2,5-DIHYDROFURANS: NEW APPROACHES BY RECYCLABLE OR COMBINED CATALYSIS

Dissertation

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2,5-DIHYDROFURANS: NEW APPROACHES BY RECYCLABLE OR COMBINED CATALYSIS

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Özge AKSIN-ARTOK
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"We must not forget that when radium was discovered no one knew that it would prove useful in hospitals. The work was one of pure science. And this is a proof that scientific work must not be considered from the point of view of the direct usefulness of it. It must be done for itself, for the beauty of science, and then there is always the chance that a scientific discovery may become like the radium a benefit for humanity."

Marie Curie (1867-1934), *Lecture at Vassar College, May 14, 1921*

Teile dieser Arbeit wurden bereits veröffentlicht:

Ö. Aksın, N. Krause, *Adv. Synth. Catal.* **2008**, *350*, 1106–1112.

Dedicated to my parents and my husband

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Abbreviations

Ac	Acetyl
aq.	Aqueous
Ar	Aryl
Bn	Benzyl
Bz	Benzoate
BMIM	1-Butyl-3-methyl-imidazolium
Boc	*tert*-butyloxycarbonyl
Bu	Butyl
Cat.	Catalytic
cod	Cyclooctadiene
d	Doublet
disp.	Dispersion
DCM	Dichloromethane
dba	Dibenzylidene acetone
DBU	1,8-Diazabicyclo [5.4.0]undec-7-ene
dd	Doublet of doublets
DCE	Dichloroethane
DMAP	4-Dimethylaminopyridine
DET	Diethyltartrate
dr	Diastereomeric ratio
dt	Doublet of triplets
ee	Enantiomeric excess
e.g.	For example (exempli gratiā)
etc.	and other things (et cetera)
equiv.	Equivalent
Eq.	Equation
Et	Ethyl
EMIM	1-Ethyl-3-methyl-imidazolium
GC	Gas Chromatography
GC-MS	Gas Chromatography Mass Spectrometry
g	Gram
h	Hour(s)
c-Hex	Cyclohexyl
HRMS	High Resolution Mass Spectra
HMDS	Hexamethyldisilazane
ICP-MS	Inductively Coupled Plasma-Mass Spectrometry
i-Pr	Iso-propyl
IPr	1,3-Bis-(2,6-diisopropyl phenyl)imidazole
IL	Ionic liquids
IR	Infrared
FT-IR	Fourier transform infrared spectroscopy
J	Coupling constant
MHz	MegaHertz
M	Molar
m	Multiplet
MALDI-TOF	Matrix Assisted Laser Desorption/Ionization)-Time-Of-Flight
m-CPBA	*meta*-Chloroperbenzoic acid
Me	Methyl
MS	Molecular sieve
Ms	Mesyl (methylsulfonyl)
mg	Milligram
min	Minutes
mL	Milliliter

μL	Microliter	RTIL's	Room temperature ionic liquids
MP	Melting point		
nbd	Norbornadiene	s	Singlet
N	Normality	sat.	Saturated
NEt_3	Triethylamine	t	Triplet
NMR	Nuclear Magnetic Resonance	TPS	Triisopropylsilyl
		TBS	*tert*-Butyldimethylsilyl
OMIM	1-octyl-3-methyl-imidazolium	Tol	Tolyl
		Tf	Triflate
o	*Ortho*	THF	Tetrahydrofuran
PG	Protecting group	TLC	Thin layer chromatography
Ph	Phenyl		
Ph_3P	Triphenylphosphine	TMEDA	Tetramethylethylene diamine
ppb	Parts per billion		
ppm	Parts per million	TMS	Trimethylsilyl
q	Quartet	*p*-Ts	*para*-Toluenesulfonyl
RT	Room Temperature		

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Preface

Five-membered heterocycles are essential building blocks that are frequently used in the pharmaceutical and chemical industry. The widespread occurrence of substituted 2,5-dihydrofuran units in a number of natural products has led to an increased recent interest in versatile and stereoselective methods for preparing such compounds. We are dedicated to developing useful approaches that can provide an access to a wide range of 2,5-dihydrofuran products.

The results of our investigations in this context form the subject matter of the thesis entitled **"2,5-DIHYDROFURANS: NEW APPROACHES BY RECYCLABLE OR COMBINED CATALYSIS"**. Each approach is discussed in the separate chapters. In each chapter, a brief *introduction* of literature examples is followed by *present study*, *conclusion* and *experimental part*. The thesis is divided into chapters which are presented as independent units and therefore the structural formulae, schemes, figures and references are numbered chapter-wise.

The thesis starts with brief introduction into allenes and literature methods for the synthesis of our target molecules, the 2,5-dihydrofurans. The definition of the research problem is also provided at the end of this chapter.

A reusable catalyst system is important for industry to reduce the loss of valuable catalysts and to avoid the formation of waste in the process. Ionic liquids are highly useful solvent systems for catalyst recycling because of their unique properties like non-volatility, non-flammability, thermal stability, etc. Therefore, we have synthesized 2,5-dihydofurans by gold-catalyzed cycloisomerization of α-hydroxyallenes in ionic liquids. The results of these studies are presented in chapter 2.

The numbers of examples where two catalysts perform sequential organic reactions in one-pot has been increasing in the last decade. We have synthesized 2,5-dihydrofurans also from alkynyl oxiranes in one-pot using a combined catalytic system by taking the advantages of two metals: rhodium and gold. The results of these studies are presented in chapter 3.

A summary of the work, also in German, is given at the end of the thesis as the last chapter.

CHAPTER 1

Introduction

1.1. ALLENES

Allenes[1] (1,2-propadiene derivatives) are an important class of compounds and have gained increasing attraction as interesting building blocks in synthetic organic chemistry. Allenes are characterized by two cumulated carbon–carbon double bonds, and their characteristic reactivity as well as unique steric properties originates in the propadienyl structures.

Allenes have been considered mostly chemical curiosities for a long period. The first report on the synthesis of an allene carried out by Burton and von Pechmann in 1887[2] was an attempt to prove the non-existence of this class of compounds. The structure of the allene was confirmed in 1954 by the use of IR and Raman spectroscopy.[3]

In recent years, allenes became highly valuable intermediates for target-oriented synthesis because they can undergo various transformations with high levels of chirality transfer. Allenes are not only important as reactive key intermediates in organic synthesis, but also as natural products and pharmacologically active compounds (Scheme 1.1).[4]

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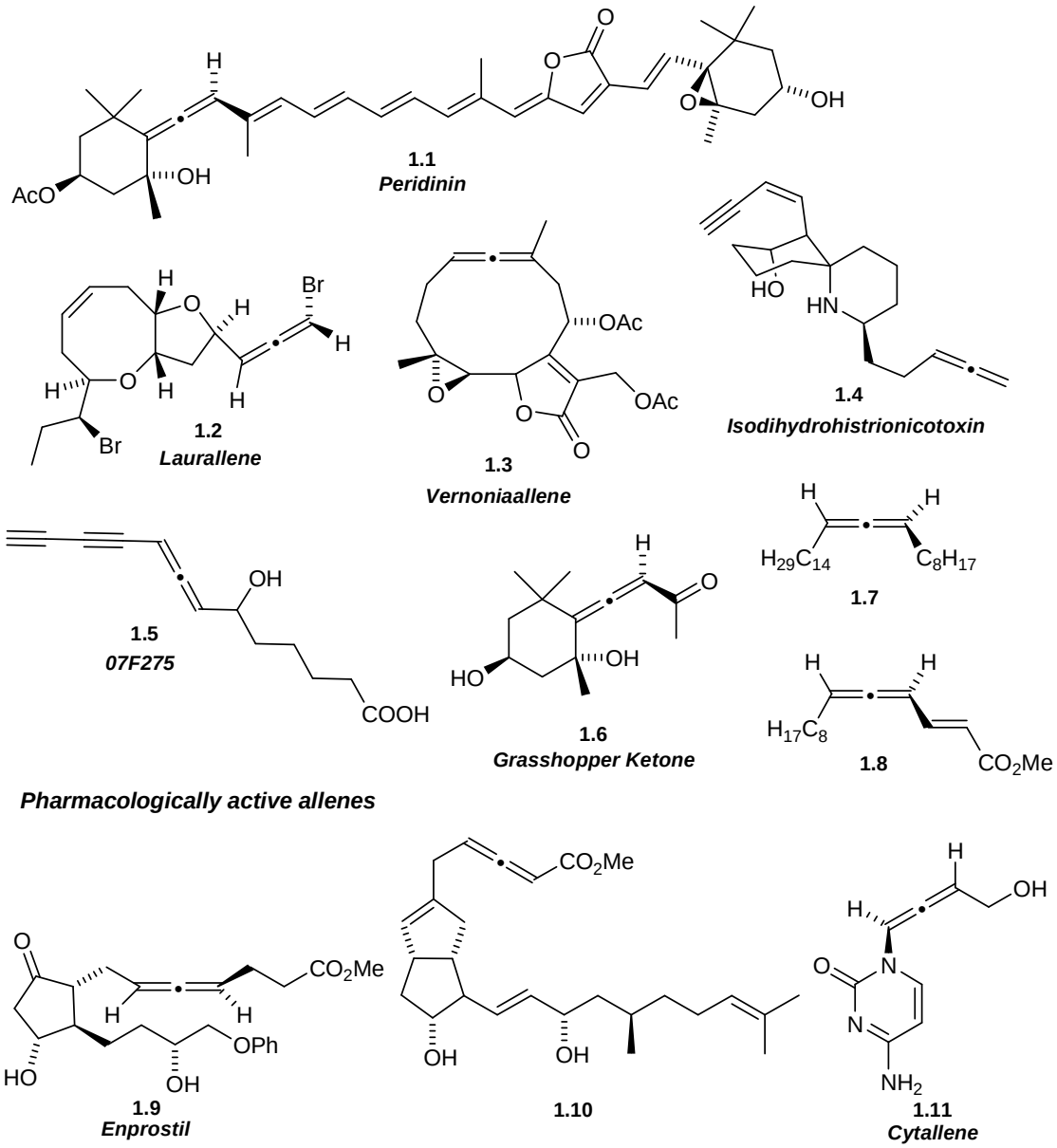
[1] a) H. F. Schuster, G. M. Coppola, *Allenes in Organic Synthesis*, Wiley, New York, **1984**; b) N. Krause, A. S. K. Hashmi, *Modern Allene Chemistry*, Wiley-VCH, Weinheim, **2004**.

[2] B. S. Burton, H. v. Pechmann, *Ber. Dtsch. Chem. Ges.* **1887**, *20*, 145–149.

[3] E. R. H. Jones, G. H. Mansfield, M. L. H. Whiting, *J. Chem. Soc.* **1954**, 3208–3212.

[4] a) M. T. Crimmins, K. A. Emmitte, *J. Am. Chem. Soc.* **2001**, *123*, 1533–1534; b) N. Furuichi, H. Hara, T. Osaki, H. Mori, S. Katsumura, *Angew. Chem.* **2002**, *114*, 1065–1068; *Angew. Chem. Int. Ed.* **2002**, *41*, 1023–1026; c) Review: A. Hoffmann-Röder, N. Krause, *Angew. Chem.* **2004**, *116*, 1216–1236; *Angew. Chem. Int. Ed.* **2004**, *43*, 1196–1216.

These characteristics gave rise to interest in the stereoselective synthesis of allenes.[5]



Scheme 1.1. Allenic natural products and pharmacologically active allenes.

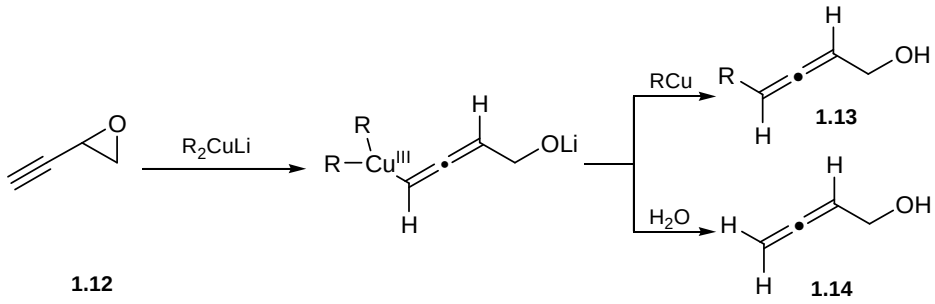
[5] Reviews: a) R. Zimmer, C. U. Dinesh, E. Nandanan, F. A. Khan, *Chem. Rev.* **2000**, *100*, 3067–3125; b) J. A. Marshall, *Chem. Rev.* **2000**, *100*, 3163–3186; c) A. S. K. Hashmi, *Angew. Chem.* **2000**, *112*, 3737–3740; *Angew. Chem. Int. Ed.* **2000**, *39*, 3590–3593; d) N. Krause, A. Hoffmann-Röder, *Modern Organocopper Chemistry* (Ed.: N. Krause), Wiley-VCH, Weinheim, **2002**, 145–166; e) A. Hoffmann-Röder, N. Krause, *Angew. Chem.* **2002**, *114*, 3057–3059; *Angew. Chem. Int. Ed.* **2002**, *41*, 2933–2935; f) N. Krause, A. Hoffmann-Röder, *Tetrahedron* **2004**, *60*, 11671–11694.

1.1.1. Synthesis of Functionalized Allenes

Allenes can be synthesized by a number of procedures.[1a] Among functionalized allenes, α-hydroxyallenes play a particular role in organic synthesis since they can be converted under mild conditions into 2,5-dihydrofurans and other hetero-substituted allenes.

Various transition metals can be used for the α-hydroxyallene formation by S_N2'-substitution of propargylic electrophiles (esters, halides, oxiranes, sulfonates, etc.).[1b,6,5a-b]

The S_N2'-substitution of propargylic oxiranes with organometallic reagents[5f] is one of the most successful procedures (*e.g.* copper-mediated[4c,5e,7] or -catalyzed[8]) for the stereoselective preparation of substituted 2,3-allenols with high *anti*-selectivity in most cases. However, Alexakis *et al*. revealed a strong halogen effect on the stereoselectivity (*anti vs. syn*) with Grignard reagents,[9] and Oehlschlager and Czyzewska *et al*. also reported that *syn*/*anti* mixtures are formed in the absence of any additives with organocuprates.[10] Moreover, the S_N2'-substitution of propargylic oxiranes **1.12** with lithium dialkylcuprates in the presence of additives like phosphines and phosphites led to the formation of reduction product **1.14** rather than the substitution product **1.13** (Scheme 1.2).



Scheme 1.2. S_N2'-substitution of propargylic oxiranes with lithium dialkylcuprates.

[6] a) S. Ma, *Chem. Rev.* **2005**, *105*, 2829–2872; b) S. Ma, *Pure Appl. Chem*. **2006**, *78*, 197–208.

[7] K. M. Brummond, J. E. DeForest, *Synthesis* **2007**, 795–818.

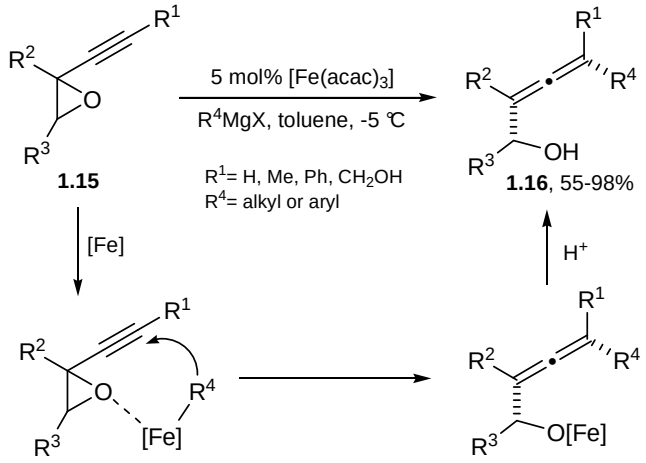
[8] a) A. Alexakis, I. Marek, P. Mangeney, J. F. Normant, *Tetrahedron* **1991**, *47*, 1677–1696; b) C. Deutsch, B. H. Lipshutz, N. Krause, *Angew. Chem.* **2007**, *119*, 1677–1681; *Angew. Chem. Int. Ed.* **2007**, *46*, 1650–1653; c) C. Deutsch, B. H. Lipshutz, N. Krause, *Org. Lett.* **2009**, *11*, 5010–5012; d) X. Tang, S. Woodward, N. Krause, *Eur. J. Org. Chem.* **2009**, 2836–2844.

[9] a) I. Marek, P. Mangeney, A. Alexakis, J. F. Normant, *Tetrahedron Lett.* **1986**, *27*, 5499–5502; b) A. Alexakis, I. Marek, P. Mangeney, J. F. Normant, *J. Am. Chem. Soc.* **1990**, *112*, 8042–8047; c) I. Marek, A. Alexakis, P. Mangeney, J. F. Normant, *Bull. Soc. Chim. Fr.* **1992**, *129*, 171–190.

[10] A. C. Oehlschlager, E. Czyzewska, *Tetrahedron Lett.* **1983**, *24*, 5587–5590.

Palladium-catalyzed reactions of propargylic oxiranes with organozinc,[11] -stannane,[12] and -boron reagents[13] and carbon monoxide[14] also yielded allenols with *anti*-selectivity.

syn-Selective S_N2'-substitutions of propargylic oxiranes **1.15** to form α-allenols **1.16** can also be achieved with Grignard reagents under iron catalysis with 55-98% yield (Scheme 1.3).[15] The diastereoselectivity is higher in a hydrocarbon solvent than in an ether medium. This is explained by the precoordination of the oxygen atom of the oxirane ring to the iron and/or the Grignard reagent and a "directed" delivery of the nucleophile to the alkyne which leads to the formation of the α-allenol.

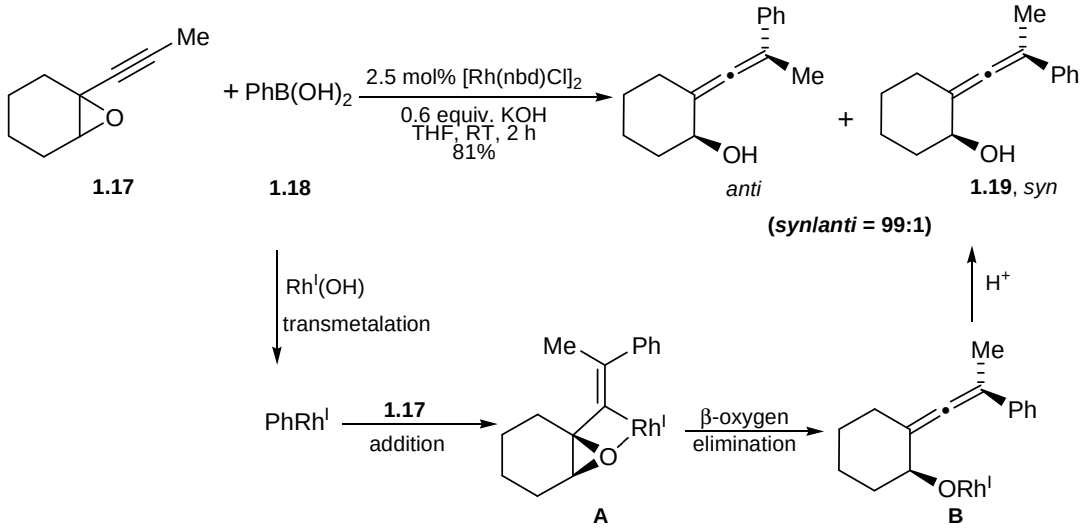


Scheme 1.3. Iron-catalyzed reaction of an alkynyl oxirane with Grignard reagents.

Excellent *syn*-selectivity was also achieved in the rhodium-catalyzed S_N2'-substitution with arylboronic acids.[16] However, alkyl- and alkenylboronic acids failed to react under these conditions. A phenylrhodium(I) species is generated by transmetalation of a hydroxorhodium(I) intermediate with **1.18**. Then, *cis*-1,2-addition of the phenylrhodium(I) species to **1.17** takes place to afford the alkenylrhodium(I) intermediate **A**. The precoordination of the oxygen atom of the oxirane ring to rhodium contributes to the high stereoselectivity as well as the high reactivity. Subsequent β-oxygen elimination occurs in a

[11] H. Kleijn, J. Meijer, G. C. Overbeek, P. Vermeer, *Rec. Trav. Chim. Pays-Bas* **1982**, *101*, 97–101.
[12] J. Kjellgren, H. Sunde´n, K. J. Szabo´, *J. Am. Chem. Soc.* **2005**, *127*, 1787–1796.
[13] M. Yoshida, H. Ueda, M. Ihara, *Tetrahedron Lett.* **2005**, *46*, 6705–6708.
[14] J. G. Knight, S. W. Ainge, C. A. Baxter, T. P. Eastman, S. J. Harwood, *J. Chem. Soc., Perkin Trans.* **2000**, *1*, 3188–3190.
[15] A. Fürstner, M. Mendez, *Angew. Chem.* **2003**, *115*, 5513–5515; *Angew. Chem. Int. Ed.* **2003**, *42*, 5355–5357.
[16] T. Miura, M. Shimada, S.Y. Ku, T. Tamai, M. Murakami, *Angew. Chem.* **2007**, *119*, 7231–7233; *Angew. Chem. Int. Ed.* **2007**, *46*, 7101–7103.

syn mode to open the oxirane ring. Protodemetalation of the resulting rhodium(I) alkoxide **B** released the product **1.19** (Scheme 1.4).



Scheme 1.4. Rh(I)-catalyzed reaction of an alkynyl oxirane with phenylboronic acid.

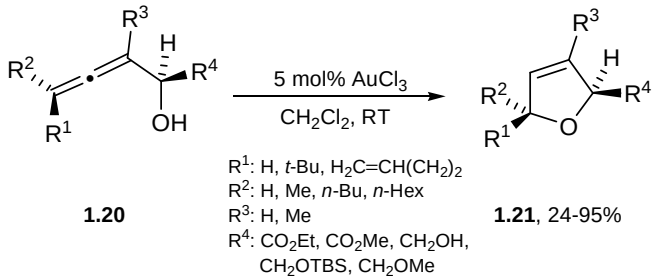
1.1.2. Gold-Catalyzed Cycloisomerization Reactions of Functionalized Allenes

Allenes are a fertile ground for new reactivity in intramolecular nucleophilic additions. A series of five- and six-membered heterocycles can be constructed using the gold-catalyzed cycloisomerization of allenes bearing nucleophiles including alcohols, esters, ketones, thiols, sulfonamides, amines, and amides.[17]

Krause *et al*. showed that α-hydroxyallenes **1.20** are converted into the corresponding 2,5-dihydrofurans **1.21** by using 5 mol% of gold(III) chloride as catalyst at room temperature. This cyclization method was applied to alkyl- and alkenyl-substituted allenes, which furnished tri- and tetra-substituted dihydrofurans in good to excellent chemical yield and with complete axis-to-center chirality transfer. Various functional groups (*e.g.*, carbonyl groups, free

[17] a) H. C. Shen, *Tetrahedron* **2008**, *64*, 3885–3903; b) N. Bongers, N. Krause, *Angew. Chem.* **2008**, *120*, 2208–2211; *Angew. Chem. Int. Ed.* **2008**, *47*, 2178–2181; c) R. A. Widenhoefer, *Chem. Eur. J.* **2008**, *14*, 5382–5391.

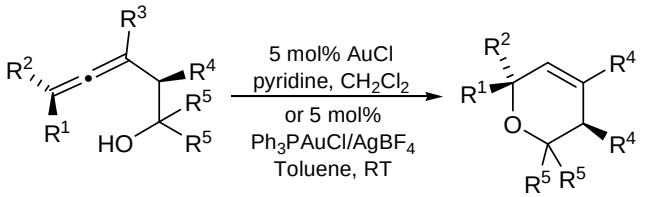
alcohols, acid-sensitive protecting groups) are tolerated under these conditions (Scheme 1.5).[18]



1.20 **1.21**, 24-95%

Scheme 1.5. Gold(III) chloride-catalyzed cyclization of α-hydroxyallenes to 2,5-dihydrofurans.

Krause *et al*. also developed an efficient and stereoselective gold(I)-catalyzed 6-*endo*-*trig* cycloisomerization of various β-hydroxyallenes **1.22** to the corresponding dihydropyrans **1.23** at room temperature in good chemical yields with axis-to-center chirality transfer. Both gold(I) and gold(III) were found to be efficient precatalysts and no trace of the 5-*exo*-isomer could be detected (Scheme 1.6).[19]



1.22 **1.23**, up to 84%

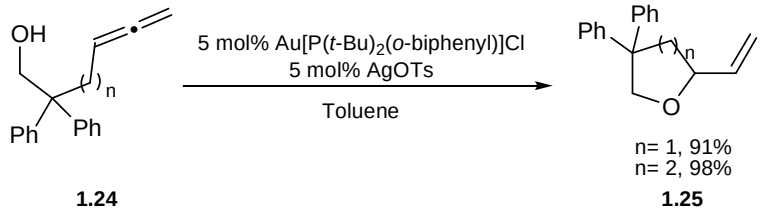
Scheme 1.6. Gold-catalyzed cycloisomerization of β-hydroxyallenes to dihydropyrans.

In 2006, Widenhoefer *et al*. reported that γ-hydroxy and δ-hydroxyallenes undergo Au-catalyzed intramolecular hydroalkoxylation within minutes at room temperature to form the corresponding oxygen heterocycles in good yield with high *exo*-selectivity. Reaction of the γ-hydroxy or δ-hydroxyallene **1.24** with a catalytic 1:1-mixture of [Au{P(*t*-Bu)$_2$(*o*-biphenyl)}Cl] and AgOTs at room temperature gave the 2-vinyltetrahydrofuran or 2-vinyltetrahydropyran **1.25** in 91% and 98% yield, respectively (Scheme 1.7).[20]

[18] a) A. Hoffmann-Röder, N. Krause, *Org. Lett.* **2001**, *3*, 2537–2538; b) N. Krause, A. Hoffmann-Röder, J. Canisius, *Synthesis* **2002**, 1759–1774; c) C. Deutsch, A. Hoffmann-Röder, A. Domke, N. Krause, *Synlett* **2007**, 737–740; d) C. Deutsch, B. Gockel, A. Hoffmann-Röder, N. Krause, *Synlett* **2007**, 1790–1794.

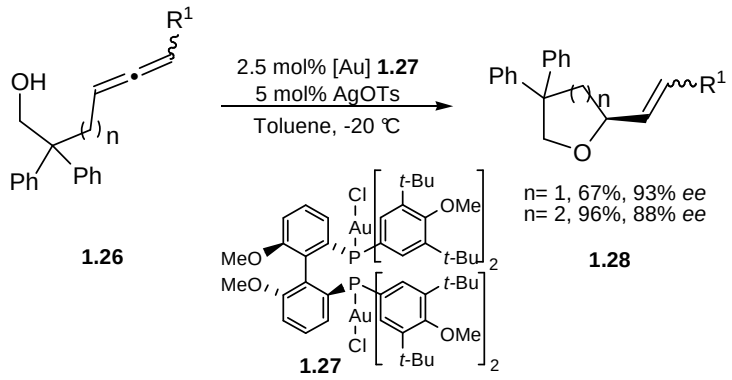
[19] B. Gockel, N. Krause, *Org. Lett.* **2006**, *8*, 4485–4488.

[20] Z. Zhang, C. Liu, R. E. Kinder, X. Han, H. Qian, R. A. Widenhoefer, *J. Am. Chem. Soc.* **2006**, *128*, 9066–9073.



Scheme 1.7. Gold(I)-catalyzed intramolecular hydroalkoxylation of γ- or δ-hydroxyallenes.

In 2007, Widenhoefer *et al*. also reported gold(I)-catalyzed intramolecular enantioselective hydroalkoxylations of allenes **1.26** for the synthesis of optically active tetrahydrofuran and tetrahydropyran derivatives **1.28** with high *ee*'s at -20 °C. This is the first example of catalytic enantioselective hydroalkoxylation of allenes catalyzed by chiral gold catalysts (Scheme 1.8).[21]

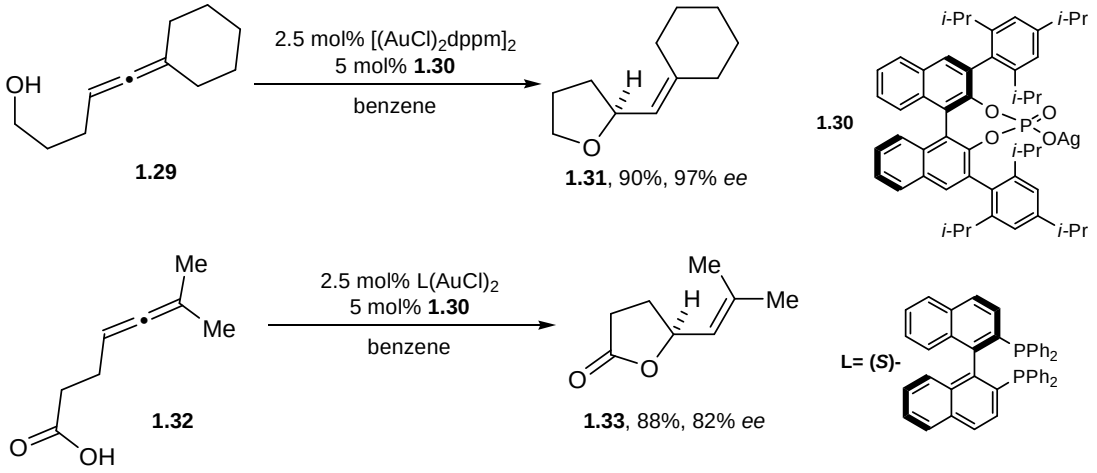


Scheme 1.8. Gold(I)-catalyzed intramolecular enantioselective hydroalkoxylation of γ- or δ-hydroxyallenes.

Toste *et al*. then reported that the use of chiral counterions, rather than chiral neutral ligands, could provide high enantioselectivity in intramolecular hydroalkoxylation of allenes.[22] The dinuclear gold complex bearing the bis(diphenylphosphinomethane) ligand (dppm) with a chiral Binol-derived phosphoric acid counterion proved as a most favourable system and provided tetrahydrofuran **1.29** from **1.31** in 90% yield and 97% *ee*.

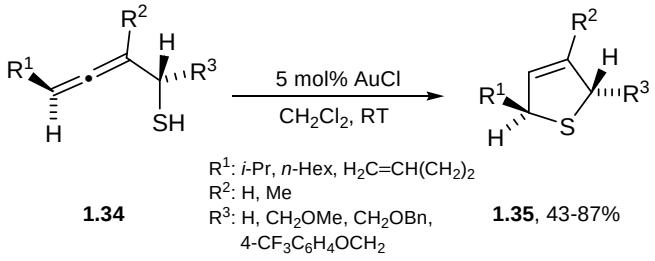
[21] Z. Zhang, R. A. Widenhoefer, *Angew. Chem.* **2007**, *119*, 287–289; *Angew. Chem. Int. Ed.* **2007**, *46*, 283–285.
[22] G. L. Hamilton, E. J. Kang, M. Mba, F. D. Toste, *Science* **2007**, *317*, 496–499.

When applying the chiral counterion strategy to the enantioselective hydrocarboxylation of allenes, neither chiral phosphine ligands nor chiral organophosphate counterions provided high enantioselectivity except the use of both chiral components together in the cyclization of **1.32** to γ-lactone **1.33** (Scheme 1.9).[22]



Scheme 1.9. Chiral counterion strategy in hydroalkoxylation and hydrocarboxylation of allenes.

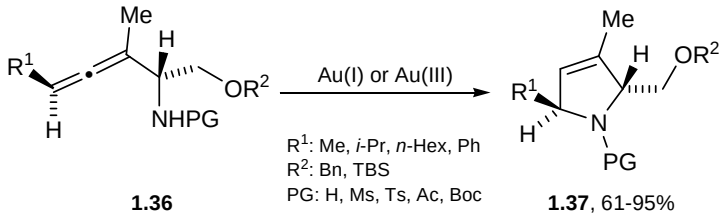
Krause *et al*. discovered the highly efficient synthesis of 2,5-dihydrothiophenes **1.35** by stereoselective cycloisomerization of α-thioallenes **1.34**, which is the first example of a gold-catalyzed carbon–sulfur bond formation. Both gold(I) and gold(III) salts can be employed as the precatalyst, with AuCl and AuI giving the highest yields. However, coordination of the gold catalyst to the sulfur atom of the α-thioallenes is probably more prominent than its coordination to the other heteroatoms, causing a lower reactivity (Scheme 1.10).[23]



Scheme 1.10. Cycloisomerization of α-thioallenes to 2,5-dihydrothiophenes.

[23] N. Morita, N. Krause, *Angew. Chem.* **2006**, *118*, 1930–1933; *Angew. Chem. Int. Ed*. **2006**, *45*, 1897–1899.

Krause *et al*. also reported that gold-catalyzed 5-*endo*-*dig* cyclization of various α-aminoallenes **1.36** gave the corresponding 3-pyrrolines **1.37** in good to high chemical yields (61-95%) and full chirality transfer. The low reactivity of the intramolecular hydroamination of unprotected α-aminoallenes with $AuCl_3$ was improved by use of gold(I) halides as the precatalyst (Scheme 1.11).[24]



1.36 **1.37**, 61-95%

Scheme 1.11. Gold-catalyzed cycloisomerization of α-aminoallenes to 3-pyrrolines.

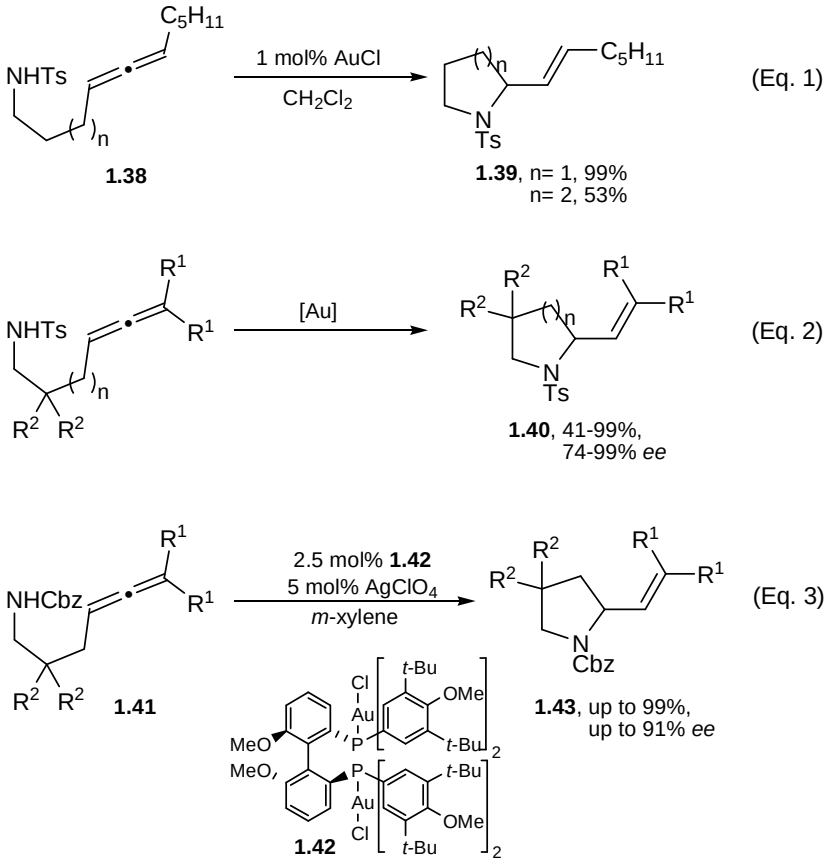
Yamamoto *et al*. have shown results concerning the Au(I)- or Au(III)-catalyzed intramolecular hydroamination of allenes **1.38** leading to pyrrolidines and piperidines **1.39** in high yields (Scheme 1.12, Eq. 1).[25a]

Toste *et al*. reported the first example of gold-catalyzed enantioselective intramolecular hydroamination of allenes for the synthesis of vinyl-substituted pyrrolidines and piperidines **1.40** with high *ee*'s. Phosphinegold(I)-bis-*p*-nitrobenzoate complexes were used as catalysts. This process was restricted to *N*-allenyl sulfonamides that have a terminally disubstituted allenyl moiety. *N*-allenyl carbamates failed to undergo hydroamination under these conditions (Scheme 1.12, Eq. 2).[25b]

Later, Widenhoefer *et al*. have demonstrated gold(I)-catalyzed enantioselective hydroaminations of *N*-allenyl carbamates with a wide range of allenes. Reaction of *N*-allenyl carbamate **1.41** with a catalytic 1:2 mixture of **1.42** and $AgClO_4$ in *m*-xylene at -40 °C for 24 h led to the formation of 2-vinylpyrrolidine **1.43** in 80-99% yield with 34-91% *ee*. Both the enantio- and diastereoselectivity were sensitive to substitution on the alkyl chain (Scheme 1.12, Eq. 3).[25c]

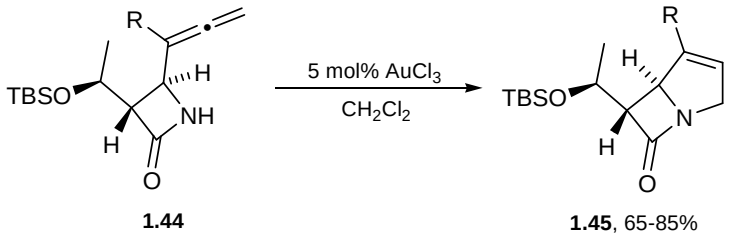
[24] a) N. Morita, N. Krause, *Org. Lett.* **2004**, *6*, 4121–4123; b) N. Morita, N. Krause, *Eur. J. Org. Chem.* **2006**, 4634–4641.

[25] a) N. T. Patil, L. M. Lutete, N. Nishina, Y. Yamamoto, *Tetrahedron Lett.* **2006**, 47, 4749–4751; b) R. L. La Londe, B. D. Sherry, E. J. Kang, F. D. Toste, *J. Am. Chem. Soc.* **2007**, *129*, 2452–2453; c) Z. Zhang, C. F. Bender, R. A.Widenhoefer, *Org. Lett.* **2007**, *9*, 2887–2889.



Scheme 1.12. Gold-catalyzed intramolecular hydroamination of allenes.

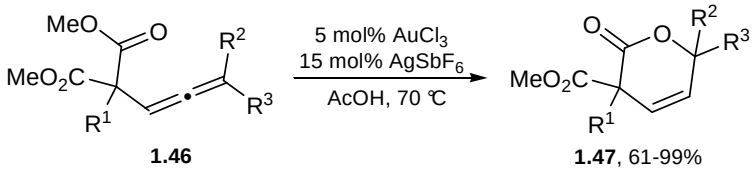
Lee *et al*. showed that the gold(III)-catalyzed intramolecular hydroamination of 4-allenyl-2-azetidinones **1.44** in CH_2Cl_2 afford the bicyclic β-lactam products **1.45** in 65-85% yield (Scheme 1.13).[26]



Scheme 1.13. $AuCl_3$-catalyzed cyclization of 4-allenyl-2-azetidinones.

[26] P. H. Lee, H. Kim, K. Lee, M. Kim, K. Noh, H. Kim, D. Seomoon, *Angew. Chem.* **2005**, *117*, 1874–1877; *Angew. Chem. Int. Ed*. **2005**, *44*, 1840–1843.

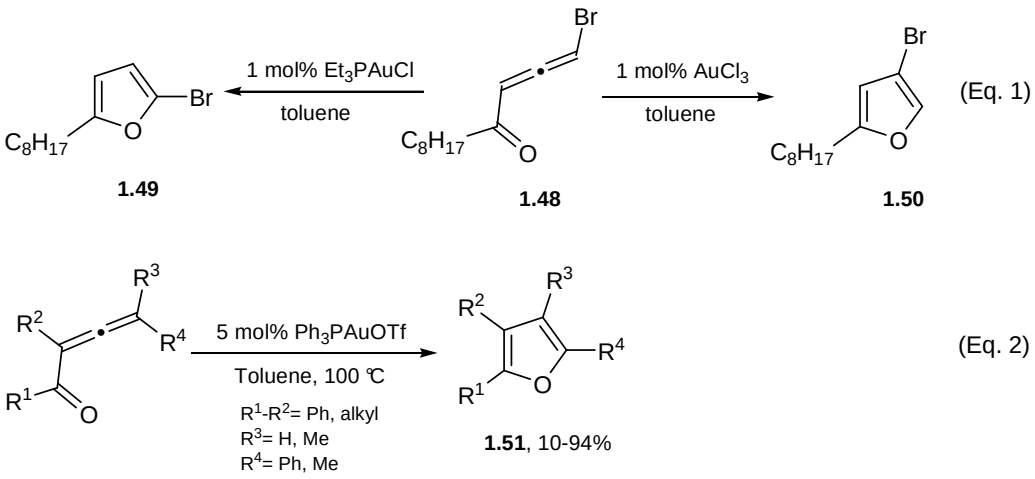
Bäckvall *et al*. developed the cyclization of allene-substituted malonates **1.46** by the intramolecular hydrocarboxylation of allenes leading to the corresponding β,γ-unsaturated δ-lactones **1.47** in 61-99% yields (Scheme 1.14).[27]



1.46 **1.47**, 61-99%

Scheme 1.14. Gold-catalyzed formation of β,γ-unsaturated δ-lactones.

In 2005, Gevorgyan *et al*. reported the cyclization of haloallenyl ketone **1.48** with divergent product distributions favouring either **1.49** or **1.50** depending upon the oxidation state of the Au precatalyst (Scheme 1.15, Eq. 1). Substrates can contain iodide, bromide, or even chloride to a lesser extent, providing yields ranging from 48-97%. They also found if the halogen is replaced with two alkyl groups, an unprecedented 1,2-alkyl shift is taking place, but harsher reaction conditions are necessary to obtain the multi-substituted furans **1.51** in 10-94% yield (Scheme 1.15, Eq. 2). [28]



1.49 **1.48** **1.50**

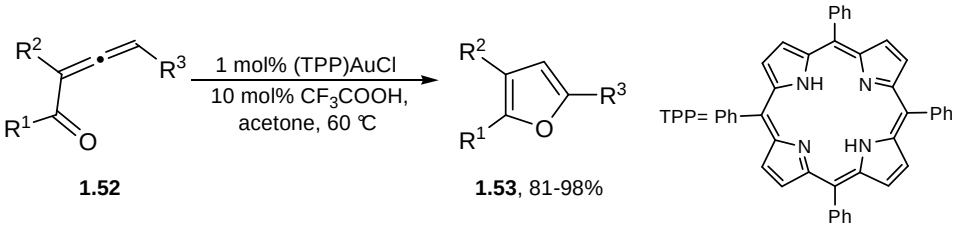
1.51, 10-94%

Scheme 1.15. Gold-catalyzed synthesis of halofurans and multi-substituted furans.

[27] J. Piera, P. Krumlinde, D. Strubing, J. E. Bäckvall, *Org. Lett.* **2007**, *9*, 2235–2237.

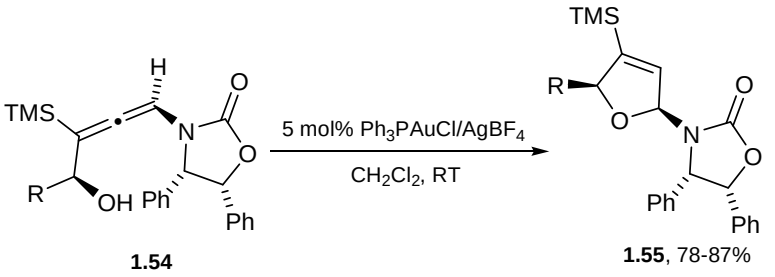
[28] a) A. W. Sromek, M. Rubina, V. Gevorgyan, *J. Am. Chem. Soc.* **2005**, *127*, 10500–10501; b) A. S. Dudnik, V. Gevorgyan, *Angew. Chem.* **2007**, *119*, 5287–5289; *Angew. Chem. Int. Ed.* **2007**, *46*, 5195–5197.

Che *et al*. reported the gold(III) porphyrin-catalyzed cycloisomerization of allenones **1.52** to the corresponding furans **1.53** in good to excellent yields (81-98%). The Au(III) catalyst was recycled ten times with TON up to 8300 (Scheme 1.16).[29]



Scheme 1.16. (TPP)AuCl-catalyzed cycloisomerization of allenones.

Hegedus *et al*. showed efficient gold-catalyzed cyclizations of chiral γ-substituted allenamides **1.54** to the highly functionalized dihydrofurans **1.55** in 78-87% yield (Scheme 1.17).[30]



Scheme 1.17. Gold-catalyzed cyclization of γ-substituted allenamides.

1.1.3. Applications of the Gold-Catalyzed Cycloisomerization of Functionalized Allenes in Total Synthesis

Gold-catalyzed reactions have already been utilized in the total synthesis of various natural products.[31] Functionalized allenes also have been utilized in recent years as highly versatile precursors for natural products by taking advantage of their inherent chirality and high reactivity in such diverse transformations as addition, cyclization/cycloaddition,

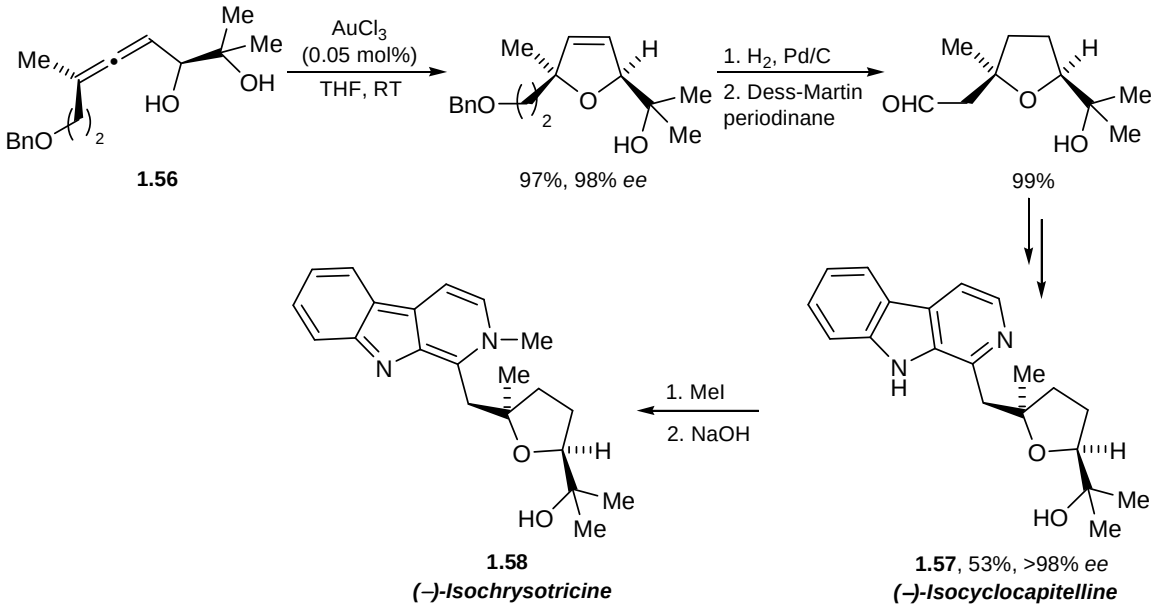
[29] C.-Y. Zhou, P. W. H. Chan, C.-M. Che, *Org. Lett.* **2006**, *8*, 325–328.

[30] C. J. T. Hyland, L. S. Hegedus, *J. Org. Chem.* **2006**, *71*, 8658–8660.

[31] a) M. D. Bachi, A. Melman, *J. Org. Chem.* **1997**, *62*, 1896–1898; b) K. Sato, N. Asao, Y. Yamamoto, *J. Org. Chem.* **2005**, *70*, 8977–8981; c) H. H. Jung, P. E. Floreancig, *J. Org. Chem.* **2007**, *72*, 7359–7366; d) Y. Li, F. Zhou, C. J. Forsyth, *Angew. Chem.* **2006**, *119*, 283–286; *Angew. Chem. Int. Ed.* **2007**, *46*, 279–282; e) X. Linghu, J. J. Kennedy-Smith, F. D. Toste, *Angew. Chem.* **2007**, *119*, 7815–7817; *Angew. Chem. Int. Ed.* **2007**, *46*, 7671–7673; f) Review: A. S. K. Hashmi, M. Rudolph, *Chem. Soc. Rev.* **2008**, *37*, 1766–1775.

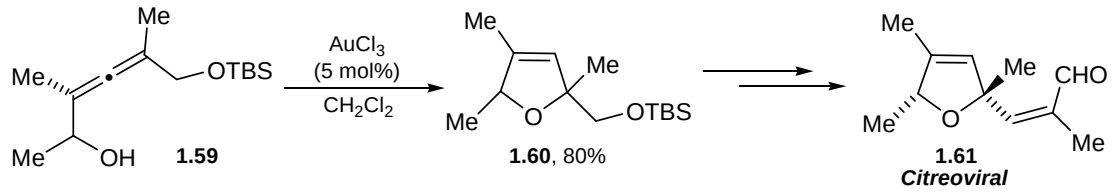
cycloisomerization, and cross-coupling reactions.[32] There are some total syntheses including the gold-catalyzed cycloisomerization of allenes which are discussed briefly in this section.

Krause *et al*. reported the first enantioselective total syntheses of the β-carboline alkaloids (–)-isochrysotricine **1.58** and (–)-isocyclocapitelline **1.57**, taking the advantage of the gold-catalyzed cycloisomerization of α-hydroxyallene **1.56**. Due to the stereo-divergent nature of the approach, both enantiomers are accessible *via* the same route (Scheme 1.18).[33]



Scheme 1.18. Total synthesis of (–)-isocyclocapitelline **1.57** and (–)-isochrysotricine **1.58**.

In 2002, Krause *et al*. reported the gold-catalyzed cycloisomerization of the α-hydroxyallene **1.59** to the corresponding dihydrofuran **1.60** which can be converted into citreoviral **1.61**, a metabolite and synthetic precursor of the mycotoxin citreoviridin (Scheme 1.19).[18b]

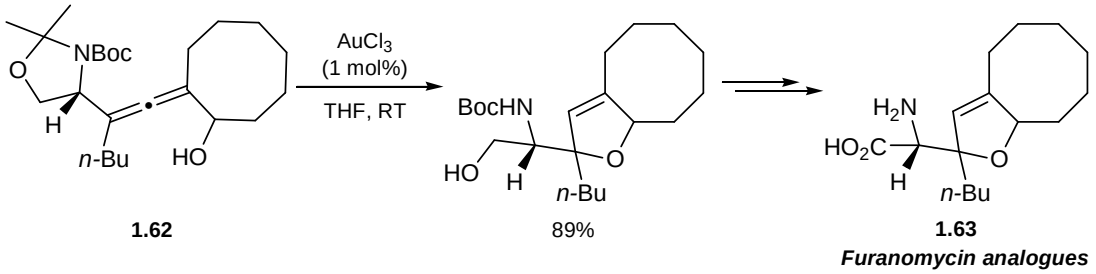


Scheme 1.19. Synthesis of racemic citreoviral **1.61** by gold-catalyzed cycloisomerization.

[32] N. Krause, A. S. K. Hashmi, *Modern Allene Chemistry*, Wiley-VCH: Weinheim, **2004**, *Vol. 2*.

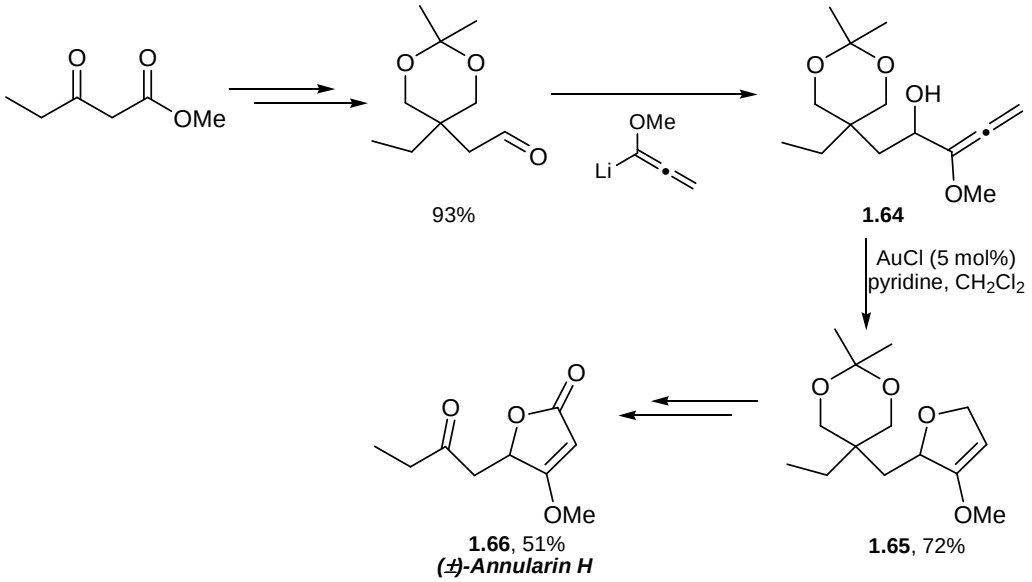
[33] a) F. Volz, N. Krause, *Org. Biomol. Chem.* **2007**, *5*, 1519–1521; b) F. Volz, S. H. Wadman, A. Hoffmann-Röder, N. Krause, *Tetrahedron* **2009**, *65*, 1902–1910.

Krause *et al*. applied the same strategy in the gold-catalyzed cyclization of α-hydroxyallenes **1.62** as the key step to synthesize novel bicyclic furanomycin analogues **1.63** as mixture of two diastereomers (Scheme 1.20).[34]



Scheme 1.20. Synthesis of furanomycin derivatives **1.63** by gold-catalyzed cycloisomerization of α-hydroxyallenes.

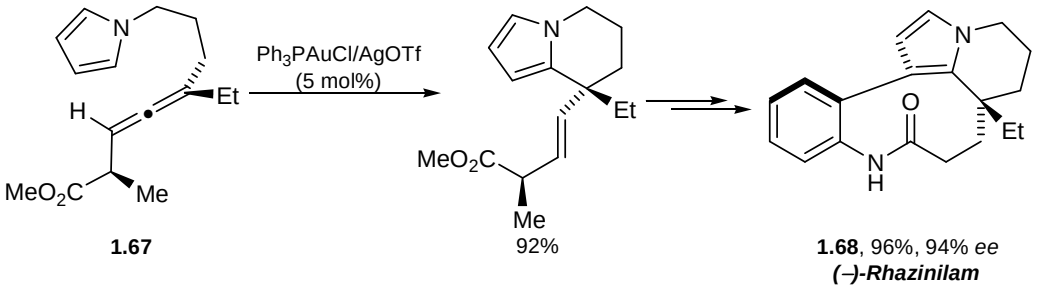
Reissig *et al*. demonstrated the utility of the 5-*endo*-cyclization of α-hydroxyallene **1.64** with AuCl/pyridine to obtain dihydrofuran **1.65**, which upon allylic oxidation and deprotection furnished the racemic natural product **1.66** with good overall efficiency (Scheme 1.21).[35]



Scheme 1.21. Gold-catalyzed total synthesis of (±)-annularin H **1.66**.

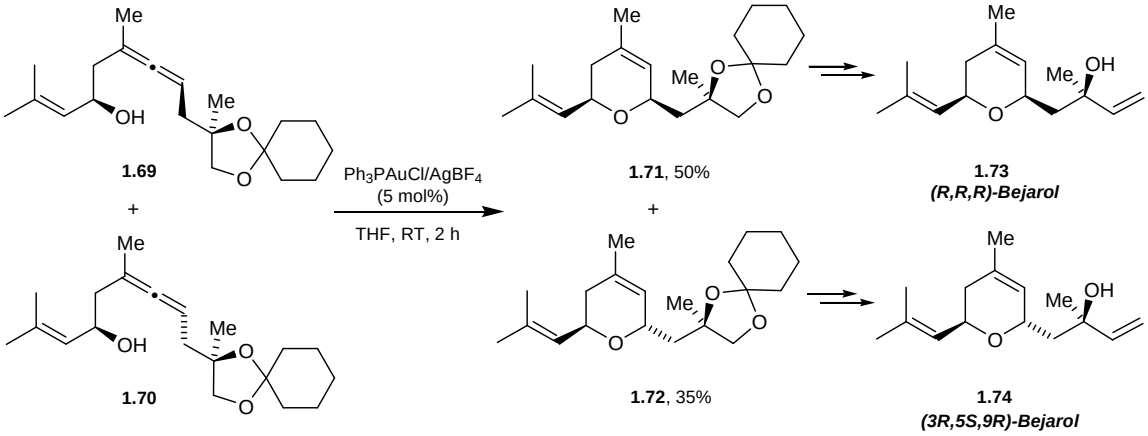
[34] J. Erdsack, N. Krause, *Synthesis* **2007**, *23*, 3741–3750.
[35] M. Brasholz, H. U. Reissig, *Synlett* **2007**, *8*, 1294–1298.

Nelson *et al*. reported an enantioselective total synthesis of (–)-rhazinilam **1.68** by utilizing a gold-catalyzed annulation of enantiomerically enriched allene **1.67** with high yield and *ee* (Scheme 1.22).[36]



Scheme 1.22. Gold-catalyzed total synthesis of (–)-rhazinilam **1.68**.

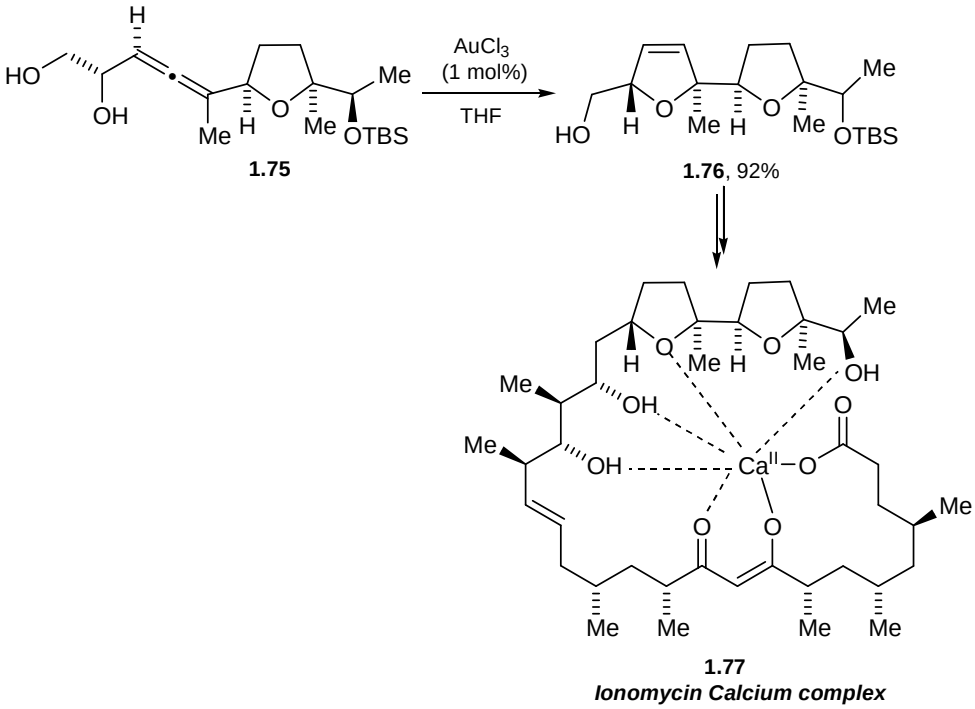
In 2009, Krause *et al*. reported the first total synthesis of (*R*,*R*,*R*)- and (3*R*,5*S*,9*R*)-bejarol **1.73**/**1.74** by application of gold-catalyzed cycloisomerization of the enantiomerically pure β-hydroxyallenes **1.69**/**1.70** to the corresponding dihydropyrans **1.71**/**1.72** as the key step (Scheme 1.23).[37]



Scheme 1.23. Total synthesis of (*R*,*R*,*R*)- and (3*R*,5*S*,9*R*)-bejarol by gold-catalyzed cycloisomerization of the β-hydroxyallenes **1.73**/**1.74**.

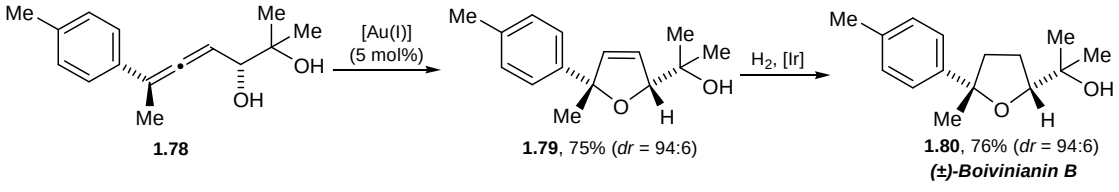
[36] Z. Liu, A. S. Wasmuth, S. G. Nelson, *J. Am. Chem. Soc.* **2006**, *128*, 10352–10353.
[37] Y. Sawama, Y. Sawama, N. Krause, *Org. Biomol. Chem.* **2008**, *6*, 3573–3579.

Kocienski *et al*. accomplished a synthesis of ionomycin calcium complex **1.77** in 33 steps from aldehyde in 0.68% overall yield. One of the noteworthy features of their approach was a highly stereoselective gold(III)-catalyzed cycloisomerization reaction of α-hydroxyallene **1.75** to 2,5-dihydrofuran **1.76** (Scheme 1.24).[38]



Scheme 1.24. Synthesis of ionomycin Calcium complex **1.77**.

Krause *et al*. and Murakami *et al*. achieved a total synthesis of (±)-boivinianin B **1.80** in a traditional multi-flask sequence with the gold-catalyzed cycloisomerization of the α-allenol **1.78** to 2,5-dihydrofuran **1.79** and subsequent the iridium-catalyzed hydrogenation (Scheme 1.25).[39]



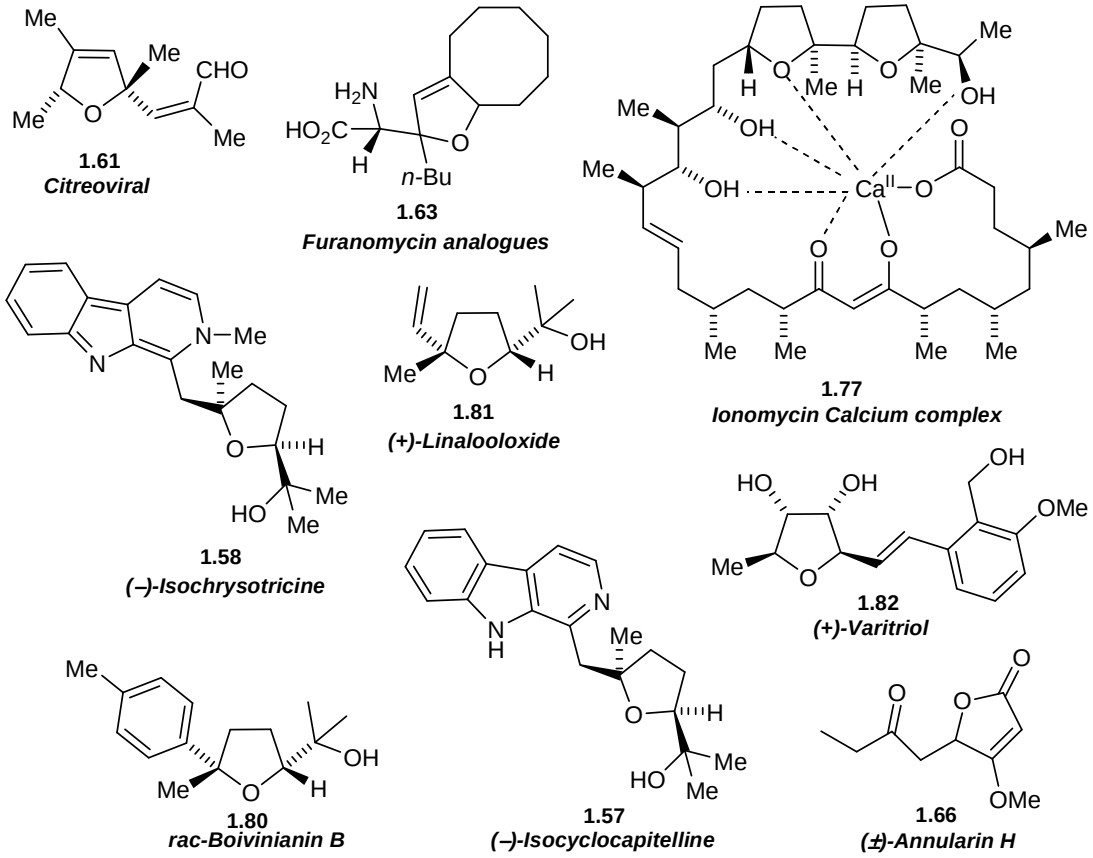
Scheme 1.25. Rhodium/Gold-catalyzed synthesis of (±)-boivinianin B **1.80**.

[38] Z. Gao, Y. Li, J. P. Cooksey, T. N. Snaddon, S. Schunk, E. M. E. Viseux, S. M. McAteer, P. J. Kocienski, *Angew. Chem.* **2009**, *121*, 5122–5125; *Angew. Chem. Int. Ed.* **2009**, *48*, 5022–5025.

[39] T. Miura, M. Shimada, P. de Mendoza, C. Deutsch, N. Krause, M. Murakami, *J. Org. Chem.* **2009**, *74*, 6050–6054.

1.2. 2,5-DIHYDROFURANS

Substituted five-membered heterocycles are a structural component of various biologically active natural or non-natural compounds. 2,5-Dihydrofurans and their derivatives bearing stereogenic centers in 2,5-positions are structural subunits that are frequent in a wide variety of natural products which find application as pharmaceuticals, flavour and fragrance compounds. They can be found in mycotoxins,[40a,b] polyether antibiotics,[40c,d] spiroketals,[40e] and even amino acids.[34]

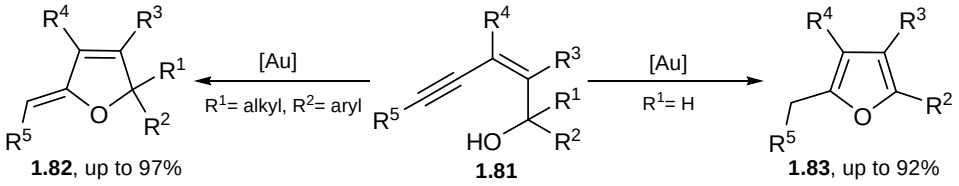


Scheme 1.26. Various natural products with 2,5-dihydrofuran building block or key step in synthesis.

[40] a) B. Franck, H.-P. Gehrken, *Angew. Chem.* **1980**, *92*, 484–486; *Angew. Chem. Int. Ed.* **1980**, *19*, 461–462; b) M. Ganguli, L. T. Burka, T. M. Harris, *J. Org. Chem.* **1984**, *49*, 3762–3766; c) T. L. B. Boivin, *Tetrahedron* **1987**, *43*, 3309–3362; d) U. Koert, M. Stein, H. Wagner, *Chem. Eur. J.* **1997**, *3*, 1170–1180; e) F. Perron, K. F. Albizati, *Chem. Rev.* **1989**, *89*, 1617–1661.

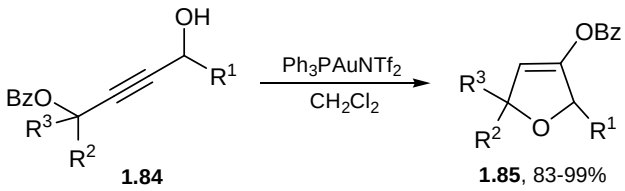
As a consequence, the development of synthetic approaches to functionalized 2,5-dihydrofurans is of major interest.[41] Transition metal-catalyzed reactions are the most attractive methods, since those reactions can construct complex molecules from readily available starting materials under mild conditions. In addition to the conventional palladium and silver catalysts,[42] gold complexes are powerful tool for the synthesis of 2,5-dihydrofuran.

Liu *et al*. reported the Au(III)- or Au(I)-catalyzed cyclization of (*Z*)-enynols **1.81**, which offers an efficient and straightforward route to highly substituted furans **1.83** or dihydrofurans **1.82** depending on the nature of the R^1 group under mild reaction conditions (Scheme 1.27).[43]



Scheme 1.27. Efficient synthesis of substituted dihydrofurans **1.82** and furans **1.83**.

Gagosz *et al*. reported the gold-catalyzed synthesis of 2,5-dihydrofurans **1.85** from substituted butynediol monobenzoates **1.84** with high yield (Scheme 1.28).[44]



Scheme 1.28. Au(I)-catalyzed synthesis of 2,5-dihydrofurans **1.85**.

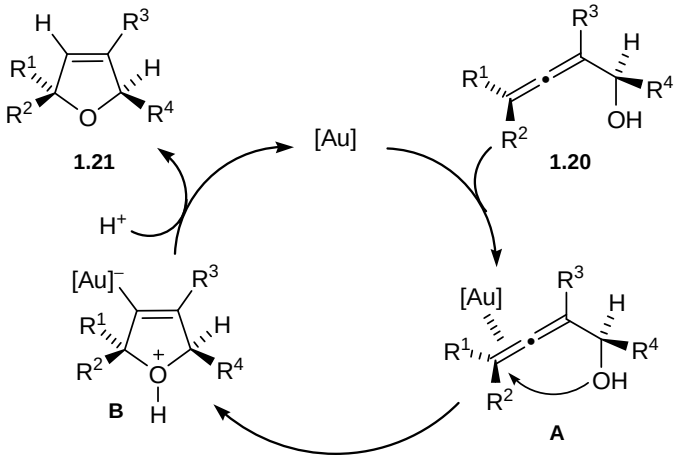
[41] Reviews: a) T. G. Kilroy, T. P. O'Sullivan, P. J. Guiry, *Eur. J. Org. Chem.* **2005**, 4929–4949; b) M. Brichacek, J. T. Njardarson, *Org. Biomol. Chem.* **2009**, *7*, 1761–1770.

[42] a) J. A. Marshall, G. S. Bartley, *J. Org. Chem.* **1994**, *59*, 7169–7171; b) J. A. Marshall, X. J. Wang, *J. Org. Chem.* **1991**, *56*, 4913–4918; c) L.-I. Olsson, A. Claesson, *Synthesis* **1979**, 743–745; d) O. Lepage, E. Kattnig, A. Fürstner, *J. Am. Chem. Soc.* **2004**, *126*, 15970–15971; e) A. Fürstner, E. Kattnig, O. Lepage, *J. Am. Chem. Soc.* **2006**, *128*, 9194–9204; f) M. P. Van Brundt, R. F. Standaert, *Org. Lett.* **2000**, *2*, 705–708.

[43] Y. Liu, F. Song, Z. Song, M. Liu, B. Yan, *Org. Lett.* **2005,** *7*, 5409–5412.

[44] A. Buzas, F. Istrate, F. Gagosz, *Org. Lett*, **2006**, *8*, 1957–1959.

Among the established methods, the cyclization of α–hydroxyallenes to 2,5-dihydrofuran with defined absolute/relative configurations is valuable for the total synthesis of the natural products. The gold-catalyzed synthesis of 2,5-dihydrofurans from α–hydroxyallenes and their role in the total synthesis of the natural products were shown in the previous section.[18,30,33,34,35,38,39]



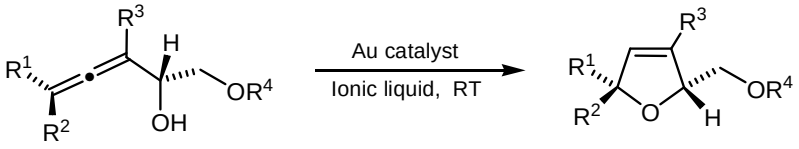
Scheme 1.29. Proposed mechanism for the gold-catalyzed cycloisomerization of α-hydroxyallenes.

The cycloisomerization for the α-hydroxyallenes **1.20** to the 2,5-dihydrofurans **1.21** can be explained with the proposed mechanism shown in Scheme 1.29. By the coordination of the gold catalyst to the terminal double bond of the allene **1.20**, the formation of the π-complex intermediate **A** is formed. Then the complex **A** undergoes an intramolecular nucleophilic attack by the heteroatom present in the molecule forming a σ-gold species **B**. Subsequent protodemetalation of the latter provides the heterocyclic product **1.21** and regenerates the gold catalyst.

1.3. DEFINITION OF THE RESEARCH PROBLEM

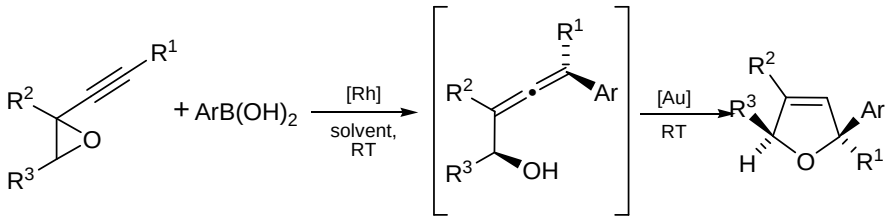
An overview of the literature reveals that, since highly substituted dihydrofurans are useful and versatile synthetic intermediates for access to natural and non-natural compounds, the development of synthetic routes that allow the facile assembly of such substituted dihydrofurans under mild conditions still remains an important objective. As a consequence, the development of practical synthetic approaches to access these target molecules is of our major interest.

We propose two efficient and economical approaches to synthesize 2,5-dihydrofurans. The first approach uses ionic liquids as solvent which affords inexpensive, recyclable and environmentally benign catalyst systems. Our goal is to establish a stable and reactive catalytic system that enables several cycles in the gold-catalyzed cycloisomerization of α-hydroxyallenes to 2,5-dihydrofurans with high chirality transfer (Scheme 1.30).



Scheme 1.30. Proposal: Gold-catalyzed synthesis of 2,5-dihydrofurans in an ionic liquids.

In the second approach, we surmised that propargylic oxiranes might be valuable precursors for the synthesis of 2,5-dihydrofuran through the sequence of a rhodium-catalyzed allenol formation and gold-catalyzed cycloisomerization (Scheme 1.31). This approach would be especially advantageous with regard to the time, yield loss associated with isolation and purification of intermediates in traditional multi-flask processes.



Scheme 1.31. Proposal: One-pot rhodium/gold-catalysis sequence.

CHAPTER 2

Gold-Catalyzed Synthesis of 2,5-Dihydrofurans in Ionic Liquids

2.1. INTRODUCTION

Homogeneous catalysts, which exist in the same phase as the reactants, offer a number of important advantages over their heterogeneous counterparts. All catalytic sites are accessible because the catalyst is usually a dissolved metal complex delivering high selectivities. Despite these advantages, compared with heterogeneous catalysts, the efficient recovery and reuse of the expensive metal catalyst require additional process steps, unavoidable loss of valuable catalyst and formation waste. From the industrial point of view, recycling of the catalyst is often fundamental for a process to be economically feasible and it is important to obtain the product free from traces of the catalyst. These are probably the main reasons that why industry often prefers recyclable catalysts. There are various concepts for catalyst recycling which are shown below to overcome this problem.[1]

❖ ***Thermal and chemical methods***: After performing the catalytic reaction in a single phase, the product is distilled off without decomposition of the catalysts. Examples are the Wacker–Hoechst process (the palladium/copper catalyzed oxidation of ethylene to acetaldehyde) or the Monsanto processes (the rhodium/iridium-catalyzed carbonylation of methanol to acetic acid).

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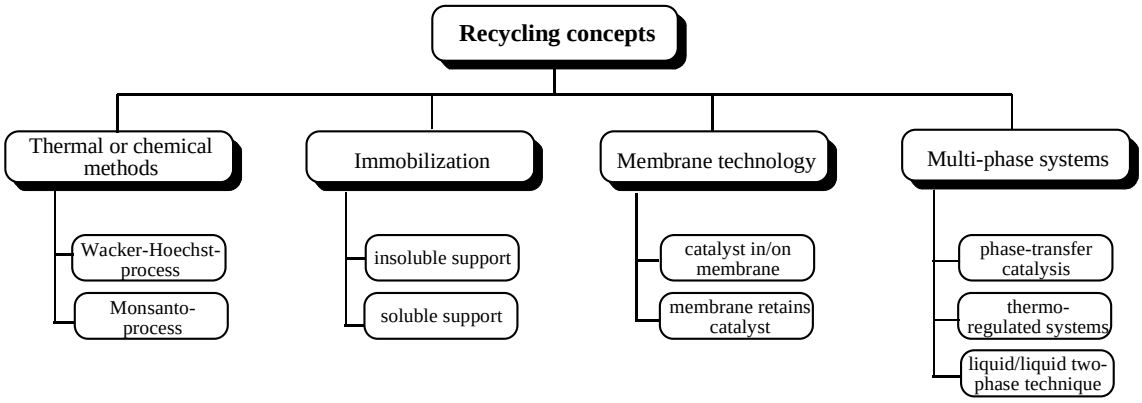
[1] a) W. Keim, *Green Chem.* **2003**, *5*, 105–111; b) D. J. Cole-Hamilton, *Science* **2003**, *299*, 1702–1706; c) A. Behr, C. Fängewisch, *Chem. Eng. Technol.* **2002**, *25*, 143–147; d) B. Cornils, W. A. Herrmann, *Applied Homogeneous Catalysis with Organometallic Compounds*, Wiley-VCH, Weinheim, **2002**, *Vol. 2*.

❖ ***Catalyst immobilization***: The catalyst is immobilized on soluble or insoluble support, and the separation is carried out by a filtration technique. Homogeneous catalysts can be immobilized onto solid materials such as inorganic oxides (often silica or zeolite) or polymers via covalent binding, adsorption, ion pair formation, or entrapment (ship in a bottle concept). The main problem is leaching of the metal and/or the ligand and activity loss of the catalyst. Polymers such as polyamides or polyglycerols which are soluble in the reaction medium can be used as supports to bind the catalyst.[2]



Scheme 2.1. Strategies to recycle catalyst.

❖ ***Membrane technology***: Depending on the size of the particles that are retained by the membrane, filtration processes can be classified into micro-, ultra- and nanofiltration and reversed osmosis. Mostly ultra- or nanofiltration is used for catalyst separation and recycling. Nanofiltration membranes rely on the difference in size between a simple organic molecule and a metal complex. They still allow solvent and product molecules to pass through, but retain the organometallic catalyst. The advantage of these systems is that optimized catalysts can be used without modification. There are two types of membranes used: organic (polymer) membranes and inorganic (ceramic) membranes.[3]

❖ ***Multi-phase systems***: The principle of multi-phase systems states that the catalyst is dissolved in one phase and the product is located in the other phase to enable the easy recovery of the catalyst. The multi-phase system can consist of two immiscible organic liquids and one phase can also be as water, fluorinated solvents, supercritical CO_2, supercritical solvents or ionic liquids.

[2] a) M. G. L. Petrucci, A. K. Kakkar, *Adv. Mater.* **1996**, *8*, 251–253; b) D. Astruc, F. Lu, J. R. Aranzaes, *Angew. Chem.* **2005**, *117*, 8062–8083; *Angew. Chem. Int. Ed.* **2005**, *44*, 7852–7872; c) P. McMorn, G. J. Hutchings, *Chem. Soc. Rev.* **2004**, *33*, 108–122.

[3] C. Müller, M. G. Nijkamp, D. Vogt, *Eur. J. Inorg. Chem.* **2005**, 4011–4021.

An alternative to multi-phase systems are thermo-regulated systems in which the reaction is carried out in monophasic conditions (*e.g.* one liquid phase) and afterwards the mixture is cooled and a phase separation occurs forming two liquid phases in which the product and catalyst exist in different phases.[4]

There are several methods which are generally called biphasic systems. Only selected ones are explained below briefly, to perform the reaction according to multi-phase system principle.[1a]

a) The catalyst is dissolved in the solvent and the products formed during the catalysis float on top of the solvent because of their insolubility in this solvent and can be decanted and the catalyst is recycled.

b) The reaction is carried out in a solvent and after the reaction; another solvent which is immiscible with the reaction medium is added. The product is soluble in the added solvent and is easily extracted from reaction medium. The catalyst which remains in the reaction medium can be recycled for the next runs.

c) There are two immiscible solvents in the reaction medium. The catalyst stays in a one solvent and the product formed during the catalysis is removed from the catalyst phase to the other phase. The phases are separated and the catalyst solution is recycled. The product is distilled from the second solvent and that pure solvent is brought back into the reaction medium.

Multi-phase systems are an efficient method to combine the advantages of homogeneous and heterogeneous system. Especially, biphasic systems are more favourable in industrial scale because they offer a wide range of applications and easy technical operations.

A number of solutions to the problem of separation of catalysts from products in catalytic reactions have been demonstrated. All of the processes have some disadvantages, such as catalyst, solvent, ligand or process may be expensive, and catalyst leaching may be high, and the environmental effect of some solvents may be severe.

In the 21st century, one of the new trends in recyclability using multi-phase systems are ionic liquids as catalyst residence. More detailed explanations are given in the following section.

[4] M. J. Muldoon, *Dalton Trans.* **2010**, *39*, 337–348.

2.1.1. Ionic Liquids

Ionic liquids are class of salts in which the ions are poorly coordinated so that they are liquid below 100 °C, or even at RT (room temperature ionic liquids, RTIL's) and in some cases even below 0 °C. Ionic liquids may be distinguished from classical molten salts by their specific properties. While a molten salt is generally thought to refer to a high-melting, highly viscous and very corrosive medium, ionic liquids are liquids already at low temperatures and have relatively low viscosity.[5]

The history of ionic liquids goes back to 1914. The first research dealt with the synthesis of ethylammonium nitrate and was reported by Walden.[6] This salt is liquid at room temperature but at that time this did not arouse great interest. In 1948, Hurley and Wier showed that the molten salts mainly ionic liquids with chloroaluminate ions were major media for electrochemical studies.[7] The use of salts based on organic cations was quite limited in this period.

In 1967, Swain *et al*. described the use of tetra-*n*-hexylammonium benzoate as a solvent for kinetic studies and electrochemical reactions.[8]

Room temperature chloroaluminate ionic liquids prompted interest with the rediscovery of this area by the groups of Osteryoung and Wilkes in the 1970s.[9,10] In the early 1980s, chloroaluminate ionic liquids began to be used by the groups of Hussey and Seddon as polar solvents for transition metal complexes for electrochemical and spectroscopic experiments.[11]

The first report on the use of this type of low melting ionic liquids as new reaction media and catalyst for organic synthesis was at the end of 1980s with regard to Friedel–Crafts reactions.[12]

[5] a) P. Wasserscheid, T. Welton, *Ionic Liquids in Synthesis*, 2nd ed., Wiley-VCH, Weinheim, **2008**, *Vol. 1*, pp. 1–7; b) K. R. Seddon, *Kinet. Catal., Engl. Transl.* **1996**, *37*, 693–697; c) K. R. Seddon, *J. Chem. Biotechnol*. **1997**, *68*, 351–356.

[6] P. Walden, *Bull. Acad. Imper. Sci. de St.-Petersburg* **1914**, 405–422.

[7] F. H. Hurley, T. P. Weir Jr., *J. Electrochem. Soc.* **1951**, *98*, 207–212.

[8] C. G. Swain, A. Ohno, D. K. Roe, R. Brown, T. Maugh II, *J. Am. Chem. Soc.* **1967**, *89*, 2648–2649.

[9] J. Robinson, R. A. Osteryoung, *J. Am. Chem. Soc.* **1979**, *101*, 323–327.

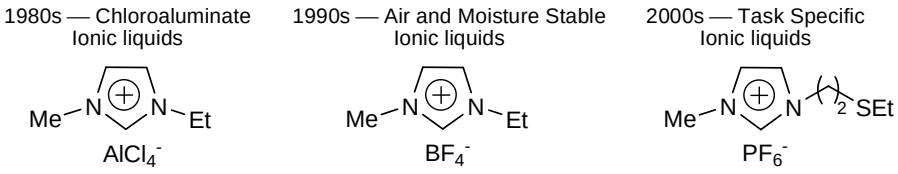
[10] J. S. Wilkes, J. A. Levisky, R. A. Wilson, C. L. Hussey, *Inorg. Chem.* **1982**, *21*, 1263–1264.

[11] a) T. B. Scheffler, C. L. Hussey, K. R. Seddon, C. M. Kear, P. D. Armitage, *Inorg. Chem.* **1983**, *22*, 2099–2100; b) D. Appleby, C. L. Hussey, K. R. Seddon, J. E. Turp, *Nature* **1986**, *323*, 614–616.

[12] J. A. Boon, J. A. Levisky, J. L. Pflug, J. S. Wilkes, *J. Org. Chem.* **1986**, *51*, 480–483.

The use of ionic liquids as solvent for homogeneous transition metal catalysts began in early 1990s by Chauvin *et al*. and Wilkes *et al*. Chauvin and coworkers reported the dimerization of propene by nickel complexes dissolved in weakly acidic chloroaluminate melts.[13] This Ziegler-Natta type reaction occurs in a typical biphasic catalytic system where the products are easily separated from the reaction mixture by simple decantation and the recovered ionic catalyst solution can be reused several times without any significant changes in catalytic performance.

Osteryoung *et al*. also used weekly acidic chloroaluminate melts in the polymerization of ethylene by Ziegler-Natta catalysts.[14] The main problem with the ionic liquids based on chloroaluminate anions, however, remained their sensitivity to water and oxygen.



Scheme 2.2. Development of ionic liquids.

A major step was achieved in 1992 when Wilkes *et al*. reported ionic liquids based on dialkylimidazolium cations (*e.g.* [EMIM][BF_4]) that solved problems associated with hydrolysis.[15] They synthesized air- and moisture-stable imidazolium salts based on anions such as BF_4^- and PF_6^- which had been successful in the rhodium-catalyzed hydrogenation of olefins.[16] These ionic liquids have since found increasing applications as reaction medium for various kinds of organic reactions.

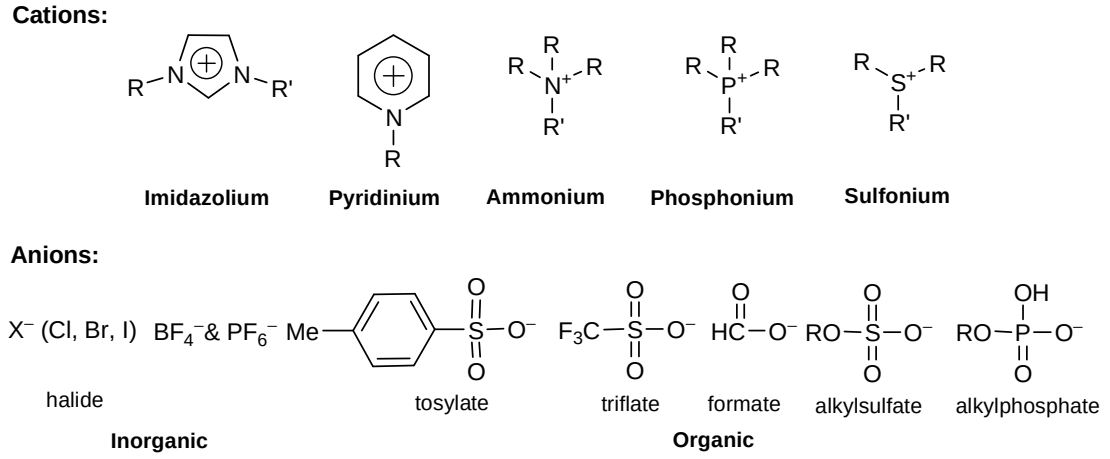
In the year 2000, the new concept of "task-specific" ionic liquids was introduced by Davis *et al*.[17] In these ionic liquids the anion, cation, or both covalently incorporate a functional group as a part of the ion structure. This allows not only control over processing of the reaction but also control over solvent-solute interactions. Since this time, the number of different ionic liquids with variable applications has expanded enormously.

[13] Y. Chauvin, B. Gilbert, I. Guibard, *J. Chem. Soc., Chem. Commun.* **1990**, 1715–1716.
[14] R. T. Carlin, R. A. Osteryoung, *J. Mol. Catal.* **1990**, *63*, 125–129.
[15] J. S. Wilkes, M. J. Zaworotko, *J. Chem. Soc., Chem. Commun.* **1992**, 965–967.
[16] A. E. Visser, R. P. Swatloski, R. D. Rogers, *Green Chem.* **2000**, *2*, 1–4.
[17] J. H. Davis, *Chem. Lett.* **2004**, *33*, 1072–1077.

2.1.1.1. Properties and Applications of Ionic Liquids

The cations of ionic liquids are generally bulky with low symmetry, *e.g.* tetraalkylammonium, tetraalkylphosphonium, *N*-alkylpyridinium, 1,3-dialkylimidazolium or trialkylsulfonium cations. Concerning the anions, they can be classified in two parts the first gives polynuclear anions, *e.g.* $Al_2Cl_7^-$, $Al_3Cl_{10}^-$. These anions are formed by the reaction of the corresponding Lewis acid, *e.g.* $AlCl_3$ with the mononuclear anion, *e.g.* $AlCl_4^-$. They are particularly air- and water-sensitive. The second class of anions corresponds to mononuclear anions which lead to neutral ionic liquids, *e.g.* BF_4^-, PF_6^-, triflate, etc. They are the most commonly used ionic liquids because of their air- and moisture-stability (Scheme 2.3).[18]

In order to be liquid at room temperature, the cation should preferably be unsymmetrical, *e.g.* R and R′ should be different alkyl groups in the dialkylimidazolium cation. It was demonstrated that water content, density, viscosity, surface tension, melting point, and thermal stability are affected by changes in alkyl chain length of the imidazolium cations and by the nature of the anions.[19]



Scheme 2.3. Most used cations and anions in ionic liquids.

Ionic liquids are fascinating new materials with unique sets of properties which are listed below.

- ❖ Remarkable dissolution properties for organic and inorganic materials,
- ❖ Liquid over a wide temperature range,
- ❖ Increase in reaction rates, selectivities and yields,

[18] J. S. Wilkes, *J. Mol. Catal. A: Chemical* **2004**, *214*, 11–17.
[19] P. Wasserscheid, W. Keim, *Angew. Chem.* **2000**, *111*, 3926–3945; *Angew. Chem. Int. Ed.* **2000**, *39*, 3772–3789.

❖ Substitutes for Volatile Organic Compounds (VOC) in chemical processes or extractions,

❖ High electrochemical stability,

❖ Non-flammable and non-explosive,

❖ High thermal stability,

❖ Non-volatile.

Ionic liquids (ILs) have attracted a great deal of scientific attention during the last decade due to their unique physical and chemical properties. Ultimately, the possible combinations of organic cations and anions place chemists in the position to design and fine-tune physical and chemical properties by introducing or combining structural motifs.

Potential and current applications of ionic liquids are in the fields of[20]

❖ Lubricant and Additives: lubricants and fuel additives,

❖ Electro elastic materials: artificial muscles and robotics,

❖ Analytics: MALDI-TOF Matrices, GC-head-space-solvents,

❖ Electrolytes: fuel cells, sensors, batteries, supercaps, metal finishing, coatings,

❖ Heat storage: thermal fluids,

❖ Liquid crystals: displays,

❖ Separation: gas separations, extractive distillation, extraction, membranes,

❖ Solvents: bio-catalysis, polymerization, nano-particle synthesis, organic reactions and catalysis.

In all these applications, the unique properties of the ionic liquids improve product performance or process efficiency. However, for all these applications it is of critical importance that the ionic liquid does not decompose under the operating conditions.

In particular, their exceptionally low vapor pressure at ambient temperatures makes them interesting substitutes for many applications for which the volatility of traditional organic solvents causes problems. Additionally, ionic liquids (ILs) have attracted increasing interest recently in the context of green organic synthesis because of their unique chemical and physical properties of non-volatility, non-flammability, thermal stability, and controlled miscibility. They continue to show their significant role in controlling reactions as solvent or catalyst.[21]

[20] a) R. D. Rogers, K. R. Seddon, *Ionic Liquids as Green Solvents, Progress and Prospects*, Oxford University Press, USA, Washington, DC, **2003**; b) N. V. Plechkova, K. R. Seddon, *Chem. Soc. Rev.* **2008**, *37*, 123–150.

[21] a) R. Sheldon, *Chem. Commun.* **2001**, 2399–2407; b) H. Olivier-Bourbigou, L. Magna, *J. Mol. Catal. A: Chemical* **2002**, *182–183*, 419–437.

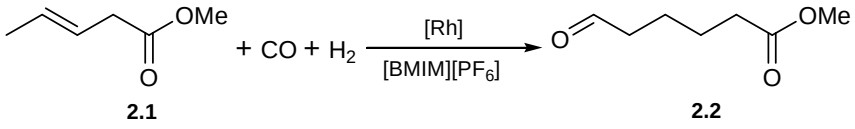
2.1.2. Ionic Liquids as Solvent for Transition Metal-Catalyzed Reactions

Ionic liquids have been shown to have a significant advantage over conventional solvents for homogeneously catalyzed reactions. Ionic liquids as reaction medium are appropriate to the isolation of soluble reaction products.[22,23]

There are various options for catalysis in and/or by ionic liquids which are defined by selected examples.

a) Monophasic systems in which the catalyst and substrate are dissolved in the ionic liquid.

Volatile products can be separated by distillation and non-volatile products can be separated by solvent extraction. Wasserscheid *et al*. reported the rhodium-catalyzed hydroformylation of methylpent-3-enoate **2.1** in [BMIM][PF_6]. The formation of the desired product requires an isomerisation step followed by hydroformylation at the end-position. The linear aldehyde product **2.2** was removed by distillation (0.2 mbar/110 °C) and the ionic liquid was recycled ten times without significant loss in activity (Scheme 2.4).[24]



2.1 **2.2**

Scheme 2.4. Example for monophasic system using an ionic liquid.

b) Monophasic systems in which the ionic liquid acts as both the solvent and the catalyst.

Ionic liquids based on Lewis acids such as $AlCl_3$ have been applied to a number of Lewis acid-catalyzed organic transformations, for example Friedel–Crafts reactions.[25] Wilkes *et al*. reported that ionic liquids derived from the reaction of [EMIM][Cl] with $AlCl_3$ show Lewis acidity depending on the molar ratio of the reactants. For example, [EMIM][Al_2Cl_7] is

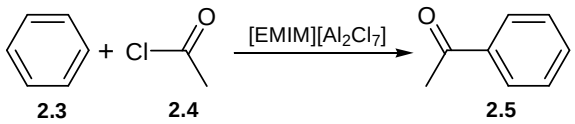
[22] Reviews: a) J. Dupont, R. F. de Souza, P. A. Z. Suarez, *Chem. Rev.* **2002**, *102*, 3667–3692; b) V. I. Parvulescu, C. Hardacre, *Chem Rev.* **2007**, *107*, 2615–2665.

[23] a) L. A. Blanchard, D. Hancu, E. J. Beckman, J. F. Brennecke, *Nature* **1999**, *399*, 28–29; b) S. Fustero, B. Pina, M. Garcia de la Torre, A. Navarro, C. Ramirez de Arellano, A. Simon, *Org. Lett.* **1999**, *1*, 977–980; c) T. Welton, *Chem. Rev.* **1999**, *99*, 2071–2083; d) M. Deetlefs, H. G. Raubenheimer, M. W. Esterhuysen, *Catalysis Today*, **2002**, *72*, 29–41; e) C. M. Gordon *Appl. Catal. A: General* **2001**, *222*, 101–117.

[24] W. Keim, D. Vogt, H. Waffenschmidt, P. Wasserscheid, *J. Catal.* **1999**, *186*, 481–484.

[25] C. J. Adams, M. J. Earle, K. R. Seddon, *Chem. Commun.* **1998**, 2097–2098.

strongly Lewis acidic and with a mixture of benzene **2.3** and acetyl chloride **2.4** afforded complete conversion to acetophenone **2.5** in 5 minutes at room temperature (Scheme 2.5).[26]

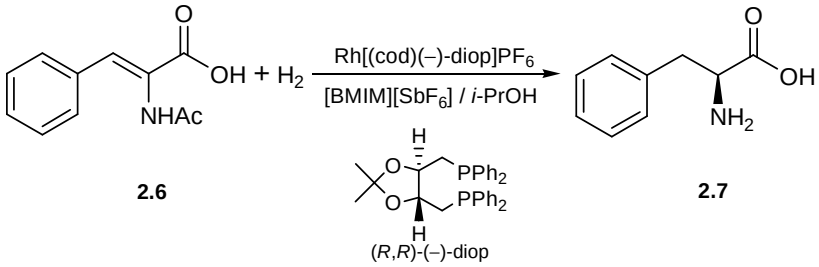


Scheme 2.5. Example for an ionic liquid acting both as catalyst and solvent.

c) Biphasic systems in which the catalyst exists in the ionic liquid and the substrate/product in a second phase or vice versa.

These biphasic systems might combine the advantages of both homogeneous (greater catalyst efficiency and mild reaction conditions) and heterogeneous (ease of catalyst recycling and separation of the products) catalysis. The reaction can take place in one (or both) of the phases or at the interface. In most cases, the products/substrates are simply removed from the reaction mixture by decantation.

Chauvin *et al*. reported that $[Rh(cod)_2(diop)]PF_6$ catalyzed the enantioselective hydrogenation of α-acetamidocinnamic acid **2.6** in a biphasic $[BMIM][SbF_6]$–isopropyl alcohol system to (*S*)-phenylalanine **2.7** with 64% *ee*. The product, contained in the isopropyl alcohol, could be separated quantitatively and the recovered ionic liquid, containing the catalyst, was reused several times (Scheme 2.6).[27]



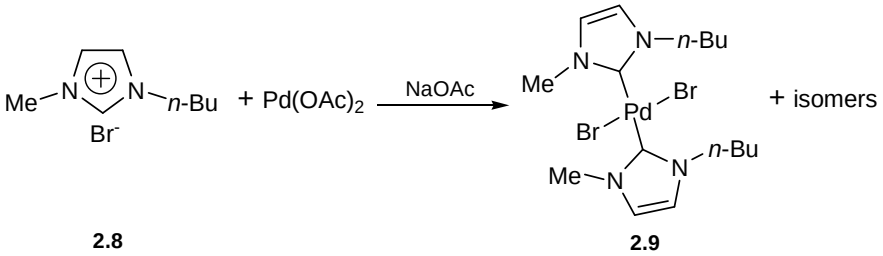
Scheme 2.6. Example for biphasic system in an ionic liquid.

[26] J. A. Boon, J. A. Levisky, J. L. Pflug, J. S. Wilkes, *J. Org. Chem.* **1986**, *51*, 480–483.

[27] Y. Chauvin, L. Mussmann, H. Olivier, *Angew. Chem.* **1995**, *107*, 2941–2943; *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 2698–2700.

d) Mono- or biphasic systems in which the anion of the ionic liquid acts as a ligand for the homogeneous catalyst.

Xiao *et al*. showed that the ionic liquid [BMIM][Br] **2.8**, when used as a solvent for the Heck reaction, forms palladium-carbene complexes **2.9** by the deprotonation of the imidazolium cation in the presence of a base (Scheme 2.7).[28]

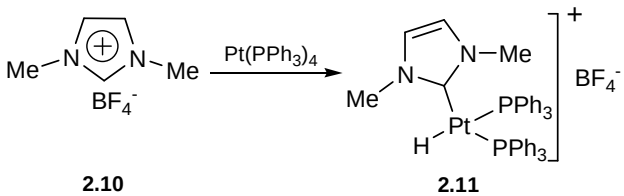


2.8 **2.9**

Scheme 2.7. Formation of carbene-Pd complex by deprotonation of the imidazolium cation.

They didn't observe the same trend in [BMIM][BF_4]. With both ionic liquids, a homogeneous yellow solution was formed during the reaction. But in the case of [BMIM][BF_4], palladium black slowly precipitated, indicating decomposition of the active palladium species. This difference was explained by the formation of the corresponding palladium–carbene complexes in the former but not in the latter.

Carbene complexes such as **2.11** can be formed also by direct oxidative addition of the ionic liquid **2.10** to a metal complex (Scheme 2.8).



2.10 **2.11**

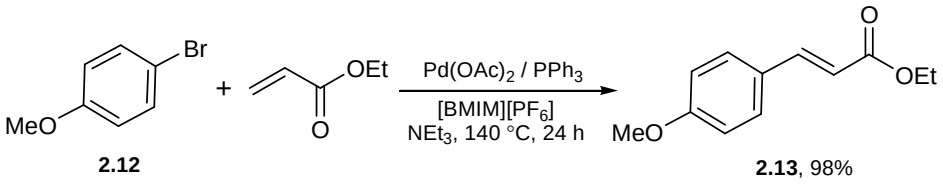
Scheme 2.8. Formation of carbene-Pt complex by oxidative addition with Pt(0).

e) Triphasic systems with an ionic liquid, water and an organic phase.

The catalyst resides in the ionic liquid, the substrate and product in the organic phase and salts formed in the reaction are extracted into the aqueous phase. Seddon *et al*. performed the $Pd(OAc)_2$–PPh_3 catalyzed Heck coupling of 4-bromoanisole **2.12** with ethyl acrylate in [BMIM][PF_6] at 140 °C which afforded ethyl 4-methoxycinnamate **2.13** in 98% yield. When

[28] L. Xu, W. Chen, J. Xiao, *Organometallics* **2000**, *19*, 1123–1127.

the reaction was over, with the addition of water and hexane, a triphasic system was obtained. The use of the hydrophobic [BMIM][PF_6] allowed the generation of a three-phase system ([BMIM][PF_6]/water/hexane). The palladium catalyst remains in the ionic liquid, the organic products remain in the hexane phase, and the salt byproducts remain in the aqueous phase (Scheme 2.9).[29]

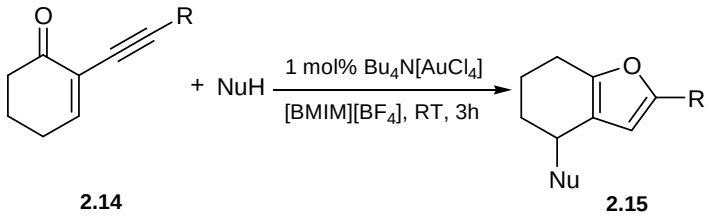


2.12 **2.13**, 98%

Scheme 2.9. Example for triphasic system using an ionic liquid.

2.1.3. Ionic Liquids as Solvent for Gold-Catalyzed Reactions

In 2006, Liang *et al*. have developed a recyclable gold catalyst in an ionic liquid for the synthesis of substituted furans **2.15** by cyclization of 2-(1-alkynyl)-2-alken-1-ones **2.14** in the presence of various nucleophiles without any loss of activity after 6 runs. The product was extracted from the reaction mixture by addition of diethyl ether and the recovered ionic liquid layer was placed under vacuum for several minutes and reused for the next reaction (Scheme 2.10).[30]



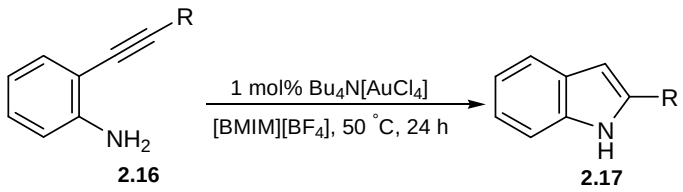
2.14 **2.15**

Scheme 2.10. $Bu_4N[AuCl_4]$-catalyzed cyclization of 2-(1-alkynyl)-2-alken-1-ones in [BMIM][BF_4].

In 2007, Marinelli *et al*. have shown that the cyclization of 2-alkynylanilines **2.16** to 2-substituted indoles **2.17** in the presence of *n*-Bu_4NAuCl_4 using [BMIM][BF_4] as the reaction

[29] A. J. Carmichael, M. J. Earle, J. D. Holbrey, P. B. McCormac, K. R. Seddon, *Org. Lett.* **1999**, *1*, 997–1000.
[30] X. Liu, Z. Pan, X. Shu, X. Duan, Y. Liang, *Synlett* **2006**, *12*, 1962–1964.

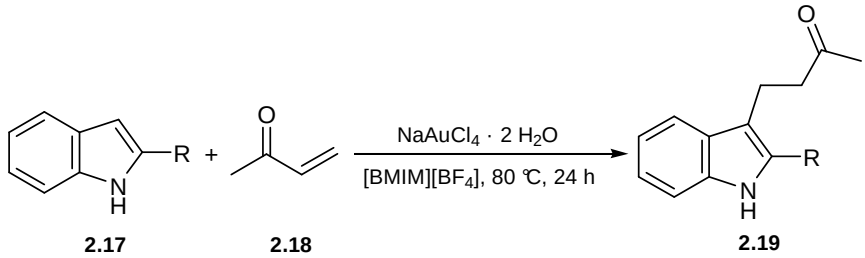
medium proceeds without any significant loss in activity after more than 5 runs (Scheme 2.11).[31]



2.16 **2.17**

Scheme 2.11. Gold-catalyzed annulation of 2-alkynylanilines to 2-substituted indoles in an ionic liquid.

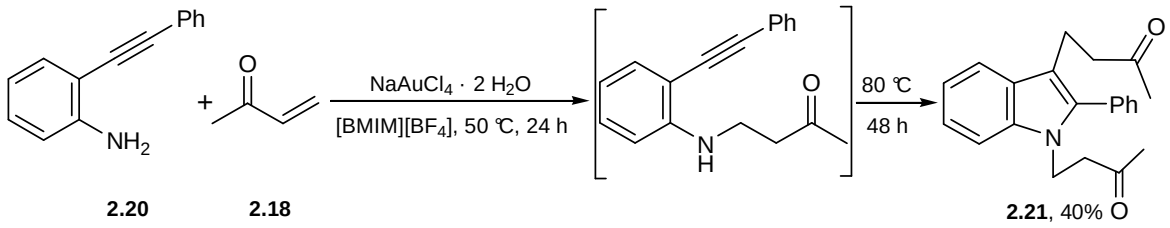
The same ionic liquid protocol was applied to synthesize 2,3-disubstituted indoles from 2-alkynylanilines and 3-buten-2-one **2.18** through a one-flask annulation–alkylation sequence.[31] 3-buten-2-one was added to the reaction mixture after completion of the annulation step and the reaction temperature was increased to 80 °C to achieve the alkylation step. 2,3-Disubstituted indoles **2.19** were obtained by alkylation of indoles **2.17** in the presence of 1 mol% of $NaAuCl_4 \cdot 2\ H_2O$ at 80 °C for 24 hours (Scheme 2.12).



2.17 **2.18** **2.19**

Scheme 2.12. Gold-catalyzed alkylation of indoles with 3-buten-2-one in an ionic liquid.

Marinelli *et al*. have also shown that 1,2,3-trisubstituted indole **2.21** are formed from **2.20** via an aza-Michael addition–annulation–alkylation process (Scheme 2.13).[31]

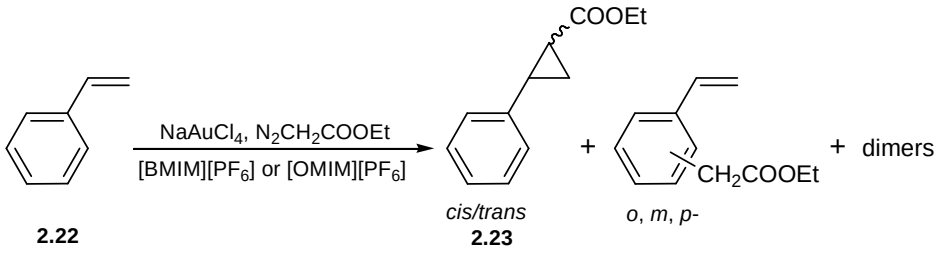


2.20 **2.18** **2.21**, 40%

Scheme 2.13. Gold-catalyzed aza-Michael addition–annulation–alkylation process in an ionic liquid.

[31] I. Ambrogio, A. Arcadi, S. Cacchi, G. Fabrizi, F. Marinelli, *Synlett* **2007**, *11*, 1775–1779.

In 2008, Corma and Sabater *et al*. have shown that gold salts ($KAuCN_2$ or $NaAuCl_4$) in different imidazolium ILs ([BMIM][PF_6] and [OMIM][PF_6]) can be used as recoverable homogeneous catalysts for the cyclopropanation reaction of alkene **2.22** with ethyldiazoacetate to give *cis*- and *trans*-cyclopropanes **2.23**. The stability of these gold salts towards the formation of gold metal agglomerates is much higher in ionic liquids and because of that higher yields of cyclopropanes can be achieved in ILs than in conventional solvents (*e.g.*, CH_2Cl_2, acetonitrile; Scheme 2.14).[32]



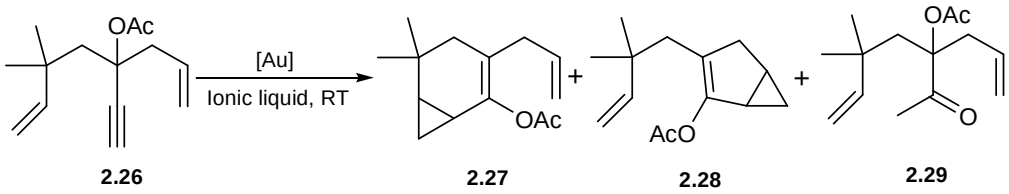
Scheme 2.14. Cyclopropanation reaction of styrene catalyzed by gold salt in ionic liquids.

In 2009, the gold-catalyzed cyclization of functionalized carboxylic acids in ionic liquids was investigated. The IL-catalysts were recycled three times without any loss in yields. Firstly, the activity of heterogeneous catalyst Au/beta-zeolite in ionic liquids was examined to compare the reactivity pattern of the ionic liquid as a catalyst in the form of [C_6MIM][$AuCl_4$] in [C_6MIM]Cl (1-hexyl-3-methylimidazolium chloride). In the case of the ionic liquid catalyst system, all the functionalized carboxylic acids **2.24** were converted to the corresponding γ-alkylidene-γ-butyrolactones **2.25** successfully at room temperature. In the case of the homogeneous catalysts like AuCl, the reaction only occurred in the presence of a base. However, ionic liquid-stabilized gold(III) chloride showed excellent reactivity in the cyclization of sterically hindered and unhindered acetylenic carboxylic acids even in the absence of a base (Scheme 2.15).[33]

Scheme 2.15. Au-catalyzed cyclization of functionalized carboxylic acids in an ionic liquid.

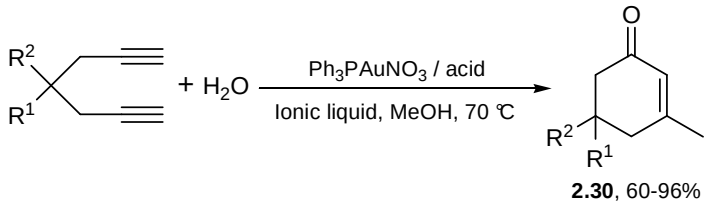
[32] A. Corma, I. Domínguez, T. Ródenas, M. J. Sabater, *Journal of Catalysis* **2008**, *259*, 26–35.
[33] F. Neaţu, V. I. Pârvulescu, V. Michelet, J. Gênet, A. Goguet, C. Hardacre, *New J. Chem.* **2009**, *33*, 102–106.

In also 2009, the groups of Fensterbank and Malacria have reported the platinum- and gold-catalyzed cycloisomerization of dienynes such as **2.26** in various ionic liquids. The reaction with the use of $AuCl_3$ in hydrophobic ionic liquids like [BMIM][PF_6] or [BMIM][NTf_2] was more selective and faster then in conventional organic solvents, *e.g.* CH_2Cl_2. The same trend was observed with the use of AuCl to obtain the mixture of **2.27** and **2.28**, but a cationic gold(I) catalyst ($Ph_3PAuCl/AgPF_6$) yielded hydration product **2.29** rather than cycloisomerization product in ionic liquid (Scheme 2.16).[34]



Scheme 2.16. Cycloisomerization of dienynes **2.26** in ionic liquids.

Recently, the hydrative cyclization of 1,6-diynes **2.30** was observed using [BMIM][BF_4] as hydrophilic IL and methanol as the co-solvent in the presence of Ph_3PAuNO_3 and methanesulfonic acid (CH_3SO_3H) at 70 °C. Hydrative cyclization of several 1,6-diynes with both acid- and base-sensitive functional groups were performed. The IL phase containing the gold catalyst was reused five times without any loss of activity (Scheme 2.17).[35]



Scheme 2.17. Gold(I)-catalyzed hydrative cyclization of 1,6-diynes in ionic liquid.

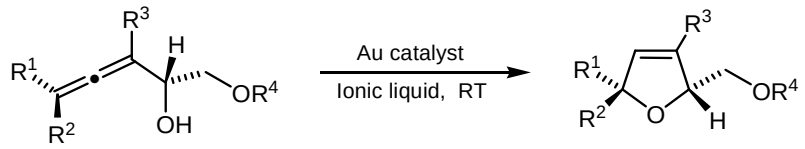
[34] X. Moreau, A. Hours, L. Fensterbank, J. P. Goddard, M. Malacria, S. Thorimbert, *J. Organomet. Chem.* **2009**, *694*, 561–565.
[35] D. M. Cui, Y. Ke, D. W. Zhuang, Q. Wang, C. Zhang, *Tetrahedron Lett*. **2010**, *51*, 980–982.

2.2. PRESENT STUDY

2,5-Dihydrofurans and their derivatives are structural subunits that are frequent in a wide variety of natural products. As a consequence, the development of synthetic approaches to functionalized 2,5-dihydrofurans is of major interest.[36] Our group has reported a highly efficient and stereoselective synthesis of 2,5-dihydrofurans by gold-catalyzed cycloisomerization of α-hydroxyallenes.[37]

One of the most important tasks for the future development of preparative chemistry is the improvement of sustainability. In the case of catalytic processes, this can be achieved by repeated use of the (often precious) catalyst, for example by immobilization on a heterogeneous support. This strategy, however, frequently suffers from decreased activities and selectivities, as well as significant catalyst leaching. An attractive alternative is the use of ionic liquids as solvent which often affords inexpensive, recyclable and therefore environmentally benign and sustainable catalyst systems. Room temperature ionic liquids are attracting much interest in many fields of chemistry and industry as an alternative to traditional organic solvents.[5] They offer a high solubility for many organic molecules, as well as transition metal catalysts, and the product can be separated easily by extraction with a non-polar organic solvent. Repeated use of the metal catalyst solution and negligible metal contamination of the product are advantages of the method.[22]

We investigated the gold-catalyzed cycloisomerization of α-hydroxyallene derivatives **2.31** to the corresponding 2,5-dihydrofurans **2.32** in room-temperature ionic liquids (Scheme 2.18). Our goal was to establish a sufficiently reactive, easy-to-handle recyclable catalyst system that displays high levels of chirality transfer in the cyclization.



2.31 **2.32**

Scheme 2.18. Gold-catalyzed cycloisomerization of functionalized α-hydroxyallenes **2.31** to 2,5-dihydrofurans **2.32**.

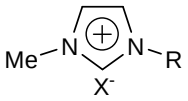
[36] a) Review on synthesis of dihydrofuran: T. G. Kilroy, T. P. O'Sullivan, P. J. Guiry, *Eur. J. Org. Chem.* **2005**, 4929–4949; b) A. Buzas, F. Istrate, F. Gagosz, *Org. Lett.* **2006**, *8*, 1957–1959; c) Y. Liu, F. Song, Z. Song, M. Liu, B. Yan, *Org. Lett.* **2005**, *7*, 5409–5412.

[37] a) A. Hoffmann-Röder, N. Krause, *Org. Lett.* **2001**, *3*, 2537–2538; b) N. Krause, A. Hoffmann-Röder, J. Canisius, *Synthesis* **2002**, 1759–1774; c) C. Deutsch, B. Gockel, A. Hoffmann-Röder, N. Krause, *Synlett* **2007**, 1790–1794.

2.3. RESULTS AND DISCUSSION

At the outset of our study, we investigated the cyclization of α-hydroxyallene **2.31a** to the corresponding 2,5-dihydrofuran **2.32a** with different Au precatalysts in various imidazolium-based ionic liquids (Scheme 2.19) at room temperature under argon (Table 2.1).

Among the gold(I) and gold(III) precatalysts tested, AuCl in [EMIM][$MeSO_3$] gave a complete conversion after just 10 min reaction time (Table 2.1, entry 1). Interestingly, addition of $AgBF_4$, as well as use of gold(III) chloride, caused a decrease of the reactivity (Table 2.1, entries 2 and 3). The same behavior was observed when $Au(OAc)_3$ or $Ph_3PAu^+BF_4^-$ (from Ph_3PAuCl and $AgBF_4$) were used (Table 2.1, entries 4 and 5).



R = Et	$X^- = MeSO_3^-$	[EMIM][$MeSO_3$]
	$X^- = EtSO_4^-$	[EMIM][$EtSO_4$]
	$X^- = BF_4^-$	[EMIM][BF_4]
	$X^- = HSO_4^-$	[EMIM][HSO_4]
	$X^- = MeSO_4^-$	[EMIM][$MeSO_4$]
	$X^- = Me(OCH_2CH_2)_2SO_4^-$	[EMIM][$Me(EG)_2SO_4$]
R = *n*-Bu	$X^- = PF_6^-$	[BMIM][PF_6]

Scheme 2.19. Imidazolium-based ionic liquids employed as solvent.

In contrast to this, $AuBr_3$ was found to be a highly effective precatalyst in [BMIM][PF_6], [EMIM][$MeSO_3$], [EMIM][$MeSO_4$], and [EMIM][HSO_4] (Table 2.1, entries 7-10), affording complete conversion after just 10 min reaction time. Only in [EMIM][BF_4], the reaction stopped after 10 min at 38% conversion (Table 2.1, entry 6).

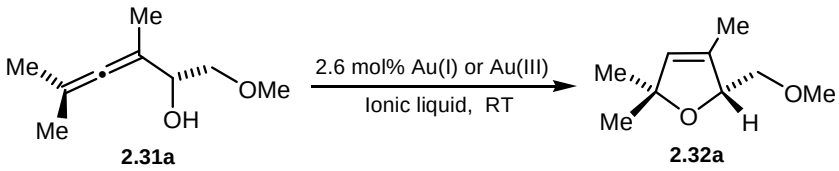
Since it is known that α-hydroxyallenes can also be cyclized to 2,5-dihydrofurans with anhydrous acid,[38] it was interesting to observe that just dissolving allene **2.31a** in the acidic ionic liquid [EMIM][HSO_4] in the absence of a gold salt also induced the cyclization to **2.32a** (Table 2.1, entry 11). Under these conditions, 48 h were required for a complete conversion, indicating that gold catalysis is much more efficient than acid catalysis for the conversion of **2.31a** into **2.32a** (Table 2.1, entry 10 vs. 11).

Having identified $AuBr_3$ as a suitable precatalyst for the cycloisomerization of allene **2.31a** in ionic liquids, we next examined the stability and recyclability of the catalyst solution. By adding new substrate to a reaction mixture after complete conversion, we could establish that $AuBr_3$ in [BMIM][PF_6] is the best combination in terms of catalyst stability. Additional advantages of this ionic liquid are its hydrophobicity, rendering the catalyst solution

[38] N. Krause, M. Laux, A. Hoffmann-Röder, *Tetrahedron Lett.* **2000**, *41*, 9613–9616.

insensitive towards water, as well as its low viscosity which makes extraction with an organic solvent easier than with other, more viscous ionic liquids.

Table 2.1. Effect of Au precatalysts and ionic liquids on the cycloisomerization of α-hydroxyallene **2.31a**.[a]



2.31a **2.32a**

Entry	Au precatalyst	Ionic liquid	Time	Conversion [%]
1	AuCl	[EMIM][$MeSO_3$]	<10 min	>99
2[b]	AuCl	[EMIM][$MeSO_3$]	~1 h	>99
3	$AuCl_3$	[EMIM][$MeSO_3$]	~1 h	>99
4	$Au(OAc)_3$	[EMIM][$MeSO_3$]	12 h	>99
5[b]	Ph_3PAuCl	[EMIM][$MeSO_3$]	24 h	20
6	$AuBr_3$	[EMIM][BF_4]	<10 min	38
7	$AuBr_3$	[BMIM][PF_6]	<10 min	>99
8	$AuBr_3$	[EMIM][$MeSO_3$]	<10 min	>99
9	$AuBr_3$	[EMIM][$MeSO_4$]	<10 min	>99
10	$AuBr_3$	[EMIM][HSO_4]	<10 min	>99
11	–	[EMIM][HSO_4]	48 h	>99

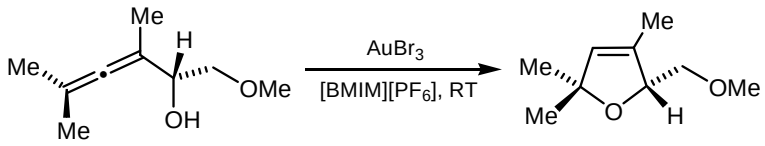
[a] The reaction was carried out using 0.25 mmol of **2.31a** and 2.6 mol% of the precatalyst in 1.0 mL of ionic liquid at RT under argon. The conversion was determined by GC. [b] $AgBF_4$ (2.0 mol%) was added.

Therefore, we concentrated on the $AuBr_3$/[BMIM][PF_6] system and examined the recyclability of the catalyst after extraction of the product with an organic solvent. Using diethyl ether for the extraction caused strongly increased reaction times in the next run; probably, the gold catalyst is extracted or destroyed partly under these conditions.

In contrast to this, the use of hexane for the extraction gave much better results (Table 2.2). With 2.6 mol% of $AuBr_3$ in [BMIM][PF_6], the activity of the catalyst was not affected by extraction of the product with hexane; even in the third run, the reaction was complete after 10 min (Table 2.2, entries 1-3). This is in strong contrast to the corresponding reaction in organic solvents (*e.g.*, CH_2Cl_2, THF) where reduction of the catalyst to (catalytically inactive) metallic gold is unavoidable.[37] Similar results were obtained with a reduced catalyst loading of 1 mol% (Table 2.2, entries 4-8) or 0.5 mol% (Table 2.2, entries 9-11). A slight loss of activity was observed after the first run when the cyclization was carried out with 0.5 mmol of **2.31a** (Table 2.2, entry 7 vs. 6, 10 vs. 9), but even under these conditions the transformation was

sufficiently fast. In order to weigh the gold precatalyst accurately, we used a catalyst loading of 1 mol% $AuBr_3$ for the subsequent studies.

Table 2.2. Repeated use of the gold catalyst in the cycloisomerization of α-hydroxyallene **2.31a** in [BMIM][PF_6].[a]



2.31a **2.32a**

Entry	Run	Time [min]	Au [mol%]	Conversion [%]
1	1	<10	2.6	>99
2	2	<10	2.6	>99
3	3	<10	2.6	>99
4	1	25	1	>99
5	2	25	1	>99
6[b]	1	<10	1	>99
7[b]	2	25	1	>99
8[b]	3	25	1	>99
9[b]	1	<10	0.5	>99
10[b]	2	30	0.5	>99
11[b]	3	40	0.5	>99

[a] The reaction was carried out using 0.25 mmol of **2.31a** in 1.0 mL of [BMIM][PF_6] at RT under argon. The conversion was determined by GC. [b] 0.5 mmol of **2.31a** in 1.0 mL of [BMIM][PF_6] was used.

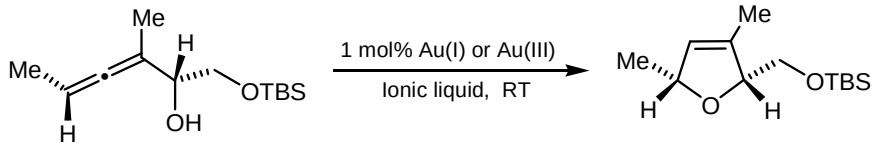
The next step was to determine the dependence of the isolated yield on the repeated use of the gold catalyst in an ionic liquid. Allene **2.31a** is not suitable for this purpose since the dihydrofuran **2.32a** is so volatile that it can be isolated only with much difficulty. Instead, we treated the α-hydroxyallene **2.31b** with different gold precatalysts in ionic liquids and determined the isolated yield after extraction with hexane (Table 2.3).

The cycloisomerization of α-hydroxyallene **2.31b** to the corresponding 2,5-dihydrofuran **2.32b** with $AuBr_3$, AuCl, $Ph_3PAuCl/AgBF_4$, or the cationic gold catalyst A[39] proceeded with good to excellent yield (70-92%) in [EMIM][HSO_4], [EMIM][$MeSO_4$], or [BMIM][PF_6] (Table 2.3). A second use of the catalyst solution after product extraction with hexane resulted in longer reaction times, but very similar chemical yields (Table 2.3, entry 3 vs. 2, 5 vs. 4, 7 vs. 6), which again demonstrates the high stability of the gold catalyst in ionic liquids. Only with

[39] C. Nieto-Oberhuber, S. Lopez, M. P. Muñoz, D. J. Cardenas, E. Buñuel, C. Nevado, A. M. Echavarren, *Angew. Chem.* **2005**, *117*, 6302–6304; *Angew. Chem. Int. Ed.* **2005**, *44*, 6146–6148.

Ph_3PAuCl as the precatalyst, a complete conversion of substrate **2.31b** could not be achieved (Table 2.3, entry 8).

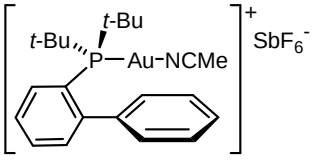
Table 2.3. Effect of Au precatalysts and ionic liquids on the cycloisomerization of α-hydroxyallene **2.31b**.[a]



2.31b **2.32b**

Entry	Run	Time	Ionic liquid	Au precatalyst	Isolated yield [%]
1	1	<10 min	[EMIM][HSO_4]	$AuBr_3$	80
2	1	<10 min	[EMIM][$MeSO_4$]	$AuBr_3$	72
3	2	3.5 h	[EMIM][$MeSO_4$]	$AuBr_3$	70
4	1	<10 min	[BMIM][PF_6]	$AuBr_3$	89
5	2	1 h	[BMIM][PF_6]	$AuBr_3$	90
6	1	<10 min	[BMIM][PF_6]	AuCl	92
7	2	2 h	[BMIM][PF_6]	AuCl	89
8	1	71 h	[BMIM][PF_6]	Ph_3PAuCl	Not completed
9[b]	1	1.5 h	[BMIM][PF_6]	Ph_3PAuCl	79
10[c]	1	<10 min	[BMIM][PF_6]	A	75

[a] The reaction was carried out using 0.5 mmol of **2.31b** and 1 mol% of the precatalyst in 1.0 mL of the ionic liquid at RT under argon. The yield was determined after extraction of the reaction mixture with dry hexane. All reactions took place with complete axis-to-center chirality transfer. [b] $AgBF_4$ (0.8 mol%) was added. [c]

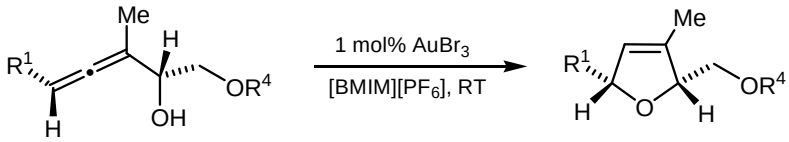


A

As with allene **2.31a**, we obtained the best results for **2.31b** with $AuBr_3$ in [BMIM][PF_6]. Subsequently, we treated various α-hydroxyallenes with this catalyst system. The results are summarized in Table 2.4.

In all cases, complete conversion of the allene was achieved. Generally, alkyl-substituted α-hydroxyallenes (Table 2.4, entries 1-12, 17-20) react faster and afford higher yields than aryl-substituted substrates (Table 2.4, entries 13-16).

Table 2.4. Cycloisomerization of α-hydroxyallenes **2.31** with $AuBr_3$ in [BMIM][PF_6].[a]



2.31 **2.32**

Entry	Run	2.31	R^1	R^4	Time	Isolated Yield 2.32 [%]
1[b]	1	**2.31b**	Me	TBS	10 min	**2.32b** 84
2[b]	2	**2.31b**	Me	TBS	3 h	**2.32b** 74
3[b]	3	**2.31b**	Me	TBS	3 h	**2.32b** 81
4[b]	4	**2.31b**	Me	TBS	3 h	**2.32b** 84
5[b]	5	**2.31b**	Me	TBS	3 h	**2.32b** 84
6	1	**2.31c**	*n*-Bu	TBS	10 min	**2.32c** 75
7	2	**2.31c**	*n*-Bu	TBS	18 h	**2.32c** 76
8	1	**2.31d**	*i*-Pr	TBS	10 min	**2.32d** 75
9	2	**2.31d**	*i*-Pr	TBS	22 h	**2.32d** 77
10	3	**2.31d**	*i*-Pr	TBS	22 h	**2.32d** 78
11	1	**2.31e**	*t*-Bu	TBS	10 min	**2.32e** 79
12	2	**2.31e**	*t*-Bu	TBS	24 h	**2.32e** 65
13[c,d]	1	**2.31f**	Ph	TBS	4 h	**2.32f** 50
14[c,d]	2	**2.31f**	Ph	TBS	6 h	**2.32f** 45
15[c,d]	1	**2.31g**	2-$MeOC_6H_4$	TBS	3 h	**2.32g** 65
16[c,d]	2	**2.31g**	2-$MeOC_6H_4$	TBS	8 h	**2.32g** 54
17	1	**2.31h**	Me	Bn	30 min	**2.32h** 88
18	2	**2.31h**	Me	Bn	30 min	**2.32h** 89
19[e]	1	**2.31h**	Me	Bn	30 min	**2.32h** 87
20[e]	2	**2.31h**	Me	Bn	30 min	**2.32h** 86

[a] The reaction was carried out using 0.5 mmol of **2.31** and 1 mol% of the precatalyst in 1.0 mL of [BMIM][PF_6] at RT under argon. The yield was determined after extraction of the reaction mixture with dry hexane. All reactions took place with complete axis-to-center chirality transfer. [b] Gold concentration in the hexane extract according to ICP-MS analysis: 318 ppb (1st run); 31 ppb (2nd run); 165 ppb (3rd run); 72 ppb (4th run); 64 ppb (5th run). [c] 0.25 mmol allene and 2.5 mol% $AuBr_3$ were used. [d] The bis-TBS ether formed by silyl transfer to the hydroxy group of substrate **2.31f/2.31g** was isolated as side product. [e] The $AuBr_3$/[BMIM][PF_6] mixture was exposed to air for 5 days prior to the reaction. The reaction was carried out under air.

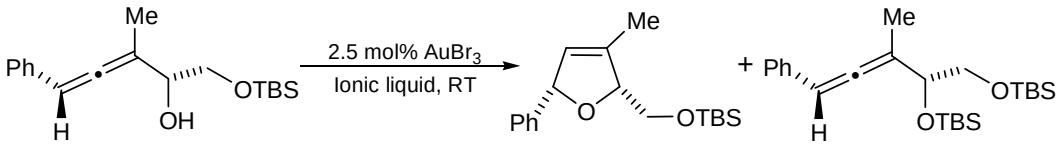
In the case of allene **2.31b**, the yield remained unchanged even after five runs (Table 2.4, entries 1-5); except for a pronounced increase of the reaction time after the first run, the reactivity of the catalyst remained constant as well (Table 2.4, entries 2-5 vs. 1). Similar trends were observed for the allenes **2.31c**-**2.31e** (Table 2.4, entries 6-12); not surprisingly, longer reaction times are required for the sterically demanding substrates **2.31d** and **2.31e** in the

second run, compared to their less bulky counterparts **2.31b** and **2.31c** (Table 2.4, entries 8-12 vs. 1-7). Nevertheless, the catalyst can be used repeatedly without compromising the conversion or isolated yield.

Interestingly, changing the TBS protecting group to a benzyl group (allene **2.31h**) resulted in high product yields without the drop in reactivity after the first run that is typical for TBS ethers **2.31b**-**2.31e** (Table 2.4, entries 17-20 vs. 1-5). The catalyst system is so stable that high yields and reactivities are observed even after exposure to air for several days (Table 2.4, entries 19 and 20).

The aryl-substituted α-hydroxyallenes **2.31f** and **2.31g** turned out to be particularly interesting substrates. When we used the standard conditions, that is, 1 mol% of $AuBr_3$ in [BMIM][PF_6], the reaction of **2.31f** took 36 h until completion. A much faster transformation could be achieved with 2.5 mol% of the precatalyst which afforded 50% of the 2,5-dihydrofuran **2.32f** after 4 h in the first run, and 45% of **2.32f** after 6 h in the second run (Table 2.4, entries 13 and 14). A similar result was obtained with the 2-methoxyphenyl-substituted allene **2.31g** (Table 2.4, entries 15 and 16). Probably due to the low reactivity, a (gold-catalyzed?) silyl transfer from the substrate or product to the starting allene is observed, leading to the isolation of the bis-silyl ether as side product.

Table 2.5. Cycloisomerization of α-hydroxyallene **2.31f** with $AuBr_3$ in ionic liquids.[a]



2.31f **2.32f** **2.33**

Entry	Time (h)	Ionic Liquid	Conversion [%]	Isolated Yield [%] (2.32f : 2.33)
1	4	[BMIM][PF_6]	>99	50:15
2	33	[EMIM][BF_4]	—	—
3	1	[EMIM][HSO_4]	>99	30:7
4	1	[EMIM][$MeSO_4$]	>99	12:57

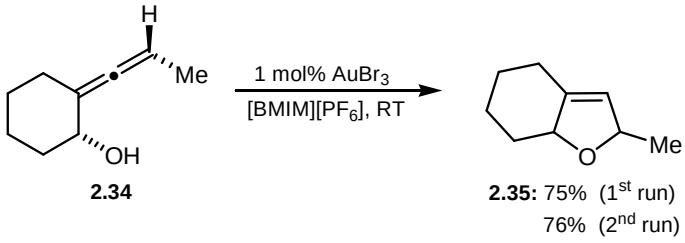
[a] The reaction was carried out using 0.25 mmol of **2.31f** and 2.5 mol% of the precatalyst in 1.0 mL of the ionic liquid at RT under argon. The yield was determined after extraction of the reaction mixture with dry hexane with respect to **2.31f**.

Other ionic liquids were examined to screen the formation of bis-silyl ether as side product in cyclization of aryl-substituted α-hydroxyallenes. When [EMIM][$MeSO_4$] was used as solvent in the cyclization of phenyl-substituted α-hydroxyallene **2.31f**, the yield of the cycloisomerization product was only 12 % and the bis-silyl ether **2.33** was the main product (57% yield) (Table 2.5, entry 4).

Previously, we had observed a facile epimerization of aryl-substituted α-hydroxyallenes when the gold-catalyzed cycloisomerization is performed in less polar solvents (*e.g.*, CH_2Cl_2).[37] This loss of stereoselectivity is attributed to the formation of zwitterionic intermediates with a benzyl cation substructure. A decrease of the Lewis acidity of the gold catalyst by using weakly coordinating additives (*e.g.*, 2,2'-bipyridine) or solvents (*e.g.*, THF) served to prevent the epimerization.[37c] In the present study, we were delighted to observe that the ionic liquid [BMIM][PF_6] can play a similar role since the phenyl-substituted dihydrofuran **2.32f** was obtained with complete axis-to-center chirality transfer (Table 2.4, entries 13 and 14).

This result indicates that the ionic liquid is not just a solvent for the catalyst and the substrate, but may have a pronounced effect on the structure and reactivity of the catalyst.[40]

The reliability of the gold-catalyzed cycloisomerization using the $AuBr_3$/[BMIM][PF_6] system was also demonstrated for the exocyclic α-hydroxyallene **2.34** (Scheme 2.20). This difficult-to-cyclize substrate[37c] afforded the desired bicyclic 2,5-dihydrofuran **2.35** with 75% yield after 10 min in the first run, and with 76% yield after 30 min in the second run.



2.34 **2.35:** 75% (1st run) 76% (2nd run)

Scheme 2.20. Cycloisomerization of α-hydroxyallene **2.34** catalyzed by $AuBr_3$ in [BMIM][PF_6].

Finally, we tested our system for metal leaching which is one of the most important criteria for recyclable catalysts, in particular if the method should be applicable to the synthesis of pharmacologically active target molecules.

Analysis of the hexane extracts obtained in the cyclization of α-hydroxyallene **2.31b** with 1 mol% $AuBr_3$ (Table 2.4, entries 1-5) by ICP-MS revealed gold contents ranging from 31-318 ppb over five runs. The highest gold loss was determined in the first run; together with the decrease of reactivity after the first run (Table 2.4, entry 2 vs. 1); this indicates a partial removal of catalytically gold species by the extraction. Overall, the five extracts contained 650 ppb of gold. Since the original catalyst loading of 1 mol% relates to 2200 ppm of gold, a loss of 650 ppb is just 0.03% of the initial amount of the catalyst. This result indicates that the solution of $AuBr_3$ in [BMIM][PF_6] is potentially recyclable several thousand times.

[40] I. Newington, J. M. Perez-Arlandis, T. Welton, *Org. Lett.* **2007**, *9*, 5247–5250.

2.4. CONCLUSION

In this study, we have demonstrated that ionic liquids are highly suitable reaction media for the gold-catalyzed cycloisomerization of α-hydroxyallenes to 2,5-dihydrofurans. The best system is $AuBr_3$ in [BMIM][PF_6]; this is air-stable and shows a very low catalyst leaching (0.03% after five runs) upon extraction with hexane. The rather low viscosity and hydrophobicity of [BMIM][PF_6] makes the catalyst solution very easy to handle and facilitates extraction of the product. The catalyst can be applied to various alkyl- or aryl-substituted α-hydroxyallenes which undergo the cycloisomerization to the corresponding 2,5-dihydrofuran with complete axis-to-center chirality transfer. We recycled the catalyst solution up to five times and often observed a pronounced decrease of the reactivity after the first run which, however, does not compromise the conversion and product yield. Due to the extremely low catalyst leaching, the $AuBr_3$/[BMIM][PF_6] solution can potentially be recycled several thousand times.

2.5. EXPERIMENTAL PART

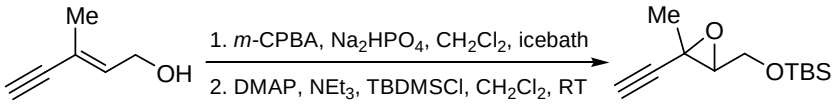
General Remarks:

Reactions were performed under an argon atmosphere if not noted otherwise. Gold precatalysts (Aldrich and Chempur) and ionic liquids (Fluka, Alfa Aeser and Solvent Innovation) were purchased from commercial sources and used without further purification. Hexane was distilled under argon from CaH_2 and stored over 3 Å molecular sieves under argon prior to use. Column chromatography was carried out with Acros silica gel 60 Å. ^1H and ^{13}C-NMR spectra were recorded with Bruker DRX 400 or DRX 500 spectrometers at room temperature in $CDCl_3$ or C_6D_6 as solvent. Chemical shifts were determined relative to the residual solvent peaks ($CHCl_3$: δ=7.26 for protons, δ=77.16 for carbon atoms; C_6H_6: δ=7.16 for protons, δ=128.06 for carbon atoms). The signals of the major component of a product mixture are marked with an asterisk (*). Reactions were monitored by both TLC and GC analysis. GC analyses were carried out with a Carlo Erba Instruments GC 8000 top gas chromatograph on a CP-SIL-5 CB capillary column (30 m x 0.32 mm x 0.25 μm) with helium as the carrier gas. GC-MS analyses were carried out with an Agilent HP 6890 as gas chromatograph on a HP-5MS column (25 m x 0.2 mm x 0.33 μm) and an Agilent HP 5973 as mass spectrometer. High-resolution mass spectral analyses were performed on a Thermo Electron system. IR spectra

were obtained with a Nicolet Avatar 320 FT-IR spectrophotometer as a liquid film between NaCl plates. ICP-MS analyses were carried out with an Agilent 7500ce spectrometer (RF Power: 1550 W, coolant gas: 15 $Lmin^{-1}$, carrier gas: 0.85 $Lmin^{-1}$, makeup gas: 0.15 $Lmin^{-1}$, Data acquisition mode: spectrum integration, time: 0.3 sec, nebulizer pumps: 0.08 rps). In order to analyze the gold content of the hexane extract, it was digested with a concentrated HNO_3/HCl mixture (3:1) with heating. After the digestion, H_2O_2 and water were added to mixture.

2.5.1. Synthesis of α-Hydroxyallenes

2.5.1.1. Synthesis of *E*-((3-Ethynyl-3-methyloxiran-2-yl)methoxy)(*t*-butyl)di methylsilane (2.37)

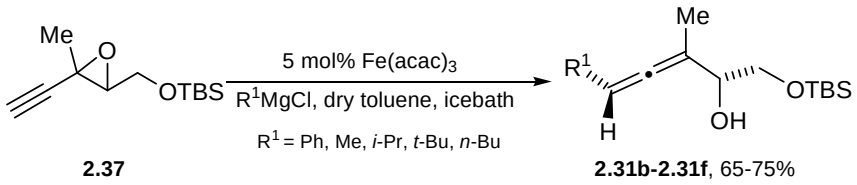


2.36 **2.37,** 82%

Step 1: Preparation of alkynyl oxirane. To a stirred solution of enynol **2.36** (9.9 g, 104 mmol) in CH_2Cl_2 (213 mL) was added *m*-CPBA (38 g, 156 mmol) and Na_2HPO_4 (17.7 g, 124.8 mmol) in an ice bath, and stirring was continued for overnight. The reaction mixture was diluted with saturated aqueous solution of Na_2CO_3, $Na_2S_2O_3$, NaOH (2 N) and extracted with CH_2Cl_2. The combined extracts were washed once more with sat. $Na_2S_2O_3$, brine and dried over anhydrous $MgSO_4$ and the solvent was evaporated under reduced pressure. The crude residue was used in the following step.

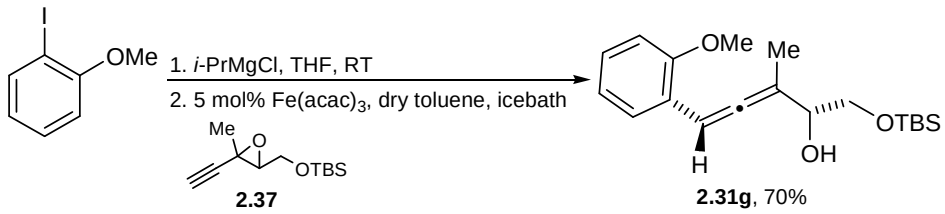
Step 2: Protection of alkynyl oxirane. A solution of crude product (10.2 g, 91.1 mmol) in CH_2Cl_2 (140 mL) was treated with DMAP (0.04 equiv., 446 mg, 3.7 mmol), triethylamine (1.2 equiv., 11.1 g, 109.3 mmol) and TBDMSCl (1.1 equiv., 15.1 g, 100.2 mmol), respectively. The reaction mixture was stirred at room temperature for overnight then was quenched with aq. sat. solution of NH_4Cl (100 mL). After extraction with CH_2Cl_2 (3 × 50 mL), the organic layer was dried with $MgSO_4$ and concentrated under vacuum. The residue was purified by column chromatography on silica gel (isohexane/EtOAc, 15:1) to give **2.37** (16.8 g, 82%) as yellow oil.

2.5.1.2. General Procedure for Synthesis of α-Hydroxyallenes (2.31b-2.31f)[41]



R^1MgCl (2 M in Et_2O, 6.5 mmol) was transferred by syringe into a solution of ((3-ethynyl-3-methyloxiran-2-yl)methoxy)(*t*-butyl)dimethylsilane (1.1 g, 5 mmol) and $Fe(acac)_3$ (89 mg, 0.25 mmol) in toluene (114 mL) in an ice bath under Ar. After stirring for 1 h, the mixture was quenched with NH_4Cl and diluted with Et_2O, the layers were separated, and the aqueous phase was extracted with Et_2O (3 × 50 mL). The combined organic layers were dried over $MgSO_4$, and the residue was purified by flash chromatography (cyclohexane/EtOAc, 14:1) to provide α-hydroxyallenes as light yellow oil.

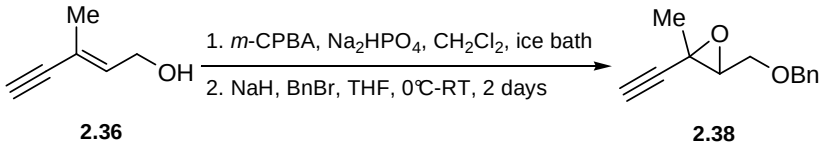
2.5.1.3. Procedure for Synthesis of α-Hydroxyallene 2.31g[41,42]



To a stirred solution of 2-iodoanisole (2.3 g, 10 mmol) in anhydrous THF (46 mL) was added *i*-PrMgCl (5.2 mL, 10.4 mmol; 2 M in THF) at room temperature. After 1 h at this temperature, the Grignard reagent was added via cannula to a cold (0 °C), freshly prepared solution of ((3-ethynyl-3-methyloxiran-2-yl)methoxy)(*t*-butyl)dimethylsilane **2.37** (906 mg, 4 mmol) and $Fe(acac)_3$ (70.6 mg, 0.2 mmol) in toluene (90 mL). The resulting solution stirred for 1 h in an ice bath, the mixture was quenched with NH_4Cl and diluted with Et_2O, the layers were separated, and the aqueous phase was extracted with Et_2O (3 × 50 mL). The combined organic layers were dried over $MgSO_4$, and the residue was purified by flash chromatography (cyclohexane/EtOAc, 10:1) to provide α-hydroxyallene **2.31g** as light yellow oil.

[41] A. Fürstner, M. Mendez, *Angew. Chem.* **2003**, *115*, 5513–5515; *Angew. Chem. Int. Ed.* **2003**, *42*, 5355–5357.
[42] C. Deutsch, A. Hoffmann-Röder, A. Domke, N. Krause, *Synlett* **2007**, *5*, 737–740.

2.5.1.4. Procedure for Synthesis of *E*-3-((Benzyloxy)methyl)-2-ethynyl-2-methyl oxirane (2.38)

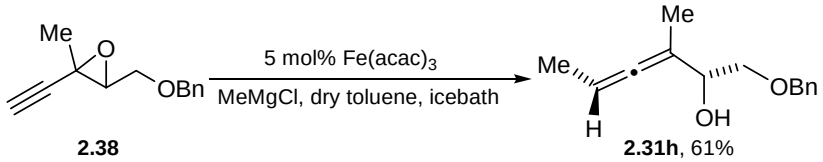


2.36 **2.38**

Step 1: Preparation of alkynyl oxirane. To a stirred solution of enynol **2.36** (5 g, 52 mmol) in CH_2Cl_2 (156 mL) was added *m*-CPBA (19 g, 78 mmol) and Na_2HPO_4 (8.9 g, 62.4 mmol) in an ice bath, and stirring was continued for overnight. The reaction mixture was diluted with saturated aqueous solution of Na_2CO_3, $Na_2S_2O_3$, NaOH (2 N) and extracted with CH_2Cl_2. The combined extracts were washed once more with sat. $Na_2S_2O_3$, brine and dried over anhydrous $MgSO_4$ and the solvent was evaporated under reduced pressure. The crude residue was used in the following step.

Step 2: Benzylation of *E*-alkynyl oxirane. To a suspension of NaH (60% disp. in oil, 1.7 equiv., 4.24 g) in absolute THF (200 mL) was the crude product (62.5 mmol) added at 0 °C and stirred for 30 min. Then at room temperature, BnBr (9.7 mL, 81.3 mmol) was added. The reaction mixture was stirred at room temperature for 2 days then was quenched with aq. saturated solution of NH_4Cl. After extraction with Et_2O, the organic layer was dried with $MgSO_4$ and concentrated under vacuum. The residue was purified by flash chromatography (cyclohexane/EtOAc, 12:1) to provide *E*-3-((benzyloxy)methyl)-2-ethynyl-2-methyl oxirane **2.38** (11.1 g, 88%) as light yellow oil.

2.5.1.5. General Procedure for Synthesis of 1-(Benzyloxy)-3-methylhexa-3,4-dien-2-ol (2.31h)[41]

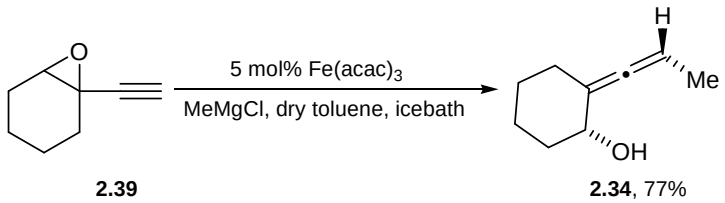


2.38 **2.31h**, 61%

MeMgCl (2 M in Et_2O, 5.2 mmol) was transferred by syringe into a solution of *E*-3-((benzyloxy)methyl)-2-ethynyl-2-methyloxirane **2.38** (809 mg, 4 mmol) and $Fe(acac)_3$ (70.6

mg, 0.2 mmol) in toluene (90 mL) in an ice bath under Ar. After stirring for 1 h, the mixture was quenched with NH_4Cl and diluted with Et_2O, the layers were separated, and the aqueous phase was extracted with Et_2O (3 × 50 mL). The combined organic layers were dried over $MgSO_4$, and the residue was purified by flash chromatography (cyclohexane/EtOAc, 10:1 to 6:1) to provide 1-(benzyloxy)-3-methylhexa-3,4-dien-2-ol **2.31h** (531.8 mg, 61%) as light yellow oil.

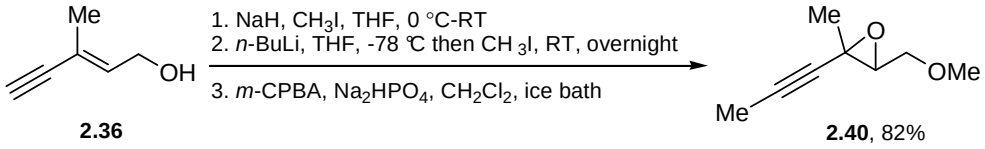
2.5.1.6. Synthesis of 2-(Prop-1-enylidene)cyclohexanol (2.34)[41]



2.39 **2.34**, 77%

MeMgCl (2 M in Et_2O, 5.2 mmol) was transferred by syringe into a solution of 1-ethynyl-7-oxa-bicyclo[4.1.0]heptane **2.39** (489 mg, 4 mmol) and $Fe(acac)_3$ (70.6 mg, 0.2 mmol) in toluene (90 mL) in an ice bath under Ar. After stirring for 1 h, the mixture was quenched with NH_4Cl and diluted with Et_2O, the layers were separated, and the aqueous phase was extracted with Et_2O (3 x 50 mL). The combined organic layers were dried over $MgSO_4$, and the residue was purified by flash chromatography (cyclohexane/EtOAc, 10:1 to 6:1) to provide 1-(benzyloxy)-3-methylhexa-3,4-dien-2-ol **2.34** (425.3 mg, 77%) as light yellow oil.

2.5.1.7. Synthesis of 3-(Methoxymethyl)-2-methyl-2-(prop-1-ynyl)oxirane (2.40)



2.36 **2.40**, 82%

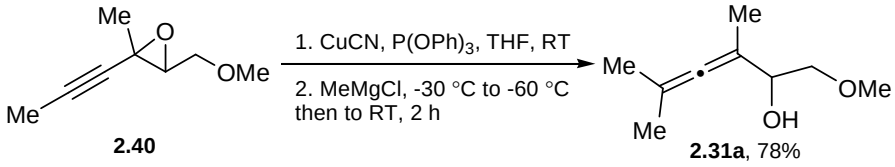
Step 1: Methylation of an alcohol. To a suspension of NaH in THF was added to *E*-3-methylpent-2-en-4-yn-1-ol **2.36** (9.6 g, 100 mmol) at 0 °C and stirred for an 30 min. Then iodomethane (7.6 mL, 120 mmol) was added and stirred for 3 h at RT. While adding the iodomethane, solution became brown. When the reaction was over, water was added and extracted with Et_2O, 10% HCl, $NaHCO_3$, and brine and dried over Na_2SO_4. The combined

organic layer was evaporated and the crude product was distilled at 64–70 °C/60 mbar to give *E*-5-methoxy-3-methylpent-3-en-1-yne (8.4 g, 77%).

Step 2: Methylation of enyne.[43] *E*-5-methoxy-3-methylpent-3-en-1-yne (8.4 g, 77.2 mmol), and dry THF 155 mL was added to flask. The flask was cooled to -78 °C, and 2.7 M *n*-BuLi in heptane (31.5 mL, 84.9 mmol) was added via syringe. After the reaction stirred for 1 h at -78 °C, iodomethane (5.8 mL, 92.6 mmol) was added dropwise. The reaction was allowed to warm to room temperature and stirred overnight. Water was added to reaction and extracted with Et_2O then dried with Na_2SO_4. Distillation under reduced pressure afforded the product as colorless oil (7.3 g, 77% yield, distilled at 83 °C/50 mbar).

For step 3; see 2.5.1.1. Synthesis of *E*-((3-ethynyl-3-methyloxiran-2-yl)methoxy)(*t*-butyl)di methylsilane **2.37**. The crude residue purified by column chromatography (cyclohexane:EtOAc, 10:1) to give **2.40** (6.7 g, 82%).

2.5.1.8. Synthesis of 1-Methoxy-3,5-dimethylhexa-3,4-dien-2-ol (2.31a)[37b,42]



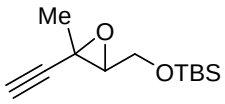
2.40 **2.31a**, 78%

$P(OPh)_3$ (14.4 mL, 55.2 mmol) was added to a suspension of CuCN (4.9 g, 55.3 mmol) in THF (414 mL) at RT. CuCN salt was dissolved in 0.5 h. The solution was cooled to -30 ºC and MeMgCl (37.2 mL, 110.4 mmol) was added and stirred for 1 h. 3-(methoxymethyl)-2-methyl-2-(prop-1-ynyl)oxirane **2.40** was added in THF at -60 °C, the solution became yellow to orange. To solution allowed to come to 0 °C and became as dark brown solution. After that solution reached to RT and stirred additional 2 h. The reaction quenched with NH_4Cl and filtrated over celite, washed with Et_2O. The ether was evaporated and the solution was washed 3 times with 5% H_2O_2 to remove Cu and excess of $P(OPh)_3$. The solution was extracted with Et_2O and concentrated under reduced pressure. The crude residue purified by column chromatography (cyclohexane:EtOAc, 10:1) to give **2.31a** (5.6 g, 78%).

[43] C. Cao, Y. Li, Y. Shi, A. L. Odom, *Chem. Commun.* **2004**, 2002–2003.

2.5.2. Characterization Data of Alkynyl Oxiranes

((3-Ethynyl-3-methyloxiran-2-yl)methoxy)(*t*-butyl)dimethylsilane (2.37)



2.37

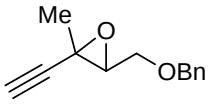
OAPHA2AT

^{1}H-NMR (400 MHz, C_6D_6)**:** δ 3.53-3.44 (m, 2H), 3.36 (t, *J*= 5.3 Hz, 1H), 1.82 (s, 1H), 1.30 (s, 3H), 0.91 (s, 9H), 0.0004 (s, 3H), -0.02 (s, 3H)

^{13}C-NMR (100 MHz, C_6D_6)**:** δ 84.5, 70.4, 63.9, 61.6, 50.3, 26.0, 18.4, -5.1, -5.3

HRMS (m/z, $[M+H]^+$)**:** 227.1389 (calculated), 227.14618 (found)

3-((Benzyloxy)methyl)-2-ethynyl-2-methyloxirane (2.38)



2.38

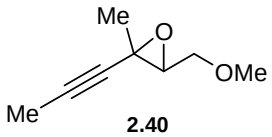
OABNEP

^{1}H-NMR (400 MHz, $CDCl_3$)**:** δ 4.67-4.52 (m, 2H), 3.68-3.54 (m, 2H), 3.43 (t, *J*= 5.3 Hz, 1H), 2.32 (s, 1H), 1.50 (s, 3H)

^{13}C-NMR (100 MHz, $CDCl_3$)**:** δ 137.7, 128.6*/128.56, 128.0/127.9*, 83.8, 73.5*/73.0, 70.5*/69.7, 67.7, 62.5/62.4*, 51.0/50.1*, 23.1, 18.5

HRMS (m/z, $[M+H]^+$)**:** 203.10666 (calculated), 203.10672 (found)

3-(Methoxymethyl)-2-methyl-2-(prop-1-ynyl)oxirane (2.40)



2.40

OAS3

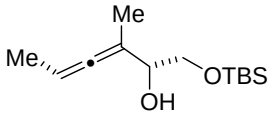
^{1}H-NMR (400 MHz, $CDCl_3$)**:** δ 3.61-3.57 (m, 1H), 3.45-3.42 (m, 1H), 3.40 (s, 3H), 3.29 (t, *J*= 5.3 Hz, 1H), 1.82 (s, 3H), 1.48 (s, 3H)

^{13}C-NMR (100 MHz, C_6D_6)**:** δ 80.5, 78.4, 70.6, 62.4, 58.6, 50.3, 19.2, 3.1

HRMS (m/z, $[M]^+$)**:** 140.0832 (calculated), 140.0834 (found)

2.5.3. Characterization Data of α-Hydroxyallenes

1-(*t*-Butyldimethylsilyloxy)-5-methyl-3-methylpenta-3,4-dien-2-ol (2.31b)



2.31b

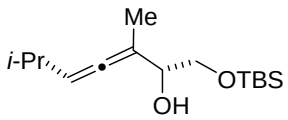
OAAL3

^{1}H-NMR (400 MHz, $CDCl_3$)**:** δ 5.21-5.12 (m, 1H), 4.03 (s, 1H), 3.69 (dd, *J*= 10.2, 3.5 Hz, 1H), 3.57-3.52 (m, 1H), 2.51 (s, 1H), 1.71 (d, *J*= 2.8 Hz, 3H), 1.65 (dd, *J*= 6.8, 1.7 Hz, 3H), 0.9 (s, 9H), 0.07 (s, 6H)

^{13}C-NMR (100 MHz, $CDCl_3$)**:** δ 201.7/201.6*, 99.04*/99.02, 87.8*/87.7, 72.73/72.66*, 66.1/66.0*, 26.1/26.0*, 18.44*/18.41, 15.9*/15.7, 14.8, -5.2

HRMS (m/z, $[M+H]^+$)**:** 243.17748 (calculated), 243.17756 (found)

1-(*t*-Butyldimethylsilyloxy)-5-*i*-propyl-3-methylpenta-3,4-dien-2-ol (2.31d)



2.31d

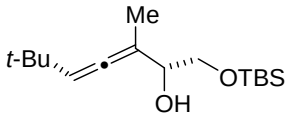
OAAL4

^{1}H-NMR (400 MHz, $CDCl_3$)**:** δ 5.25-5.19 (m, 1H), 4.05-4.02 (m, 1H), 3.71-3.67 (m, 1H), 3.57-3.53 (m, 1H), 2.48 (d, *J*= 4.0 Hz, 1H), 2.34-2.22 (m, 1H), 1.74-1.73 (m, 3H), 0.99 (d, *J*= 6.8 Hz, 6H), 0.90 (s, 9H), 0.08 (s, 6H)

^{13}C-NMR (100 MHz, $CDCl_3$)**:** δ 199.3/199.1*, 101/100.9*, 100.8/100.6*, 72.8/72.6*, 66.3, 28.3, 26.1*/26.0, 22.73*/22.70, 18.5*/18.4, 16.3/15.8, -5.2

HRMS (m/z, $[M+H]^+$)**:** 271.20878 (calculated), 271.20880 (found)

1-(*t*-Butyldimethylsilyloxy)-5-*t*-butyl-3-methylpenta-3,4-dien-2-ol (2.31e)



2.31e

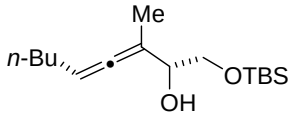
OAAL5

^{1}H-NMR (400 MHz, $CDCl_3$)**:** δ 5.22-5.21 (m, 1H), 4.04-4.03 (m, 1H), 3.70 (d, *J*= 10.2 Hz, 1H), 3.57-3.53 (m, 1H), 2.45 (s, 1H), 1.74 (d, *J*= 3.0 Hz, 3H), 1.02 (s, 9H), 0.90 (s, 9H), 0.08 (s, 6H)

^{13}C-NMR (100 MHz, $CDCl_3$)**:** δ 197.8, 105.3*/105.0, 101.5*/101.3, 72.8/72.6*, 66.4, 32.3, 30.4, 26.1, 18.5, 16.4*/15.8, -5.2

HRMS (m/z, $[M]^+$)**:** 284.2166 (calculated), 284.2161 (found)

1-(*t*-Butyldimethylsilyloxy)-5-*n*-butyl-3-methylpenta-3,4-dien-2-ol (2.31c)



2.31c

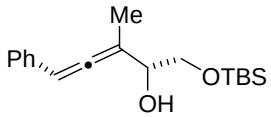
OAAL6

^{1}H-NMR (400 MHz, $CDCl_3$)**:** δ 5.23-5.16 (m, 1H), 4.04-4.03 (m, 1H), 3.70 (dd, *J*= 10.0, 3.3 Hz, 1H), 3.57-3.53 (m, 1H), 2.50 (d, *J*= 4.0 Hz, 1H), 2.01-1.96 (m, 2H), 1.72 (d, *J*= 2.5 Hz, 3H), 1.38-1.31 (m, 4H), 0.90 (s, 9H + 3H), 0.08 (s, 6H)

^{13}C-NMR (100 MHz, $CDCl_3$)**:** δ 200.8/200.7*, 99.52*/99.45, 93.3*/93.1, 72.8/72.6*, 66.2, 31.5, 28.9, 26.0, 22.3, 18.5, 16.1, 15.8, 14.1, -5.2

HRMS (m/z, $[M+H]^+$)**:** 285.22443 (calculated), 285.22460 (found)

1-(*t*-Butyldimethylsilyloxy)-5-phenyl-3-methylpenta-3,4-dien-2-ol (2.31f)



2.31f

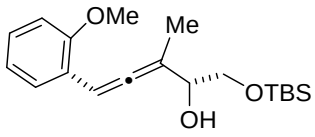
OAPHA3A

^{1}H-NMR (400 MHz, $CDCl_3$)**:** δ 7.30-7.29 (m, 4H), 7.21-7.17 (m, 1H), 6.24-6.19 (m, 1H), 4.20 (m, 1H), 3.80-3.77 (m, 1H), 3.70-3.64 (m, 1H), 2.63-2.59 (m, 1H), 1.87 (d, *J*= 2.8 Hz, 3H), 0.92-0.92 (s, 9H), 0.09-0.07 (m, 6H)

^{13}C-NMR (100 MHz, $CDCl_3$)**:** δ 202.4/202.2*, 134.9, 128.7, 127.0, 126.91*/126.9, 104.3*/104.0, 96.5*/96.2, 72.8/72.6*, 66.0/65.9*, 26.04*/26.0, 18.5*/18.4, 15.6*/15.4, -5.18/-5.2*

HRMS (m/z, $[M]^+$)**:** 304.1853 (calculated), 304.1861 (found)

1-(*t*-Butyldimethylsilyloxy)-5-(2-methoxyphenyl)-3-methylpenta-3,4-dien-2-ol (2.31g)



2.31g

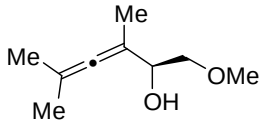
OAAL9

^{1}H-NMR (400 MHz, $CDCl_3$)**:** δ 7.36 (d, *J*= 7.6 Hz, 1H), 7.17 (t, *J*= 7.7 Hz, 1H), 6.90 (t, *J*= 7.1 Hz, 1H), 6.86 (d, *J*= 8.0 Hz, 1H), 6.61 (dt, *J*= 18.0, 2.6 Hz, 1H), 4.2 (m, 2H), 3.84 (s, 3H), 3.80-3.76 (m, 1H), 3.69-3.63 (m, 1H), 2.60 (dd, *J*= 21.2, 4.2 Hz, 1H), 1.85 (d, *J*= 1.8 Hz, 3H), 0.91 (s, 9H), 0.09-0.07 (m, 6H)

^{13}C-NMR (100 MHz, $CDCl_3$)**:** δ 202.7/202.5*, 157.2/156.2*, 131.6, 128.7, 128.1*/128.0, 123.3, 120.9*/120.5, 111.3/111.1*, 103.4*/103.2, 90.4*/90.3, 72.9/72.7*, 66.2/66.1*, 55.9/55.7*, 26.1, 18.5, 15.6*/15.5, -5.2

HRMS (m/z, $[M]^+$)**:** 334.1959 (calculated), 334.1970 (found)

1-Methoxy-3,5-dimethylhexa-3,4-dien-2-ol (2.31a)



2.31a

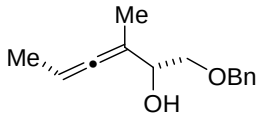
OA2S4TT

^{1}H-NMR (400 MHz, $CDCl_3$)**:** δ 4.15-4.11 (m, 1H), 3.47 (d, *J*= 9.8 Hz, 1H), 3.40 (s, 3H), 3.36-3.31 (m, 1H), 2.21 (s, 1H), 1.70 (s, 9H)

^{13}C-NMR (125 MHz, $CDCl_3$)**:** δ 198.1, 98.2, 97.7, 75.9, 71.6, 59.2, 20.9, 16.0

HRMS (m/z, $[M]^+$)**:** 156.1145 (calculated), 156.1142 (found)

1-(Benzyloxy)-3-methylhexa-3,4-dien-2-ol (2.31h)



2.31h

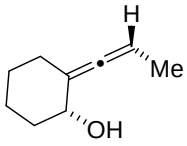
OAAL8

^{1}H-NMR (400 MHz, $CDCl_3$)**:** δ 7.35-7.27 (m, 5H), 5.22-5.17 (m, 1H), 4.58 (s, 2H), 4.22 (s, 1H), 3.62-3.59 (m, 1H), 3.50-3.45 (m, 1H), 2.38 (s, 1H), 1.72 (d, *J*= 2.5 Hz, 3H), 1.65 (dd, *J*= 6.6, 3.4 Hz, 3H)

^{13}C-NMR (100 MHz, $CDCl_3$)**:** δ 201.4, 138.2, 128.6, 127.9*/127.8, 99.2*/99.1, 88.2/88.1*, 73.5, 73.3/73.31*, 71.5/71.4, 15.9/15.8*, 14.74*/14.72

HRMS (m/z, $[M+Na]^+$)**:** 241.11990 (calculated), 241.11996 (found)

2-(Prop-1-enylidene)cyclohexanol (2.34)



2.34

OAAL12

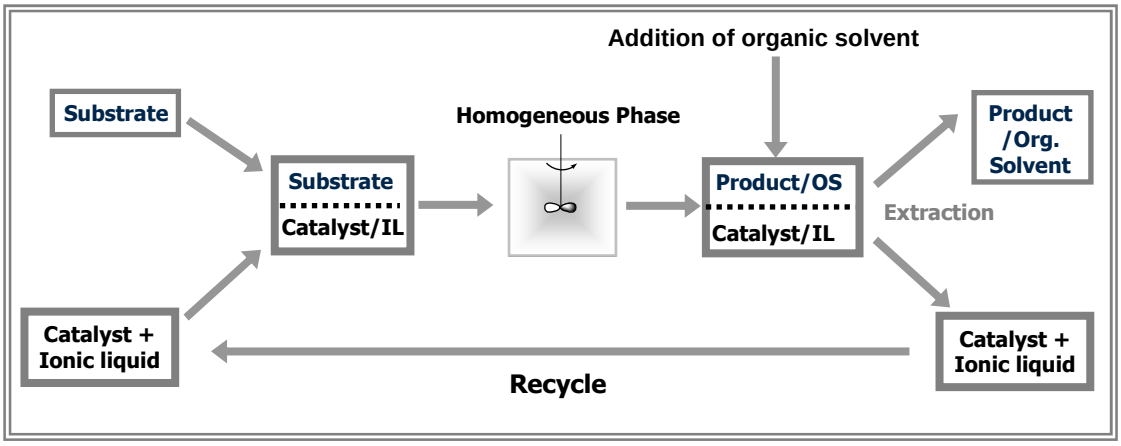
^{1}H-NMR (400 MHz, $CDCl_3$)**:** δ 5.36-5.27 (m, 1H), 3.96-3.94 (m, 1H), 2.37 (d, *J*= 13.0 Hz, 1H), 2.07-1.89 (m, 3H), 1.80-1.79 (m, 1H), 1.71-1.67 (m, 1H), 1.69 (s, 3H), 1.39-1.32 (m, 3H)

^{13}C-NMR (100 MHz, $CDCl_3$)**:** δ 195.7*/195.6, 107.5/107.4*, 90.54/90.5*, 69.1*/68.9, 36.24*/36.2, 30.2/30.0*, 26.9*/26.7, 24.0, 15.6*/15.3

HRMS (m/z, $[M]^+$)**:** 138.1039 (calculated), 138.1040 (found)

2.5.4. General Procedure for the Gold-Catalyzed Cycloisomerization of α-Hydroxyallenes to 2,5-Dihydrofurans in Ionic Liquids

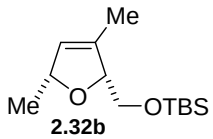
The Au precatalyst (1 mol%), the ionic liquid (1 mL), and the α-hydroxyallene (0.5 mmol) were introduced into a 25 mL two-necked round bottom flask under argon, and the mixture was stirred vigorously with a magnetic stirrer at room temperature. Small samples were periodically withdrawn by a glass Pasteur pipette; they were washed with diethyl ether, and the extract was analyzed by TLC and GC. The reaction was continued until no further α-hydroxyallene was detected. Upon completion, the product was extracted from the reaction mixture with dry hexane (5 × 10 mL). The combined organic layers were concentrated in vacuo. The crude product was purified by column chromatography on silica gel with isohexane/ethyl acetate (10:1) to give the 2,5-dihydrofuran. The ionic liquid layer containing the gold catalyst was exposed to oil pump vacuum for several minutes and reused (Scheme 2.21).



Scheme 2.21. Monophasic catalytic reaction in an ionic liquid.

2.5.5. Characterization Data of 2,5-Dihydrofurans

5-*t*-Butyl-2-(*t*-butyldimethylsilyloxymethyl)-3-methyl-2,5-dihydrofuran (2.32b)



2.32b

OAR45/OARR39

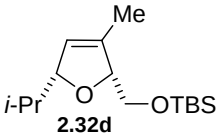
Yield: 84% of **2.32b** as light yellow oil.

^{1}H-NMR (400 MHz, $CDCl_3$)**:** δ 5.41 (s, 1H), 4.88-4.81 (m, 1H), 4.62-4.55 (m, 1H), 3.67-3.66 (m, 2H), 1.72 (s, 3H), 1.21 (dd, *J*= 6.0, 2.5 Hz, 3H), 0.89 (s, 9H), 0.06 (s, 6H)

^{13}C-NMR (100 MHz, $CDCl_3$)**:** δ 136.44*/136.4, 127.0/126.8*, 88.5*/88.2, 81.5/81.4*, 65.8*/65.1, 26.1*/26.0, 22.9*/22.3, 18.5*/18.4, 12.9/12.8*, -5.2/-5.3*

HRMS (m/z, $[M+H]^+$)**:** 243.18 (calculated), 243.18 (found)

2-(*t*-Butyldimethylsilyloxymethyl)-3-methyl-5-(1-methylethyl)-2,5-dihydrofuran (2.32d)



2.32d

OAR46

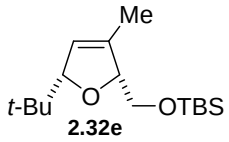
Yield: 75% of **2.32d** as light yellow oil.

^{1}H-NMR (400 MHz, $CDCl_3$)**:** δ 5.45 (s, 1H), 4.55 (s, 1H), 4.41-4.40 (m, 1H), 3.67 (d, *J*= 4.5 Hz, 2H), 1.74 (s, 3H), 1.70-1.60 (m, 1H), 0.92-0.84 (2d, *J*= 6.8 Hz, 6H), 0.89 (s, 9H), 0.06 (2s, 6H)

^{13}C-NMR (125 MHz, $CDCl_3$)**:** δ 137.8, 123.9, 90.8, 88.1, 66.0, 33.9, 26.1, 18.9, 18.5, 18.3, 13.04, -5.27/-5.29

HRMS (m/z, $[M+H]^+$)**:** 271.20878 (calculated), 271.20895 (found)

5-*t*-Butyl-2-(*t*-butyldimethylsilyloxymethyl)-3-methyl-2,5-dihydrofuran (2.32e)



2.32e

OAR47

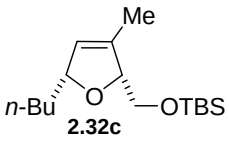
Yield: 79% of **2.32e** as light yellow oil.

^{1}H-NMR (400 MHz, $CDCl_3$)**:** δ 5.41 (s, 1H), 4.56-4.55 (m, 1H), 4.37-4.36 (m, 1H), 3.68 (d, *J*= 5.0 Hz, 2H), 1.75 (s, 3H), 0.89 (s, 9H), 0.85 (s, 9H), 0.07 (2s, 6H)

^{13}C-NMR (100 MHz, C_6D_6)**:** δ 139.0, 123.5, 93.6, 88.2, 66.5, 34.5, 26.18/26.15, 25.8 18.5, 13.0/12.9, -5.15, -5.23

HRMS (m/z, $[M+H]^+$)**:** 285.22443 (calculated), 285.22411 (found)

5-Butyl-2-(*t*-butyldimethylsilyloxymethyl)-3-methyl-2,5-dihydrofuran (2.32c)



2.32c

OAR48

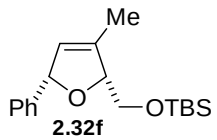
Yield: 75% of **2.32c** as light yellow oil.

^{1}H-NMR (400 MHz, $CDCl_3$)**:** δ 5.43 (s, 1H), 4.75-4.67 (m, 1H), 4.58-4.55 (m, 1H), 3.68-3.67 (m, 2H), 1.73 (s, 3H), 1.53-1.31 (m, 6H), 0.89 (s, 9H), 0.88 (s, 3H), 0.06 (s, 6H)

^{13}C-NMR (100 MHz, $CDCl_3$)**:** δ 136.8/136.7*, 125.6*/125.56, 88.2*/88.1, 85.7/85.6*, 65.8*/65.2, 37.0*/36.4, 28.0*/27.6, 26.1*/26.0, 23.0/22.9*, 18.5*/18.4, 14.2, 13.0/12.96*, -5.2/-5.3*

HRMS (m/z, $[M+H]^+$)**:** 285.22443 (calculated), 285.22470 (found)

2-(*t*-Butyldimethylsilyloxymethyl)-5-phenyl-3-methyl-2,5-dihydrofuran (2.32f)



2.32f

OA2R58

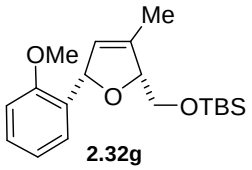
Yield: 50% of **2.32f** as light yellow oil.

^{1}H-NMR (400 MHz, $CDCl_3$)**:** δ 7.40 (d, *J*= 7.8 Hz, 2H), 7.32 (t, *J*= 7.2 Hz, 3H), 5.67 (s, 1H), 5.52 (s, 1H), 4.83-4.71 (m, 1H), 3.83-3.79 (m, 2H), 1.82 (s, 3H), 0.91 (s, 9H), 0.09-0.06 (2s, 6H)

^{13}C-NMR (100 MHz, $CDCl_3$)**:** δ 142.9/142.6*, 137.6, 128.5/128.3*, 127.8*/127.7, 127.1*/126.5, 125.74/125.7*, 89.0/88.7*, 87.5/87.0*, 65.5*/65.0, 26.1*/26.0, 18.5, 12.9/12.8*, -5.2/-5.26*, -5.3/-5.4*

HRMS (m/z, $[M+H]^+$)**:** 305.19313 (calculated), 305.19348 (found)

2-(*t*-Butyldimethylsilyloxymethyl)-5-(2-methoxyphenyl)-3-methyl-2,5-dihydro furan (2.32g)



2.32g

OAR62

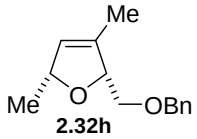
Yield: 65% of **2.32g** as light yellow oil.

^{1}H-NMR (400 MHz, $CDCl_3$)**:** δ 7.5/7.4 (d, *J*= 7.4 Hz, 1H), 7.22 (t, *J*= 7.8 Hz, 1H), 6.9 (m, 1H), 6.84 (d, *J*= 8.0 Hz, 1H), 6.05 (s, 1H), 5.64/5.63* (m, 1H), 4.82/4.72* (m, 1H), 3.84 (s, 3H), 3.81-3.79 (m, 2H), 1.79/1.78* (s, 3H), 0.91/0.90* (s, 9H), 0.09 (s, 3H), 0.05 (2s, 6H)

^{13}C-NMR (100 MHz, $CDCl_3$)**:** δ 156.4/156.2*, 136.9/136.5*, 131.5*/131.1, 128.32*/128.28, 127.2*/126.5, 125.2*/125.0, 120.8/120.7, 110.3/110.1*, 88.6/88.4*, 82.0/81.1*, 65.8/65.3*, 55.5, 26.1, 18.5, 13.0, -5.19*/-5.24, -5.26*/-5.25

HRMS (m/z, $[M]^+$)**:** 334.1959 (calculated), 334.1960 (found)

2-((Benzyloxy)methyl)-3,5-dimethyl-2,5-dihydrofuran (2.32h)



2.32h

OAR52

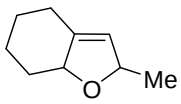
Yield: 88% of **2.32h** as light yellow oil.

^{1}H-NMR (400 MHz, $CDCl_3$)**:** δ 7.34-7.27 (m, 5H), 5.47 (d, *J*= 8.5 Hz, 1H), 4.96-4.71 (m, 2H), 4.64-4.56 (m, 2H), 3.61-3.49 (m, 2H), 1.71 (s, 3H), 1.24 (dd, *J*= 10.2, 6.4 Hz, 3H)

^{13}C-NMR (100 MHz, $CDCl_3$)**:** δ 138.6/138.5*, 135.8/135.6*, 128.4, 127.8*/127.7, 127.6*/127.59, 127.4*/127.2, 87.1*/86.8, 81.5, 73.6*/73.5, 72.5/71.7*, 22.9/22.2*, 12.73*/12.72

HRMS (m/z, $[M]^+$)**:** 218.1301 (calculated), 218.1297 (found)

2,4,5,6,7,7a-Hexahydro-2-methylbenzofuran (2.35)



2.35

OAR53

Yield: 75% of **2.35** as light yellow oil.

^{1}H-NMR (400 MHz, $CDCl_3$)**:** δ 5.28 (d, *J*= 10.3 Hz, 1H), 4.92-4.86 (m, 1H), 4.54-4.41 (m, 1H), 2.23-2.13 (m, 1H), 2.0-1.93 (m, 1H), 1.79-1.75 (m, 2H), 1.37-1.15 (m, 5H)

^{13}C-NMR (100 MHz, $CDCl_3$)**:** δ 142.0/141.7*, 121.2*/120.8, 84.8*/84.0, 81.6*/81.4, 37.1/35.6*, 27.3*/27.2, 27.0/26.8*, 23.6*/23.5, 23.4*/22.5

HRMS (m/z, $[M]^+$)**:** 138.1039 (calculated), 138.1036 (found)

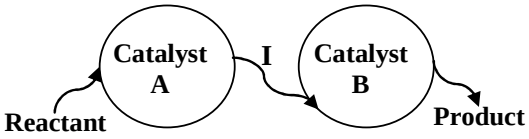
CHAPTER 3

Combined Rhodium/Gold Catalysis: From Propargyl Oxiranes to 2,5-Dihydrofurans in One Pot

3.1. INTRODUCTION

While transition metal catalyzed processes have enabled transformative developments in organic synthesis, the major problems are the handling of waste (compatibility with the environment, ecological problems, safety, etc.) and production cost (laboratory operations, quantities of chemicals and solvents used, etc.). However, it would be much more efficient if the reactions are carried out in a single reaction vessel with multiple catalysts operating simultaneously. This could avoid the time and yield losses associated with the isolation and purification of intermediates in multistep sequences. In recent years, therefore much interest on tandem/one-pot processes in which two catalysts perform sequential organic transformations via the first step is carried out by one catalyst **A** to afford certain intermediates **I** and then another reagent or second catalyst **B** is added and lead to the final product (Scheme 3.1). The challenges in these transformations are the compatibility of the second catalyst to the conditions of the first catalytic reaction and every step should proceed in the designed sequence to avoid side reactions.[1]

[1] a) D. E. Fogg, E. N. dos Santos, *Coordination Chem. Rev.* **2004**, *248*, 2365–2379; b) L. F. Tietze, *Chem. Rev.* **1996**, *96*, 115–136; c) R. A. Bunce, *Tetrahedron* **1995**, *51*, 13103–13159; d) H. Sun, F. Z. Su, J. Ni, Y. Cao, H. Y. He, K. N. Fan, *Angew. Chem.* **2009**, *121*, 4454–4457; *Angew. Chem. Int. Ed.* **2009**, *48*, 4390–4393; e) X. Z.



Scheme 3.1. Proposal of bimetallic sequential one-pot reaction.

Over the last years, the combination of efficient catalytic methods in tandem or one-pot processes like multiple metal catalysts,[2-7,14,15] gold/organocatalyst,[8-12] gold/enzymes[13] were published.

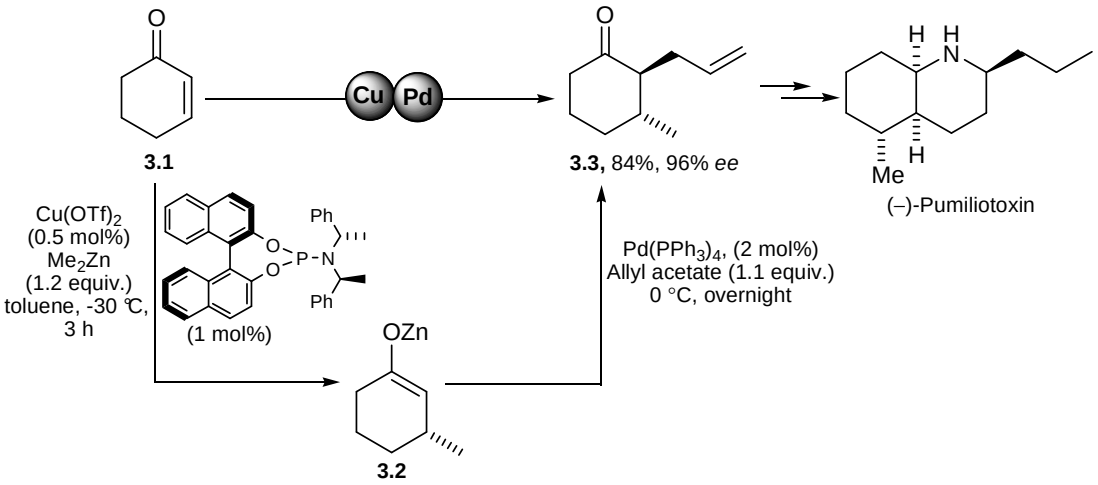
3.1.1. Tandem Reactions Catalyzed by Multiple Metal Catalysts

The combination of different metal complexes for catalytic reactions is rather limited, probably owing to the fact that the presence of multiple metal catalysts will lead to the competitive coordination of metals to the chiral ligand used, which makes the chiral environmental unpredictable and unsuitable for a given reaction. Nevertheless, there are some examples of this concept.

In 2004, Feringa *et al*. reported the asymmetric synthesis of (–)-pumiliotoxin C via a Cu/Pd-catalyzed tandem asymmetric conjugate addition–allylic substitution and a tandem Heck-allylic substitution reaction (Scheme 3.2). The copper-phosphoramidite catalyzed addition of dimethylzinc to 2-cyclohexenone **3.1** formed the intermediate **3.2**, a zinc enolate which reacted with catalytic $Pd(PPh_3)_4$ and allyl acetate to give **3.3**. After this key step of the synthesis, eight additional steps were needed to complete the synthesis of (–)-pumiliotoxin C (Scheme 3.2).[2]

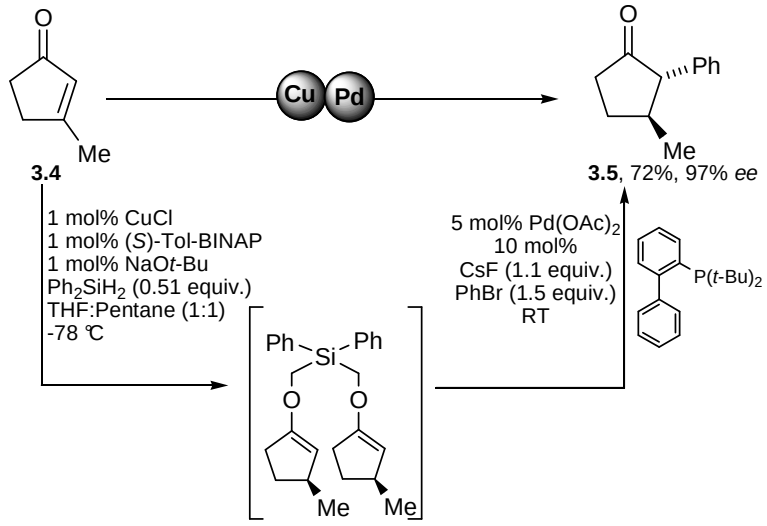
Shu, X. Y. Liu, K. G. Ji, H. Q. Xiao, Y. M. Liang, *Chem. Eur. J.* **2008**, *14*, 5282–5289; f) J. C. Wasilke, S. J. Obrey, R. T. Baker, G. C. Bazan, *Chem. Rev.* **2005**, *105*, 1001–1020; g) J. M. Lee, H. Youngim, C. S. Hoon, *Chem. Soc. Rev.* **2004**, *33*, 302–312; h) L. F. Tietze, U. Beifuss, *Angew. Chem.* **1993**, *105*, 137–170; *Angew. Chem. Int. Ed.* **1993**, *32*, 131–312.

[2] E. W. Dijk, L. Panella, P. Pinho, R. Naasz, A. Meetsma, A. J. Minnaard, B. L. Feringa, *Tetrahedron* **2004**, *60*, 9687–9693.



Scheme 3.2. Combination of copper catalysis and palladium catalysis.[2]

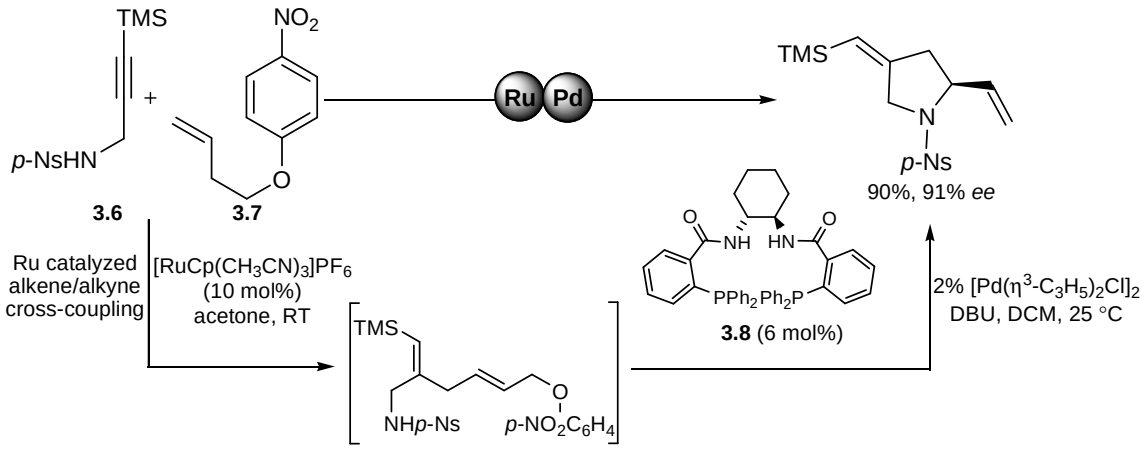
In 2004, Buchwald *et al*. reported a one-pot tandem copper-catalyzed asymmetric conjugate reduction of cyclopentenone **3.4** and palladium-catalyzed arylation reaction in the presence of CsF, providing α-arylated cycloalkanone **3.5** with excellent enantiomeric and diastereomeric purity. In addition, this procedure can be carried out in one pot without isolation of the intermediate diphenylsilyl enol ether (Scheme 3.3).[3]



Scheme 3.3. Combination of copper catalysis and palladium catalysis.[3]

[3] J. Chae, J. Yun, S. L. Buchwald, *Org. Lett.* **2004**, *6*, 4809–4812.

In 2006, Trost *et al*. reported a one-pot synthesis of enantiopure N- and O-heterocyclic compounds using the combination of a ruthenium catalyst and a chiral palladium complex. After the completion of the ruthenium-catalyzed alkene/alkyne cross coupling reaction of **3.6** and **3.7**, the chiral ligand **3.8** and the palladium catalyst were added to induce the enantioselective intramolecular heterocyclization reaction. This tandem reaction was employed for the synthesis of ring B of bryostatin (Scheme 3.4).[4]

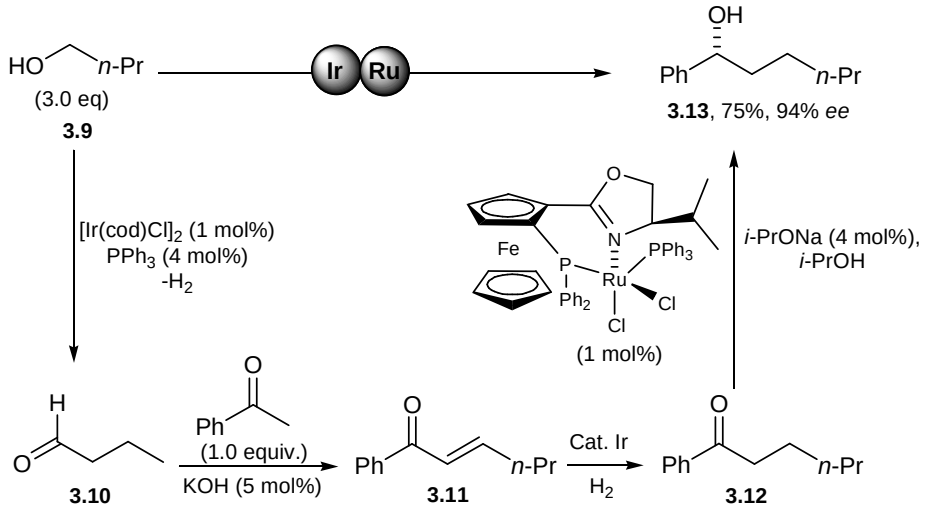


Scheme 3.4. Combination of ruthenium catalysis and palladium catalysis.[4]

In 2006, Nishibayashi *et al*. have shown that an iridium catalyst can be compatible with a ruthenium catalyst in one pot. The first step was the catalytic dehydrogenation of primary alcohol **3.9** by the iridium complex to form the corresponding aldehyde **3.10**, which underwent a base-catalyzed aldol condensation with acetophenone to afford the α,β-unsaturated ketone **3.11**. The following iridium-catalyzed hydrogenation gave α-alkylated ketone **3.12**. Finally, ruthenium-catalyzed enantioselective hydrogenation of the α-alkylated ketone resulted in formation of the enantiomerically enriched alcohol **3.13** (Scheme 3.5).[5]

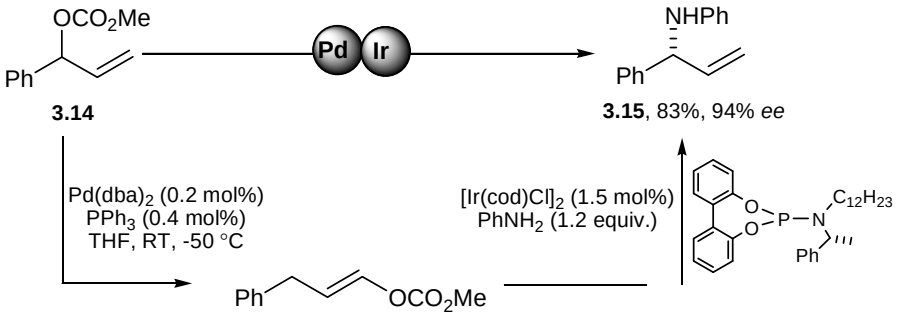
[4] B. M. Trost, M. R. Machacek, B. D. Faulk, *J. Am. Chem. Soc.* **2006**, *128*, 6745–6754.

[5] G. Onodera, Y. Nishibayashi, S. Uemura, *Angew. Chem.* **2006**, *118*, 3903–3906; *Angew. Chem. Int. Ed.* **2006**, *45*, 3819–3822.



Scheme 3.5. Combination of iridium catalysis and ruthenium catalysis.[5]

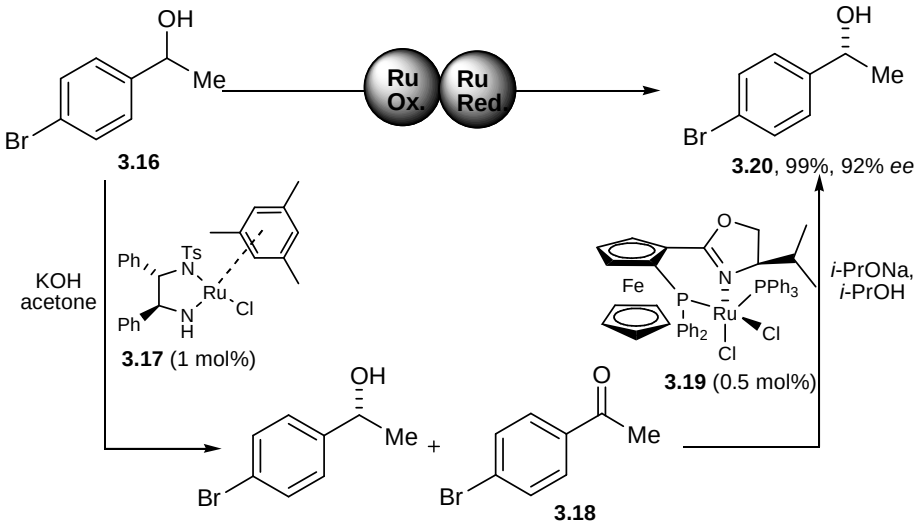
Hartwig *et al*. reported a sequential palladium-catalyzed isomerization and iridium-catalyzed asymmetric allylic substitution reaction. The transformation of branched aromatic esters **3.14** to branched allylic products **3.15** was carried out with several nucleophiles in good yield and excellent regio- and enantioselectivity (Scheme 3.6).[6]



Scheme 3.6. Combination of palladium catalysis and iridium catalysis.[6]

In 2007, Nishibayashi *et al*. reported deracemization of secondary benzylic alcohols by a two-step process with the combination of two different chiral ruthenium catalysts in the oxidation and reduction steps. The first step was the selective oxidation of the *S*-enantiomer of the racemic alcohol **3.16** to the corresponding ketone **3.18** by chiral ruthenium complex **3.17**. Then the ketone **3.18** was enantioselectively reduced to the *R*-enantiomer **3.20** by the second chiral ruthenium catalyst **3.19** (Scheme 3.7).[7]

[6] S. Shekhar, B. Trantow, A. Leitner, J. F. Hartwig, *J. Am. Chem. Soc.* **2006**, *128*, 11770–11771.
[7] Y. Shimada, Y. Miyake, H. Matsuzawa, Y. Nishibayashi, *Chem. Asian J.* **2007**, *2*, 393–396.



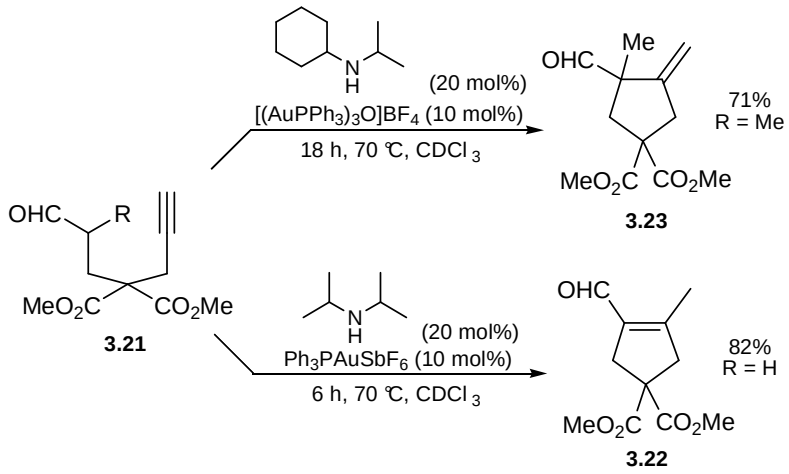
Scheme 3.7. Combination of two different ruthenium complexes.[7]

3.1.2. Tandem Reactions Catalyzed by the Combination of Gold and Organocatalysts

The combination of transition metal catalysis with organocatalysis has become a useful strategy for the development of new and valuable reactions; it is still a challenge to develop a tandem reaction catalyzed by the combination of two types of catalysts. While organocatalysis is dominated by Lewis-basic catalysts, such as amines, carbenes, and tertiary phosphines, a metal catalyst usually needs to have an empty coordination site to interact and activate a given substrate to facilitate a reaction. Nevertheless, there have some examples of tandem reactions catalyzed by gold and organocatalysts.

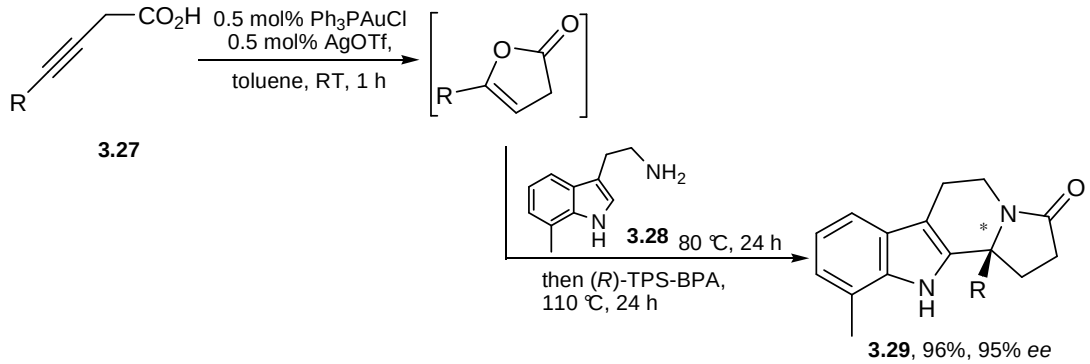
In 2008, Kirsch *et al*. have shown that formyl alkynes undergo previously unknown cyclizations on activation with catalytic amounts of a Au(I) complex and an amine, thus opening a new entry into the direct α-functionalization of aldehydes with unactivated alkynes. In fact, treatment of formyl alkyne **3.21** with both $Ph_3PAuSbF_6$ (10 mol%) and *i*-Pr_2NH (20 mol%) in $CDCl_3$ at 70 °C resulted in the formation of the cyclization product **3.22** in 82% isolated yield. With R= Me, reactions of α-branched aldehydes should be conducted utilizing $[(AuPPh_3)_3O]BF_4$ as π-acidic catalyst; in the presence of 20 mol% of HN(*i*-Pr)(*c*-Hex) at 70 °C in $CDCl_3$, the cyclization product **3.23** is formed in 71% isolated yield (Scheme 3.8).[8]

[8] J. T. Binder, B. Crone, T. T. Haug, H. Menz, S. F. Kirsch, *Org.Lett.* **2008**, *10*, 1025–1028.



Scheme 3.8. Combining gold catalysis with enamine catalysis.[8]

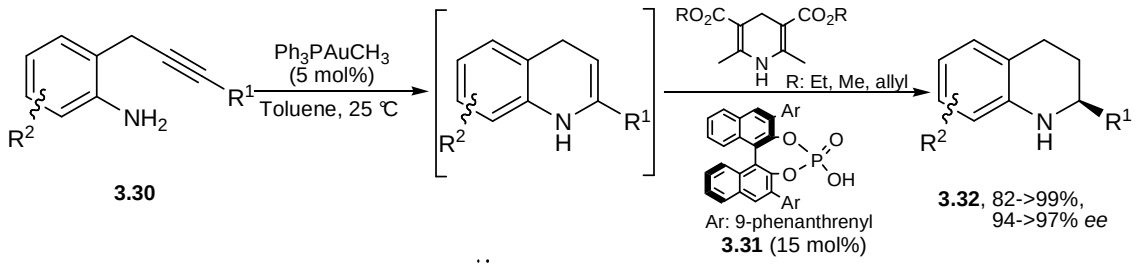
In 2009, Dixon *et al*. have shown an *in situ* enol lactone-forming by gold(I)-catalyzed cycloisomerization of alkynoic acids **3.27** and a chiral Brønsted acid-catalyzed dehydrative condensation of an enol lactone and an amine **3.28**. Alkynoic acids were treated with gold(I)triphenylphosphine triflate (0.5 mol%) and then tryptamine **3.28** in the presence (*R*)-TPS-BPA (10 mol%), and the cyclized products **3.29** were isolated in good yields and with high *ee*'s (Scheme 3.9).[9]



Scheme 3.9. One-pot cycloisomerization/*N*-acyliminium cyclization reaction.[9]

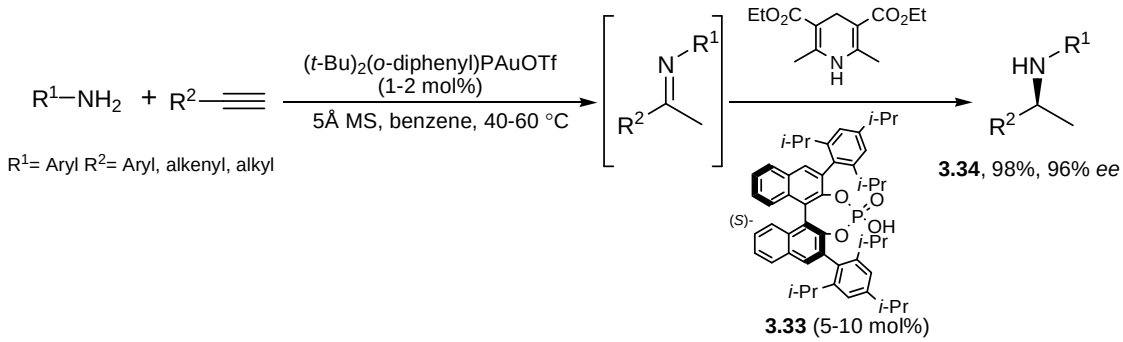
[9] M. E. Muratore, C. A. Holloway, A. W. Pilling, R. I. Storer, G. Trevitt, D. J. Dixon, *J. Am. Chem. Soc.* **2009**, *131*, 10796–10797.

Also in 2009, Gong *et al*. reported an Au-catalyzed intramolecular hydroamination of a C-C triple bond combined with a chiral phosphoric acid-catalyzed enantioselective transfer hydrogenation reaction. The transformation of 2-(2-propynyl)aniline **3.30** bearing either aromatic or aliphatic substituents on the propynyl moiety into tetrahydroquinolines **3.32** using a binary catalyst system consisting of Ph_3PAuCH_3 (5 mol%) and Brønsted acid **3.31** (15 mol%) were developed in high yields (82->99%) with excellent enantioselectivity ranging from 94% to >99% *ee* (Scheme 3.10).[10]



Scheme 3.10. One-pot hydroamination/transfer hydrogenation reaction.[10]

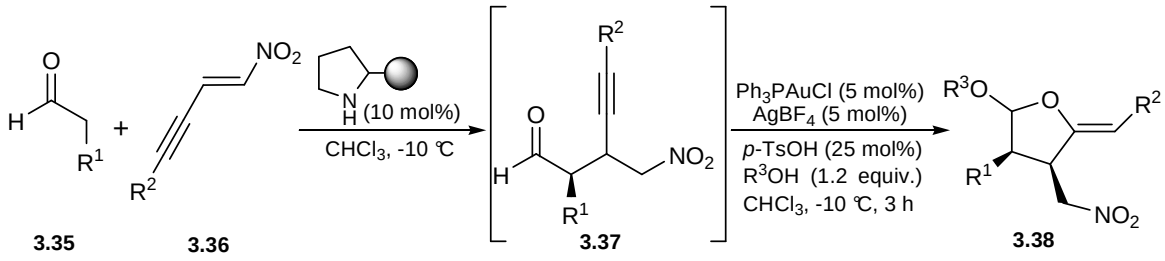
Almost at the same time, Che *et al*. applied the same strategy to the one-pot synthesis of chiral secondary amines through tandem intermolecular hydroamination/transfer hydrogenation of alkynes using a cooperative catalytic system composed of a gold(I) complex and the chiral Brønsted acid **3.33**. Various aryl, alkenyl and aliphatic alkynes were coupled with anilines to afford chiral secondary amine **3.34** in up to 98% yield and up to 96% *ee* under mild conditions (Scheme 3.11).[11]



Scheme 3.11. Combination of gold catalysis with Brønsted acid catalysis.[11]

[10] Z. Y. Han, H. Xiao, X. H. Chen, L. Z. Gong, *J. Am. Chem. Soc.* **2009**, *131*, 9182–9183.
[11] X. Y. Liu, C. M. Che, *Org. Lett.* **2009**, *11*, 4204–4207.

In 2009, Alexakis *et al*. investigated a one-pot reaction consisting of an enantioselective organocatalytic Michael addition of aldehydes **3.35** to nitroenyne **3.36**, and a subsequent gold-catalyzed tandem acetalization/cyclization of the corresponding adduct **3.37** which leads to nitro-substituted tetrahydrofuranyl ethers **3.38** with high diastereo- and enantioselectivities (Scheme 3.12).[12]

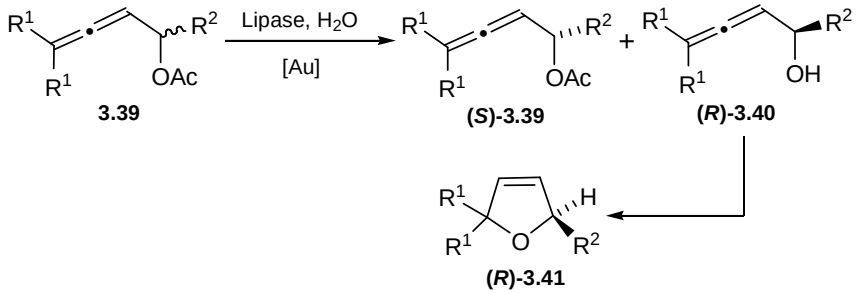


3.35 **3.36** **3.37** **3.38**

Scheme 3.12. Enantioselective one-pot organocatalytic Michael addition/Gold-catalyzed tandem acetalization/cyclization.[12]

3.1.3. Tandem Reactions Catalyzed by the Combination of Gold and Enzymes

The first example for the combination of enzymes and gold catalysts is based on the Burkholderia cepacia (PS Amano SD) lipase-catalyzed kinetic resolution of racemic α-allenic acetates **3.39** and the $HAuCl_4$-catalyzed cycloisomerization of the resulting enantiomerically enriched α-hydroxyallenes **3.40** to the corresponding 2,5-dihydrofurans **3.41** in one pot. The one-pot kinetic resolution/cycloisomerization afforded 2,5-dihydrofurans (*R*)-**3.41**, as well as unreacted starting material (*S*)-**3.39**, with 28-50% isolated yield and 86-98% *ee*.[13]



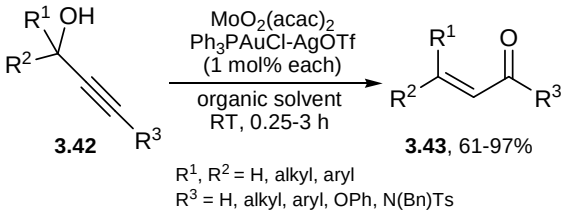
3.39 **(*S*)-3.39** **(*R*)-3.40** **(*R*)-3.41**

Scheme 3.13. Combination of gold catalysis with enzymes.[13]

[12] S. Belot, K. A. Vogt, C. Besnard, N. Krause, A. Alexakis, *Angew.Chem.* **2009**, *121*, 9085–9088; *Angew. Chem. Int. Ed.* **2009**, *48*, 8923–8926.
[13] M. Asikainen, N. Krause, *Adv. Synth. Catal*. **2009**, *351*, 2305–2309.

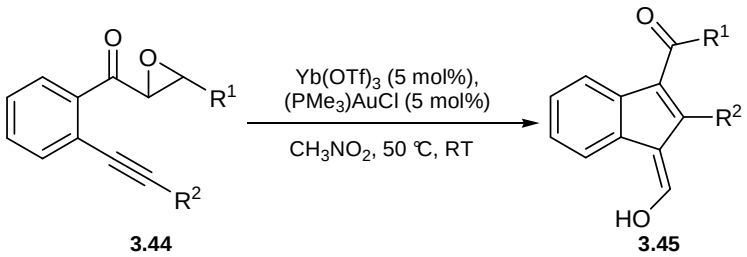
3.1.4. Tandem Reactions Catalyzed by the Combination of Gold and Other Metal Catalysts

In the field of gold catalysis, only two reports in which gold and another transition metal were used in one pot have appeared so far. Akai *et al*. have published a 1,3-rearrangement of propargyl alcohols **3.42** to α,β-unsaturated carbonyl compounds **3.43** with the combination of 1 mol% each of $MoO_2(acac)_2$, Ph_3PAuCl and AgOTf. It has provided good to excellent isolated yields of unsaturated ketones from primary, secondary, and tertiary propargyl alcohols (Scheme 3.14).[14]



Scheme 3.14. Combination of gold catalysis and molybdenum catalysis.[14]

Shi *et al*. have reported that a combination of $(PMe_3)AuCl$ and $Yb(OTf)_3$ catalyzes the domino isomerisation of epoxy alkynes to give functionalized indene derivatives in good yields under mild conditions. They envisaged a cascade reaction using epoxy alkynes as substrates, that ketone-substituted epoxides **3.44** in the presence of acid might undergo isomerization to give 1,3-diketones and subsequent intramolecular cyclization could occur via nucleophilic addition of an oxygen or a carbon atom to the alkyne to give **3.45** (Scheme 3.15).[15]



Scheme 3.15. Combination of gold catalysis and ytterbium catalysis.[15]

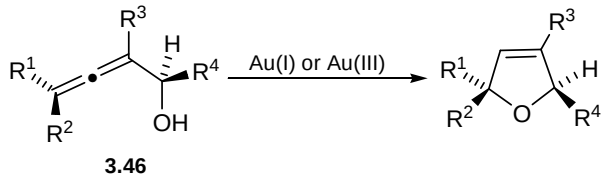
[14] M. Egi, Y. Yamaguchi, N. Fujiwara, S. Akai, *Org. Lett.* **2008**, *10*, 1867–1870.

[15] a) L. Z. Dai, M. Shi, *Eur. J. Org. Chem.* **2009**, 3129-3133; b) L. Z. Dai, M. Shi, *Chem. Eur. J.* **2010**, *16*, 2496–2502.

3.2. PRESENT STUDY

Our interest in the synthesis of 2,5-dihydrofurans from alkynyl oxiranes by S_N2'-substitution and subsequent cycloisomerization offers a unique opportunity for the development of such a new tandem or one-pot process involving gold and a second transition metal.

2,5-Dihydrofurans are the structural subunits that are found in an abundance of natural products and pharmacologically active molecules. The development of synthetic approaches to functionalized 2,5-dihydrofurans is of major interest.[16] Our group has developed a highly efficient and stereoselective synthesis of 2,5-dihydrofurans by gold-catalyzed cycloisomerization of α-hydroxyallenes **3.46**,[17] a method that has found various applications in target-oriented synthesis[18] (Scheme 3.16).



3.46

Scheme 3.16. Gold-catalyzed cycloisomerization of α-hydroxyallenes.

α-Hydroxyallenes which are the starting materials for the 2,5-dihydrofurans are also versatile building blocks for organic synthesis because of the inherent reactivity of their axially chiral backbone.[19] The α-hydroxyallenes are normally prepared by copper-mediated[20] or

[16] a) Review on synthesis of dihydrofuran: T. G. Kilroy, T. P. O'Sullivan, P. J. Guiry, *Eur. J. Org. Chem.* **2005**, 4929–4949; b) A. Buzas, F. Istrate, F. Gagosz, *Org. Lett.* **2006**, *8*, 1957–1959; c) Y. Liu, F. Song, Z. Song, M. Liu, B. Yan, *Org. Lett.* **2005**, *7*, 5409–5412.

[17] a) A. Hoffmann-Röder, N. Krause, *Org. Lett.* **2001**, *3*, 2537–2538; b) N. Krause, A. Hoffmann-Röder, J. Canisius, *Synthesis* **2002**, 1759–1774; c) C. Deutsch, B. Gockel, A. Hoffmann-Röder, N. Krause, *Synlett* **2007**, 1790–1794; d) Ö. Aksın, N. Krause, *Adv. Synth. Catal.* **2008**, *350*, 1106–1112; e) M. Poonoth, N. Krause, *Adv. Synth. Catal.* **2009**, *351*, 117–122; f) C. Winter, N. Krause, *Green Chem.* **2009**, *11*, 1309–1312; g) N. Krause, V. Belting, C. Deutsch, J. Erdsack, H.-T. Fan, B. Gockel, A. Hoffmann-Röder, N. Morita, F. Volz, *Pure Appl. Chem.* **2008**, *80*, 1063–1069; h) N. Krause, Ö. Aksin-Artok, V. Breker, C. Deutsch, B. Gockel, M. Poonoth, Y. Sawama, Y. Sawama, T. Sun, C. Winter, *Pure Appl. Chem.* **2010**, *82*, 1529–1536.

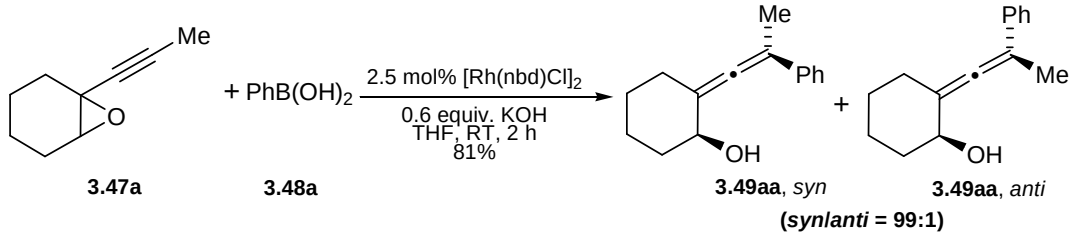
[18] a) F. Volz, N. Krause, *Org. Biomol. Chem.* **2007**, *5*, 1519–1521; b) J. Erdsack, N. Krause, *Synthesis* **2007**, 3741–3750; c) Y. Sawama, Y. Sawama, N. Krause, *Org. Biomol. Chem.* **2008**, *6*, 3573–3579; d) F. Volz, S. H. Wadman, A. Hoffmann-Röder, N. Krause, *Tetrahedron* **2009**, *65*, 1902–1910; e) Z. Gao, Y. Li, J. P. Cooksey, T. N. Snaddon, S. Schunk, E. M. E. Viseux, S. M. McAteer, P. J. Kocienski, *Angew. Chem.* **2009**, *121*, 5122–5125; *Angew. Chem. Int. Ed.* **2009**, *48*, 5022–5025.

[19] For selected reviews, see: a) J. A. Marshall, *Chem. Rev.* **2000**, *100*, 3163–3185; b) R. Zimmer, C. U. Dinesh, E. Nandanan, F. A. Khan, *Chem. Rev.* **2000**, *100*, 3067–3125; c) S. Ma, *Acc. Chem. Res.* **2003**, *36*, 701–712; d) A. S. K. Hashmi, *Angew. Chem. Int. Ed.*. **2000**, *39*, 3590–3593.

[20] Reviews: a) A. Hoffmann-Röder, N. Krause, *Angew. Chem.* **2002**, *114*, 3057–3059; *Angew. Chem. Int. Ed.* **2002**, *41*, 2933–2935; b) A. Hoffmann-Röder, N. Krause, *Angew. Chem.* **2004**, *116*, 1216–1236; *Angew. Chem.*

-catalyzed[21] S_N2'-substitution of alkynyl oxiranes and related electrophiles which takes place with high *anti*-selectivity in most cases. α-Allenols are also synthesized with *anti*-selectivity in the presence of organozinc,[22] stannane,[23] and -boron reagents[24] or carbon monoxide[25] from propargylic oxiranes under palladium catalysis.

In contrast to this, the rhodium-catalyzed S_N2'-substitution of alkynyl oxiranes with boronic acids developed recently by Murakami and coworkers[26] permits the construction of *syn*-configured α-allenols with high levels of diastereoselectivity under mild conditions. A pre-coordination of the oxirane oxygen atom is likely to contribute strongly to the high stereoselectivity and reactivity observed in this transformation (Scheme 3.17).



Scheme 3.17. Rh(I)-catalyzed reaction of an alkynyl oxirane with phenylboronic acid.[26]

Krause *et al*. and Murakami *et al*. applied this rhodium-catalyzed addition of arylboronic acids to alkynyl oxiranes together with the gold-catalyzed cycloisomerization of the corresponding allenol and the iridium-catalyzed hydrogenation to achieve a total synthesis of (±)-boivinianin B in a traditional multi-flask sequence (Scheme 3.18).[27]

Int. Ed. **2004**, *43*, 1196–1216; c) N. Krause, A. Hoffmann-Röder, *Tetrahedron* **2004**, *60*, 11671–11694; d) K. M. Brummond, J. E. DeForest, *Synthesis* **2007**, 795–818.

[21] a) A. Alexakis, I. Marek, P. Mangeney, J. F. Normant, *Tetrahedron* **1991**, *47*, 1677–1696; b) C. Deutsch, B. H. Lipshutz, N. Krause, *Angew. Chem.* **2007**, *119*, 1677–1681; *Angew. Chem. Int. Ed.* **2007**, *46*, 1650–1653; c) C. Deutsch, B. H. Lipshutz, N. Krause, *Org. Lett.* **2009**, *11*, 5010–5012; d) X. Tang, S. Woodward, N. Krause, *Eur. J. Org. Chem.* **2009**, 2836–2844.

[22] H. Kleijn, J. Meijer, G. C. Overbeek, P. Vermeer, *Rec. Trav. Chim. Pays-Bas* **1982**, *101*, 97–101.

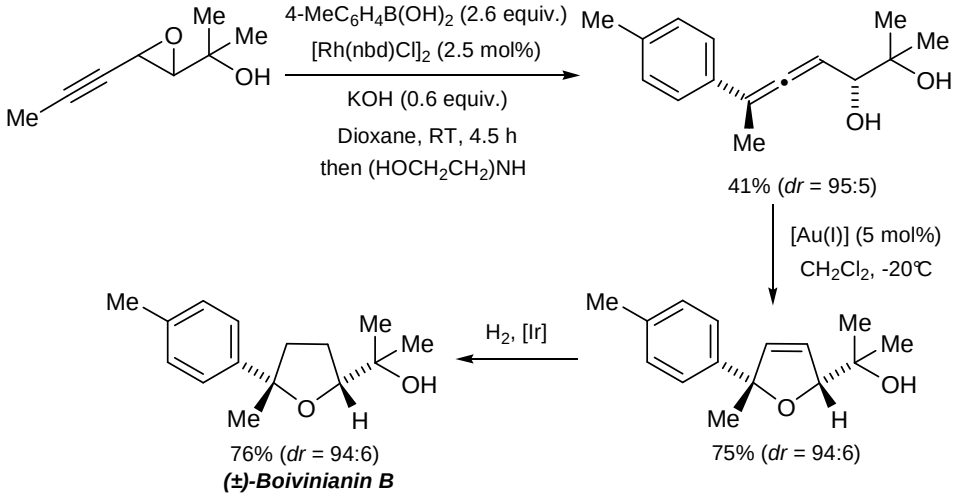
[23] J. Kjellgren, H. Sunde´n, K. J. Szabo´, *J. Am. Chem. Soc.* **2005**, *127*, 1787–1796.

[24] M. Yoshida, H. Ueda, M. Ihara, *Tetrahedron Lett.* **2005**, *46*, 6705–6708.

[25] J. G. Knight, S. W. Ainge, C. A. Baxter, T. P. Eastman, S. J. Harwood, *J. Chem. Soc., Perkin Trans.* **2000**, *1*, 3188–3190.

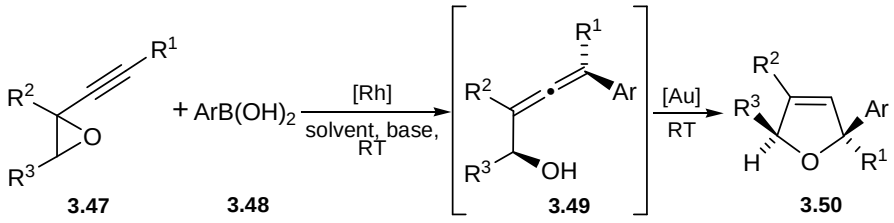
[26] T. Miura, M. Shimada, S.Y. Ku, T. Tamai, M. Murakami, *Angew. Chem.* **2007**, *119*, 7231–7233; *Angew. Chem. Int. Ed.* **2007**, *46*, 7101–7103.

[27] T. Miura, M. Shimada, P. de Mendoza, C. Deutsch, N. Krause, M. Murakami, *J. Org. Chem.* **2009**, *74*, 6050–6054.



Scheme 3.18. Traditional multiflask sequence in the synthesis of the natural product (±)-Boivinianin B.

Multiple catalysts operating simultaneously in one pot could circumvent the time and yield losses associated with the isolation and purification of intermediates in multistep sequences. The examples where two catalysts perform sequential organic transformations in a single vessel are significantly increasing in recent years. In many aspects, this approach of one-pot or tandem catalysis makes the processes more economical and time saving compared to the traditional one-catalyst one-reaction routes. Nevertheless, tandem/one-pot reactions with gold and other frequently used transition metals (Pd, Rh etc.) are still the field to examine.



Scheme 3.19. Proposal: One-pot rhodium/gold-catalysis sequence.

In this respect, our aim is to synthesize 2,5-dihydrofurans **3.50** by a sequential one pot reaction consisting of a rhodium-catalyzed S_N2'-substitution of alkynyl oxiranes **3.47** with arylboronic acids **3.48** to furnish α-allenols **3.49**, followed by cycloisomerization of the α-allenols **3.49** by gold catalysis (Scheme 3.19). This two-step, one-pot formation of the 2,5-dihydrofurans **3.50** would represent the first example of combined rhodium/gold catalysis and an ecological and economical way to access novel and complex molecules from simple, readily available starting materials.

3.3. RESULTS AND DISCUSSION

In order to examine the compatibility of the rhodium- and gold-catalyzed step in one-pot, we first investigated the reaction of alkynyl oxirane **3.47a** with phenylboronic acid **3.48a** which should afford bicyclic dihydrofuran **3.50aa** via α-hydroxyallene **3.49aa** (Table 3.1).

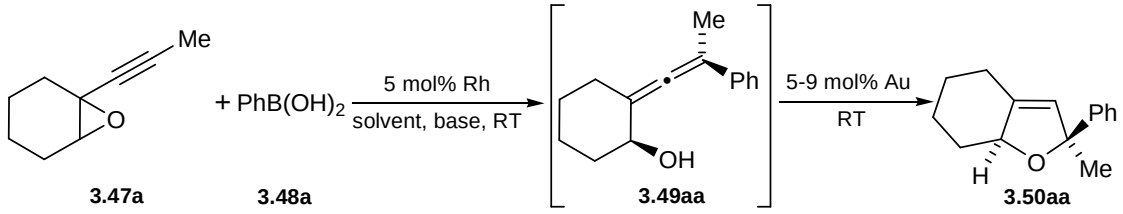
We performed the rhodium-catalyzed step by adopting the Murakami's method with the only difference that KOH was added as an aqueous solution (THF:water 100:1) to simplify the addition of small amounts of KOH to reaction mixture. The conversion of **3.47a** was complete as determined by TLC analysis. Subsequently 5 mol% of $HAuCl_4 \cdot 3\,H_2O$ was added to the reaction mixture to achieve the cyclization step. Unfortunately, the cycloisomerization was slow and yielded only 39% of **3.50aa** (Table 3.1, entry 1). The cycloisomerization was faster and yielded 71% of **3.50aa** when we increased the gold amount to 8 mol% (Table 3.1, entry 2). When 1,4-dioxane was used as solvent, the rhodium-catalyzed S_N2'-substitution was much slower and did not go to completion (Table 3.1, entry 3).

We assumed that the base could be detrimental for the gold-catalyzed cycloisomerization of the allenol. It is known that [Rh]-OH species is formed *in situ* with $[Rh(nbd)Cl]_2$ and KOH.[26] From that knowledge, to eliminate the base effect on the gold-catalyzed step, preformed $[Rh(cod)OH]_2$ (5% Rh, cod: cycloocta-1,5-diene) complex was used for the allenol formation in THF without additional base. Under these conditions, both the Rh- and Au-catalyzed step were fast and yielded 36% of **3.50aa** with side products (Table 3.1, entry 4). When THF:H_2O (100:5) was used, the overall yield was decreased to 29% (Table 3.1, entry 5). It is observed that the amount of water is important for the one-pot reaction. With 1% or 0.5% of H_2O in the reaction mixture, better yields of the 2,5-dihydrofuran (50-58%) were obtained (Table 3.1, entries 6-8). 1,4-Dioxane or dichloroethane turned out to be not effective solvents for the one-pot reaction (Table 3.1, entries 9 and 10).

In the presence of the $[Rh(cod)OMe]_2$ complex (5% Rh) in MeOH with $HAuCl_4 \cdot 3\,H_2O$, **3.50aa** was obtained in an NMR yield of 46% (Table 3.1, entry 11). However, $[Rh(cod)OMe]_2$ in THF was less effective then in MeOH, and both the Rh- and Au-catalyzed step were rather slow with low yield (Table 3.1, entry 12).

Since the base-free conditions did not offer an advantage, we turned back to the previous procedure. When K_2CO_3 was used as a base to eliminate the side product formation with $[Rh(cod)OH]_2$, nearly no change was observed compared to the reactions without base (Table 3.1, entry 13).

Table 3.1. Optimization of the 1st step (Rh catalysis) of the one-pot synthesis of 2,5-dihydrofuran **3.50aa** from alkynyl oxirane **3.47a** using phenylboronic acid **3.48a**.[a]



3.47a **3.48a** **3.49aa** **3.50aa**

	Rh-catalyzed S_N2'-substitution				Au-catalyzed cycloisomerization	
Entry	**Rh (5 mol%)**	**Base (equiv.)**	**Solvent**	**Time (h)**	**Time (h)**	**Yield 3.50aa [%][b]**
1[c]	$[Rh(nbd)Cl]_2$	KOH (0.6)	THF:H_2O (100:1)	1	23	39
2[d]	$[Rh(nbd)Cl]_2$	KOH (0.6)	THF:H_2O (100:1)	1	15	71
3[e]	$[Rh(nbd)Cl]_2$	KOH (0.6)	Dioxane:H_2O (100:1)	17	—	—
4	$[Rh(cod)OH]_2$	—	THF	2	0.75	36
5[e]	$[Rh(cod)OH]_2$	—	THF:H_2O (100:5)	22	0.5	29
6	$[Rh(cod)OH]_2$	—	THF:H_2O (100:1)	1	0.5	58
7[f]	$[Rh(cod)OH]_2$	—	THF:H_2O (100:1)	2	1	50
8	$[Rh(cod)OH]_2$	—	THF:H_2O (100:0.5)	1	0.5	55
9[e]	$[Rh(cod)OH]_2$	—	Dioxane:H_2O (100:1)	4	0.5	41
10[e]	$[Rh(cod)OH]_2$	—	DCE:H_2O (100:1)	7	—	—
11	$[Rh(cod)OMe]_2$	—	MeOH	1	0.5	46
12[e]	$[Rh(cod)OMe]_2$	—	THF	3	0.5	23
13	$[Rh(cod)OH]_2$	K_2CO_3 (0.6)	THF:H_2O (100:1)	1	0.5	58
14[e]	$[Rh(cod)Cl]_2$	KOH (0.6)	THF:H_2O (100:1)	47	24	17
15	$[Rh(nbd)Cl]_2$	K_3PO_4 (1)	THF:H_2O (100:1)	1	24	53
16	$[Rh(nbd)Cl]_2$	$CsOH \cdot H_2O$ (0.4)	THF:H_2O (100:1)	1	24	52
17	$[Rh(nbd)Cl]_2$	NBu_4OH (0.6)	THF:H_2O (100:1)	1	24	—
18[c]	**$[Rh(nbd)Cl]_2$**	**KOH (0.4)**	**THF:H_2O (100:1)**	**2**	**0.5,10,21**	**73-80**

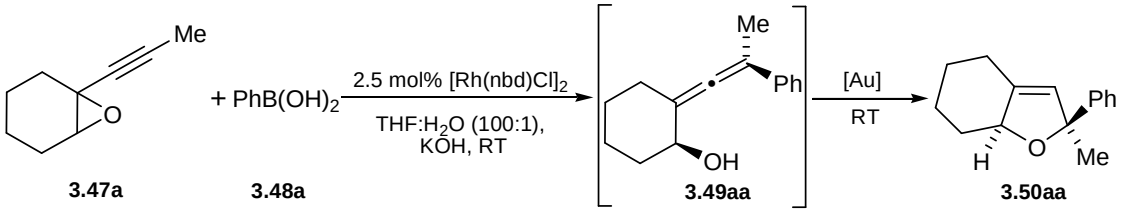
[a] Reaction conditions: 0.2 mmol of **3.47a**, different amount of bases in different amounts of H_2O (or without), 0.3 mmol of phenylboronic acid **3.48a**, 5 mol% of Rh in 2.0 mL solvent at RT under Ar. When the alkynyl oxirane **3.47a** is consumed (TLC control), 5-9 mol% $HAuCl_4 \cdot 3\ H_2O$ was added. [b] Calculated by ^1H NMR relative to an internal standard (1,3-dimethoxybenzene). [c] With 5 mol% of $HAuCl_4 \cdot 3\ H_2O$. [d] With 8 mol% of $HAuCl_4 \cdot 3\ H_2O$. [e] The 1st step was discontinued and gold catalyst was added to reaction mixture. [f] 5-6 mol% $AuBr_3$ was used instead of $HAuCl_4 \cdot 3\ H_2O$.

Interestingly, the analogous $[Rh(cod)Cl]_2$ complex proved less effective in basic THF solution, indicating that nbd is a better ligand than cod for this reaction (Table 3.1, entry 14).

Based on the best result for the one-pot reaction that we obtained with $[Rh(nbd)Cl]_2$/KOH in a THF:H_2O solvent system (Table 3.1, entry 2), we investigated the effect of bases for the second step, the gold-catalyzed cycloisomerization of the allenol, to increase the overall yield in shorter reaction times.

Bases like K_3PO_4 (1 equiv.) or $CsOH \cdot H_2O$ (0.4 equiv.) afforded complete conversion in the Rh-catalyzed step, but the gold-catalyzed cycloisomerization stopped after 24 h (Table 3.1, entries 15 and 16). Even NBu_4OH (0.6 equiv.) was an effective base for Rh catalysis; however the Au-catalyzed cycloisomerization did not take place at all (Table 3.1, entry 17). Unfortunately, other bases like Cs_2CO_3 (1 equiv.), NaOH (0.4 equiv.), K_2CO_3 (1equiv.) or $LiOH \cdot H_2O$ (0.4 equiv.) yielded only 12-30% of **3.50aa** after incomplete conversion of **3.47a** in the first step. When K_3PO_4 (0.4 equiv.) was used, the Rh-catalyzed step did not work at all. Coming back to KOH as a base, lowering the amount from 0.6 to 0.4 equiv. afforded short reaction times in both Rh- and Au-catalyzed steps with promising yields. The reactivity of the gold-catalyzed cycloisomerization strongly depends on the quality of the catalyst; whereas a fresh sample of $HAuCl_4 \cdot 3\ H_2O$ gave complete conversion of **3.49aa** to **3.50aa** within 30 min, older samples required up to 21 h. Yields, however, remained constant (Table 3.1, entry 18).

Table 3.2. Effect of gold precatalysts on the one-pot synthesis of 2,5-dihydrofuran **3.50aa** from alkynyl oxirane **3.47a** using phenylboronic acid **3.48a** with $[Rh(nbd)Cl]_2$.[a]



3.47a **3.48a** **3.49aa** **3.50aa**

Entry	[Au] (5 mol%)	Time (h)	NMR Yield 3.50aa [%][b]
1	**$HAuCl_4 \cdot 3\ H_2O$**	**0.5, 10, 21**	**73-80**
2	$HAuCl_4 \cdot 3\ H_2O$ (9%)	0.5	77
3	$NaAuCl_4$	21	10
4	$AuCl_3$	24	32
5	AuCl	24	14
6	Ph_3PAuCl/AgOTf	24	3
7	AuIPrCl/AgOTf	24	6
8	**$AuBr_3$**	**3**	**72**

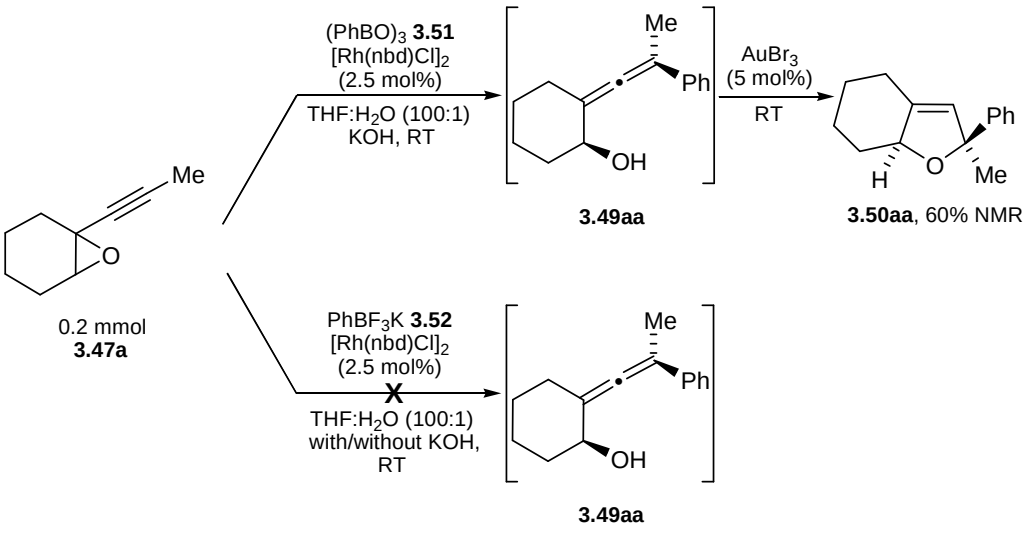
[a] Reaction conditions: 0.2 mmol of **3.47a**, 0.08 mmol of KOH in 20 µL H_2O, 0.3 mmol of **3.48a**, 2.5 mol% of $[Rh(nbd)Cl]_2$ (5 mol% of Rh) in 2.0 mL THF at RT under Ar. When the alkynyl oxirane **3.47a** was consumed (2 h, TLC control), 5 mol% of gold catalyst was added. [b] Calculated by ^1H NMR relative to an internal standard (1,3-dimethoxybenzene).

In contrast to this, the allene formation did not work at all with just 0.2 equiv. of KOH.

From this base screening, KOH (0.4 equiv.) in THF:H_2O (100:1) emerged as the best system for the rhodium-/gold-catalyzed reaction in one-pot. Next, we tested different gold(I) and gold(III) precatalysts (5 mol%) to solve the problem of inconsistent reaction time which we had with $HAuCl_4 \cdot 3\,H_2O$ (Table 3.2, entry 1).

Increasing the gold amount from 5 mol% to 9 mol% helped the consistency of reaction time. The reaction was over after 0.5 h with 77% yield of **3.50aa** (Table 3.2, entry 2). When we tried $NaAuCl_4$ instead of $HAuCl_4 \cdot 3\,H_2O$, the yield of **3.50aa** decreased dramatically to 10% (Table 3.2, entry 3). A similar behavior was observed when AuCl and $AuCl_3$ were used (Table 3.2, entries 4 and 5). Cationic gold source like $Ph_3PAu^+OTf^-$ (from Ph_3PAuCl and AgOTf) and the gold complex bearing an *N*-heterocyclic carbene ligand (*N*,*N*′-bis(2,6-diisopropylphenyl)imidazol-2-ylidene) turned out to be not efficient in this cycloisomerization (Table 3.2, entries 6 and 7). On the contrary, 5 mol% of $AuBr_3$ was found to be a highly effective precatalyst for the cycloisomerization of the allenol in a one-pot reaction with 72% NMR yield in 3 h (Table 3.2, entry 8). This is more efficient then the use of 9 mol% of $HAuCl_4 \cdot 3\,H_2O$.

We investigated the cycloisomerization also with silver catalysts in one-pot. After the complete conversion of **3.47a** was observed in the optimized rhodium-catalyzed reaction, 5 mol% of $AgNO_3$ was added, but no conversion of α-allenol **3.49aa** was observed.



Scheme 3.20. One-pot reaction with different organoboranes.

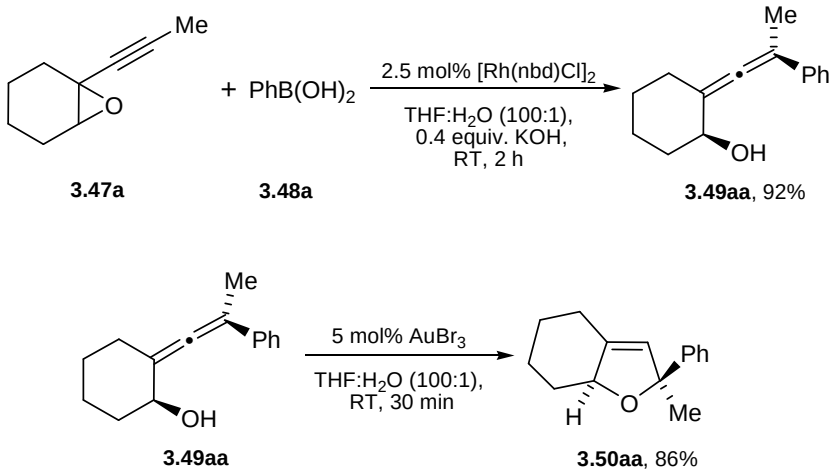
We also changed the organoboron type from arylboronic acid to arylboroxine. Unfortunately, the Rh-catalyzed reaction between phenylboroxine **3.51** (0.5 equiv., 0.1 mmol) and **3.47a** was not completed after 17 h, subsequent addition of 5 mol% $AuBr_3$ to reaction

mixture afforded 60% of **3.50aa** (NMR). In contrast, when potassium phenyltrifluoroborate ($PhBF_3K$) **3.52** was used as phenyl source, the Rh-catalyzed S_N2'-substitution did not proceed (Scheme 3.20).

After optimizing the one-pot reaction, the next step was to determine the reliability of the NMR yield; the isolated yield of 2,5-dihydrofuran **3.50aa** (72 mol%) was same as the NMR yield.

When the rhodium-catalyzed step was performed under air, no oxirane conversion was observed. However, after performing the rhodium-catalyzed reaction under argon, the reaction medium was exposed to air for the gold-catalyzed cycloisomerization, and 69% of **3.50aa** was isolated.

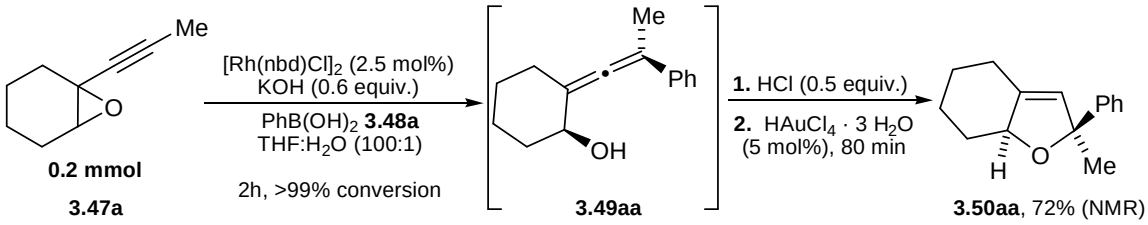
We then compared the efficiency of the one-pot sequence with the traditional multiflask sequence. The rhodium-catalyzed S_N2'-substitution of alkynyl oxirane **3.47a** with phenylboronic acid **3.48a** afforded 92 mol% isolated yield of α-allenol **3.49aa** under the optimum conditions. The allenol **3.49aa** underwent cycloisomerization in the absence of base with 5 mol% $AuBr_3$ to afford 86% of 2,5-dihydrofuran **3.50aa** in 30 minutes (Scheme 3.21). Thus, the overall yield of the traditional multiflask sequence was 79% **3.50aa** which was slightly higher than that of one-pot Rh/Au sequence (72%, isolated yield).



Scheme 3.21. Traditional multiflask sequence to obtain 2,5-dihydrofuran **3.50aa**.

Another alternative to perform the one-pot reaction was the neutralization of base which we have assumed to decrease the reactivity of the gold catalyst. For that purpose, the allenol formation reaction was carried out using 0.2 mmol of **3.47a**, 0.6 equiv. of KOH in 20 µL H_2O, 0.3 mmol of **3.48a**, 2.5 mol% of $[Rh(nbd)Cl]_2$ (5 mol% of Rh) in 2.0 mL THF at RT under Ar.

When the alkynyl oxirane **3.47a** was consumed, KOH was neutralized with 16.7 μL (0.5 equiv.) of HCl and then 5 mol% $HAuCl_4 \cdot 3\ H_2O$ was added to reaction mixture which yielded 72% (NMR) of **3.50aa** in 80 minutes (Scheme 3.22).



Scheme 3.22. Neutralization of base to accelerate the cycloisomerization step.

With the optimized conditions for the one-pot reaction in hand, we investigated the scope of the reaction with the oxirane **3.47a** and various arylboronic acids **3.48** in the presence of $[Rh(nbd)Cl]_2$ in THF/H_2O with KOH at RT for the first step. After completion of the allenol formation; 5 mol% of $AuBr_3$ was directly added at RT to the reaction mixture (Table 3.3).

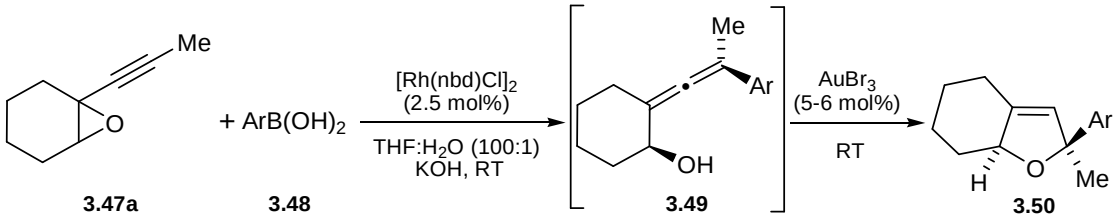
As shown in Table 3, the one-pot rhodium/gold-catalyzed reaction of **3.47a** with different substituents on *o*-, *m*- and *p*-positions of the phenyl ring of boronic acids and heteroarylboronic acid **3.48** was achieved with stereoselectivities higher than 90:10, except in the case of the sterically hindered *o*-tolylboronic acid.

Strongly electron withdrawing groups on the phenyl ring of the boronic acid such as 4-(trifluoromethyl)phenylboronic acid **3.48c** afforded 79% of 2,5-dihydrofuran **3.50ac** formation in one-pot. The electron-poor 4-acetylphenylboronic acid **3.48d** and 4-fluorophenylboronic acid **3.48e** also gave good isolated yields of 90% of **3.50ad** and 78% of **3.50ae**, respectively (Table 3.3, entries 3-5).

When electron-rich *p*-substituted arylboronic acids **3.48b** and **3.48f** were used, 80% of **3.50ab** and 68% of **3.50af** were isolated with high selectivity (Table 3.3, entries 2 and 6). Expectedly, the basic medium lowered the activity of 4-hydroxyphenylboronic acid **3.48g** towards oxirane **3.47a** and also resulted in low 2,5-dihydrofuran yield, albeit with high diastereoselectivity. When we changed the $[Rh(nbd)Cl]_2$ catalyst to $[Rh(cod)OH]_2$ (7.5% Rh) in the absence of KOH, 68% of **3.50ag** was isolated and diastereoselectivity decreased to *76:24* (Table 3.3, entries 7 and 8).

The reaction of sterically hindered 3-chlorophenylboronic acid **3.48h** with **3.47a** required a higher Rh concentration (7.5%) to afford a high yield of the corresponding 2,5-dihydrofuran **3.50ah**. Reaction conditions also tolerated the *m*-formylphenylboronic acid **3.48i**, and 77% of **3.50ai** was formed selectively (Table 3.3, entry 9-11).

Table 3.3. Scope of one-pot rhodium/gold-catalyzed reaction.[a]



3.47a **3.48** **3.49** **3.50**

		Au-catalyzed cycloisomerization	
Entry	**$ArB(OH)_2$ 3.48**	**Time (h)**	**Isolated Yield 3.50 [%] (*dr*)**
1	**3.48a** Ar= Ph	3	**3.50aa** 72 (*99:1*)
2	**3.48b** Ar= 4-MeC_6H_4	3	**3.50ab** 80 (*99:1*)
3	**3.48c** Ar= 4-$F_3CC_6H_4$	5	**3.50ac** 79 (*99:1*)
4	**3.48d** Ar= 4-$MeOCC_6H_4$	2	**3.50ad** 90 (*99:1*)
5	**3.48e** Ar= 4-FC_6H_4	2	**3.50ae** 78 (*99:1*)
6	**3.48f** Ar= 4-$MeOC_6H_4$	2	**3.50af** 68 (*99:1*)
7[b]	**3.48g** Ar= 4-HOC_6H_4	3	**3.50ag** 36 (*97:3*)
8[c]	**3.48g** Ar= 4-HOC_6H_4	1	**3.50ag** 68 (*74:26*)
9	**3.48h** Ar= 3-ClC_6H_4	2	**3.50ah** 60 (*99:1*)
10[b]	**3.48h** Ar= 3-ClC_6H_4	2	**3.50ah** 79 (*99:1*)
11	**3.48i** Ar= 3-$HOCC_6H_4$	4	**3.50ai** 77 (*99:1*)
12[e]	**3.48j** Ar= 2-MeC_6H_4	30	**3.50aj** 50 (*56:44*)
13[d,e]	**3.48j** Ar= 2-MeC_6H_4	48	**3.50aj** 63 (*56:44*)
14	**3.48k** Ar= 2-FC_6H_4	2	**3.50ak** 78 (*99:1*)
15	**3.48l** Ar= 2-thiophene	4	**3.50al** 64 (*90:10*)
16	**3.48m** Ar= 2-Naphthyl	6	**3.50am** 76 (*99:1*)

[a] Reaction conditions: 0.2 mmol of **3.47a**, 0.08 mmol of KOH in 20 µL H_2O, 0.3 mmol of **3.48**, 2.5 mol% of $[Rh(nbd)Cl]_2$ (5 mol% of Rh) in 2.0 mL THF at RT under Ar in 2-5 h. When the alkynyl oxirane **3.47a** was consumed (TLC control), 5-6 mol% of $AuBr_3$ was added to reaction mixture. [b] 7.5 mol% Rh. [c] 7.5 mol% Rh, $[Rh(cod)OH]_2$ in the absence of KOH. [d] 7.5 mol% $AuBr_3$, 12% of corresponding allenol was recovered. [e] For **3.50aj,** it is not clear that the ratio *56:44* represents atropisomerism or cis/trans isomerism.

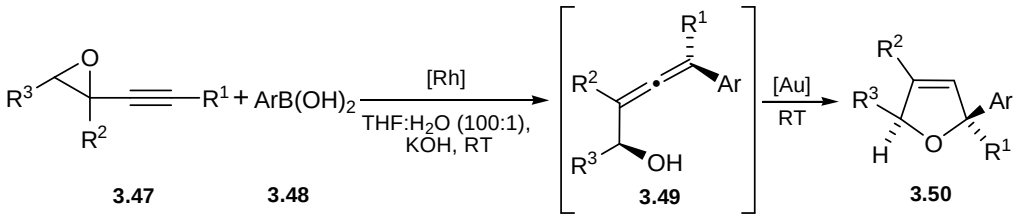
Reaction of sterically hindered *o*-tolylboronic acid with **3.47a** entailed higher Rh and Au concentrations (7.5%) to afford a moderate yield of the corresponding 2,5-dihydrofuran **3.50aj** in longer reaction times than other arylboronic acids (Table 3.3, entries 12 and 13). However, one-pot reaction of *o*-fluorophenyl boronic acid **3.48k** with **3.47a** succeeded to give 78% of **3.50ak** (Table 3.3, entry 14).

Moderate to high yields were also obtained with heteroarylboronic acid *e.g.*, 2-thiopheneboronic acid **3.48l,** and 2-napthaleneboronic acid **3.48m** (Table 3.3, entries 15 and 16).

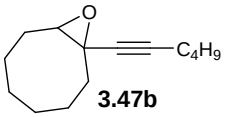
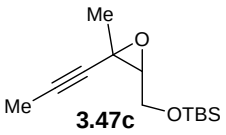
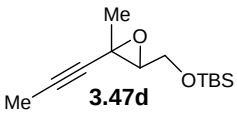
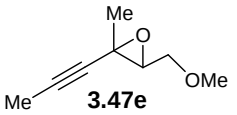
It must be noted, that *o*-hydroxyphenylboronic acid failed to undergo cycloisomerization of the allenol which was formed by Rh-catalysis. Under the optimized one-pot reaction

conditions, only 40% of the corresponding allenol was recovered. Even when 7.5 mol% of Rh and 5 mol% of $HAuCl_4 \cdot 3\,H_2O$ were used, 48% of the corresponding allenol was recovered, and the gold-catalyzed cycloisomerization did not proceed.

Table 3.4. Scope of the one-pot rhodium/gold-catalyzed reaction.[a]



3.47 **3.48** **3.49** **3.50**

			Au-catalyzed cycloisomerization	
Entry	**Alkynyl oxirane 3.47**	**$ArB(OH)_2$ 3.48**	**Time (h)**	**Isolated Yield 3.50 [%] (*dr*)**
1		**3.48a** Ar= Ph	8	**3.50ba** 73 (*99:1*)
2[b]	 **3.47b**	**3.48a** Ar= Ph	8	**3.50ba** 78 (*99:1*)
3		**3.48b** Ar= 4-MeC_6H_4	5	**3.50bb** 75 (*99:1*)
4		**3.48d** Ar= 4-$MeOCC_6H_4$	4	**3.50bd** 70 (*99:1*)
5	 **3.47c**	**3.48a** Ar= Ph	6	**3.50ca** 64 (*53:47*)
6		**3.48b** Ar= 4-MeC_6H_4	6	**3.50cb** 66 (*56:44*)
7		**3.48d** Ar= 4-$MeOCC_6H_4$	7-19	**3.50cd** 65 (*44:56*)
8	 **3.47d**	**3.48a** Ar= Ph	4	**3.50da** 76 (*99:1*)
9		**3.48b** Ar= 4-MeC_6H_4	4	**3.50db** 81 (*99:1*)
10		**3.48d** Ar= 4-$MeOCC_6H_4$	5	**3.50dd** 70 (*99:1*)
11	 **3.47e**	**3.48a** Ar= Ph	5	**3.50ea** 86 (*99:1*)
12		**3.48d** Ar= 4-$MeOCC_6H_4$	9	**3.50ed** 64 (*99:1*)

[a] Reaction conditions: 0.2 mmol of **3.47**, 0.08 mmol of KOH in 20 µL H_2O, 0.3 mmol of **3.48**, 2.5 mol% of $[Rh(nbd)Cl]_2$ (5 mol% of Rh) in 2.0 mL THF at RT under Ar in 2-5 h. When the alkynyl oxirane **3.47** was consumed (TLC control), 5-6 mol% of $AuBr_3$ was added to reaction mixture. [b] 7.5 mol% Au.

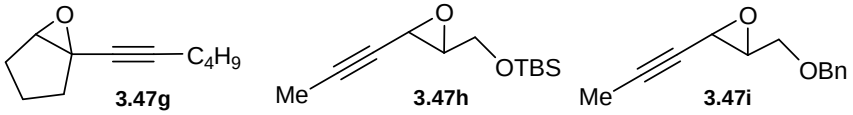
As shown in Table 3.4, the one-pot rhodium/gold catalyzed reaction of different alkynyl oxiranes **3.47** with substituted phenylboronic acids **3.48** also took place with high diastereoselectivities (99:1), except in the case of the *Z*-configured acyclic substrate **3.47c**.

Substrate **3.47b** with an eight-membered-ring structure gave the respective products **3.50ba**, **3.50bb** and **3.50bd** stereoselectively in high yields (Table 3.4, entries 1-4). In addition, the *E*-configured acyclic substrate **3.47d** also reacted with high yields (70-81%) and stereoselectively with electron-poor and -rich arylboronic acids (Table 3.4, entries 8-10).

Reaction of methyl ether of *E*-configured acyclic substrate **3.47e** with **3.48a** and **3.48d** afforded 84% of **3.50ea** and 64% of **3.50ed** with high selectivity, respectively (Table 3.4, entries 11 and 12).

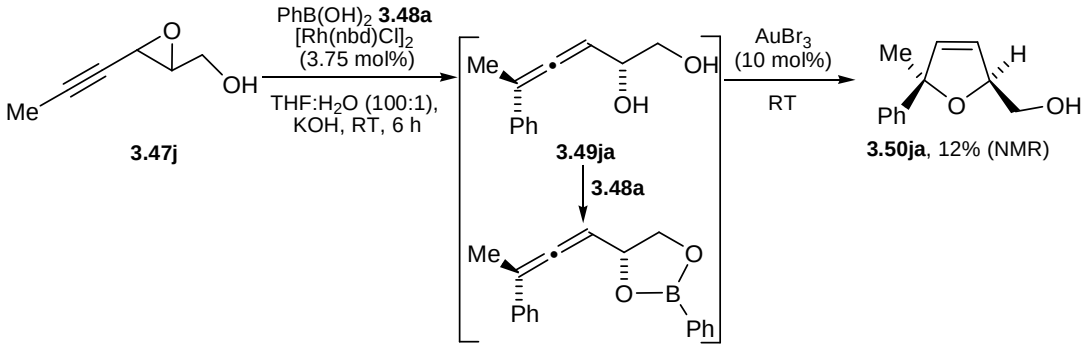
Interestingly, the *Z*-configured acyclic substrate **3.47c** also reacted with high yields but while the gold-catalyzed reactions were performed, epimerization took place and approximately 1:1-mixtures of diastereomers were isolated (Table 3.4, entries 5-7). We examined the gold precatalyst effect on the epimerization and have found out that the reaction of *Z*-configured acyclic substrate **3.47c** was accompanied by epimerization even in the presence of AuCl or $HAuCl_4 \cdot 3\ H_2O$.[17c]

Unfortunately, five-membered-ring substrate **3.47g** had failed to undergo gold-catalyzed cycloisomerization of the allenol which was formed in the Rh-catalyzed step (7.5% Rh), and 58% of the corresponding allenol was recovered. Decomposition occurred when the cycloisomerization of the corresponding allenol of **3.47g** was performed with 5 mol% $AuBr_3$ in CH_2Cl_2. Alkynyl oxiranes **3.47h** and **3.47i** gave complex mixtures (Scheme 3.23).



Scheme 3.23. Alkynyl oxiranes which were not efficient.

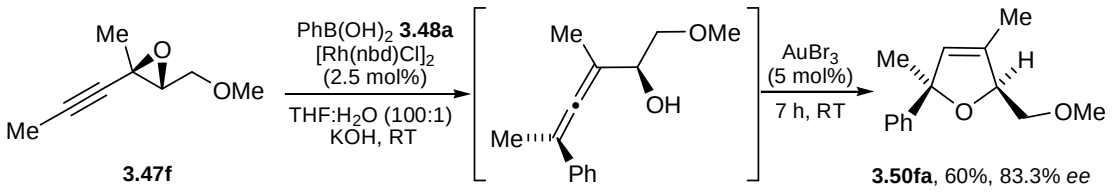
Reaction of unprotected alkynyl oxirane **3.47j** with phenylboronic acid **3.48a** yielded 12% of corresponding the 2,5-dihydrofuran **3.50ja** in the presence of 7.5% Rh and 10 mol% Au, respectively. Possible formation of a cyclic boronate which was formed by esterification of the allenediol did not permit efficient formation of the 2,5-dihydrofuran **3.50ja**. To achieve the synthesis of 2,5-dihydrofuran **3.50ja**, the cyclic boronate should be cleaved with diethanolamine to furnish the free diol for the cycloisomerization (Scheme 3.24).[27]



Scheme 3.24. The one-pot reaction between unprotected alkynyl oxirane **3.47j** and phenylboronic acid.

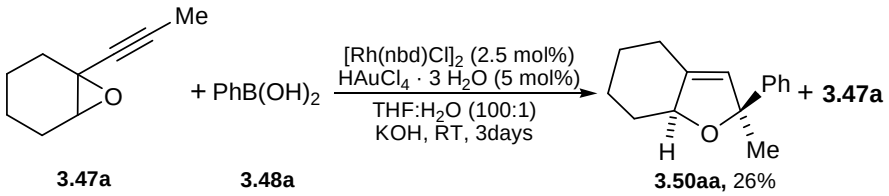
It was shown that the one-pot synthesis of 2,5-dihydrofurans from different alkynyl oxiranes with various arylboronic acids via combined rhodium-gold catalysis carried the diastereoselective information to next step with high yields.

Moreover, reaction of enantiomerically enriched alkynyl oxirane **3.47f** (84.5% *ee*) with **3.48a** afforded the 2,5-dihydrofuran **3.50fa** (83.3% *ee*) with almost complete chirality transfer (Scheme 3.25).



Scheme 3.25. Chirality transfer in the one-pot conversion of alkynyl oxirane **3.47f** to dihydrofuran **3.50fa**.

We also investigated the simultaneous addition of the rhodium and gold catalyst to the reaction flask together from the beginning of reaction. However, the reaction was rather slow, compared to the sequential one-pot reaction; incomplete addition of phenylboronic acid **3.48a** to **3.47a** to form **3.49aa** and complete cyclization of allenol **3.49aa** to 2,5-dihydrofuran **3.50aa** (26%) were achieved with $[Rh(nbd)Cl]_2$ (5% Rh) and $HAuCl_4 \cdot 3\,H_2O$ (5% Au) in basic THF solution in 3 days (Scheme 3.26).

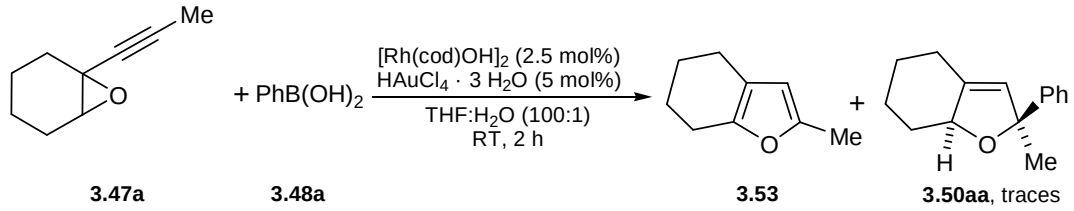


Scheme 3.26. Rhodium/gold tandem reaction.

Without base and with $[Rh(cod)OH]_2$–$AuBr_3$ catalysts the reaction preferred to provide furan **3.53** (27%) by direct gold-catalyzed cycloisomerization of oxirane **3.47a**.[28]

When we changed the gold source from $AuBr_3$ to $HAuCl_4 \cdot 3\,H_2O$, alkynyl oxirane **3.47a** was consumed in 2 h and furan **3.53** formation was observed in TLC, accompanied by traces of 2,5-dihydrofuran **3.50aa** (Scheme 3.27).

[28] A. S. K. Hashmi, S. Pradipta, *Adv. Synth. Catal.* **2004**, *346*, 432–438.



Scheme 3.27. Rhodium/gold-catalyzed reaction in the absence of base.

3.4. CONCLUSION

In summary, an efficient, one-pot synthesis of 2,5-dihydrofurans was developed by sequential rhodium-gold catalysis with high yields and selectivities under mild conditions. The one-pot procedure can be applied to various oxiranes and arylboronic acids. The crucial issue is the high *syn*-selectivity of the rhodium-catalyzed S_N2'-substitution which was transferred to the 2,5-dihydrofuran in the subsequent gold-catalyzed cycloisomerization with center-to-axis-to-center chirality transfer.

3.5. EXPERIMENTAL PART

General Remarks:

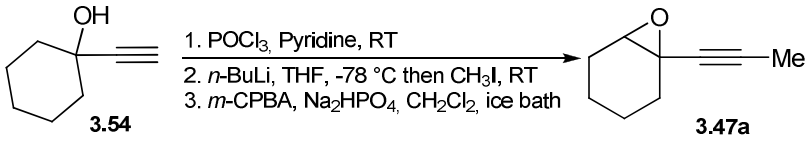
Reactions were performed under an argon atmosphere if not noted otherwise. Gold precatalysts were purchased from commercial sources (Acros, Sigma-Aldrich and Chempur) and used without further purification. $[Rh(nbd)Cl]_2$[29] was purchased from Sigma-Aldrich and purified based on the literature. Rhodium complexes $[Rh(cod)Cl]_2$[30], $[Rh(cod)OH]_2$[31] and $[Rh(cod)OMe]_2$[31] were synthesized according to the literature. Column chromatography was carried out with Macherey-Negel silica gel 60. ^{1}H-NMR and ^{13}C-NMR spectra were recorded with Bruker DRX 400 or DRX 500 spectrometers in C_6D_6 as solvent. Chemical shifts were determined relative to the residual solvent peaks (C_6H_6: δ = 7.16 for protons, δ = 128.06 for carbon atoms). The signals of the major component of a product mixture are marked with an asterisk (*). Reactions were monitored by both TLC and GC analysis. GC analyses were carried out with a Carlo Erba Instruments GC 8000 top gas chromatograph on a CP-SIL-5 CB

[29] E. W. Abel, M.A. Bennett, G. Wilkonson, *J. Chem. Soc.* **1959**, 3178–3182.
[30] G. Giordano, R. H. Crabtree, *Inorg. Synth.* **1979**, *19***,** 218–220.
[31] R. Uson, L. A. Oro, J. A. Cabeza, *Inorg. Synth.* **1985**, *23*, 126–130.

capillary column (30 m x 0.32 mm x 0.25 μm) with helium as the carrier gas. GC-MS analyses were carried out with an Agilent HP 6890 as gas chromatograph on a HP-5MS column (25 m x 0.2mm x 0.33 μm) and an Agilent HP 5973 as mass spectrometer. High-resolution mass spectral analyses were performed on a Thermo Electron system. IR spectra were obtained with a Nicolet Avatar 320 FT-IR spectrophotometer as a liquid film between NaCl plates. Optical rotations were measured on Perkin Elmer Polarimeter 341. Melting points were recorded on a Reichert Thermovar melting point apparatus and are uncorrected.

3.5.1. Synthesis of Alkynyl Oxiranes

3.5.1.1. Synthesis of 1-(Prop-1-ynyl)-7-oxa-bicyclo[4.1.0]heptane (3.47a)



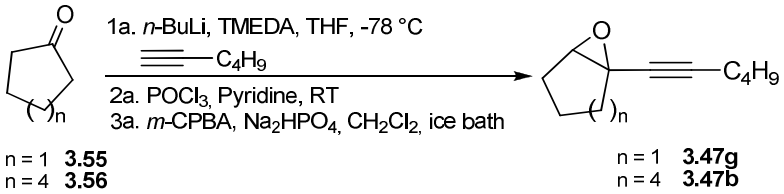
Step 1: Preparation of enyne.[32] To a stirred solution of alkynyl alcohol **3.54** (4.97 g, 40 mmol) in pyridine (21.5 mL) was added $POCl_3$ (5.7 mL, 61.6 mmol) at 0 °C, and the stirring was continued for 5 h at RT. Ice was added to reaction mixture at 0 °C and layers were separated and the aqueous layer was extracted with Et_2O. The combined extracts were washed with 10% HCl, water and sat. $NaHCO_3$ and dried over anhydrous $MgSO_4$ and the solvent was evaporated under reduced pressure. The crude residue was purified by column chromatography on silica gel with cyclohexane.

Step 2: Methylation of enyne.[33] 1-ethynylcyclohexene (2.5 g, 23.6 mmol), and dry THF (26 mL) was added to flask. The flask was cooled to -78 °C, and 2.5 M *n*-BuLi in hexanes (9.7 mL, 24.1 mmol) was added via syringe. After the reaction stirred for 1 h at -78 °C, iodomethane (1.52 mL, 24.1 mmol) was added dropwise. The reaction was allowed to warm to room temperature and stirred an additional 2 h. Water was added to reaction and extracted with Et_2O then dried with $MgSO_4$. Distillation under reduced pressure afforded the product as colorless oil (2.2 g, 77% yield, b.p. 33 °C_0.2 mm Hg).

[32] M. Yoshida, M. Hayashi, K. Shishido, *Org. Lett.* **2007**, *9*, 1643–1646.
[33] C. Cao, Y. Li, Y. Shi, A. L. Odom, *Chem. Commun.* **2004**, 2002–2003.

Step 3: Preparation of alkynyl oxirane. To a stirred solution of enyne (2.2 g, 18.3 mmol) in CH_2Cl_2 (60 mL) was added *m*-CPBA (6.3 g, 27.4 mmol) and Na_2HPO_4 (3.1 g, 22 mmol) in an ice bath, and stirring was continued for overnight. The reaction mixture was diluted with saturated aqueous solution of Na_2CO_3, $Na_2S_2O_3$, NaOH (2 N) and extracted with CH_2Cl_2. The combined extracts were washed once more with sat. $Na_2S_2O_3$, brine and dried over anhydrous $MgSO_4$ and the solvent was evaporated under reduced pressure. The crude residue was purified by column chromatography on silica gel (cyclohexane/EtOAc, 18:1) afforded 1.37 g (55%) of **3.47a**.as colorless oil.

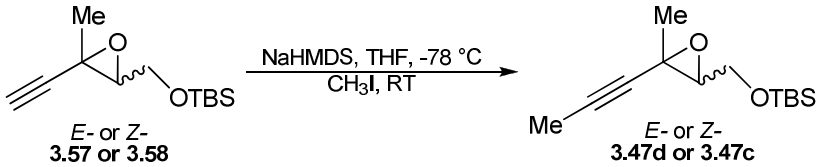
3.5.1.2. General Procedure for Synthesis of 1-(Hex-1-ynyl)-6-oxa-bicyclo[3.1.0] hexane (3.47g) and 1-(hex-1-ynyl)-9-oxa-bicyclo[6.1.0]nonane (3.47b)



Step 1a: Preparation of alkynyl alcohols.[32] To a stirred solution of 1-hexyne (2.9 mL, 24.1 mmol) in THF (61 mL) were added 1.6 M hexane solution of *n*-BuLi (16.3 mL, 26.1 mmol) and TMEDA (3.6 mL, 24.1 mmol) at -78 °C. After stirring was continued for 1 h, cyclic ketone **3.55/3.56** (20 mmol) was added dropwise to the reaction mixture at the same temperature, and stirring was continued for 2 h at the same temperature. The reaction mixture was diluted with water and then extracted with EtOAc. The combined extracts were washed with brine and residue obtained when the organic layer was separated and dried over anhydrous $MgSO_4$ and the solvent was evaporated under reduced pressure. The crude residue was purified by column chromatography on silica gel.

For step 2a and 3a; see 3.5.1.1. Synthesis of 1-(Prop-1-ynyl)-7-oxa-bicyclo[4.1.0]heptane (**3.47a**).

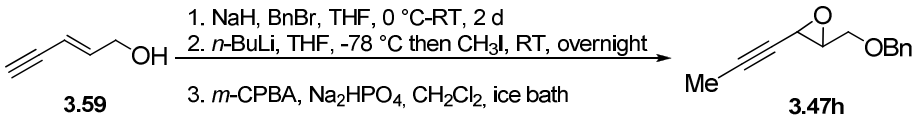
3.5.1.3. General Procedure for Synthesis of *E*- and *Z*-((3-Methyl-3-(prop-1-ynyl) oxirane-2-yl)methoxy)(*t*-butyl)dimethylsilane (3.47d and 3.47c)



For synthesis of *E*- and *Z*-alkynyl oxirane; see Chapter 2, 2.5.1.Synthesis of α-Hydroxyallenes.

Methylation of *E*- and *Z*-alkynyl oxirane. To a stirred solution of alkynyl oxirane **3.57/3.58** (678 mg, 3 mmol) in THF (4 mL) were added NaHMDS (1.55 mL, 3.1 mmol) at -78 °C. After stirring was continued for 1 h, iodomethane (0.2 mL, 3.1 mmol) was added dropwise to the reaction mixture at the same temperature. The reaction was allowed to warm to room temperature and stirred an additional 5 h. The reaction mixture was diluted with water and then extracted with Et_2O. The combined extracts were washed with brine and residue obtained when the organic layer was separated and dried over anhydrous $MgSO_4$ and the solvent was evaporated under reduced pressure. The crude residue was purified by column chromatography on silica gel (isohexane/EtOAc, 20:1).

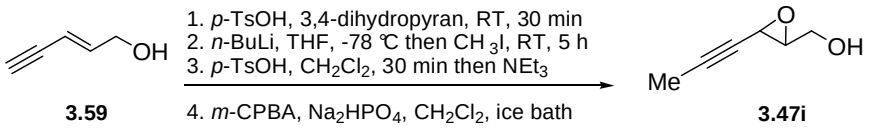
3.5.1.4. General Procedure for Synthesis of *E*-2-((Benzyloxy)methyl)-3-(prop-1-ynyl)oxirane (3.47h)



Step 1: Benzylation of *E*-enynol. To a suspension of NaH (60% disp. in oil, 204 mg, 5.1 mmol) in THF (10 mL) was **3.59** added at 0 °C and stirred for 30 min. Then at room temperature, BnBr (700 mg, 3.9 mmol) was added. The reaction mixture was stirred at room temperature for 2 d then was quenched with aq. sat. solution of NH_4Cl. After extraction with Et_2O, the organic layer was dried with $MgSO_4$ and concentrated under vacuum. The residue was used for the next steps.

For step 2 and 3; see 3.5.1.1. Synthesis of 1-(Prop-1-ynyl)-7-oxa-bicyclo[4.1.0]heptane (**3.47a**).

3.5.1.5. General Procedure for Synthesis of *E*-(3-(Prop-1-ynyl)oxiran-2-yl)methanol (3.47i)



3.59 **3.47i**

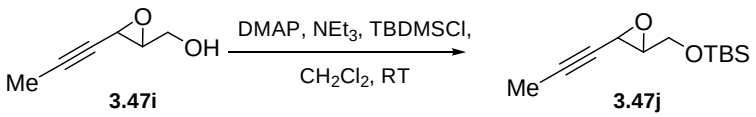
Step 1 and 2.[34] To a solution of commercial *E*-pent-2-en-4-yn-1-ol **3.59** (1.6 g, 20 mmol) and 3,4-dihydropyran (2.2 mL) was added *p*-toluenesulfonic acid (44 mg, 0.02 mmol) and stirred for 30 min at room temperature. Then the mixture was diluted with 40 mL dry THF under argon and cooled to -78 °C. At that temperature 1.5 M *n*-BuLi in hexanes (16 mL, 24 mmol) was added via syringe. After the reaction stirred for 30 min at -78 °C, iodomethane (2.5 mL, 40 mmol) was added dropwise. The reaction was allowed to warm to room temperature and stirred an additional 5 h. Quenched with sat. NH_4Cl and extracted with Et_2O and washed with water. The organic layer was dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was used in the following step without any other purification.

Step 3.[34] A solution of the preceding crude compound in methanol (60 mL) was treated with *p*-toluenesulfonic acid (1.2 g, 6 mmol) and stirred at RT for 30 min. Then triethylamine was added (1.8 mL), and the solution was concentrated under reduced pressure. The mixture was taken in dichloromethane and washed with water. The combined extracts were washed with brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Purification by column chromatography on silica gel (isohexane/EtOAc, 7:1) gave corresponding enynol (1.66 g, 86%, for 3 steps) as light yellow oil.

For step 4; see 3.5.1.1. Synthesis of 1-(Prop-1-ynyl)-7-oxa-bicyclo[4.1.0]heptane (**3.47a**). Purification by column chromatography on silica gel (isohexane/EtOAc, 7:1) gave **3.47i** (166.2 mg, 21%) as a light yellow oil.

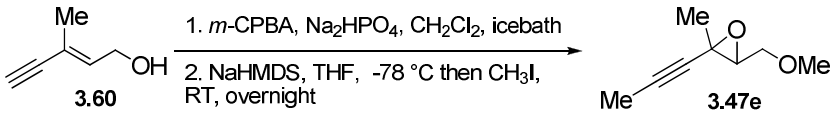
[34] J. F. Betzer, F. Delaloge, B. Muller, A. Pancrazi, J. Prunet, *J. Org. Chem.* **1997**, *62*, 7768–7780.

3.5.1.6. General Procedure for Synthesis of *E*-((3-(Prop-1-ynyl)oxiran-2-yl)methoxy)(tert-butyl)dimethylsilane (3.47j)



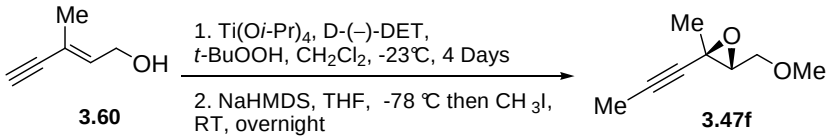
A solution of **3.47i** (199 mg, 0.89 mmol) in CH_2Cl_2 (4 mL) was treated with DMAP (5 mg, 0.04 mmol), triethylamine (108 mg, 1.07 mmol) and TBDMSCl (148 mg, 0.98 mmol), respectively. The reaction mixture was stirred at room temperature for overnight then was quenched with aq. sat. solution of NH_4Cl (10 mL). After extraction with CH_2Cl_2 (3 × 25 mL), the organic layer was dried with $MgSO_4$ and concentrated under vacuum. The residue was purified by column chromatography on silica gel (isohexane/EtOAc, 15:1) to give **3.47j** (135.3 mg, 67%) as a yellow oil.

3.5.1.7. General Procedure for Synthesis of *E*-3-(Methoxymethyl)-2-methyl-2-(prop-1-ynyl)oxirane (3.47e)



For step 1; see 3.5.1.1. Synthesis of 1-(Prop-1-ynyl)-7-oxa-bicyclo[4.1.0]heptane (**3.47a**) and for step 2; see 3.5.1.3. Synthesis of *E*- and *Z*-((3-Methyl-3-(prop-1-ynyl)oxiran-2-yl)methoxy)(*t*-butyl)dimethylsilane (**3.47d** and **3.47c**). Purification by column chromatography on silica gel (cyclohexane/EtOAc, 12:1) gave **3.47e** (713.6 mg, 51%, for 2 steps) as a light yellow oil.

3.5.1.8. General Procedure for Synthesis of (*2R,3R*)-3-(Methoxymethyl)-2-methyl-2-(prop-1-ynyl)oxirane (3.47f)



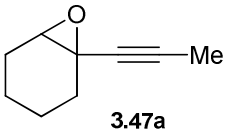
Step1.[35] To a suspension of powdered, activated molecular sieves (4Å, 2 g) in CH_2Cl_2 (35 mL) were D-(–)-DET (0.495 g, 2.4 mmol) and Ti(O*i*-Pr)$_4$ (0.4 mL, 2.0 mmol) added at -30 °C. After being stirred at -30 °C for 20 min was **3.60** (1.1 mL, 10.0 mmol) added dropwise over 10 min. The mixture was stirred for additional 40 min at -30 °C then cooled to -50 °C. *t*-Butyl hydroperoxide (TBHP, 3.8M solution in toluene, 16 mL, 60 mmol, predried with 1.6 g powdered, activated molecular sieves 4Å) was slowly added over a period of 10 min. The reaction mixture was further stirred at -30 °C for 1 h before it was put in fridge with an inner temperature of -23 °C. After 5 days the reaction mixture was transferred in a bigger flask at 0 °C, the molecular sieves should not be transferred if possible. To this mixture a precooled (with ice bath) solution of $FeSO_4 \cdot 7\ H_2O$ (60 g, 216 mmol) and tartaric acid (1.2 g, 8 mmol) in H_2O (240 mL) was added. The mixture was stirred at 0 °C for 1 h then allowed to warm up to room temperature. After extraction with Et_2O (6 × 100 mL), was the organic layer dried with $MgSO_4$ and concentrated under vacuum (up to 300 mbar). The crude product, which was a solution mainly of alkynyl oxirane and D-(–)-DET in toluene, was direct applied in the next step.

For step 2; see 3.5.1.3. Synthesis of *E*- and *Z*-((3-Methyl-3-(prop-1-ynyl)oxiran-2-yl)methoxy)(*t*-butyl)dimethylsilane (**3.47d** and **3.47c**). Purification by column chromatography on silica gel (isohexane/EtOAc, 12:1 to 8:1) gave **3.47f** (523.3 mg, 38%, for 2 steps) as a light yellow oil.

[35] Tao Sun, Ph.D Thesis, Dortmund University of Technology.

3.5.2. Characterization Data of Alkynyl Oxiranes

1-(Prop-1-ynyl)-7-oxa-bicyclo[4.1.0]heptane (3.47a)



3.47a

OAA3PT

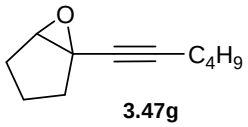
^{1}H-NMR (400 MHz, C_6D_6)**:** δ 3.24 (d, *J*= 3.8 Hz, 1H), 2.20-2.14 (m, 1H), 1.95-1.88 (m, 1H), 1.67-1.60 (m, 1H), 1.44 (s, 3H), 1.45-1.37 (m, 1H), 1.31-1.12 (m, 2H), 1.01-0.92 (m, 1H), 0.88-0.78 (m, 1H)

^{13}C-NMR (100 MHz, C_6D_6)**:** δ 81.0, 78.2, 59.5, 50.4, 30.6, 24.5, 19.8, 19.4, 3.2

IR (ν_{max}/cm^{-1})**:** 2940, 2861, 2252, 1774, 1435, 1384, 1358, 1294, 1226, 1122, 960, 848, 761

HRMS (m/z, $[M]^+$)**:** 136.0883 (calculated), 136.0880 (found)

1-(Hex-1-ynyl)-6-oxa-bicyclo[3.1.0]hexane (3.47g)



3.47g

OAB3T

Purification by column chromatography on silica gel (cyclohexane/ethyl acetate, 20:1) afforded 1.33 g (40%) of **3.47g** as colorless oil.

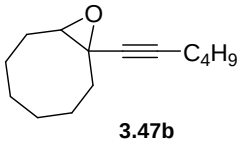
^{1}H-NMR (400 MHz, C_6D_6)**:** δ 3.43 (s, 1H), 2.09 (dd, *J*= 13.8, 8.0 Hz, 1H), 2.02 (t, *J*= 6.8 Hz, 3H), 1.67-1.59 (m, 2H), 1.36-1.21 (m, 5H), 1.18-1.09 (m, 2H), 0.75 (t, *J*= 7.2 Hz, 3H)

^{13}C-NMR (100 MHz, C_6D_6)**:** δ 84.9, 77.9, 64.5, 56.0, 32.5, 30.9, 27.7, 22.2, 19.5, 18.8, 13.7

IR (ν_{max}/cm^{-1})**:** 3024, 2958, 2933, 2873, 2242, 1773, 1727, 1466, 1434, 1403, 1382, 1328, 1296, 1263, 1213, 1096, 1053, 938, 876, 855, 794

HRMS (m/z, $[M]^+$)**:** 164.1196 (calculated), 164.1191 (found)

1-(Hex-1-ynyl)-9-oxa-bicyclo[6.1.0]nonane (3.47b)



3.47b

OAC3

Purification by column chromatography on silica gel (isohexane/ethyl acetate, 42:1) afforded 0.435 g (42%) of **3.47b** as colorless oil.

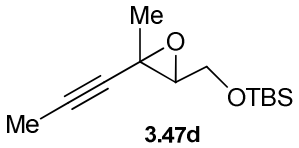
^{1}H-NMR (400 MHz, C_6D_6)**:** δ 3.06 (*J*= 9.7, 4.1 Hz, 1H), 2.23 (dt, *J*= 13.4, 3.4 Hz, 1H), 2.00 (t, *J*= 6.8 Hz, 2H), 1.91-1.79 (m, 2H), 1.56-1.05 (m, 13H), 0.75 (t, *J*= 7.0 Hz, 3H)

^{13}C-NMR (100 MHz, C_6D_6)**:** δ 83.0, 81.1, 63.3, 53.8, 31.5, 31.0, 27.6, 26.7, 26.4, 25.5, 22.2, 18.7, 13.7

IR (ν_{max}/cm^{-1})**:** 2957, 2929, 2858, 2244, 1728, 1469, 1383, 1327, 1267, 1195, 1159, 1118, 928, 879, 849

HRMS (m/z, $[M+H]^+$)**:** 207.17434 (calculated), 207.17431 (found)

E-((3-Methyl-3-(prop-1-ynyl)oxiran-2-yl)methoxy)(*t*-butyl)dimethylsilane (3.47d)



3.47d

OAEOX2/OAEOX3T

Yield: 0.344 g (48%) of **3.47d** as light yellow oil.

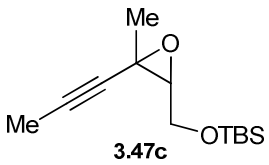
^{1}H-NMR (400 MHz, C_6D_6)**:** δ 3.64-3.54 (m, 2H), 3.44 (t, *J*= 5.4 Hz, 1H), 1.41 (s, 3H), 1.37 (s, 3H), 0.93 (s, 9H), 0.03 (s, 3H), 0.01 (s, 3H)

^{13}C-NMR (100 MHz, C_6D_6)**:** δ 80.6, 78.4, 64.2, 62.0, 50.9, 26.0, 19.2, 18.4, 3.1, -5.1, -5.3

IR (ν_{max}/cm^{-1})**:** 2956, 2930, 2886, 2858, 2247, 1472, 1463, 1383, 1362, 1258, 1132, 1090, 1070, 838, 778

HRMS (m/z, $[M+H]^+$)**:** 241.16183 (calculated), 241.16190 (found)

Z-((3-Methyl-3-(prop-1-ynyl)oxiran-2-yl)methoxy)(*t*-butyl)dimethylsilane (3.47c)



3.47c

OAZM

Yield: 570 mg (58%) of **3.47c** as light yellow oil.

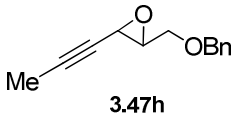
^{1}H-NMR (400 MHz, C_6D_6)**:** δ 4.10-3.95 (m, 2H), 2.95 (t, *J*= 5.2 Hz, 1H), 1.38 (s, 3H), 1.37 (s, 3H), 0.99 (s, 9H), 0.12 (s, 3H), 0.11 (s, 3H)

^{13}C-NMR (100 MHz, C_6D_6)**:** δ 80.9, 77.7, 64.3, 63.9, 52.0, 26.1, 23.8, 18.5, 3.2, -5.0, -5.1

IR (ν_{max}/cm^{-1})**:** 2956, 2930, 2885, 2858, 2245, 1726, 1472, 1464, 1380, 1361, 1309, 1255, 1136, 1091, 838, 778

HRMS (m/z, $[M+H]^+$)**:** 241.16183 (calculated), 241.16193 (found)

E-2-((Benzyloxy)methyl)-3-(prop-1-ynyl)oxirane (3.47h)



3.47h

OAG

Yield: 131.6 mg (22%) of **3.47h** as light yellow oil.

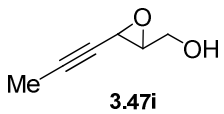
^{1}H-NMR (500 MHz, C_6D_6)**:** δ 7.20-7.06 (m, 5H), 4.24 (s, 2H), 3.25-3.17 (m, 3H), 3.11-3.08 (m, 1H), 1.38 (s, 3H)

^{13}C-NMR (125 MHz, C_6D_6)**:** δ 138.6, 128.6, 128.4, 127.8, 80.4, 76.6, 73.3, 69.3, 58.7, 43.3, 3.2

IR (ν_{max}/cm^{-1})**:** 3063, 3030, 3001, 2919, 2858, 2242, 1772, 1727, 1496, 1453, 1384, 1363, 1318, 1240, 1096, 877, 739

HRMS (m/z, $[M]^+$)**:** 202.0988 (calculated), 202.0981 (found)

E-(3-(Prop-1-ynyl)oxiran-2-yl)methanol (3.47i)



3.47i

OAHT

Yield: 166.2 g (21%) of **3.47i** as light yellow oil.

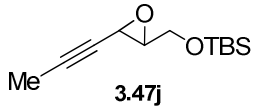
^{1}H-NMR (500 MHz, C_6D_6)**:** δ 3.28-3.22 (m, 2H), 3.12-3.11 (m, 1H), 2.098-2.97 (m, 1H), 1.38 (s, 3H), 1.14 (s, 1H)

^{13}C-NMR (125 MHz, C_6D_6)**:** δ 80.5, 76.5, 60.6, 59.9, 43.1, 3.2

IR (ν_{max}/cm^{-1})**:** 3442, 2996, 2921, 2857, 1620, 1453, 1384, 1330, 1224, 1161, 1073, 1025, 878

HRMS (m/z, $[M]^+$)**:** 112.0519 (calculated), 112.0518 (found)

E-((3-(Prop-1-ynyl)oxiran-2-yl)methoxy)(*t*-butyl)dimethylsilane (3.47j)



3.47j

OAIT

Yield: 135.3 mg (67%) of **3.47j** as light yellow oil.

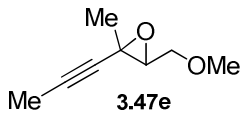
^{1}H-NMR (400 MHz, C_6D_6)**:** δ 3.49-3.45 (m, 1H), 3.37-3.33 (m, 1H), 3.29 (s, 1H), 3.15 (m, 1H), 1.37 (s, 3H), 0.90 (s, 9H), -0.01 (s, 6H)

^{13}C-NMR (100 MHz, C_6D_6)**:** δ 80.3, 76.7, 62.4, 60.1, 43.2, 25.9, 18.5, 3.2, -5.3

IR (ν_{max}/cm^{-1})**:** 2956, 2929, 2886, 2857, 1472, 1463, 1439, 1389, 1362, 1255, 1135, 1100, 1045, 1006, 949, 882, 837, 778

HRMS (m/z, $[M+H]^+$)**:** 227.1389 (calculated), 227.14618 (found)

E-3-(Methoxymethyl)-2-methyl-2-(prop-1-ynyl)oxirane (3.47e)



3.47e

OAKT

Yield: 713.6 mg (51%) of **3.47e** as colorless oil.

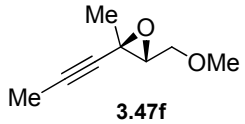
^{1}H-NMR (400 MHz, C_6D_6)**:** δ 3.42 (t, *J*= 5.1 Hz, 1H), 3.24-3.14 (m, 2H), 3.03 (s, 3H), 1.38 (s, 3H), 1.35 (s, 3H)

^{13}C-NMR (100 MHz, C_6D_6)**:** δ 80.5, 78.4, 70.6, 62.4, 58.6, 50.3, 19.2, 3.1

IR (ν_{max}/cm^{-1})**:** 2987, 2923, 2823, 2246, 1450, 1383, 1360, 1263, 1197, 1127, 1096, 1073, 1042, 947, 922, 846, 777

HRMS (m/z, $[M]^+$)**:** 140.0832 (calculated), 140.0834 (found)

(*2R,3R*)-3-(Methoxymethyl)-2-methyl-2-(prop-1-ynyl)oxirane (3.47f)



3.47f

OAJT

Yield: 523.3 mg (38%) of **3.47f** as colorless oil.

^{1}H-NMR (500 MHz, C_6D_6)**:** δ 3.42 (t, *J*= 5.0 Hz, 1H), 3.21-3.17 (m, 2H), 3.04 (s, 3H), 1.38 (s, 3H), 1.35 (s, 3H)

^{13}C-NMR (125 MHz, C_6D_6)**:** δ 80.6, 78.3, 70.6, 62.4, 58.7, 50.3, 19.2, 3.1

IR (ν_{max}/cm^{-1}): 2986, 2921, 2895, 2857, 2823, 2389, 1380, 1330, 1264, 1197, 1129, 1098, 1073, 1043, 825, 813

HRMS (m/z, $[M+H]^+$)**:** 141.09101 (calculated), 141.09075 (found)

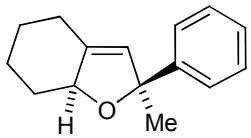
Optical rotation (589 nm, d = 10 cm)**:** $[\alpha]^{20}_D$ = + 10.8 (*c* 1.52, $CHCl_3$)

3.5.3. General Procedure for the Rhodium- and Gold-Catalyzed One-Pot Synthesis of 2,5-Dihydrofurans from Alkynyl Oxiranes with Arylboronic Acids

In a Schlenk flask flushed with Ar, 2.5-3.75 mol% of $[Rh(nbd)Cl]_2$ (5-7.5 mol% Rh, 0.01-0.015 mmol) and arylboronic acid (1.5 equiv., 0.3 mmol) were dissolved in THF (1 mL, Argon purged). After that KOH (0.4 equiv., 0.08 mmol) in H_2O (20 µL, Argon purged) was successively added and the mixture was stirred for ~2 minutes. Then the corresponding alkynyl oxirane (0.2 mmol) dissolved in THF (1 mL) was added. The reaction mixture was stirred at room temperature until the complete consumption of alkynyl oxirane was monitored by Thin Layer Chromatography (TLC). When the alkynyl oxirane was consumed, 5-7.5 mol% of gold catalyst was added to reaction mixture. Even incomplete conversion of the alkynyl oxirane was observed in 24 h, the gold catalyst was added. The reaction was monitored by TLC until the complete conversion of allenol to 2,5-dihydrofuran. The solvent was removed under reduced pressure and the residue was purified by column chromatography (isohexane/EtOAc, 12:1) to give 2,5-dihydrofuran.

3.5.4. Characterization Data of 2,5-Dihydrofurans

2,4,5,6,7,7a-Hexahydro-2-methyl-2-phenylbenzofuran (3.50aa)



3.50aa

R194/R205/R206/R215

Yield: 72% of **3.50aa** as light yellow oil.

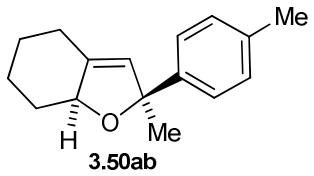
^{1}H-NMR (400 MHz, C_6D_6)**:** δ 7.56 (d, *J*= 8.0 Hz, 2H), 7.24 (t, *J*= 7.8 Hz, 2H), 7.10 (t, *J*= 7.3 Hz, 1H), 5.33 (s, 1H), 4.62-4.58 (m, 1H), 2.24-2.17 (m, 2H), 1.75-1.68 (m, 1H), 1.66 (s, 3H), 1.44-1.36 (m, 2H), 1.33-1.27 (m, 1H), 1.05-0.94 (m, 1H), 0.92-0.81 (m, 1H)

^{13}C-NMR (100 MHz, C_6D_6)**:** δ 148.5, 140.5, 128.4, 126.6, 125.3, 125.0, 90.3, 84.2, 36.1, 29.6, 27.2, 26.8, 23.5

IR (ν_{max}/cm^{-1})**:** 3085, 3061, 3025, 2970, 2934, 2857, 1672, 1601, 1493, 1445, 1365, 1338, 1254, 1191, 1073, 1051, 1028, 951, 900, 821, 761

HRMS (m/z, $[M+H]^+$)**:** 215.14304 (calculated), 215.14300 (found)

2,4,5,6,7,7a-Hexahydro-2-methyl-2-*p*-tolylbenzofuran (3.50ab)



3.50ab

OAR210/OAR222

Yield: 80% of **3.50ab** as colorless oil.

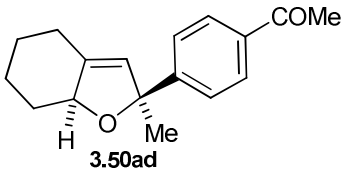
^{1}H-NMR (400 MHz, C_6D_6)**:** δ 7.50 (d, *J*= 8.0 Hz, 2H), 7.09 (d, *J*= 7.8 Hz, 2H), 5.37 (s, 1H), 4.64-4.60 (m, 1H), 2.26-2.18 (m, 2H), 2.16 (s, 3H), 1.76-1.71 (m, 1H), 1.69 (s, 3H), 1.46-1.39 (m, 2H), 1.37-1.30 (m, 1H), 1.07-0.84 (m, 2H)

^{13}C-NMR (100 MHz, C_6D_6)**:** δ 145.6, 140.4, 135.8, 129.1, 125.4, 125.2, 90.3, 84.2, 36.2, 29.6, 27.2, 26.9, 23.6, 21.0

IR (ν_{max}/cm^{-1})**:** 3090, 3063, 3022, 2969, 2934, 2857, 2360, 1672, 1510, 1445, 1364, 1338, 1321, 1254, 1186, 1089, 1075, 1052, 1020, 951, 935, 900, 816

HRMS (m/z, $[M+H]^+$)**:** 229.15869 (calculated), 229.15862 (found)

1-(4-(2,4,5,6,7,7a-Hexahydro-2-methylbenzofuran-2-yl)phenyl)ethanone (3.50ad)



3.50ad

OAR223

Yield: 90% of **3.50ad** as white solid. **MP:** 75-76 °C

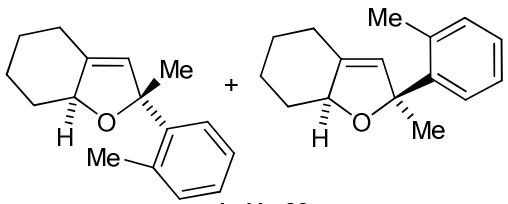
^{1}H-NMR (400 MHz, C_6D_6)**:** δ 7.86 (d, *J*= 8.5 Hz, 2H), 7.48 (d, *J*= 8.5 Hz, 2H), 5.25 (s, 1H), 4.60-4.56 (m, 1H), 2.24-2.17 (m, 2H), 2.14 (s, 3H), 1.74-1.65 (m, 1H), 1.59 (s, 3H), 1.46-1.39 (m, 2H), 1.32-1.22 (m, 1H), 1.05-0.94 (m, 1H), 0.91-0.80 (m,1H)

^{13}C-NMR (100 MHz, C_6D_6)**:** δ 196.3, 153.3, 141.2, 136.1, 128.6, 125.3, 124.1, 90.3, 84.4, 36.1, 29.5, 27.2, 26.8, 26.2, 23.5

IR (ν_{max}/cm^{-1})**:** 3063, 2970, 2935, 2858, 1683, 1606, 1446, 1404, 1357, 1269, 1075, 1052, 1015, 953, 901, 834

HRMS (m/z, $[M+H]^+$)**:** 257.15361 (calculated), 257.15359 (found)

2,4,5,6,7,7a-Hexahydro-2-methyl-2-*o*-tolylbenzofuran (3.50aj)



***dr* 44 : 66**
3.50aj

OAR224/OAR230

Yield: 63% of **3.50aj** as yellow paste.

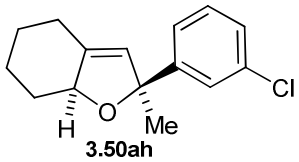
^{1}H-NMR (400 MHz, C_6D_6)**:** δ 7.83*/7.72 (d, *J*= 7.8 Hz, 1H), 7.10-7.06 (m, 3H), 5.71*/5.65 (s, 1H), 4.58-4.54*/4.37-4.33 (m, 1H), 2.482*/2.478 (s, 3H), 2.29-2.22*/2.14-2.11 (m, 2H), 1.77-1.59 (m, 1H), 1.71/1.69* (s, 3H), 1.49-1.29 (m, 2H), 1.26-1.17 (m, 1H), 1.06-0.80 (m, 2H)

^{13}C-NMR (100 MHz, C_6D_6)**:** δ 146.4*/145.9, 141.7*/141.6, 134.5/134.3*, 132.32/132.28*, 126.99/126.91*, 126.07*/126.04, 126.02/125.99*, 123.9/123.3*, 91.3*/90.7, 83.7*/83.0, 36.8/35.9*, 30.3/29.3*, 27.3*/27.2, 26.91*/26.87, 23.6*/23.4, 22.1*/21.9

IR (ν_{max}/cm^{-1})**:** 3060, 3015, 2967, 2933, 2857, 1673, 1483, 1445, 1383, 1364, 1338, 1293, 1234, 1090, 1075, 1051, 951, 035, 901, 818, 758

HRMS (m/z, $[M+H]^+$)**:** 229.15869 (calculated), 229.15863 (found)

2-(3-Chlorophenyl)-2,4,5,6,7,7a-hexahydro-2-methylbenzofuran (3.50ah)



3.50ah

OAR225/OAR229

Yield: 79% of **3.50ah** as colorless oil.

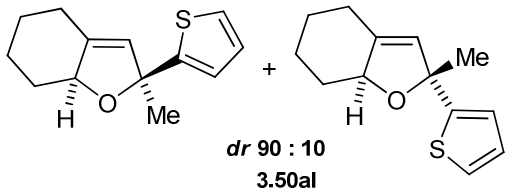
^{1}H-NMR (400 MHz, C_6D_6)**:** δ 7.69 (s, 1H), 7.27 (d, *J*= 6.8 Hz, 1H), 7.08-7.06 (m, 1H), 6.91 (t, *J*= 7.8 Hz, 1H), 5.15 (s, 1H), 4.54-4.50 (m, 1H), 2.19-2.09 (m, 2H), 1.69-1.61 (m, 1H), 1.51 (s, 3H), 1.39-1.36 (m, 2H), 1.26-1.16 (m, 1H), 0.99-0.88 (m, 1H), 0.87-0.85 (m, 1H)

^{13}C-NMR (100 MHz, C_6D_6)**:** δ 150.8, 141.1, 134.5, 129.8, 126.8, 125.7, 124.2, 123.4, 89.9, 84.3, 36.0, 29.4, 27.1, 26.7, 23.4

IR (ν_{max}/cm^{-1})**:** 3069, 2970, 2935, 2858, 1596, 1571, 1471, 1445, 1384, 1366, 1247, 1190, 1075, 1052, 952, 936, 901, 822, 784

HRMS (m/z, $[M+H]^+$)**:** 249.10407 (calculated), 249.10418 (found)

2,4,5,6,7,7a-Hexahydro-2-methyl-2-(thiophen-2-yl)benzofuran (3.50al)



***dr* 90 : 10**

3.50al

OAR226

Yield: 64% of **3.50al** as yellow oil.

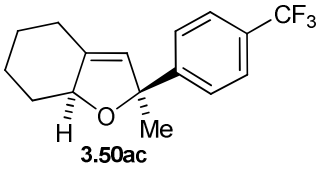
^{1}H-NMR (400 MHz, C_6D_6)**:** δ 6.90-6.89 (m, 1H), 6.84-6.83 (m,1H), 6.79-6.77 (m, 1H), 5.27/5.23* (s, 1H), 4.61-4.47/4.53-4.49* (m, 1H), 2.23-2.17 (m, 2H), 1.75/1.72* (s, 3H), 1.69-1.63 (m, 1H), 1.58-1.51 (m, 1H), 1.48-1.42 (m, 2H), 1.02-0.94 (m, 2H)

^{13}C-NMR (100 MHz, C_6D_6)**:** δ153.6, 141.0, 126.9/126.85*, 125.1*/124.6, 124.3*/124.0, 122.3*/122.0, 88.3, 84.4, 36.9/36.3*, 30.1/28.8*, 27.1*/27.0, 26.9/26.8*, 23.5*/23.4

IR (ν_{max}/cm^{-1})**:** 3107, 3072, 2972, 2936, 2857, 2269, 1619, 1447, 1384, 1330, 1246, 1158, 1075, 1044, 951, 899, 812

HRMS (m/z, $[M+H]^+$)**:** 221.09946 (calculated), 221.09946 (found)

2-(4-(Trifluoromethyl)phenyl)-2,4,5,6,7,7a-hexahydro-2-methylbenzofuran (3.50ac)



3.50ac

OAR227

Yield: 79% of **3.50ac** as colorless oil.

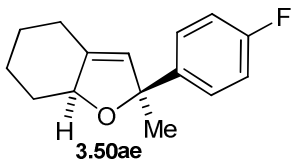
^{1}H-NMR (400 MHz, C_6D_6)**:** δ 7.43-7.36 (m, 4H), 5.18 (s, 1H), 4.56-4.52 (m, 1H), 2.22-2.12 (m, 2H), 1.72-1.66 (m, 1H), 1.51 (s, 3H), 1.45-1.40 (m, 2H), 1.22-1.14 (m, 1H), 1.03-0.93 (m, 1H), 0.90-0.81 (m, 1H)

^{13}C-NMR (100 MHz, C_6D_6)**:** δ 152.4 (d, *J*= 1.9 Hz), 141.3, 125.6, 125.4 (q, *J*= 10.6 Hz), 124.0, 90.0, 84.4, 36.1, 29.5, 27.1, 26.7, 23.4, 22.8, 11.7

IR (ν_{max}/cm^{-1})**:** 3072, 2971, 2936, 2860, 1618, 1447, 1408, 1394, 1367, 1327, 1164, 1124, 1074, 1053, 1016, 953, 901, 843, 821

HRMS (m/z, $[M+H]^+$)**:** 283.13043 (calculated), 283.13057 (found)

2-(4-Fluorophenyl)-2,4,5,6,7,7a-hexahydro-2-methylbenzofuran (3.50ae)



3.50ae

OAR228

Yield: 78% of **3.50ae** as colorless oil.

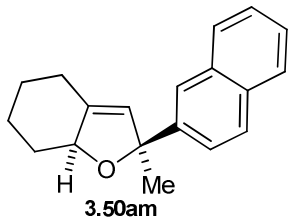
^{1}H-NMR (400 MHz, C_6D_6)**:** δ 7.34-7.31 (m, 2H), 6.90-6.86 (m, 2H), 5.23 (s, 1H), 4.57-4.54 (m, 1H), 2.24-2.13 (m, 2H), 1.73-1.67 (m, 1H), 1.56 (s, 3H), 1.45-1.40 (m, 2H), 1.27-1.19 (m, 1H), 1.04-0.95 (m, 1H), 0.92-0.83 (m, 1H)

^{13}C-NMR (100 MHz, C_6D_6)**:** δ 162.1 (d, *J*= 242 Hz), 144.2 (d, *J*= 3.9 Hz), 140.7, 127.0 (d, *J*= 7.6 Hz), 124.8, 115.0 (d, *J*= 21 Hz), 89.8, 84.2, 36.1, 29.4, 27.1, 26.8, 23.5

IR (ν_{max}/cm^{-1})**:** 3067, 2970, 2935, 2858, 1602, 1507, 1446, 1384, 1366, 1251, 1228, 1156, 1090, 1075, 1052, 1014, 951, 900, 834, 821

HRMS (m/z, $[M+H]^+$)**:** 233.13362 (calculated), 233.13352 (found)

2,4,5,6,7,7a-Hexahydro-2-methyl-2-(naphthalen-3-yl)benzofuran (3.50am)



3.50am

OAR231

Yield: 76% of **3.50am** as white solid. **MP:** 52-55 °C

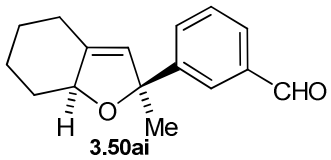
^{1}H-NMR (400 MHz, C_6D_6)**:** δ 8.10 (s, 1H), 7.75-7.70 (m, 2H), 6.67-7.64 (m, 2H), 7.30-7.24 (m, 2H), 5.44 (s, 1H), 4.69-4.65 (m, 1H), 2.28-2.24 (m, 2H), 1.78-1.70 (m, 1H), 1.75 (s, 3H), 1.46-1.32 (m, 3H), 1.08-0.97 (m, 1H), 0.95-0.83 (m, 1H)

^{13}C-NMR (100 MHz, C_6D_6)**:** δ 145.9, 140.9, 134.1, 133.0, 128.5, 126.2, 125.7, 124.8, 124.6, 123.4, 90.5, 84.4, 36.2, 29.6, 27.3, 26.8, 23.6

IR (ν_{max}/cm^{-1})**:** 3057, 3019, 2968, 2933, 2856, 1672, 1631, 1600, 1505, 1444, 1366, 1351, 1338, 1271, 1127, 1089, 1076, 1051, 951, 901, 855, 817, 746

HRMS (m/z, $[M+H]^+$)**:** 265.15869 (calculated), 265.15870 (found)

3-(2,4,5,6,7,7a-Hexahydro-2-methylbenzofuran-2-yl)benzaldehyde (3.50ai)



3.50ai

OAR232

Yield: 77% of **3.50ai** as yellow oil.

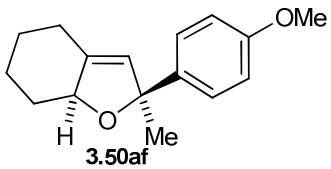
^{1}H-NMR (400 MHz, C_6D_6)**:** δ 9.74 (s, 1H), 8.04 (s, 1H), 7.65 (d, *J*= 7.8 Hz, 1H), 7.45 (d, *J*= 7.6 Hz, 1H), 7.09 (t, *J*= 7.7 Hz, 1H), 5.20 (s, 1H), 4.57-4.53 (m, 1H), 2.21-2.13 (m, 2H) ,1.71-1.63 (m, 1H), 1.55 (s, 3H), 1.43-1.37 (m, 2H), 1.28- 1.18 (m, 1H), 1.02-0.91 (m, 1H), 0.89-0.77 (m, 1H)

^{13}C-NMR (100 MHz, C_6D_6)**:** δ 191.6, 149.5, 141.2, 137.2, 131.0, 129.0, 126.1, 124.2, 90.0, 84.3, 36.1, 29.4, 27.1, 26.7, 23.4

IR (ν_{max}/cm^{-1})**:** 3065, 2970, 2934, 2857, 2725, 1698, 1600, 1583, 1446, 1383, 1338, 1205, 1158, 1075, 1052, 953, 935, 899

HRMS (m/z, $[M+H]^+$)**:** 243.13796 (calculated), 243.13805 (found)

2,4,5,6,7,7a-Hexahydro-2-(4-methoxyphenyl)-2-methylbenzofuran (3.50af)



3.50af

OAR237

Yield: 68% of **3.50af** as colorless oil.

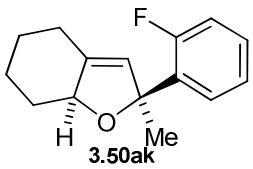
^{1}H-NMR (400 MHz, C_6D_6)**:** δ 7.48 (d, *J*= 8.8 Hz, 2H), 6.87 (d, *J*= 8.8 Hz, 2H), 5.35(s, 1H), 4.64-4.60 (m, 1H), 3.34 (s, 3H), 2.28-2.19 (m, 2H), 1.77-1.71 (m, 3H), 1.69 (s, 3H), 1.48-1.31 (m, 3H), 1.08-0.87 (m, 2H)

^{13}C-NMR (100 MHz, C_6D_6)**:** δ 158.9, 140.6, 140.3, 126.6, 125.4, 113.8, 90.0, 84.1, 54.8, 36.2, 29.4, 27.2, 26.9, 23.6

IR (ν_{max}/cm^{-1})**:** 3061, 3037, 2967, 2933, 2856, 2835, 1611, 1510, 1462, 1444, 1301, 1244, 1177, 1074, 1050, 1035, 951, 935, 900, 829, 807

HRMS (m/z, $[M+H]^+$)**:** 245.15361 (calculated), 245.15355 (found)

2-(2-Fluorophenyl)-2,4,5,6,7,7a-hexahydro-2-methylbenzofuran (3.50ak)



3.50ak

OAR238

Yield: 78% of **3.50ak** as colorless oil.

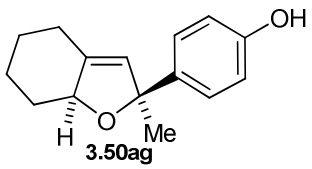
^{1}H-NMR (500 MHz, C_6D_6)**:** δ 8.02-7.98 (m, 1H), 6.97-6.94 (m, 1H), 6.90-6.81 (m, 2H), 5.88 (s, 1H), 4.59-4.55 (m, 1H), 2.20-2.15 (m, 2H), 1.79 (s, 3H), 1.70-1.64 (m, 1H), 1.42-1.34 (m, 2H), 1.28-1.20 (m, 1H), 1.02-0.93 (m, 1H), 0.83-0.74 (m, 1H)

^{13}C-NMR (125 MHz, C_6D_6)**:** δ 159.3 (d, *J*= 242 Hz), 141.1, 135.8 (d, *J*= 14.3 Hz), 128.5 (d, *J*= 8.6 Hz), 127.4 (d, *J*= 4.8 Hz), 124.5 (d, *J*= 2.9 Hz), 123.2 (d, *J*= 4.8 Hz), 115.7 (d, *J*= 22.9 Hz), 88.9 (d, *J*= 3.8 Hz), 84.1, 36.2, 29.0 (d, *J*= 2.9 Hz), 27.2, 26.7, 23.5

IR (ν_{max}/cm^{-1})**:** 3082, 3037, 2971, 2935, 2859, 1673, 1614, 1582, 1482, 1443, 1384, 1366, 1339, 1292, 1269, 1212, 1187, 1109, 1090, 1076, 1053, 1031, 954, 902, 821, 758

HRMS (m/z, $[M+H]^+$)**:** 233.13362 (calculated), 233.13361 (found)

4-(2,4,5,6,7,7a-Hexahydro-2-methylbenzofuran-2-yl)phenol (3.50ag)



3.50ag

OAR260

Yield: 36% and 68% of **3.50ag** as light yellow oil.

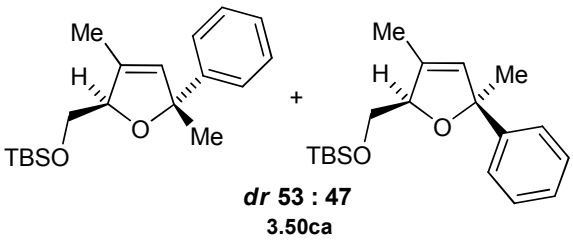
^{1}H-NMR (500 MHz, C_6D_6)**:** δ 7.38 (d, *J*= 8.8 Hz, 2H), 6.59 (d, *J*= 8.4 Hz, 2H), 5.30 (s, 1H), 4.60-4.57 (m, 1H), 4.21 (s, 1H), 2.25-2.16 (m, 2H), 1.76-1.68 (m, 1H), 1.65 (s, 3H), 1.45-1.41 (m, 2H), 1.36-1.28 (m, 1H), 1.05-0.96 (m, 1H), 0.96-0.86 (m, 1H)

^{13}C-NMR (125 MHz, C_6D_6)**:** δ 155.1, 140.2, 128.4, 126.7, 125.4, 115.1, 90.1, 84.1, 36.2, 29.3, 27.2, 26.9, 23.6

IR (ν_{max}/cm^{-1})**:** 3437, 2969, 2935, 2857, 1673, 1613, 1594, 1513, 1445, 1384, 1368, 1338, 1227, 1173, 1070, 1048, 1034, 951, 935, 831

HRMS (m/z, $[M+H]^+$)**:** 231.13796 (calculated), 231.13801 (found)

((2,5-Dihydro-3,5-dimethyl-5-phenylfuran-2-yl)methoxy)(*t*-butyl)dimethylsilane (3.50ca)



***dr* 53 : 47**

3.50ca

OAR235

Yield: 64% of **3.50ca** as colorless oil.

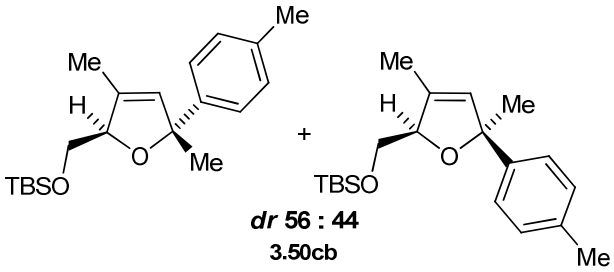
^{1}H-NMR (400 MHz, C_6D_6)**:** δ 7.53/7.48 (d, *J*= 7.6 Hz, 2H), 7.26-7.21 (m, 2H), 7.12-7.08 (m, 1H), 5.47 (s, 1H), 4.80/4.67* (s, 1H), 3.79-3.65 (m, 2H), 1.68*/1.61 (s, 3H), 1.59/1.52* (s, 3H), 0.99*/0.91 (s, 9H), 0.10*/0.010 (s, 3H), 0.10*/-0.03 (s, 3H)

^{13}C-NMR (100 MHz, C_6D_6)**:** δ 148.3*/148.1, 136.0*/135.4, 130.4*/130.3, 128.5, 126.71/126.69*, 125.4/125.1*, 90.0*/89.8, 88.4*/88.0, 65.9/65.6*, 30.3*/29.7, 26.2*/26.1, 18.9*/18.5, 12.9/12.6*, -5.1/-5.2/-5.4

IR (ν_{max}/cm^{-1})**:** 3061, 3026, 2956, 2928, 2897, 2857, 2388, 1724, 1618, 1493, 1471, 1462, 1446, 1385, 1362, 1330, 1254, 1137, 1084, 1028, 1007, 898, 838, 812, 777, 761

HRMS (m/z, $[M+H]^+$)**:** 319.2088 (calculated), 319.2089 (found)

((2,5-Dihydro-3,5-dimethyl-5-*p*-tolylfuran-2-yl)methoxy)(*t*-butyl)dimethylsilane (3.50cb)



OAR236

Yield: 66% of **3.50cb** as colorless oil.

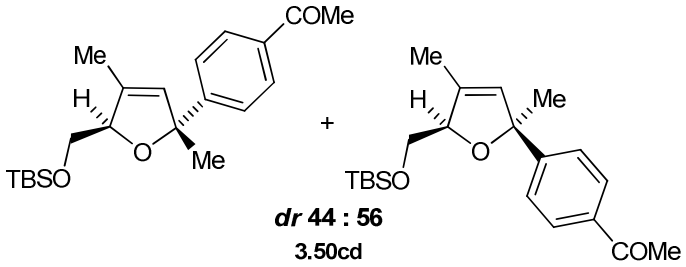
^{1}H-NMR (400 MHz, C_6D_6)**:** δ 7.47/7.43* (d, *J*= 8.3 Hz, 2H), 7.10-7.06 (m, 2H), 5.50 (s, 1H), 4.81/4.70* (s, 1H), 3.80-3.67 (m, 2H), 2.16-2.15* (s, 3H), 1.71*/1.64 (s, 3H), 1.61/1.54* (s, 3H), 1.00*/0.93 (s, 9H), 0.10*/0.03 (s, 3H), 0.09*/-0.01 (s, 3H)

^{13}C-NMR (100 MHz, C_6D_6)**:** δ 145.4*/145.2, 135.95/135.92*, 135.9/135.3*, 130.6*/130.5, 129.1*/129.0, 125.5/125.1*, 89.9*/89.7, 88.4/88.0*, 66.1/65.6*, 30.3*/29.6, 26.2*/26.1, 21.0, 18.6*/18.5, 12.9/12.6*, -5.1/-5.2/-5.3/-5.4

IR (ν_{max}/cm^{-1})**:** 3062, 3023, 2955, 2928, 2898, 2857, 2738, 2709, 1727, 1667, 1511, 1471, 1462, 1446, 1384, 1362, 1254, 1137, 1084, 1020, 1006, 898, 838, 814, 776

HRMS (m/z, $[M+H]^+$)**:** 333.22443 (calculated), 333.22452 (found)

((2,5-Dihydro-3,5-dimethyl-5-(4-acetylphenyl)furan-2-yl)methoxy)(*t*-butyl)di methylsilane (3.50cd)



***dr* 44 : 56**

3.50cd

OAR249

Yield: 65% of **3.50cd** as white solid. **MP:** 90-95 °C

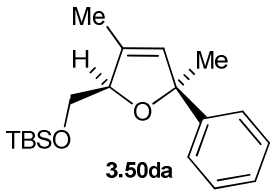
^{1}H-NMR (400 MHz, C_6D_6)**:** δ 7.89*/7.86 (d, *J*= 8.5 Hz, 2H), 7.48*/7.41 (d, *J*= 8.3 Hz, 2H), 5.40*/5.39 (s, 1H), 4.76*/4.64 (s, 1H), 3.79-3.63 (m, 2H), 2.15*/2.13 (s, 3H), 1.62*/1.56 (s, 3H), 1.55/1.51* (s, 3H), 1.00/0.88* (s, 9H), 0.102/0.002* (s, 3H), 0.100/-0.03* (s, 3H)

^{13}C-NMR (100 MHz, C_6D_6)**:** δ 196.2, 153.0/152.9*, 136.5/136.2*, 136.0, 129.6/129.5*, 128.7/128.5*, 125.4*/125.1, 89.9/89.8*, 88.6/88.2*, 65.6*/65.3, 30.0/29.6*, 26.2/26.1*, 26.0, 18.9/18.4*, 12.8*/12.5, -5.2/-5.3/-5.38/-5.40

IR (ν_{max}/cm^{-1})**:** 2984, 2928, 2857, 1686, 1606, 1471, 1463, 1446, 1404, 1384, 1360, 1268, 1137, 1082, 1014, 898, 837, 777

HRMS (m/z, $[M+H]^+$)**:** 361.21935 (calculated), 361.21941 (found)

((2,5-Dihydro-3,5-dimethyl-5-phenylfuran-2-yl)methoxy)(*t*-butyl)dimethylsilane (3.50da)



3.50da

OAR239

Yield: 76% of **3.50da** as colorless oil.

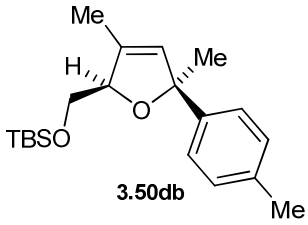
^{1}H-NMR (500 MHz, C_6D_6)**:** δ 7.53 (d, *J*= 7.3 Hz, 2H), 7.24 (t, *J*= 7.7 Hz, 2H), 7.10 (t, *J*= 7.3 Hz, 1H), 5.48 (s, 1H), 4.79 (s, 1H), 3.73-3.66 (m, 2H), 1.61 (s, 3H), 1.60 (s, 3H), 0.91 (s, 9H), 0.02 (s, 3H), -0.03 (s, 3H)

^{13}C-NMR (125 MHz, C_6D_6)**:** δ 148.1, 136.1, 130.4, 128.4, 126.7, 125.4, 89.8, 88.0, 66.0, 29.6, 26.1, 18.5, 12.8, -5.4

IR (ν_{max}/cm^{-1})**:** 3086, 3062, 3027, 2955, 2928, 2898, 2857, 1494, 1471, 1463, 1446, 1385, 1362, 1254, 1138, 1085, 1028, 1006, 895, 837, 776

HRMS (m/z, $[M+H]^+$)**:** 319.20878 (calculated), 319.20889 (found)

((2,5-Dihydro-3,5-dimethyl-5-*p*-tolylfuran-2-yl)methoxy)(*t*-butyl)dimethylsilane (3.50db)



3.50db

OAR240

Yield: 81% of **3.50db** as colorless oil.

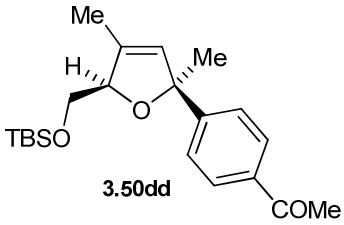
^{1}H-NMR (500 MHz, C_6D_6)**:** δ 7.47 (d, *J*= 8.0 Hz, 2H), 7.08 (d, *J*= 8.0 Hz, 2H), 5.51 (s, 1H), 4.81 (s, 1H), 3.76-3.68 (m, 2H), 2.16 (s, 3H), 1.64 (s, 3H), 1.61 (s, 3H), 0.92 (s, 9H), 0.03 (s, 3H), -0.01 (s, 3H)

^{13}C-NMR (125 MHz, C_6D_6)**:** δ 145.3, 136.0, 135.9, 130.6, 129.0, 128.4, 125.5, 89.8, 88.0, 66.1, 29.6, 26.1, 21.0, 18.5, 12.9, -5.32, -5.34

IR (ν_{max}/cm^{-1})**:** 3094, 3060, 3022, 2954, 2927, 2899, 2856, 1667, 1512, 1471, 1462, 1445, 1385, 1362, 1253, 1183, 1137, 1113, 1084, 1020, 1005, 895, 837, 814, 775

HRMS (m/z, $[M+H]^+$)**:** 333.22443 (calculated), 333.22451 (found)

((2,5-Dihydro-3,5-dimethyl-5-(4-acetylphenyl)furan-2-yl)methoxy)(*t*-butyl)di methylsilane (3.50dd)



3.50dd

OAR258

Yield: 70% of **3.50dd** as colorless oil.

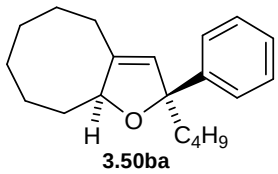
^{1}H-NMR (400 MHz, C_6D_6)**:** δ 7.89 (d, *J*= 8.6 Hz, 2H), 7.48 (d, *J*= 8.3 Hz, 2H), 5.40 (s, 1H), 4.77 (s, 1H), 3.67-3.66 (m, 2H), 2.15 (s, 3H), 1.57 (s, 3H), 1.55 (s, 3H), 0.89 (s, 9H), 0.003 (s, 3H), -0.03 (s, 3H)

^{13}C-NMR (100 MHz, C_6D_6)**:** δ 196.3, 152.9, 136.5, 136.2, 129.5, 128.5, 125.4, 89.8, 88.2, 65.6, 29.6, 26.2, 26.0, 18.4, 12.3, -5.39, -5.40

IR (ν_{max}/cm^{-1})**:** 3065, 2954, 2928, 2897, 2857, 1685, 1606, 1471, 1463, 1446, 1405, 1385, 1359, 1268, 1189, 1137, 1083, 1015, 946, 896, 837, 777

HRMS (m/z, $[M+H]^+$)**:** 361.21935 (calculated), 361.21943 (found)

2-Butyl-2,4,5,6,7,8,9,9a-octahydro-2-phenylcycloocta[*b*]furan (3.50ba)



3.50ba

OAR254P

Yield: 78% of **3.50ba** as colorless oil.

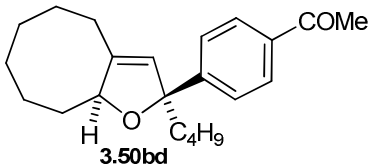
^{1}H-NMR (400 MHz, C_6D_6)**:** δ 7.54 (d, *J*= 7.5 Hz, 2H), 7.26 (t, *J*= 7.7 Hz, 2H), 7.09 (t, *J*= 7.4 Hz, 1H), 5.56 (s, 1H), 4.92-4.91 (m, 1H), 2.32-2.25 (m, 1H), 2.02-1.74 (m, 5H), 1.53-1.46 (m, 2H), 1.42-1.22 (m, 9H), 1.16-1.12 (m, 1H), 0.85 (t, *J*= 7.1 Hz, 3H)

^{13}C-NMR (100 MHz, C_6D_6)**:** δ 147.6, 142.5, 129.3, 126.4, 125.4, 92.0, 87.2, 43.4, 32.4, 28.3, 27.7, 26.9, 26.8, 25.7, 23.5, 22.6, 14.4

IR (ν_{max}/cm^{-1})**:** 3084, 3059, 3024, 2929, 2855, 1600, 1492, 1463, 1446, 1378, 1181, 1084, 1056, 1030, 988, 832, 761

HRMS (m/z, $[M+H]^+$)**:** 285.22129 (calculated), 285.22125 (found)

2-Butyl-2,4,5,6,7,8,9,9a-octahydro-2-(4-acetylphenyl)cycloocta[b]furan (3.50bd)



3.50bd

OAR256PT

Yield: 70% of **3.50bd** as colorless oil.

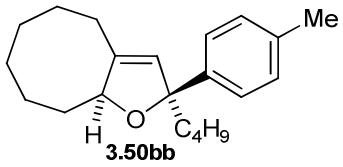
^{1}H-NMR (400 MHz, C_6D_6)**:** δ 7.88 (d, *J*= 8.3 Hz, 2H), 7.46 (d, *J*= 8.3 Hz, 2H), 5.46 (s, 1H), 4.89-4.88 (m, 1H), 2.31-2.24 (m, 1H), 2.12 (s, 3H), 2.00-1.94 (m, 1H), 1.89-1.72 (m, 4H), 1.50-1.08 (m, 12H), 0.86 (t, *J*= 6.9 Hz, 3H)

^{13}C-NMR (100 MHz, C_6D_6)**:** δ196.3, 152.4, 143.1, 135.9, 128.6, 125.4, 92.0, 87.3, 43.1, 32.3, 28.3, 27.7, 26.8, 26.7, 26.2, 25.6, 23.5, 22.6, 14.4

IR (ν_{max}/cm^{-1})**:** 2929, 2855, 1683, 1605, 1462, 1404, 1384, 1357, 1268, 1181, 1059, 956, 836

HRMS (m/z, $[M+H]^+$)**:** 327.23186 (calculated), 327.23181 (found)

2-Butyl-2,4,5,6,7,8,9,9a-octahydro-2-*p*-tolylcycloocta[*b*]furan (3.50bb)



3.50bb

OAR257P

Yield: 75% of **3.50bb** as colorless oil.

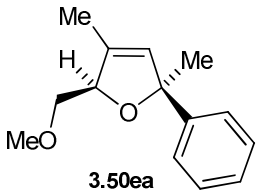
^{1}H-NMR (400 MHz, C_6D_6)**:** δ 7.47 (d, *J*= 8.0 Hz, 2H), 7.09 (d, *J*= 8.0 Hz, 2H), 5.59 (s, 1H), 4.93 (s, 1H), 2.24-2.27 (m, 1H), 2.15 (s, 3H), 2.05-1.75 (m, 5H), 1.59-1.49 (m, 2H), 1.44-1.26 (m, 9H), 1.18-1.14 (m, 1H), 0.86 (t, *J*= 7.3 Hz, 3H)

^{13}C-NMR (100 MHz, C_6D_6)**:** δ 144.7, 142.2, 135.5, 129.5, 129.0, 125.4, 92.0, 87.1, 43.5, 32.4, 28.4, 27.8, 26.92, 26.87, 25.7, 23.6, 22.6, 21.1, 14.4

IR (ν_{max}/cm^{-1})**:** 3089, 3053, 3022, 2929, 2855, 1511, 1462, 1445, 1384, 1183, 1109, 1058, 1041, 988, 816

HRMS (m/z, $[M+H]^+$)**:** 299.23694 (calculated), 299.23697 (found)

2,5-Dihydro-5-(methoxymethyl)-2,4-dimethyl-2-phenylfuran (3.50ea)



3.50ea

OAR278P

Yield: 86% of **3.50ea** as colorless oil.

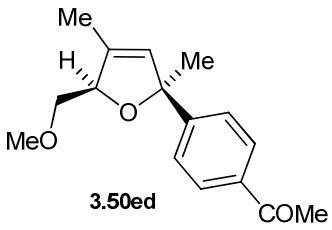
^{1}H-NMR (500 MHz, C_6D_6)**:** δ 7.53 (dd, *J*= 8.4, 1.2 Hz, 2H), 7.23 (t, *J*= 7.6, 2H), 7.12-7.09 (m, 1H), 5.45-5.44 (m, 1H), 4.90-4.88 (m, 1H), 3.40-3.32 (m, 2H), 3.08 (s, 3H), 1.61 (s, 3H), 1.52 (s, 3H)

^{13}C-NMR (125 MHz, C_6D_6)**:** δ 148.2, 135.9, 130.2, 128.3, 126.7, 125.4, 90.0, 86.5, 75.4, 58.9, 29.6, 12.6

IR (ν_{max}/cm^{-1})**:** 3085, 3061, 3025, 2973, 2922, 2879, 2827, 1669, 1601, 1493, 1446, 1365, 1277, 1239, 1197, 1130, 1087, 1028, 997, 944, 824, 761, 700

HRMS (m/z, $[M+H]^+$)**:** 219.13796 (calculated), 219.13803 (found)

2,5-Dihydro-5-(methoxymethyl)-2,4-dimethyl-2-(4-acetylphenyl)furan (3.50ed)



3.50ed

OAR281P

Yield: 64% of **3.50ed** as colorless oil.

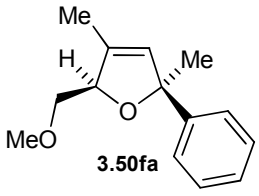
^{1}H-NMR (500 MHz, C_6D_6)**:** δ 7.86 (d, *J*= 8.5 Hz, 2H), 7.47 (d, *J*= 8.5 Hz, 2H), 5.37-5.36 (m, 1H), 4.85-4.83 (m, 1H), 3.33-3.32 (m, 2H), 3.08 (s, 3H), 2.14 (s, 3H), 1.54 (s, 3H), 1.50 (s, 3H)

^{13}C-NMR (125 MHz, C_6D_6)**:** δ 196.3, 152.9, 136.3, 136.2, 129.5, 128.5, 125.4, 89.9, 86.7, 75.1, 58.9, 29.5, 26.2, 12.6

IR (ν_{max}/cm^{-1})**:** 3061, 2973, 2923, 2882, 2362, 1683, 1606, 1568, 1448, 1404, 1358, 1268, 1197, 1129, 1081, 998, 957, 834, 813

HRMS (m/z, $[M+H]^+$)**:** 261.14852 (calculated), 261.14846 (found)

(2*S*,5*R*)-2,5-Dihydro-5-(methoxymethyl)-2,4-dimethyl-2-phenylfuran (3.50fa)



3.50fa

OAR279P

Yield: 60% of **3.50fa** as colorless oil.

^{1}H-NMR (500 MHz, C_6D_6)**:** δ 7.53 (dd, *J*= 8.3, 1.3 Hz, 2H), 7.24 (t, *J*= 7.7 Hz, 2H), 7.12-7.09 (m, 1H), 5.45-5.44 (m, 1H), 4.90-4.87 (m, 1H), 3.40-3.31 (m, 2H), 3.08 (s, 3H), 1.61 (s, 3H), 1.52 (s, 3H)

^{13}C-NMR (125 MHz, C_6D_6)**:** δ 148.2, 135.9, 130.3, 128.3, 126.7, 125.4, 90.0, 86.5, 75.4, 58.9, 29.6, 12.6

IR (ν_{max}/cm^{-1})**:** 3085, 3061, 3025, 2972, 2922, 2879, 2827, 1670, 1601, 1493, 1446, 1365, 1278, 1239, 1197, 1130, 1087, 1028, 997, 944, 824, 762, 700

HRMS (m/z, $[M+H]^+$)**:** 219.13796 (calculated), 219.13800 (found)

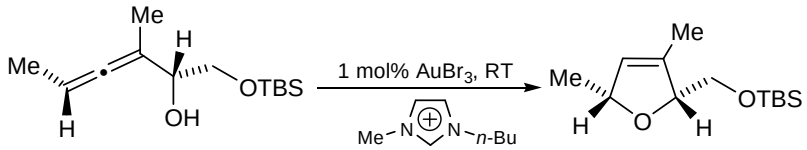
Optical rotation (589 nm, d = 10 cm)**:** $[\alpha]^{20}_D$ = + 30.5 (*c* 1.17, $CHCl_3$)

CHAPTER 4

Summary

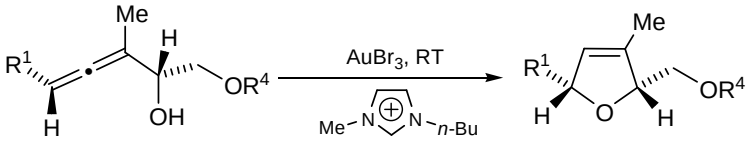
The thesis entitled '**2,5-DIHYDROFURANS: NEW APPROACHES BY RECYCLABLE OR COMBINED CATALYSIS**' describes new routes to synthesize 2,5-dihydrofurans by transition metal catalysis with high yields and selectivities. The result of our investigations on the synthesis of 2,5-dihydrofurans was summarized in each chapter as each approach.

Chapter 2 deals with a recyclable, efficient, and environmentally benign catalytic system for the synthesis of 2,5-dihydrofurans. We achieved 74-84% yield of 2,5-dihydrofuran **2.32b** over 5 cycles using a $AuBr_3$/ionic liquid system without loss of activity.



2.31b **2.32b**, 74-84%, ***5 cycles***

Other α-hydroxyallenes also showed similar reactivity in the $AuBr_3$/ionic liquid catalytic system over 3 cycles. Even when the $AuBr_3$/ionic liquid solution was exposed to air for several days, no drop in reactivity of the recyclable catalyst was observed. The reaction can also be applied to the cyclic α-hydroxyallenes.



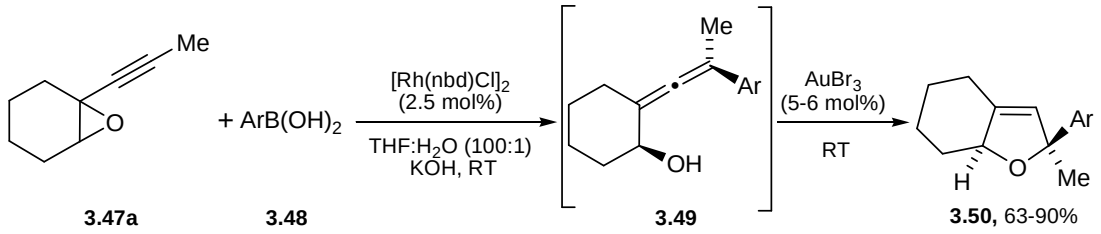
2.31 **2.32**, 50-89%, ***2 or 3 cycles***

R^1= Me, *n*-Bu, *i*-Pr, *t*-Bu, Ph, 2-$MeOC_6H_4$

R^4= TBS, Bn

Chapter 3 deals with a one-pot synthesis of 2,5-dihydrofurans by sequential rhodium-gold catalysis. This combined metal catalysis in one-pot offers an efficient and economical

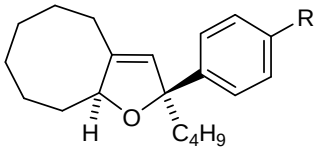
route to synthesize complex molecules from simple starting materials. The one-pot procedure was applied to various substituted- and hetero-arylboronic acids **3.48** and afforded the desired 2,5-dihydrofurans with high yields (63-90%) and selectivities under mild conditions.



3.47a **3.48** **3.49** **3.50,** 63-90%

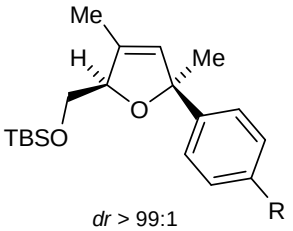
Ar= Ph, 4-MeC_6H_4, 4-$F_3CC_6H_4$, 4-FC_6H_4, 4-$MeOCC_6H_4$, 4-$MeOC_6H_4$, 4-HOC_6H_4, 3-ClC_6H_4, 3-$HOCC_6H_4$, 2-MeC_6H_4, 2-FC_6H_4, 2-thiophene, 2-Naphthyl

This method was also applied to various oxiranes, in most cases with high diastereoselectivity (*dr* >99:1) and 64-86% yield.



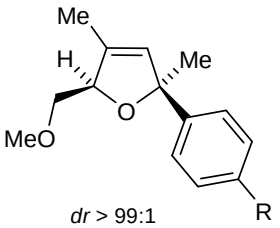
dr > 99:1

R= H, **3.50ba**, 78%
R= Me, **3.50bb**, 75%
R= COMe, **3.50bd**, 70%



dr > 99:1

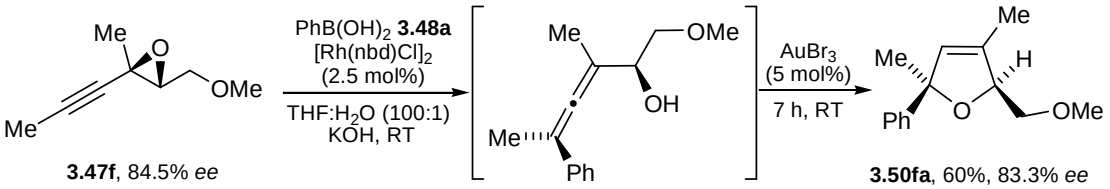
R= H, **3.50da**, 76%
R= Me, **3.50db**, 81%
R= COMe, **3.50dd**, 70%



dr > 99:1

R= H, **3.50ea**, 86%
R= COMe, **3.50ed**, 64%

An important issue was the high *syn*-selectivity of the rhodium-catalyzed S_N2'-substitution which was transferred to 2,5-dihydrofuran in the subsequent gold-catalyzed cycloisomerization. The enantiomerically enriched alkynyl oxirane **3.47f** afforded the 2,5-dihydrofuran **3.50fa** with complete chirality transfer.



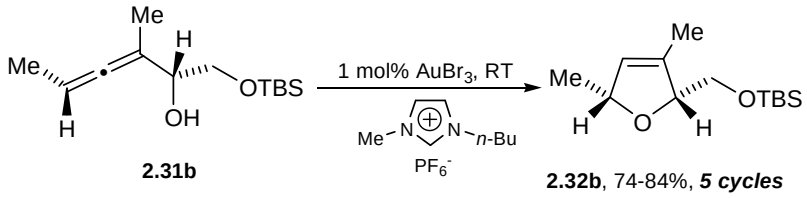
3.47f, 84.5% *ee* **3.50fa**, 60%, 83.3% *ee*

In conclusion, the new approaches for the synthesis of pharmaceutically and industrially important 2,5-dihydrofuran that we present in this thesis may inable industry to reduce the production cost.

Zusammenfassung

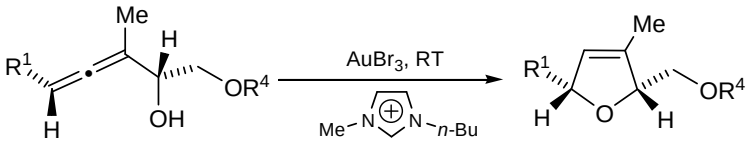
Die Arbeit mit dem Titel '**2,5-DIHYDROFURANS: NEW APPROACHES BY RECYCLABLE OR COMBINED CATALYSIS**' beschreibt die möglichen Wege zur Synthese von 2,5-Dihydrofuranen mittels Übergangsmetallkatalyse mit hohen Ausbeuten und Selektivitäten. Die Ergebnisse unserer Untersuchungen bezüglich der Synthese von 2,5-Dihydrofuranen sind für jedes Kapitel jeweils zusammengefasst.

Kapitel 2 ist einem recyclisierbaren, effizienten und umweltfreundlichen katalytischen System für die Synthese von 2,5-Dihydrofuranen gewidmet. Das katalytische System aus $AuBr_3$ und der ionischen Flüssigkeit [BMIM][PF_6] wurde fünf mal zur Bildung des 2,5-Dihydrofurans **2.32b** mit 74-84% Ausbeute ohne Aktivitätsverlust verwendet.



2.31b **2.32b**, 74-84%, ***5 cycles***

Andere α-Hydroxyallene zeigten über drei Cyclen ähnliche Reaktivitäten gegenüber dem katalytischen System aus $AuBr_3$ und einer ionischen Flüssigkeit. Selbst das mehrtägige Aussetzen der Katalysatorlösung gegenüber Luft und Feuchtigkeit verursachte keinen Reaktivitätsverlust. Auch cyclische α-Hydroxyallene werden bei den Reaktionsbedingungen mit hohen Ausbeuten umgesetzt.



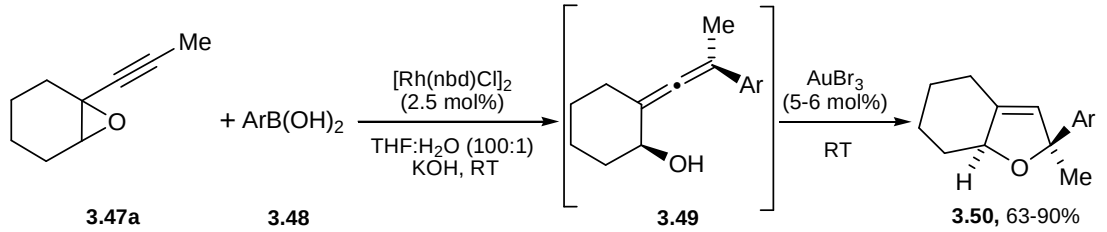
2.31 **2.32**, 50-89%, ***2 or 3 cycles***

R^1= Me, *n*-Bu, *i*-Pr, *t*-Bu, Ph, 2-$MeOC_6H_4$

R^4= TBS, Bn

Kapitel 3 behandelt die Eintopfsynthese von 2,5-Dihydrofuranen aus Propargyloxiranen und Arylboronsäure durch sequentielle Rhodium-Gold-Katalyse. Diese kombinierte Eintopf-Metallkatalyse bietet eine effiziente und ökonomische Route zur Synthese von komplexen Molekülen aus einfachen Startmaterialien. Das Eintopfverfahren findet Anwendung auf

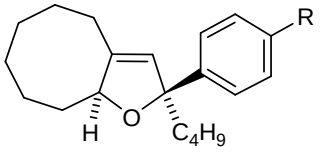
zahlreiche Arylboronsäuren **3.48** die die gewünschten 2,5-Dihydrofurane **3.50** mit hohen Ausbeuten (63-90%) und Selektivitäten unter milden Bedingungen ergaben.



3.47a **3.48** **3.49** **3.50,** 63-90%

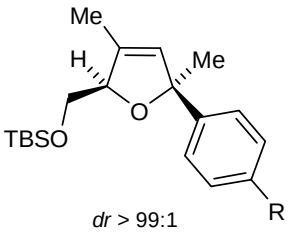
Ar= Ph, 4-MeC_6H_4, 4-$F_3C$$C_6H_4$, 4-F$C_6H_4$, 4-MeO$CC_6H_4$, 4-Me$OC_6H_4$, 4-HO$C_6H_4$, 3-Cl$C_6H_4$, 3-HO$CC_6H_4$, 2-Me$C_6H_4$, 2-F$C_6H_4$, 2-Thiophen, 2-Naphthyl

Diese Methode konnte zudem auf zahlreiche Epoxide übertragen werden. In den meisten Fällen liefert sie eine Diastereoselektivität von *dr*>99:1 sowie Ausbeuten von 64-86%.



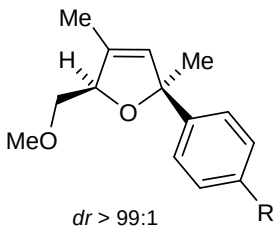
dr > 99:1

R= H, **3.50ba**, 78%
R= Me, **3.50bb**, 75%
R= COMe, **3.50bd**, 70%



dr > 99:1

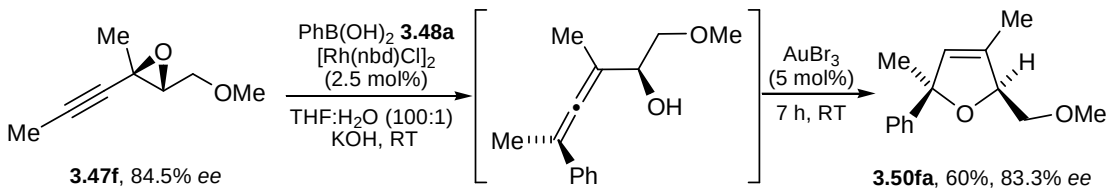
R= H, **3.50da**, 76%
R= Me, **3.50db**, 81%
R= COMe, **3.50dd**, 70%



dr > 99:1

R= H, **3.50ea**, 86%
R= COMe, **3.50ed**, 64%

Eine wichtige Eigenschaft ist der Transfer der bei der Rhodium-katalysierten S_N2'-Substitution erzielten hohen *syn*-Selektivität auf das 2,5-Dihydrofuran während der anschließenden Gold-katalysierten Cycloisomerisierung. Das enantiomerenangereicherte Epoxid **3.47f** lieferte das 2,5-Dihydrofuran **3.50fa** unter vollständigem Chiralitätstransfer.



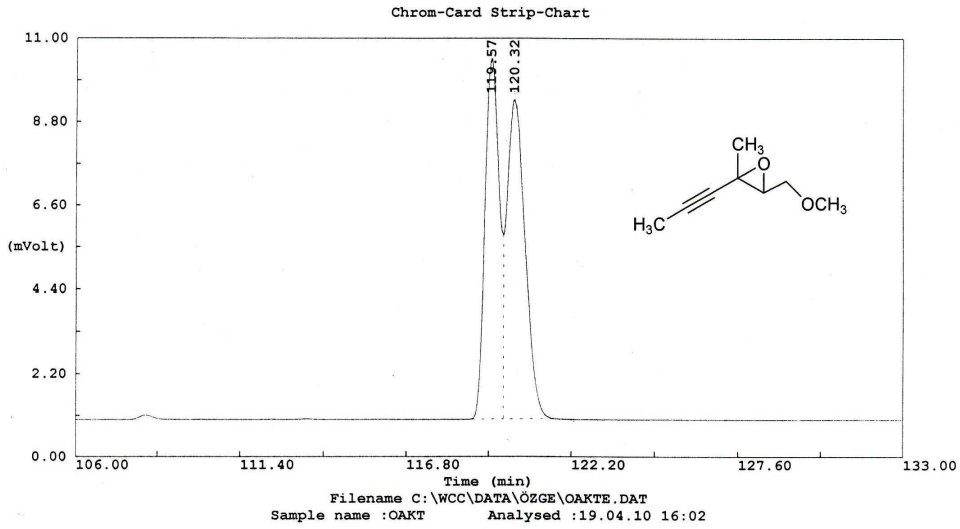
3.47f, 84.5% *ee* **3.50fa**, 60%, 83.3% *ee*

Schlussfolgernd lässt sich sagen, dass die Zugänge zur Synthese von pharmazeutisch und industriell wichtigen 2,5-Dihydrofuranen, die in dieser Dissertation beschrieben werden, für die Industrie zur Senkung der Produktionskosten entscheidend sind.

APPENDIX

Chiral GC Analysis (Chapter 3)

E-3-(Methoxymethyl)-2-methyl-2-(prop-1-ynyl)oxirane (3.47e)



Chrom-Card Report

Operator ID : Peri
Company Name : AK Krause
Method Name : özge
Method File : OZGECHI1.MTH
Analysed : 19.04.10 16:02
Printed : 23.04.2010 14:38

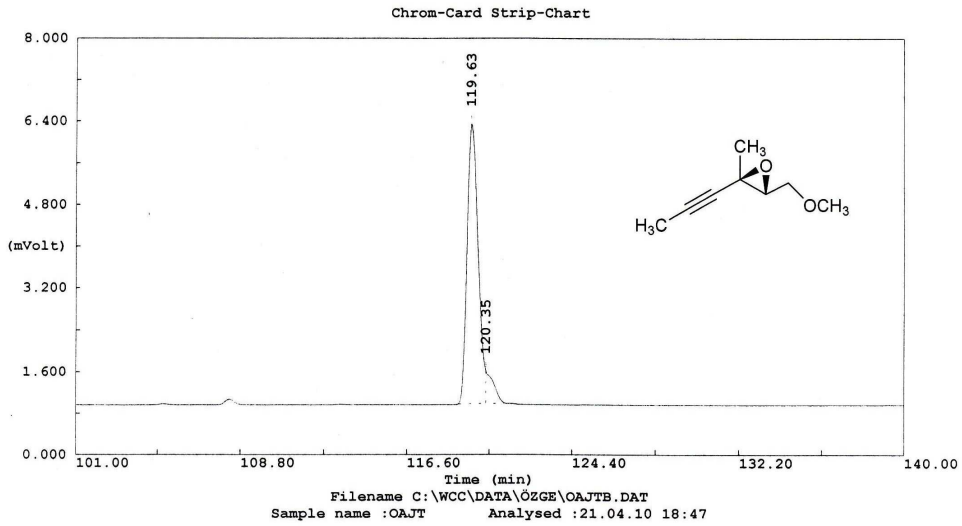
Sample ID : OAKT
Channel : Channel C
Analysis Type : UnkNown (Area)
Calc. Method : Area %
Chromatogram : C:\WCC\DATA\ÖZGE\OAKTE.DAT

Warning Chromatogram has been subjected to manual integration.

Peak Number #	Area %	Ret.Time	Area	BC
1	47.1664	119.57	3089520	mi
2	52.8336	120.32	3460732	mi
Totals	100.0000		6550252	

Column: Hyhdodex-beta-3P 25m,0.25mm ID
Detektor: FID, 280°C
Injektor: 280°C
Oven program: Isotemp.1: 40°C, Isotime1:45 min,
Rate1:0.3°C/min, Isotemp.2:100°C/min, Isotime2: 0 min
Rate1:40°C/min, Isotemp.2:200°C/min, Isotime2: 0 min
Split: 35

(*2R,3R*)-3-(Methoxymethyl)-2-methyl-2-(prop-1-ynyl)oxirane (3.47f)



Chrom-Card Report

Operator ID : Peri
Company Name : AK Krause
Method Name : özge
Method File : OZGECHI1.MTH
Analysed : 21.04.10 18:47
Printed : 23.04.2010 14:41

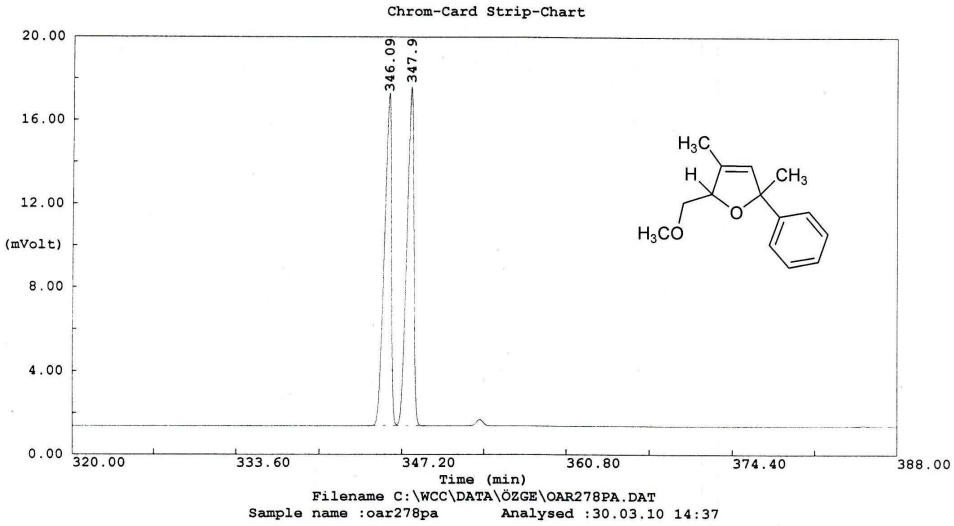
Sample ID : OAJT
Channel : Channel C
Analysis Type : UnkNown (Area)
Calc. Method : Area %
Chromatogram : C:\WCC\DATA\ÖZGE\OAJTB.DAT

Warning Chromatogram has been subjected to manual integration.

Peak Number #	Area %	Ret.Time	Area	BC
1	92.4901	119.63	1939803	mi
2	7.5099	120.35	157506	mi
Totals	100.0000		2097309	

Column: Hyhdodex-beta-3P 25m,0.25mm ID
Detektor: FID, 280°C
Injektor: 280°C
Oven program: Isotemp.1: 40°C, Isotime1:45 min,
Rate1:0.3°C/min, Isotemp.2:100°C/min, Isotime2: 0 min
Rate1:40°C/min, Isotemp.2:200°C/min, Isotime2: 0 min
Split: 35

2,5-Dihydro-5-(methoxymethyl)-2,4-dimethyl-2-phenylfuran (3.50ea)



Chrom-Card Report

Operator ID : Peri
Company Name : AK Krause
Method Name : özge
Method File : OZGECHI1.MTH
Analysed : 30.03.10 14:37
Printed : 23.04.2010 14:28

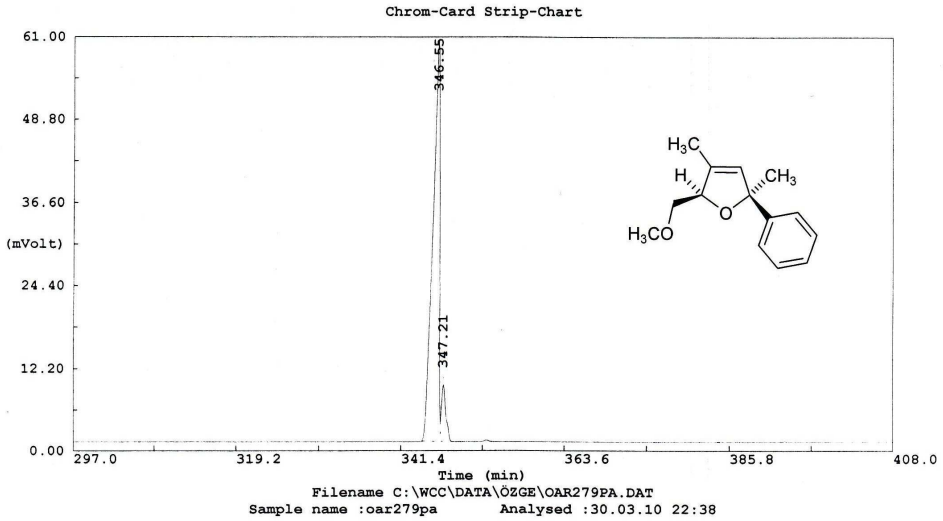
Sample ID : oar278pa
Channel : Channel C
Analysis Type : UnkNown (Area)
Calc. Method : Area %
Chromatogram : C:\WCC\DATA\ÖZGE\OAR278PA.DAT

Warning Chromatogram has been subjected to manual integration.

Peak Number #	Area %	Ret.Time	Area	BC
1	49.4780	346.09	6336773	mi
2	50.5220	347.90	6470479	mi
Totals	100.0000		12807250	

Column: Hyhdodex-beta-3P 25m,0.25mm ID
Detektor: FID, 280°C
Injektor: 280°C
Oven program: Isotemp.1: 40°C, Isotime1:15 min,
Rate1:0.2°C/min, Isotemp.2:130°C/min, Isotime2: 0 min
Rate1:20°C/min, Isotemp.2:200°C/min, Isotime2: 5 min
Split: 35

(2*S*,5*R*)-2,5-Dihydro-5-(methoxymethyl)-2,4-dimethyl-2-phenylfuran (3.50fa)



Chrom-Card Report

Operator ID : Peri
Company Name : AK Krause
Method Name : özge
Method File : OZGECHI1.MTH
Analysed : 30.03.10 22:38
Printed : 23.04.2010 14:32

Sample ID : oar279pa
Channel : Channel C
Analysis Type : UnkNown (Area)
Calc. Method : Area %
Chromatogram : C:\WCC\DATA\ÖZGE\OAR279PA.DAT

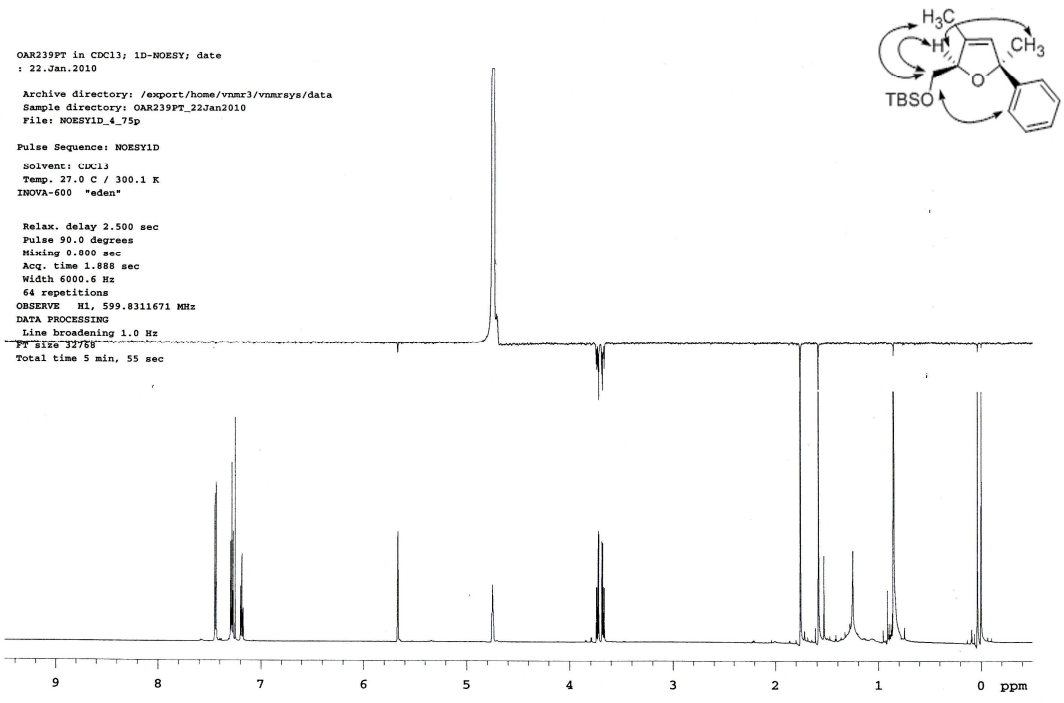
Warning Chromatogram has been subjected to manual integration.

Peak Number #	Area %	Ret.Time	Area	BC
1	91.6446	346.55	37900960	mi
2	8.3554	347.21	3455504	mi
Totals	100.0000		41356470	

Column: Hyhdodex-beta-3P 25m,0.25mm ID
Detektor: FID, 280°C
Injektor: 280°C
Oven program: Isotemp.1: 40°C, Isotime1:15 min,
Rate1:0.2°C/min, Isotemp.2:130°C/min, Isotime2: 0 min
Rate1:20°C/min, Isotemp.2:200°C/min, Isotime2: 5 min
Split: 35

NOE (Chapter 3)

((2,5-Dihydro-3,5-dimethyl-5-phenylfuran-2-yl)methoxy)(*t*-butyl)dimethylsilane (3.50da)



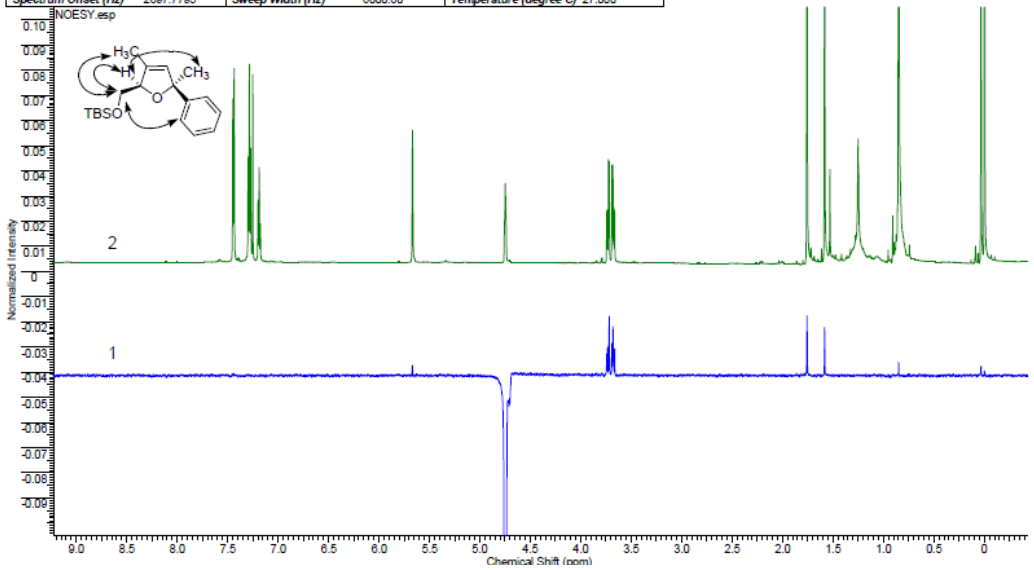
Spectrum : 1

OAR239PT in CDCl3; 1D-NOESY

Acquisition Time (sec)	1.8883	*Comment*	OAR239PT in CDCl3; 1D-NOESY; date			*Date*	Jan 22 2010
Date Stamp	Jan 22 2010	*File Name*	C:\NMR GERMANY\OAR239PT_22Jan2010\NOESY1D_4_75p				
Frequency (MHz)	599.83	*Nucleus*	1H	*Number of Transients*	64	*Original Points Count*	11331
Points Count	16384	*Pulse Sequence*	NOESY1D	*Receiver Gain*	40.00	*Solvent*	CHLOROFORM-d
Spectrum Offset (Hz)	2697.7800	*Sweep Width (Hz)*	6000.60	*Temperature (degree C)*	27.000		

Spectrum : 2

Acquisition Time (sec)	1.8883	*Comment*	OAR239PT in CDCl3; 1D-NOESY; date			*Date*	Jan 22 2010
Date Stamp	Jan 22 2010	*File Name*	C:\NMR GERMANY\OAR239PT_22Jan2010\PROTON			*Frequency (MHz)*	599.83
Nucleus	1H	*Number of Transients*	16	*Original Points Count*	11331	*Points Count*	16384
Pulse Sequence	s2pul	*Receiver Gain*	32.00	*Solvent*	CHLOROFORM-d		
Spectrum Offset (Hz)	2697.7795	*Sweep Width (Hz)*	6000.60	*Temperature (degree C)*	27.000		



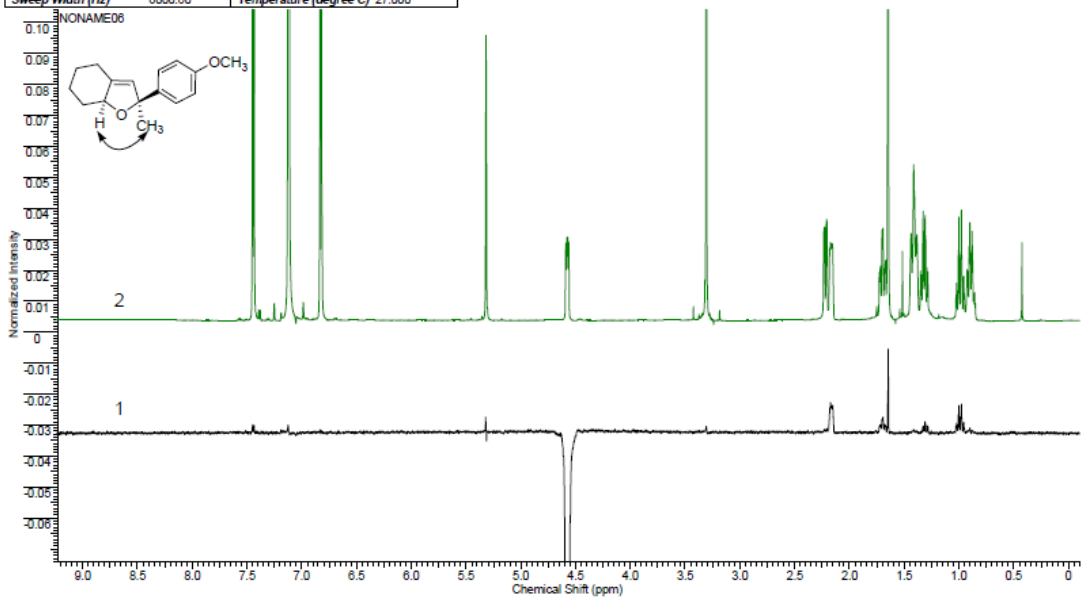
2,4,5,6,7,7a-Hexahydro-2-(4-methoxyphenyl)-2-methylbenzofuran (3.50af)

Spectrum : 1 OAR237PN in C6D6; 1D-NOESY

Acquisition Time (sec)	1.8883	*Comment*	OAR237PN in C6D6; 1D-NOESY; date:			*Date*	Jan 22 2010
Date Stamp	Jan 22 2010	*File Name*	C:\NMR GERMANY\OAR237PN_22Jan2010\NOESY1D_4_58p				
Frequency (MHz)	599.83	*Nucleus*	1H	*Number of Transients*	64	*Original Points Count*	11331
Points Count	16384	*Pulse Sequence*	NOESY1D	*Receiver Gain*	34.00	*Solvent*	Benzene
Spectrum Offset (Hz)	2699.2939	*Sweep Width (Hz)*	6000.60	*Temperature (degree C)*	27.000		

Spectrum : 2

Acquisition Time (sec)	1.8883	*Comment*	OAR237PN in C6D6; 1D-NOESY; date:			*Date*	Jan 22 2010
Date Stamp	Jan 22 2010	*File Name*	C:\NMR GERMANY\OAR237PN_22Jan2010\PROTON			*Frequency (MHz)*	599.83
Nucleus	1H	*Number of Transients*	16	*Original Points Count*	11331	*Points Count*	16384
Pulse Sequence	s2pul	*Receiver Gain*	26.00	*Solvent*	Benzene	*Spectrum Offset (Hz)*	2699.2942
Sweep Width (Hz)	6000.60	*Temperature (degree C)*	27.000				



Compound Characterization Checklist

Compound, structure, or table-entry number	New	Known	MP	IR	UV-Vis	^{1}H-NMR	^{13}C-NMR	MS	HRMS	Optical Rotation	*ee*	Note
2.31a	x					x	x		x			—
2.31b		x				x	x					*Org. Lett.* **2001**, *3*, 2537–2538
2.31c	x					x	x		x			—
2.31d		x				x	x					*Green Chem.* **2009**, *11*, 1309–1312
2.31e	x					x	x		x			—
2.31f		x				x	x		x			*J. Org. Chem.* **2009**, 74, 6050–6054
2.31g		x				x	x		x			*Synlett* **2007**, 5, 737–740
2.31h	x					x	x		x			—
2.32b		x				x	x		x			*Org. Lett.* **2001**, *3*, 2537–2538
2.32c	x					x	x		x			—
2.32d		x				x	x		x			*Green Chem.* **2009**, *11*, 1309–1312
2.32e	x					x	x		x			—
2.32f		x				x	x		x			*Synlett* **2007**, *11*, 1790–1794
2.32g	x					x	x		x			—
2.32h	x					x	x		x			—
2.34		x				x	x		x			*Angew. Chem. Int. Ed.* **2003**, *42*, 5355–5357
2.35	x					x	x		x			—
2.37		x				x	x		x			*J. Org. Chem.* **1993,** *58*, 3435–3443
2.38		x				x	x		x			*J. Org. Chem.* **2002,** *67*, 3930–3932
2.40		x				x	x		x			*Synlett* **2007**, 5, 737–740
3.47a		x		x		x	x		x			*J. Org. Chem.* **1998**, *63*, 6425–6426
3.47b	x			x		x	x		x			—
3.47c		x		x		x	x		x			*J. Org. Chem.* **2009**, *74*, 6050–6054
3.47d		x		x		x	x		x			*J. Org. Chem.* **1994,** *59***,** 1457–1464
3.47e		x		x		x	x		x			*Synlett* **2007**, *5*, 737–740
3.47f	x			x		x	x		x	x	x	—

Compound, structure, or table-entry number	New	Known	MP	IR	UV-Vis	^{1}H-NMR	^{13}C-NMR	MS	HRMS	Optical Rotation	*ee*	Note
3.47g	x			x		x	x		x			—
3.47h	x			x		x	x		x			—
3.47i	x			x		x	x		x			—
3.47j	x			x		x	x		x			—
3.49aa		x		x		x	x		x			*Angew. Chem. Int. Ed.* **2007**, *46*, 7101–7103
3.50aa	x			x		x	x		x			—
3.50ab	x			x		x	x		x			—
3.50ac	x			x		x	x		x			—
3.50ad	x		x	x		x	x		x			—
3.50ae	x			x		x	x		x			—
3.50af	x			x		x	x		x			—
3.50ag	x			x		x	x		x			—
3.50ah	x			x		x	x		x			—
3.50ai	x			x		x	x		x			—
3.50aj	x			x		x	x		x			—
3.50ak	x			x		x	x		x			—
3.50al	x			x		x	x		x			—
3.50am	x		x	x		x	x		x			—
3.50ba	x			x		x	x		x			—
3.50bb	x			x		x	x		x			—
3.50bd	x			x		x	x		x			—
3.50ca	x			x		x	x		x			—
3.50cb	x			x		x	x		x			—
3.50cd	x		x	x		x	x		x			—
3.50da	x			x		x	x		x			—
3.50db	x			x		x	x		x			—
3.50dd	x			x		x	x		x			—
3.50ea	x			x		x	x		x			—
3.50ed	x			x		x	x		x			—
3.50fa	x			x		x	x		x	x	x	—

Eidesstattliche Erklärung

Ich versichere hiermit, dass ich die vorliegende Dissertation selbstständig und ohne unzulässige fremde Hilfe erbracht habe. Ich habe keine anderen als die angegebenen Quellen und Hilfsmittel benutzt, sowie wörtliche und sinngemäße Zitate kenntlich gemacht.

Dortmund, den 23 Juli 2010

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Lebenslauf

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Studium

01/2007–09/2010	:	Promotion im Arbeitkreis von Prof. Dr. Norbert Krause, Technische Universität Dortmund, Dortmund-Deutschland Thema: "2,5-Dihydrofurans: New Approaches by Recyclable or Combined Catalysis"
09/2003–08/2005	:	Masterarbeit Izmir Instutute of Technology, Izmir-Türkei Thema: "The Activity of Silica Immobilized Palladium N-Heterocyclic Carbene Complexes Toward Mizoroki-Heck Reaction and Their Characterization"

Tätigkeiten

04/2009–06/2009	:	Praktikum bei Solvias AG, Basel (Schweiz)
04/2009–11/2008	:	Projekt Betreuer im Arbeitkreis von Prof. Dr. Simon Woodward, The University of Nottingham, England

Stipendien

01/2007–12/2009	:	Marie Curie Early Stage Training Stipendium

Posterpräsentationen

"Gold-Catalyzed Synthesis of 2,5-Dihydrofurans In Ionic Liquids", Ö. Aksın-Artok, N. Krause

- ❖ Tag der Chemie, Technische Universität Dortmund, März 2010, Dortmund-Deutschland;
- ❖ Minisymposium of the IRTG Münster-Nagoya, Oktober 2009, Münster-Deutschland;
- ❖ 5th Asian-European Symposium on Metal-Mediated Efficient Organic Synthesis, Mai 2008, Strasbourg-Frankreich.

Vorträge

"Combined Rhodium/Gold Catalysis: From Propargyl Oxiranes to 2,5-Dihydrofurans in One Pot", COST D40, Innovative Catalysis: New Processes & Selectivities, Gazi Universität, Mai 2010, Ankara, Türkei.

Publikationen von Promotion

"Gold-Catalyzed Synthesis of 2,5-Dihydrofurans in Ionic Liquids", Ö. Aksın, N. Krause, *Adv. Synth. Catal.* **2008**, *350*, 1106–1112.