), 787 (69, [2M+Na]$^+$), 683 (12), 421 (27, [M+K]$^+$), 405 (100, [M+Na]$^+$), 383 (47, [M+H]$^+$); **HR-MS** (ESI-pos): *m/z* calcd. for [M+H]$^+$: 383.14892, found: 383.14895.

4.2.6 Tin-Lithium Exchange Reactions

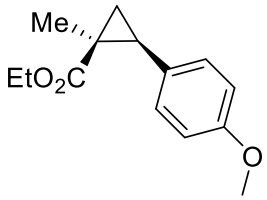
<u>Representative procedure for tin-lithium exchange</u>: *ent*-82a: In a Schlenk flask, ***cis*-57b**



(25 mg), 0.065 mmol) was dissolved in THF (1 mL). The solution was cooled to -78°C and methyllithium (0.188 M in Et_2O, 0.38 mL, 0.071 mmol) was added. After 3 min of stirring, methyl iodide (10 µL, 0.16 mmol) was added and the mixture was stirred at -78°C for 2 min. The cooling bath was removed and the mixture was warmed to room temperature. Upon completion of the reaction (monitored by TLC), the reaction mixture was diluted with MTBE. The crude product was immobilized on Celite and purified *via* flash chromatography (SiO_2, hexane/EtOAc 15:1) to afford the title compound as a light yellow oil (12 mg, 0.051 mmol, 78 %). $[\alpha]_D^{20}$ = 71.8° (c = 1.0, $CHCl_3$). **^{1}H-NMR** (400 MHz, $CDCl_3$): δ = 7.13 (d, *J* = 8.6 Hz, 2H), 6.78 (d, *J* = 8.7 Hz, 2H), 3.86 – 3.70 (m, 5H), 2.27 (t, *J* = 8.0 Hz, 1H), 1.89 (dd, *J* = 7.2 Hz, 4.9 Hz, 1H), 1.47 (s, 3H), 1.08 (dd, *J* = 8.7 Hz, 4.9 Hz, 1H), 0.88 (t, *J* = 7.2 Hz, 3H) ppm; **^{13}C{^{1}H}-NMR** (101 MHz, $CDCl_3$): δ = 172.8, 158.3, 130.3, 129.6, 113.3, 60.3, 55.4, 33.2, 27.6, 21.4, 19.0, 14.0 ppm; **IR (film, ATR)**: $\tilde{\nu}$ [cm^{-1}] = 2978, 2934, 2836, 1715, 1612, 1514, 1463, 1442, 1370, 1325, 1299, 1244, 1174, 1150, 1114, 1031, 945, 836, 802, 770, 730,

686, 560, 543; **EI-MS**: *m/z* (%) = 234 (10, [M]), 205(6), 188 (33), 177 (30), 161 (100), 145 (17), 115 (14), 91 (18), 77 (5); **HR-MS** (GC-EI): *m/z* calcd. for [M]: 234.12505, found: 234.12502.

Compound 82a: Prepared according to the representative procedure for tin-lithium exchange



from ***trans*-57b** (20 mg, 0.052 mmol) to afford the title compound as a colourless oil (9.7 mg, 0.041 mmol, 79 %). $[\alpha]_D^{20}$ = −46.9° (c = 0.97, $CHCl_3$). Other analytical data *vide supra*.

The formation of two enantiomers depending on whether ***cis*-57b** or ***trans*-57b** is used as a starting material is also supported by chiral HPLC (150 mm Chiralpak IB-N, 3 µm, 4.6 mm, *n*-heptane/2-propanol 95:5, 1.0 mL·min^{-1}, 298 K): 3.08 min (***ent*-82a** from ***cis*-57b**) and 3.23 min (**82a** from ***trans*-57b**).

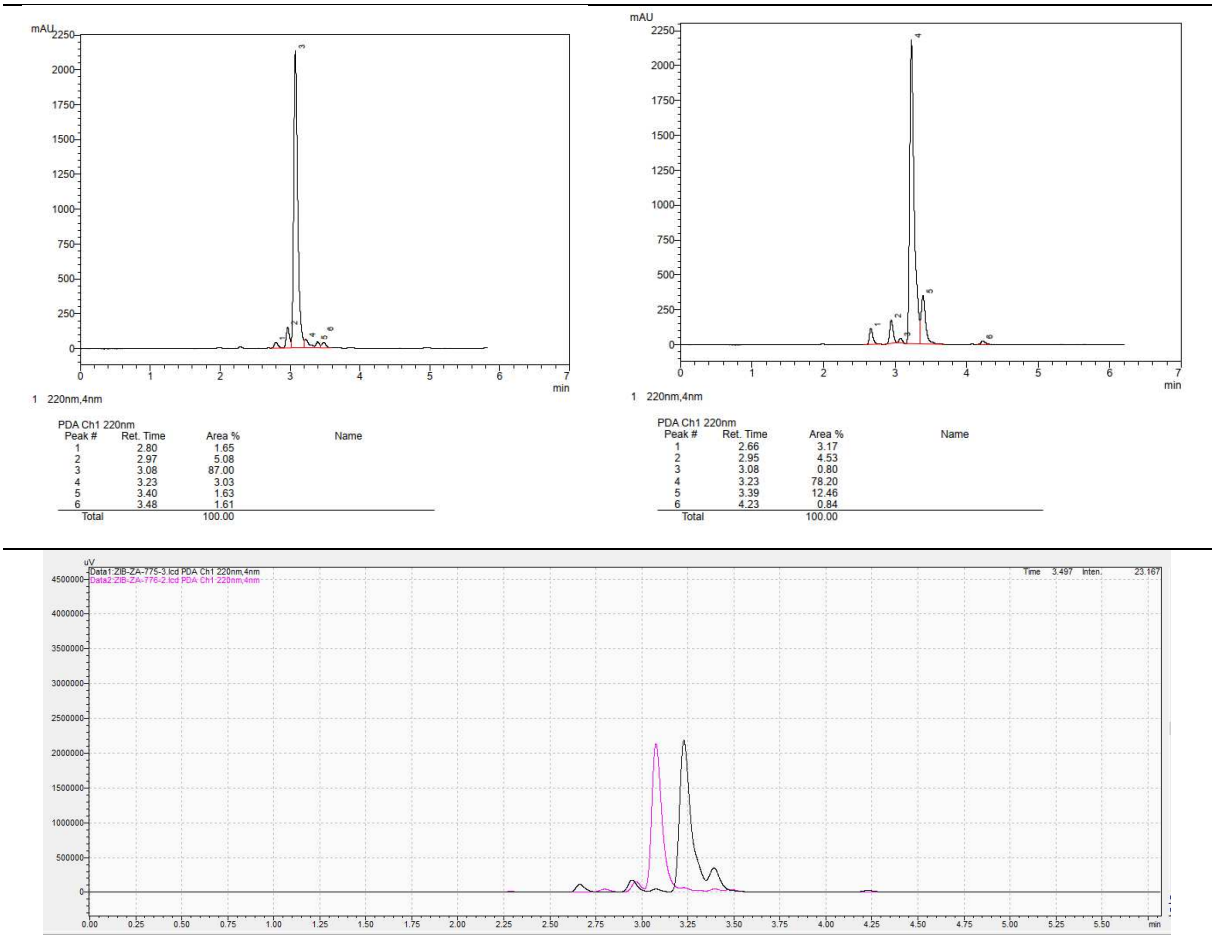
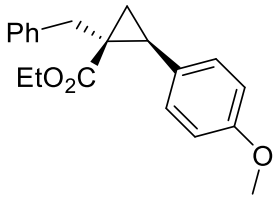


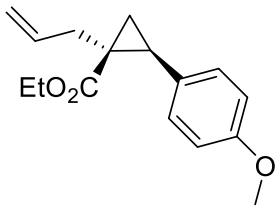
Figure 50. HPLC traces of *ent*-82a (from *cis*-57b, top left), 82a (from *trans*-57b, top right) and an overlay of the two chromatograms (bottom).

Compound 82b: Prepared according to the representative procedure for tin-lithium exchange



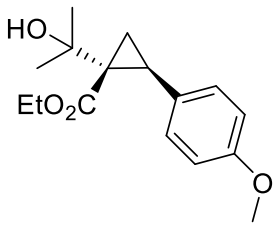
from ***trans*-57b** (20 mg, 0.052 mmol) and benzyl bromide (15 µL, 0.13 mmol) to afford the title compound as a colourless oil (10 mg, 0.032 mmol, 62 %). $[\alpha]_D^{20}$ = −51.3° (c = 1.0, $CHCl_3$). **^{1}H-NMR** (400 MHz, $CDCl_3$): δ = 7.31 – 7.27 (m, 4H), 7.24 – 7.18 (m, 1H), 7.14 (d, *J* = 8.2 Hz, 2H), 6.79 (d, *J* = 8.7 Hz, 2H), 3.82 – 3.69 (m, 5H), 3.67 (d, *J* = 13.8 Hz, 1H), 2.67 (d, *J* = 14.7 Hz, 1H), 2.39 (t, *J* = 8.0 Hz, 1H), 1.98 (ddd, *J* = 7.2 Hz, 5.1 Hz, 1.1 Hz, 1H), 1.28 – 1.24 (m, 1H), 0.83 (t, *J* = 7.1 Hz, 3H) ppm; **^{13}C{^{1}H}-NMR** (101 MHz, $CDCl_3$): δ = 171.7, 158.4, 139.6, 130.2, 129.2, 129.1, 128.4, 126.5, 113.4, 60.4, 55.4, 40.5, 33.5, 31.5, 17.0, 14.0 ppm; **IR (film, ATR)**: $\tilde{\nu}$ [cm^{-1}] = 2980, 2933, 2836, 1718, 1612, 1515, 1496, 1454, 1371, 1344, 1298, 1247, 1180, 1138, 1034, 836, 745, 700, 552; **EI-MS**: *m/z* (%) = 310 (11, [M]), 264 (14), 235 (9), 219 (16), 203 (5), 186 (16), 165 (10), 145 (100), 129 (28), 103 (7), 91 (36), 77 (7); **HR-MS** (GC-EI): *m/z* calcd. for [M]: 310.15635, found: 310.15664.

Compound 82c: Prepared according to the representative procedure for tin-lithium exchange



from ***trans*-57b** (25 mg, 0.065 mmol) and allyl iodide (15 µL, 0.16 mmol) to afford the title compound as a colourless oil (11 mg, 0.042 mmol, 65 %). $[\alpha]_D^{20}$ = −87.0° (c = 0.99, $CHCl_3$). **^{1}H-NMR** (400 MHz, $CDCl_3$): δ = 7.13 (d, *J* = 8.9 Hz, 2H), 6.78 (d, *J* = 8.7 Hz, 2H), 5.99 – 5.86 (m, 1H), 5.15 – 5.03 (m, 2H), 3.83 – 3.73 (m, 5H), 2.85 (dd, *J* = 14.8 Hz, 8.2 Hz, 1H), 2.36 – 2.29 (m, 1H), 2.15 (dd, *J* = 14.8 Hz, 6.5 Hz, 1H), 1.91 (dd, *J* = 6.8 Hz, 5.5 Hz, 1H), 1.14 (dd, *J* = 8.9 Hz, 5.1 Hz, 1H), 0.88 (t, *J* = 7.2 Hz, 3H) ppm; **^{13}C{^{1}H}-NMR** (101 MHz, $CDCl_3$): δ = 171.9, 158.4, 135.7, 130.2, 129.3, 116.7, 113.4, 60.3, 55.4, 39.4, 32.1, 31.5, 17.2, 14.0 ppm; **IR (film, ATR)**: $\tilde{\nu}$ [cm^{-1}] = 2980, 2934, 2836, 1717, 1640, 1612, 1581, 1515, 1464, 1442, 1371, 1341, 1297, 1246, 1203, 1176, 1149, 1114, 1035, 916, 836, 771, 557; **EI-MS**: *m/z* (%) = 260 (6, [M]), 231 (7), 219 (7), 199 (6), 187 (55), 171 (10), 159 (25), 145 (100), 121 (25), 115 (14), 103 (7), 91 (15), 77 (7); **HR-MS** (GC-EI): *m/z* calcd. for [M]: 260.1407, found: 260.1406.

Compound 82d: Prepared according to the representative procedure for tin-lithium exchange



from ***trans*-57b** (25 mg, 0.065 mmol) and acetone (20 µL, 0.27 mmol) to afford the title compound as a colourless oil (14 mg, 0.05 mmol, 77 %). $[\alpha]_D^{21}$ = −35.9° (c = 0.99, $CHCl_3$). **^{1}H-NMR** (400 MHz, $CDCl_3$): δ = 7.14 (d, *J* = 8.6 Hz, 2H), 6.78 (d, *J* = 8.7 Hz, 2H), 3.96 (s, 1H), 3.80 – 3.72 (m, 4H), 3.68 – 3.57 (m, 1H), 2.65 (t, *J* = 8.2 Hz, 1H), 1.90 (dd, *J* = 7.4 Hz, 5.4 Hz, 1H), 1.44 (s, 3H), 1.28 (dd, *J* = 9.1 Hz, 5.5 Hz, 1H), 1.19 (s, 3H), 0.80 (t, *J* = 7.2 Hz, 3H) ppm; **^{13}C{^{1}H}-NMR** (101 MHz, $CDCl_3$): δ = 172.8, 158.5, 130.2, 129.2, 113.5, 71.1, 60.6, 55.4, 40.6, 29.0, 27.2, 25.6, 14.4, 13.7 ppm; **IR (film, ATR)**: $\tilde{\nu}$ [cm^{-1}] = 3505, 2977, 2935, 2836, 1713, 1613, 1515,

1464, 1370, 1305, 1246, 1213, 1177, 1149, 1110, 1036, 957, 835, 558; **EI-MS**: *m/z* (%) = 278 (< 1, [M]), 260 (2), 245 (3), 215 (2), 187 (7), 172 (9), 158 (4), 145 (8), 137 (100), 109 (14), 96 (4); **HR-MS** (ESI-pos): *m/z* calcd. for $[M+Na]^+$: 301.14103, found: 301.14125.

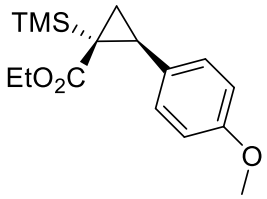
Compound *ent*-82e: Prepared according to the representative procedure for tin-lithium exchange from ***cis*-57b** (20 mg, 0.052 mmol) and pentanoyl chloride (19 µL, 0.16 mmol) to afford the title compound as a colourless oil (9 mg, 0.03 mmol, 57 %). $[\alpha]_D^{21}$ = 248.2° (c = 0.9, $CHCl_3$). **^{1}H-NMR** (400 MHz, $CDCl_3$): δ = 7.11 (d, *J* = 8.5 Hz, 2H), 6.79 (d, *J* = 8.9 Hz, 2H), 3.84 (dddd, *J* = 17.9 Hz, 10.8 Hz, 7.2 Hz, 3.6 Hz, 2H), 3.77 (s, 3H), 3.22 (t, *J* = 8.6 Hz, 1H), 2.91 (ddd, *J* = 17.0 Hz, 8.4 Hz, 6.5 Hz, 1H), 2.67 (ddd, *J* = 17.1 Hz, 8.2 Hz, 6.5 Hz, 1H), 2.15 (dd, *J* = 8.0 Hz, 4.5 Hz, 1H), 1.67 – 1.57 (m, 3H), 1.38 – 1.29 (m, 2H), 0.92 (t, *J* = 7.1 Hz, 6H) ppm; **^{13}C{^{1}H}-NMR** (101 MHz, $CDCl_3$): δ = 204.9, 168.5, 159.0, 130.1, 127.1, 113.6, 61.2, 55.4, 44.6, 41.7, 34.4, 26.3, 22.5, 21.6, 14.0, 13.9 ppm; **IR (film, ATR)**: $\tilde{\nu}$ [cm^{-1}] = 2958, 2933, 2872, 2838, 1721, 1693, 1613, 1516, 1464, 1441, 1371, 1315, 1248, 1205, 1178, 1156, 1116, 1041, 838, 807, 762, 534; **ESI-MS**: *m/z* (%) = 631 (28, $[2M+Na]^+$), 343 (6, $[M+K]^+$), 327 (100, $[M+Na]^+$), 305 (58, $[M+H]^+$); **HR-MS** (ESI-pos): *m/z* calcd. for $[M+Na]^+$: 327.15668, found: 327.15676.

Compound 82f (= 79a): Prepared according to the representative procedure for tin-lithium exchange from ***trans*-57b** (20 mg, 0.052 mmol) and benzoyl chloride (15 µL, 0.13 mmol) to afford the title compound as a colourless solid (12 mg, 0.037 mmol, 71 %). **^{1}H-NMR** (400 MHz, $CDCl_3$): δ = 7.90 (d, *J* = 7.5 Hz, 2H), 7.54 (t, *J* = 7.4 Hz, 1H), 7.44 (d, *J* = 15.3 Hz, 2H), 7.23 (d, *J* = 8.6 Hz, 2H), 6.83 (d, *J* = 8.7 Hz, 2H), 3.78 (s, 3H), 3.70 (tt, *J* = 10.8Hz, 6.0 Hz, 2H), 3.52 (t, *J* = 8.6 Hz, 1H), 2.40 (dd, *J* = 8.1 Hz, 4.8 Hz, 1H), 1.66 (dd, *J* = 9.1 Hz, 4.8 Hz, 1H), 0.70 (t, *J* = 7.1 Hz, 3H) ppm; **^{13}C{^{1}H}-NMR** (101 MHz, $CDCl_3$): δ = 195.3, 168.6, 158.9, 137.6, 132.9, 130.3, 128.6, 128.3, 126.9, 113.6, 61.2, 55.4, 42.5, 30.4, 20.4, 13.7 ppm. The analytical data matches with the respective compound obtained from carbonylative cross coupling (*vide supra*).

Compound 82g: Prepared according to the representative procedure for tin-lithium exchange from ***trans*-57b** (20 mg, 0.052 mmol) and furan-2-carbonyl chloride (16 µL, 0.16 mmol) to afford the title compound as a white solid (13 mg, 0.041 mmol, 79 %). $[\alpha]_D^{21}$ = −26.7° (c = 0.96, $CHCl_3$). **^{1}H-NMR** (400 MHz, $CDCl_3$): δ = 7.58 (d, *J* = 1.0 Hz, 1H), 7.25 – 7.18 (m, 3H), 6.82 (d, *J* = 8.7 Hz, 2H), 6.55 (dd, *J* = 3.6 Hz, 1.7 Hz, 1H), 3.91 – 3.81 (m, 2H), 3.78 (s, 3H), 3.48 (t, *J* = 8.7 Hz, 1H), 2.29 (dd, *J* = 8.1 Hz, 4.9 Hz, 1H), 1.60 (dd, *J* = 9.1 Hz, 4.9 Hz, 1H), 0.85 (t, *J* = 7.1 Hz, 3H) ppm; **^{13}C{^{1}H}-NMR** (101 MHz, $CDCl_3$): δ = 182.9, 168.1, 158.9, 152.3, 146.4, 130.3, 126.8, 117.8, 113.6, 112.5, 61.3, 55.4, 42.0, 30.0, 20.1, 13.9 ppm; **IR (film,**

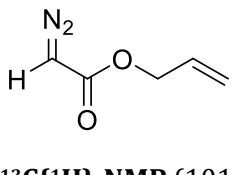
ATR): $\tilde{\nu}$ [cm^{-1}] = 2980, 2935, 2837, 1731, 1669, 1612, 1568, 1515, 1465, 1392, 1370, 1306, 1248, 1178, 1149, 1116, 1095, 1034, 916, 885, 834, 767, 551; **EI-MS**: *m/z* (%) = 314 (8, [M]), 268 (16), 240 (15), 200 (21), 187 (100), 145 (23), 115 (9), 95 (17); **HR-MS** (GC-EI): *m/z* calcd. for [M]: 314.11488, found: 314.11513.

Compound 82h: Prepared according to the representative procedure for tin-lithium exchange from ***trans*-57b** (20 mg, 0.052 mmol) and TMS-I (20 µL, 0.14 mmol) to afford the title compound as a light yellow oil (9 mg, 0.031 mmol, 59 %). **^{1}H-NMR** (400 MHz, $CDCl_3$): δ = 7.11 (d, *J* = 8.4 Hz, 2H), 6.78 (d, *J* = 8.7 Hz, 2H), 3.86 – 3.71 (m, 5H), 2.33 (d, *J* = 6.7 Hz, 1H), 1.87 (dd, *J* = 6.6 Hz, 4.8 Hz, 1H), 1.16 (dd, *J* = 7.9 Hz, 4.8 Hz, 1H), 0.95 (t, *J* = 7.2 Hz, 3H), 0.13 (s, 9H) ppm; **^{13}C{^{1}H}-NMR** (101 MHz, $CDCl_3$): δ = 172.6, 158.4, 129.9, 129.4, 113.4, 60.3, 55.4, 27.8, 23.1, 14.4, 14.2, -2.2 ppm. The analytical data is consistent with the literature[134].

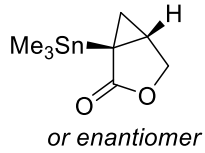


4.2.7 Synthesis of Salinilactones B and C

Allyl 2-diazoacetate (105): The compound was prepared following the same procedure as diazo compound **14.** It was obtained as a bright yellow oil (562 mg, 4.17 mmol, 90 %). **^{1}H-NMR** (400 MHz, $CDCl_3$): δ = 5.92 (ddt, *J* = 17.1 Hz, 10.4 Hz, 5.7 Hz, 1H), 5.36 – 5.20 (m, 2H), 4.77 (s, 1H), 4.66 (dt, *J* = 5.7 Hz, 1.4 Hz, 2H) ppm; **^{13}C{^{1}H}-NMR** (101 MHz, $CDCl_3$): δ = 132.3, 118.4, 65.5, 46.4 ppm; **IR (ATR)**: $\tilde{\nu}$ [cm^{-1}] = 3121, 3099, 2110, 1689, 1447, 1383, 1340, 1237, 1180, 1098, 1026, 992, 935, 741, 485; **ESI-MS**: *m/z* (%) = 351 (6), 321 (10), 289 (20), 237 (9), 217 (12), 197 (14), 143 (15), 125 (100, [M-H]$^-$), 115 (32); **HR-MS** (ESI-neg): *m/z* calcd. for [M-H]$^-$: 125.03565, found: 125.03565. The analytical data is consistent with the literature[255].

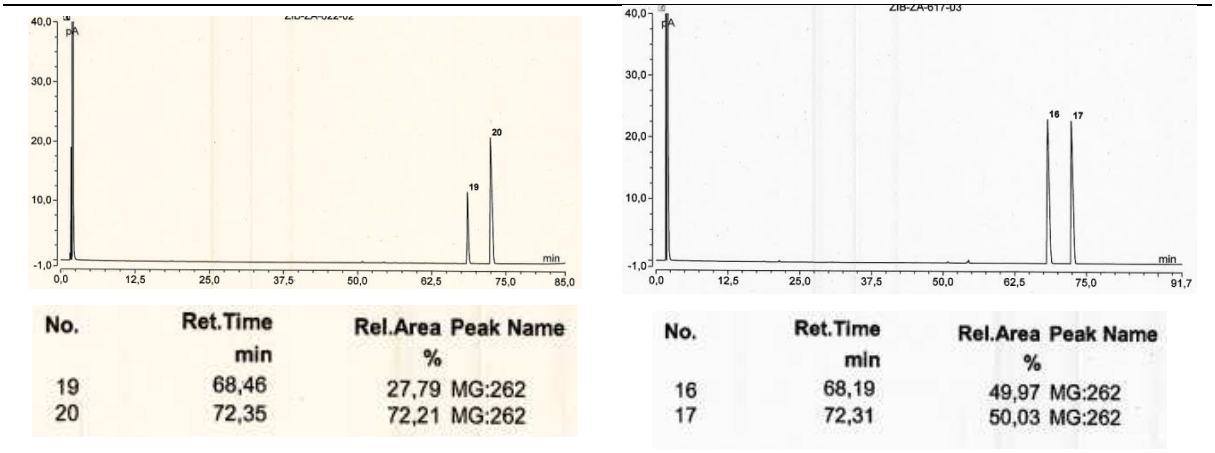


Compound 102 or *ent*-102: In a Schlenk flask, diazoacetate **105** (100 mg, 0.79 mmol) was dissolved in Et_2O (4 mL). Dimethylamino trimethyltin (0.13 mL, 0.80 mmol) was added and the mixture was stirred at room temperature overnight. The solvent was carefully evaporated under vacuum and the remaining material was dissolved in pentane (3 mL). In a cooling Schlenk flask, complex **C3** (6.5 mg, 3.8 µmol) was dissolved in pentane (5 mL) and the solution was cooled to - 20°C. Then the solution of freshly prepared stannyl diazo compound **103** was added and the mixture was stirred at -20 °C overnight. The reaction mixture was warmed to room temperature and the solvent was evaporated. The crude product was purified *via* flash chromatography (SiO_2 hexane/EtOAc 20:1 to 10:1) to obtain the title compound as a colourless oil (62 mg, 0.24 mmol, 30 %, 44 % *ee*). **^{1}H-NMR** (400 MHz, $CDCl_3$): δ = 4.35 – 4.26 (m, 2H), 2.04 (dtd, *J* = 6.7 Hz, 4.3 Hz, 1.1 Hz, 1H), 1.19 – 1.04 (m, 1H), 1.00 (t, *J* = 4.2 Hz, 1H), 0.22 (s, 9H) ppm; **^{13}C{^{1}H}-NMR** (101 MHz,



$CDCl_3$): δ = 181.1, 69.4, 21.9, 16.6, 14.1, -10.0 ppm; **^{119}Sn-NMR** (149 MHz, $CDCl_3$): δ = 10.1 ppm; **IR (ATR)**: $\tilde{\nu}$ [cm^{-1}] = 2970, 2903, 1746, 1366, 1248, 1206, 1181, 1110, 1067, 1033, 989, 921, 861, 768, 703, 633, 532; **ESI-MS**: *m/z* (%) = 547 (28, $[2M+Na]^+$), 285 (100, $[M+Na]^+$), 280 (61, $[M+NH_4]^+$), 263 (8, $[M+H]^+$), 247 (80); **HR-MS** (ESI-pos): *m/z* calcd. for $[M+NaH]^+$: 284.9908, found: 284.99088.

The optical purity was determined by chiral GC (G-TA 0.25/?df, 30 m, carrier gas H_2, 0.6 bar, temperature gradient 220/60 °C) **[t_R]** = 68.64 min (minor), 72.35 min (major).

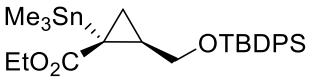


No.	Ret.Time min	Rel.Area %	Peak Name
19	68,46	27,79	MG:262
20	72,35	72,21	MG:262

No.	Ret.Time min	Rel.Area %	Peak Name
16	68,19	49,97	MG:262
17	72,31	50,03	MG:262

Figure 51. GC traces of enantioenriched 102 from C3 (left), and of racemic 102 (right).

Compound 109: Prepared according to a modified representative procedure for



cyclopropanations (*reaction was run at room temperature instead of – 20°C*) using complex **C3** to afford the title compound as a colourless oil (119 mg, 0.22 mmol, 81 %, *trans*/cis > 20:1 (^{1}H-NMR), 95 % *ee*). **$[\alpha]_D^{20}$** = −4.8° (c = 0.98, $CHCl_3$); **^{1}H-NMR** (400 MHz, $CDCl_3$): δ = 7.72 – 7.61 (m, 4H), 7.45 – 7.33 (m, 6H), 4.18 – 4.07 (m, 1H), 4.01 (dq, *J* = 10.8 Hz, 7.1 Hz, 1H), 3.89 (dd, *J* = 10.9 Hz, 5.6 Hz, 1H), 3.69 (dd, *J* = 11.0 Hz, 8.5 Hz, 1H), 1.52 – 1.31 (m, 1H), 1.22 (t, *J* = 7.2 Hz, 4H), 1.04 (s, 9H), 0.83 (dd, *J* = 7.6 Hz, 4.6 Hz, 1H), 0.13 (s, 9H) ppm; **^{13}C{^{1}H}-NMR** (101 MHz, $CDCl_3$): δ = 175.3, 135.72, 135.68, 134.2, 134.1, 129.68, 129.65, 127.7, 63.7, 60.8, 26.9, 26.8, 19.3, 15.6, 14.4, 14.0, -9.6 ppm; **^{119}Sn-NMR** (149 MHz, $CDCl_3$): δ = 21.8 ppm; **IR (ATR)**: $\tilde{\nu}$ [cm^{-1}] = 2959, 2931, 2857, 1710, 1472, 1390, 1363, 1281, 1182, 1159, 1108, 1076, 1008, 850, 823, 767, 739, 700, 612, 503; **ESI-MS**: *m/z* (%) = 1115 (5, $[2M+Na]^+$), 569 (100, $[M+Na]^+$), 547 (29, $[M+H]^+$), 501 (23); **HR-MS** (ESI-pos): *m/z* calcd. for $[M+Na]^+$: 569.15044, found: 569.1504.

The optical purity was determined by HPLC (Chiralpak IB N-3, 150 mm, 4.6 mm, i.D., *n*-heptane/MTBE 98:2, 1.0 mL/min) **[t_R]** = 4.70 min (major), 5.48 min (minor).

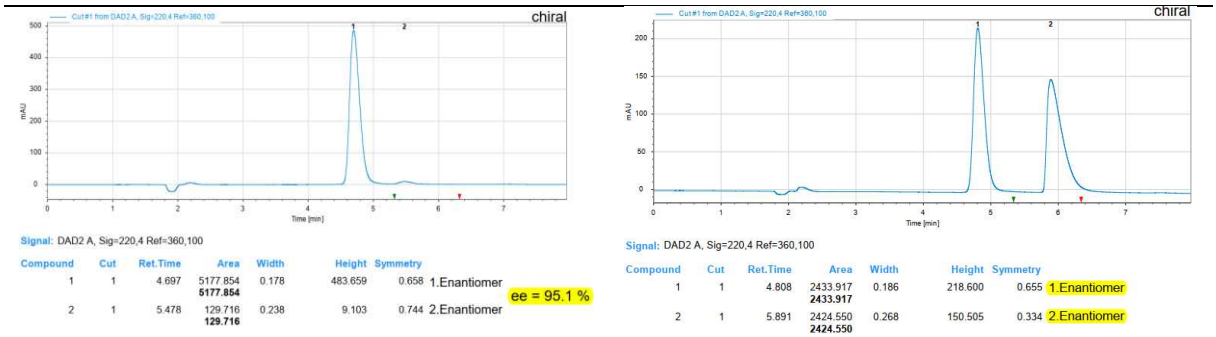
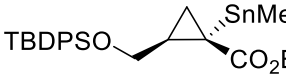


Figure 52. HPLC traces of enantioenriched 109 from C3 (left), and of racemic 109 (right).

Compound *ent*-109: Prepared according to a modified representative procedure for



cyclopropanations (*reaction was run at 0°C instead of – 20°C*) using complex ***ent*-C3** to afford the title compound as a colourless oil (176 mg, 0.32 mmol, 69 %, *trans/cis* > 30:1 (^{1}H-NMR), 96 % *ee*). $[\alpha]_D^{20}$ = 5.5° (c = 1.01, $CHCl_3$); **^{1}H-NMR** (400 MHz, $CDCl_3$): δ = 7.71 – 7.61 (m, 4H), 7.45 – 7.32 (m, 6H), 4.12 (dq, *J* = 10.8 Hz, 7.1 Hz, 1H), 4.00 (dq, *J* = 10.8 Hz, 7.2 Hz, 1H), 3.92 – 3.85 (m, 1H), 3.68 (dd, *J* = 11.0 Hz, 8.5 Hz, 1H), 1.49 – 1.32 (m, 1H), 1.21 (t, *J* = 7.2 Hz, 4H), 1.03 (s, 9H), 0.82 (dd, *J* = 7.6 Hz, 4.6 Hz, 1H), 0.12 (s, 9H) ppm; **^{13}C{^{1}H}-NMR** (101 MHz, $CDCl_3$): δ = 175.3, 135.73, 135.68, 134.2, 134.1, 129.68, 129.66, 127.7, 63.7, 60.8, 26.9, 26.8, 19.4, 15.6, 14.4, 14.0, -9.6 ppm; **^{119}Sn-NMR** (149 MHz, $CDCl_3$): δ = 21.8 ppm; **IR (ATR)**: $\tilde{\nu}$ [cm^{-1}] = 3071, 2959, 2931, 2858, 1711, 1472, 1428, 1390, 1363, 1282, 1183, 1159, 1111, 1079, 823, 769, 739, 702, 613, 505; **ESI-MS**: *m/z* (%) = 1115 (7, $[2M+Na]^+$), 569 (100, $[M+Na]^+$), 547 (15, $[M+H]^+$); **HR-MS** (ESI-pos): *m/z* calcd. for $[M+Na]^+$: 569.15037, found: 569.15076.

The optical purity was determined by HPLC (Chiralpak IB N-3, 150 mm, 4.6 mm, i.D., *n*-heptane/MTBE 98:2, 1.0 mL/min) **[t_R]** = 4.80 min (minor), 5.36 min (major).

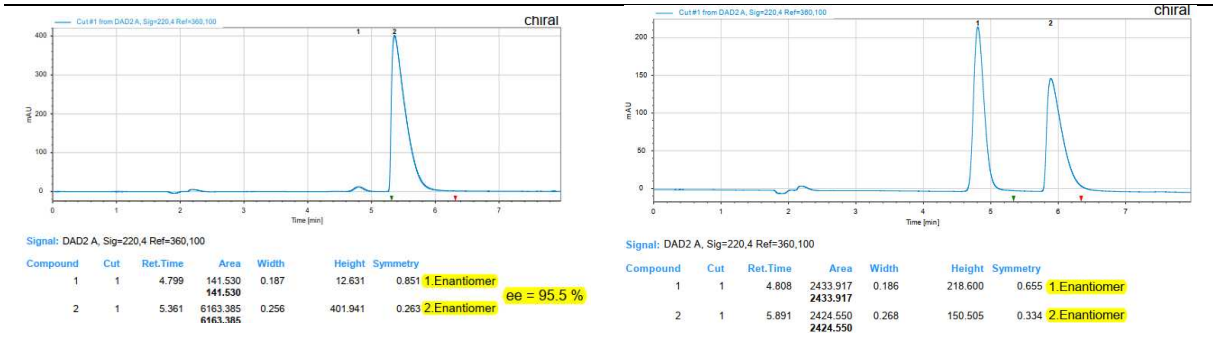
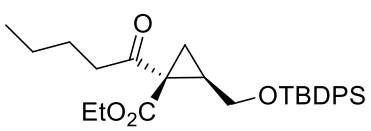


Figure 53. HPLC traces of enantioenriched *ent*-109 from C3 (left), and of racemic 109 (right).

Compound 110a Prepared according to the representative procedure for tin-lithium exchange



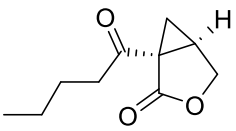
from **109** and pentanoyl chloride to afford the title compound as a colourless oil (24 mg, 0.051 mmol, 88 %). $[\alpha]_D^{21}$ = −30.0° (c = 0.99, $CHCl_3$). **^{1}H-NMR** (400 MHz, $CDCl_3$): δ = 7.70 – 7.59 (m,

4H), 7.45 – 7.35 (m, 6H), 4.28 – 4.09 (m, 2H), 3.82 (dd, *J* = 11.3 Hz, 5.7 Hz, 1H), 3.68 (dd, *J* = 11.3 Hz, 7.9 Hz, 1H), 2.83 (ddd, *J* = 17.0 Hz, 8.3, 6.6 Hz, 1H), 2.68 (ddd, *J* = 17.0 Hz, 8.2 Hz, 6.7 Hz, 1H), 2.28 – 2.12 (m, 1H), 1.65 – 1.52 (m, 2H), 1.52 – 1.43 (m, 1H), 1.35 – 1.27 (m, 3H), 1.25 (t, *J* = 7.2 Hz, 3H), 1.03 (s, 9H), 0.91 (t, *J* = 7.4 Hz, 3H) ppm; **^{13}C{^{1}H}-NMR** (101 MHz, $CDCl_3$): δ = 205.1, 169.6, 135.70, 135.65, 133.64, 133.62, 129.9, 129.8, 127.9, 127.8, 62.07, 61.6, 41.4, 40.1, 31.8, 26.9, 26.4, 22.5, 21.0, 19.3, 14.2, 14.0 ppm; **IR (film, ATR)**: $\tilde{\nu}$ [cm^{-1}] = 2958, 2932, 2858, 1722, 1701, 1464, 1428, 1367, 1311, 1258, 1182, 1159, 1106, 1030, 823, 797, 739, 700, 612, 504, 488; **ESI-MS**: *m/z* (%) = 955 (11, [2M+Na]$^+$), 505 (14, [M+K]$^+$), 489 (100, [M+Na]$^+$), 467 (7, [M+H]$^+$); **HR-MS** (ESI-pos): *m/z* calcd. for [M+Na]$^+$: 489.24316, found: 489.24309.

Compound *ent*-110a: Prepared according to the representative procedure for tin-lithium exchange from ***ent*-109** and pentanoyl chloride to afford the title compound as a colourless oil (20 mg, 0.043 mmol, 75 %). $[\alpha]_D^{21}$ = 26.7° (c = 0.99, $CHCl_3$). **^{1}H-NMR** (400 MHz, $CDCl_3$): δ = 7.68 – 7.61 (m, 4H), 7.45 – 7.34 (m, 7H), 4.28 – 4.09 (m, 2H), 3.81 (dd, *J* = 11.3 Hz, 5.7 Hz, 1H), 3.68 (dd, *J* = 11.3 Hz, 7.9 Hz, 1H), 2.83 (ddd, *J* = 16.9 Hz, 8.2 Hz, 6.7 Hz, 1H), 2.67 (ddd, *J* = 16.9 Hz, 8.1 Hz, 6.7 Hz, 1H), 2.25 – 2.12 (m, 1H), 1.62 – 1.54 (m, 2H), 1.47 (dd, *J* = 7.5 Hz, 4.2 Hz, 1H), 1.35 – 1.27 (m, 3H), 1.24 (t, *J* = 7.2 Hz, 3H), 1.02 (s, 9H), 0.91 (t, *J* = 7.4 Hz, 3H) ppm; **^{13}C{^{1}H}-NMR** (101 MHz, $CDCl_3$): δ = 205.1, 169.6, 135.7, 135.7, 133.7, 129.9, 129.8, 127.9, 127.8, 62.1, 61.6, 41.4, 40.1, 31.8, 26.9, 26.4, 22.5, 21.0, 19.3, 14.2, 14.0 ppm; **IR (film, ATR)**: $\tilde{\nu}$ [cm^{-1}] = 2958, 2931, 2858, 1724, 1700, 1464, 1428, 1368, 1312, 1259, 1182, 1159, 1110, 1030, 823, 740, 702, 613, 505; **ESI-MS**: *m/z* (%) = 955 (9, [2M+Na]$^+$), 505 (2, [M+K]$^+$), 489 (100, [M+Na]$^+$), 484 (30, [M+NH_4]$^+$), 467 (15, [M+H]$^+$); **HR-MS** (ESI-pos): *m/z* calcd. for [M+Na]$^+$: 489.24316, found: 489.24357.

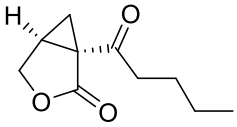
Compound *ent*-110b: Prepared according to the representative procedure for tin-lithium exchange from ***ent*-109** and 4-methylvaleryl chloride to afford the title compound as a colourless oil (15 mg, 0.031 mmol, 61 %). $[\alpha]_D^{21}$ = 34.6° (c = 1.01, $CHCl_3$). **^{1}H-NMR** (400 MHz, $CDCl_3$): δ = 7.64 (td, *J* = 8.1 Hz, 1.6 Hz, 4H), 7.46 – 7.32 (m, 6H), 4.31 – 4.07 (m, 2H), 3.82 (dd, *J* = 11.3 Hz, 5.6 Hz, 1H), 3.68 (dd, *J* = 11.3 Hz, 8.0 Hz, 1H), 2.83 (ddd, *J* = 16.9 Hz, 9.3 Hz, 5.9 Hz, 1H), 2.69 (ddd, *J* = 16.9 Hz, 9.1 Hz, 6.0 Hz, 1H), 2.20 (dtd, *J* = 9.1 Hz, 7.9 Hz, 5.7 Hz, 1H), 1.61 – 1.44 (m, 4H), 1.36 – 1.29 (m, 1H), 1.25 (t, *J* = 7.2 Hz, 3H), 1.03 (s, 9H), 0.89 (d, *J* = 6.3 Hz, 6H) ppm; **^{13}C{^{1}H}-NMR** (101 MHz, $CDCl_3$): δ = 205.3, 169.6, 135.7, 135.7, 133.6, 133.6, 129.9, 129.8, 127.8, 62.1, 61.6, 40.1, 39.8, 33.1, 31.8, 27.9, 26.9, 22.5, 22.5, 21.0, 19.3, 14.2 ppm; **IR (film, ATR)**: $\tilde{\nu}$ [cm^{-1}] = 3071, 2956, 2931, 2858, 1724, 1701, 1469, 1428, 1312, 1260, 1182, 1108, 1030, 823, 799, 740, 702, 613, 505; **ESI-MS**: *m/z* (%) = 983 (9, [2M+Na]$^+$), 519 (7, [M+K]$^+$), 503 (100, [M+Na]$^+$), 498 (15, [M+NH_4]$^+$), 481 (8, [M+H]$^+$); **HR-MS** (ESI-pos): *m/z* calcd. for [M+Na]$^+$: 503.25881, found: 503.25909.

Compound *ent*-92a: In a Schlenk flask, compound **110a** (70 mg, 0.15 mmol) was dissolved in



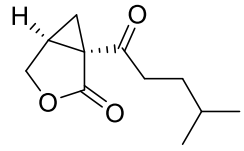
MeOH (3 mL) and the solution was cooled to 0°C. Acetyl chloride (1 µL, 14 µmol) was added and the mixture was stirred at room temperature overnight. The mixture was diluted with CH_2Cl_2 (3 mL) and quenched with aqueous $NaHCO_3$ (10%, 5 mL). The aqueous layer was extracted once with CH_2Cl_2. The combined organic layers were washed with water and dried over Na_2SO_4. The crude product was immobilized on Celite and purified *via* flash chromatography (SiO_2, CH_2Cl_2/MeOH 400:1). The title compound was obtained as a pale brown liquid (15 mg, 0.082 mmol, 55 %). $\mathbf{[\alpha]_D^{21}}$ = −58.7° (c = 1.5, $CHCl_3$); **^{1}H-NMR** (400 MHz, $CDCl_3$): δ = 4.33 (dd, *J* = 9.4 Hz, 4.8 Hz, 1H), 4.19 (d, *J* = 9.4 Hz, 1H), 3.12 (ddd, *J* = 17.9 Hz, 8.6 Hz, 6.4 Hz, 1H), 2.87 (ddd, *J* = 17.6 Hz, 8.4 Hz, 6.3 Hz, 1H), 2.76 (dt, *J* = 7.9 Hz, 5.1 Hz, 1H), 2.05 (dd, *J* = 8.2 Hz, 4.0 Hz, 1H), 1.59 (h, *J* = 7.4 Hz, 6.8 Hz, 2H), 1.42 – 1.29 (m, 3H), 0.92 (t, *J* = 7.4 Hz, 3H) ppm; **^{13}C{^{1}H}-NMR** (101 MHz, $CDCl_3$): δ = 203.0, 173.0, 67.4, 41.5, 36.3, 29.8, 25.7, 23.9, 22.3, 14.0 ppm; **IR (film, ATR)**: $\tilde{\nu}$ [cm^{-1}] = 2959, 2932, 2873, 1766, 1696, 1465, 1438, 1382, 1300, 1262, 1211, 1114, 1081, 1047, 1030, 993, 766, 704, 570; **EI-MS**: *m/z* (%) = 183 (< 1, $[M+H]^+$), 167 (4), 153 (31), 140 (34), 122 (100), 94 (29), 83 (24), 66 (23); **HR-MS** (GC-EI): *m/z* calcd. for [M]: 182.09375, found: 182.09386.

Compound 92a (Salinilactone B): Prepared analogously to ***ent*-92a** from ***ent*-110a** to afford the



title compound as a pale brown liquid (13 mg, 0.071 mmol, 67 %). $\mathbf{[\alpha]_D^{21}}$ = 107.2° (c = 1.25, $CHCl_3$); **^{1}H-NMR** (400 MHz, $CDCl_3$): δ = 4.33 (dd, *J* = 9.5 Hz, 4.8 Hz, 1H), 4.19 (d, *J* = 9.4 Hz, 1H), 3.12 (ddd, *J* = 17.7 Hz, 8.4 Hz, 6.5 Hz, 1H), 2.86 (ddd, *J* = 17.6 Hz, 8.2 Hz, 6.4 Hz, 1H), 2.80 – 2.70 (m, 1H), 2.04 (dd, *J* = 8.4 Hz, 3.8 Hz, 1H), 1.67 – 1.51 (m, 2H), 1.41 – 1.29 (m, 3H), 0.92 (t, *J* = 7.3 Hz, 3H) ppm; **^{13}C{^{1}H}-NMR** (101 MHz, $CDCl_3$): δ = 203.0, 173.0, 67.4, 41.5, 36.3, 29.8, 25.7, 23.9, 22.3, 14.0 ppm; **IR (film, ATR)**: $\tilde{\nu}$ [cm^{-1}] = 2959, 2933, 2873, 1766, 1696, 1466, 1438, 1383, 1301, 1211, 1115, 1082, 1047, 993, 766, 704, 631, 570; **ESI-MS**: *m/z* (%) = 387 (9, $[2M+Na]^+$), 205 (100, $[M+Na]^+$), 183 (17, $[M+H]^+$); **HR-MS** (ESI-pos): *m/z* calcd. for $[M+Na]^+$: 205.08351, found: 205.08354. The analytical data is consistent with the literature[179].

Compound 92b (Salinilactone C): Prepared analogously to ***ent*-92a** from ***ent*-110b** to afford the



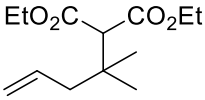
title compound as a colourless oil (10 mg, 0.051 mmol, 45 %). $\mathbf{[\alpha]_D^{21}}$ = 95.3° (c = 1.0, $CHCl_3$); **^{1}H-NMR** (400 MHz, $CDCl_3$): δ = 4.33 (dd, *J* = 9.5 Hz, 4.8 Hz, 1H), 4.19 (d, *J* = 9.4 Hz, 1H), 3.20 – 3.03 (m, 1H), 2.87 (ddd, *J* = 17.6 Hz, 9.3 Hz, 5.8 Hz, 1H), 2.75 (dt, *J* = 7.9 Hz, 4.8 Hz, 1H), 2.05 (dd, *J* = 8.0 Hz, 4.2 Hz, 1H), 1.62 – 1.41 (m, 3H), 1.38 (dd, *J* = 5.6 Hz, 4.1 Hz, 1H), 0.91 (dd, *J* = 6.5 Hz, 1.8 Hz, 6H) ppm; **^{13}C{^{1}H}-NMR** (101 MHz, $CDCl_3$): δ = 203.2, 172.9, 67.4, 39.9, 36.3, 32.4, 29.8, 27.8, 24.0, 22.6, 22.5 ppm; **IR (film, ATR)**: $\tilde{\nu}$ [cm^{-1}] = 2957, 2930, 2871, 1768, 1697, 1468, 1384, 1301, 1210, 1116,

1083, 1048, 1000, 767, 702, 631; **ESI-MS**: *m/z* (%) = 415 (6, $[2M+Na]^+$), 235 (3, $[M+K]^+$), 219 (100, $[M+Na]^+$), 214 (14, $[M+NH_4]^+$), 197 (10, $[M+H]^+$); **HR-MS** (ESI-pos): *m/z* calcd. for $[M+Na]^+$: 219.09916, found: 219.09932. The analytical data is consistent with the literature[179].

4.2.8 Synthesis of Integrifolian-1,5-dione and Derivatives

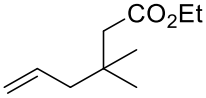
4.2.8.1 Compounds from Open-Chain Cyclization Approach

Compound 143: The compound was prepared according to a literature procedure[227]. Colourless



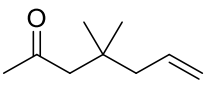
oil (529 mg, 2.18 mmol, 86 %) **^{1}H-NMR** (400 MHz, $CDCl_3$): δ = 5.88 – 5.74 (m, 1H), 5.12 – 5.00 (m, 2H), 4.17 (q, *J* = 7.1 Hz, 4H), 3.30 (s, 1H), 2.23 (d, *J* = 7.6 Hz, 2H), 1.26 (t, *J* = 7.1 Hz, 6H), 1.11 (s, 6H) ppm; **^{13}C{^{1}H}-NMR** (101 MHz, $CDCl_3$): δ = 168.5, 134.3, 118.6, 61.0, 59.4, 45.3, 36.5, 25.2, 14.3 ppm; **IR (film, ATR)**: $\tilde{\nu}$ [cm^{-1}] = 2980, 1753, 1730, 1466, 1447, 1390, 1368, 1316, 1228, 1138, 1096, 1038, 918; **GC-MS**: *m/z* (%) = 242 (< 1, [M]), 201 (10), 173 (7), 151 (40), 133 (47), 115 (17), 99 (100), 87 (30), 71 (6), 67 (18); **HR-MS** (ESI-pos): *m/z* calcd. for $[M+Na]^+$: 265.14103, found: 265.14102. The analytical data is consistent with the literature[227].

Compound 141b: The compound was prepared according to a literature procedure[227]. Orange



oil (19 mg, 0.11 mmol, 17 %) **^{1}H-NMR** (400 MHz, $CDCl_3$): δ = 5.90 – 5.74 (m, 1H), 5.11 – 4.98 (m, 2H), 4.11 (q, *J* = 7.2 Hz, 2H), 2.18 (s, 2H), 2.07 (d, *J* = 7.5 Hz, 2H), 1.25 (t, *J* = 7.2 Hz, 3H), 1.00 (s, 6H) ppm; **^{13}C{^{1}H}-NMR** (101 MHz, $CDCl_3$): δ = 172.4, 135.0, 117.8, 60.0, 46.7, 45.9, 33.6, 27.3, 14.5 ppm; **IR (film, ATR)**: $\tilde{\nu}$ [cm^{-1}] = 3078, 2962, 2931, 1731, 1466, 1448, 1368, 1329, 1260, 1217, 1134, 1035, 915, 805; **GC-MS**: *m/z* (%) = 170 (1, [M]), 155 (21), 129 (15), 109 (7), 97 (12), 87 (100), 82 (35), 69 (16), 59 (33); **HR-MS** (EI-MS): *m/z* calcd. for $[M]^+$: 170.13013, found: 170.13003. The analytical data is consistent with the literature[227].

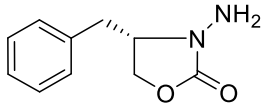
Compound 144: In a Schlenk flask, mesityl oxide (2.4 mL, 20.9 mmol, 1.0 eq) was dissolved in



CH_2Cl_2 (30 mL) and a solution of $TiCl_4$ (1 M in CH_2Cl_2, 21 mL, 21.0 mmol, 1.0 eq) was slowly added at room temperature. After 5 min of stirring of the mixture, a solution of allyltrimethylsilane (4.3 mL, 27.1 mmol, 1.3 eq) in CH_2Cl_2 (30 mL) was slowly added and the reaction mixture was stirred at room temperature for 0.5 h. Water was added to the mixture and the aqueous layer was extracted with MTBE (3x). The combined organic layers were washed with sat. aq. $NaHCO_3$ and brine, dried over Na_2SO_4, and the solvent evaporated. The crude productwas purified *via* flash chromatography (SiO_2 hexane/MTBE 97:3) to obtain the title compound as a yellow oil (2.13 g, 15.2 mmol, 73 %). **^{1}H-NMR** (400 MHz, $CDCl_3$): δ = 5.79 (ddt, *J* = 16.9 Hz, 10.3 Hz, 7.5 Hz, 1H), 5.08 – 4.97 (m, 2H), 2.31 (s, 2H), 2.11 (s, 3H), 2.08 (dt, *J* = 7.5 Hz, 1.2 Hz, 2H), 1.00 (s, 6H) ppm; **^{13}C{^{1}H}-NMR** (101 MHz, $CDCl_3$): δ = 208.9, 135.2, 117.7, 53.5, 46.6,

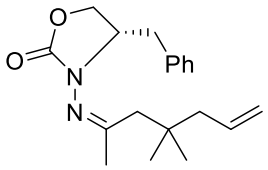
33.7, 32.6, 27.3 ppm; **IR (film, ATR)**: $\tilde{\nu}$ [cm^{-1}] = 3077, 2957, 2873, 1713, 1639, 1470, 1384, 1359, 1248, 1210, 1149, 997, 914, 856, 835, 598, 586, 527; **GC-MS**: *m/z* (%) = 140 (< 1, [M]), 125 (23), 107 (6), 99 (8), 82 (52), 67 (50), 43 (100); **HR-MS** (ESI-pos): *m/z* calcd. for [M+H]$^+$: 141.12739, found: 141.12745. The analytical data is consistent with the literature[258].

Compound 145b: In a Schlenk flask, oxazolidinone (200 mg, 1.13 mmol, 1.0 eq) was dissolved in



THF (5 mL). Sodium hydride (72 mg, 3.0 mmol, 2.7 eq) was added and the mixture was stirred at room temperature for 1 h. Then NH_2Cl (0.1 M in Et_2O, 20 mL, 2.0 mmol, 1.77 eq, prepared according to a literature procedure[259]) was added and the mixture was kept stirring for 4 h. The reaction was quenched upon addition of aq. $Na_2S_2O_3$ and the aqueous layer was extracted with MTBE (3x). The combined organic layers were dried over $MgSO_4$ and the solvent was evaporated. The title compound was obtained as a yellow oil (195 mg, 1.01 mmol, 90 %). **^{1}H-NMR** (400 MHz, $CDCl_3$): δ = 7.37 – 7.29 (m, 2H), 7.29 – 7.24 (m, 1H), 7.17 (dd, *J* = 6.7, 1.6 Hz, 2H), 4.22 – 4.13 (m, 1H), 4.03 – 3.84 (m, 4H), 3.31 (dd, *J* = 13.6, 3.6 Hz, 1H), 2.72 (dd, *J* = 13.5, 8.9 Hz, 1H) ppm; **^{13}C{^{1}H}-NMR** (101 MHz, $CDCl_3$): δ = 159.4, 135.7, 129.3, 129.1, 127.3, 66.3, 59.9, 37.6 ppm; **IR (film, ATR)**: $\tilde{\nu}$ [cm^{-1}] = 3337, 2916, 1753, 1410, 1239, 1092, 1025, 703; **ESI-MS**: *m/z* (%) = 215 (100, [M+Na]$^+$), 193 (17, [M+H]$^+$); **HR-MS** (ESI-pos): *m/z* calcd. for [M+Na]$^+$: 215.0791, found: 215.07914. The analytical data is consistent with the literature[259].

Compound 147: In a Schlenk flask, auxiliary **145b** (162 mg, 0.84 mmol, 1.0 eq) was dissolved in



CH_2Cl_2 (5 mL). Ketone **144** (122 mg, 0.87 mmol, 1.03 eq) was added, followed by *para*-toluenesulfonic acid (326 mg, 1.7 mmol, 2.0 eq) and the mixture was kept stirring at room temperature for 20 h. The reaction was quenched with sat. aq. $NaHCO_3$ and extracted with CH_2Cl_2 (3x). The combined organic layers were washed with brine, dried over $MgSO_4$, and the solvent was evaporated. The crude product was purified *via* flash chromatography (silica, hexanes/EtOAc 9:1 to 8:1) to afford the title compound as an orange oil (43 mg, 0.14 mmol, 16 %). **^{1}H-NMR** (400 MHz, $CDCl_3$): δ = 7.38 – 7.22 (m, 4H), 7.21 – 7.06 (m, 2H), 5.88 (ddt, *J* = 16.7, 10.3, 7.4 Hz, 1H), 5.15 – 4.97 (m, 2H), 4.36 (tdd, *J* = 9.1, 7.6, 3.9 Hz, 1H), 4.25 (dd, *J* = 8.6, 7.6 Hz, 1H), 4.04 (t, *J* = 8.9 Hz, 1H), 3.17 (dd, *J* = 13.6, 4.0 Hz, 1H), 2.73 (dd, *J* = 13.6, 9.2 Hz, 1H), 2.40 – 2.26 (m, 2H), 2.11 (dd, *J* = 7.4, 1.3 Hz, 2H), 2.06 (s, 3H), 1.03 (d, *J* = 5.8 Hz, 6H) ppm; **^{13}C{^{1}H}-NMR** (101 MHz, $CDCl_3$): δ = 175.6, 154.4, 135.7, 135.3, 129.3, 129.0, 127.3, 117.7, 66.8, 60.8, 50.5, 47.4, 38.6, 34.6, 27.6, 27.4, 22.5 ppm; **IR (film, ATR)**: $\tilde{\nu}$ [cm^{-1}] = 2959, 1760, 1366, 1215, 1030, 700; **EI-MS**: *m/z* (%) = 299 (4), 273 (6), 232 (10), 176 (7), 141 (50), 124 (24), 117 (100), 97 (17); **HR-MS** (GC-CI): *m/z* calcd. for [M+H]$^+$: 315.2067, found: 315.2066.

Compound 148: In a Schlenk flask, LiHMDS (30 mg, 0.18 mmol, 1.4 eq) was dissolved in THF (2 mL) and the solution was cooled to -78 °C. Then hydrazone **147** (40 mg, 0.13 mmol, 1.0 eq) was added as a solution in THF (2 mL) and the mixture was stirred at -78 °C for 1 h. Methyl iodide (0.02 mL, 0.32 mmol, 2.5 eq) was added and after 5 min of stirring the cooling bath was removed. The mixture was further stirred for 20 min and the reaction was quenched with water. The aqueous layer was extracted with MTBE (3x), the combined organic layers were washed with brine, dried over $MgSO_4$, and the solvent was evaporated. The crude product was immobilized on Celite and purified *via* flash chromatography (silica, hexanes/EtOAc 9:1) to afford the title compound as a colourless oil (35 mg, 0.11 mmol, 84 %). **^{1}H-NMR** (400 MHz, $CDCl_3$): δ = 7.35 – 7.22 (m, 3H), 7.22 – 7.12 (m, 2H), 5.95 – 5.78 (m, 1H), 5.13 – 4.96 (m, 2H), 4.39 – 4.29 (m, 1H), 4.28 – 4.21 (m, 1H), 4.04 (t, *J* = 8.8 Hz, 1H), 3.18 (dd, *J* = 13.6, 3.9 Hz, 1H), 2.71 (dd, *J* = 13.6, 9.4 Hz, 1H), 2.59 (dt, *J* = 14.7, 7.5 Hz, 1H), 2.40 – 2.24 (m, 3H), 2.13 (dt, *J* = 7.4, 1.1 Hz, 2H), 1.11 (t, *J* = 7.6 Hz, 3H), 1.04 (d, *J* = 4.6 Hz, 6H) ppm; **^{13}C{^{1}H}-NMR** (101 MHz, $CDCl_3$): δ = 180.0, 154.7, 135.7, 135.3, 129.1, 128.8, 127.1, 117.5, 66.7, 60.8, 47.2, 45.5, 38.5, 34.7, 27.4, 27.3, 27.2, 11.0 ppm; **IR (film, ATR)**: $\tilde{\nu}$ [cm^{-1}] = 1960, 1761, 1454, 1213, 1092, 700; **EI-MS**: *m/z* (%) = 313 (4), 287 (4), 246 (10), 217 (2), 176 (8), 155 (40), 138 (40), 117 (100), 91 (17), 70 (10), 44 (13); **HR-MS** (GC-CI): *m/z* calcd. for $[M+H]^+$: 329.22235, found: 329.22281.

Compound 152: The title compound was prepared from ketone **144** according to the representative procedure for cyclopropanations using ***ent*-C3**. Light brown oil (146 mg, 0.38 mmol, 43 %, *trans/cis* > 20:1 (^{1}H-NMR), 98 % *ee*). $[\alpha]_D^{20}$ = 32.2° (c = 1.01, $CHCl_3$); **^{1}H-NMR** (400 MHz, $CDCl_3$): δ = 4.17 – 3.98 (m, 2H), 2.42 – 2.29 (m, 2H), 2.12 (s, 3H), 1.59 (dd, *J* = 14.6 Hz, 5.8 Hz, 1H), 1.37 (dd, *J* = 14.1 Hz, 6.8 Hz, 1H), 1.24 (t, *J* = 7.2 Hz, 3H), 1.16 – 1.06 (m, 2H), 1.03 (d, *J* = 4.2 Hz, 6H), 0.93 – 0.85 (m, 1H), 0.11 (s, 9H) ppm; **^{13}C{^{1}H}-NMR** (101 MHz, $CDCl_3$): δ = 208.9, 175.6, 60.7, 54.4, 41.2, 34.4, 32.7, 27.3, 27.2, 20.6, 16.3, 16.1, 14.6, -9.7 ppm; **^{119}Sn-NMR** (149 MHz, $CDCl_3$): δ = 22.2 ppm; **IR (film, ATR)**: $\tilde{\nu}$ [cm^{-1}] = 2960, 2931, 1707, 1446, 1362, 1282, 1179, 1125, 1098, 1022, 974, 844, 765, 528; **EI-MS**: *m/z* (%) = 375 (69), 329 (50), 287 (11), 249 (9), 231 (14), 207 (8), 165 (100), 151 (28), 135 (41); **HR-MS** (ESI-pos): *m/z* calcd. for $[M+Na]^+$: 413.11084, found: 413.11132.

The optical purity was determined by HPLC (Chiralpak IC-3, 4.6 mm i.D, acetonitrile/water 50:50, 1.0 mL/min) **[t_R]** = 12.31 min (minor), 16.61 min (major).

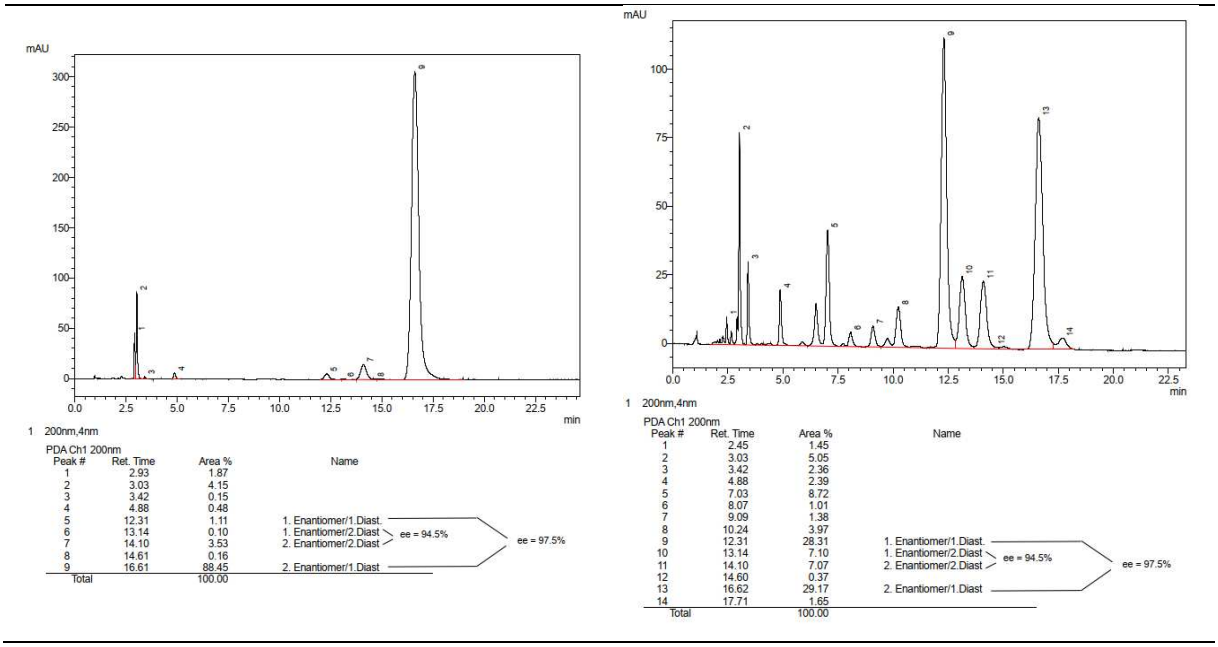
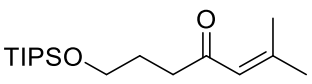


Figure 54. HPLC traces of enantioenriched 152 from *ent*-C3 (left), and of racemic 152 (right).

Preparation of Grignard Reagents: General Procedure. In a two neck round bottom flask equipped with a reflux condenser, magnesium turnings (3.0 eq.) are suspended in THF and a catalytic amount of iodine is added. The mixture is stirred at room temperature for 15 min and then heated to 50 °C until the solution turns colourless. Then the respective alkyl bromide (1.0 eq.) is added and the reaction mixture is heated to reflux temperature for > 1 h. The concentration of the resulting Grignard solution is determined by iodometric titration.

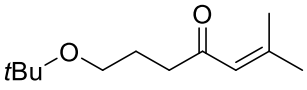
Fe-catalyzed Cross-Coupling of Grignard Reagents and Acid Chloride: General Procedure. In a Schlenk flask, $Fe(acac)_3$ (0.03 eq.) is dissolved in THF and acid chloride **140** (1.15 eq.) is added. The mixture is cooled to -78 °C and the previously prepared solution of the respective Grignard reagent (1.0 eq) is added slowly. The mixture is kept stirring at -78°C until full consumption of the starting material is observed by TLC (ca. 1 h) and then quenched with sat. aq NH_4Cl and extracted with MTBE. The combined organic layers are dried over $MgSO_4$ and the solvent is evaporated. The crude product is ultimately purified *via* flash chromatography to obtain the desired product.

Compound 154b: Prepared according to the general procedure for Fe-catalyzed cross couplings.



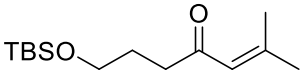
Colourless oil (405 mg, 1.36 mmol, 68 %). **^{1}H-NMR** (400 MHz, $CDCl_3$): δ = 6.09 (p, J = 1.3 Hz, 1H), 3.70 (t, J = 6.1 Hz, 2H), 2.52 (t, J = 7.4 Hz, 2H), 2.14 (d, J = 1.3 Hz, 3H), 1.88 (d, J = 1.5 Hz, 3H), 1.86 – 1.78 (m, 2H), 1.05 (q, J = 3.7 Hz, 23H) ppm; **^{13}C{^{1}H}-NMR** (101 MHz, $CDCl_3$): δ = 201.2, 124.1, 62.7, 40.7, 27.8, 27.6, 20.8, 18.2, 12.1 ppm; **IR (film, ATR)**: $\tilde{\nu}$ [cm^{-1}] = 2942, 2866, 1691, 1623, 1463, 1382, 1249, 1104, 1069, 1014, 962, 882, 681, 658; **GC-MS**: *m/z* (%) = 255 (100), 213 (5), 171 (7), 157 (7), 125 (30), 103 (25), 75 (88), 61 (14); **HR-MS** (GC-CI): *m/z* calcd. for $[M+H]^+$: 299.24008, found: 299.24001.

Compound 154c: Prepared according to the general procedure for Fe-catalyzed cross couplings.



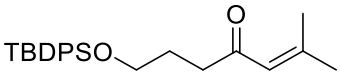
Light yellow oil (225 mg, 1.14 mmol, 55 %). **^{1}H-NMR** (400 MHz, $CDCl_3$): δ = 6.08 (p, J = 1.4 Hz, 1H), 3.35 (t, J = 6.3 Hz, 2H), 2.48 (t, J = 7.2 Hz, 2H), 2.13 (d, J = 1.4 Hz, 3H), 1.87 (d, J = 1.4 Hz, 3H), 1.85 – 1.75 (m, 2H), 1.16 (s, 9H) ppm; **^{13}C{^{1}H}-NMR** (101 MHz, $CDCl_3$): δ = 201.1, 154.7, 124.1, 72.7, 60.8, 41.1, 27.8, 27.7, 25.3, 20.8 ppm; **IR (film, ATR)**: $\tilde{\nu}$ [cm^{-1}] = 2973, 2933, 2870, 1687, 1620, 1443, 1383, 1362, 1232, 1197, 1122, 1081, 1034, 967, 873, 824, 458; **GC-MS**: *m/z* (%) = 141 (43), 125 (34), 95 (13), 83 (100), 67 (4), 57 (6), 55 (13); **HR-MS** (ESI-pos): *m/z* calcd. for [M+Na]$^+$: 221.1512, found: 221.15134.

Compound 154a: Prepared according to the general procedure for Fe-catalyzed cross couplings.



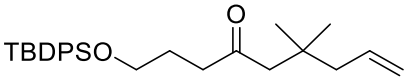
Light yellow oil (312 mg, 1.22 mmol, 72 %). **^{1}H-NMR** (400 MHz, $CDCl_3$): δ = 6.08 (h, J = 1.3 Hz, 1H), 3.62 (t, J = 6.2 Hz, 2H), 2.48 (t, J = 7.3 Hz, 2H), 2.14 (d, J = 1.4 Hz, 3H), 1.88 (d, J = 1.4 Hz, 3H), 1.80 (ddd, J = 13.4, 7.4, 6.2 Hz, 2H), 0.88 (s, 9H), 0.04 (s, 6H) ppm; **^{13}C{^{1}H}-NMR** (101 MHz, $CDCl_3$): δ = 201.0, 154.9, 124.0, 62.5, 40.7, 27.8, 27.4, 26.0, 20.8, 18.5, -5.3 ppm.

Compound 154d: in a Schlenk flask, TIPS-protected enone **154b** (190 mg, 0.64 mmol, 1.0 eq) was



dissolved in THF (5 mL) and the solution was cooled to 0°C. Then TASF (285 mg, 1.0 mmol, 1.6 eq) was added and the mixture was stirred at 0°C for 4 h and then warmed to room temperature. No full conversion was observed by TLC, so TBAF (1 M in THF, 2.0 mL, 2.0 mmol, 3.1 eq) was added and the mixture was stirred at room temperature for another 30 min. The reaction was quenched with sat. aq. $NaHCO_3$ and extracted with MTBE (3x). The combined organic layers were washed with water and brine, dried over $MgSO_4$, and solvent evaporated. The crude product was dissolved in CH_2Cl_2 (5 mL) and imidazole (87 mg, 1.3 mmol, 2.0 eq) was added, followed by TBDPSCl (0.18 mL, 0.69 mmol, 1.08 eq). The mixture was stirred at room temperature overnight. The reaction was quenched with water and extracted with CH_2Cl_2 (3x). The combined organic layers were dried over $MgSO_4$ and the solvent evaporated. The crude product was purified *via* flash chromatography (SiO_2 hexane/EtOAc 30:1) to obtain the title compound as a light yellow oil (128 mg, 0.34 mmol, 53 %). **^{1}H-NMR** (400 MHz, $CDCl_3$): δ = 7.69 – 7.60 (m, 4H), 7.45 – 7.33 (m, 6H), 6.07 (p, J = 1.3 Hz, 1H), 3.68 (t, J =6.1 Hz, 2H), 2.53 (t, J = 7.4 Hz, 2H), 2.14 (d, J = 1.4 Hz, 3H), 1.91 – 1.80 (m, 5H), 1.04 (s, 9H) ppm; **^{13}C{^{1}H}-NMR** (101 MHz, $CDCl_3$): δ = 201.0, 154.9, 135.7, 134.1, 129.7, 127.8, 124.0, 63.3, 40.8, 27.8, 27.2, 27.0, 20.9, 19.4 ppm.

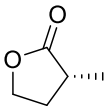
Compound 155d: In a Schlenk flask, enone **154d** (120 mg, 0.32 mmol, 1.0 eq) was dissolved in



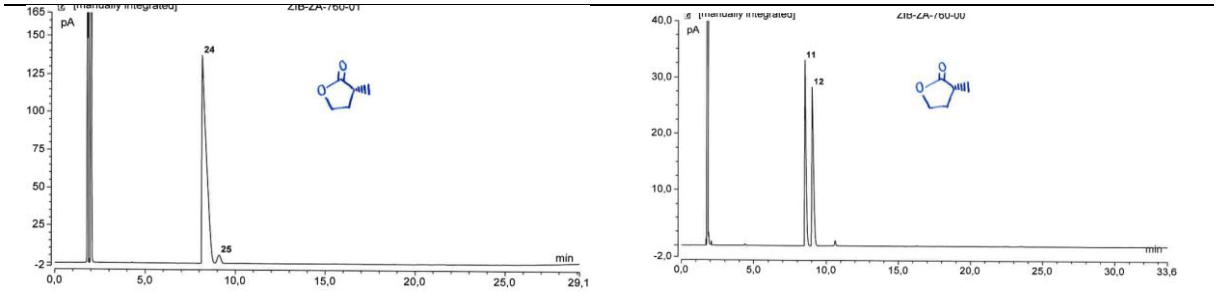
CH_2Cl_2 (5 mL) and the solution was cooled to 0 °C. Then $TiCl_4$ (1 M in CH_2Cl_2, 0.63 mL, 0.63 mmol, 2.0 eq) was added and the mixture was stirred at room temperature for 1 h. The reaction was quenched with water and the

mixture was stirred for another five minutes. The aqueous layer was extracted with MTBE (3x) and the combined organic layers were dried over Na_2SO_4. The solvent was evaporated and the crude product was purified *via* flash chromatography (SiO_2 hexane/EtOAc 30:1). The title compound was obtained as a colourless oil (87 mg, 0.21 mmol, 65 %). **^{1}H-NMR** (400 MHz, $CDCl_3$): δ = 7.65 (dd, J = 8.0, 1.6 Hz, 4H), 7.43 – 7.35 (m, 6H), 5.88 – 5.68 (m, 1H), 5.08 – 4.96 (m, 2H), 3.66 (t, J = 6.1 Hz, 2H), 2.50 (t, J = 7.4 Hz, 2H), 2.28 (s, 2H), 2.08 (dt, J = 7.5, 1.3 Hz, 2H), 1.85 – 1.72 (m, 2H), 1.04 (s, 9H), 0.99 (s, 6H) ppm; **^{13}C{^{1}H}-NMR** (101 MHz, $CDCl_3$): δ = 210.8, 135.7, 135.2, 134.0, 129.8, 127.8, 117.7, 63.1, 52.8, 46.7, 41.5, 33.9, 27.4, 27.0, 26.7, 19.4 ppm.

Compound 156: The title compound was prepared according to a literature procedure[260]. *ee* = 94 %. **^{1}H-NMR** (400 MHz, $CDCl_3$): δ = 4.32 (td, J = 8.7, 2.8 Hz, 1H), 4.21 – 4.11 (m, 1H), 2.65 – 2.52 (m, 1H), 2.47 – 2.35 (m, 1H), 1.97 – 1.83 (m, 1H), 1.27 (d, J = 7.2 Hz, 3H) ppm; The analytical data is consistent with the literature[260].



The optical purity was determined by chiral GC (BGB-176/BGB-15, 30 m, carrier gas H_2, 0.6 bar, temperature gradient 220/95 °C) **[t_R]** = 8.14 min (major), 9.1 min (minor).

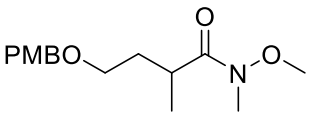


No.	Ret.Time min	Rel.Area %	Peak Name
24	8,14	96,97	
25	9,10	3,03	

No.	Ret.Time min	Rel.Area %	Peak Nam
11	8,52	49,93	
12	9,02	50,07	

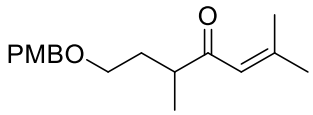
Figure 55. GC traces of enantioenriched 156 (left) and racemic 156 (right).

Compound *rac*-162: In a Schlenk flask, *N*,*O*-dimethylhydroxylamine hydrochloride (1.56 g, 16.0 mmol, 1.5 eq) was suspended in CH_2Cl_2 (10 mL) and the mixture was cooled to 0°C. Then DIBAL-H (1 M in hexanes, 15.6 mL, 15.6 mmol, 1.5 eq) was added slowly (gas evolution!) and the mixture was stirred for 1 h. Lactone ***rac*-156** (1.0 mL, 10.4 mmol, 1.0 eq) was added and the cooling bath was removed. The mixture was stirred at room temperature for 2.5 h, cooled to 0 °C again and quenched with aq. $NaHSO_4$ (1 M). The aqueous layer was extracted with CH_2Cl_2 (3x), the combined organic layers dried over Na_2SO_4, and the solvent evaporated. The crude product was dissolved in CH_2Cl_2 (5 mL) and cooled to 0 °C. PMBTC (3.0 mL, 14.5 mmol, 1.4 eq) and CSA (128 mg, 0.55 mmol, 0.05 eq) were added to the mixture and the cooling bath removed. The mixture was stirred at room temperature overnight. The reaction was quenched with sat. aq. $NaHCO_3$ and the aqueous



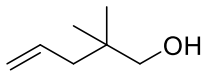
layer extracted with CH_2Cl_2 (3x). The combined organic layers were dried over Na_2SO_4 and the solvent was evaporated. The crude product was purified *via* flash chromatography (SiO_2 hexane/EtOAc 7:3 to 3:7) to obtain the title compound as a pale yellow oil (1.95 g, 6.9 mmol, 67 %). **^{1}H-NMR** (400 MHz, $CDCl_3$): δ = 7.26 – 7.20 (m, 2H), 6.90 – 6.82 (m, 2H), 4.40 (s, 2H), 3.80 (s, 3H), 3.65 (s, 3H), 3.52 – 3.36 (m, 2H), 3.17 – 3.10 (m, 4H), 2.07 – 1.96 (m, 1H), 1.72 – 1.58 (m, 1H), 1.12 (d, *J* = 7.0 Hz, 3H) ppm; **^{13}C{^{1}H}-NMR** (101 MHz, $CDCl_3$): δ = 159.3, 130.8, 129.4, 113.9, 72.7, 68.1, 61.6, 55.4, 33.7, 32.2, 17.8 ppm; **IR (film, ATR)**: $\tilde{\nu}$ [cm^{-1}] = 2936, 2860, 1656, 1612, 1512, 1462, 1385, 1301, 1245, 1173, 1091, 1032, 993, 818, 741, 515; **EI-MS**: *m/z* (%) = 241 (1), 145 (5), 121 (100), 85 (3), 78 (3); **HR-MS** (ESI-pos): *m/z* calcd. for $[M+Na]^+$: 304.15192, found: 304.15188. The analytical data is consistent with the literature[261].

Compound *rac*-163: In a Schlenk flask, Weinreb amide ***rac*-162** (155 mg, 0.55 mmol, 1.0 eq) was



dissolved in THF (2 mL) and the solution was cooled to -78 °C. Isobutenylmagnesium bromide solution (0.5 M in THF, 3.3 mL, 1.65 mmol, 3.0 eq) was slowly added and the mixture was warmed to room temperature overnight. The mixture was cooled to -78 °C and the reaction quenched with sat. aq. NH_4Cl. The aqueous layer was extracted with MTBE (3x), the combined organic layers were dried over Na_2SO_4, and the solvent was evaporated. The crude product was purified *via* flash chromatography (SiO_2 hexane/MTBE 5:1 to 1:1) to obtain the title compound as a colourless oil (83 mg, 0.3 mmol, 55 %). **^{1}H-NMR** (400 MHz, $CDCl_3$): δ = 7.26 – 7.20 (m, 2H), 6.91 – 6.83 (m, 2H), 6.14 – 6.04 (m, 1H), 4.40 (s, 2H), 3.80 (s, 3H), 3.53 – 3.31 (m, 2H), 2.69 (h, *J* = 6.9 Hz, 1H), 2.12 (s, 3H), 2.01 (dq, *J* = 13.7, 6.4 Hz, 1H), 1.88 (s, 3H), 1.65 – 1.51 (m, 1H), 1.07 (d, *J* = 7.1 Hz, 3H) ppm; **^{13}C{^{1}H}-NMR** (101 MHz, $CDCl_3$): δ = 204.4, 159.3, 155.8, 130.8, 129.4, 123.4, 113.9, 72.7, 68.0, 55.4, 43.9, 33.1, 27.9, 20.9, 16.8 ppm; **IR (film, ATR)**: $\tilde{\nu}$ [cm^{-1}] = 2933, 2859, 1682, 1614, 1512, 1443, 1360, 1301, 1246, 1173, 1096, 1034, 821; **EI-MS**: *m/z* (%) = 276 (< 1, [M]), 261 (2), 176 (1), 137 (7), 121 (100), 83 (62); **HR-MS** (ESI-pos): *m/z* calcd. for $[M+Na]^+$: 299.16176, found: 299.16153.

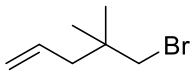
Compound 169: In a Schlenk flask, diisopropylamine (2.7 mL, 19.3 mmol) was dissolved in THF



(30 mL) and the solution was cooled to -78°C. *n*-Butyllithium (1.6 M in hexanes, 11.2 ml, 17.9 mmol) was slowly added and the mixture stirred for 0.5 h. Ethyl isobutyrate **166** (2.0 mL, 14.9 mmol) was added and the mixture kept stirring at -78°C for another 0.5 h. Allyl bromide **167** (1.42 mL, 16.4 mmol) was added and stirring of the mixture was continued at -78°C for 1 h. The mixture was warmed to room temperature and stirred overnight. The reaction was quenched with water and the aqueous layer extracted with diethyl ether. The combined organic layers were washed with water, aq. HCl (1 M) and brine, dried over $MgSO_4$, and the solvent carefully evaporated. The crude product was dissolved in diethyl ether (10 mL) and cooled to 0°C. A suspension of $LiAlH_4$ (0.9 g, 23.7 mmol) in diethyl ether (20 mL) was added and

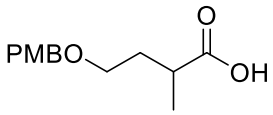
the mixture was stirred at 0°C for 1 h. After careful quenching of the reaction with water, the aqueous layer was extracted with diethyl ether, the combined organic layers were washed with water, aq. HCl (1 M) and brine, dried over $MgSO_4$, and the solvent evaporated. Purification *via* flash chromatography (SiO_2 pentane/Et_2O 3:1 to 1:1) afforded the title compound as a colourless oil (1.7 g, 14.9 mmol, *quant.*). **^{1}H-NMR** (400 MHz, $CDCl_3$): δ = 5.93 – 5.74 (m, 1H), 5.12 – 4.97 (m, 2H), 3.33 (s, 2H), 2.02 (dt, J = 7.5, 1.2 Hz, 2H), 0.89 (s, 6H) ppm; **^{13}C{^{1}H}-NMR** (101 MHz, $CDCl_3$): δ = 135.5, 117.3, 71.9, 43.5, 35.7, 24.0 ppm; **IR (film, ATR)**: $\tilde{\nu}$ [cm^{-1}] = 3346, 2957, 2928, 2871, 1039, 995, 911, 624; **ESI-MS**: *m/z* (%) = 360 (9), 287 (31, [2(M•H_2O)+Na]$^+$), 265 (11, [2(M•H_2O)+H]$^+$), 195 (16), 155 (100, [M•H_2O+Na]$^+$), 133 (6, [M•H_2O+H]$^+$), 115 (12, [M+H]$^+$); **HR-MS** (ESI-pos): *m/z* calcd. for [M+H]$^+$: 115.11174, found: 115.11202. The analytical data is consistent with the literature[233].

Compound 165: In a pressure Schlenk flask, triphenyl phosphine (1.63 g, 6.2 mmol, 1.2 eq) was



dissolved in DMF (3 mL). Then bromine (0.29 mL, 5.7 mmol, 1.1 eq) and imidazole (417 mg, 6.1 mmol, 1.2 eq) were added, followed by alcohol **169** (600 mg, 5.3 mmol, 1.0 eq). The mixture was heated to 115 °C overnight. It was cooled to room temperature and the reaction mixture was directly applied on a plug of silica to elute the product with pentane. The title compound was obtained as a colourless solution in pentane, which was not fully removed due to volatility of the product (697 mg, 3.9 mmol, 75 %). **^{1}H-NMR** (400 MHz, $CDCl_3$): δ = 5.84 – 5.67 (m, 1H), 5.11 (d, J = 2.8 Hz, 1H), 5.08 (dt, J = 2.5, 1.1 Hz, 1H), 3.28 (s, 2H), 2.11 (dt, J = 7.6, 1.1 Hz, 2H), 1.02 (s, 6H) ppm; **^{13}C{^{1}H}-NMR** (101 MHz, $CDCl_3$): δ = 134.3, 118.3, 46.4, 44.3, 35.0, 25.8 ppm; **IR (film, ATR)**: $\tilde{\nu}$ [cm^{-1}] = 3077, 2962, 1639, 1468, 1366, 1239, 997, 917, 661, 619; **EI-MS**: *m/z* (%) = 178 (< 1), 135 (68), 109 (7), 97 (21), 81 (10), 69 (9), 55 (100), 41 (8); **HR-MS** (GC-EI): *m/z* calcd. for [M]$^+$: 176.01953, found: 176.01947. The analytical data is consistent with the literature[262].

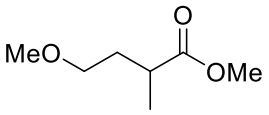
Compound *rac*-172: In a pressure Schlenk flask, lactone ***rac*-156** (0.1 mL, 1.0 mmol, 1.0 eq) was



dissolved in toluene (3 mL) and KOH (300 mg, 5.3 mmol, 5.1 eq) was added. The mixture was stirred at 120°C for 1 h. *p*-Methoxybenzyl chloride **171** (0.35 mL, 2.6 mmol, 2.5 eq) was added as a solution in toluene (1 mL) and the mixture was kept stirring at 120°C for 2 h. The mixture was diluted with EtOAc and washed with water (3x), the organic layer was discarded. The aqueous layer was acidified with aq. HCl (2 M) to pH~1 and a white precipitate formed. The aqueous layer was then extracted with EtOAc (3x) and the obtained combined organic layers were dried over $MgSO_4$, and the solvent evaporated. The title compound was obtained without further purification as a yellow oil (249 mg, 1.0 mmol, *quant.*). **^{1}H-NMR** (400 MHz, $CDCl_3$): δ = 7.28 – 7.20 (m, 2H), 6.90 – 6.84 (m, 2H), 4.43 (d, J = 2.4 Hz, 2H), 3.80 (s, 3H), 3.51 (t, J = 6.2 Hz, 2H), 2.67 (dq, J = 14.1, 7.1 Hz, 1H), 2.09 – 1.96 (m, 1H), 1.75 – 1.63 (m, 1H), 1.20 (d, J = 7.1 Hz, 3H) ppm; **^{13}C{^{1}H}-NMR** (101 MHz,

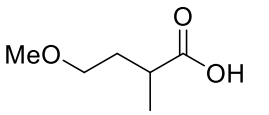
$CDCl_3$): δ = 181.8, 159.3, 130.4, 129.4, 113.9, 72.8, 67.6, 55.4, 36.6, 33.3, 17.1 ppm; **IR (film, ATR)**: $\tilde{\nu}$ [cm^{-1}] = 2973, 1704, 1512, 1245, 1173, 1082, 1032, 819; **EI-MS**: *m/z* (%) = 238 (< 1, [M]), 191 (1), 137 (100), 121 (91), 109 (22), 91 (8), 77 (10); **HR-MS** (GC-EI): *m/z* calcd. for $[M]^+$: 238.11996, found: 238.11988. The analytical data is consistent with the literature[261].

Compound *rac*-175: In a pressure Schlenk flask, lactone ***rac*-156** (1.0 mL, 10.4 mmol, 1.0 eq) and



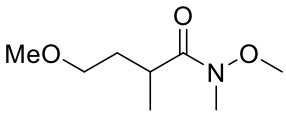
trimethyl orthoformiate (2.3 mL, 21.0 mmol, 2.0eq) were dissolved in methanol (5 mL). A few drops of concentrated H_2SO_4 were added and the mixture was stirred at 50 °C overnight. The mixture was diluted with water and the aqueous layer was extracted with CH_2Cl_2 (3x). The combined organic layers were dried over Na_2SO_4 and the solvent evaporated. The crude product was purified *via* flash chromatography (SiO_2 hexane/MTBE 9:1) to obtain the title compound as a colourless oil (1.3 g, 8.9 mmol, 86 %). **^{1}H-NMR** (400 MHz, $CDCl_3$): δ = 3.67 (s, 3H), 3.38 (tt, *J* = 6.0, 3.0 Hz, 2H), 3.30 (s, 3H), 2.60 (dq, *J* = 14.1, 7.1 Hz, 1H), 1.96 (ddt, *J* = 13.9, 7.9, 6.3 Hz, 1H), 1.65 (dq, *J* = 14.1, 6.2 Hz, 1H), 1.17 (d, *J* = 7.1 Hz, 3H) ppm; **^{13}C{^{1}H}-NMR** (101 MHz, $CDCl_3$): δ = 177.1, 70.5, 58.8, 51.7, 36.5, 33.6, 17.2 ppm; **IR (film, ATR)**: $\tilde{\nu}$ [cm^{-1}] = 2951, 2876, 1733, 1435, 1197, 1169, 1114; **EI-MS**: *m/z* (%) = 115 (28), 99 (7), 88 (100), 71 (17), 57 (61), 45 (34); **HR-MS** (GC-CI): *m/z* calcd. for $[M+H]^+$: 147.10157, found: 147.10176. The analytical data is consistent with the literature[263].

Compound *rac*-176: In a pressure Schlenk flask, lactone ***rac*-156** (0.25 mL, 2.6 mmol, 1.0 eq) and



trimethylorthoformiate (0.57 mL, 5.2 mmol, 2.0 eq) were dissolved in methanol (2.5 mL). A few drops of concentrated H_2SO_4 were added and the mixture was stirred at 50°C overnight. The mixture was then diluted with MTBE and the solvent evaporated. The residue was dissolved in THF (5 mL) and water (2 mL) and lithium hydroxide (160 mg, 6.7 mmol, 2.6 eq) were added. The mixture was stirred at 50 °C for 1.5 h. It was then acidified with aq. H_2SO_4 (2 M) and the aqueous layer extracted with MTBE (3x). The combined organic layers were dried over $MgSO_4$ and the solvent was evaporated. The title compound was obtained without further purification as a collourless oil (360 mg, 2.7 mmol, *quant.*) **^{1}H-NMR** (400 MHz, $CDCl_3$): δ = 3.45 (t, *J* = 6.3 Hz, 2H), 3.34 (s, 3H), 2.70 – 2.58 (m, 1H), 2.06 – 1.93 (m, 1H), 1.69 (dq, *J* = 14.2, 6.1 Hz, 1H), 1.22 (d, *J* = 7.1 Hz, 3H) ppm; **^{13}C{^{1}H}-NMR** (101 MHz, $CDCl_3$): δ = 182.0, 70.4, 58.8, 36.5, 33.2, 17.1 ppm; **IR (film, ATR)**: $\tilde{\nu}$ [cm^{-1}] = 2932, 2877, 1703, 1462, 1183, 1113, 947, 837; **EI-MS**: *m/z* (%) = 114 (6), 99 (7), 85 (9), 74 (92), 59 (58), 45 (100); **HR-MS** (GC-EI): *m/z* calcd. for $[M]^+$: 132.0781, found: 132.0781. The analytical data is consistent with the literature[236].

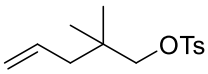
Compound *rac*-182: In a jacketed cooling Schlenk flask, methyl ester ***rac*-175** (500 mg, 3.4 mmol,



1.0 eq) and *N*,*O*-dimethylhydroxylamine hydrochloride (850 mg, 8.7 mmol, 2.5 eq) were dissolved in THF (3 mL) and the solution was

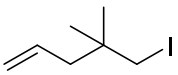
cooled to -30 °C. Isopropylmagnesium chloride (2 M in THF, 8.5 mL, 17 mmol, 5.0 eq) was slowly added with a syringe pump over a course of 30 min and the mixture was stirred at 0 °C for 1.5 h. The reaction was quenched with sat. aq. NH_4Cl and warmed to room temperature. The aqueous layer was extracted with MTBE (3x), the combined organic layers dried over Na_2SO_4, and the solvent evaporated. The crude product was purified *via* flash chromatography (SiO_2 hexane/EtOAc 1:1 to 1:2) to obtain the title compound as a colourless liquid (535 mg, 3.05 mmol, 89 %). **^{1}H-NMR** (400 MHz, $CDCl_3$): δ = 3.69 (s, 3H), 3.44 – 3.26 (m, 5H), 3.19 (s, 3H), 3.08 (d, J = 4.3 Hz, 1H), 2.03 – 1.91 (m, 1H), 1.68 – 1.57 (m, 1H), 1.12 (d, J = 7.0 Hz, 3H) ppm; **^{13}C{^{1}H}-NMR** (101 MHz, $CDCl_3$): δ = 177.8, 70.6, 61.6, 58.6, 33.6, 32.4, 32.1, 17.7 ppm; **IR (film, ATR)**: $\tilde{\nu}$ [cm^{-1}] = 2935, 2874, 1657, 1462, 1385, 1179, 1116, 993; **EI-MS**: *m/z* (%) = 144 (1), 115 (100) 87 (31), 57 (26), 45 (55); **HR-MS** (GC-CI): *m/z* calcd. for $[M+H]^+$: 176.12812, found: 176.12816.

Compound 179: In a Schlenk flask, alcohol **169** (500 mg, 4.4 mmol, 1.0 eq) was dissolved in



CH_2Cl_2 (10 mL) and DMAP (840 mg, 6.9 mmol, 1.6 eq) was added. The mixture was cooled to 0 °C and tosyl chloride (946 mg, 5.0 mmol, 1.1 eq) was added. The mixture was warmed to room temperature and stirred overnight. The reaction was quenched with water, the aqueous layer was extracted with CH_2Cl_2 (3x) and the combined organic layers were dried over $MgSO_4$, and the solvent was evaporated. The crude product was purified *via* flash chromatography (SiO_2 hexane/EtOAc 25:1) to obtain the title compound as a colourless liquid (973 mg, 3.6 mmol, 83 %). **^{1}H-NMR** (400 MHz, $CDCl_3$): δ = 7.81 – 7.76 (m, 2H), 7.34 (d, J = 7.9 Hz, 2H), 5.71 – 5.59 (m, 1H), 5.04 – 4.92 (m, 2H), 3.68 (s, 2H), 2.45 (s, 3H), 1.98 (d, J = 7.5 Hz, 2H), 0.87 (s, 6H) ppm; **^{13}C{^{1}H}-NMR** (101 MHz, $CDCl_3$): δ = 144.8, 133.7, 133.2, 129.9, 128.1, 118.4, 42.9, 34.5, 23.9, 21.8 ppm; **IR (film, ATR)**: $\tilde{\nu}$ [cm^{-1}] = 2967, 1357, 1174, 1098, 964, 836, 812, 665, 553; **EI-MS**: *m/z* (%) = 227 (1), 173 (2), 155 (100), 119 (15), 96 (22), 91 (71), 81 (34); **HR-MS** (GC-CI): *m/z* calcd. for $[M+H]^+$: 269.12059, found: 269.12081. The analytical data is consistent with the literature[264].

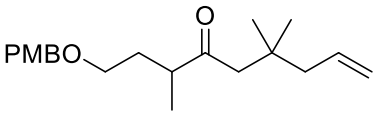
Compound 180: In a Schlenk flask, alcohol **169** (834 mg, 7.3 mmol, 1.0 eq) was dissolved in



CH_2Cl_2 (8 mL) and the solution was cooled to -78 °C. Lutidine (0.94 mL, 8.1 mmol, 1.11 eq) was added followed by Tf_2O (1.3 mL, 7.7 mmol, 1.1 eq) and the cooling bath changed to 0 °C. The mixture was stirred for 30 min at 0 °C, then the reaction was quenched with sat. aq. NH_4Cl. The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (3x). The combined organic layers were washed with water and brine, dried over $MgSO_4$, and the solvent was evaporated. The crude product was dissolved in DMF (10 mL) and NaI (3.3 g, 22.1 mmol, 3.0 eq) was added. The mixture was stirred at room temperature for 1 h, diluted with water and pentane and the reaction was quenched with sat. aq. $Na_2S_2O_3$. The aqueous layer was extracted with pentane (3x), the combined organic layers were washed with sat. aq. $Na_2S_2O_3$, dried over $MgSO_4$, and the solvent partially evaporated. The title compound was obtained without

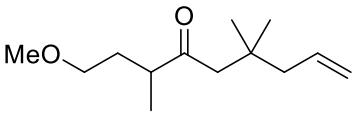
further purification as a colourless solution in pentane, which was not fully removed due to expected volatility of the product (1.68 g, 7.5 mmol, *quant.*). **^{1}H-NMR** (400 MHz, $CDCl_3$): δ = 5.74 (ddt, *J* = 16.7, 10.4, 7.5 Hz, 1H), 5.14 – 5.09 (m, 1H), 5.08 (t, *J* = 1.1 Hz, 1H), 3.14 (s, 2H), 2.09 (dt, *J* = 7.5, 1.1 Hz, 2H), 1.03 (s, 6H) ppm; **^{13}C{^{1}H}-NMR** (101 MHz, $CDCl_3$): δ = 134.4, 118.3, 45.2, 33.8, 26.8, 24.0 ppm; **IR (film, ATR)**: $\tilde{\nu}$ [cm^{-1}] = 3076, 2961, 1639, 1466, 1383, 1366, 1213, 1153, 996, 916, 598; **EI-MS**: *m/z* (%) = 224 (3, [M]), 183 (100), 155 (7), 97 (34), 69 (14), 55 (52); **HR-MS** (GC-EI): *m/z* calcd. for $[M]^+$: 224.00565, found: 224.00577. The analytical data is consistent with the literature[233].

Compound *rac*-164: In a Schlenk flask, alkyl iodide **180** (60 mg, 0.27 mmol, 1.5 eq) was dissolved



in pentane (3 mL) and the solution was cooled to -78 °C. *tert*-Butyllithium (1.7 M in pentane, 0.23 mL, 0.39 mmol, 2.2 eq) was added and the mixture was stirred at -78 °C for 30 min. A solution of Weinreb amide ***rac*-162** (50 mg, 0.18 mmol, 1.0 eq) in THF (2 mL) was added and stirring continued at -78 °C for 45 min. The reaction was quenched with brine and warmed to room temperature. The aqueous layer was extracted with MTBE (3x), the combined organic layers were dried over $MgSO_4$, and the solvent evaporated. The crude product was immobilized on Celite and purified *via* flash chromatography (SiO_2 hexane/EtOAc 20:1) to yield the title compound as a light yellow oil (11 mg, 0.04 mmol, 19 %). **^{1}H-NMR** (400 MHz, $CDCl_3$): δ = 7.26 – 7.19 (m, 2H), 6.92 – 6.82 (m, 2H), 5.77 (ddt, *J* = 17.9, 10.3, 7.5 Hz, 1H), 5.07 – 4.91 (m, 2H), 4.39 (s, 2H), 3.80 (s, 3H), 3.41 (qdd, *J* = 9.5, 6.7, 5.6 Hz, 2H), 2.68 (h, *J* = 7.0 Hz, 1H), 2.40 – 2.23 (m, 2H), 2.09 (dd, *J* = 7.5, 1.1 Hz, 2H), 1.96 (dtd, *J* = 14.1, 7.0, 5.6 Hz, 1H), 1.59 – 1.46 (m, 1H), 1.02 (d, *J* = 7.0 Hz, 3H), 0.97 (s, 6H) ppm; **^{13}C{^{1}H}-NMR** (101 MHz, $CDCl_3$): δ = 214.2, 159.3, 135.4, 130.6, 129.5, 117.5, 113.9, 72.8, 67.7, 55.4, 51.4, 46.4, 44.3, 33.7, 32.8, 27.4, 27.4, 16.6 ppm; **IR (film, ATR)**: $\tilde{\nu}$ [cm^{-1}] = 2956, 2870, 1709, 1613, 1513, 1247, 1094, 1037, 821; **EI-MS**: *m/z* (%) = 274 (1), 197 (1), 179 (2), 137 (17), 121 (100), 109 (3), 91 (3), 77 (3); **HR-MS** (GC-CI): *m/z* calcd. for $[M+H]^+$: 319.22677, found: 319.2272.

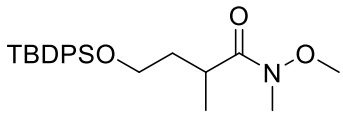
Compound *rac*-178: In a Schlenk flask, *tert*-butyllithium (1.7 M in pentane, 0.39 mL, 0.66 mmol,



2.0 eq) was diluted in pentane (1 mL) at -78 °C. A solution of alkyl iodide **180** (75 mg, 0.33 mmol, 1.0 eq) in diethyl ether (1 mL) was added and the mixture was stirred at -78 °C for 3 h. A solution of Weinreb amide ***rac*-182** (88 mg, 0.5 mmol, 1.5 eq) in diethyl ether (1 mL) was added and stirring continued at -78 °C for 1 h. The reaction was quenched with sat. aq. NH_4Cl and warmed room temperature. The aqueous layer was extracted with pentane (3x). The combined organic layers were dried over $MgSO_4$ and the solvent evaporated. The crude product was purified *via* flash chromatography (SiO_2 pentane/Et_2O 9:1) to obtain the title compound as a colourless oil (12 mg, 0.06 mmol, 17 %). **^{1}H-NMR** (400 MHz, $CDCl_3$): δ = 5.85 – 5.71 (m, 1H), 5.06 – 4.96 (m, 2H),

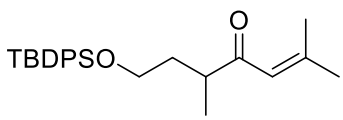
3.40 – 3.30 (m, 2H), 3.29 (s, 3H), 2.65 (h, *J* = 7.0 Hz, 1H), 2.35 (d, *J* = 1.0 Hz, 2H), 2.11 (dt, *J* = 7.5, 1.1 Hz, 2H), 1.94 (dtd, *J* = 14.2, 7.0, 5.7 Hz, 1H), 1.56 – 1.42 (m, 1H), 1.04 (d, *J* = 7.0 Hz, 4H), 0.99 (s, 6H) ppm; **^{13}C{^{1}H}-NMR** (101 MHz, $CDCl_3$): δ = 214.1, 135.4, 117.5, 70.5, 58.7, 51.4, 46.4, 44.3, 33.7, 32.7, 27.4, 16.6 ppm; **IR (film, ATR)**: $\tilde{\nu}$ [cm^{-1}] = 2959, 2873, 1706, 1460, 1364, 1193, 1117, 1052, 997, 914; **EI-MS**: *m/z* (%) = 197 (1) 180 (3), 165 (5), 154 (38), 139 (40), 130 (22), 112 (93), 97 (49), 87 (67), 74 (50), 59 (100), 41 (58); **HR-MS** (ESI-pos): *m/z* calcd. for [M+Na]$^{+}$: 235.16685, found: 235.16707.

Compound *rac*-184: In a Schlenk flask, lactone ***rac*-156** (0.25 mL, 2.65 mmol, 1.0 eq) was



dissolved in THF (5 mL) and *N*,*O*-dimethylhydroxylamine hydrochloride (364 mg, 3.7 mmol, 1.4 eq) was added. The mixture was cooled to 0 °C, followed by slow addition of isopropylmagnesium chloride•LiCl (1.3M in THF, 5.3 mL, 6.9 mmol, 2.6 eq) *via* syringe. The mixture was kept stirring at 0 °C for another 5 min, then the cooling bath was removed and stirring continued at room temperature for 1.5 h. The mixture was cooled to 0 °C again and the reaction carefully quenched with phosphate buffer solution. The aqueous layer was extracted with CH_2Cl_2 (5x), the combined organic layers dried over $MgSO_4$, and the solvent evaporated. The crude product was dissolved in CH_2Cl_2, then imidazole (375 mg, 5.5 mmol, 2.1 eq) and TBDPSCl (0.76 mL, 2.9 mmol, 1.1 eq) were added. The mixture was stirred at room temperature for 3 h, then the reaction was quenched with water. The aqueous layer was extracted with MTBE (3x). The combined organic layers were dried over $MgSO_4$ and the solvent evaporated. The crude product was purified *via* flash chromatography (silica, hexane/EtOAc 5:1 to 4:1) to obtain the title compound as a colourless liquid (971 mg, 2.43 mmol, 92 %). **^{1}H-NMR** (400 MHz, $CDCl_3$): δ = 7.70 – 7.61 (m, 4H), 7.46 – 7.34 (m, 6H), 3.76 – 3.63 (m, 5H), 3.18 (s, 4H), 2.04 – 1.93 (m, 1H), 1.63 – 1.52 (m, 1H), 1.10 (d, *J* = 7.0 Hz, 3H), 1.05 (s, 9H) ppm; **^{13}C{^{1}H}-NMR** (101 MHz, $CDCl_3$): δ = 178.0, 135.7, 135.7, 134.0, 129.7, 129.7, 127.8, 127.8, 61.8, 61.6, 36.4, 31.7, 27.0, 19.4, 17.2 ppm; **IR (film, ATR)**: $\tilde{\nu}$ [cm^{-1}] = 2932, 2857, 1661, 1427, 1107, 1087, 997, 822, 739, 700, 612, 503, 430; **EI-MS**: *m/z* (%) = 384 (1), 342 (100), 310 (1), 282 (2), 213 (7), 183 (6), 135 (11), 105 (2); **HR-MS** (ESI-pos): *m/z* calcd. for [M+Na]$^{+}$: 422.2122, found: 422.2126.

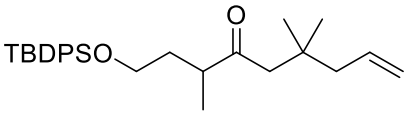
Compound *rac*-187: In a Schlenk flask, *tert*-butyllithium (1.7 M in pentane, 4.2 mL, 7.14 mmol,



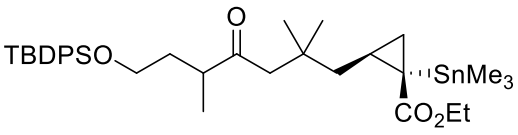
4.0 eq) was diluted diethyl ether (10 mL) at 0 °C. Isobutenyl bromide **185** (0.4 mL, 3.9 mmol, 2.2 eq) was slowly added and the mixture was stirred at 0 °C for 1.5 h. The obtained solution was then added to a solution of Weinreb amide ***rac*-184** (717 mg, 1.79 mmol, 1.0 eq) in diethyl ether (10 mL) at 0 °C. The mixture was stirred at 0 °C for 45 min. The reaction was quenched with sat. aq. NH_4Cl and the aqueous layer was extracted with MTBE (3x). The combined organic layers were dried over $MgSO_4$ and the solvent evaporated. The crude product was purified *via* flash

chromatography (silica, hexane/EtOAc 30:1) to obtain the title compound as a colourless oil (641 mg, 1.62 mmol, 91 %). **^{1}H-NMR** (400 MHz, $CDCl_3$): δ = 7.65 (ddd, J = 8.0, 3.4, 1.6 Hz, 4H), 7.45 – 7.34 (m, 6H), 6.11 (p, J = 1.4 Hz, 1H), 3.67 (t, J = 6.3 Hz, 2H), 2.76 (q, J = 6.9 Hz, 1H), 2.13 (d, J = 1.3 Hz, 3H), 2.01 – 1.90 (m, 1H), 1.89 (d, J = 1.4 Hz, 3H), 1.51 (dd, J = 13.8, 7.0 Hz, 1H), 1.07 – 1.00 (m, 12H) ppm; **^{13}C{^{1}H}-NMR** (101 MHz, $CDCl_3$): δ = 204.5, 155.7, 135.7, 134.0, 134.0, 129.7, 127.8, 123.4, 61.9, 43.5, 35.9, 27.9, 27.0, 20.9, 19.4, 16.5 ppm; **IR (film, ATR)**: $\tilde{\nu}$ [cm^{-1}] = 2931, 2857, 1686, 1620, 1428, 1106, 822, 738, 700, 613, 503; **ESI-MS**: *m/z* (%) = 811 (24, $[2M+Na]^+$), 471 (7), 417 (100, $[M+Na]^+$), 395 (23, $[M+H]^+$), 317 (8); **HR-MS** (ESI-pos): *m/z* calcd. for $[M+Na]^+$: 417.222, found: 417.2218.

Compound *rac*-188: In a Schlenk flask, *tert*-butyllithium (1.7 M in pentane, 5.5 mL, 9.35 mmol, 3.9 eq) was diluted in diethyl ether (10 mL) at -78 °C. Then alkyl iodide **180** (58 wt% solution in pentane, 2.67 g, 6.9 mmol, 2.8 eq) was added dropwise and the mixture was kept stirring at -78 °C for 2 h. The obtained solution was added to a solution of Weinreb amide ***rac*-184** (970 mg, 2.4 mmol, 1.0 eq) in diethyl ether (20 mL) at -78 °C. The mixture was stirred for 30 min, the reaction quenched with sat. aq. NH_4Cl and warmed to room temperature. The aqueous layer was extracted with MTBE (3x), combined organic layers were dried over $MgSO_4$, and the solvent evaporated. The crude product was purified *via* flash chromatography (silica, hexane/EtOAc 50:1 to 40:1) to obtain the title compound as a light yellow oil (953 mg, 2.18 mmol, 90 %). **^{1}H-NMR** (400 MHz, $CDCl_3$): δ = 7.71 – 7.59 (m, 4H), 7.47 – 7.32 (m, 6H), 5.85 – 5.71 (m, 1H), 5.05 – 4.95 (m, 2H), 3.65 (t, J = 6.1 Hz, 2H), 2.81 – 2.70 (m, 1H), 2.41 – 2.26 (m, 2H), 2.09 (dq, J = 7.5, 1.0 Hz, 2H), 1.94 – 1.84 (m, 1H), 1.44 (ddt, J = 13.3, 7.4, 6.0 Hz, 1H), 1.06 (s, 9H), 1.02 – 0.95 (m, 9H) ppm; **^{13}C{^{1}H}-NMR** (101 MHz, $CDCl_3$): δ = 214.4, 135.7, 135.3, 133.9, 133.9, 129.8, 127.8, 117.6, 61.6, 51.4, 46.5, 43.8, 35.5, 33.8, 27.4, 27.4, 27.0, 19.4, 16.1 ppm; **IR (film, ATR)**: $\tilde{\nu}$ [cm^{-1}] = 3072, 2931, 2858, 1710, 1428, 1106, 997, 913, 822, 736, 700, 613, 502, 487; **EI-MS**: *m/z* (%) = 379 (50), 337 (26), 297 (52), 219 (68), 199 (100), 163 (20), 135 (31), 83 (41), 55 (58); **HR-MS** (ESI-pos): *m/z* calcd. for $[M+Na]^+$: 459.26898, found: 459.26941.

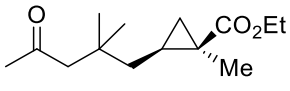


Compound 189: In a Schlenk flask, ***ent*-C3** (20 mg, 0.01 mmol, 0.02 eq) was dissolved in pentane (6 mL) and olefin ***rac*-188** (490 mg, 1.1 mmol, 2.0 eq) was added. The mixture was cooled to 0 °C and a solution of diazo compound **56** (152 mg, 0.55 mmol, 1.0 eq) in pentane (4 mL) was added. The mixture was stirred at 0 °C for 1 h, then the solvent was evaporated and the crude material purified *via* flash chromatography (silica, hexane/EtOAc 50:1 to 9:1). The title compound was obtained as a colourless oil (201 mg, 0.29 mmol, 53 %, *cis*/*trans* = 1:18, ^{1}H-NMR). **^{1}H-NMR** (400 MHz, $CDCl_3$): δ = 7.65 (dt, J = 8.0, 1.2 Hz, 4H), 7.46 – 7.34 (m, 6H), 4.18 – 3.97 (m, 2H), 3.65 (t, J = 6.2 Hz, 2H), 2.75 (h, J = 7.0 Hz, 1H), 2.44 – 2.28 (m, 2H),



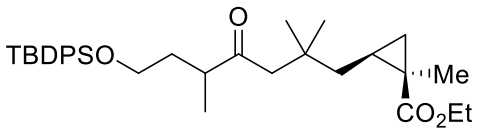
1.90 (dqd, *J* = 12.4, 6.4, 1.7 Hz, 1H), 1.59 (dt, *J* = 13.8, 5.6 Hz, 1H), 1.49 – 1.31 (m, 2H), 1.24 (d, *J* = 7.1 Hz, 3H), 1.12 (ddt, *J* = 6.1, 4.1, 2.2 Hz, 1H), 1.08 (dd, *J* = 6.1, 0.9 Hz, 1H), 1.05 (s, 9H), 1.03 – 0.97 (m, 9H), 0.87 (ddd, *J* = 7.5, 4.1, 1.2 Hz, 1H), 0.10 (s, 9H) ppm; **^{13}C{^{1}H}-NMR** (101 MHz, $CDCl_3$): δ = 214.3, 175.6, 135.7, 133.9, 133.9, 129.8, 127.8, 61.6, 60.6, 52.2, 52.1, 44.0, 41.2, 41.2, 35.4, 35.3, 34.4, 34.4, 27.3, 27.3, 27.1, 27.0, 20.6, 19.4, 16.3, 16.1, 16.0, 14.6, -9.7 ppm; **^{119}Sn{^{1}H}-NMR** (149 MHz, $CDCl_3$): δ = 22.1 ppm; **IR (film, ATR)**: $\tilde{\nu}$ [cm^{-1}] = 2959, 2931, 1708, 1282, 1179, 1104, 736, 701, 613, 503; **ESI-MS**: *m/z* (%) = 1393 (21, [2M+Na]$^+$), 1056 (1), 1048 (1), 849 (12), 709 (100, [M+Na]$^+$), 704 (32, [M+NH_4]$^+$); **HR-MS** (ESI-pos): *m/z* calcd. for [M+Na]$^+$: 228.12074, found: 709.2705. Doubled signals in ^{13}C-NMR observed due to presence of diastereoisomers.

Compound 190: In a pressure Schlenk flask, $Pd_2(dba)_3$ (3 mg, 0.003 mmol, 0.05 eq), JackiePhos



(20 mg, 0.025 mmol, 0.4 eq), CuCl (32 mg, 0.32 mmol, 5.0 eq) and KF (8 mg, 0.14 mmol, 2.1 eq) were mixed and dissolved in THF (2 mL). Then stannane **152** (25 mg, 0.06 mmol, 1.0 eq) and methyl iodide (0.02 mL, 0.32 mmol, 5.0 eq) were added and the mixture was stirred at 70°C for four days. Heating was stopped, the reaction mixture was diluted with MTBE and filtered through filter paper. The solvent was removed and the crude product was immobilized on Celite and purified *via* flash chromatography (SiO_2, hexane/EtOAc 20:1) to obtain the title compound as a light yellow oil (11 mg, 0.046 mmol, 71 %). **^{1}H-NMR** (400 MHz, $CDCl_3$): δ = 4.19 – 4.05 (m, 2H), 2.35 (d, *J* = 3.4 Hz, 2H), 2.12 (s, 3H), 1.54 (dd, *J* = 9.6, 6.0 Hz, 2H), 1.29 (s, 3H), 1.28 – 1.22 (m, 4H), 1.18 – 1.11 (m, 1H), 1.00 (d, *J* = 4.8 Hz, 6H), 0.80 (dd, *J* = 8.6, 4.2 Hz, 1H) ppm; **^{13}C{^{1}H}-NMR** (101 MHz, $CDCl_3$): δ = 208.8, 174.3, 60.4, 54.2, 39.5, 34.0, 32.6, 27.1, 27.0, 26.2, 23.7, 21.4, 21.3, 14.4 ppm; **IR (film, ATR)**: $\tilde{\nu}$ [cm^{-1}] = 2961, 1715, 1365, 1324, 1279, 1174, 1154, 1137, 1029; **EI-MS**: *m/z* (%) = 225 (43), 179 (73), 151 (17), 136 (100), 121 (45), 109 (93), 93 (32), 81 (17), 67 (49); **HR-MS** (ESI-pos): *m/z* calcd. for [M+H]$^+$: 241.17982, found: 241.17983.

Compound 191: In a pressure Schlenk flask, $Pd_2(dba)_3$ (7 mg, 0.008 mmol, 0.05 eq), JackiePhos



(46 mg, 0.06 mmol, 0.4 eq), KF (17 mg, 0.30 mmol, 2.0 eq) and CuCl (31 mg, 0.31 mmol, 2.1 eq) were mixed and dissolved in THF (2 mL). In another Schlenk flask, stannane **189** (100 mg, 0.15 mmol, 1.0 eq) and methyl iodide (0.09 mL, 1.5 mmol, 10 eq) were dissolved in THF (1 mL) and this solution was then added to the mixture in the pressure Schlenk flask. The mixture was heated to 70 °C for 16 h. After cooling to room temperature, the mixture was diluted with MTBE, filtered and the solvent evaporated. The crude product was immobilized on Celite and purified *via* flash chromatography (silica hexane/EtOAc 30:1) to yield the title compound as a colourless oil obtained (42 mg, 0.078 mmol, 54 %). **^{1}H-NMR** (400 MHz, $CDCl_3$): δ = 7.65 (dt, *J* = 8.0, 1.2 Hz, 4H), 7.46 – 7.33 (m, 6H), 4.18 – 4.05 (m, 2H), 3.65 (t, *J* = 6.3 Hz, 2H),

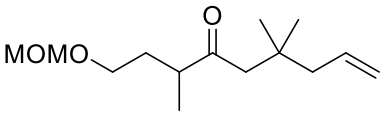
2.81 – 2.70 (m, 1H), 2.45 – 2.27 (m, 2H), 1.95 – 1.83 (m, 1H), 1.60 – 1.50 (m, 2H), 1.44 (td, *J* = 13.5, 5.9 Hz, 1H), 1.28 (s, 2H), 1.24 (d, *J* = 7.1 Hz, 3H), 1.14 (dd, *J* = 7.6, 4.6 Hz, 1H), 1.05 (s, 10H), 1.02 – 0.96 (m, 9H), 0.78 (dd, *J* = 9.4, 4.2 Hz, 1H) ppm; **^{13}C{^{1}H}-NMR** (101 MHz, $CDCl_3$): δ = 214.3, 174.4, 135.7, 133.9, 133.9, 129.8, 127.8, 61.6, 60.6, 52.0, 44.0, 39.8, 35.4, 34.2, 27.2, 27.1, 27.0, 26.4, 23.8, 21.5, 21.5, 19.4, 16.0, 14.5 ppm; **IR (film, ATR)**: $\tilde{\nu}$ [cm^{-1}] = 2932, 1714, 1279, 1173, 1109, 738, 702, 613, 504; **ESI-MS**: *m/z* (%) = 1096 (12, $[2M+Na]^+$), 824 (5, $[3M+Ca]^{2+}$), 575 (2, $[M+K]^+$), 559 (100, $[M+Na]^+$), 554 (16, $[M+NH_4]^+$), 537 (6, $[M+H]^+$); **HR-MS** (ESI-pos): *m/z* calcd. for $[M+Na]^+$: 559.32141, found: 559.32116. Doubled signals in ^{13}C-NMR observed due to presence of diastereoisomers.

Compound *rac*-193: In a Schlenk flask, *N*,*O*-dimethylhydroxylamine hydrochloride (790 mg, 8.1 mmol, 1.5 eq) and lactone ***rac*-156** (0.5 mL, 5.3 mmol, 1.0 eq) were suspended in THF (10 mL) and the mixture was cooled to 0 °C. Isopropylmagnesium chloride (2 M in THF, 8.0 mL, 16.0 mmol, 3.0 eq) was added and the cooling bath removed. Stirring of the mixture was continued at room temperature for 2 h. More *N*,*O*-dimethylhydroxylamine hydrochloride (300 mg, 3.1 mmol, 0.6 eq) and isopropylmagnesium chloride (2 M in THF, 3.0 mL, 6.0 mmol, 1.1 eq) were added and the mixture was stirred for another hour. The reaction was then quenched with phosphate buffer solution and the aqueous layer extracted with CH_2Cl_2 (3x). The combined organic layers were dried over $MgSO_4$ and the solvent evaporated. The crude product was dissolved in CH_2Cl_2 (10 mL) and MOMCl (1.2 mL, 15.8 mmol, 3.0 eq) and diisopropylethylamine (1.4 mL, 8.0 mmol, 1.5 eq) were added. The mixture was stirred at room temperature overnight. The reaction was quenched with sat. aq. NH_4Cl and the aqueous layer extracted with CH_2Cl_2 (3x). The combined organic layers were dried over $MgSO_4$ and the solvent evaporated. The crude product was purified *via* flash chromatography (silica, hexane/MTBE 1:1 to 1:2) to obtain the title compound as a colourless liquid (764 mg, 3.72 mmol, 70 %). **^{1}H-NMR** (400 MHz, $CDCl_3$): δ = 4.58 (s, 2H), 3.68 (s, 3H), 3.57 – 3.43 (m, 2H), 3.33 (s, 3H), 3.17 (s, 3H), 3.08 (d, *J* = 7.0 Hz, 1H), 2.05 – 1.94 (m, 1H), 1.69 – 1.58 (m, 1H), 1.13 (d, *J* = 7.0 Hz, 3H) ppm; **^{13}C{^{1}H}-NMR** (101 MHz, $CDCl_3$): δ = 177.7, 96.6, 65.8, 61.6, 55.3, 33.6, 32.4, 32.2, 17.7 ppm; **IR (film, ATR)**: $\tilde{\nu}$ [cm^{-1}] = 2935, 2881, 1657, 1463, 1385, 1141, 1109, 1045, 994, 917, 731; **EI-MS**: *m/z* (%) = 174 (< 1), 160 (1), 144 (38), 115 (100), 105 (7), 74 (48), 59 (20), 45 (53); **HR-MS** (ESI-pos): *m/z* calcd. for $[M+Na]^+$: 228.12063, found: 228.12074.

Compound *rac*-194: In a Schlenk flask, alcohol ***rac*-192** (500 mg, 3.1 mmol, 1.0 eq) was dissolved in DMF (6 mL) and the solution was cooled to -10 °C. Benzyl bromide (0.92 mL, 7.7 mmol, 2.5 eq) and sodium hydride (130 mg, 5.4 mmol, 1.7 eq) were added and the mixture was kept stirring at -10 °C for 30 min. The reaction was quenched with sat. aq. NH_4Cl and the organic layer was washed with

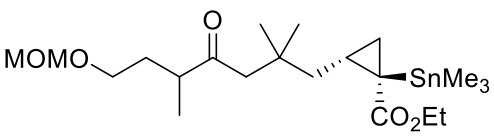
water and brine, then dried over $MgSO_4$ and the solvent evaporated. The crude product was purified *via* flash chromatography (SiO_2 hexane/EtOAc 2:1) to obtain the title compound as a colourless oil (348 mg, 1.39 mmol, 45 %). **^{1}H-NMR** (400 MHz, $CDCl_3$): δ = 7.39 – 7.23 (m, 5H), 4.47 (s, 2H), 3.65 (s, 3H), 3.59 – 3.38 (m, 2H), 3.17 (s, 4H), 2.12 – 1.95 (m, 1H), 1.74 – 1.59 (m, 1H), 1.13 (d, *J* = 6.8 Hz, 3H) ppm; **^{13}C{^{1}H}-NMR** (101 MHz, $CDCl_3$): δ = 177.6, 138.7, 128.5, 127.8, 127.6, 73.0, 68.4, 61.6, 33.7, 32.2, 17.8 ppm; **IR (film, ATR)**: $\tilde{\nu}$ [cm^{-1}] = 2935, 2861, 1656, 1454, 1385, 1176, 1094, 993, 736, 698, 601; **EI-MS**: *m/z* (%) = 191 (1), 151 (3), 117 (2), 91 (100), 65 (4); **HR-MS** (GC-CI): *m/z* calcd. for [M+H]$^+$: 252.15942, found: 252.15972.

Compound *rac*-195: The compound was prepared from Weinreb amide ***rac*-193** analogously to the TBDPS-derivative ***rac*-188**. Colourless lquid (147 mg, 0.6 mmol, 69 %). **^{1}H-NMR** (400 MHz, $CDCl_3$): δ = 5.78 (ddt, *J* = 17.6, 10.3, 7.5 Hz, 1H), 5.08 – 4.92 (m, 2H), 4.57 (s, 3H), 3.56 – 3.43 (m, 3H), 3.34 (s, 3H), 2.65 (h, *J* = 7.0 Hz, 1H), 2.42 – 2.25 (m, 2H), 2.11 (dt, *J* = 7.5, 1.1 Hz, 2H), 2.03 – 1.86 (m, 1H), 1.62 – 1.45 (m, 1H), 1.05 (d, *J* = 7.0 Hz, 3H), 0.98 (s, 6H) ppm; **^{13}C{^{1}H}-NMR** (101 MHz, $CDCl_3$): δ = 213.8, 135.3, 117.5, 96.5, 65.6, 55.4, 51.2, 46.4, 44.3, 33.6, 32.7, 27.4, 27.4, 26.3, 16.5 ppm; **IR (film, ATR)**: $\tilde{\nu}$ [cm^{-1}] = 2954, 1704, 1461, 1365, 1110, 1045, 917; **EI-MS**: *m/z* (%) = 210 (< 1), 195 (3), 183 (6), 163 (9), 154 (21), 139 (34), 125 (21), 115 (92), 98 (100), 83 (48), 67 (49), 55 (42), 45 (47); **HR-MS** (ESI-pos): *m/z* calcd. for [M+Na]$^+$: 265.17741, found: 265.17773.



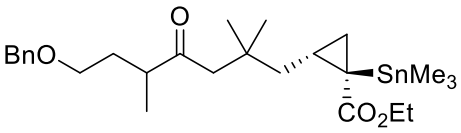
Compound *rac*-196: The compound was prepared from Weinreb amide ***rac*-194** analogously to the TBDPS-derivative ***rac*-188**. Colourless liquid (166 mg, 0.58 mmol, 70 %). **^{1}H-NMR** (400 MHz, $CDCl_3$): δ = 7.37 – 7.26 (m, 5H), 5.84 – 5.71 (m, 1H), 5.06 – 4.94 (m, 2H), 4.46 (s, 2H), 3.44 (qdd, *J* = 9.5, 6.7, 5.6 Hz, 2H), 2.75 – 2.65 (m, 1H), 2.41 – 2.26 (m, 2H), 2.10 (dd, *J* = 7.5, 1.3 Hz, 2H), 1.98 (dtd, *J* = 14.1, 7.0, 5.6 Hz, 1H), 1.60 – 1.49 (m, 1H), 1.04 (d, *J* = 7.1 Hz, 3H), 0.97 (s, 6H) ppm; **^{13}C{^{1}H}-NMR** (101 MHz, $CDCl_3$): δ = 214.2, 138.5, 135.4, 128.5, 127.9, 127.8, 117.5, 73.1, 68.1, 51.4, 46.4, 44.3, 33.7, 32.8, 27.4, 27.4, 16.6 ppm; **IR (film, ATR)**: $\tilde{\nu}$ [cm^{-1}] = 2960, 1712, 1455, 1365, 1274, 1101, 915, 713; **EI-MS**: *m/z* (%) = 229 (1), 202 (5), 188 (10), 154 (4), 139 (8), 112 (13), 91 (100); **HR-MS** (ESI-pos): *m/z* calcd. for [M+Na]$^+$: 311.19815, found: 311.19848.

Compound 197: In a Schlenk flask, **C3** (11 mg, 0.006 mmol, 0.01 eq) was dissolved in pentane (5 mL) and olefin ***rac*-195** (150 mg, 0.62 mmol, 1.0 eq) was added. Then a solution of diazo stannane **56** (392 mg, 1.4 mmol, 2.3 eq) in pentane (4 mL) was added over a course of 8 h *via* syringe pump and the mixture stirred overnight afterwards. It was then diluted with pentane, filtered through filter paper and the solvent evaporated. The crude

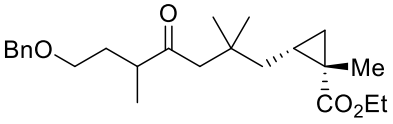


product was purified *via* flash chromatography (silica, hexane/EtOAc 15:1 to 4:1) to obtain the title compound as colourless liquid (147 mg, 0.3 mmol, 48 %, *cis*/*trans* = 1:18, ^{1}H-NMR). **^{1}H-NMR** (400 MHz, $CDCl_3$): δ = 4.57 (s, 2H), 4.18 – 3.96 (m, 2H), 3.54 – 3.44 (m, 2H), 3.34 (s, 3H), 2.65 (h, *J* = 7.0 Hz, 1H), 2.50 – 2.30 (m, 2H), 2.02 – 1.91 (m, 1H), 1.63 – 1.47 (m, 2H), 1.42 – 1.34 (m, 1H), 1.23 (t, *J* = 7.2 Hz, 3H), 1.17 – 1.07 (m, 2H), 1.06 (d, *J* = 7.0 Hz, 3H), 1.02 (d, *J* = 4.9 Hz, 6H), 0.88 (ddd, *J* = 7.4, 3.9, 1.3 Hz, 1H), 0.10 (s, 9H)ppm; **^{13}C{^{1}H}-NMR** (101 MHz, $CDCl_3$): δ = 213.8, 213.8, 175.6, 96.5, 65.6, 60.6, 55.4, 52.1, 52.1, 44.5, 44.5, 41.1, 41.1, 34.4, 34.3, 32.6, 32.6, 27.2, 27.1, 27.1, 20.6, 16.4, 16.4, 16.3, 16.1, 16.1, 14.6, -9.7 ppm; **^{119}Sn{^{1}H}-NMR** (149 MHz, $CDCl_3$): δ = 22.0 ppm; **IR (film, ATR)**: $\tilde{\nu}$ [cm^{-1}] = 2927, 1710, 1283, 1180, 1107, 1049, 769, 531; **ESI-MS**: *m/z* (%) = 1007 (4, $[2M+Na]^+$), 657 (8), 557 (4), 515 (100, $[M+Na]^+$), 510 (23, $[M+NH_4]^+$), 493 (6, $[M+H]^+$), 477 (11); **HR-MS** (ESI-pos): *m/z* calcd. for $[M+Na]^+$: 515.17899, found: 515.17915. Doubled signals in ^{13}C-NMR observed due to presence of diastereoisomers.

Compound 198: In a Schlenk flask, **C3** (12 mg, 0.007 mmol, 0.01 eq) was dissolved in pentane (4 mL) and olefin ***rac*-196** (160 mg, 0.55 mmol, 1.0 eq) was added. Then a solution of diazo stannane **56** (394 mg, 1.42 mmol, 2.6 eq) in pentane (4 mL) and CH_2Cl_2 (1 mL) was added over a course of 10 h *via* syringe pump and the mixture stirred overnight. The mixture was diluted with pentane, filtered through filter paper and the solvent evaporated. The crude product was purified *via* flash chromatography (silica, hexane/EtOAc 30:1 to 10:1) to yield the title compound as a colourless oil (230 mg, 0.43 mmol, 77 %, *cis*/*trans* = 1:14, ^{1}H-NMR). **^{1}H-NMR** (400 MHz, $CDCl_3$): δ = 7.38 – 7.27 (m, 5H), 4.46 (s, 2H), 4.17 – 3.96 (m, 2H), 3.50 – 3.37 (m, 2H), 2.70 (q, *J* = 6.7 Hz, 1H), 2.46 – 2.29 (m, 2H), 2.04 – 1.92 (m, 1H), 1.64 – 1.50 (m, 2H), 1.43 – 1.32 (m, 1H), 1.22 (d, *J* = 7.1 Hz, 3H), 1.14 – 1.09 (m, 1H), 1.08 (d, *J* = 5.7 Hz, 1H), 1.04 (d, *J* = 7.1 Hz, 3H), 1.00 (dd, *J* = 4.3, 2.0 Hz, 6H), 0.91 – 0.81 (m, 1H), 0.10 (s, 9H) ppm; **^{13}C{^{1}H}-NMR** (101 MHz, $CDCl_3$): δ = 214.1, 214.1, 175.6, 138.5, 128.5, 127.8, 127.7, 73.1, 68.1, 60.6, 52.2, 52.2, 44.4, 44.4, 41.1, 41.1, 34.4, 34.3, 32.7, 32.7, 27.3, 27.2, 27.1, 27.1, 20.6, 16.5, 16.5, 16.3, 16.3, 16.1, 16.1, 14.6, 14.3, -9.7 ppm; **^{119}Sn{^{1}H}-NMR** (149 MHz, $CDCl_3$): δ = 22.0 ppm; **IR (film, ATR)**: $\tilde{\nu}$ [cm^{-1}] = 2965, 2872, 1706, 1282, 1178, 1099, 766, 735, 698, 529; **ESI-MS**: *m/z* (%) = 1099 (5, $[2M+Na]^+$), 593 (10), 561 (100, $[M+Na]^+$), 539 (16, $[M+H]^+$), 493 (6); **HR-MS** (ESI-pos): *m/z* calcd. for $[M+Na]^+$: 561.19973, found: 561.20002. Doubled signals in ^{13}C-NMR observed due to presence of diastereoisomers.

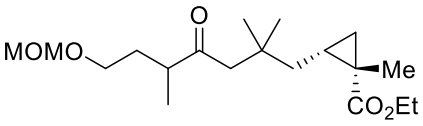


Compound 200: In a microwave vial, JackiePhos-Pd-G4 (14 mg, 0.01 mmol, 0.2 eq), KF (10 mg, 0.17 mmol, 3.1 eq) and CuCl (11 mg, 0.11 mmol, 2.0 eq) were suspended in THF (2 mL). In another Schlenk flask, stannane **198** (30 mg, 0.06 mmol, 1.0 eq) and methyl iodide (0.1 mL, 1.6 mmol, 29.0 eq) were dissolved in THF (2 mL) and added to the catalyst solution. The mixture



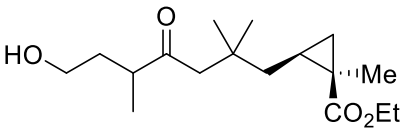
was stirred at 100°C in the microwave for 20 h. The mixture was diluted with MTBE, filtered through filter paper and the crude product was immobilized on Celite. After purification *via* flash chromatography (silica, hexane/EtOAc 15:1 to 9:1), the title compound was obtained as a colourless soild (11 mg, 0.028 mmol, 51 %). **^{1}H-NMR** (400 MHz, $CDCl_3$): δ = 7.40 – 7.27 (m, 5H), 4.46 (s, 2H), 4.20 – 4.00 (m, 2H), 3.52 – 3.36 (m, 2H), 2.70 (h, *J* = 7.0 Hz, 1H), 2.48 – 2.25 (m, 2H), 2.04 – 1.93 (m, 1H), 1.60 – 1.49 (m, 3H), 1.33 – 1.20 (m, 6H), 1.13 (dd, *J* = 7.2, 4.1 Hz, 1H), 1.06 – 0.96 (m, 9H), 0.96 – 0.87 (m, 1H), 0.77 (dd, *J* = 8.6, 4.2 Hz, 1H) ppm; **^{13}C{^{1}H}-NMR** (101 MHz, $CDCl_3$): δ = 214.2, 214.2, 174.4, 138.5, 128.5, 127.8, 127.7, 73.1, 68.1, 60.5, 52.0, 52.0, 44.5, 39.7, 39.7, 34.1, 32.7, 32.7, 27.2, 27.2, 27.1, 27.0, 26.4, 23.8, 21.5, 21.5, 16.5, 14.5 ppm. Doubled signals in ^{13}C-NMR observed due to presence of diastereoisomers.

Compound 199: In a microwave vial, JackiePhos-Pd-G4 (15 mg, 0.01 mmol, 0.2 eq), JackiePhos



(29 mg, 0.04 mmol, 0.6 eq), KF (12 mg, 0.21 mmol, 3.4 eq) and CuCl (13 mg, 0.13 mmol, 2.2 eq) were suspended in THF (2 mL). In another Schlenk flask, stannane **197** (30 mg, 0.06 mmol, 1.0 eq) and methyl iodide (0.2 mL, 3.2 mmol, 53.0 eq) were dissolved in THF (2 mL) and added to the catalyst solution. The mixture was stirred at 100°C in the microwave for 22 h. The mixture was diluted with MTBE, filtered through filter paper and the crude product was immobilized on Celite. After purification *via* flash chromatography (silica, hexane/EtOAc 5:1), the title compound was obtained as a light brown liquid (8 mg, 0.023 mmol, 38 %). **^{1}H-NMR** (400 MHz, $CDCl_3$): δ = 4.57 (s, 2H), 4.17 – 4.06 (m, 2H), 3.34 (s, 3H), 2.65 (q, *J* = 6.8 Hz, 1H), 2.49 – 2.30 (m, 2H), 2.02 – 1.92 (m, 1H), 1.57 – 1.48 (m, 3H), 1.29 (s, 3H), 1.25 (t, *J* = 7.2 Hz, 3H), 1.19 (s, 2H), 1.16 – 1.12 (m, 1H), 1.06 (d, *J* = 7.1 Hz, 3H), 1.00 (d, *J* = 5.3 Hz, 6H), 0.94 (d, *J* = 6.8 Hz, 1H), 0.79 (dd, *J* = 9.1, 3.7 Hz, 1H) ppm.

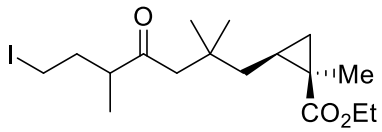
Compound 201: In a Schlenk flask, TBDPS ether **191** (200 mg, 0.37 mmol, 1.0 eq) was dissolved



in THF (5 mL) and the solution was cooled to 0 °C. TBAF (1 M in THF, 0.75 mL, 0.75 mmol, 2.0 eq) was added and the mixture was stirred overnight while warming to room temperature. The reaction was quenched with sat. aq. NH_4Cl, the aqueous layer extracted with MTBE (3x) and the combined organic layers were dried over $MgSO_4$. The solvent was evaporated and the crude product was purified *via* flash chromatography (silica, hexane/EtOAc 3:1 to 2:1) to obtain the title compound as a colourless oil (35 mg, 0.12 mmol, 31 %). **^{1}H-NMR** (400 MHz, $CDCl_3$): δ = 4.10 (qq, *J* = 10.9, 7.1 Hz, 2H), 3.61 (q, *J* = 6.0 Hz, 2H), 2.76 – 2.62 (m, 1H), 2.50 – 2.26 (m, 2H), 1.93 – 1.84 (m, 1H), 1.59 – 1.47 (m, 3H), 1.27 (s, 3H), 1.24 (t, *J* = 7.1 Hz, 3H), 1.13 (dt, *J* = 7.2, 3.7 Hz, 1H), 1.06 (d, *J* = 6.5 Hz, 3H), 1.02 – 0.97 (m, 6H), 0.97 – 0.90 (m, 1H), 0.78 (dd, *J* = 8.9, 4.7 Hz, 1H) ppm; **^{13}C{^{1}H}-NMR** (101 MHz, $CDCl_3$): δ = 214.8, 174.6, 174.5, 60.6, 60.6, 52.1, 44.6, 44.6, 39.6, 39.5,

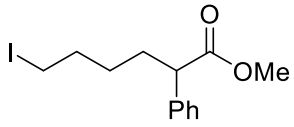
35.3, 34.2, 27.3, 27.2, 27.1, 27.1, 26.9, 26.4, 23.8, 23.8, 21.5, 21.5, 21.4, 16.6, 16.5, 14.4 ppm. Doubled signals in ^{13}C-NMR observed due to presence of diastereoisomers.

Compound 138: In a Schlenk flask, alcohol **201** (35 mg, 0.12 mmol, 1.0 eq) was dissolved in THF



(2 mL) and the solution was cooled to 0 °C. Triphenyl phosphine (43 mg, 0.16 mmol, 1.4 eq) and imidazole (20 mg, 0.29 mmol, 2.5 eq) were added, followed by iodine (36 mg, 0.14 mmol, 1.2 eq). The mixture was stirred overnight while warming to room temperature. The mixture was diluted with MTBE and water, sat. aq. $Na_2S_2O_3$ was added and the aqueous layer was extracted with MTBE (3x). The combined organic layers were dried over $MgSO_4$ and the solvent evaporated. The crude product was immobilized on Celite and purified *via* flash chromatography (silica, hexane/EtOAc 25:1) to obtain the title compound as a brown oil (24 mg, 0.06 mmol, 50 %). **^{1}H-NMR** (400 MHz, $CDCl_3$): δ = 4.12 (ttd, J = 10.9, 7.2, 3.7 Hz, 2H), 3.23 – 3.09 (m, 2H), 2.67 (h, J = 6.8 Hz, 1H), 2.47 – 2.32 (m, 2H), 2.17 (dq, J = 13.9, 6.9 Hz, 1H), 1.73 (dq, J = 13.7, 6.9 Hz, 1H), 1.64 – 1.48 (m, 2H), 1.29 (s, 3H), 1.26 (t, J = 7.2 Hz, 3H), 1.17 – 1.11 (m, 1H), 1.06 (d, J = 7.0 Hz, 3H), 1.00 (dd, J = 4.9, 2.5 Hz, 6H), 0.97 – 0.90 (m, 1H), 0.80 (dd, J = 8.6, 4.2 Hz, 1H) ppm; **^{13}C{^{1}H}-NMR** (101 MHz, $CDCl_3$): δ = 213.0, 174.4, 60.6, 52.2, 48.1, 39.6, 39.6, 35.9, 34.3, 27.3, 27.2, 27.2, 27.1, 26.4, 23.8, 23.8, 21.5, 21.5, 21.4, 16.0, 14.5, 4.8, 4.7 ppm; **EI-MS**: *m/z* (%) = 408 (54, [M]), 363 (29), 280 (17), 211 (78), 183 (80), 136 (100), 95 (47), 69 (51), 55 (93); **HR-MS** (ESI-pos): *m/z* calcd. for $[M+Na]^+$: 431.10536, found: 431.10559. Doubled signals in ^{13}C-NMR observed due to presence of diastereoisomers.

Compound *rac*-211: In a Schlenk flask, diisopropylamine (0.74 mL, 5.28 mmol, 1.3 eq) was

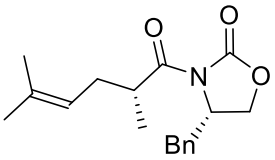


dissolved in THF (15 mL) and the solution was cooled to -78 °C. *n*-Butyllithium (1.6 M in hexanes, 3.0 mL, 4.8 mmol, 1.17 eq) was added and the mixture was stirred for 5 min. Methyl phenylacetate (0.63 mL, 4.5 mmol, 1.1 eq) was added and after stirring for another 20 min followed by the addition of 1-chloro-4-iodobutane (0.5 mL, 4.1 mmol, 1.0 eq). The mixture was stirred at -78 °C for 45 min, then the cooling bath was removed and stirring continued at room temperature for 16 h. The reaction was quenched with sat. aq. NH_4Cl, the aqueous layer extracted with MTBE (3x) and the combined organic layers were dried over $MgSO_4$. The crude product was dissolved in acetone (10 mL) and transferred into a pressure Schlenk flask. Sodium iodide (2.37 g, 16.0 mmol, 3.9 eq) was added and the mixture was heated to 60 °C for 72 h. The reaction was quenched with brine and the aqueous layer extracted with CH_2Cl_2 (3x). The combined organic layers were dried over $MgSO_4$ and the solvent was evaporated. The crude product was purified *via* flash chromatography (silica, hexane/EtOAc 20:1) to afford the title compound as a yellow oil (1.11 g, 3.33 mmol, 82 % over two steps). **^{1}H-NMR** (400 MHz, $CDCl_3$): δ = 7.36 – 7.23 (m, 5H), 3.66 (s, 3H), 3.54 (t, J = 7.7 Hz, 1H), 3.15 (t, J = 6.8 Hz, 2H), 2.14 – 1.98 (m, 1H), 1.90 – 1.72 (m, 3H), 1.44 – 1.23 (m, 2H) ppm;

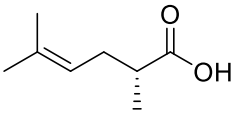
$^{13}C\{^1H\}$-NMR (101 MHz, $CDCl_3$): δ = 174.4, 139.0, 128.8, 128.0, 127.5, 52.2, 51.5, 33.3, 32.5, 28.6, 6.5 ppm; **IR (film, ATR)**: $\tilde{\nu}$ [cm^{-1}] = 2947, 1731, 1433, 1198, 1160, 731, 697, 508; **EI-MS**: *m/z* (%) = 332 (39, [M]), 273 (10), 205 (40), 145 (100), 117 (15), 91 (74); **HR-MS** (ESI-pos): *m/z* calcd. for $[M+Na]^+$: 355.01655, found: 355.01657.

4.2.8.2 Compounds from Ring Expansion Approach

Compound 222: In a Schlenk flask, NaHMDS (557 mg, 3.04 mmol, 1.3 eq) was dissolved in THF (10 mL) and the solution was cooled to -78 °C. A solution of oxazolidinone **221** (550 mg, 2.36 mmol, 1.0 eq) in THF (5 mL) was added slowly and the mixture was stirred at -78°C for 0.5 h. Prenyl bromide **226** (0.55 mL, 4.76 mmol, 2.0 eq) was added and after another 15 min the mixture was warmed to 0°C. The reaction was quenched after stirring for 1 h at 0°C upon addition of sat. aq. NH_4Cl. The aqueous layer was extracted with MTBE (3x), the combined organic layers dried over $MgSO_4$, and the solvent evaporated. The crude product was purified *via* flash chromatography (silica, hexane/EtOAc 5:1) to afford the title compound as a colourless oil (624 mg, 2.07 mmol, 88 %). $[\alpha]_D^{20}$ = 51.7° (c = 1.1, $CHCl_3$); **^{1}H-NMR** (400 MHz, $CDCl_3$): δ = 7.37 – 7.30 (m, 2H), 7.30 – 7.25 (m, 1H), 7.22 (dd, *J* = 6.7, 1.7 Hz, 2H), 5.17 (tp, *J* = 7.4, 1.4 Hz, 1H), 4.69 (ddt, *J* = 9.6, 7.6, 3.3 Hz, 1H), 4.23 – 4.11 (m, 2H), 3.80 (h, *J* = 6.8 Hz, 1H), 3.24 (dd, *J* = 13.4, 3.4 Hz, 1H), 2.71 (dd, *J* = 13.4, 9.6 Hz, 1H), 2.45 (ddd, *J* = 13.9, 7.5, 6.5 Hz, 1H), 2.20 (p, *J* = 7.3 Hz, 1H), 1.70 (d, *J* = 1.3 Hz, 3H), 1.65 (d, *J* = 1.3 Hz, 3H), 1.17 (d, *J* = 6.8 Hz, 3H) ppm; **$^{13}C\{^1H\}$-NMR** (101 MHz, $CDCl_3$): δ = 177.2, 153.3, 135.5, 134.1, 129.6, 129.1, 127.5, 121.2, 66.1, 55.4, 38.1, 38.0, 32.5, 26.0, 18.0, 16.6 ppm; **IR (film, ATR)**: $\tilde{\nu}$ [cm^{-1}] = 2971, 2917, 1778, 1698, 1385, 1212, 1101, 703; **EI-MS**: *m/z* (%) = 301 (2, [M]), 233 (100), 204 (6), 178 (31), 160 (11), 134 (32), 117 (81), 96 (35), 81 (60); **HR-MS** (GC-EI): *m/z* calcd. for $[M]^+$: 301.16724, found: 301.16717. The analytical data is consistent with the literature[265].

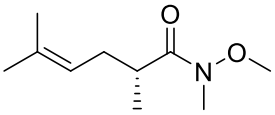


Compound 223: In a round bottom flask, oxazolidinone derivative **222** (700 mg, 2.3 mmol, 1.0 eq) was dissolved in THF (5 mL) and water (5 mL) and the solution was cooled to 0°C. Then an aqueous solution of hydrogen peroxide (35 wt%, 0.9 mL, 9.26 mmol, 4.0 eq) was added, followed by LiOH (129 mg, 5.4 mmol, 2.3 eq). The cooling bath was removed and the mixture was stirred at room temperature for 1.5 h. The organic solvent was partially evaporated and the remaining mixture diluted with CH_2Cl_2. The organic layer was washed with aqueous NaOH (1 M, 3x) and the combined aqueous layers were extracted with CH_2Cl_2 (2x). The aqueous layer was acidified with conc. HCl (pH approx. 1) and then again extracted with CH_2Cl_2 (3x). The second organic layer was then dried over $MgSO_4$ and the solvent evaporated. The obtained crude product was used in the next step without further



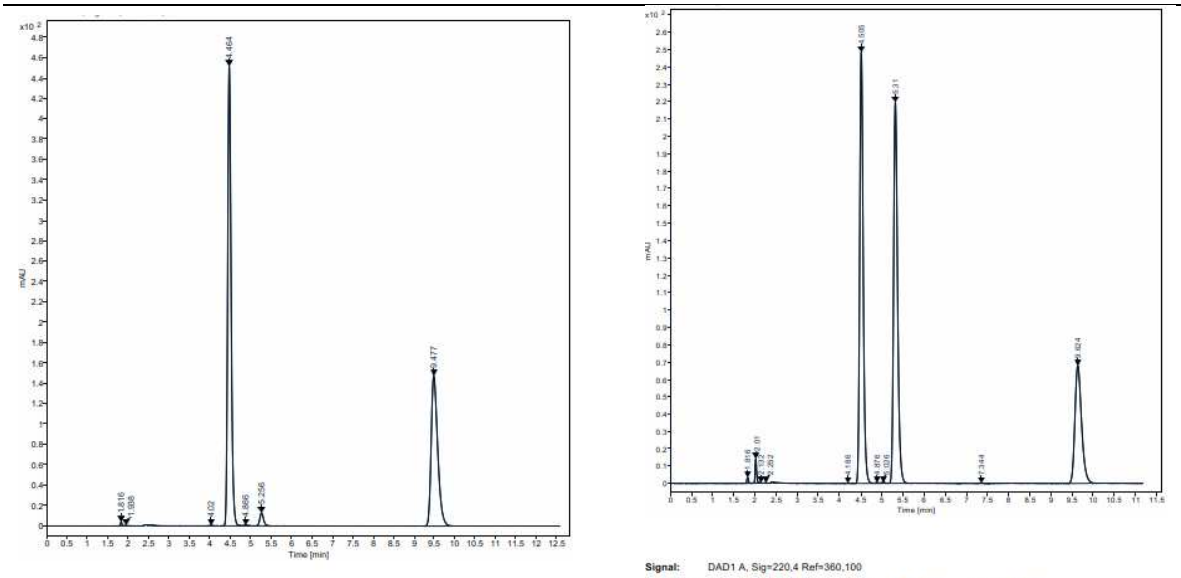
purification. $[\alpha]_D^{20}$ = −5.9° (c = 1.0, $CHCl_3$); **^{1}H-NMR** (400 MHz, $CDCl_3$): δ = 5.10 (dddd, *J* = 8.4, 7.0, 2.9, 1.5 Hz, 1H), 2.48 (h, *J* = 7.0 Hz, 1H), 2.37 (dt, *J* = 13.4, 6.8 Hz, 1H), 2.22 – 2.11 (m, 1H), 1.70 (d, *J* = 1.3 Hz, 3H), 1.62 (d, *J* = 1.3 Hz, 3H), 1.17 (d, *J* = 7.0 Hz, 3H) ppm; **^{13}C{^{1}H}-NMR** (101 MHz, $CDCl_3$): δ = 183.2, 134.2, 121.0, 39.9, 32.0, 25.9, 18.0, 16.4 ppm; **IR (film, ATR)**: $\tilde{\nu}$ [cm^{-1}] = 2972, 2917, 2658, 1702, 1461, 1416, 1286, 1225, 932; **EI-MS**: *m/z* (%) = 142 (59, [M]), 124 (27), 109 (24), 96 (24), 87 (81), 81 (30), 69 (100), 41 (98); **HR-MS** (GC-EI): *m/z* calcd. for $[M]^+$: 142.09883, found: 142.09899. The analytical data is consistent with the literature[266].

Compound 220 (from auxiliary approach): The crude carboxylic acid **223** was dissolved in



CH_2Cl_2 (10 mL) and the solution was cooled to 0°C. Carbonyldiimidazole **227** (452 mg, 2.8 mmol, 1.2 eq) was added and the mixture was kept stirring at 0°C for 1 h. *N*,*O*-dimethylhydroxylamino hydrochloride (600 mg, 6.2 mmol, 2.6 eq) was added and the mixture was warmed to room temperature and stirred overnight. The precipitate that had formed during the reaction was filtered off through filter paper and the filtrate was washed with aq. HCl (1 M). The organic layer was dried over $MgSO_4$ and the crude product was purified *via* flash chromatography (silica, hexane/EtOAc 3:1) to yield the title compound as colourless liquid (351 mg, 1.9 mmol, 82 % over 2 steps, *ee* = 94 %). Analytical data *vide infra*.

The optical purity was determined by HPLC (Chiralpak IB-N3, 150 mm, 4.6 mm, i.D., *n*-heptane/isopropanol 99:1, 1.0 mL/min) **[t_R]** = 4.46 min (major), 5.26 min (minor).



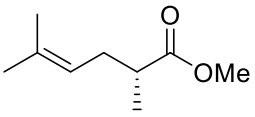
Signal: DAD1 A, Sig=220,4 Ref=360,100

RT [min]	Type	Width [min]	Area	Height	Area%	Name
1.816	BV	0.0392	9.8445	3.8723	0.2262	
1.938	VV	0.0341	0.9407	0.3642	0.0216	
4.020	VV	0.0673	1.7676	0.3108	0.0406	
4.464	BV	0.0897	2618.4551	451.5494	60.1658	1. enantiomer
4.866	VV	0.0938	6.3322	0.7963	0.1455	ee = 93.9%
5.256	VB	0.0980	82.3042	12.8929	1.8912	2. enantiomer
9.477	BB	0.1681	1632.4247	147.4685	37.5092	
		Sum	4352.0690			

Signal: DAD1 A, Sig=220,4 Ref=360,100

RT [min]	Type	Width [min]	Area	Height	Area%	Name
1.816	BV	0.0399	9.0134	3.5217	0.2468	
2.010	VV	0.0361	33.9635	14.1244	0.9299	
2.132	VB	0.0345	0.7831	0.3155	0.0214	
2.252	VB	0.0366	1.0702	0.4085	0.0293	
4.186	BB	0.0707	1.9863	0.3398	0.0544	
4.505	BV	0.0882	1424.2473	248.9362	38.9944	1. enantiomer
4.876	VV	0.0766	2.4594	0.3872	0.0673	
5.026	VB	0.0777	3.2437	0.4963	0.0888	
5.310	BB	0.0998	1429.8149	219.9577	39.1469	2. enantiomer
7.344	BB	0.1030	2.9233	0.3517	0.0800	
9.624	BB	0.1652	742.9323	67.8661	20.3407	
		Sum	3652.4374			

Figure 56. HPLC trace of enantioenriched 220 (left) and racemic 220 (right).

Compound 225: 

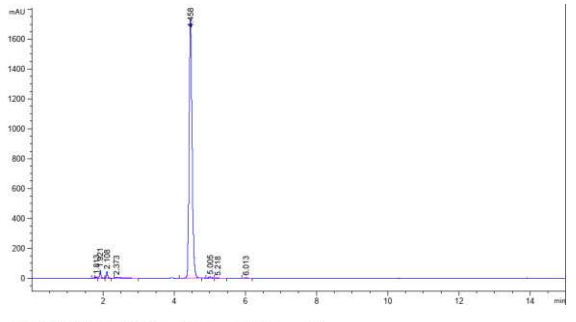
In a Schlenk flask, CuCl (22 mg, 0.22 mmol, 0.2 eq) and $MnBr_2$ (67 mg, 0.31 mmol, 0.3 eq) were suspended in DMPU (2 mL). (*S*)-(-)-3-Bromoisobutyric acid methyl ester **224** (0.37 mL, 2.9 mmol, 3.0 eq) was added, followed by dropwise addition of a solution of diethyl zinc (1.0 M in hexanes, 2.2 mL, 2.2 mmol, 2.3 eq) and the mixture was stirred at room temperature overnight. The obtained biphasic mixture was transferred into a solution of Pd(dppf)•CH_2Cl_2 (41 mg, 0.05 mmol, 0.05 eq) and 1-bromo-2-methyl-1-propene **185** (0.1 mL, 0.98 mmol, 1.0 eq) in THF (5 mL) at 0°C. The mixture was stirred at room temperature for 30 min and heated to 65°C overnight. Upon full conversion of starting material **185** (monitored by TLC), the reaction was quenched with sat. aq. NH_4Cl and diluted with water and MTBE. The layers were separated and the aqueous layer was extracted with MTBE (3x). The combined organic layers were washed with brine (3x), then dried over $MgSO_4$, and the solvent evaporated. The crude product was purified *via* flash chromatography (silica, hexane/MTBE 50:1) to obtain the title compound as a colourless oil (137 mg, 0.88 mmol, 90 %). $[\alpha]_D^{20}$ = −15.7° (c = 1.22, $CHCl_3$); **^{1}H-NMR** (400 MHz, $CDCl_3$): δ = 5.06 (tdt, *J* = 7.1, 2.7, 1.4 Hz, 1H), 3.66 (s, 3H), 2.45 (h, *J* = 7.0 Hz, 1H), 2.32 (dtd, *J* = 13.8, 6.8, 1.0 Hz, 1H), 2.13 (dtd, *J* = 14.3, 7.4, 1.0 Hz, 1H), 1.68 (s, 3H), 1.60 (s, 3H), 1.13 (d, *J* = 7.0 Hz, 3H) ppm; **^{13}C{^{1}H}-NMR** (101 MHz, $CDCl_3$): δ = 177.1, 133.9, 121.3, 51.6, 40.0, 32.3, 25.9, 17.9, 16.7 ppm; **IR (film, ATR)**: $\tilde{\nu}$ [cm^{-1}] = 2972, 1736, 1456, 1435, 1377, 1253, 1200, 1160, 1121, 1084,

1052, 986, 819; **ESI-MS**: *m/z* (%) = 211 (19), 195 (32), 193 (30), 179 (100, $[M+Na]^+$), 157 (34, $[M+H]^+$), 151 (28); **HR-MS** (ESI-pos): *m/z* calcd. for $[M+Na]^+$: 179.10425, found: 179.10441.

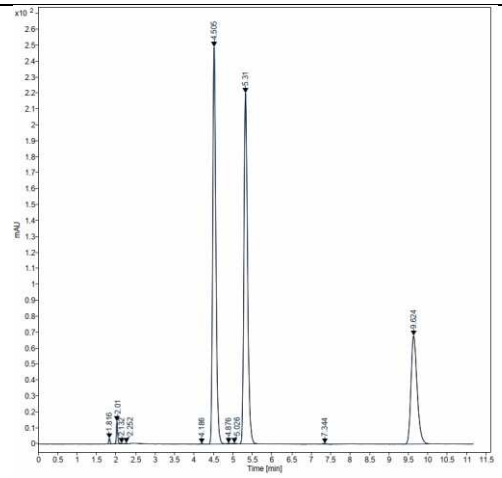
Compound 220 (from Roche ester derivative 225): Methyl ester **225** (789 mg, 5.05 mmol, 1.0 eq) and *N*,*O*-dimethylhydroxylamine hydrochloride (1.20 g, 12.3 mmol, 2.4 eq) were dissolved in THF (20 mL) and the solution was cooled to −30°C. A solution of isopropylmagnesium chloride–lithium chloride (1.3 M in THF, 14 mL, 18.2 mmol, 3.6 eq) was slowly added over a course of 30 min. The mixture was stirred at 0°C for 1 h, then the reaction was quenched with sat. aq. NH_4Cl and the mixture warmed to room temperature. The layers were separated and the aqueous layer was extracted with MTBE (3x), the combined organic layers dried over $MgSO_4$ and the solvent was evaporated. The title compound was obtained without further purification as a light yellow oil (931 mg, 5.03 mmol, > 99 %, *ee* > 99 %). $\mathbf{[\alpha]_D^{20}}$ = −11.8° (c = 1.03, $CHCl_3$); **^{1}H-NMR** (400 MHz, $CDCl_3$): δ = 5.09 (ddp, J_H = 8.2, 6.8, 1.4 Hz, 1H), 3.67 (s, 3H), 3.18 (s, 3H), 2.86 (d, *J* = 6.5 Hz, 1H), 2.31 (dt, *J* = 13.9, 6.9 Hz, 1H), 2.09 (dt, *J* = 14.2, 7.6 Hz, 1H), 1.68 (d, *J* = 1.4 Hz, 3H), 1.61 (d, *J* = 1.0 Hz, 3H), 1.10 (d, *J* = 6.8 Hz, 3H) ppm; **^{13}C{^{1}H}-NMR** (101 MHz, $CDCl_3$): δ = 177.9, 133.5, 122.0, 61.5, 35.8, 32.2, 25.9, 17.9, 17.0 ppm; **IR (film, ATR)**: $\tilde{\nu}$ [cm^{-1}] = 2969, 2934, 1659, 1462, 1416, 1381, 1309, 1175, 1114, 1042, 995, 432; **EI-MS**: *m/z* (%) = 185 (3, [M]), 170 (3), 154 (21), 125 (15), 117 (57), 109 (15), 97 (100), 87 (20), 81 (20), 69 (72), 61 (23), 55 (86), 41 (35); **HR-MS** (GC-EI): *m/z* calcd. for $[M]^+$: 185.14103, found: 185.14109.

The racemic sample was prepared following the same procedure, starting from the racemic ethyl ester derivative of compound **225**.

The optical purity was determined by HPLC (Chiralpak IB-N3, 150 mm, 4.6 mm, i.D., *n*-heptane/isopropanol 99:1, 1.0 mL/min) **[t_R]** = 4.46 min (major), 5.22 min (minor).



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %	
1	1.813	VV T	0.0367	24.13440	10.36417	0.2281	
2	1.921	VV R	0.0376	148.77136	57.68918	1.4062	
3	2.108	VB	0.0398	118.06242	44.70730	1.1160	
4	2.373	BB	0.1801	82.81191	5.56457	0.7828	
5	4.458	VB	0.0910	1.01191e4	1724.24194	95.6491	1.Enantiomer
6	5.005	BV	0.0825	48.96862	8.71999	0.4629	ee = 99.8 %
7	5.218	VB	0.0829	11.33524	2.05480	0.1071	2.Enantiomer
8	6.013	BB	0.1011	26.21549	3.84423	0.2478	

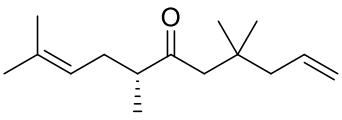


Signal: DAD1 A, Sig=220,4 Ref=360,100

RT [min]	Type	Width [min]	Area	Height	Area%	Name
1.816	BV	0.0399	9.0134	3.5217	0.2468	
2.010	VV	0.0361	33.9635	14.1244	0.9299	
2.132	VB	0.0345	0.7831	0.3155	0.0214	
2.252	VB	0.0366	1.0702	0.4085	0.0293	
4.186	BB	0.0707	1.9863	0.3398	0.0544	
4.505	BV	0.0882	1424.2473	248.9362	38.9944	1. enantiomer
4.876	VV	0.0766	2.4594	0.3872	0.0673	
5.026	VB	0.0777	3.2437	0.4963	0.0888	
5.310	BB	0.0998	1429.8149	219.9577	39.1469	2. enantiomer
7.344	BB	0.1030	2.9233	0.3517	0.0800	
9.624	BB	0.1652	742.9323	67.8661	20.3407	

Figure 57. HPLC traces of enantioenriched 220 (left) and racemic 220 (right).

Compound 219: In a Schlenk flask, *tert*-butyllithium (1.7 M in pentane, 3.3 mL, 5.6 mmol, 3.5 eq)



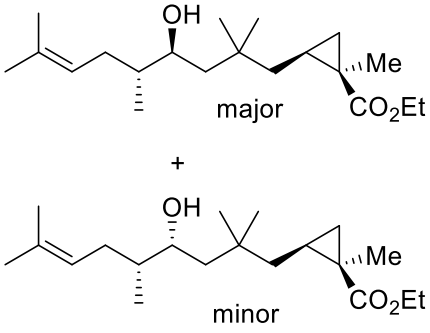
was diluted in Et_2O (5 mL) at -78 °C. Iodide **180** (50 wt% solution in pentane, 1.9 g, 4.2 mmol, 2.6 eq) was added and the mixture was stirred at -78 °C for 1.5 h. The obtained milky solution was then added to a solution of Weinreb amide **220** (300 mg, 1.62 mmol, 1.0 eq) in Et_2O (5 mL) at −78 °C and stirred for 30 min. The reaction was quenched at -78 °C by adding sat. aq. NH_4Cl. After warming to room temperature, the layers were separated and the aqueous layer was extracted with MTBE (3x). The combined organic layers were dried over $MgSO_4$ and the solvent evaporated. The crude product was purified *via* flash chromatography (silica, hexane/EtOAc 50:1) to obtain the title compound as a colourless liquid (319 mg, 1.44 mmol, 89 %). $\boldsymbol{[\alpha]_D^{20}}$ = −26.9° (c = 1.36, $CHCl_3$); **^{1}H-NMR** (400 MHz, $CDCl_3$): δ = 5.78 (ddt, *J* = 16.7, 10.3, 7.5 Hz, 1H), 5.09 – 4.95 (m, 3H), 2.48 (h, *J* = 6.9 Hz, 1H), 2.31 (d, *J* = 3.2 Hz, 2H), 2.29 – 2.21 (m, 1H), 2.10 (dt, *J* = 7.5, 1.2 Hz, 2H), 2.03 – 1.93 (m, 1H), 1.68 (d, *J* = 1.3 Hz, 3H), 1.59 (d, *J* = 1.3 Hz, 3H), 1.01 (d, *J* = 7.0 Hz, 3H), 0.98 (s, 6H) ppm; **^{13}C{^{1}H}-NMR** (101 MHz, $CDCl_3$): δ = 214.3, 135.4, 133.6, 121.8, 117.5, 51.6, 48.0, 46.4, 33.7, 31.6, 27.4, 25.9, 17.9, 16.1 ppm; **IR (film, ATR)**: $\tilde{\nu}$ [cm^{-1}] = 2963, 2930, 2913, 2872, 1709, 1639, 1453, 1364, 1038, 998, 913, 630; **EI-MS**: *m/z* (%) = 222 (3, [M]), 207 (20), 154 (24), 140 (34), 125 (58), 107 (33), 97 (100), 83 (42), 69 (49), 55 (51), 41 (67); **HR-MS** (GC-EI): *m/z* calcd. for $[M]^+$: 222.19782, found: 222.19788.

Compound 218: In a Schlenk flask, ***ent*-C3** (40 mg, 0.02 mmol, 0.01 eq) was dissolved in pentane (10 mL) and olefin **219** (520 mg, 2.34 mmol, 1.0 eq) was added at room temperature. Then diazo stannane **56** (1.5 g, 5.42 mmol, 2.3 eq) was added as a solution in pentane (9 mL) over a course of 9 h *via* syringe pump and the mixture was left to stir overnight afterwards. The solvent was then evaporated and the crude product purified *via* flash chromatography (silica, hexane/EtOAc 50:1 to 20:1) to obtain the title compound as a colourless oil (894 mg, 1.90 mmol, 81 %, *cis*/*trans* = 1:12, ^{1}H-NMR). $\mathbf{[\alpha]_D^{20}}$ = 9.1° (c = 1.53, $CHCl_3$); **^{1}H-NMR** (400 MHz, $CDCl_3$): δ = 5.03 (tp, *J* = 7.4, 1.5 Hz, 1H), 4.08 (ddq, *J* = 39.5, 10.8, 7.1 Hz, 2H), 2.48 (h, *J* = 6.8 Hz, 1H), 2.42 – 2.30 (m, 2H), 2.25 (ddd, *J* = 14.4, 7.3, 6.2 Hz, 1H), 1.98 (dt, *J* = 14.2, 7.5 Hz, 1H), 1.68 (d, *J* = 1.3 Hz, 3H), 1.61 – 1.55 (m, 4H), 1.38 (dd, *J* = 14.1, 6.8 Hz, 1H), 1.24 (t, *J* = 7.2 Hz, 3H), 1.12 (dd, *J* = 6.1, 3.7 Hz, 1H), 1.10 – 1.04 (m, 1H), 1.03 – 0.98 (m, 9H), 0.91 – 0.84 (m, 1H), 0.10 (s, 9H) ppm; **^{13}C{^{1}H}-NMR** (101 MHz, $CDCl_3$): δ = 214.3, 175.6, 133.6, 121.8, 60.6, 52.4, 48.1, 41.2, 34.4 31.6, 27.2, 27.1, 25.9, 20.6, 17.9, 16.3, 16.1, 16.0, 14.6, -9.7 ppm; **^{119}Sn{^{1}H}-NMR** (149 MHz, $CDCl_3$): δ = 22.0 ppm; **IR (film, ATR)**: $\tilde{\nu}$ [cm^{-1}] = 2968, 2930, 2913, 2873, 1708, 1453, 1364, 1282, 1179, 1125, 1103, 1044, 844, 767, 529; **EI-MS**: *m/z* (%) = 472 (< 1, [M+H]), 457 (100), 411 (39), 331 (9), 289 (7), 231 (11), 165 (56), 97 (10), 69 (18); **HR-MS** (ESI-pos): *m/z* calcd. for $[M+Na]^+$: 495.18916, found: 495.18885.

Compound 229: In a pressure Schlenk flask, $Pd_2(dba)_3$, (20 mg, 0.02 mmol, 0.1 eq), JackiePhos (135 mg, 0.17 mmol, 0.8 eq), KF (25 mg, 0.43 mmol, 2.0 eq) and CuCl (105 mg, 1.06 mmol, 5.0 eq) were suspended in THF (3 mL). In a second Schlenk flask, stannane **218** (100 mg, 0.21 mmol, 1.0 eq) and methyl iodide (0.8 mL, 12.9 mmol, 61 eq) were dissolved in THF (2 mL) and added to the catalyst solution. The mixture was stirred at 70 °C for three days. The mixture was cooled to room temperature and diluted with MTBE. After filtering through filter paper, the crude product was immobilized on Celite and purified *via* flash chromatography (silica, hexanes/MTBE 30:1). The title compound was obtained as a light yellow oil (38 mg, 0.12 mmol, 56 %). $\mathbf{[\alpha]_D^{20}}$ = −28.7° (c = 1.2, $CHCl_3$); **^{1}H-NMR** (600 MHz, $CDCl_3$): δ = 5.04 (tp, *J* = 7.3, 1.5 Hz, 1H), 4.17 – 4.06 (m, 2H), 2.48 (h, *J* = 6.9 Hz, 1H), 2.40 – 2.29 (m, 2H), 2.29 – 2.22 (m, 1H), 2.02 – 1.95 (m, 1H), 1.68 (d, *J* = 1.4 Hz, 3H), 1.59 (d, *J* = 0.9 Hz, 3H), 1.57 – 1.49 (m, 2H), 1.29 (s, 3H), 1.26 (t, *J* = 7.2 Hz, 3H), 1.14 (dd, *J* = 7.1, 4.3 Hz, 1H), 1.00 (dd, *J* = 13.3, 6.6 Hz, 9H), 0.94 (dd, *J* = 8.6, 7.0 Hz, 1H), 0.79 (dd, *J* = 8.7, 4.3 Hz, 1H) ppm; **^{13}C{^{1}H}-NMR** (101 MHz, $CDCl_3$): δ = 214.4, 174.5, 133.6, 121.8, 60.6, 52.2, 48.1, 39.7, 34.1, 31.6, 27.2, 27.1, 26.4, 25.9, 23.8, 21.5, 21.5, 17.9, 16.0, 14.5 ppm; **IR (film, ATR)**: $\tilde{\nu}$ [cm^{-1}] = 2964, 2931, 2873, 1714, 1460, 1366, 1324, 1279, 1172, 1153, 1032, 863; **EI-MS**: *m/z* (%) = 322 (18, [M]), 307 (27), 254 (66), 179 (24), 136 (84), 125 (35), 109 (100),

97 (75), 69 (79), 55 (70), 41 (51); **HR-MS** (ESI-pos): *m/z* calcd. for $[M+Na]^+$: 345.24001, found: 345.24015.

Compounds (*R*)- and (*S*)-230: In a Schlenk flask, ketone **229** (30 mg, 0.09 mmol, 1.0 eq) was dissolved in THF (5 mL) and the solution was cooled to −78°C. A solution of $NaBHEt_3$ (1 M in THF, 0.14 mL, 0.14 mmol, 1.5 eq) was added and the mixture was stirred at −78°C for 6 h. Upon full conversion of starting material **229** (monitored by TLC), the reaction was quenched with sat. aq. NH_4Cl and the mixture warmed to room temperature. The aqueous layer was extracted with MTBE, the combined organic layers were dried over $MgSO_4$ and the solvent was evaporated. The crude product was purified *via* flash chromatography (silica, hexanes/MTBE 7:1) to obtain the product as a 5:1 mixture (*S*:*R*, based on ^{1}H-NMR) of diastereoisomers. Colourless oil (27 mg, 0.08 mmol, 89 %). Analytical Data: *vide infra.*

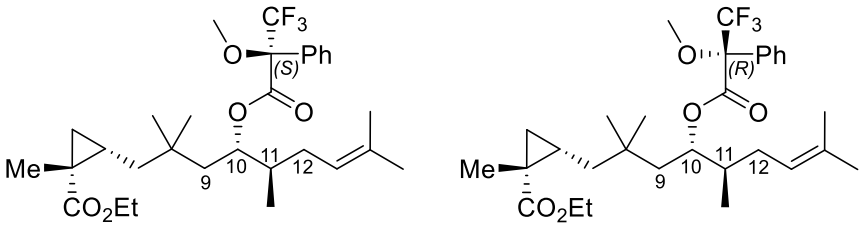


Cross coupling and reduction as a telescoped two-step process:

In a pressure Schlenk flask, $Pd_2(dba)_3$, (41 mg, 0.04 mmol, 0.1 eq), JackiePhos (271 mg, 0.34 mmol, 0.8 eq), KF (30 mg, 0.52 mmol, 1.2 eq) and CuCl (440 mg, 4.4 mmol, 10 eq) were suspended in THF (5 mL). In a second Schlenk flask, stannane **218** (200 mg, 0.42 mmol, 1.0 eq) and methyl iodide (1 mL, 16 mmol, 38 eq) were dissolved in THF (5 mL) and added to the catalyst solution. The mixture was then stirred at 70 °C for three days. The mixture was cooled to room temperature and diluted with MTBE. After filtering through filter paper, the crude product was passed through a short column (silica, hexane/MTBE 25:1) in order to remove major impurities. The obtained material (still containing some minor impurities, approx. 108 mg) was then subjected to the next step. The material was transferred into a jacketed cooling Schlenk flask, dissolved in THF (5 mL) and the solution was cooled to -70°C. A solution of $NaBHEt_3$ (1 M in THF, 0.4 mL, 0.4 mmol, 1.2 eq; based on 108 mg of crude material) was added and the mixture was stirred at −70°C for 16 h. Upon full conversion of starting material **229** (monitored by TLC), the reaction was quenched with sat. aq. NH_4Cl and the mixture warmed to room temperature. The aqueous layer was extracted with MTBE, the combined organic layers were dried over $MgSO_4$ and the solvent was evaporated. The crude product was purified *via* flash chromatography (silica, hexanes/MTBE 9:1) to obtain the product as a mixture of diastereoisomers, which could partially be separated for analytical purposes. Colourless oil (89 mg, 0.27 mmol, 65 % combined yield over two steps). Major diastereomer; **(*S*)-230**: $[\alpha]_D^{20}$ = −13.4° (c = 1.1, $CHCl_3$); **^{1}H-NMR** (400 MHz, $CDCl_3$): δ = 5.14 (ddt, *J* = 8.1, 6.7, 1.3 Hz, 1H), 4.11 (qq, *J* = 10.9, 7.1 Hz, 2H), 3.63 (ddd, *J* = 8.7, 4.9, 1.6 Hz, 1H), 2.06 (dt, *J* = 14.4, 5.4 Hz, 1H), 1.92 – 1.80 (m, 1H), 1.70 (s, 3H), 1.61 (s, 3H), 1.53 (dd, *J* = 14.3, 7.0 Hz,

2H), 1.46 – 1.42 (m, 1H), 1.41 – 1.37 (m, 1H), 1.29 (s, 3H), 1.25 (t, *J* = 7.1 Hz, 4H), 1.13 (dd, *J* = 7.2, 4.2 Hz, 1H), 1.03 – 0.95 (m, 4H), 0.91 (s, 3H), 0.87 (d, *J* = 6.8 Hz, 3H), 0.79 (dd, *J* = 8.6, 4.1 Hz, 1H) ppm; **^{13}C{^{1}H}-NMR** (101 MHz, $CDCl_3$): δ = 174.6, 132.5, 123.3, 72.8, 60.5, 46.0, 41.4, 40.2, 33.4, 30.7, 27.8, 27.4, 26.6, 26.0, 23.9, 21.7, 21.5, 18.0, 15.5, 14.5 ppm; **IR (film, ATR)**: $\tilde{\nu}$ [cm^{-1}] = 3508, 2960, 2929, 1718, 1462, 1367, 1324, 1174, 1154, 1030, 863, 773; **EI-MS**: *m/z* (%) = 309 (< 1), 263 (2), 237 (5), 177 (12), 153 (22), 121 (37), 109 (100), 95 (33), 81 (41), 67 (34); **HR-MS** (ESI-pos): *m/z* calcd. for [M+Na]$^+$: 347.25566, found: 347.25604. Minor diastereomer; **(*R*)-230**: $[\alpha]_D^{20}$ = 12.9° (c = 1.1, $CHCl_3$); **^{1}H-NMR** (400 MHz, $CDCl_3$): δ = 5.14 (t, *J* = 7.3 Hz, 1H), 4.11 (qq, *J* = 10.9, 7.1 Hz, 2H), 3.70 (d, *J* = 2.5 Hz, 1H), 2.17 – 2.01 (m, 1H), 1.87 (dt, *J* = 14.4, 7.5 Hz, 1H), 1.70 (d, *J* = 1.4 Hz, 3H), 1.62 (d, *J* = 1.1 Hz, 3H), 1.53 – 1.41 (m, 3H), 1.41 – 1.31 (m, 2H), 1.29 (s, 3H), 1.25 (t, *J* = 7.1 Hz, 3H), 1.15 (dd, *J* = 7.1, 4.2 Hz, 1H), 1.00 – 0.96 (m, 1H), 0.93 (d, *J* = 3.0 Hz, 6H), 0.85 (d, *J* = 6.8 Hz, 3H), 0.79 (dd, *J* = 8.6, 4.2 Hz, 1H) ppm; **^{13}C{^{1}H}-NMR** (101 MHz, $CDCl_3$): δ = 174.6, 132.7, 123.3, 71.9, 60.5, 47.1, 41.3, 40.0, 33.4, 31.9, 27.6, 27.5, 26.7, 26.0, 23.9, 21.6, 21.5, 18.0, 14.5, 13.7 ppm; **IR (film, ATR)**: $\tilde{\nu}$ [cm^{-1}] = 3525, 2961, 2930, 1719, 1464, 1368, 1325, 1175, 1155, 1030; **EI-MS**: *m/z* (%) = 309 (< 1), 278 (1), 263 (1), 237 2), 209 (4), 183 (13), 153 (19), 137 (23), 121 (32), 109 (100), 95 (37), 81 (42), 67 (39); **HR-MS** (ESI-pos): *m/z* calcd. for [M+Na]$^+$: 347.25567, found: 347.25575.

The absolute configuration of **(*S*)-230** was determined *via* Mosher-Ester analysis.

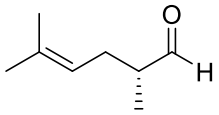


(*S*)-MTPA-ester (*R*)-MTPA-ester

# H	δ (^{1}H) *S*-MTPA ester	δ (^{1}H) *R*-MTPA ester	δ(*S*) – δ(*R*)
9a	1.46	1.49	-0.03
9b	1.39	1.43	-0.04
10	5.19	5.20	-0.01
11	1.85	1.79	0.06
12a	1.98	1.96	0.02
12b	1.81	1.77	0.04

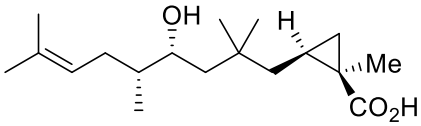
All chemical shifts given in ppm. Measured in $CDCl_3$ at 600 MHz.

Compound 232: In a Schlenk flask, methyl ester **225** (200 mg, 1.3 mmol, 1.0 eq) was dissolved in



CH_2Cl_2 (5 mL) and the solution was cooled to −78 °C. DIBAL-H (1 M in hexanes, 1.5 mL, 1.5 mmol, 1.2 eq) was added dropwise over a course of 10 min and the mixture was kept stirring at −78 °C for 1 h. The reaction was quenched with sat. aq. NH_4Cl and methanol and the mixture was diluted with aqueous HCl (2 M). The aqueous layer was extracted with CH_2Cl_2 (3x), the combined organic layers dried over $MgSO_4$ and the solvent partially evaporated. Due to a presence of primary alcohol as a result of overreduction, the obtained crude material (solution in CH_2Cl_2) was treated with DMP (541 mg, 1.3 mmol, 1.0 eq) at room temperature. After stirring of the mixture for 2.5 h, the reaction was quenched upon addition of water. The aqueous layer was extracted with CH_2Cl_2 (3x), the combined organic layers dried over $MgSO_4$ and the solvent evaporated. The crude product was purified *via* flash chromatography (silica, CH_2Cl_2 only) to obtain the title compound as a colourless liquid (85 mg, 0.67 mmol, 53 % mg). $\mathbf{[\alpha]_D^{20}}$ = −26.3° (c = 1.03, $CHCl_3$); **^{1}H-NMR** (400 MHz, $CDCl_3$): δ = 9.64 (d, *J* = 1.5 Hz, 1H), 5.13 – 5.05 (m, 1H), 2.44 – 2.29 (m, 2H), 2.21 – 1.98 (m, 1H), 1.70 (d, *J* = 1.3 Hz, 3H), 1.62 (d, *J* = 1.3 Hz, 3H), 1.08 (d, *J* = 7.0 Hz, 3H) ppm; **^{13}C{^{1}H}-NMR** (101 MHz, $CDCl_3$): δ = 205.2, 134.1, 120.6, 46.8, 29.2, 25.8, 17.8, 13.1 ppm; **IR (film, ATR)**: $\tilde{\nu}$ [cm^{-1}] = 3442, 2968, 2928, 2718, 1728, 1455, 1378, 1114, 1063, 983, 926, 801; **EI-MS**: *m/z* (%) = 126 (12, [M]), 111 (78), 108 (46), 93 (100), 69 (28), 41 (95); **HR-MS** (GC-CI): *m/z* calcd. for $[M]^+$: 126.10392, found: 126.10416. The analytical data is consistent with the literature[267].

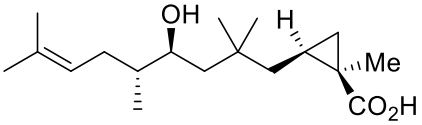
Compound (*R*)-217: In a pressure Schlenk flask, ester **(*R*)-230** (30 mg, 0.09 mmol, 1.0 eq) was



dissolved in THF (3 mL) and KOTMS (31 mg, 0.24 mmol, 2.6 eq) was added. The mixture was stirred at 50°C for 20 h. Upon full conversion of starting material **(*R*)-230** (monitored by TLC), the mixture was diluted with MTBE and the organic layer was washed with aqueous NaOH (1 M, 3x) followed by water (2x) and then discarded. The combined aqueous layers were acidified with conc. HCl and then extracted with MTBE (3x). The combined organic layers were dried over $MgSO_4$ and the solvent was evaporated. The title compound was obtained without further purification as a light yellow oil (21 mg, 0.07 mmol, 77 %). $\mathbf{[\alpha]_D^{20}}$ = 12.1° (c = 1.0, $CHCl_3$); **^{1}H-NMR** (400 MHz, $CDCl_3$): δ = 5.14 (tdt, *J* = 6.5, 3.7, 1.6 Hz, 1H), 3.71 (ddd, *J* = 7.9, 3.5, 2.3 Hz, 1H), 2.09 (ddd, *J* = 14.1, 6.8, 5.8 Hz, 1H), 1.92 – 1.81 (m, 1H), 1.70 (s, 3H), 1.62 (s, 3H), 1.59 – 1.50 (m, 2H), 1.48 – 1.43 (m, 1H), 1.41 – 1.33 (m, 2H), 1.30 (s, 3H), 1.23 – 1.19 (m, 1H), 1.13 – 1.04 (m, 1H), 0.95 (d, *J* = 5.4 Hz, 6H), 0.91 – 0.87 (m, 1H), 0.85 (d, *J* = 6.8 Hz, 3H) ppm; **^{13}C{^{1}H}-NMR** (101 MHz, $CDCl_3$): δ = 181.1, 132.7, 123.3, 72.0, 47.0, 41.3, 39.9, 33.5, 31.9, 27.9, 27.6, 27.5, 26.0, 23.7, 22.7, 21.3, 18.0, 13.8 ppm; **IR (film, ATR)**: $\tilde{\nu}$ [cm^{-1}] = 3429, 2961, 2927, 1687, 1465, 1384, 1326, 1183, 902, 865; **EI-MS**: *m/z* (%) = 278 (3), 263 (1), 235 (2), 221 (3), 209 (7), 193 (16), 153 (10),

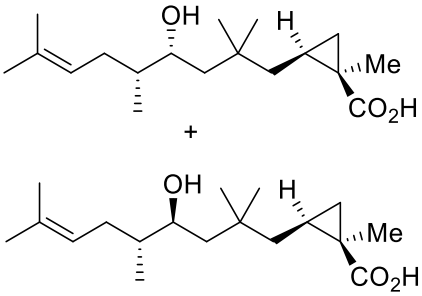
137 (20), 121 (28), 109 (100), 95 (34), 81 (39), 67 (38); **HR-MS** (ESI-pos): *m/z* calcd. for $[M+Na]^+$: 319.22436, found: 319.22445.

Compound (*S*)-217: The compound was prepared from **(*S*)-230** analogously to **(*R*)-217**. Yellow



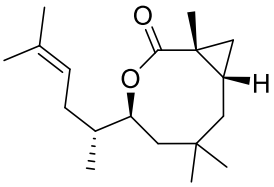
oil (37 mg, 0.125 mmol, 99 %). $[\alpha]_D^{20}$ = -11.2° (c = 1.0, $CHCl_3$); **^{1}H-NMR** (400 MHz, $CDCl_3$): δ = 5.18 – 5.09 (m, 1H), 3.64 (ddd, *J* = 8.7, 4.8, 1.6 Hz, 1H), 2.05 (dt, *J* = 12.9, 6.1 Hz, 1H), 1.86 (dt, *J* = 15.3, 8.1 Hz, 1H), 1.70 (s, 3H), 1.65 – 1.58 (m, 4H), 1.56 – 1.44 (m, 2H), 1.41 (dd, *J* = 14.7, 1.6 Hz, 1H), 1.34 – 1.28 (m, 4H), 1.22 – 1.16 (m, 1H), 1.14 – 1.07 (m, 1H), 0.98 (s, 3H), 0.94 (s, 3H), 0.91 – 0.85 (m, 4H) ppm; **^{13}C{^{1}H}-NMR** (101 MHz, $CDCl_3$): δ = 180.5, 132.5, 123.3, 72.8, 45.8, 41.4, 40.0, 33.4, 30.8, 28.0, 27.8, 27.4, 26.0, 23.6, 22.6, 21.3, 18.1, 15.4 ppm; **IR (film, ATR)**: $\tilde{\nu}$ [cm^{-1}] = 3402, 2960, 2927, 1686, 1464, 1383, 1326, 1184, 902, 864; **ESI-MS**: *m/z* (%) = 615 (8, $[2M+Na]^+$), 335 (7, $[M+K]^+$), 319 (100, $[M+Na]^+$), 297 (8, $[M+H]^+$); **HR-MS** (ESI-pos): *m/z* calcd. for $[M+Na]^+$: 319.22437, found: 319.22488.

Combined Saponification of (*R*)- and (*S*)-217: A mixture of both diastereoisomers of ester **230**



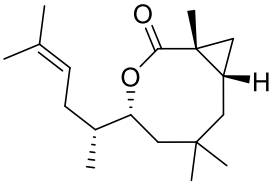
(169 mg, 0.52 mmol, 1.0 eq) was dissolved in THF (15 mL) and KOTMS (660 mg, 5.1 mmol, 9.9 eq.) was added portionwise. The mixture was stirred at room temperature for 3 h and then heated to 30 °C for another 20 h. The mixture was diluted with MTBE and the organic layer was washed with aqueous NaOH (1 M, 3x) and water (3x). The aqueous layer was then acidified with conc. HCl to a pH of approx. 1 and then extracted with MTBE (3x). The obtained organic layer was washed with aqueous HCl (1 M, 3x) to remove silanol residues, dried over $MgSO_4$ and the solvent was evaporated. The title compound was obtained as a light yellow oil and could be used in the next step without further purification (131 mg, 0.44 mmol, 85 %). Analytical data *vide supra*.

Compound (*S*)-216: In a Schlenk flask, carboxylic acid **(*S*)-217** (35 mg, 0.12 mmol, 1.0 eq) was

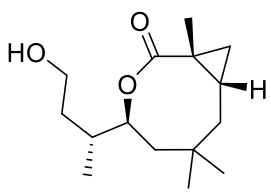


dissolved in THF (2 mL) and the solution was cooled to 0°C. Triethylamine (0.02 mL, 0.14 mmol, 1.2 eq) was added, followed by dropwise addition of 2,4,6-trichlorobenzoyl chloride (0.02 mL, 0.13 mmol, 1.08 eq). The cooling bath was removed and the mixture was stirred at room temperature for 5 h. The formed slurry was filtered through a syringe filter and diluted with toluene (4 mL). This solution was added to solution of DMAP (87 mg, 0.71 mmol, 6.0 eq) in toluene (200 mL) at 80 °C *via* syringe pump over the course of 1 h. The mixture was kept stirring at 80 °C afterwards overnight. After cooling to room temperature, the toluene was evaporated and the crude material dissolved in MTBE. The organic layer was washed with

aqueous HCl (1 M) and aqueous NaOH (1 M), dried over $MgSO_4$, and the solvent evaporated. The crude product was immobilized on Celite and purified *via* flash chromatography (silica, hexane/MTBE 25:1). The title compound was obtained as a colourless liquid (22 mg, 0.079 mmol, 67 %). $\mathbf{[\alpha]_D^{20}}$ = 73.1° (c = 1.2, $CHCl_3$); **^{1}H-NMR** (400 MHz, $CDCl_3$): δ = 5.15 (ddt, *J* = 8.1, 6.7, 1.4 Hz, 1H), 3.64 (t, *J* = 10.3 Hz, 1H), 2.47 (d, *J* = 13.9 Hz, 1H), 2.06 (dqt, *J* = 16.5, 6.6, 3.4 Hz, 1H), 1.95 – 1.84 (m, 1H), 1.81 – 1.74 (m, 1H), 1.71 – 1.64 (m, 5H), 1.61 (d, *J* = 0.9 Hz, 3H), 1.37 (d, *J* = 16.0 Hz, 1H), 1.25 (s, 3H), 1.22 (dd, *J* = 6.4, 4.0 Hz, 1H), 1.13 – 1.04 (m, 1H), 0.98 (s, 3H), 0.96 (dd, *J* = 8.1, 3.9 Hz, 1H), 0.90 (s, 3H), 0.77 (d, *J* = 6.7 Hz, 3H) ppm; **^{13}C{^{1}H}-NMR** (101 MHz, $CDCl_3$): δ = 181.4, 132.8, 122.6, 83.8, 42.1, 41.3, 38.2, 33.5, 31.3, 30.4, 29.0, 28.4, 27.6, 26.1, 23.8, 21.0, 18.0, 16.1 ppm; **IR (film, ATR)**: $\tilde{\nu}$ [cm^{-1}] = 2956, 2931, 2869, 1716, 1460, 1378, 1340, 1109, 1023, 993, 962, 878; **EI-MS**: *m/z* (%) = 278 (1, [M]), 177 (11), 163 (12), 149 (9), 137 (19), 125 (33), 109 (100), 95 (33), 81 (55), 67 (45); **HR-MS** (GC-EI): *m/z* calcd. for $[M]^+$: 278.22403, found: 278.22396.

Compound (*R*)-216:  The compound was prepared from **(*R*)-217** (20 mg, 0.07 mmol) analogously to lactone **(*S*)-216**. Colourless oil (11 mg, 0.04 mmol, 59 %). $\mathbf{[\alpha]_D^{20}}$ = 15.3° (c = 0.98, $CHCl_3$); **^{1}H-NMR** (400 MHz, $CDCl_3$): δ = 5.17 – 5.06 (m, 1H), 4.85 (ddd, *J* = 7.2, 5.3, 1.3 Hz, 1H), 2.22 – 2.12 (m, 1H), 1.96 – 1.84 (m, 2H), 1.70 (s, 3H), 1.66 – 1.55 (m, 5H), 1.54 – 1.47 (m, 1H), 1.36 (s, 3H), 1.05 (s, 4H), 0.94 (d, *J* = 6.8 Hz, 3H), 0.90 (s, 3H), 0.84 (dd, *J* = 15.0, 12.0 Hz, 1H), 0.74 – 0.63 (m, 2H) ppm; **^{13}C{^{1}H}-NMR** (101 MHz, $CDCl_3$): δ = 175.7, 133.3, 122.6, 79.4, 48.1, 43.2, 40.4, 33.6, 33.2, 31.3, 26.0, 25.8, 25.6, 22.5, 21.7, 18.2, 17.4, 14.0 ppm; **IR (film, ATR)**: $\tilde{\nu}$ [cm^{-1}] = 2985, 2927, 1726, 1454, 1382, 1323, 1242, 1150, 1016, 980, 934, 810, 581; **EI-MS**: *m/z* (%) = 278 (1, [M]), 235 (2), 209 (2), 193 (6), 177 (13), 163 (15), 109 (100), 95 (39), 81 (55), 67 (48); **HR-MS** (GC-EI): *m/z* calcd. for $[M]^+$: 278.22403, found: 278.22414.

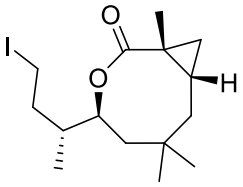
Compound 216 from mixture of diastereoisomers of carboxylic acid 217: When a mixture of diastereomers of carboxylic acid **217** (40 mg, 0.13 mmol) was treated according to the above described procedure, both isomers of the lactone **216** were obtained (30 mg, 0.108 mmol, overall yield of 80 %) and could be easily separated *via* flash chromatography. Major **(*S*)-216** (20 mg, 0.072 mmol) and minor **(*R*)-216** (10 mg, 0.036 mmol). Analytical data *vide supra*.

Compound (*S*)-237: In a Schlenk flask, olefin **(*S*)-216** (20 mg, 0.07 mmol, 1.0 eq) was dissolved  in CH_2Cl_2 (2 mL) and the solution was purged with argon for 1 min. It was then cooled to – 78 °C and ozone was bubbled through the solution until a light blue colour persisted (approx.. 1 min). It was purged with argon again until the blue colour dissipated. Dimethyl sulfide (0.01 mL 0.14 mmol, 1.9 eq) was added and the mixture was stirred for another 5 min. The cooling bath

was removed and the reaction quenched with water. The layers were separated and organic layer was dried over $MgSO_4$. The crude material was dissolved in abs. EtOH (1 mL) and cooled to 0°C. $NaBH_4$ (5 mg, 0.13 mmol, 1.8 eq) was added and the mixture was stirred at 0 °C for 30 min. The reaction was quenched with sat. aq. NH_4Cl and the mixture was diluted with water. The aqueous layer was extracted with MTBE, the combined organic layers were washed with sat. aq. $NaHCO_3$ and brine, then dried over $MgSO_4$ and solvent evaporated. The crude product was immobilized on Celite and purified *via* flash chromatography (silica, hexane/MTBE 4:1 to 2:1) to obtain the title compound as a colourless liquid (12 mg, 0.047 mmol, 66 %). $\mathbf{[\alpha]_D^{20}}$ = 59.1° (c = 1.2, $CHCl_3$); **^{1}H-NMR** (400 MHz, $CDCl_3$): δ = 3.84 – 3.75 (m, 1H), 3.71 – 3.60 (m, 2H), 2.18 (dtd, *J* = 14.4, 10.5, 6.6 Hz, 1H), 2.13 – 2.02 (m, 1H), 1.84 – 1.74 (m, 1H), 1.74 – 1.64 (m, 2H), 1.52 – 1.36 (m, 2H), 1.30 – 1.20 (m, 5H), 1.17 – 1.09 (m, 1H), 0.99 (d, *J* = 3.9 Hz, 4H), 0.92 (s, 3H), 0.85 (d, *J* = 6.7 Hz, 3H) ppm; **^{13}C{^{1}H}-NMR** (101 MHz, $CDCl_3$): δ = 182.4, 84.5, 61.1, 42.1, 41.6, 36.5, 34.3, 33.4, 30.3, 28.9, 28.4, 27.9, 24.4, 20.9, 17.5 ppm; **IR (film, ATR)**: $\tilde{\nu}$ [cm^{-1}] = 3429, 2955, 2933, 2869, 1716, 1469, 1381, 1336, 1112, 1060, 1039, 1023, 995; **EI-MS**: *m/z* (%) = 221 (2), 193 (6), 175 (5), 168 (13), 153 (23), 135 (49), 123 (68), 109 (100), 95 (74), 85 (24), 81 (56), 67 (53); **HR-MS** (ESI-pos): *m/z* calcd. for [M+Na]$^+$: 277.17742, found: 277.17771.

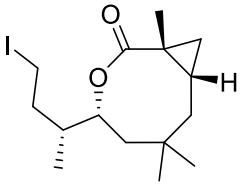
Compound (*R*)-237: In a Schlenk flask, olefin **(*R*)-216** (14 mg, 0.05 mmol, 1.0 eq) was dissolved in CH_2Cl_2 (2 mL) and MeOH (0.5 mL) and the solution was purged with argon for 1 min. It was then cooled to −78 °C and ozone was bubbled through the solution until a light blue colour persisted (ca. 1 min). It was purged with oxygen until the blue colour dissipated. $NaBH_4$ (17 mg, 0.45 mmol, 9.0 eq) was added and the mixture was stirred at -78 °C for 1.5 h. The reaction was quenched with sat. aq NH_4Cl, the mixture warmed to ambient temperature and diluted with water. The aqueous layer was extracted with CH_2Cl_2 (3x), the combined organic layers were dried over $MgSO_4$, and the solvent was evaporated. The crude product was immobilized on Celite and purified *via* flash chromatography (silica, hexane/MTBE 1:1 to 1:2) to obtain the title compound as a light yellow oil (11 mg, 0.043 mmol, 86 %). $\mathbf{[\alpha]_D^{20}}$ = 24.3° (c = 1.1, $CHCl_3$); **^{1}H-NMR** (400 MHz, $CDCl_3$): δ = 4.87 (ddd, *J* = 7.2, 4.1, 1.4 Hz, 1H), 3.78 (ddd, *J* = 10.5, 6.7, 5.1 Hz, 1H), 3.69 (ddd, *J* = 10.6, 8.0, 6.1 Hz, 1H), 1.97 – 1.89 (m, 1H), 1.89 – 1.76 (m, 2H), 1.58 – 1.49 (m, 2H), 1.48 – 1.40 (m, 1H), 1.37 (s, 3H), 1.12 – 1.03 (m, 4H), 0.99 (d, *J* = 7.0 Hz, 3H), 0.91 (s, 3H), 0.83 (dd, *J* = 15.0, 12.0 Hz, 2H), 0.74 – 0.63 (m, 2H) ppm; **^{13}C{^{1}H}-NMR** (101 MHz, $CDCl_3$): δ = 175.4, 79.8, 60.9, 47.3, 43.2, 36.0, 35.4, 33.6, 33.2, 25.7, 25.6, 22.5, 21.8, 17.3, 14.4 ppm; **IR (film, ATR)**: $\tilde{\nu}$ [cm^{-1}] = 3433, 2956, 2926, 2873, 1726, 1326, 1174, 1156, 1052; **EI-MS**: *m/z* (%) = 221 (3), 193 (10), 168 (18), 153 (16), 135 (48), 123 (92), 109 (100), 95 (99), 81 (78), 67 (75); **HR-MS** (ESI-pos): *m/z* calcd. for [M+Na]$^+$: 277.17742, found: 277.17708.

Compound (*S*)-215: In a Schlenk flask, alcohol **(*S*)-237** (11 mg, 0.04 mmol, 1.0 eq) was dissolved



in CH_2Cl_2 (2 mL) and the solution was cooled to 0 °C. Triphenylphosphine (30 mg, 0.11 mmol, 2.6 eq), imidazole (7 mg, 0.1 mmol, 2.4 eq) and iodine (22 mg, 0.07 mmol, 2.0 eq) were added and the cooling bath was removed. The mixture was stirred at room temperature overnight. The reaction was quenched with sat. aq. $Na_2S_2O_3$ and the aqueous layer extracted with MTBE. The combined organic layers were dried over $MgSO_4$ and the solvent was evaporated. The crude product was immobilized on Celite and purified *via* flash chromatography (silica, hexane/MTBE 25:1) to obtain the title compound as a colourless oil (14 mg, 0.038 mmol, 89 %). $[\alpha]_D^{20}$ = 65.2° (c = 1.4, $CHCl_3$); **^{1}H-NMR** (400 MHz, $CDCl_3$): δ = 3.63 (t, *J* = 9.7 Hz, 1H), 3.32 (td, *J* = 9.7, 4.7 Hz, 1H), 3.17 (td, *J* = 9.4, 7.4 Hz, 1H), 2.44 (dddd, *J* = 13.7, 10.1, 7.4, 3.5 Hz, 1H), 2.08 (dddq, *J* = 13.2, 9.8, 6.6, 3.4 Hz, 1H), 1.82 – 1.61 (m, 4H), 1.36 (d, *J* = 15.8 Hz, 1H), 1.25 (s, 3H), 1.21 (dd, *J* = 6.5, 4.1 Hz, 1H), 1.13 – 1.07 (m, 1H), 0.98 (d, *J* = 3.8 Hz, 4H), 0.90 (s, 3H), 0.83 (d, *J* = 6.7 Hz, 3H) ppm; **^{13}C{^{1}H}-NMR** (101 MHz, $CDCl_3$): δ = 181.3, 83.1, 42.1, 41.6, 39.1, 37.6, 33.5, 30.4, 28.9, 28.5, 27.7, 23.9, 20.9, 15.9, 4.4 ppm; **IR (film, ATR)**: $\tilde{\nu}$ [cm^{-1}] = 2955, 2932, 2868, 1715, 1469, 1380, 1335, 1109, 1037, 993, 962, 878; **EI-MS**: *m/z* (%) = 308 (2), 277 (4), 250 (6), 221 (7), 195 (14), 181 (11), 163 (19), 155 (41), 135 (45), 123 (83), 109 (100), 95 (88), 81 (82), 67 (75), 41 (48); **HR-MS** (ESI-pos): *m/z* calcd. for $[M+Na]^+$: 387.07915, found: 387.0787.

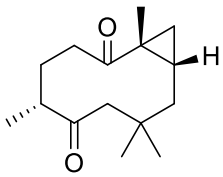
Compound (*R*)-215: In a Schlenk flask, alcohol **(*R*)-237** (10 mg, 0.04 mmol, 1.0 eq) was dissolved



in THF (2 mL). Triphenylphosphine (26 mg, 0.1 mmol, 2.5 eq) was added and the mixture was cooled to 0°C. Imidazole (6 mg, 0.09 mmol, 2.2 eq) and iodine (20 mg, 0.04 mmol, 2.0 eq) were added and the cooling bath was removed. The mixture was stirred at room temperature for 1.5 h. The reaction was quenched with sat. aq. $Na_2S_2O_3$ and the mixture was diluted with water. The aqueous layer was extracted with MTBE (3x), the combined organic layers were dried over $MgSO_4$, and the solvent was evaporated. The crude product was immobilized on Celite and purified *via* flash chromatography (silica, hexanes/MTBE 10:1). In order to remove last minor impurities, the product was again flushed through a column (silica, CH_2Cl_2 only). The title compound was obtained as a white solid (13 mg, 0.036 mmol, 91 %). $[\alpha]_D^{20}$ = 32.6° (c = 1.3, $CHCl_3$); **^{1}H-NMR** (400 MHz, $CDCl_3$): δ = 4.91 – 4.78 (m, 1H), 3.40 – 3.28 (m, 1H), 3.23 – 3.08 (m, 1H), 2.15 – 2.01 (m, 1H), 1.94 (dt, *J* = 15.0, 2.7 Hz, 1H), 1.85 – 1.69 (m, 2H), 1.62 – 1.46 (m, 2H), 1.36 (s, 3H), 1.05 (s, 4H), 0.96 (d, *J* = 6.6 Hz, 3H), 0.91 (s, 3H), 0.83 (dd, *J* = 15.0, 12.0 Hz, 1H), 0.75 – 0.65 (m, 2H) ppm; **^{13}C{^{1}H}-NMR** (101 MHz, $CDCl_3$): δ = 175.3, 79.0, 47.7, 43.1, 40.5, 36.5, 33.6, 33.2, 25.7, 25.5, 22.6, 21.8, 17.4, 13.0, 4.6 ppm; **IR (film, ATR)**: $\tilde{\nu}$ [cm^{-1}] = 2956, 2926, 1728, 1456, 1384, 1366, 1324, 1242, 1150, 981; **EI-MS**: *m/z* (%) = 308 (9), 250 (14), 221 (12), 181 (24), 163 (37), 123 (100), 95 (75), 81 (65), 67 (51); **HR-MS** (ESI-pos): *m/z* calcd. for $[M+Na]^+$: 387.07915, found: 387.07906.

Compound **(*R*)-215** can also be prepared directly from the crude material obtained after ozonolysis without prior purification of the primary alcohol **(*R*)-237**. Starting from olefin **(*R*)-216** (29 mg, 0.1 mmol, 1.0 eq), which was treated with ozone and $NaBH_4$ (40 mg, 1.1 mmol, 10 eq) according to the previously described procedure, the obtained crude product was dissolved in THF (5 mL). Triphenylphosphine (70 mg, 0.27 mmol, 2.6 eq), imidazole (19 mg, 0.28 mmol, 2.7 eq) and iodine (48 mg, 0.19 mmol, 1.8 eq) were added as described above. After aqueous workup and flash chromatography (silica, hexanes/MTBE 10:1) the title compound was obtained as a white solid (31 mg, 0.085 mmol, 82 % over two steps). Analytical data: *vide supra*.

Integrifolian-1,5-dione 113: In a Schlenk flask, *tert*-butyllithium (1.7 M in pentane, 0.04 mL, 0.07 mmol, 3.5 eq) was diluted in THF (2 mL) at −78 °C. A solution of **(*S*)-215** (7 mg, 0.02 mmol, 1.0 eq) in THF (1 mL) was added dropwise and the mixture was stirred at −78°C for 1 h. The reaction was quenched with sat. aq. NH_4Cl and extracted with MTBE (3x). The combined organic layers were dried over $MgSO_4$ and the solvent evaporated. The crude product was dissolved in CH_2Cl_2 (3 mL) and DMP (48 mg, 0.11 mmol, 6.0 eq) and $NaHCO_3$ (17 mg, 0.2 mmol, 10.5 eq) were added. The mixture was stirred at room temperature under air for 17 h. The reaction was quenched with water and the aqueous layer extracted with CH_2Cl_2 (3x). The combined organic layers were dried over $MgSO_4$ and the solvent evaporated. The crude product was immobilized on Celite and purified *via* flash chromatography (silica, hexanes/MTBE 9:1) to obtain the title compound as a white solid (2.6 mg, 0.011 mmol, 57 % *over two steps*). $[\alpha]_D^{20}$ = −24.9° (c = 1.0, $CHCl_3$); **^{1}H-NMR** (600 MHz, $CDCl_3$): δ = 3.14 (ddd, *J* = 16.9, 11.7, 1.4 Hz, 1H), 2.51 (d, *J* = 19.0 Hz, 1H), 2.39 – 2.33 (m, 1H), 2.32 – 2.21 (m, 2H), 2.02 (dd, *J* = 19.2, 1.6 Hz, 1H), 1.61 (dddd, *J* = 13.5, 7.9, 4.2, 1.6 Hz, 1H), 1.53 (dd, *J* = 15.2, 11.6 Hz, 1H), 1.46 (s, 3H), 1.43 (dt, *J* = 15.2, 2.1 Hz, 1H), 1.34 (dd, *J* = 7.3, 3.8 Hz, 1H), 1.18 (s, 3H), 1.08 (dddd, *J* = 11.5, 8.7, 7.3, 2.6 Hz, 1H), 0.99 (d, *J* = 6.6 Hz, 3H), 0.92 (s, 3H), 0.64 (dd, *J* = 8.8, 3.8 Hz, 1H) ppm; **^{13}C{^{1}H}-NMR** (151 MHz, $CDCl_3$): δ = 212.9, 207.8, 52.7, 46.9, 38.6, 35.1, 32.3, 31.7, 30.4, 29.7, 29.6, 28.9, 21.5, 20.3, 17.2 ppm; **IR (film, ATR)**: $\tilde{\nu}$ [cm^{-1}] = 2919, 1708, 1684, 1391, 1369, 1035; **EI-MS**: *m/z* (%) = 236 (3, [M]), 221 (10), 203 (11), 179 (10), 165 (16), 150 (36), 137 (30), 123 (31), 109 (100), 95 (47), 81 (28), 67 (23), 41 (19); **HR-MS** (GC-EI): *m/z* calcd. for $[M]^+$: 236.17708, found: 236.1771. The analytical data is consistent with the literature[203].



The title compound was obtained from **(*R*)-215** (10 mg, 0.028 mmol) as well, following the previously described procedure. White solid (4.4 mg, 0.018 mmol, 67 % *over two steps*). Analytical data *vide supra*.

Aldol Addition Product 115a: In a Schlenk flask, integrifolian-1,5-dione **113** (6 mg, 0.025 mmol, 1.0 eq) was dissolved in methanol (2 mL). Cesium carbonate (16 mg, 0.05 mmol, 1.9 eq) was added and the mixture was stirred at room temperature for three days. The reaction was quenched with water and the aqueous layer extracted with CH_2Cl_2 (3x). The combined organic layers were dried over $MgSO_4$ and the solvent evaporated. The crude product was immobilized on Celite and purified *via* flash chromatography (silica, hexanes/MTBE 3:1). It was possible to re-isolate unreacted starting material **113** after flash chromatography, which was re-subjected to the aforementioned conditions. The title compound was obtained as a white solid (2.8 mg, 0.012 mmol, 41 % (56 % *brsm*) after two cycles). $\mathbf{[\alpha]_D^{20}}$ = −115.1° (c = 0.35, $CHCl_3$); **^{1}H-NMR** (600 MHz, $CDCl_3$): δ = 2.39 (dp, *J* = 13.3, 6.9, 6.3 Hz, 1H), 2.14 (td, *J* = 14.0, 13.7, 4.6 Hz, 1H), 2.01 (ddt, *J* = 14.0, 4.5, 2.5, 2.4 Hz, 1H), 1.96 (dddd, *J* = 13.4, 6.9, 4.6, 2.5 Hz, 1H), 1.84 – 1.74 (m, 3H), 1.28 (d, *J* = 2.0 Hz, 1H), 1.24 – 1.20 (m, 1H), 1.13 (d, *J* = 1.2 Hz, 3H), 1.11 (d, *J* = 0.6 Hz, 3H), 1.10 – 1.06 (m, 1H), 1.05 (d, *J* = 6.3 Hz, 3H), 0.76 (s, 3H), 0.55 (dd, *J* = 8.9, 4.6 Hz, 1H), 0.25 (t, *J* = 5.4, 4.6 Hz, 1H) ppm; **^{13}C{^{1}H}-NMR** (151 MHz, $CDCl_3$): δ = 214.3, 76.7, 66.8, 43.9, 42.9, 34.6, 32.3, 30.4, 29.9, 26.2, 26.2, 23.0, 22.1, 20.7, 14.9 ppm; **IR (film, ATR)**: $\tilde{\nu}$ [cm^{-1}] = 3486, 2963, 2934, 2872, 1680, 1456, 1376, 1173, 1131, 989, 916; **EI-MS**: *m/z* (%) = 236 (1, [M]), 218 (34), 203 (84), 175 (31), 161 (36), 147 (64), 133 (100), 119 (64), 105 (76), 91 (54), 83 (20); **HR-MS** (ESI-pos): *m/z* calcd. for $[M+Na]^+$: 259.16685, found: 259.16668.

Lippifoli-1(6)-en-5-one 114. In a Schlenk flask, aldol addition product **115a** (3 mg, 0.013 mmol, 1.0 eq) was dissolved in THF (1 mL). Burgess reagent (6 mg, 0.025 mmol, 2.0 eq) was added as a solution in THF (0.6 mL). The mixture was stirred at room temperature for 3 h. The solvent was evaporated, the crude product was immobilized on Celite and purified *via* flash chromatography (silica, hexanes/EtOAc 50:1) to obtain an approx. 1:3 mixture of the title compound and the unconjugated double bond isomer. The mixture was dissolved in THF (1 mL), catalytic amounts of DBU were added and the mixture was heated to 70 °C for 48 h, resulting in double bond migration, which was monitored by GC-MS. After cooling of the mixture to room temperature, the solvent was removed, the crude product immobilized on Celite and purified *via* flash chromatography (silica, hexanes/EtOAc 100:1) to yield 1.5 mg of the title compound, which contained trace amounts of the 4-Me-epimer. The reaction was repeated with 4 mg of aldol addition product **115a**, eventually yielding 1.9 mg of a similar mixture of title compound and C4-epimer. The combined amounts were submitted to HPLC purification to separate the epimers and obtain the title compound in pure form as a colourless film (1 mg, 0.005 mmol, 15 % overall yield). **^{1}H-NMR** (600 MHz, $CDCl_3$): δ = 2.45 (ddd, *J* = 17.8, 11.5, 4.6 Hz, 1H), 2.34 (ddd, *J* = 17.8, 4.5, 3.4 Hz, 1H), 2.19 (dqd, *J* = 12.7, 7.0, 4.8 Hz 1H), 1.97 (dtd, *J* = 12.7, 4.8, 4.6, 3.4 Hz, 1H), 1.86 (dd, *J* = 14.1, 8.1 Hz, 1H), 1.50

(tdd, *J* = 12.7, 11.5, 4.5 Hz, 1H), 1.19 (s, 6H), 1.17 (s, 3H), 1.16 – 1.13 (m, 1H), 1.12 (d, *J* = 6.9 Hz, 3H), 1.10 – 1.07 (m, 1H), 0.83 (dd, *J* = 7.8, 3.8 Hz, 1H), 0.29 – 0.26 (m, 1H) ppm; **$^{13}C\{^1H\}$-NMR** (151 MHz, $CDCl_3$): δ = 201.5, 160.3, 140.2, 43.6, 42.6, 33.7, 30.3, 29.0, 28.8, 27.6, 26.4, 23.0, 20.6, 19.2, 16.8 ppm; **IR (film, ATR)**: $\tilde{\nu}$ [cm^{-1}] = 2954, 2922, 2851, 1662, 1458, 1379, 1259, 1093, 1017, 798; **EI-MS**: *m/z* (%) = 218 (12, [M]), 203 (36), 175 (17), 161 (26), 148 (15), 133 (100), 119 (18), 105 (28), 91 (16); **HR-MS** (GC-EI): *m/z* calcd. for $[M]^+$: 218.16652, found: 218.16657. The analytical data is consistent with the literature[197a, 203].

4.3 Supporting Crystallographic Information

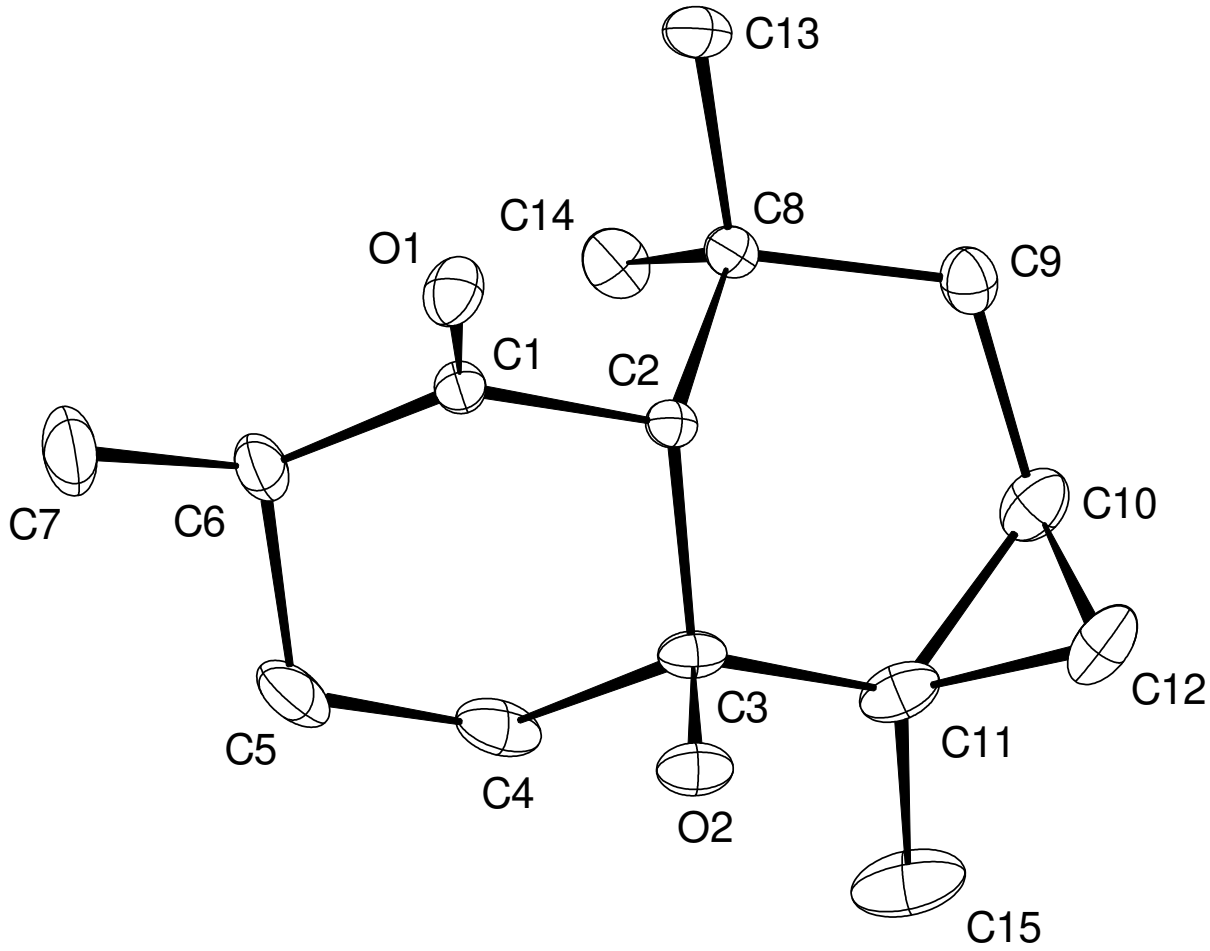


Figure 58. Crystal structure of aldol addition product 115a from X-ray diffraction analysis.

Identification code	15713	
Empirical formula	C_{15} H_{24} O_2	
Color	colourless	
Formula weight	236.357 g·mol^{-1}	
Temperature	100(2) K	
Wavelength	0.71073 Å	
Crystal system	Orthorhombic	
Space group	$P2_12_12_1$, (no. 19)	
Unit cell dimensions	a = 5.8165(3) Å	α= 90°.
	b = 11.7639(5) Å	β= 90°.
	c = 19.7105(9) Å	γ = 90°.
Volume	1348.69(11) Å^3	
Z	4	
Density (calculated)	1.164 Mg·m^{-3}	
Absorption coefficient	0.075 mm^{-1}	
F(000)	520.298 e	

Crystal size	0.24 x 0.14 x 0.101 mm^3	
θ range for data collection	2.02 to 31.10°.	
Index ranges	$-8 \leq h \leq 8$, $-17 \leq k \leq 17$, $-28 \leq l \leq 28$	
Reflections collected	60654	
Independent reflections	4329 [R_{int} = 0.0294]	
Reflections with I>2σ(I)	4066	
Completeness to θ = 25.2417°	99.93 %	
Absorption correction	Gaussian	
Max. and min. transmission	0.99589 and 0.98730	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	4329 / 0 / 370	
Goodness-of-fit on F^2	1.1885	
Final R indices [I>2σ(I)]	R_1 = 0.0166	wR^2 = 0.0276
R indices (all data)	R_1 = 0.0198	wR^2 = 0.0282
Absolute structure parameter	0.05(15)	
Largest diff. peak and hole	0.0940 and -0.0965 e·$Å^{-3}$	
Refinement special details	non-spherical atom form factors	

5 Abbreviations

Ac	acetyl
Acac	acetylacetonate
acam	acetamidate
aq.	aqueous
Ar	aryl
atm.	atmosphere
Bn	benzyl
Boc	*tert*-butyloxycarbonyl
brsm	based on recovered starting material
Bu	butyl
c	concentration
calcd.	calculated
cat.	catalyst, catalytic
CDI	1,1'-carbonyldiimidazole
conc.	concentrated
CSA	camphorsulfonic acid
Cy	cyclohexyl
dba	dibenzylideneacetone
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
DCC	*N*,*N*'-dicyclohexylcarbodiimide
DEAD	diethyl azodicarboxylate
DFT	density functional theory
DIBAL-H	diisobutylaluminium hydride
DMAP	*N*,*N*-dimethyl-4-aminopyridine
DMF	*N*,*N*-dimethylformamide
DMP	Dess-Martin periodinane
DMPU	*N*,*N*′-dimethylpropyleneurea
DMS	dimethyl sulfide
DMSO	dimethyl sulfoxide
DPP	diphenylphosphinate

d.r.	diastereomeric ratio
EDC	1-ethyl-3-(3-dimethylaminopropyl)carbodiimide
EDG	electron-donating group
ee	enantiomeric excess
ent	enantiomeric
eq	equivalent(s)
EI	electron ionisation
ESI	electrospray ionisation
Et	ethyl
et al.	and others
EWG	electron-withdrawing group
exp.	experimental
g	grams(s)
GC	gas chromatography
h	hour(s)
h•ν	irradiation
Hal	halogen
HMDS	hexamethyldisilazane
HMPA	hexamethylphosphoramide
HPLC	high-performance liquid chromatography
HR-MS	high resolution mass spectrometry
i	*iso*
i.e.	that is
IR	infrared spectroscopy
kcal	kilocalorie(s)
LDA	lithium diisopropylamide
LG	leaving group
Lit.	literature
m	*meta*
M	molar
Me	methyl
mg	milligram(s)

MHz	megahertz
μwave	microwave
min	minute(s)
mL	milliliter(s)
mmol	millimole(s)
mol	mole(s)
MOM	methoxymethyl
MS	mass spectrometry, molecular sieves
Ms	mesyl
MTBE	methyl *tert*-butyl ether
MTPA	α-methoxy-α-trifluoromethylphenylacetic acid
Nap	naphthyl
NBS	*N*-bromosuccinimide
neg	negative
NIS	*N*-iodosuccinimide
NMP	*N*-methyl-2-pyrrolidon
NMR	nuclear megnatic resonance
No.	number
NOE	nuclear Overhauser effect
NOESY	nuclear Overhauser effect spectroscopy
Nu	nucleophile
o	*ortho*
p	*para*
P	product
Ph	phenyl
p-ABSA	4-acetamidobenzenesulfonyl azide
p-TsOH	*para*-toluenesulfonic acid
PG	protecting group
pin	pinacol
PMB	*para*-methoxybenzyl
pos.	positive
ppm	parts per million

PPTS	pyridinium *para*-toluenesulfonate
Pr	propyl
pyr	pyridine
quant.	quantitative
rt	room temperature
sat.	saturated
SM	starting material
t	*tert*
T	temperature
TBAF	tetra-n-butylammonium fluoride
TBAI	tetra-n-butylammonium iodide
TBDPS	*tert*-butyldiphenylsilyl
TBS	*tert*-butyldimethylsilyl
Tf	trifluoromethanesulfonyl
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TIPS	tri-*iso*-propylsilyl
TLC	thin-layer chromatography
TM	transition metal
TMEDA	*N*,*N*,*N*',*N*'-tetramethylenediamine
TMS	trimethylsilyl
TON	turnover number
TS	transition state
Ts	toluenesulfonyl

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