Metal-catalysed cyclisation reactions in sustainable reaction media

DISSERTATION

zur Erlangung des Akademischen Grades
Doktor der Naturwissenschaften
(Dr. rer. nat.)

vorgelegt
der Fakultät Chemie und Chemische Biologie
der Technischen Universität Dortmund
von

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Dortmund, 2019

Die vorliegende Arbeit wurde in der Zeit vom Juli 2015 bis Oktober 2018 am Lehrstuhl für Organische Chemie der Technischen Universität Dortmund unter der Leitung von Herrn Prof. Dr. Norbert Krause erstellt.

Erstgutachter: Prof. Dr. Norbert Krause

Zweitgutachter: Prof. Dr. Klaus Jurkschat

Eingereicht am: 29.05.19

“[…]Und wenn ich so auf den Planet runter schau dann, denke ich, dass ich mich bei euch wohl leider entschuldigen muss. […]in Wirklichkeit ist es uns Menschen schon sehr klar, dass wir im Moment den Planeten mit Kohlendioxid verpesten; dass wir das Klima zum Kippen bringen; dass wir Wälder roden; dass wir die Meere mit Müll verschmutzen; dass wir die limitierten Ressourcen viel zu schnell verbrauchen; und dass wir zum Großteil sinnlose Kriege führen. [...] Und ich würde mir wünschen, dass wir nicht bei euch als die Generation in Erinnerung bleiben, die eure Lebensgrundlage egoistisch und rücksichtslos zerstört hat.

Ich bin mir sicher, dass ihr die Dinge inzwischen sehr viel besser versteht, als meine Generation. Und wer weiß, vielleicht lernen wir ja auch noch was dazu: Dass ein Blick von außen immer hilft; dass dieses zerbrechliche Raumschiff Erde sehr viel kleiner ist, als die aller meisten Menschen sich das vorstellen können; wie zerbrechlich seine Biosphäre ist und wie limitiert seine Ressourcen; dass es sich lohnt, mit seinen Nachbarn gut auszukommen; dass Träume wertvoller sind, als Geld und dass man ihnen eine Chance geben muss; dass Jungen und Mädchen Dinge genauso gut können, aber dass doch jeder von euch eine Sache hat, die er besser kann, als alle anderen; dass die einfachen Erklärungen oft die falschen sind und dass die eigene Sichtweise eigentlich immer unvollständig ist; dass die Zukunft wichtiger ist, als die Vergangenheit und dass man niemals ganz erwachsen werden soll; dass Gelegenheiten immer nur einmal kommen. Und dass man für Dinge die es wert sind, auch mal ein Risiko eingehen muss; dass ein Tag, an dem man etwas neues entdeckt hat, über seinen Horizont hinaus geschaut hat, ein guter Tag ist[…]”

„Nachricht an meine Enkelkinder“
Internationale Raumstation
Kommandant der Expedition 57
Alexander Gerst
25 November 2018
400 km über der Erdoberfläche

Danksagung

Mein herzlichster Dank gilt Prof. Dr. Norbert Krause für die Aufnahme in seine Arbeitsgruppe und für dieses interessante und herausfordernde Promotionsthema, welches mich vor allem durch den Bezug zur grünen Chemie sehr erfüllt hat. Weiterhin möchte ich ihm für die Unterstützung und das entgegengebrachte Vertrauen sehr bedanken, vor allem die Freiheit der Forschung, die ich genießen durfte waren mir sehr viel wert.

Herrn Prof. Dr. Klaus Jurkschat möchte ich für die bereitwillige Übernahme des Zweitgutachtens und die Anteilnahme an dieser Arbeit danken.

Des Weiteren möchte ich allen gegenwärtigen und ehemaligen Arbeitskreismitgliedern für ihre Unterstützung und das angenehme und meist sehr lustige Arbeitsumfeld innerhalb und außerhalb des Labors danken: Dr. Anja Wiegand, Dr. Bernd Wagner, Evelyn Grochulski, Dr. Gen Onodera, Dr. Gürkan Eray Akpinar, Dr. Hülya Sak, Indre Versinskaite, Johannes Rath, Justin Schieven, Katharina Müller, Dr. Katrin Belger, Dr. Linda Lempke, Martin Körner, Matthias Mawick, Monika Ballmann, Sebastian Kampling, Vera Wiese, Yang Zhang.
Außerdem möchte ich Kim Vogt danken, vor allem für unsere gemeinsamen Bastelstunden an der Mikrowelle und GC, sowie Katja Weber, Andreas Hammer, Kerstin Hammerschmidt-Aßmann, Dr. Ljuba Iovkova und Dr. Alexandra Behler und Silvia Lessing für ihre tatkräftige Unterstützung.

Mein Dank gilt auch der gesamten NMR-Abteilung für das zügige Messen meiner zahlreichen NMR-Proben, sowie der HRMS-Abteilung und Sylvia Marzian und Stephanie Schulz für die massenspektroskopischen Analysen. Weiterhin möchte ich auch Dr. Ulrike Kroesen und Dr. Kathrin Louven für die Messung meiner GC-MS Proben sowie durchgeführter DFT Rechnungen danken.

Außerdem möchte ich meinen Studenten und Azubis Andrea Machalica, Anna Krupp, David Podlesainski, Hendrik Busen, Kathrin Ludwigs, Nicholas Jankowski, Niklas Wild, Nils Kampling, Paul Ruer für die schöne Zeit, ihr Interesse und ihre Unterstützung danken. Es hat mir immer sehr viel Spaß gemacht mit euch!

Ich möchte mich auch für die Möglichkeit am Forschungscluster SusChemSys teilzunehmen bedanken, welcher mir ermöglichte, mich persönlich und fachlich weiterzubilden sowie einen Blick über den Tellerrand hinaus ermöglichte.

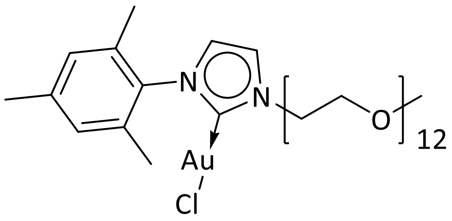
Schließlich möchte ich mich bei all meinen Freunden, die mich in den letzten Jahren begleitet haben ganz herzlich für die schöne Zeit und ihre Unterstützung danken, insbesondere bei Matthias, Benedikt, Peter, Sven, Claudius und Felix, sowie Ilka für ihre steten Ermutigungen und Unterstützung in stressigen Zeiten und bei Misserfolgen. Besonderer Dank gilt auch meinem Vater für seine Unterstützung, auf die ich stets und bedingungslos zählen konnte.

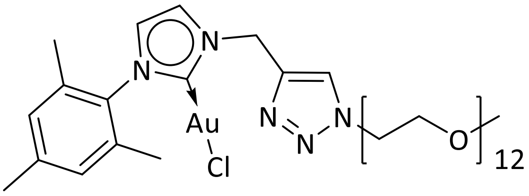
Vielen Dank auch an die fleißigen Korrekturleser dieser Arbeit.

Abstract

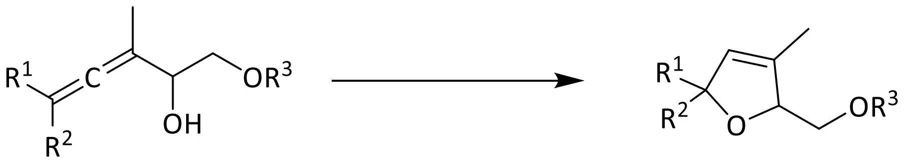
Since an increased attention has been paid to the sustainability of reactions in chemistry, it is envisaged to develop and implement new, more sustainable catalyst/solvent systems. Important approaches and concepts to fulfil the need of a greener chemistry are in particular catalysts which can be easily separated from their products and thereby reused.

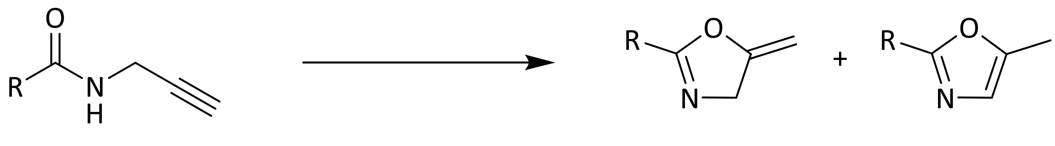
To this end, were hydrophilic and therefore easily separable NHC-gold complexes synthesised. In order to ensure the water solubility hydrophilic polyethylene glycol (PEG) side chains were introduced to imidazole-based NHC complexes.





Moreover, a new and sustainable class of solvents, so-called Deep Eutectic Solvent (DES) were tested on chosen gold-catalysed reactions and were optimised regarding their recyclability. Furthermore, the catalytic activity of the hydrophilic gold complexes was examined, in the following test reactions conducted in green solvents.

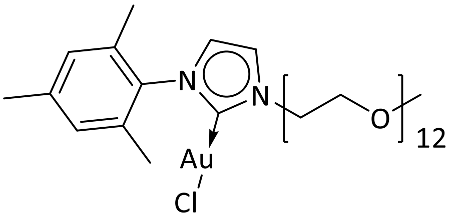


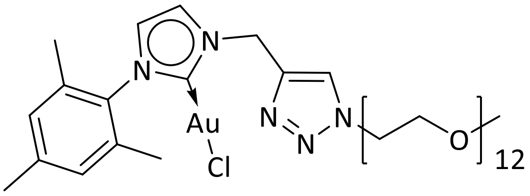


Abstrakt

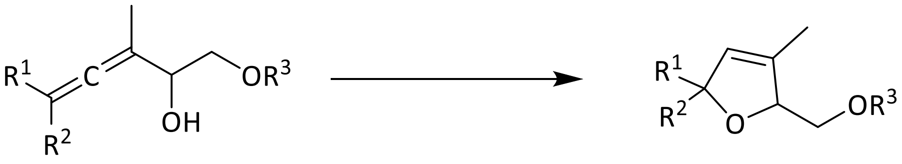
Da der Nachhaltigkeit von Reaktionen in der Chemie immer mehr Aufmerksamkeit geschenkt wird, ist die Entwicklung und Implementierung neuer, nachhaltigerer Katalysator-/Lösemittelsysteme wünschenswert. Wichtige Ansätze und Konzepte auf dem Weg zu einer grüneren Chemie sind insbesondere Katalysatoren, die sich leicht von ihren Produkten trennen und damit wiederverwenden lassen.

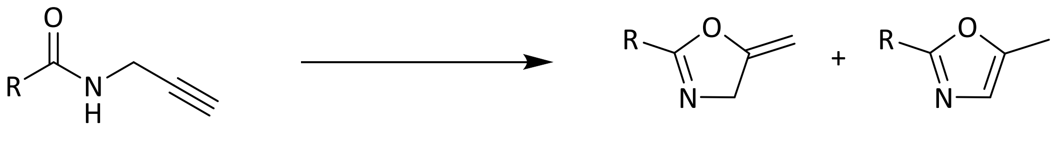
Zu diesem Zweck wurden hydrophile und damit leicht abtrennbare NHC-Gold-Komplexe synthetisiert. Um die Wasserlöslichkeit zu gewährleisten, wurden hydrophile Polyethylenglykol (PEG)-Seitenketten in imidazolbasierten NHC-Komplexe eingeführt.





Darüber hinaus wurde eine neue und nachhaltige Klasse von Lösemitteln, die sogenannten Deep Eutectic Solvents (DES), an ausgewählten goldkatalysierten Reaktionen getestet und hinsichtlich ihrer Recyclingfähigkeit optimiert. Weiterhin wurde die katalytische Aktivität der hydrophilen Goldkomplexe in den folgenden Testreaktionen in grünen Lösungsmitteln untersucht.





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The following abbreviations are used in this doctoral thesis:

°C	Degree Celsius
Å	Ångström
Ac	Acetyl
acac	Acetylacetone
Acc	Acceptor
Ar	Aryl
BetHCl	Betaine hydrochloride
Bn	Benzyl
Boc	tert-Butyloxycarbonyl protecting group
Bu	Butyl
CHCl	Choline chloride
Conc.	Concentrated
CuAAC	Copper(I)-catalysed Azide-Alkyne Cycloaddition
Cy	Cyclohexane
D	Day(s)
DCM	Dichloromethane
DES	Deep Eutectic Solvent
DFT	Density functional theory
DIAD	Diisopropyl azodicarboxylate
DIBAL-H	Diisobutylaluminium hydride
DMAP	4-Dimethylaminopyridine
DMF	N,N-Dimethylformamide
DMSO	Dimethylsulfoxide
EDTA	Ethylenediaminetetraacetic acid
eq.	equivalents
ESI	Electrospray ionisation
Et	Ethyl
EtOAc	Ethyl acetate
EtOH	Ethanol
g	gram
GC	Gas chromatography
h	hour(s)
HCl	Hydrochloric acid
HPLC	High performance liquid chromatography
Hz	Hertz
IMes	1,3-Bis(2,4,6-trimethylphenyl)-1,3-dihydro-2H-imidazol-2-ylidene

IPr	1,3-bis(2,6-diisopropylphenyl)imidazol-2-ylidene
*i*Pr	*iso*-Propyl
IR	Infrared
KHMDS	Potassium bis(trimethylsilyl)amide
KO*t*Bu	Potassium tert-butoxide
L	Litre
LDA	Lithium diisopropylamide
M	Molar concentration
m-CPBA	*meta*-Chloroperoxybenzoic acid
Me	Methyl
MeCN	Acetonitrile
MeOH	Methanol
Mes	Mesityl
mg	Milligram
MIC	Mesoionic carbene
min	minute(s)
mL	Millilitre
mmol	Millimole
MPEG	monomethylated PEG
Ms	Mesyl
nBu	normal Butyl

nBuLi	n-Butyllithium
NHC	N-heterocyclic carbene
nm	Nanometre
NMR	Nuclear magnetic resonance
NSAID	Nonsteroidal anti-inflammatory drug
Nu	Nucleophile
OTf	Triflate
PEG	Polyethylene glycol
Pg	Protecting group
Ph	Phenyl
PPG	Polypropylene glycol
ppm	parts per million
p-TsOH	p-Toluenesulfonic acid
quant.	quantitative
rt	room temperature
Sat.	saturated
TBS	tert-Butyldimethylsilyl ether
*t*Bu, *t*-Bu	tert-Butyl
TDG	thiodiglycol
THF	Tetrahydrofuran
TIPS	Triisopropylsilyl ether
TLC	Thin-layer chromatography
Ts	Tosyl

UV	Ultraviolet		
δ	Chemical shift	μL	Microlitre

1. General introduction

1.1. The necessity of Green Chemistry

Ban Ki-moon the Eighth Secretary-General of the United Nations said on the World Economic Forum in Davos: *"We are the first generation to be able to end poverty, and the last generation that can take steps to avoid the worst impacts of climate change. Future generations will judge us harshly if we fail to uphold our moral and historical responsibilities."*[1]

In the last years, the limitation of natural resources on earth has become more omnipresent than ever. Mankind's lifestyle is far beyond the borders of regenerative capacity of the earth and its biosphere.[2] According to a report of the Global Footprint Network, humanity exceed the regenerative capacity by 70% and the calculated Earth Overshoot Day was on the 1. August of 2018 ("Earth Overshoot Day marks the date when humanity has exhausted nature's budget for the year").[3] The consequences are known: polluted drinking water, overfished and polluted oceans, extinction of entire species, erosion of fertile soil and climate changes with all their associated negative impacts.[4] The strains have become so large that in maintaining this way of life in 2035 a demand for a second earth would be inevitable to guarantee a sufficient satisfaction of our needs.[5] In fact, the global population will exceed nine billion people, who all rely on a liveable environment, a stable climate and availability of clean drinking water.[6] Furthermore, our water consumption is constantly increasing and will surpass our current water supply by 40% in 2030.[7]

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[1] United Nations, accessed 14.05.19, https://www.un.org/sg/en/content/sg/statement/2015-01-23/secretary-generals-remarks-world-economic-forum-plenary-session;

[2] J. Cohen, *Science* **1995**, *269*, 341-346.

[3] *Earth Overshoot Day 2018: is August 1, the earliest date since ecological overshoot started in the early 1970s?*, Global Footprint Network, **2018**.

[4] M. Carley, P. Spapens, *Sharing the World. London: Routledge*, Routledge, London, **1997**.

[5] S. H. Chris Hails, J. Loh, S. Goldfinger,*Living Planet Report 2008,* WWF, **2008**.

[6] *World Population Prospects*, Department of Economic and Social Affairs, Population Division, New York, **2015**.

[7] C. Douglas, The 2030 Water Resources Group, **2009**.

Already today, our advanced sewage treatment plants can no longer ensure a removal of all organic contaminants, not even mentioning the situation in developing countries.[8] Chemical- and pharmaceutical industry is jointly responsible for this urgent situation and has to face the challenge of utter sustainability, despite the increasing need for chemical products like polymers, fine- and special chemicals, as well as, pharmaceuticals.[9]

These circumstances require a development of sustainable solutions and processes in the spirit of green chemistry, which were established by Anastas, Warner, Sheldon and Trost in the early 1990s.[10] Their definition reads as follows: „Green Chemistry efficiently utilises (preferably renewable) raw materials, eliminates waste and avoids the use of toxic and/or hazardous reagents and solvents in the manufacture and application of chemical products.“[11]

Additionally, twelve general principles regarding green chemistry were introduced by Anastas and Warner in 1998 (see figure 1).[[12]]

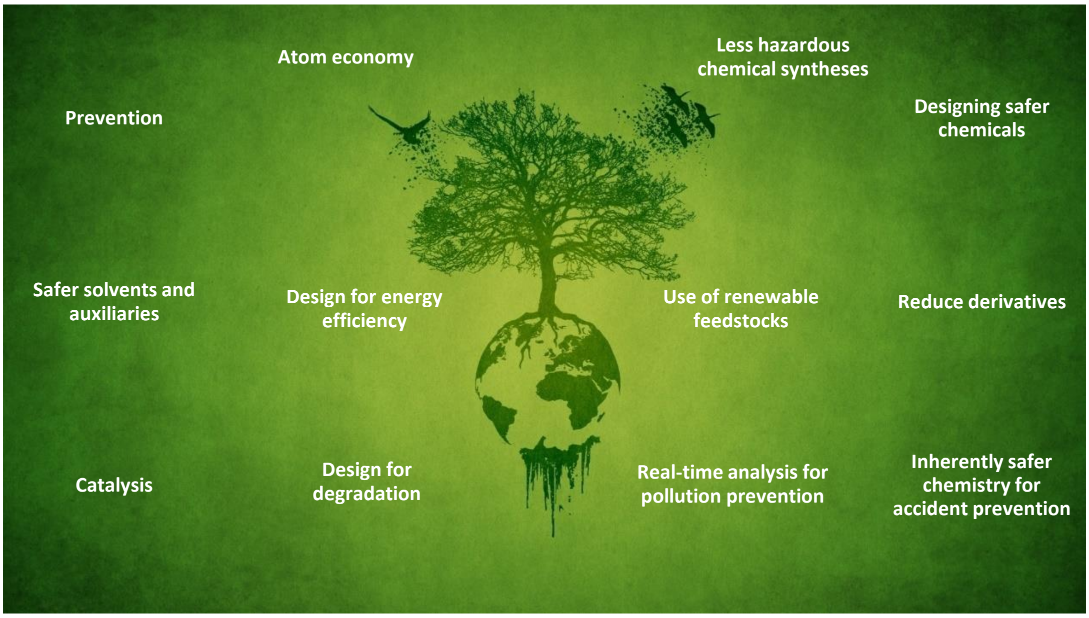

Figure 1 Twelve general principles regarding green chemistry image taken from http://neomatrixblog.blogspot.com/2013/04/save-blue-planetbecause-its-actually.html, accessed 15.11.2018

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[8] M. Kucera, *Gut gefiltert in Gelsenkirchen, kma, Georg Thieme Verlag KG Stuttgart* **2014**, *19*, 52-54.

[9] M. M. V. Sarathy, J. Gotpagar, J. Bebiak, *2017 Chemicals Industry Trends; Delivering profitable growth in a hypercompetitive, low-growth world,* PwC’s Strategy&, **2017**.

[10] J. C. W. P. T. Anastas, *Green Chemistry. Theory and Practice*, Oxford University Press, **1998**; R. A. Sheldon, *Chem. Ind. (London),* **1992**, 903–906; R. A. Sheldon, *CHEMTECH;(United States)* **1994**, *24*; B. M. Trost, *Science,* **1991**, 254, 5037, 1471-1477.

[11] I. A. R. A. Sheldon, U. Hanefeld, *Green Chemistry and Catalysis*, Wiley-VCH, **2007**.

[12] J. C. W. P. T. Anastas, *Green Chemistry. Theory and Practice*, Oxford University Press, **1998**.

Six years later, the OECD (Organisation for Economic Cooperation and Development) in tandem with the German Federal Environment Agency stipulated five criteria for a sustainable way of chemistry:[13]

- "**Qualitative development:** Use of harmless substances, or where this is impossible, substances involving a low risk for humans and the environment, and manufacturing of long-life products in a resource-saving manner;"
- "**Quantitative development:** Reduction of the consumption of natural resources, which should be renewable wherever possible, avoidance or minimisation of emission or introduction of chemicals or pollutants into the environment. Such measures will help to save costs;"
- "**Comprehensive life cycle assessment:** Analysis of raw material production, manufacture, processing, use and disposal of chemicals and discarded products in order to reduce the consumption of resources and energy and to avoid the use of dangerous substances;"
- "**Action instead of reaction:** Avoidance, already at the stage of development and prior to marketing, of chemicals that endanger the environment and human health during their life cycle and make excessive use of the environment as a source or sink; reduction of damage costs and the associated economic risks for enterprises and remediation costs to be covered by the state;"
- "**Economic innovation:** Sustainable chemicals, products and production methods produce confidence in industrial users, private consumers and customers from the public sector and thus, result in competitive advantages."

In the words of Nobel laureate professor Ryoji Noyori "Green Chemistry is not just a mere catch phrase; it is the key to the survival of mankind."[14]

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[13] Umweltbundesamt, Nachhaltige Chemie, accessed 23.06.218
https://www.umweltbundesamt.de/themen/chemikalien/chemikalienmanagement/

[14] R. Noyori, *Tetrahedron,* **2010**, 1028.

1.2. Role of solvents

Many of these criteria could be satisfied by the development and utilisation of highly active, selective and recyclable catalysts in combination with separation processes as well as lastly, and importantly the application of green solvents.[15] The usage of solvents is a significant factor due to their ubiquitous role in chemistry:[16]

- >80% of the material usage for Active Pharmaceutical Ingredient (API) manufacture are caused by solvents;
- Solvents consume about 60% of the overall energy;
- Solvents are responsible for 50% of the post treatment greenhouse gas emissions;
- Recovery efficiencies are typically between 50–80%;[17]
- Solvents are often volatile organic compounds (VOCs) causing further problems:
    - Accumulation in the atmosphere causing unintentional changes
    - Flammability
    - Often high toxicity
    - Mostly not biodegradable

Thusly it is very desirable to dismiss the use of any solvents. Examples are given but often it is not applicable to give up on solvents.[18]

In consequence, there is a compelling need of alternate solvents, which can provide the demanded specifications on the one hand and are able to overcome the known drawbacks of classic organic solvents on the other hand.

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[15] P. T. Anastas, L. B. Bartlett, M. M. Kirchhoff, T. C. Williamson, *Catal. Today*, **2000**, *55*, 11-22;
C. K. Z. Andrade, A. R. Dar, *Tetrahedron,* **2016**, *72*, 7375-7391.

[16] R. K. Henderson, C. Jiménez-González, D. J. C. Constable, S. R. Alston, G. G. A. Inglis, G. Fisher, J. Sherwood, S. P. Binks, A. D. Curzons, *Green Chem.,,* **2011**, *13*, 854-862;
R. A. Sheldon, *Green Chem.,,* **2005**, *7*, 267-278;
D. J. C. Constable, A. D. Curzons, V. L. Cunningham, *Green Chem.,* **2002**, *4*, 521-527.

[17] G. P. Taber, D. M. Pfisterer, J. C. Colberg, *Org. Process Res. Dev.,* **2004**, *8*, 385-388.

[18] P. J. Walsh, H. Li, C. A. de Parrodi, *Chem. Rev.,,* **2007**, *107*, 2503-2545; R. S. Varma, *Green Chem.,* **1999**, *1*, 43-55.

They should possess the following properties:[19]

- Low toxicity, vapor pressure and flammability
- biodegradability and environmentally harmless
- Low synthetic expanse and based on natural resources
- Simple recyclability and separation
- Chemically inert
- Cheap and economical

The following table shows some of the most important classes of alternative solvents and some examples:

Water
- Micelles
- Biphasic systems

Supercritical fluids
- Carbon dioxide

Alcohols and Ethers
- Glycerol
- Methanol, Ethanol
- 2-Methyltetrahydrofuran

Organic carbonates
- Propylene carbonate
- Dimethyl carbonate

Ionic Liquids
- 1-Butyl-3-methylimidazolium hexafluorophosphate (BMIM-PF_6)

Polyfluorinated solvents

Liquid polymers
- PEG (Polyethylene glycol)

Switchable solvent systems
- DBU/Alcohol/carbon dioxide

Deep Eutectic Solvents
- Cholin/urea

Figure 2: Most important classes of alternative solvents

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[19] R. M. Francesca Kerton, *Alternative Solvents for Green Chemistry*, 2nd ed., The Royal Society of Chemistry, **2013**.

1.3. Green metrics

Another crucial challenge is to take all process steps into account in order to determine the "greenness" of the whole process. This is an important consideration due to the fact that the used amount of solvents for purification and separation processes can exceed the solvent amount for the reaction itself by 30 times.[20] As a consequence, it is not sufficient to just consider the reaction media, but also on the whole process of the desired product. Obviously, there is no absolute "greenness", but in recent years some appropriate green metrics could be introduced, which allow a relative comparison of "greenness".

Atom economy

Atom economy (AE) was introduced by *B.M. Trost* in 1991 in order to raise awareness for the number of reactants which end up in the product, referred to as atom economy. AE offers a simple method for the "greenness" of an organic reaction by just calculate how much atoms of the reactants remain in the final product. In this manner, the ideal reaction would include all atoms of all reactants for the purpose of waste avoidance as well as a more effective use of limited resources. However, the simplicity of AE is also a drawback because factors like solvents, energy or the purification steps are not taken into account.[21]

E-Factor

The E-Factor (environmental factor) is one attempt to describe the sustainability of a chemical manufacturing process and their environmental impact, introduced by *Roger Sheldon* 1992.[22] It is defined as a quotient between the actual weight amount of waste divided by the mass of the desired product.[23]

$$\frac{\text{Mass of waste}}{\text{Mass of product}} = \text{E-Factor}$$

Equation 1: Calculation of the E-Factor

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[20] A. A. Donna G. Blackmond, V. Coombe, A. Wells, *Angew. Chem.* **2007**, 3872 – 3874.

[21] B. M. Trost, *Science,* **1991**, 254, 5037, 1471-1477.

[22] R. A. Sheldon, *Chem. Ind. (London)* **1992**, 903–906.

[23] R. A. Sheldon, *CHEMTECH;(United States),* **1994**, *24*.

The advantages are clear: The E-factor is easy to calculate, and it takes many factors into account like the chemical yield, all reagents, solvents losses and all process aids. It is even basically possible to include the required energy because of the waste generation in the form of carbon dioxide. Noteworthy, water is generally excluded from the calculation because it claimed to lead to difficult comparisons. With this in mind, it is easy to see that a higher E-factor means a greater negative environmental impact whereas the ideal E-factor is zero. Typical E-factors are shown in Table 1.[24]

Table 1: Typical E-factors

Industry Segment	**Volume (tons/annum)**	**E Factor (kg waste/kg product)**
Bulk Chemicals	10^4–10^6	<1–5
Fine chemicals	10^2–10^4	5– >50
Pharmaceutical Industry	10–10^3	25– >100

The concept of E-factors is widely established by now and led to a paradigm shift: an aged approach exclusively focused on chemical yield changed slightly in favour of a modern more sustainable one that is focused on waste elimination and optimisation of raw materials utilisation in chemical industry.[25]

Life-cycle assessment

Life-cycle assessment (LCA) is a method to determine the environmental impact of a product by taking all stages of a product's life like raw materials, processing, production, distribution, use, repair as well as disposal or recycling into account. Obviously, this method is one of the most time-consuming and can be very costly, which limits its use as analysis technique.[26]

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[24] R. A. Sheldon, *Chem. Soc. Rev.,* **2012**, *41*, 1437-1451.

[25] R. A. Sheldon, *Green Chem.,* **2007**, *9*, 1273-1283.

[26] U. E. P. Agency; A. White, K. Shapiro, *Environ. Sci. Technol.,* **1993**, *27*, 1016-1017.

1.4. Catalysis

The usage of catalysis has become an indispensable technology in today's chemistry, this obviously can be derived from the numbers: About 90% of all manufactured products from chemical industry are produced with the assistance of a catalyst including fuels, agrochemicals, synthetic materials, dyes or pharmaceuticals.[27] A definition that still holds true today was given by *Ostwald* 1894: “a catalyst accelerates a chemical reaction without affecting the position of the equilibrium” (see Figure 3).[28] It is noteworthy that the catalyst does not change the thermodynamics of the reaction, furthermore, under ideal conditions the catalyst would not be consumed in this reaction even though this is often not the case in practice. Because of the above stated challenges that lie ahead to the global population (chapter 1.1), it is more important than ever before, to develop and establish more efficient and sustainable processes in chemical industry, wherein catalysis owes a central role as a key technology.

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[27] M. Baerns, A. Behr, A. Brehm, J. Gmehling, H. Hofmann, U. Onken, *Technische Chemie*, John Wiley & Sons, **2013**;
A. Behr, D. W. Agar, J. Jörissen, *Einführung in die technische Chemie*, Springer, **2010**.

[28] W. Ostwald, *Zeitschrift für physikalische Chemie,* **1894**, *15*, 705-706.

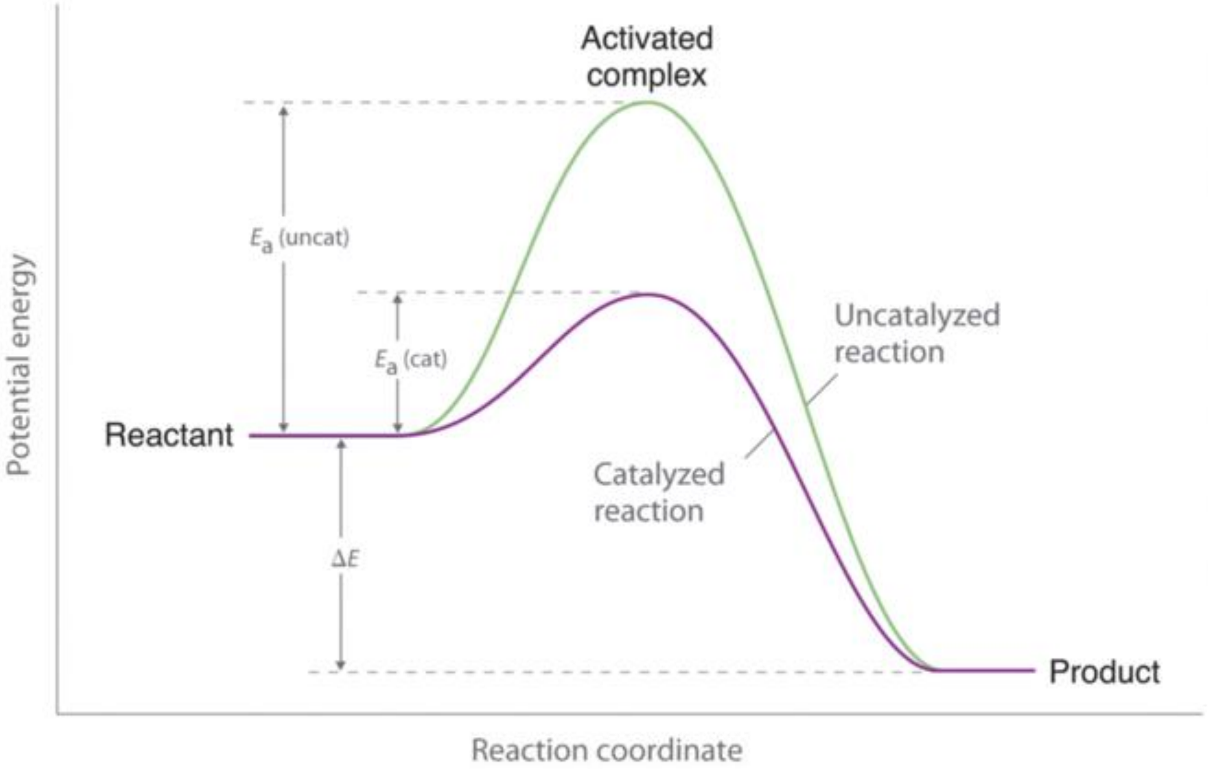

Figure 3 Activation energy of a reaction in the presence and absence of a catalyst[29]

1.4.1. Gold catalysis

Even though gold was considered as a catalytically inactive element for a long time it has become an important tool in synthetic chemistry and is furthermore a fast-growing field of modern catalysis.[30] In the 1970s, hydrogenations of olefins over supported gold catalysts[31] were reported, later oxidation of CO[32] and hydrochlorinations of ethyne to vinyl chloride[33] could be sufficiently achieved with gold catalysts. One of the most important steps for a key role in homogenous catalysis was the addition of nucleophiles to alkynes investigated for alcohols, water, and amines.[34]

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[29] L. libraries, accessed 24.10.18, https://chem.libretexts.org/Textbook_Maps/General_Chemistry/Map%3A_A_Molecular_Approach_(Tro)/14%3A_Chemical_Kinetics/14.7%3A_Catalysis

[30] M. Rudolph, A. S. K. Hashmi, *Chem. Soc. Rev.,* **2012**, *41*, 2448-2462.

[31] G. C. Bond, P. A. Sermon, G. Webb, D. A. Buchanan, P. B. Wells, *J. Chem. Soc., Chem. Commun.,* **1973**, 444b-445.

[32] M. Haruta, T. Kobayashi, H. Sano, N. Yamada, *Chem. Lett.,* **1987**, *16*, 405-408.

[33] G. J. Hutchings, *J. Catal.,* **1985**, *96*, 292-295.

[34] Y. Fukuda, K. Utimoto, *J. Org. Chem.,* **1991**, *56*, 3729-3731;
J. H. Teles, S. Brode, M. Chabanas, *Angew. Chem., Int. Ed.,,* **1998**, *37*, 1415-1418.

The mechanism for the gold-induced carbophilic activation often follows the same pattern (see Figure 4). In stage **A** the active carbophilic gold species coordinates to the multiple bond (*π*-complex) and facilitates an attack by a nucleophile. The addition of the inter- or intramolecularly attacking nucleophile proceeds in general in *anti* position. This observation is best described by an outer sphere mechanism, whereas a substitution in *syn* position would proceed through an inner-sphere mechanism, which can be assumed in rare cases and only in the presence of strongly coordinating nucleophiles.[35] The resulting σ-complex **B** undergoes a protodeauration subsequently generating the addition product and regenerating the catalysts (shown in **C**). It is noteworthy that the last step can also work with other electrophiles like electrophilic iodine.[36]

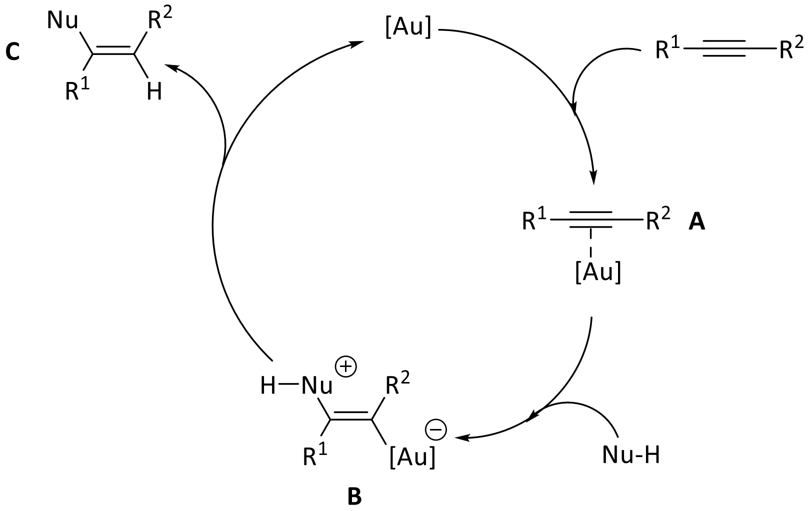

Figure 4 Proposed mechanism for the gold-induced carbophilic activation

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[35] A. S. K. Hashmi, *Angew. Chem., Int. Ed.,,* **2010**, *49*, 5232-5241.

[36] A. Buzas, F. Gagosz, *Synlett,* **2006**, *2006*, 2727-2730;
S. F. Kirsch, J. T. Binder, B. Crone, A. Duschek, T. T. Haug, C. Liébert, H. Menz, *Angew.Chem.Int.Ed.,* **2007**,46,2310–2313
L.-P. Liu, B. Xu, M. S. Mashuta, G. B. Hammond, *J. Am. Chem. Soc.,* **2008**, *130*, 17642-17643.

Another interesting fact is the strong relativistic effect that gold is bearing. Therefore, the characteristics of the electronic structure like the golden colour, large Au–L bond strength, linear structure, aurophilicity and the alkynophilicty are the consequence.[37] This effect is due to the fact that the relativistic mass increases with the velocity. This becomes important in heavier elements, where the electrons can reach several per cent of the speed of light resulting in an increase in mass, which corresponds to a decrease in radius.

That is why the electrons are closer the nucleus and have higher ionisation energies, especially the *d* and *f* orbitals receive an exceptional shielding by the electrons in the *s* and *p* orbitals, resulting in a weaker nuclear attraction. It is noteworthy that the most important fact in favour of gold catalysis is the superior ("soft") Lewis acidity of gold compared with other group 11 metals, which is also a consequence of relativistic effects. Since the relativistic contraction of the valence 6*s* or 6*p* orbitals resulting in a low-lying LUMO, which corresponds to a strong Lewis acidity.[38]

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[37] D. R. McKelvey, *J. Chem. Educ.,* **1983**, *60*, 112;
P. Pyykko, J. P. Desclaux, *Acc. Chem. Res.,* **1979**, *12*, 276-281;
J. Desclaux, P. Pyykkö, *Chem. Phys. Lett.,* **1976**, *39*, 300-303;
F. Scherbaum, A. Grohmann, B. Huber, C. Krüger, H. Schmidbaur, *Angew. Chem., Int. Ed., Engl.,* **1988**, *27*, 1544-1546.

[38] P. A. M. Dirac, *Proc. R. Soc. Lond. A* **1928**, *117*, 610-624;
A. Einstein, *Ann. Phys.,* **1905**, *322*, 891-921;
D. J. Gorin, F. D. Toste, *Nature* **2007**, *446*, 395.

2. First steps into sustainability: Synthesis of recyclable NHC-catalysts

2.1. Carbenes

Carbenes are reactive neutral molecules, which contain a divalent carbon atom with two unshared valence electrons bearing either an antiparallel spin, so-called singlet carbene or a parallel spin named triplet carbene.[39] Despite numerous important previous achievements in this field by *M. Hermann*[40], *A. Geuther*[41], *M. Gomberg*[42], *H. Staudinger*[43] and *H. Meerwein*[44], the true nature of the carbenes remained hidden from them in consequence of limited analysis methods.

The existence of carbenes could first be proven only in 1954 by *W. Doering* through his ground-breaking studies on the addition of dichlormethylene to olefins via a carbene intermediate.[45]

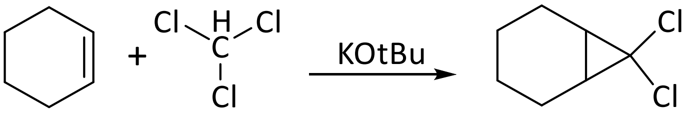

Figure 5: Addition of dichlormethylene to olefins

Even though carbenes play a crucial role as intermediates in important chemical industry processes, like gas to liquids (GTL) process or difluorocarbene as the precursor to Teflon (difluorocarbene is the most commercially available carbene), they were considered as not isolable intermediates in chemistry text books due to their high reactivity for a long time.[46]

A few years later, *Wanzlick* pursued the idea to synthesise a stable carbene and claimed to have found the carbene in equilibrium with its corresponding dimer by an α-elimination of chloroform.

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[39] M. Regitz, *Angew. Chem. Int. Ed. Engl.*, **1991**, 30, No. 6
[40] M. Hermann*, Justus Liebigs Ann. Chem.*, ***1855****, 95, 211-225.*
[41] A. Geuther*, Ann. Chem. Pharm.*, ***1862****, 123, 121-122.*
[42] M. Gomberg*, J. Am. Chem. Soc.*, ***1900****, 22, 757-771.*
[43] H. Staudinger*, O. Kupfer, Ber. Dtsch. Chem. Ges.*, ***1911****, 44, 2194-2197.*
[44] H. Meerwein, H. Rathjen, H. Werner*, Ber. Dtsch. Chem. Ges., (A and B Series)* ***1942****, 75, 1610-1622.*
[45] W. von E. Doering, A. K. Hoffmann, *J. Am. Chem. Soc.*, **1954**, *76*, 6162-6165.
[46] A. J. Arduengo, R. Krafczyk, *Chem. Unserer Zeit*, **1998**, *32*, 6-14.

As well as a benzothiazole-carbene by deprotonation of a vitamin B_1 derivate three years later.[47] Although this abovementioned equilibrium was called "*Wanzlick equilibrium*" later investigations showed that this equilibrium does not exist in the mentioned reactions and the balance is shifted fully to the side of the dimer.[48]

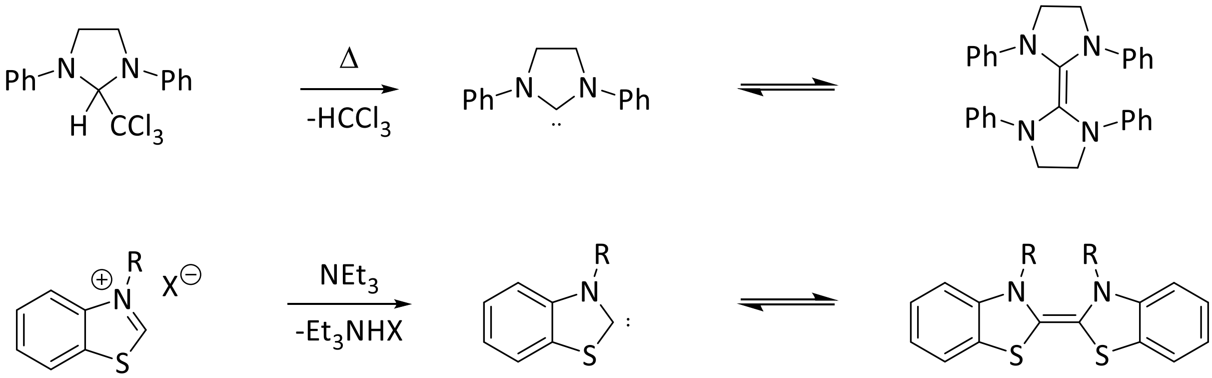

Figure 6 "Stable carbenes" in equilibrium with their corresponding dimers claimed by *Wanzlick*

Decades later, it could be demonstrated that the "*Wanzlick equilibrium*" is applicable only to special cases, demonstrated with disubstituted benzimidazoles.[49]

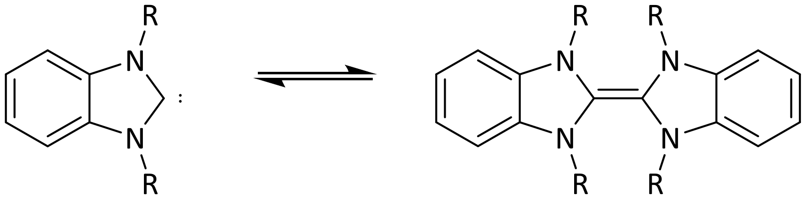

Figure 7 Equilibrium between an *N*-heterocyclic carbene and its dimer (R = alkyl substituents)

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[47] H.-W. Wanzlick, E. Schikora, *Angew. Chem. Int.,* **1960** 72,14, 494.;
H.-W. Wanzlick, E. Schikora, *Chem. Ber.,* **1961**, 94, 2389-2393;
H. W. Wanzlick, H. J. Kleiner, I. Lasch, H. U. Füldner, H. Steinmaus, *Justus Liebigs Ann. Chem.,* **1967**, *708*, 155-169.

[48] D. M. Lemal, R. A. Lovald, K. I. Kawano, *J. Am. Chem. Soc.,* **1964**, *86*, 2518-2519;
H. Quast, S. Hünig, *Chem. Ber.,* **1966**, *99*, 2017-2038;
H. Quast, S. Hünig, *Angew. Chem. Int.,* **1964** 3,12, 800-801.
Y. Liu, D. M. Lemal, *Tetrahedron Lett.,* **2000**, *41*, 599-602.

[49] V. P. W. Böhm, W. A. Herrmann, *Angew. Chem., Int. Ed.,* **2000**, *39*, 4036-4038;
W. Kirmse, *Angew. Chem., Int. Ed.,* **2010**, *49*, 8798-8801;
F. E. Hahn, L. Wittenbecher, D. Le Van, R. Fröhlich, *Angew. Chem., Int. Ed.,* **2000**, *39*, 541-544.

However, it was to take years until *Bertrand et al.* were able to isolate a stable λ^3-phosphinocarbene[50] in 1988 and three years later the first stable *N*-heterocyclic carbenes (NHC) synthesised by *Arduengo et al.*.[51] These findings resulted in a veritable boom on this field and a dramatically increased understanding of carbene chemistry.[52]

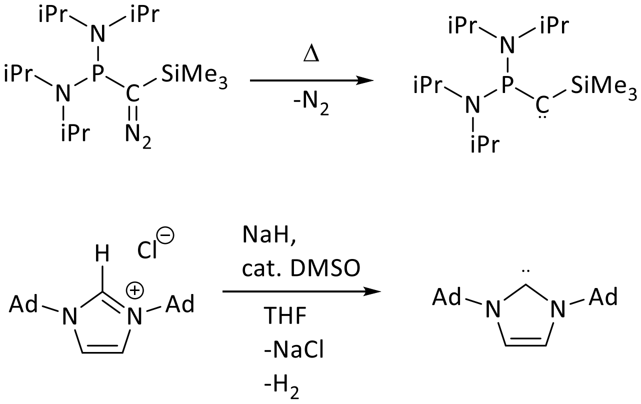

Figure 8: Synthesis of a stable λ^3-Phosphinocarbene from the diazo compound and stable crystalline *N*-heterocyclic carbene by deprotonation of 1,3-di-l-adamantylimidazoliumchloride

2.1.1. Properties of carbenes

The question arises what makes carbenes, especially NHCs, so special? The answer lies in their unique characteristics and the resulting applications. As mentioned before, carbenes contain a divalent carbon atom with two unshared valence electrons. Furthermore, the spin multiplicity and stability can be influenced by substituents. The spin multiplicity can adopt a singlet state with antiparallel spin or a triplet state with parallel spin. Their geometry can be linear or bent caused by hybridisation. The geometry of the much rarer linear carbene can be explained through a sp-hybridisation resulting in a carbene centre with two nonbonding degenerated orbitals (p_x and p_y).

The singlet carbene bearing an antiparallel spin, the carbon atom is sp^2- hybridised resulting in a bending of the molecule and a stabilisation of the p_x orbital through the increased s character, called σ. While the p_y orbital maintains mostly unchanged and is called p_π.[53]

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[50] A. Igau, H. Grutzmacher, A. Baceiredo, G. Bertrand, *J. Am. Chem. Soc.,* **1988**, *110*, 6463-6466.
[51] *A. J. Arduengo III, R. L. Harlow, M. Kline, J. Am. Chem. Soc., **1991**, 113, 361-363.*
[52] D. Bourissou, O. Guerret, F. P. Gabbai, G. Bertrand, *Chem. Rev.,* **2000**, *100*, 39-92.
[53] D. Bourissou, O. Guerret, F. P. Gabbai, G. Bertrand, *Chem. Rev.,* **2000**, *100*, 39-92.

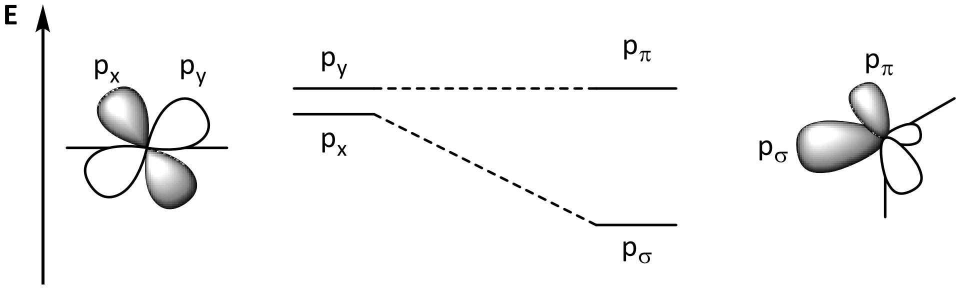

Figure 9 Bond angles and frontier orbitals of linear and bended carbenes

The reactivity of carbenes is ruled by the ground-state spin multiplicity, which is related to the relative energy of the two characterising orbitals σ and p_π.[54] Whereby, a large separation of σ and p_π facilitates the more favourable singlet ground state.[55] Substituents have a crucial influence on the σ - p_π separation:

- **Inductive effects:** σ-electron-withdrawing substituents increase the s character, while the p_π orbital remains nearly unchanged resulting in an inductive stabilisation of the nonbonding orbital, increasing of the σ - p_π separation. This effect causes the singlet status to be preferred. Quite to the contrary, σ-electron-donating substituents lead to a decreased σ - p_π separation and a favoured triplet state.[56]
- **Mesomeric effects:** In most instances, mesomeric effects are even more substantial. It consists of the interaction of the carbon orbitals (σ, p_π) and the regarding p or π orbitals of the two substituents and can be divided in three groups:
    - Two σ-electron-donating substituents: The lone pairs of the substituents interacting with the vacant p_π orbital resulting in an increased energy level, while the σ orbital remains nearly unchanged. This gives rise to an increased σ - p_π separation and the singlet state is favoured as a result. Another result of this is a polarised four-electron three-centre π-system, which possesses a multiple bond character.[57] Typical examples are diaminocarbenes like NHCs.

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[54] G. B. Schuster, *Adv. Phys. Org. Chem.*, **1987**, *22*, 311-361.

[55] R. Hoffmann, *J. Am. Chem. Soc.*, **1968**, *90*, 1475-1485.

[56] K. K. Irikura, W. Goddard III, J. Beauchamp, *J. Am. Chem. Soc.*, **1992**, *114*, 48-51.

[57] P. H. Mueller, N. G. Rondan, K. Houk, J. F. Harrison, D. Hooper, B. H. Willen, J. F. Liebman, *J. Am. Chem. Soc.*, **1981**, *103*, 5049-5052.

  - Two σ-electron-withdrawing substituents: These carbenes are predicted to be linear singlet carbenes arising from an interaction of the p_π orbital with the vacant p orbitals of the substituents.[58] Typical examples are diborylcarbenes, which can only be isolated in their masked analogues[59] or as metal-complexes[60].
  - σ-electron-donating and withdrawing substituents: These carbenes combine both effects described above. Both of them stabilise and favour the singlet state leading to a quasi-linear polarised allene-type system like phosphinosilyl- and phosphinophosphoniocarbenes.[61]
- **Steric effect:** In the case of insignificant electronic effects the steric effects of the substituents have considerable influence on the ground-state spin multiplicity, although bulky substituents are able to stabilise all types of carbenes. Since a linear geometry favours the triplet state, bulky substituents provoke a broadening of the carbene bond angle and facilitates the triplet state.[62] As a result, relatively small cyclic carbenes like imidazol-ylidenes have a singlet state because of their angle restriction combined with aromaticity.[63]

By their nature, NHCs are one of the most interesting classes of carbenes, therefore, the following parts are focused on their history as well as the properties and applications of their metal complexes.

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[58] P. H. Mueller, N. G. Rondan, K. Houk, J. F. Harrison, D. Hooper, B. H. Willen, J. F. Liebman, *J. Am. Chem. Soc.*, **1981**, *103*, 5049-5052.

[59] A. Berndt, *Angew. Chem., Int. Ed., Engl.*, **1993**, *32*, 985-1009.

[60] A. Gunale, H. Pritzkow, W. Siebert, D. Steiner, A. Berndt, *Angew. Chem., Int. Ed., Engl.*, **1995**, *34,10*, 1111-1113.

[61] A. Baceiredo, G. Bertrand, G. Sicard, *J. Am. Chem. Soc.*, **1985**, *107*, 4781-4783.

[62] B. Gilbert, D. Griller, A. Nazran, *J. Org. Chem.*, **1985**, *50*, 4738-4742.

[63] D. Bourissou, O. Guerret, F. P. Gabbai, G. Bertrand, *Chem. Rev.*, **2000**, *100*, 39-92.

2.1.2. A short history of NHCs

At the end of the 1960s, *Wanzlick* as well as *Öfele* could isolate NHC-metal-complexes. *Wanzlick* used 1,3-diphenylimidazoliumperchlorate in the presence of mercury(II) acetate resulting in bis(1,3-diphenylimidazolio)mercury-diperchlorate.[64] *Öfele* heated a 1,3-dimethylimidazoliumhydrogenchromiumpentacarbonyl-(II)-salt under high vacuum to generate the corresponding pentacarbonyl(2,3-diphenylcyclopropenyliden)-chrom(0)[65] followed by further findings of metal complexes of ruthenium, osmium and nickel by *Lappert*[66] as stated. However, it was not before 1991, when the first stable and crystalline carbene could be isolated.[67]

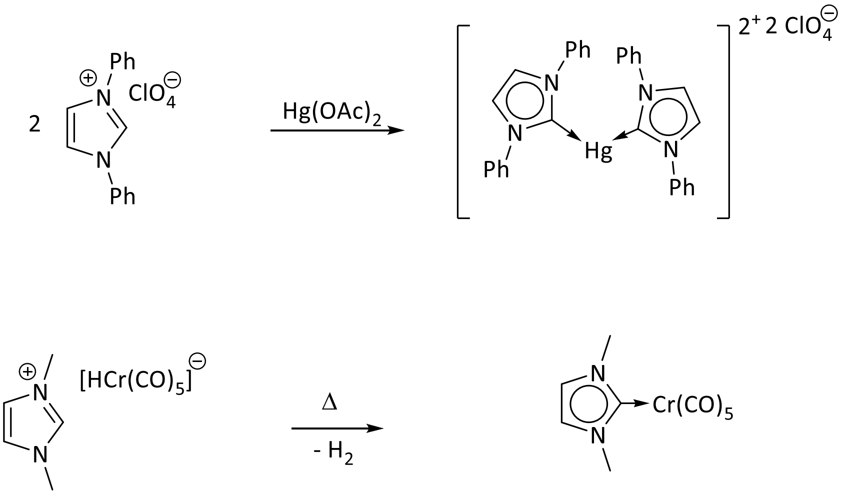

Figure 10 Mercury and chromium NHC-metal-complexes

In the next years, further synthetic routes became known like reduction of imidazol-thiones with potassium[68] or among one of the first commercially available carbene 1,2,4-triazol-5-ylidene by thermal elimination of methanol in vacuo.[69] These synthetic routes are obviously not restricted to imidazoles but also heterocycles containing sulphur-, oxygen-, phosphorous- or carbon as well as six membered cycles are suitable.

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[64] H. W. Wanzlick, H. J. Schönherr, *Angew. Chem., Int. Ed., Engl.*, **1968**, *7,2*, 141-142.

[65] K. Öfele, *Angew. Chem., Int. Ed., Engl.,***1968**, *7,12*, 950.

[66] *M. F. Lappert, P. L. Pye, J. Chem. Soc., Dalton Trans.,* ***1978****, 837-844.*

[67] A. J. Arduengo III, R. L. Harlow, M. Kline, *J. Am. Chem. Soc.,* **1991**, *113*, 361-363.

[68] N. Kuhn, T. Kratz, *Synthesis,* **1993**, *1993*, 561-562.

[69] D. Enders, K. Breuer, G. Raabe, J. Runsink, J. H. Teles, J. P. Melder, K. Ebel, S. Brode, *Angew. Chem., Int. Ed., Engl.,* **1995**, *34*, 1021-1023.

It is therefore hardly surprising that a large number of stable NHCs have been isolated using almost every imaginable eligible heterocycle.[70]

2.1.3. NHC metal complexes

The chemistry of NHC metal complexes and their applications have been extensively investigated in the last years, as a result a corresponding complex from nearly every metal is known.[71] This is due to their excellent properties as a ligand by reason of their remarkable strong NHC-metal bonds, which permits a particular stability of the catalyst.[72]

First, it was assumed that the unexpected stability of NHC-complexes was comparable to the bonding properties of electron-rich trialkylphosphanes, thus an almost pure σ-donor.[73] In fact, the high stability exclusive of the σ-donation from the NHC σ-donor orbital to an orbital of a transition metal acceptor is in contrast with classical carbene ligands, as they require a π-backdonation from the metal into p_π-orbitals like "*Fischer*"-Carbenes.[74] However, recent theoretical studies have shown various degrees of π-bonding as well as an ambivalent character, depending on the metal coordinated to the carbene.[75]

Indeed, the contribution ranges from 10% to almost 35% of the total orbital interaction energy and is therefore not negligible. Furthermore, the maximum is reached for group 11 metals with the strongest π-bonding for gold within this group.[76]

In addition, further investigations have determined a cyclic electron stabilisation, which would mean that the imidazol-2-ylidenes possess a certain aromatic character. However, the aromaticity would only be an additional stabilising factor.[77]

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[70] S. Diez-Gonzalez, N. Marion, S. P. Nolan, *Chem. Rev.,* **2009**, *109*, 3612-3676.
[71] N. Kuhn, A. Al-Sheikh, *Coord. Chem. Rev.,***2005**, *249*, 829-857.
[72] T. Strassner, in *Metal Carbenes in Organic Synthesis*, Springer, **2004**, pp. 1-20.
[73] U. Radius, F. M. Bickelhaupt, *Coord. Chem. Rev.,***2009**, *253*, 678-686.
[74] H. Jacobsen, A. Correa, A. Poater, C. Costabile, L. Cavallo, *Coord. Chem. Rev.,***2009**, *253*, 687-703.
[75] L. Cavallo, A. Correa, C. Costabile, H. Jacobsen, *J. Organomet. Chem.,* **2005**, *690*, 5407-5413.
[76] U. Radius, F. M. Bickelhaupt, *Coord. Chem. Rev.,***2009**, *253*, 678-686.
[77] S. Díez-González, S. P. Nolan, *Coord. Chem. Rev.,***2007**, *251*, 874-883.

In conclusion, three interactions contribute to the stability of these complexes (see also Figure 11):

- σ-donation from the carbene to a metal acceptor orbital
- π-backdonation from an occupied metal d-orbital to the p_π-orbital of the carbene carbon atom
- A delocalisation between the π-system of the NHC and the empty metal orbitals

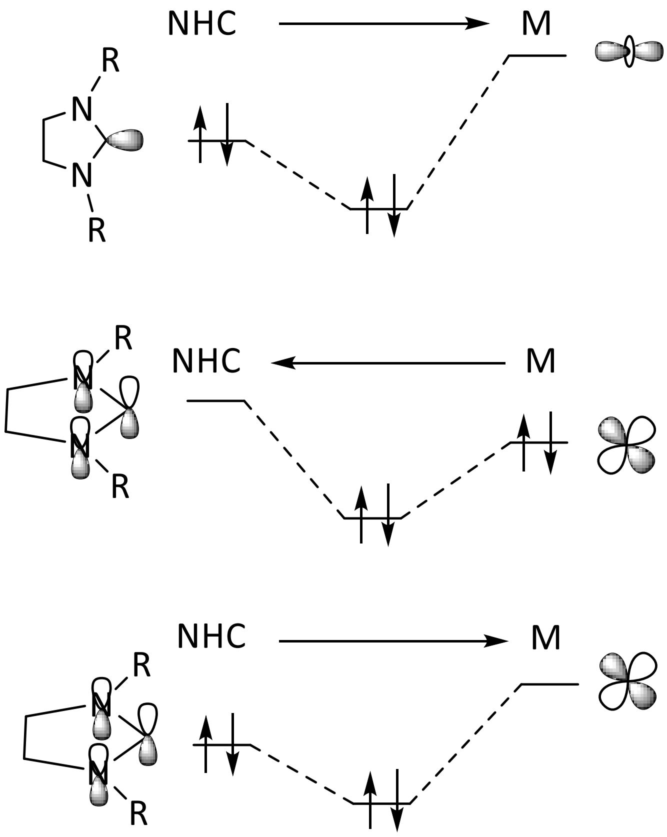

Figure 11 Three interactions contribute to the stability of NHC-metal-complexes

The synthesis of NHC-metal complexes can be mostly achieved by using the free carbene in situ or isolated in combination with the corresponding metal salt. For this a broad range of suitable bases are known like NaOH[78], Potassium bis(trimethylsilyl)amide[79], KO*t*Bu[80], Grignard reagents[81], K_2CO_3[82], NBu_4(acac)[83] or $KHCO_3$[84]. Even though, most carbenes are accessible by deprotonation, sometimes it is preferable to use another common way called transmetalation. In doing so, silver(I)oxide is used as a mild base leading to an NHC-silver-complex, which can be easily transformed to the desired NHC-metal-complex. The precipitation of insoluble silver chloride by adding the desired metal salt strongly facilitates this reaction.[85]

2.1.4. Abnormal/mesoionic carbenes (MICs)

Abnormal/mesoionic carbenes (aNHCs or MICs) are a relatively new subclass of NHCs. They are characterised by a lack of an uncharged resonance form.[86] The development of these complexes began in 2001, when *Crabtree* et al. reported a complex, in which the metal is bound at the C5 position of the imidazole ring.[87]

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[78] H. Ibrahim, P. de Fremont, P. Braunstein, V. Thery, L. Nauton, F. Cisnetti, A. Gautier, *Adv. Synth. Catal.,* **2015**, *357*, 3893-3900.

[79] D. Mendoza-Espinosa, R. González-Olvera, G. E. Negrón-Silva, D. Angeles-Beltrán, O. R. Suárez-Castillo, A. Álvarez-Hernández, R. Santillan, *Organometallics,* **2015**, *34*, 4529-4542.

[80] W. Wang, J. Wu, C. Xia, F. Li, *Green Chem.,* **2011**, *13*, 3440-3445.

[81] M. W. Wallasch, D. Weismann, C. Riehn, S. Ambrus, G. Wolmershäuser, A. Lagutschenkov, G. Niedner-Schatteburg, H. Sitzmann, *Organometallics,* **2010**, *29*, 806-813.

[82] R. Visbal, A. Laguna, M. C. Gimeno, *Chem. Commun.,* **2013**, *49*, 5642-5644.

[83] A. Johnson, M. C. Gimeno, *Chem. Commun.,* **2016**, *52*, 9664-9667.

[84] M. v. Fèvre, J. Pinaud, A. Leteneur, Y. Gnanou, J. Vignolle, D. Taton, K. Miqueu, J.-M. Sotiropoulos, *J. Am. Chem. Soc.,* **2012**, *134*, 6776-6784.

[85] H. M. Wang, I. J. Lin, *Organometallics,* **1998**, *17*, 972-975;
P. de Frémont, N. M. Scott, E. D. Stevens, S. P. Nolan, *Organometallics,* **2005**, *24*, 2411-2418.

[86] O. Schuster, L. Yang, H. G. Raubenheimer, M. Albrecht, *Chem. Rev.,* **2009**, *109*, 3445-3478.

[87] S. Gründemann, A. Kovacevic, M. Albrecht, J. W. Faller, R. H. Crabtree, *J. Am. Chem. Soc.,* **2002**, *124*, 10473-10481;
S. Gründemann, A. Kovacevic, M. Albrecht, J. W. Faller Robert, H. Crabtree, *Chem. Commun.,* **2001**, 2274-2275.

Followed by studies of *Huynh* et al. and *Albrecht* et al. which reported pyrazolium[88] and triazolium[89] metal complexes (see Figure 12)

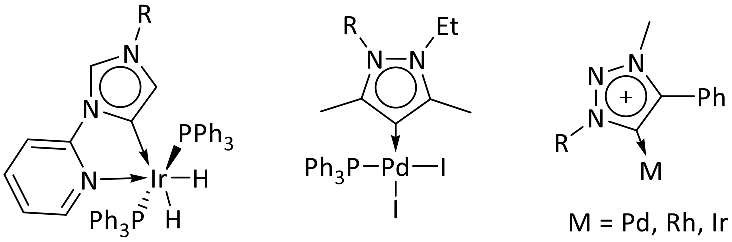

Figure 12 First abnormal NHCs metal complexes

Interestingly, experimental and theoretical data suggest that these carbenes are even stronger electron-donating species than normal NHCs and bear an appreciably large singlet–triplet separation, which is a good marker for their stability.[90]

Especially, the 1,2,3-triazoles benefit from their straightforward and broad synthetic flexibility of their ligand precursors via the easily accessible copper(I) catalysed azide-alkyne cycloaddition (CuAAC or "click-chemistry").[91]

2.2. Aim of the Recyclable NHC-catalysts project

One key element of sustainability in chemistry is catalysis. Its ability to influence reactivity and selectivity was refined, perfected and has become an integral part in chemistry, which gives rise to a broad range of applications into the whole field of chemistry. One of the most important challenges in the idea of green chemistry is the recyclability of catalysts. It is envisaged as a solution to counteract their often-high costs and environmentally unfriendly waste production. In order to eradicate these flaws, the catalyst system should allow in its design an easy separation from the products.

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[88] Y. Han, H. V. Huynh, G. K. Tan, *Organometallics,* **2007**, *26*, 6581-6585;
Y. Han, L. J. Lee, H. V. Huynh, *Organometallics,* **2009**, *28*, 2778-2786.

[89] P. Mathew, A. Neels, M. Albrecht, *J. Am. Chem. Soc.,* **2008**, *130*, 13534-13535.

[90] G. Guisado-Barrios, J. Bouffard, B. Donnadieu, G. Bertrand, *Angew. Chem., Int. Ed.,* **2010**, *49*, 4759-4762.

[91] V. V. Rostovtsev, L. G. Green, V. V. Fokin, K. B. Sharpless, *Angew. Chem., Int. Ed.,* **2002**, *41*, 2596-2599.

In the last years, several resourceful approaches connected to this challenge could be established, such as immobilisation on a suitable carrier framework[92], biphasic systems with water[93], ionic liquids[94] or liquid carbon dioxide[95] to name but a few. Another promising approach is that strong polar catalysts capable to be solved in water or other strongly polar media by its design. This allows an easy separation of the products, which usually lack of water solubility, so the products can be filtered or extracted, whereas the catalyst remains in the reaction media.[96]

There exist a few pathways to ensure the hydrophilicity of a ligand or rather a catalyst. One of the first were phosphine ligands combined with anionic substituents like a sulfonate group[97] but also hydrophilic NHCs flourished in this effort: *Herrmann* et al. as well as *Shaughnessy* et al. were pioneers on this field and published the first hydrophilic NHC-transition metal complexes using polyethers, amines, alkylsulfonates or alkylcarboxylates and their corresponding salts.[98] Followed by the use of hydrophilic polymers, alcohols, carbohydrates or other cationic or anionic functional groups furthermore, the ability to recycle this kind of catalysts systems could be proved.[99] In fact, our own group was able to contribute two kinds of hydrophilic gold catalysts (shown in Figure 13) bearing ammonium salts, which showed a good reactivity and could be recycled easily.[100]

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[92] P. McMorn, G. J. Hutchings, *Chem. Soc. Rev.,* **2004**, *33*, 108-122;
L. Canali, D. C. Sherrington, *Chem. Soc. Rev.,* **1999**, *28*, 85-93;
A. Rosevear, *J. Chem. Technol. Biotechnol.,* **1984**, *34*, 127-150;
B. M. Dioos, I. F. Vankelecom, P. A. Jacobs, *Adv. Synth. Catal.,* **2006**, *348*, 1413-1446.

[93] B. Cornils, *J. Mol. Catal. A: Chem.,* **1999**, *143*, 1-10;
B. Cornils, *Org. Process Res. Dev.,* **1998**, *2*, 121-127.

[94] J. Dupont, G. S. Fonseca, A. P. Umpierre, P. F. P. Fichtner, S. R. Teixeira, *J. Am. Chem. Soc.,* **2002**, *124*, 4228-4229.

[95] R. A. Brown, P. Pollet, E. McKoon, C. A. Eckert, C. L. Liotta, P. G. Jessop, *J. Am. Chem. Soc.,* **2001**, *123*, 1254-1255;
F. Jutz, J.-M. Andanson, A. Baiker, *Chem. Rev.,* **2011**, *111*, 322-353.

[96] L.-A. Schaper, S. J. Hock, W. A. Herrmann, F. E. Kühn, *Angew. Chem., Int. Ed.,* **2013**, *52*, 270-289;
N. Pinault, D. W. Bruce, *Coord. Chem. Rev.,* **2003**, *241*, 1-25.

[97] S. Ahrland, J. Chatt, N. Davies, A. Williams, *J. Chem. Soc.,* **1958**, 276-288.

[98] W. A. Herrmann, L. J. Gooβen, M. Spiegler, *J. Organomet. Chem.,* **1997**, *547*, 357-366;
L. R. Moore, S. M. Cooks, M. S. Anderson, H.-J. Schanz, S. T. Griffin, R. D. Rogers, M. C. Kirk, K. H. Shaughnessy, *Organometallics,* **2006**, *25*, 5151-5158.

[99] K. H. Shaughnessy, *Chem. Rev.,* **2009**, *109*, 643-710.

[100] K. Belger, N. Krause, *Eur. J. Org. Chem.,* **2015**, *2015*, 220-225;
K. Belger, N. Krause, *Org. Biomol. Chem.,***2015**, *13*, 8556-8560.

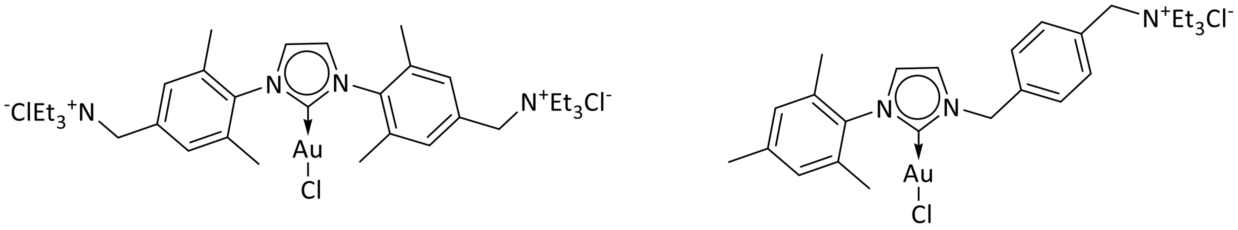

Figure 13 Two representatives of ammonium salt tagged gold catalysts

This is simultaneously the point of departure for this project, which has the following aims:

2.2.1. Polyethylen glycol (PEG)-linked NHC gold complexes

The synthesis of easily accessible and hydrophilic imidazolium-based gold complexes was another aim of this project. Hence, many water-soluble gold complexes lack from an elaborate synthesis. In this way, the cheap and nontoxic PEG group is supposed to fulfil the desired hydrophilicity. This concept is well established by now and there are many PEG linked transition metal complexes known.[101]

In 2015, *Johnson* et al. reported the synthesis of a simple accessible PEGylated *N*-heterocyclic carbene for gold-nanoparticle surfaces and could show their water stability. However, no catalysis was performed with this gold-complexes.[102]

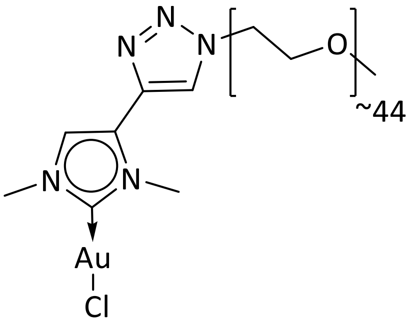

Figure 14 PEGylated *N*-heterocyclic carbene

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[101] S. Varray, R. Lazaro, J. Martinez, F. Lamaty, *Organometallics,* **2003**, *22*, 2426-2435;
W. J. Sommer, M. Weck, *Coord. Chem. Rev.,***2007**, *251*, 860-873;
J.-W. Kim, J.-H. Kim, D.-H. Lee, Y.-S. Lee, *Tetrahedron Lett.,* **2006**, *47*, 4745-4748.

[102] M. J. MacLeod, J. A. Johnson, *J. Am. Chem. Soc.,* **2015**, *137*, 7974-7977.

2.2.2. Water soluble MIC gold complexes

The synthesis of a triazole based ammonium salt tagged gold catalyst, which would be a mesoionic NHC and should benefit from higher stability due to their stronger electron-donating properties as well as from their straightforward synthesis, was envisaged (see 2.1.4). Despite limited examples of triazole based gold complexes[103], as far as it is known, this would be the first hydrophilic triazole based gold catalyst.

Furthermore, oxazole and thiazole gold complexes are also conceivable, despite the fact that oxazoles and thiazoles used for decades as organocatalysts[104] only limited metal-complexes are known. In 2011, *Bertrand* et al. reported a thiazol-5-ylidene transition metal complex with gold, palladium or ruthenium but showed also that thiazole carbenes are in principle relatively unstable (Figure 15).[105] Moreover, three years later a water soluble copper-complex of vitamin B_1 was reported and successfully tested in a CuAAC click reaction (Figure 15).[106] In the case of oxazole complexes, no gold-complex was reported so far.

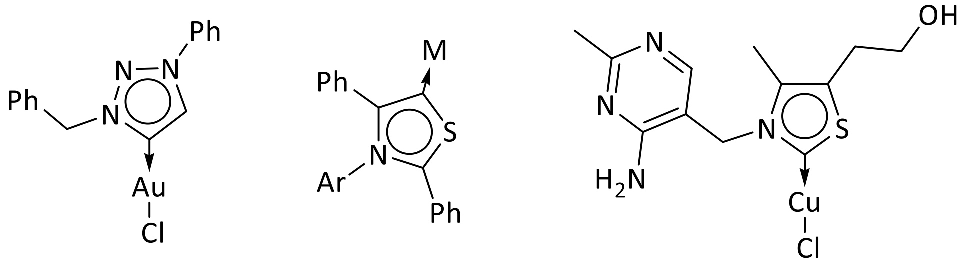

Figure 15 Selected representatives of MIC transition metal complexes[107]

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[103] D. Mendoza-Espinosa, R. González-Olvera, G. E. Negrón-Silva, D. Angeles-Beltrán, O. R. Suárez-Castillo, A. Álvarez-Hernández, R. Santillan, *Organometallics,* **2015**, *34*, 4529-4542;
K. J. Kilpin, U. S. Paul, A.-L. Lee, J. D. Crowley, *Chem. Commun.,* **2011**, *47*, 328-330;
L. Hettmanczyk, S. Manck, C. Hoyer, S. Hohloch, B. Sarkar, *Chem. Commun.,* **2015**, *51*, 10949-10952.

[104] A. T. Biju, F. Glorius, *Angew. Chem., Int. Ed.,* **2010**, *49*, 9761-9764;
K. Hirano, A. T. Biju, I. Piel, F. Glorius, *J. Am. Chem. Soc.,* **2009**, *131*, 14190-14191;
R. Lebeuf, K. Hirano, F. Glorius, *Org. Lett.,***2008**, *10*, 4243-4246;
D. Enders, T. Balensiefer, *Acc. Chem. Res.* **2004**, *37*, 534-541;
I. Piel, M. D. Pawelczyk, K. Hirano, R. Fröhlich, F. Glorius, *Eur. J. Org. Chem.,* **2011**, *2011*, 5475-5484.

[105] D. Mendoza-Espinosa, G. Ung, B. Donnadieu, G. Bertrand, *Chem. Commun.,* **2011**, *47*, 10614-10616.

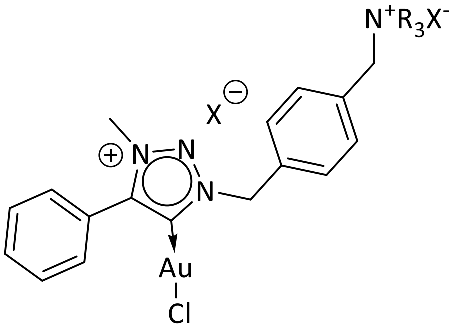
[106] V. B. Purohit, S. C. Karad, K. H. Patel, D. K. Raval, *RSC Adv.,* **2014**, *4*, 46002-46007.

[107] K. J. Kilpin, U. S. Paul, A.-L. Lee, J. D. Crowley, *Chem. Commun.,* **2011**, *47*, 328-330;
D. Mendoza-Espinosa, G. Ung, B. Donnadieu, G. Bertrand, *Chem. Commun.,* **2011**, *47*, 10614-10616;
V. B. Purohit, S. C. Karad, K. H. Patel, D. K. Raval, *RSC Adv.,* **2014**, *4*, 46002-46007.

2.3. Results and discussion

2.3.1. Ammonium-salt tagged triazole based MIC (Cat1)

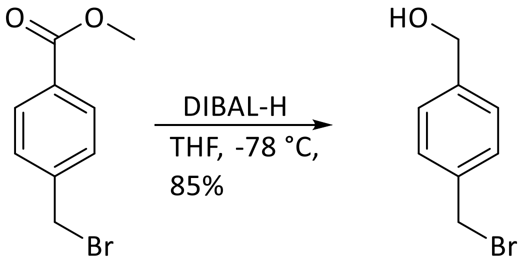
As mentioned above, the desired molecule **Cat1** was envisioned to bear a quaternary ammonium salt group ensuring the hydrophilicity and a triazole based carbene core. Figure 16 is showing the general structure.[108]



2.1
Cat1

Figure 16 Ammonium-salt tagged triazole based MIC **Cat1**

As starting material, the methylbenzoate **2.2** was conceived and reduced by DIBAL-H in THF. The alcohol **2.3** could be obtained in 85% yield (Figure 17).



2.2 **2.3**

Figure 17 Reduction of **2.2** to the corresponding alcohol **2.3**

In a next step, the corresponding azide of **2.3** was synthesised in situ by just adding sodium azide to the reaction mixture, followed by a CuAAC coupling using copper(II)sulphate in combination with sodium ascorbate as reducing agent, since Cu(I) ions are necessary for the reaction and sodium carbonate as a base (Figure 18).

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[108] The most work was done in the context of a bachelor thesis A. Machalica, TU Dortmund (Dortmund), **2016**.

This mild and green reaction showed excellent yields as well as the advantageous easy access to triazoles. **2.7** could be obtained quantitatively and no further purification was necessary. It could be determined by ^{1}H-, ^{13}C-NMR and ESI.

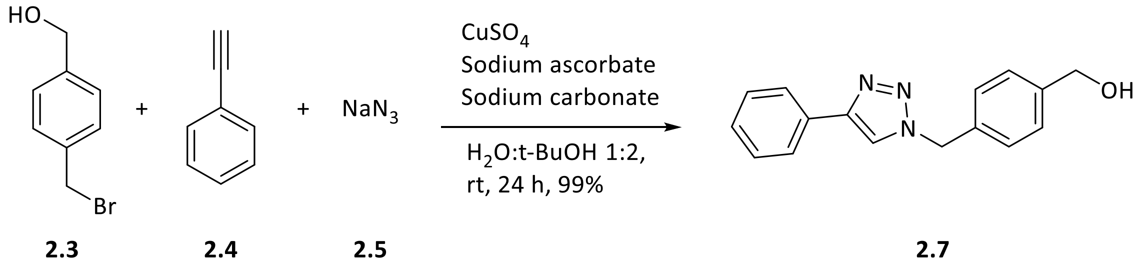


Figure 18 CuAAC reaction to **2.7**

Another route to synthesise molecule **2.7**, was to first click the methylbenzoate **2.2** (89% yield) followed by a reduction (47 %) to the desired alcohol (Figure 19), but on this way lower yields were obtained and therefore discarded.

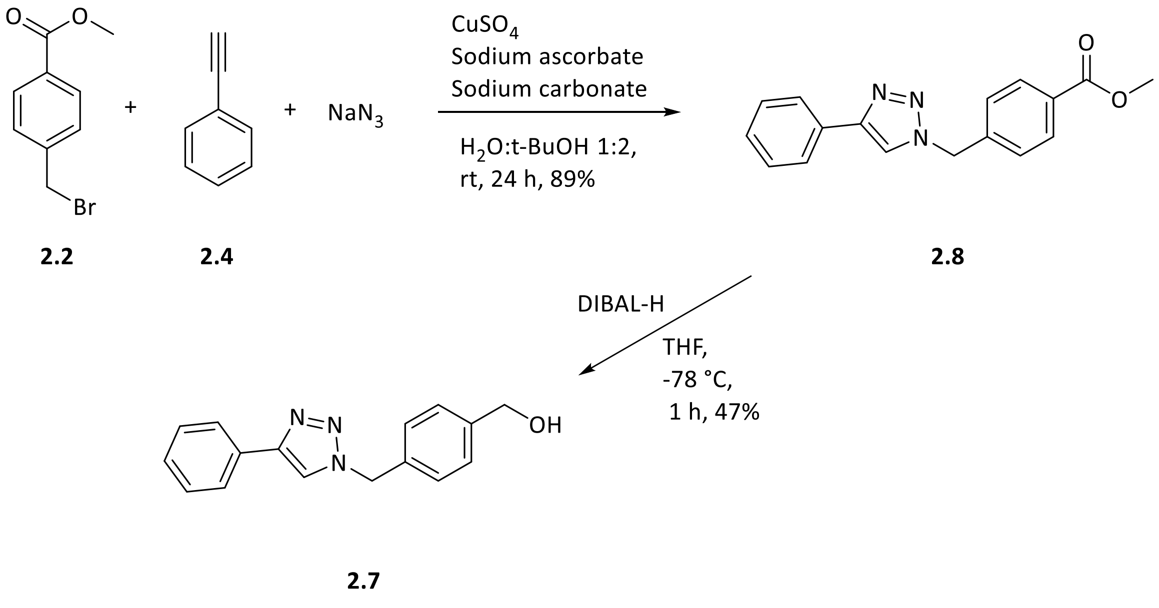
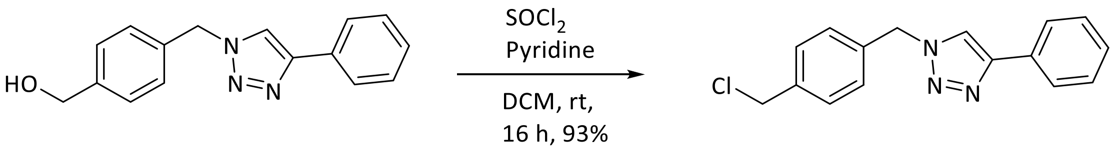


Figure 19 Alternative route to **2.7**

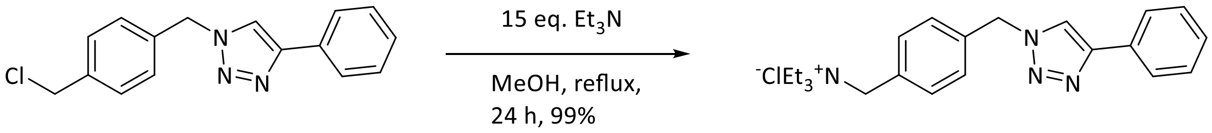
For the planned quaternary ammonium group a better leaving group is mandatory. In doing so, the benzyl alcohol was substituted by chloride using the entrenched *Darzens* halogenation protocol[109] with thionyl chloride and pyridine with a very good yield of 93% (Figure 20).



2.7 **2.9**

Figure 20 Nucleophilic substitution to benzyl chloride **2.9**

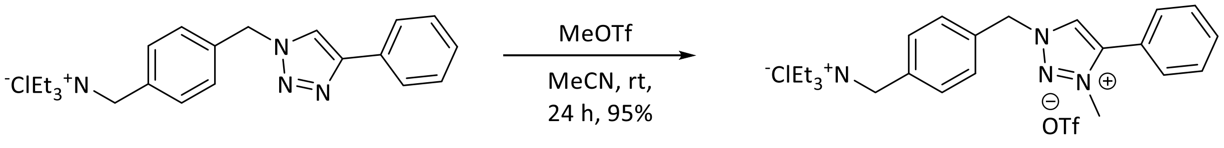
The molecule **2.9** has now a suitable leaving group and could be obtained without the need for further purification and was determined by ^{1}H-, ^{13}C-NMR and ESI. With **2.9** in hand the hydrophilic quaternary ammonium salt group could be introduced by a simple S$_N$2 reaction (Figure 21). For this purpose, **2.9** was refluxed with triethylamine and the formed ionic product **2.10** could be precipitated by adding EtOAc yielding in 99% of pure **2.10**.



2.9 **2.10**

Figure 21 S$_N$2 reaction of **2.9** to the ammonium salt triazole **2.10**

In a last step molecule **2.10** was methylated in N^1-position in order to pave the way for the following formation of the carbene (Figure 22).



2.10

2.11
L1

Figure 22 Methylation of **L1**

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[109] G. Darzens, *Comptes Rendus,* **1911**, *152*, 1314-1317;

Initially, methyl iodide was used for the methylation, however, the methylated product could not be observed. Therefore, the much stronger reagent methyltriflate was used and afforded a good yield of 95%. The product could be easily precipitated by addition of EtOAc and no further purification was necessary. The ligand **L1** could be verified by ^1H-, ^{13}C-, ^{15}N (HMBC)-, ^{19}F-NMR, ESI and X-ray diffraction analysis. The ^{15}N (HMBC)-NMR, which has the advantage that it can be performed using the natural abundance of the ^{15}N isotope, showed clearly the predicted methylation on the most nucleophilic N^1-position as Figure 23 indicates. It is noteworthy that there is coupling between N^3 and $C^3(CH_3)$ observable, which proves that the nucleophilic substitution took place on N^1.

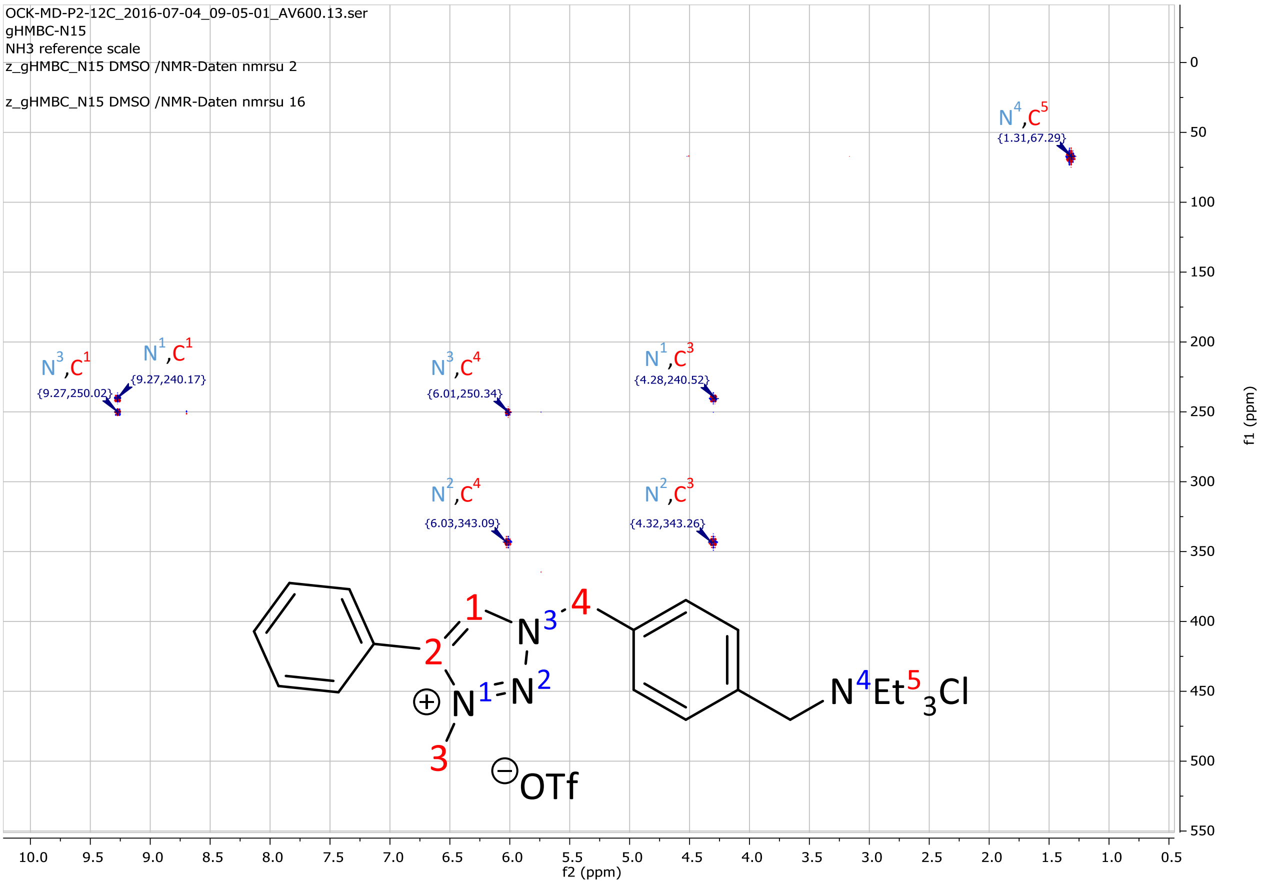

Figure 23 ^1H, ^{15}N-HMBC-NMR of **L1**

Mass spectroscopy showed particularly a m/z of 513.3 which corresponds to the bicationic complex with one triflate counterion $[C_{24}H_{32}N_4SF_3O_3]^+$. Molecule fragments with chloride as counterion were not found. It is conceivable that an exchange between the chloride and the triflate anion during the methylation took place.

The X-ray diffraction analysis showed clearly the formation of **L1** and supports this assumption hence, molecule **L1** has two triflate and no chloride counterions embedded in the crystal lattice (Figure 24). Furthermore, the analysis showed the two “arms” of the molecule bearing the cationic groups are on the same side and facing each other.

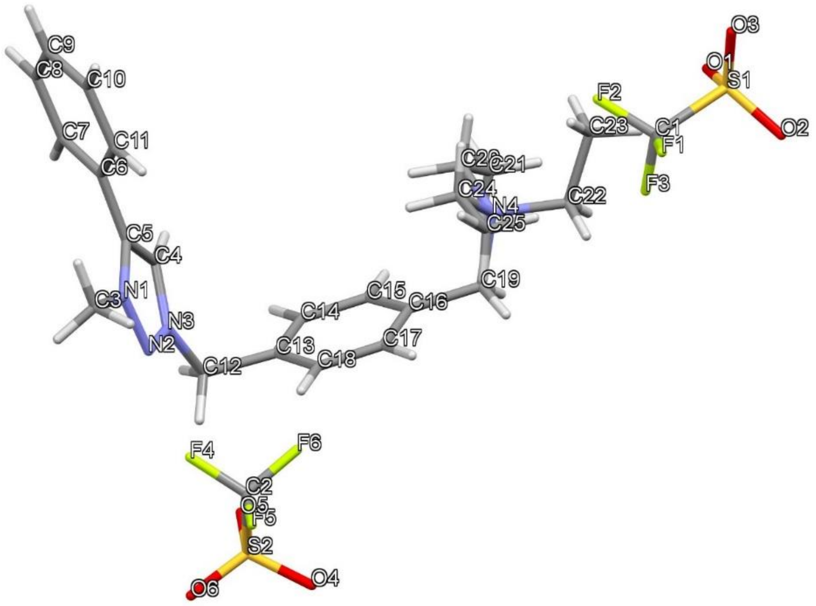

Figure 24 X-ray diffraction analysis of **L1** (green: Fluor, yellow: Sulphur, red: Oxygen, blue: Nitrogen, light grey: Hydrogen, dark grey: Carbon), performed by Dr. Ljuba Iovkova-Berends

A further implemented DFT calculation for molecule **L1** in vacuum showed a similar structure (Figure 25).

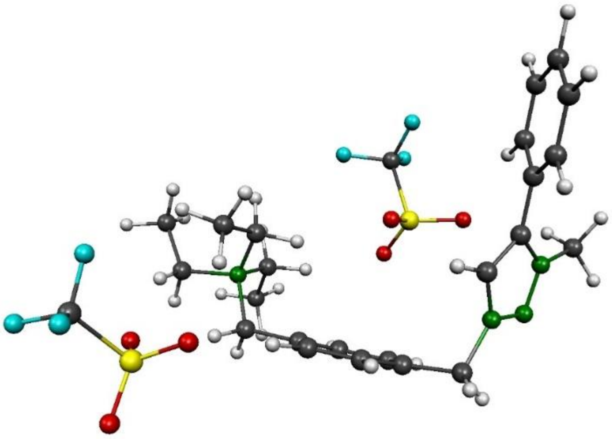

Figure 25 DFT-Calculation (B3LYP/6-31+gcd) of **L1** (turquoise: Fluor, yellow: Sulphur, red: Oxygen, green: Nitrogen, light grey: Hydrogen, dark grey: Carbon), performed by Dr. Ulrike Kroesen

Hereinafter, multifarious protocols to generate the desired gold-complex **Cat1** were tested. In a first attempt, the metal complexation by generating the free carbene in situ and adding a suitable metal salt was selected as first method of choice. In doing so, various bases were tested.

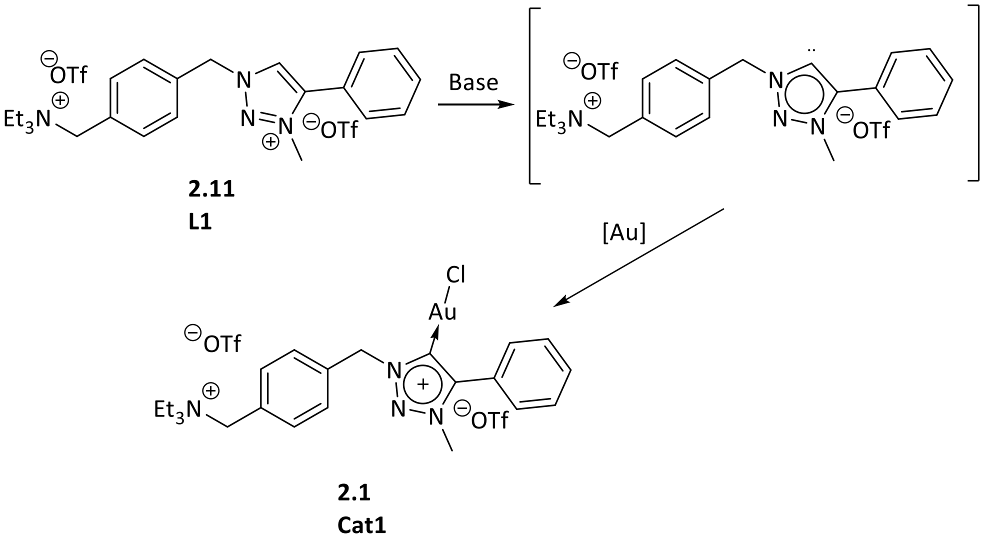

Figure 26 Complexation of **L1** by using the free carbene protocol

At first KO*t*Bu was used as a base, because it has proven performance in the generation of other NHC gold complexes, like the presented in Figure 13[110]. Due to the high polarity of **L1** was resorted to polar solvents like MeOH or MeCN. **L1** was dissolved in the respective solvent and the respective base was added at room temperature shortly thereafter the gold species was added. The product was precipitated with Et_2O.

Table 2 Complexation of **L1** using the free carbene protocol with KO*t*Bu

Entry	Solvent	Temp.	Time	Base	Gold species	Result
1	MeOH	rt	12 h	KO*t*Bu (1 eq.)	$Au(SMe_2)Cl$ (1 eq.)	No conversion
2	MeOH	70 °C	12 h	KO*t*Bu (1.2 eq.)	$Au(SMe_2)Cl$ (1.1 eq.)	No conversion
3	MeCN	rt	12 h	KO*t*Bu (1 eq.)	$Au(SMe_2)Cl$ (1 eq.)	No conversion

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[110] K. Belger, N. Krause, *Org. Biomol. Chem.,* **2015**, *13*, 8556-8560.

Unfortunately, KO*t*Bu proved to be unsuitable, even though a reaction could be observed by adding the base. NMR analysis debunked this first observation in showing only educt **L1** in all reactions. Even a temperature rising (Table 2,entry 2) or the switch of solvent to acetonitrile (Table 2, entry 3) did not facilitate this reaction.

In a next step, another strong, non-nucleophilic base was used: Potassium bis(trimethylsilyl)amide (KHMDS). As mentioned above, *Mendoza-Espinosa* et al. were able to synthesise a similar MIC rhodium, palladium and gold complexes by using KHMDS[111], a related protocol should be applied in this case (Table 3). **L1** was dissolved at -78 °C and the base as well as the gold species were added followed by a warming to room temperature. The product was precipitated with Et_2O.

Herein, Chloro(tetrahydrothiophene)gold(I) was tested as alternative gold reagent, which revealed in some cases better leaving group properties.[112]

Table 3 Complexation of **L1** by using the free carbene protocol with KHMDS

Entry	Solvent	Temp.	Time	Base	Gold species	Result
1	THF	rt	12 h	KHMDS (1.2 eq.)	$Au(SMe_2)Cl$ (1.1 eq.)	No conversion
2	MeCN	rt	12 h	KHMDS (1.2 eq.)	$Au(SMe_2)Cl$ (1.1 eq.)	No conversion
3	DMF	rt	12 h	KHMDS (1.2 eq.)	$Au(SMe_2)Cl$ (1.1 eq.)	No conversion
4	DMF	60 °C	12 h	KHMDS (1.2 eq.)	$Au(SMe_2)Cl$ (1.1 eq.)	No conversion
5	DMF	rt	12 h	KHMDS (1.2 eq.)	$Au(SC_4H_8)Cl$ (1.1 eq.)	No conversion

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[111] D. Mendoza-Espinosa, R. González-Olvera, G. E. Negrón-Silva, D. Angeles-Beltrán, O. R. Suárez-Castillo, A. Álvarez-Hernández, R. Santillan, *Organometallics,* **2015**, *34*, 4529-4542.

[112] A. S. K. Hashmi, T. Hengst, C. Lothschütz, F. Rominger, *Adv. Synth. Catal.,* **2010**, *352*, 1315-1337.

In the original protocol, THF was used as solvent. Therefore, it was herein used first resulting in the isolation of only educt **L1** (Table 3, entry 1). Although, a colour change from yellow to purple and later dark brown could be observed. Subsequent, the solvent was changed to more polar ones: MeCN (Table 3, entry 2) and DMF (Table 3, entry 3) with the same unsatisfactory result. The addition of the base and reactants had to be made at higher temperatures due to the higher melting point of the solvents (MeCN -45 °C and DMF -61 °C). Even a heating after the addition at 60 °C could not facilitate the formation of **Cat1** and only educt **L1** could be isolated (Table 3, entry 4) as well as the change to another gold species at room temperature showed no conversion (Table 3, entry 5).

In 2013, *Gimeno* et al. reported a mild and efficient method starting from an imidazolium and a gold salt in the presence of the mild base K_2CO_3 (Figure 27).[113]

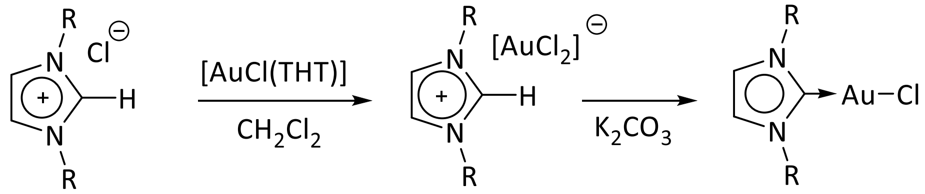

Figure 27 Complexation protocol by *Gimeno* et al.

This method was applied with amendments to molecule **L1** resulting in no conversion although a colour change could be observed (Table 4). As gold species the related [AuCl(SMe_2)] was used as well as MeCN as solvent because of the poor solubility of **L1**. Furthermore, **L1** is not a neat chloride salt but primary a triflate salt, which maybe could explain the bad reactivity. Admittedly, this method was never tested with MICs.

Table 4 Outcome of the complexation using K_2CO_3

Entry	Solvent	Temp.	Time	Base	Gold species	Result
1	MeCN	1. 60 °C 2. 60 °C	1. 2 h 2. 2 h	K_2CO_3	Au(SMe_2)Cl (1 eq.)	No conversion

---

[113] R. Visbal, A. Laguna, M. C. Gimeno, *Chem. Commun.,* **2013**, *49*, 5642-5644.

In the next step, another method involving a mild base published by the same group was tested. The use of tetrabutylammonium acetylacetonate, NBu_4(acac), a mild base is well-established within organometallic chemistry for the preparation of metal complexes and was recently used for the preparation of NHC-gold-complexes under mild conditions.[114] The NBu_4(acac) could be easily synthesised by letting tetrabutylammonium hydroxide and acetylacetone react. Certainly, in this case, too, only educt **L1** could be observed after precipitation.

Vignolle and *Taton* introduced another relatively new method including an anion metathesis of imidazolium chlorides with $KHCO_3$ resulting in air stable imidazolium hydrogen carbonates, which can react as masked NHCs and form metal complexes (Figure 28).[115]

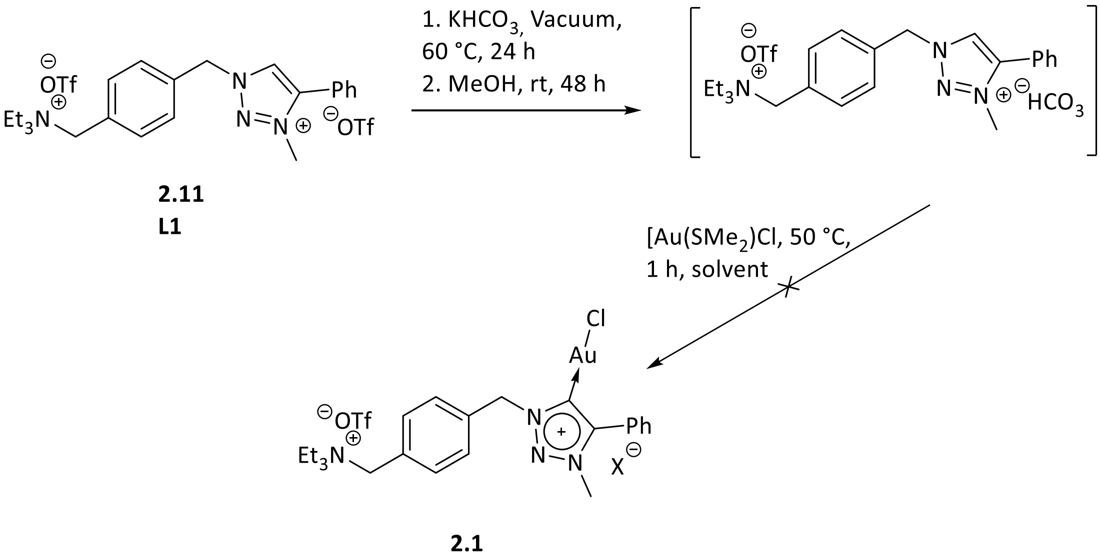

Figure 28 Gold complexation using imidazolium hydrogen carbonates

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[114] A. Johnson, M. C. Gimeno, *Chem. Commun.,* **2016**, *52*, 9664-9667.

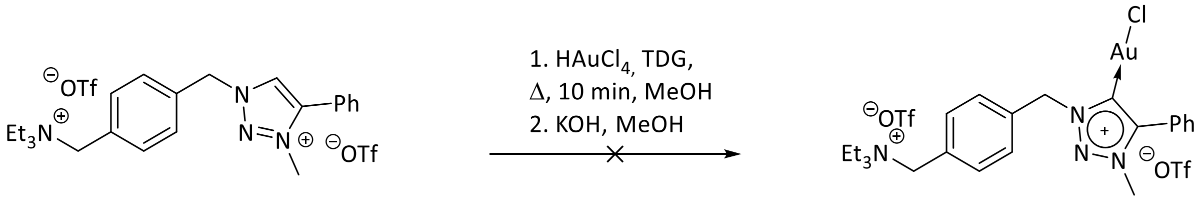
[115] M. v. Fèvre, J. Pinaud, A. Leteneur, Y. Gnanou, J. Vignolle, D. Taton, K. Miqueu, J.-M. Sotiropoulos, *J. Am. Chem. Soc.,* **2012**, *134*, 6776-6784.

In the described protocol THF was used as solvent for the metal complexation and was also tested first in this case (entry 1). However, it appears that the solubility was not sufficient in THF so that the usage of alternative solvents was deemed necessary (Table 5, Entry 2 and 3). Furthermore, the reaction was carried out in the presence of molecular sieves to assure the exclusion of humidity (Table 5, entry 4). Unfortunately, all attempts were unsucessfull to synthesise the desired gold complex, instead only educt **L1** could be isolated.

Table 5 Outcome of the complexation using imidazolium hydrogen carbonates

Entry	Solvent	Temp.	Time	Base	Gold species	Result
1	THF	50 °C	1 h	$KHCO_3$ (1.05 eq.)	$[Au(SMe_2)Cl]$ (1 eq.)	No conversion
2	DMF	50 °C	1 h	$KHCO_3$ (1.05 eq.)	$[Au(SMe_2)Cl]$ (1 eq.)	No conversion
3	MeCN	50 °C	1 h	$KHCO_3$ (1.05 eq.)	$[Au(SMe_2)Cl]$ (1 eq.)	No conversion
4	MeCN + molecular sieves (3 Å)	50 °C	1 h	$KHCO_3$ (1.05 eq.)	$[Au(SMe_2)Cl]$ (1 eq.)	No conversion

Additionally, a method was tested, which has already been successful in the complexation of a bicationic hydrophilic Imidazole-gold-complex.[116] It includes KOH as base and a gold species, which is generated by the reaction of $HAuCl_4$ with thiodiglycol (TDG) (Figure 29).



2.11
L1

2.1
Cat1

Figure 29 Gold complexation using KOH and $HAuCl_4$ with TDG

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[116] H. Ibrahim, P. de Fremont, P. Braunstein, V. Thery, L. Nauton, F. Cisnetti, A. Gautier, *Adv. Synth. Catal.*, **2015**, *357*, 3893-3900.

The generation of the gold species went very smoothly, a colour change from yellow to colourless could be observed like in the literature. Followed by the addition of KOH as well as ligand **L1** and stirring at room temperature for 2 hours, but also in this case the desired product **Cat1** could not be observed (Table 6, entry 1). Therefore, the temperature was risen (Table 6, entry 2) and the reaction time increased (Table 6, entry 3) but to no avail.

Table 6 Results of the gold complexation using KOH and $HAuCl_4$ with tdg

Entry	Solvent	Temp.	Time	Base	Gold species	Result
1	MeOH	rt	2 h	KOH (4.5 eq.)	$HAuCl_4$ + tdg (1.1 eq.+ 6 eq.)	No conversion
2	MeOH	65 °C	2 h	KOH (4.5 eq.)	$HAuCl_4$ + tdg (1.1 eq.+ 6 eq.)	No conversion
3	MeOH	65 °C	4 h	KOH (4.5 eq.)	$HAuCl_4$ + tdg (1.1 eq.+ 6 eq.)	No conversion

In consequence of the failure of the free carbene methods another solution had to be found, in doing so transmetalation became its tool. This method involves the formation of a metal complex, which then itself undergoes a transmetalation to the desired complex.

As a result, a metathesis through a Grignard interstage was envisaged, therefore, the iodine derivate had to be synthesised, which could be done by deprotonation of **L1** followed by the addition of elemental iodine at -60 °C. In the next step, the Grignard molecule should be formed by the addition of *i*PrMgCl at -40 °C and subsequently $[Au(SMe_2)Cl]$ at room temperature. However, NMR analysis showed a decomposition of the molecule.

A widely accepted method, involving a transmetalation with the respective in situ generated Ag(I)-NHC salt, was introduced by *Nolan* et al. in 2005 (Figure 30).[117] In the most cases this protocol realises better yields, no decomposition to metallic gold and lesser side products, like dimerisation.

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[117] P. de Frémont, N. M. Scott, E. D. Stevens, S. P. Nolan, *Organometallics,* **2005**, *24*, 2411-2418.

Step 1 **Step 2**

$$\mathrm{NHC\text{-}HCl} \xrightarrow{Ag_2O} \mathrm{Ag(NHC)Cl} \xrightarrow{[Au(SMe)_2Cl]} \mathrm{Au(NHCH_2)Cl} + \mathrm{AgCl}\downarrow + \mathrm{SMe_2}$$

Figure 30 Synthesis of *N*-heterocyclic carbene gold(I) complexes via silver transmetalation[117]

In doing so, the silver(I)oxide reacts as a mild base, subsequently the solution must be filtered after the first step followed by the addition of the gold species. Furthermore, the following precipitation of the nascent insoluble silver(I)chloride strongly facilitates this reaction.

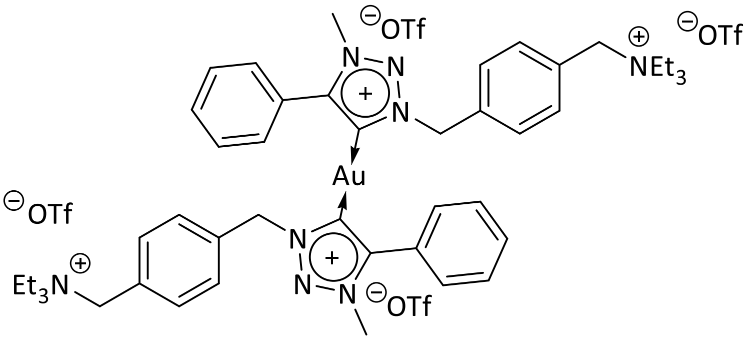
The reaction was implemented in line with the published reaction pattern with one exception in respect of the solubility in THF. Therefore, MeCN was used. Furthermore, unlike the procedure, the reaction was carried out under inert conditions to avoid any interference with oxygen or humidity.

Table 7 Outcomes of the silver transmetalation protocol

Entry	Solvent	Temp. Step 1/2	Time Step 1/2	Silver salt	Gold species	Result
1	MeCN	rt/rt	24 h/24 h	Ag_2O (0.65 eq.)	$[Au(SMe_2)Cl]$ (1 eq.)	No conversion
2	MeCN	82 °C/82 °C	24 h/24 h	Ag_2O (0.65 eq.)	$[Au(SMe_2)Cl]$ (1 eq.)	40 %*

* Mixture of Mono- and Dimer

At first the reaction was carried out at room temperature, which showed no conversion (Table 7, entry 1). Subsequent, the reaction was repeated under reflux during both steps (Table 7, entry 2). After precipitation of the product ^{1}H- and ^{13}C- NMR spectroscopy indicated the formation of the desired gold complex **Cat1** especially since the triazole proton signal had vanished. These findings were supported by mass spectroscopy, which showed complex **Cat1** as well as the corresponding dimer **2.12** (Figure 31). It is also noteworthy that a coupling between the triazole proton and the neighboured nitrogen atoms could no longer been detected.



2.12

Figure 31 The corresponding dimer **2.12**

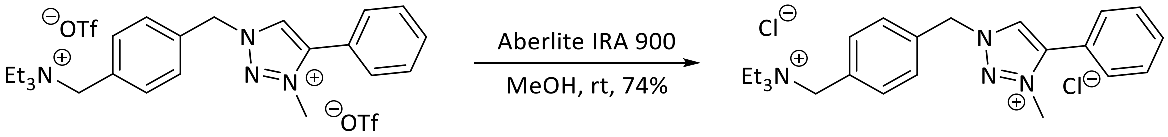
Hereinafter, the results should be reproduced, and the reaction conditions altered in order to shift the outcome to the desired monomer **Cat1**.

Table 8 Outcomes of the silver transmetalation protocol with altered reaction conditions

Entry	Solvent	Temp. Step 1/2	Time Step 1/2	Silver salt	Gold species	Result
1	MeCN	82 °C/82 °C	24 h/24 h	Ag_2O (1 eq.)	$[Au(SMe_2)Cl]$ (1.2 eq.)	No conversion
2	MeCN	82 °C/82 °C	48 h/12 h	Ag_2O (0.65 eq.)	$[Au(SMe_2)Cl]$ (1.2 eq.)	No conversion
3	MeCN	82 °C/82 °C	60 h/24 h	Ag_2O (0.65 eq.)	$[Au(SMe_2)Cl]$ (1.2 eq.)	No conversion
4	MeOH	65 °C/65 °C	12 h/12 h	Ag_2O (1 eq.)	$[Au(SMe_2)Cl]$ (1.2 eq.)	No conversion
5	DMF	40 °C/40 °C	24 h/64 h	Ag_2O (1 eq.)	$[Au(SMe_2)Cl]$ (1.2 eq.)	No conversion
6	DMF	100 °C/100 °C	24 h/64 h	Ag_2O (1 eq.)	$[Au(SMe_2)Cl]$ (1.2 eq.)	No conversion
7	DMF	100 °C/100 °C	48 h/24 h	Ag_2O (1 eq.)	$[Au(SMe_2)Cl]$ (1.2 eq.)	No conversion
8	DMF	100 °C/100 °C	72 h/72 h	Ag_2O (1 eq.)	$[Au(SMe_2)Cl]$ (1.2 eq.)	No conversion

Despite numerous research activities and all the efforts undertaken to reproduce the initial findings, it was not possible to synthesise **Cat1** again, even under the same conditions (Table 8, entry 1). Because of this, the reaction time was prolongated to 48 h (Table 8, entry 2) or 60 h (Table 8, entry 3) without any improvement, however. Since the dimerisation is also depending on the solvent, Methanol was chosen as alternative and the reaction was carried out under reflux, but no product formation could be detected (Table 8, entry 4). In a last attempt, DMF was used at different temperatures ranging from 40 °C to 100 °C and different reaction times up to 72 h without any impact on the conversion of **L1** (Table 8, entry 5-8). In sum, only the educt **L1** could be isolated.

A second consideration consisted of an anion change from the weak coordinating triflate anion to the stronger coordinating chloride anion, since in the majority of the transmetalation reactions of this pattern NHC-chlorides were used. For this purpose, the NHC ligand **L1** was dissolved in methanol and *Amberlite* IRA 900 was added as ion exchanger (Figure 32). After filtration, the chloride salt **L2** could be obtained in 74% yield. The absence of triflate anions could be determined by ^{19}F-NMR spectroscopy since, no fluorine could be detected anymore.



2.11
L1

2.13
L2

Figure 32 Anion exchange with *Amberlite* IRA 900

With the chloride NHC **L2** in hand, the transmetalation reaction was repeated in hope for a better outcome.

Table 9 Outcomes of the silver transmetalation protocol with the NHC **L2**

Entry	Solvent	Temp. Step 1/2	Time Step 1/2	Silver salt	Gold species	Result
1	MeCN	82 °C/82 °C	48 h/48 h	Ag_2O (1 eq.)	[Au(SMe$_2$)Cl] (1.2 eq.)	No conversion
2	MeOH	65 °C/65 °C	48 h/48 h	Ag_2O (1 eq.)	[Au(SMe$_2$)Cl] (1.2 eq.)	No conversion
3	MeCN	82 °C/82 °C	60 h/60 h	Ag_2O (0.65 eq.)	[Au(SMe$_2$)Cl] (1 eq.)	No conversion
4*	MeCN	82 °C/82 °C	24 h/24 h	Ag_2O (0.65 eq.)	[Au(SMe$_2$)Cl] (1 eq.)	No conversion

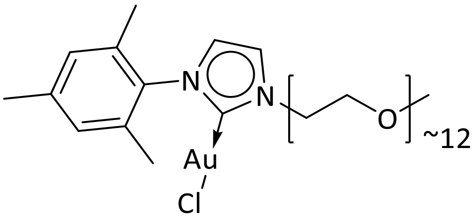
* Addition of 1 eq. KOH

At first, the initial conditions with MeCN under reflux was tested with an increased reaction time of 48 h (Table 9, entry 1). However, no conversion was noticed. In the next step the solvent was altered to methanol, while the other conditions were retained with the same degree of success (Table 9, entry 2). As a last resort, the reaction time was extended to 60 h for both steps, but exclusively the educt **L2** could be recovered (Table 9, entry 3). The addition of an auxiliary base like KOH was also ineffective (Table 9, entry 4).

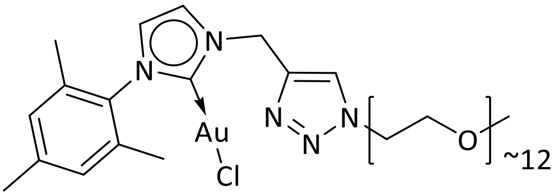
To sum up, the gold complex **Cat1** could be synthesised only once using the mentioned silver transmetalation protocol. Admittedly, complex **Cat1** could not be synthesised without dimerisation, all attempts to solve this problem and to reproduce the synthesis failed.

2.3.2. Polyethylene glycol (PEG)-linked NHC gold complexes

The introduction of polyethylene glycol groups is an easy and well-established possibility to add hydrophilicity to a ligand, which paves the way for water solubility. This project was aimed for the generation of two easily accessible water-soluble gold-complexes (Figure 33).[118] In addition to complex **AuPEG**, complex **AuPEGTriazole** bears a triazole group between the NHC and the hydrophilic PEG group in which one of the nitrogen atoms could possibly provide a coordination and thus a supplementary stabilisation to the gold atom.



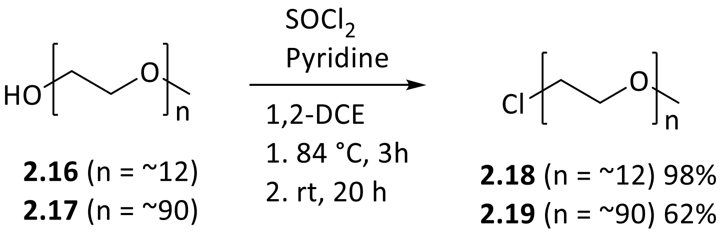
2.14
Cat2
AuPEG



2.15
Cat3
AuPEGTriazole

Figure 33 Aimed gold complexes of this project

As the general basis of the synthesis it was necessary to synthesise PEG entities with suitable leaving groups for the following substitution reactions. In doing so, two different lengths of the PEG-monomethylether chains were used, one with average 12 entities and an average molecular weight of 550 g/mol and the second with an average chain length of 90 and a corresponding weight of 4000 g/mol. In a first step, both polymers were chlorinated with thionyl chloride and pyridine, 1,2-DCE was chosen as solvent because of the needed higher temperatures than usually due to the low reactivity of these polymers (Figure 34).



2.16 (n = ~12)
2.17 (n = ~90)

2.18 (n = ~12) 98%
2.19 (n = ~90) 62%

Figure 34 Chlorination of the polymers **2.16** and **2.17**

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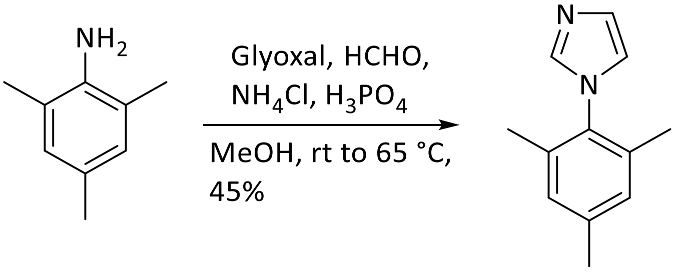
[118] Parts of this work were done in context of a bachelor thesis N. Jankowski, TU Dortmund (Dortmund), **2017**.

In the case of the shorter polymer **2.16** the chlorination went very well, and the product could be obtained in nearly quantitative yield of 98% and could be determined by ^{1}H- and ^{13}C-NMR spectroscopy. In the other case, it was clearly noticeable that the longer polymer has an even lower reactivity, hence the yield under the same conditions declined to 62%. The product could be characterised in the same way as before.

Another basic substance needed for the synthesis of the desired NHC ligands is an imidazole unit. Therefore, 1-mesityl-1H-imidazole **2.21** needed to be generated (Figure 35). It could be synthesised by a known procedure in a moderate yield of 45%, which coincides with results known from the literature.[119] The product could be identified by NMR spectroscopy.



2.20 **2.21**

Figure 35 Synthesis of 1-mesityl-1H-imidazole **2.21**

Next, the hydrophilic PEG group were introduced into the molecule by an S_N2 reaction with the free nitrogen atom, which simultaneously generates the imidazolium salt (Figure 36). On the basis of the lower reactivity of the polymers, microwave assisted heating was chosen to facilitate the substitution. Microwave reactors allow a more directly heating, shorter reaction times and the use of solvents greatly exceeding their normal boiling point.

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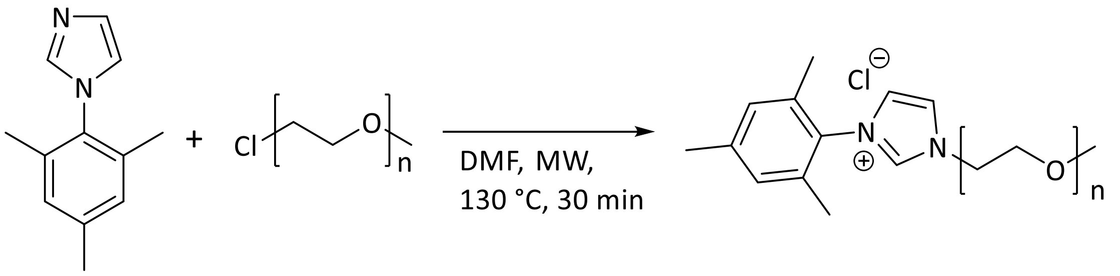
[119] J. Liu, J. Chen, J. Zhao, Y. Zhao, L. Li, H. Zhang, *Synthesis,* **2003**, 2661-2666.



2.21

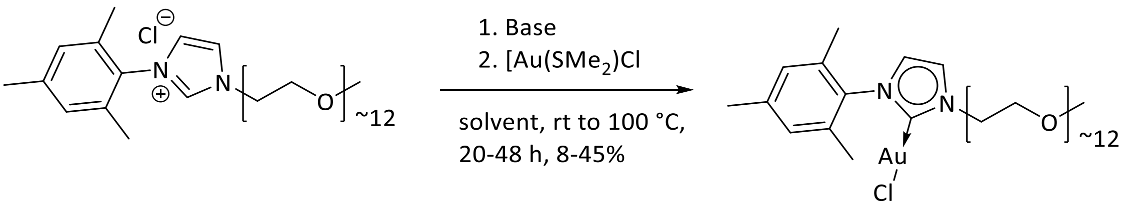
2.18 (n = ~12)
2.19 (n = ~90)

2.22, L3 (n = ~12) 82%
2.23, L4 (n = ~90) 0%

Figure 36 Generation of the PEG linked imidazolium salt

The shorter PEG-chloride **2.18** proceeded well in this reaction and the product could be isolated as brown oil with a yield of 82% and was characterised by NMR and mass spectroscopy. However, the longer version failed in the attempt to generate ligand **L4**. Only a product mixture could be isolated, which proved to be not separable. As a consequence, it was focused on the shorter imidazolium salt **L3**, in the following.

The ligand **L3**, which could be synthesised in just three steps with a total yield of 36% opens the possibility to coordinate to a metal, in this case gold was the metal of choice (Figure 37).



2.22
L3

2.14
Cat2
AuPEG

Figure 37 Complexation of ligand **L3**

At a first attempt, a well-known transmetalation reaction with silver(I)oxide as a mild base was applied, (see 2.3.1). Since, however, the polymers possess a low reactivity as experienced in the steps before, the reaction conditions were adapted.

Table 10 Outcome of the complexation of Ligand **L3**

Entry	Solvent	Temp. Step 1/2	Time Step 1/2	Base	Gold species	Result
1	DCM	rt/rt	24 h/24 h	Ag_2O (0.6 eq.)	[Au(SMe_2)Cl] (1 eq.)	8%
2	1,2-DCE	80 °C/80 °C	24 h/24 h	Ag_2O (1 eq.)	[Au(SMe_2)Cl] (1 eq.)	45%
3	DMF	100 °C/100 °C	24 h/24 h	Ag_2O (1 eq.)	[Au(SMe_2)Cl] (1 eq.)	24%
4	DMF	100 °C/100 °C	48 h/48 h	Ag_2O (1 eq.)	[Au(SMe_2)Cl] (1 eq.)	14%
5	MeCN	82 °C/82 °C	20 h	KO*t*Bu (1 eq.)	[Au(SMe_2)Cl] (1 eq.)	35%

Initially, the reaction was carried out in DCM at room temperature resulting in a very low yield of 8% (Table 10, entry 1). Therefore, the solvent was changed to the related 1,2-DCE, which enables an increase of the reaction temperature to 80 °C. Furthermore, the amount of Ag_2O was enhanced to 1 eq. leading to a much better result: The gold complex **AuPEG** could be isolated in 45% yield (Table 10, entry 2). To improve this result, the solvent was changed to another aprotic polar one, DMF. In addition, the temperature was increased to 100 °C, these conditions decreased the yield to 24% (Table 10, entry 3), even with a longer reaction time the outcome decreased even more to 14% (Table 10, entry 4). A possible explanation for this result is the low stability of the NHC-silver complex, in any case DMF does not seem to be compatible. Another approach was the use of a stronger base to generate the free carbene in situ, which should then in the presence of a suitable gold salt lead to a complexation. A known protocol for similar NHC ligands was applied (see 2.3.1), which led to a moderate yield of 35%. The isolated **AuPEG** was a red-brown solid and was identified by ^{1}H-,^{13}C-NMR-spectroscopy and mass spectrometry.

In order to generate another easily accessible PEG linked ligand **L5**, which can be synthesised in a straightforward manner by using a CuAAC-reaction, the formation of a PEG azide was needed.

An earlier attempt failed to accomplish a one pot CuAAC-reaction in which the PEG azide should be generated in situ due to the low reactivity of **2.18**. Therefore, the azide **2.24** was generated by the addition of sodium azide to the chlorinated PEG **2.18**, dissolved in DMF and heated under microwave radiation to 130 °C for 30 min (Figure 38). It could be isolated as a colourless liquid in very good yields of 91%. The identification was acquired by ^{1}H- and ^{13}C-NMR spectroscopy.

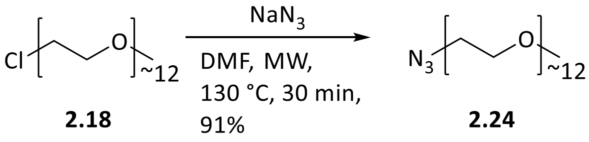


Figure 38 Synthesiss of PEG azide **2.24**

With the PEG azide **2.24** in one hand and the mesitylimidazole **2.21** in the other the desired ligand could be completed in one big step (Figure 39).

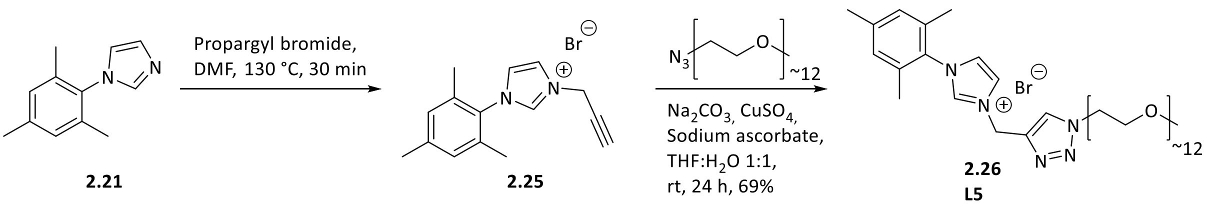
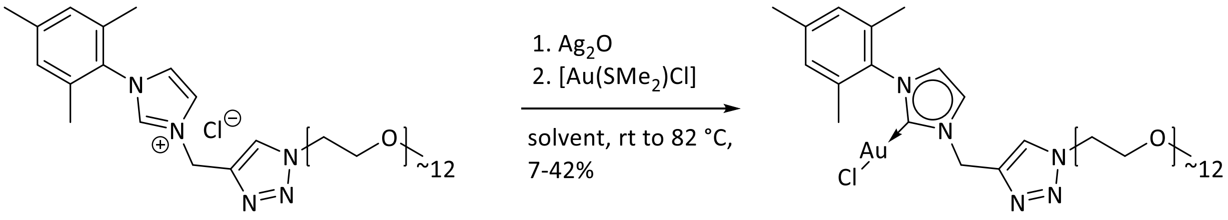


Figure 39 Synthesis of ligand **L5**

As first step, mesitylimidazole and propargylbromide reacted in a S_n2 reaction to generate the propargyl imidazolium salt **2.25**, which was precipitated from the reaction solution with Et_2O. Substance **2.25** was used directly in the following CuAAC reaction leading to a quite good yield of 69%. The product could be determined by ^{1}H-,^{13}C-NMR spectroscopy as well as ^{1}H-^{15}N-HMBC and mass spectrometry and appeared to be a brown oil.

The synthesised ligand **L5** could now be used for a complexation with a gold species, for this purpose the silver transmetalation protocol was applied (Figure 40).



2.26
L5

2.15
Cat3
AuPEGTriazole

Figure 40 Transmetalation reaction to generate gold complex **AuPEGTriazole**

Initially, the reaction was carried out at room temperature with DCM as solvent for 12 h in each step. Unfortunately, the desired gold complex could only be isolated in a very low yield of 7% (Table 11, entry 1). The desired product could be characterised by NMR and mass spectrometry. In order to improve this result, it was envisaged to increase the temperature therefore, the solvent needed to be changed to one with a higher boiling point. Furthermore, the free carbene route was tested, too (Table 11).

Table 11 Outcome of the complexation of Ligand **L5**

Entry	Solvent	Temp. Step 1/2	Time Step 1/2	Base	Gold species	Result
1	DCM	rt/rt	24 h/24 h	Ag_2O (0.6 eq.)	$[Au(SMe_2)Cl]$ (1 eq.)	7%
2	1,2-DCE	80 °C/80 °C	20 h/20 h	Ag_2O (1 eq.)	$[Au(SMe_2)Cl]$ (1 eq.)	21%
3	MeCN	82 °C/82 °C	20 h/20 h	Ag_2O (1 eq.)	$[Au(SMe_2)Cl]$ (1 eq.)	27%
4	MeCN	82 °C/82 °C	20 h	KO*t*Bu (1.2 eq.)	$[Au(SMe_2)Cl]$ (1 eq.)	42%

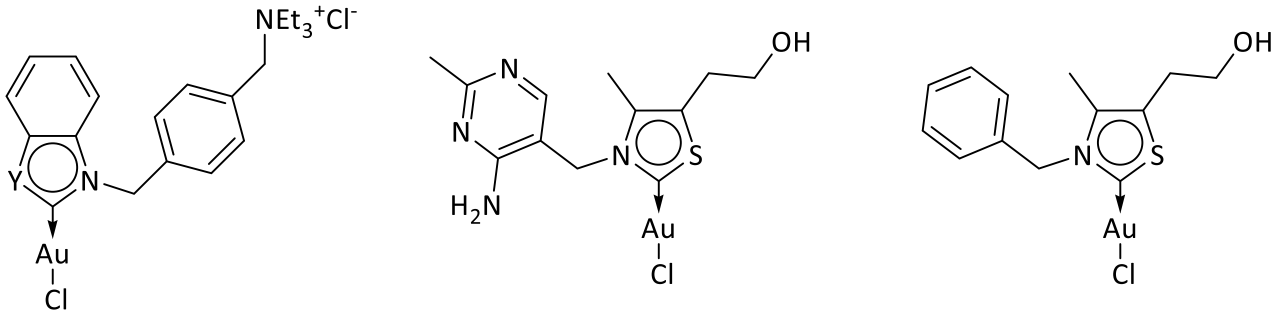
Using higher temperatures in the very similar solvent 1,2-DCE compared to DCM, the yield could be increased to 21% (Table 11, entry 2). When the more polar aprotic solvent acetonitrile was used the yield rose slightly to 27% (Table 11, entry 3).

The use of the free carbene route with KO*t*Bu as base in acetonitrile led to a moderate increase in yield up to 42% (Table 11, entry 4).

To sum up, both desired gold complexes **AuPEG** and **AuPEGTriazole** could be successfully synthesised in a total yield of 16% for complex **AuPEG** and 12% for complex **AuPEGTriazole**.

2.3.3. Oxazole and thiazole based MICs

As mentioned in chapter 2.1.4, there have been only a few reported gold complexes with oxazoles or thiazoles up till now and none of them were water soluble. To achieve such a target, a small number of desired molecules were envisaged (Figure 41).



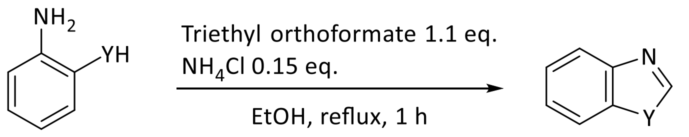
2.27a, Cat4a (Y = O)
2.27b, Cat4b (Y = S)

2.28
Cat5

2.29
Cat6

Figure 41 Desired gold complexes **Cat4, Cat5** and **Cat6**

Initially, the required benzoxazole and thiazole were synthesised starting with the ammonium chloride-catalysed reaction of ortho-aminophenol or ortho-aminothiophenol and triethyl orthoformate based on a synthesis of *Bunce* et al. (Figure 42).[120]



2.30 (Y = O)
2.31 (Y = S)

2.32 (y = O) 87%
2.33 (y = S) 90%

Figure 42 Synthesise of **2.32** and **2.33**

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[120] C. Fortenberry, B. Nammalwar, R. A. Bunce, *Org. Prep. Proced. Int.,* **2013**, *45*, 57-65.

This reaction pattern enabled an easy access to the desired heterocycles. Fortunately, the reaction proceeded in a straightforward manner and good yields of 87 % for the benzoxazole and 90 % for the thiazole could be achieved and were determined by ^{1}H- and ^{13}C-NMR spectroscopy.

In a next step, **2.33** should be coupled with the already known **2.3** from chapter 2.3.1. In doing so, the two components were refluxed in MeCN with a poor outcome of 15 % (Figure 43). The product could be determined by ^{1}H- and ^{13}C-NMR-spectroscopy as well as mass spectrometry. The corresponding benzoxazole derivate could not be isolated.

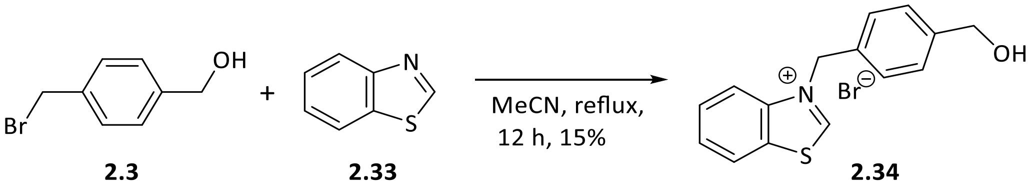


Figure 43 Nucleophilic substitution to **2.34**

Following the known procedure, the alcohol group should be changed to a better leaving group in order to facilitate the subsequent nucleophilic substitution. Therefore, it was pondered to use the *Darzens* halogenation protocol with thionyl chloride and pyridine (Figure 44). However, **2.34** bears a poor solubility in DCM, even in MeCN as a result, a mixture of DCM and MeCN was used (1:2) and stirred for 48 hours. Nevertheless, the chlorinated product **2.35** could not be observed.

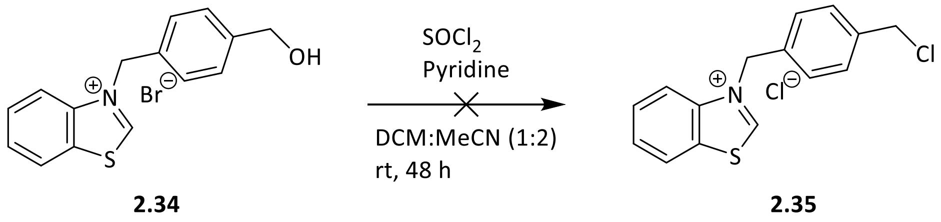
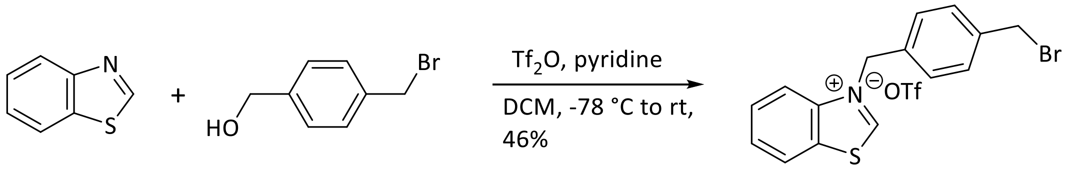


Figure 44 Chlorination of **2.34**

To circumvent this challenging step, two steps were combined. The benzyl alcohol **2.3** was in situ converted to a triflate group, one of the best leaving groups in S_N2 reactions and was then able to react with the benzthiazole in an S_N2 reaction (Figure 45). The product could be obtained in a moderate yield of 46% and could be identified by ^{1}H- and ^{13}C-NMR-spectroscopy as well as mass spectrometry.



2.33 **2.3** **2.36**

Figure 45 Alternative synthesis for **3.36** using an in situ generated triflate

To enable the water solubility of the ligand a hydrophilic group must be introduced into the molecule. Therefore, like in chapter 2.3.1 a quaternary ammonium salt was intended. For this purpose, **2.36** was dissolved in MeOH, Et_3N was added and the mixture was refluxed for three hours. Subsequent, a black solid could be isolated, however the NMR spectrum showed a decomposition. A consequential shortening of the reaction time to 30 min resulted in the same output.

As consequence, the project to synthesise ammonium salt-tagged benzothiazole ligands was discontinued at this point due to the poor yields of the previous steps and the lability of the benzothiazole.

Alternative thiazoles are vitamin B_1 (Thiamin) derivates, since a water-soluble copper complex could already be reported using them.[121] This complex could be synthesised by using the free carbene method with vitamin B_1, deprotonation could be achieved with NaO*t*Bu. Some of the protocols used in 2.3.1 were also applied in this project.

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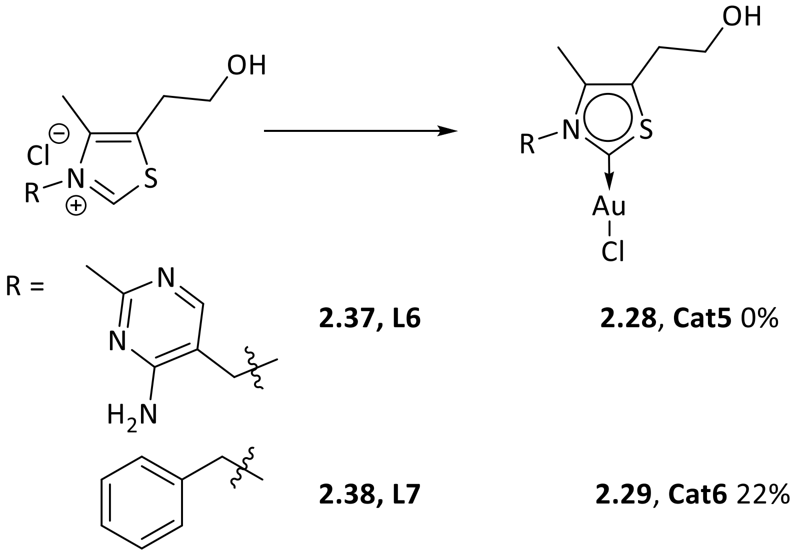
[121] V. B. Purohit, S. C. Karad, K. H. Patel, D. K. Raval, *RSC Adv.,* **2014**, *4*, 46002-46007.



2.37, L6 **2.28**, **Cat5** 0%

2.38, L7 **2.29**, **Cat6** 22%

Figure 46 Synthesis of Thiamin gold complexes

Initially, thiamine **2.37** and a thiamine derivate **2.38** were used as cheap starting substrates. In a first step, several deprotonation methods were tested followed by the addition of [Au(SMe$_2$)Cl].

Table 12 Outcome of the free carbene protocol

Entry	**Thiazole**	**Solvent**	**Temp.**	**Time**	**Base**	**Metal addition**	**Result**
1	**L6**	MeCN	82 °C	12 h	KO*t*Bu (1 eq.)	[Au(SMe$_2$)Cl] (1 eq.)	decomposition
2	**L6**	THF	rt	3 h	KO*t*Bu (1 eq.)	[Au(SMe$_2$)Cl] (1 eq.)	decomposition
3	**L6**	THF	rt	5 h	KO*t*Bu (1 eq.)	CuCl (1 eq.)	No conversion
4	**L7**	MeOH	65 °C	12 h	KO*t*Bu (1.1 eq.)	[Au(SMe$_2$)Cl] (1 eq.)	decomposition
5	**L7**	MeOH	rt	2 h	NaOMe (10 eq.)	[Au(SMe$_2$)Cl] (1 eq.)	decomposition
6	**L7**	MeOH	rt	2 h	KOH (4.5 eq.)	HAuCl$_4$ + TDG (1.1 eq.+ 6 eq.)	No conversion

Thiamin **L6** proved to be very labile, which corresponded with some publications about vitamin B_1.[122] Therefore, only decomposition could be obtained by the deprotonation with KO*t*Bu (Table 12, entry 1). The decomposition could be observed even at room temperature (Table 12, entry 2). Even though the similar reaction conditions from the published copper complex were applied no reaction could be observed. It was not possible to reproduce the findings of *Raval* et al. (Table 12, entry 3). That is why the thiamine was changed to the more stable **L7**, which is also cheap and easy to acquire.

It was then treated with two bases, on the one hand KO*t*Bu (Table 12, entry 4) and on the other hand NaOMe (Table 12, entry 5) in methanol, which both ended in a decomposition. Thereupon, an established method known from 2.3.1 involving a thiodiglycol (TDG) gold species was used. However, no conversion could be observed and the educt could be recovered.

Another mild tool to generate the gold complexes is transmetalation, Table 13 indicates the outcome of this method.

Table 13 Outcome of the transmetalation method

Entry	**Thiazole**	**Solvent**	**Temp.**	**Time**	**Silver salt**	**Gold species**	**Result**
1	**L6**	MeCN	1. rt 2. rt	1. 12 h 2. 12 h	Ag_2O (0.5 eq.)	$[Au(SMe_2)Cl]$ (1 eq.)	Decomposition
2	**L7**	MeCN	1. rt 2. rt	1. 12 h 2. 4 h	Ag_2O (0.5 eq.)	$[Au(SMe_2)Cl]$ (1 eq.)	22 %
3	**L7**	MeCN	1. rt 2. rt	1. 24 h 2. 12 h	Ag_2O (0.7 eq.)	$[Au(SMe_2)Cl]$ (1 eq.)	No conversion
4	**L7**	MeOH	1. rt 2. rt	1. 12 h 2. 4 h	Ag_2O (0.7eq.)	$[Au(SMe_2)Cl]$ (1 eq.)	No conversion
5	**L7**	MeCN	1. 80 °C 2. 80 °C	1. 12 h 2. 12 h	Ag_2O (1 eq.)	$[Au(SMe_2)Cl]$ (1.2 eq.)	No conversion
6	**L7**	MeOH	1. 65 °C 2. 65 °C	1. 12 h 2. 12 h	Ag_2O (1 eq.)	$[Au(SMe_2)Cl]$ (1.2 eq.)	No conversion

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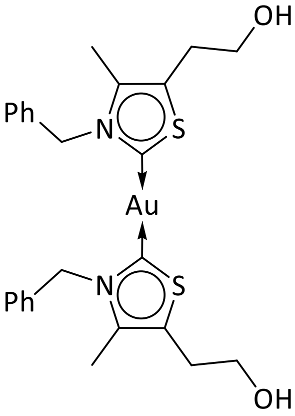
[122] D. Pachapurkar, L. N. Bell, *J. Food Sci.,* **2005**, *70*, c423-c426;
F. C. McIntire, D. V. Frost, *J. Am. Chem. Soc.,* **1944**, *66*, 1317-1318.

As a result of the poor solubility of the thiazole ligand in DCM, the standard solvent for this transmetalation reactions could not be used and was replaced by acetonitrile. The first attempt with vitamin B_1 failed due to a decomposition (Table 13, entry 1), but by using thiazole **L7** a gold complex could be obtained and characterised by NMR spectroscopy and mass spectrometry, which showed primarily the formation of a dimer (Table 13, entry 2) (see Figure 47).

However, it was not possible to reproduce this finding, even if the reaction time was prolonged, the amount of reagents increased, the solvent changed or the temperature increased no formation of a gold complex could be detected (Table 13, entries 3-6).

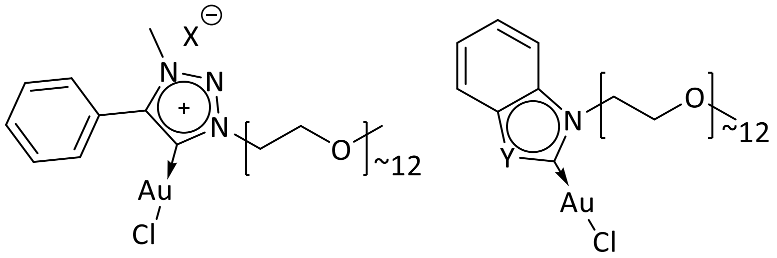


2.39

Figure 47 Observed dimer after the gold complexation of **L7**

2.3.4. Polyethylene glycol (PEG)-linked MIC complexes

Following the successful integration of PEG groups into NHCs in order to ensure their water solubility (see 2.2.1 and 2.3.2), it was also considered to use this concept for MIC ligands. Therefore, two kinds of MICs were envisaged in this project (see Figure 48).



2.40, Cat7 (n = ~12)

2.41, **Cat8** (Y = O)
2.42, **Cat9** (Y = S)

Figure 48 Polyethylene glycol (PEG)-linked MIC gold-complexes **Cat7**-**Cat9**

To generate the preceding ligand for complex **Cat7**, PEG azide **2.24** was used in a CuAAC-reaction with phenylacetylene in a mixture of THF and water (1:1) leading to ligand **2.43** in a good yield of 80% as yellow solid (Figure 49).

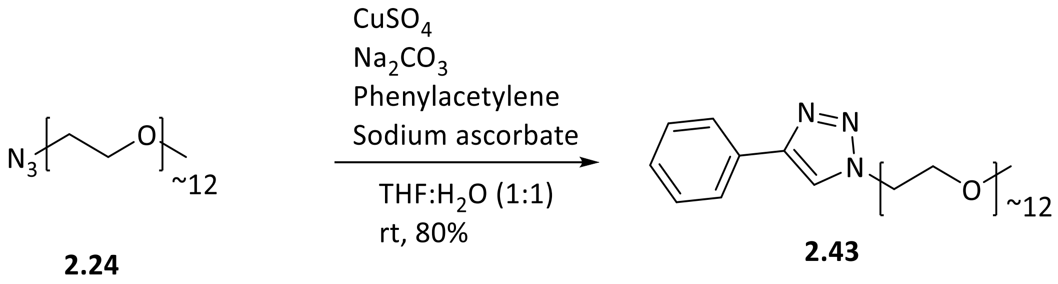


Figure 49 CuAAC-reaction to generate ligand **2.43**

Product **2.43**, which could be determined by NMR spectroscopy was then methylated to facilitate the following complexation (Figure 50). Even though methyl triflate, as very strong methylation agent was used only a yield of 60% of product **L8** could be isolated as brown viscous oil, which was identified by NMR spectroscopy.

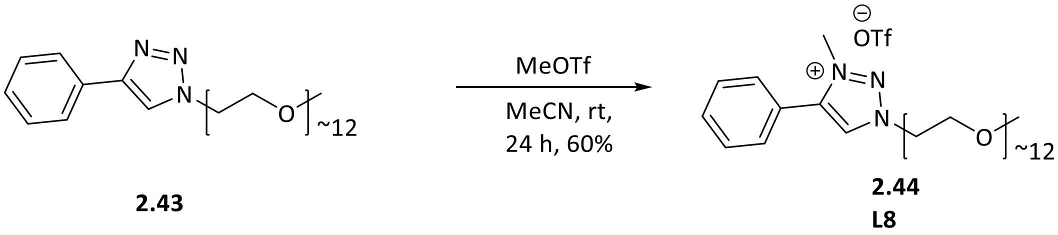
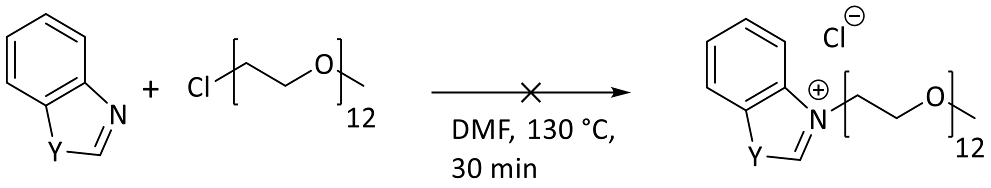


Figure 50 Methylation of **2.43**

Finally, gold should be introduced to the ligand **L8.** In doing so the transmetalation method was used in 1,2-DCE at 60 °C as well as the free carbene method with KO*t*Bu as base in methanol at 65 °C. Unfortunately, no product formation could be observed, and only educt **L8** could be recovered. Based on the negative experience of these triazole based ligands in chapter 2.3.1 this project discontinued at this point.

The same happened to the PEG linked oxa- and thiazole based ligands, since it was not possible to do an S_n2 reaction to generate the regarding PEG linked salt **L9** and **L10** (Figure 51).



2.32 (y = O)
2.33 (y = S)

2.18

2.44, **L9** (y = O)
2.45, **L10** (y = S)

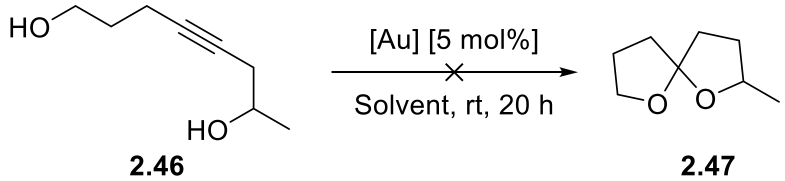
Figure 51 PEGylation of **2.32** and **2.33**

Based on the experiences of S_n2 reactions with PEG chloride, a high temperature achieved using microwave irradiation was applied here. However, this led presumably to a decomposition of the heterocycle.

2.3.5. First application: Cycloisomerisation of functionalised alkynediols

The cyclisation of an alkynediol was chosen as a first test reaction since its performance is well-known in the *Krause* group and the respective diols from former projects could be used.[123]

Table 14 Outcome of the cyclisation of an alkynediol



Entry	**Solvent**	**Catalyst**	**Additive**	**Yield**
1	H_2O	**AuPEG**	-	No conversion
2	H_2O	**AuPEGTriazole**	-	No conversion
3	H_2O	**AuPEG**	AgOTf [5 mol%]	No conversion
4	H_2O	**AuPEGTriazole**	AgOTf [5 mol%]	No conversion
5	DCM	**AuPEG**	AgOTf [5 mol%]	No conversion
6	DCM	**AuPEGTriazole**	AgOTf [5 mol%]	No conversion

Initially, the catalysts **AuPEG** and **AuPEGTriazole** were used in water without the addition of a silver salt since it could be shown that water is often polar enough to facilitate a dissociation of the chloride. [110], [123] However, no conversion could be detected with both used catalysts (Table 14, entries 1 and 2). Even though, a silver salt to generate the active gold cation was added no conversion could be determined (Table 14, entries 3 and 4). The same goes for the change of solvent to DCM (Table 14, entries 5 and 6).

The catalysts **AuPEG** and **AuPEGTriazole** were also used in two other test reactions, the outcome can be seen in the following chapters 3.4.2 and 4.3.2.

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[123] K. Belger, N. Krause, *Eur. J. Org. Chem.*, **2015**, *2015*, 220-225.

2.3.6. Excursus: Main Group metal NHC

In addition, it was envisaged to coordinate the main group metals gallium, indium and bismuth to some of the previously used NHCs (some originate from a former project)**Fehler! Textmarke nicht definiert.**. In doing so, the ligands were exposed to several typical bases like Ag_2O or KO*t*Bu to generate the free carbene or the silver NHC complex, which then should react with the respective metal chloride. Despite numerous efforts with different bases and reaction conditions the desired metal complexes could not be generated.

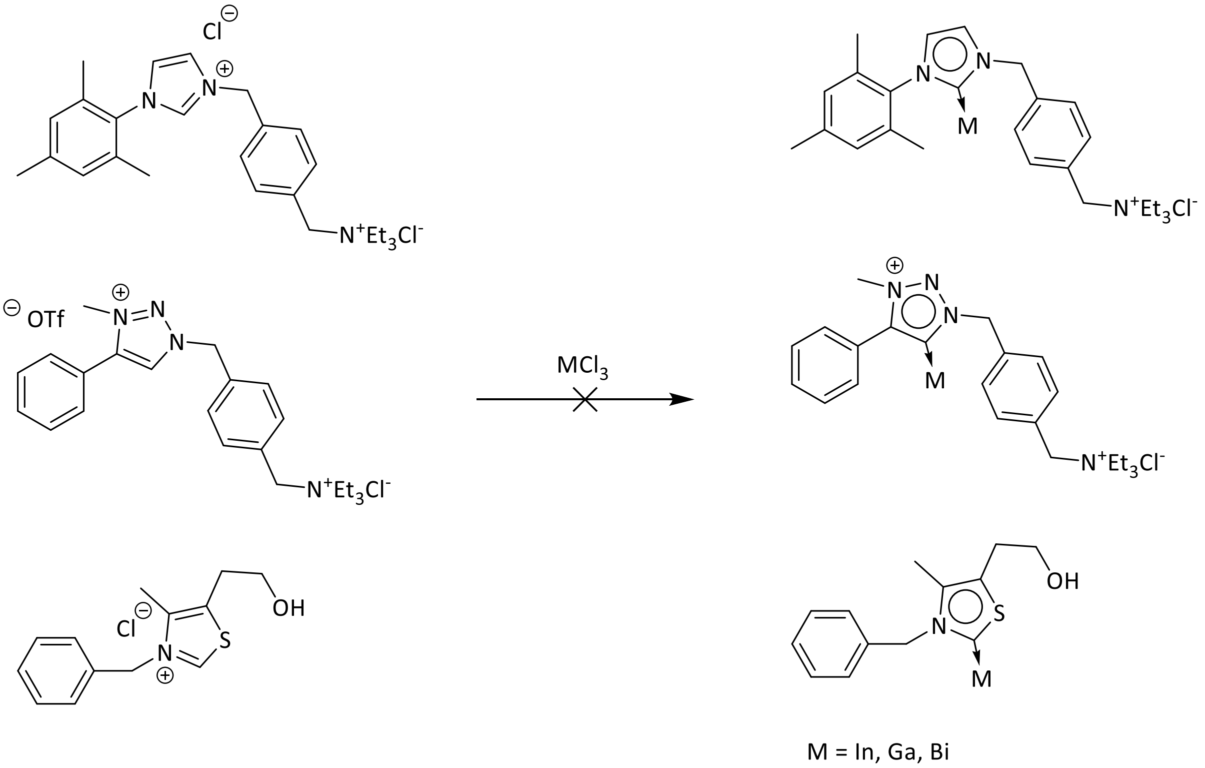


Figure 52 Outcome of the syntheses of main group metal NHC complexes

2.4. Conclusion

In the context of this project, a large part of the envisaged easily accessible ligands could be synthesised and identified. The easy accessibility becomes particularly obvious considering the PEG linked ligands **AuPEG** and **AuPEGTriazole**, since the synthesis does not include more than three steps and the products could be obtained in high yields. Especially the CuAAC-reaction showed once again it's superior effectiveness even with less reactive substances like PEG-azides.

Nonetheless, it proved to be challenging to introduce gold to the respective ligands and succeeded reliable, only in the case of PEG-linked imidazolium ligands **L3** and **L5** in expandable yields of 45% and 42% (Figure 53 and Figure 54). For **AuPEGTriazole**, it could be shown that the generation of the free carbene with the non-nucleophilic base KOtBu and subsequent complexation with chloro(dimethyl sulfide)gold(I) was superior to the transmetalation methods, where the silver carbene complex is generated initially followed by a transmetalation with chloro(dimethyl sulfide)gold(I) (Figure 54).

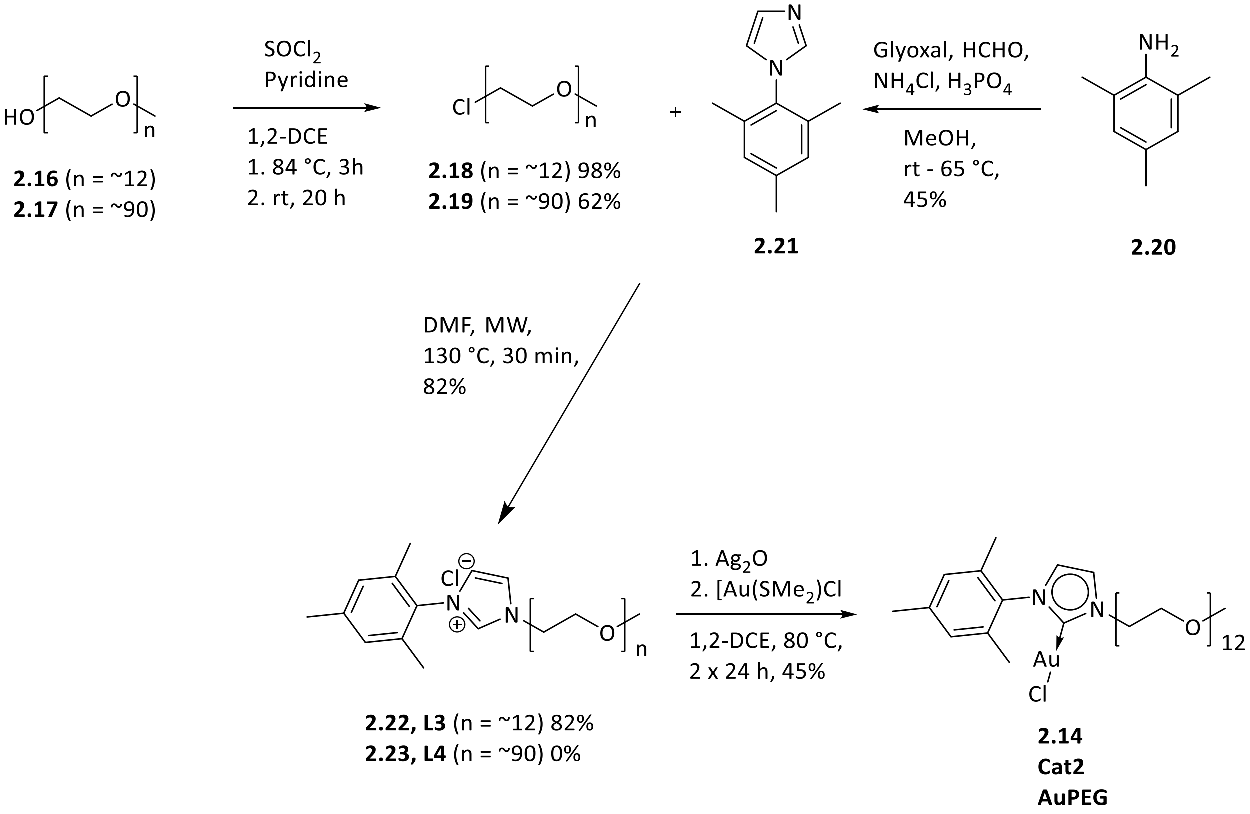


Figure 53 Synthesis of gold complex **AuPEG**

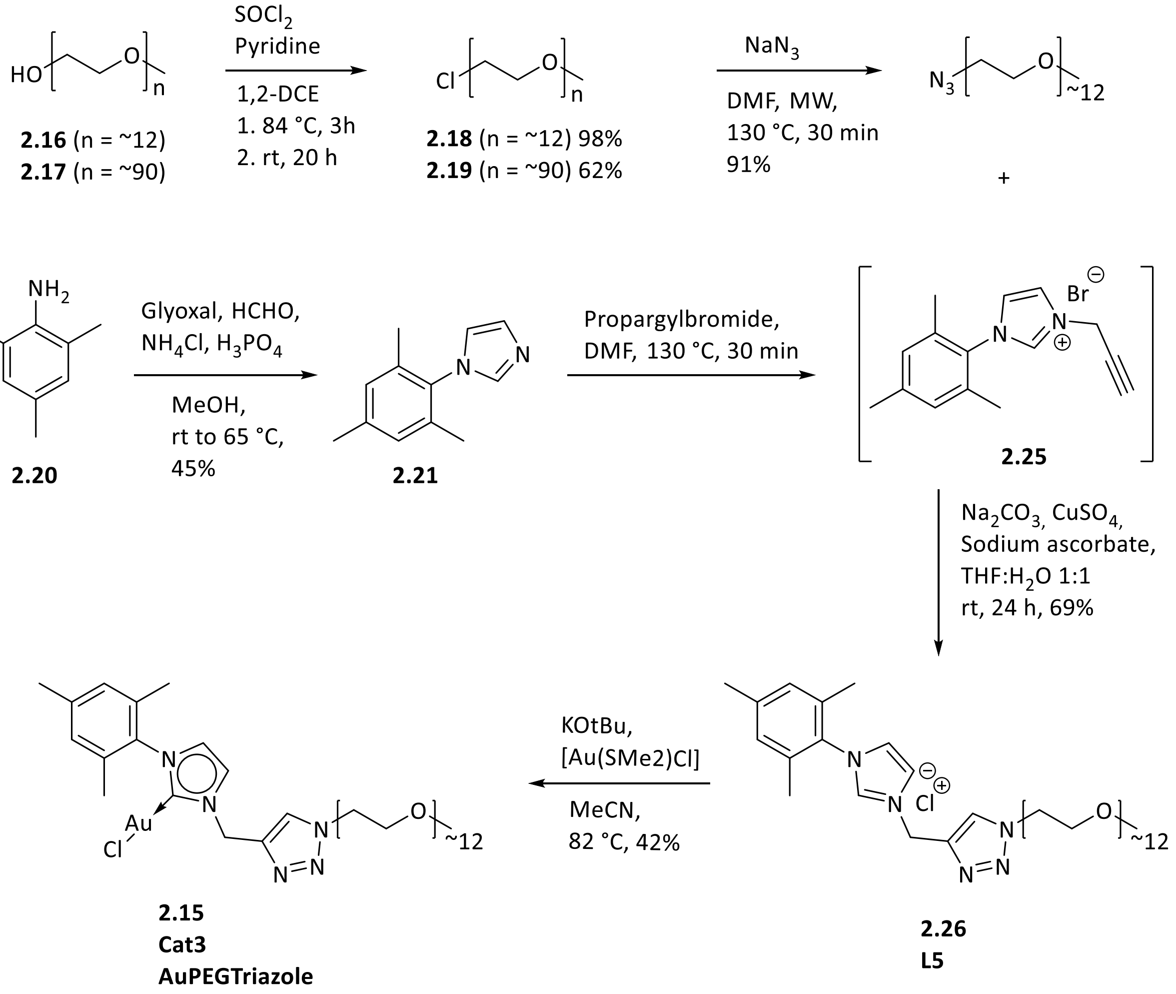


Figure 54 Synthesis of gold complex **AuPEGTriazole**

The triazole based ammonium salt-tagged ligand **L1** could be synthesised in good yields (Figure 55).

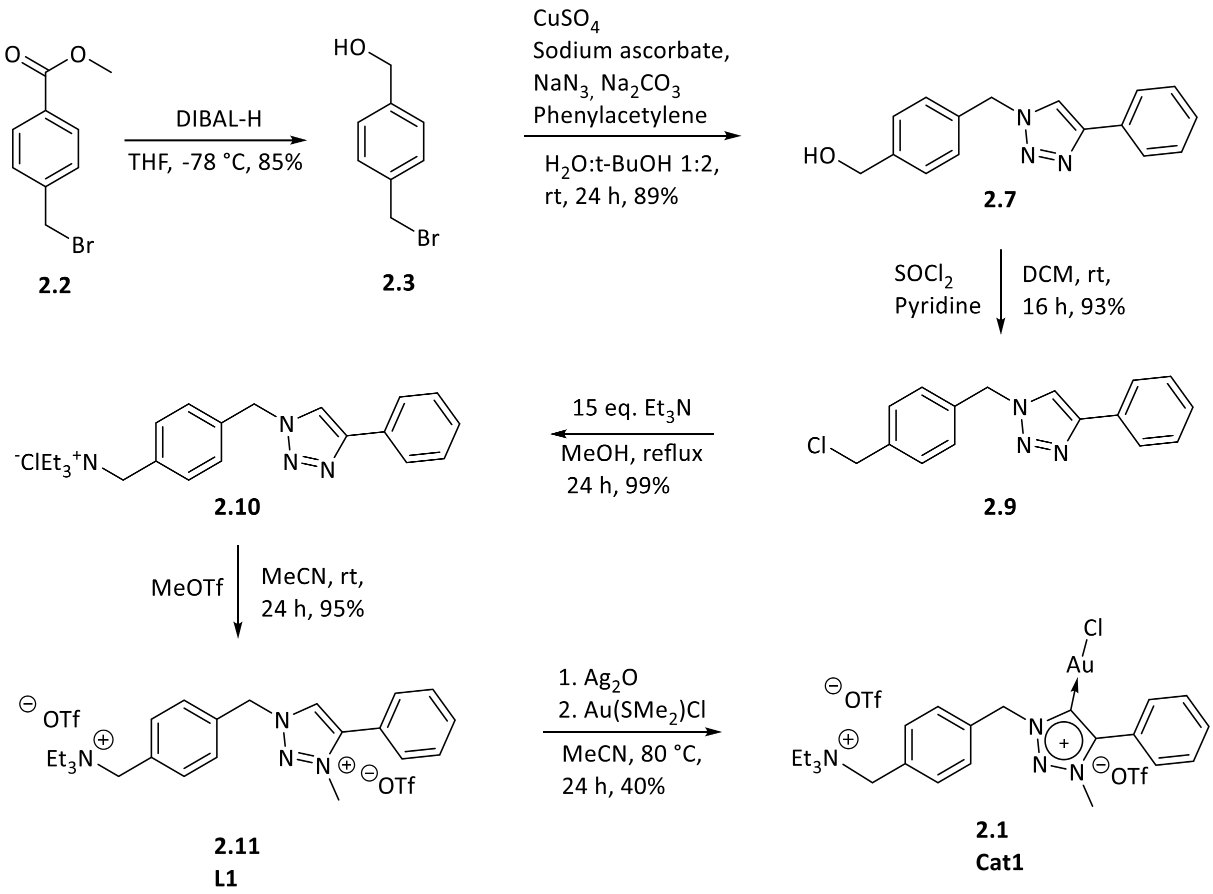


Figure 55 Synthesis of the triazole based ammonium salt-tagged gold complex **Cat1**

However, gold complex **Cat1** could only be formed once as monomer/dimer mixture (Figure 56). Even though, a broad range of known complexation methods were tested the following attempts to reproduce or improve this finding failed.

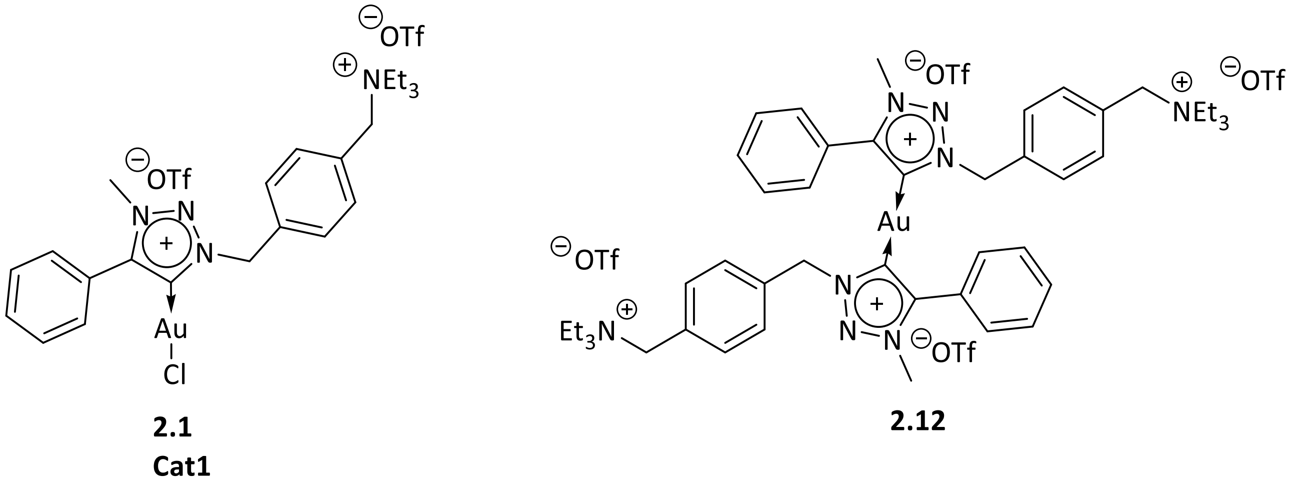
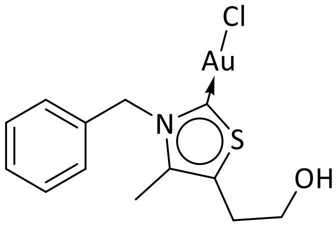


Figure 56 Triazole based ammonium salt-tagged gold complex **Cat1** and the corresponding dimer **2.12**

Similar behaviour could also be seen for the generation of the gold thiazole complex **Cat6** (Figure 57). The ligand **L7** is a water-soluble vitamin B_1 derivate, which could be introduced to gold only once via the transmetalation method.



2.29
Cat6

Figure 57 Thiazole based gold complex **Cat6**

In order to evaluate the performance of catalysts **AuPEG** and **AuPEGTriazole**, the cyclisation of an alkynediol to their corresponding spiro acetal was tested (Figure 58). However, it was not possible to observe any conversion, even with the addition of a silver salt with a non-coordinating anion.

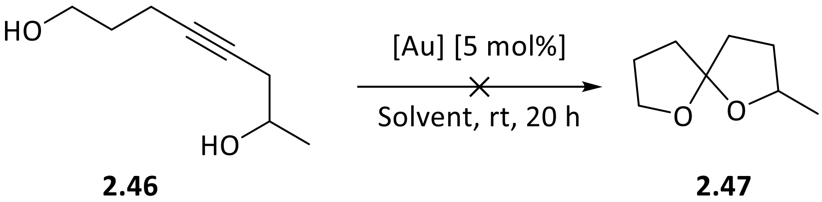


Figure 58 Cyclisation of an alkynediol

2.5. Experimental

Notes and list of abbreviations

In the text, superscript Arabic numerals in square brackets indicate to references.

Numbers of molecules are in bold in the text as well as in the figures and tables. The lower-case letters a, b, c, etc. or roman numerals following on compound numbers are used to distinguish compounds of the same skeleton but different substitution patterns.

Reagents and Solvents

Unless otherwise stated, all moisture and air-sensitive reactions were carried out in heated glassware under argon atmosphere as protective gas. The reagents were added in argon counterflow or by injection through a septum. The solvents tetrahydrofuran, dichloromethane, diethyl ether, toluene, acetonitrile and dimethylformamide were taken from the solvent-drying system MB-SPS 800 from MBRAUN. Other dry solvents as well as deuterated solvents were purchased commercially unless otherwise specified. The chemicals used were purchased from ABCR, Acros, Alfa Aesar, Chempur, Sigma Aldrich, Carbolution, J&K Scientific, Deutero and TCI and are usually used directly.

Chromatography

Column chromatographic separations were carried out on silica gel from MACHEREY-NAGEL (silica gel 60M, particle size 0.04-0.063 mm). The solvents used were technical solvents from company without further purification. Column chromatography was performed at a slight overpressure using a double blower. For filtration over celite Hyflo Super Gel from the company FLUKA was used.

Reaction controls were carried out by thin layer chromatography on silica gel plates from MERCK (Kieselgel 60 F254). In addition to the detection of fluorescence quenching with a UV lamp (λ = 254 nm), the chromatograms were stained by immersion in one of the following solutions and subsequent heating with a heat gun.

- Solution of potassium permanganate: 9 g $KMnO_4$, 12.6 g K_2CO_3, 15 ml NaOH (5% in Water), 900 ml deionised water
- Solution of anisic aldehyde: 12.8 ml anisic aldehyde, 4.8 ml acetic acid, 13.2 ml conc. H_2SO_4, 200 ml deionised water
- Solution of ammonium molybdate: 2 g $Ce(SO_4)_2 \cdot 4H_2O$, 4.2 g $(NH_4)_6Mo_7O_{24} \cdot 4H_2O$, 20 ml conc. H_2SO_4, 200 ml deionised water

Gas chromatography

Gas chromatographic spectroscopy was carried out on a gas chromatograph GC 8000 TOP from CE INSTRUMENTS using helium as the carrier gas (usually 70 kPa) and the capillary column CP-SIL-5CB (30 m, 0.32 mm ID, DF 0.25 µm). Octadecane was used as internal standard.

Mass spectroscopy

High resolution Bruker "compact QTOF" mass spectrometer with ESI source, coupled to an "Agilent 1260" HPLC system with UV-VIS-DAD / fluorescence detector.

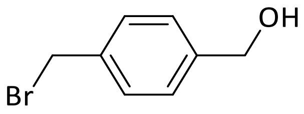
NMR spectroscopy

The recorded spectra were taken on the devices AV 400 Avance III HD Nanobay (400 MHz) and AV 500 Avance III HD (500 MHz) from BRUKER and Agilent Technologies DD2. The chemical shifts δ are given in ppm and refer to the respective solvent signal as an internal standard. The coupling constant J is shown in Hz. The solvents used here are $CDCl_3$, C_6D_6, DMSO-d_6, CD_3CN, Aceton-d_6 and MeOD. The spectra were evaluated with the software MestReNova from Mestrelab Research S.L.

For the listing of the spin multiplicities the following abbreviations were used: s (Singlet), d (doublet), t (triplet), q (quartet), dd (doublet of doublet), dt (doublet of triplet), td (triplet of doublet), ddt (doublet of doublet of triplet), dq (doublet of quartet), br (broad), m (multiplet).

(4-(bromomethyl)phenyl)methanol (**2.3**)

MD-P8-1



5.00 g methyl 4-(bromomethyl)benzoate (27.1 mmol, 1 eq.) was dissolved in dry THF under argon atmosphere at -78 °C, followed by a slow addition of 70 ml of a 1.9 M DIBAL-H solution in THF (47.5 g, 54.6 mmol, 2 eq.) holding this temperature. The solution was warmed slowly to 0 °C subsequently and ice was added into the solution. The precipitation was dissolved by the addition of conc. HCL (approx. 75 ml) and the THF was removed in vacuo. The residual solution was extracted with DCM (7 x 50 ml), the combined organic phases were dried by $MgSO_4$ and the solvent was removed in vacuo resulting in 85% of **2.3** as white solid (3.41 g, 21.7 mmol).

^1H NMR (600 MHz, Chloroform-*d*) δ 7.44 – 7.33 (m, 4H), 4.71 (d, *J* = 4.8 Hz, 2H), 4.59 (s, 1H), 4.50 (s, 1H)

^{13}C NMR (151 MHz, Chloroform-*d*) δ 141.3, 137.0, 129.4, 129.0, 127.5, 127.4, 65.1, 46.1

Known compound[124]

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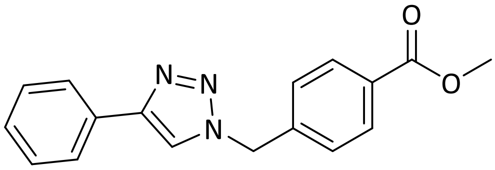
[124] E. Allard, J. Delaunay, J. Cousseau, *Org. Lett.,* **2003**, *5*, 2239-2242.

Methyl 4-((4-phenyl-1H-1,2,3-triazol-1-yl)methyl)benzoate (**2.8**)

MD-P2-8



1.73 g of benzoate 4-(bromomethyl)benzoate (7.54 mmol, 1 eq.) and 0.89 g sodium azide (13.7 mmol, 2 eq.) were dissolved in 8 ml MeCN in a microwave flask and heated 15 min at 150 °C. To the solution were then 0.18 g sodium carbonate (1.71 mmol, 0.25 eq.), 0.34 g sodium ascorbate (1.71 mmol, 0.25 eq.), 0.20 g copper sulphate (1.37 mmol, 0.2 eq.), 0.75 ml phenylacetylene (0.7 g, 6.85 mmol, 1 eq.) and 50 ml of a mixture of H_2O:*t*-BuOH (1:2) added. Then, the mixture was stirred overnight and filtered through celite subsequent. The remaining solution was extracted with DCM (3 x 25 ml), the combined organic phases were washed with 50 ml sat. solution of ammonium chloride and dried by $MgSO_4$. Removing of the solvent leading to the product as light-yellow solid in a yield of 89% (1.79 g, 6.10 mmol).

^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.09 – 8.02 (m, 2H), 7.85 (s, 1H), 7.48 – 7.39 (m, 3H), 7.35 (dd, *J* = 7.7, 4.1 Hz, 4H), 5.64 (s, 2H), 3.91 (d, *J* = 1.0 Hz, 3H)
^{13}C NMR (101 MHz, Chloroform-*d*) δ 166.6, 140.4, 132.1, 130.4, 130.1, 128.9, 128.3, 127.9, 127.8, 125.7, 54.3, 52.2
MS (ESI (m/z) $[C_{17}H_{18}N_3O_2 + H]^+$) calculated: m/z = 294.1164; found: 294.0
Known compound[125]

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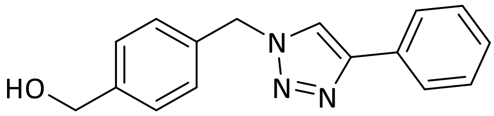
[125] F. Sebest, J. J. Dunsford, M. Adams, J. Pivot, P. D. Newman, S. Díez-González, *ChemCatChem,* **2018**, *10*, 2041-2045.

(4-((4-phenyl-1*H*-1,2,3-triazol-1-yl)methyl)phenyl)methanol (**2.7**)

MD-P2-4, MD-P2-9



Method 1 2.57 g of **2.3** (12.8 mmol, 1 eq.) was dissolved in 150 ml of a mixture of H_2O:*t*-BuOH (1:2) followed by the addition of 1.66 g sodium azide (25.6 mmol, 2 eq.), 0.34 g sodium carbonate (3.20 mmol, 0.25 eq.), 0.63 g sodium ascorbate (3.20 mmol, 0.25 eq.), 0.41 g copper sulphate (2.56 mmol, 0.2 eq.) and 2.11 ml phenylacetylene (1.96 g, 19.2 mmol, 1.5 eq.). Then, the mixture was stirred for 24 h and filtered through celite subsequent. The remaining solution was extracted with DCM (6 x 20 ml), the combined organic phases were washed with 100 ml sat. solution of ammonium chloride and dried by $MgSO_4$. Removing of the solvent led to the product as light-yellow solid in a yield of 99% (3.36 g, 12.7 mmol).

Method 2 2.46 g of benzoate **2.8** (8.39 mmol, 1 eq.) was dissolved in dry THF under argon atmosphere at -78 °C, followed by a slow addition of 29.4 ml of a 1 M DIBAL-H solution in THF (4.17 g, 29.4 mmol, 3.5 eq.). The solution was warmed slowly to 0 °C, after stirring for 30 min ice was added slowly into the solution. The precipitation was dissolved by the addition of conc. HCL (approx. 50 ml) and the THF was removed in vacuo. The residual solution was extracted with DCM (3 x 50 ml) and the combined organic phases were dried by $MgSO_4$ and the solvent was removed in vacuo resulting in 47% of **2.7** as white solid (1.06 g, 8.39 mmol).

^{1}H NMR (500 MHz, DMSO-d_6) δ 8.60 (s, 1H), 7.86 – 7.79 (m, 2H), 7.41 (t, *J* = 7.7 Hz, 2H), 7.30 (s, 5H), 5.60 (s, 2H), 4.46 (d, *J* = 5.7 Hz, 2H)

^{13}C NMR (126 MHz, DMSO-d_6) δ 146.6, 142.6, 134.3, 130.7, 128.9, 127.9, 127.8, 126.8, 125.1, 121.5, 62.5, 52.9

MS (ESI (m/z) [$C_{16}H_{17}N_3$ +H]$^+$) calculated: m/z = 266.1215; found: 266.1

Known compound[126]

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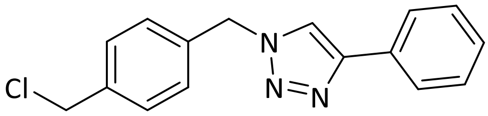
[126] S. Pan, S. Yan, T. Osako, Y. Uozumi, *ACS Sustainable Chem. Eng.*, **2017**, *5*, 10722-10734.

1-(4-(chloromethyl)benzyl)-4-phenyl-1*H*-1,2,3-triazole (2.9)

MD-P2-10



Method 1 3.36 g of triazole **2.7** (12.7 mmol, 1 eq.) and 51.07 mml pyridine (50.2 mg, 0.64 mmol 0.05 eq.) were dissolved under argon atmosphere in 150 ml dry DCM followed by a slow addition of 1.84 ml thionyl chloride (3.01 g, 25.3 mmol, 3 eq.). The solution was stirred over night at room temperature and then quenched by the addition of 50 ml sat. solution of sodium bicarbonate. Subsequent, the mixture was extracted with DCM (3 x 25 ml), the combined organic phases were dried by $MgSO_4$ and the solvent removed. Product **2.9** could be obtained as light-yellow solid in 93 % yield (3.28, 11.8 mmol).

Method 2 3.22 ml of trifluoromethanesulfonic anhydride (5.40 g, 19.2 mmol, 1.5 eq.) was dissolved in 50 ml dry DCM under argon atmosphere at – 80 °C. 2 g of the alcohol **2.7** (12.77 mmol, 1 eq.) and 3.09 ml pyridine (3.03 g, 38.3 mmol, 3 eq.) were filled in a mounted dropping funnel and subsequently dropped slowly into the solution resulting in a white precipitation. The mixture was stirred for 15 min and then warmed to room temperature for 20 min followed by a filtration through celite under argon. 1.25 g sodium azide (19.2 mmol, 1.5 eq.) and 1.35 g Na_2CO_3 (25.5 mmol, 2 eq.) were added and stirred for 30 min. The solvent was evaporated, and the remaining residue resolved in H_2O:*t*-BuOH (1:2) and 1.4 ml phenylacetylene (1.25 g, 12.8 mmol, 1 eq.), 0.41 g copper sulphate (2.55 mmol, 0.2 eq.) and 0.63 g sodium ascorbate (3.19 mmol, 0.25 eq.) were added and the solution was stirred for 24 h. The solution was filtered through celite and was extracted with EtOAc (3 x 20 ml), the combined organic phases were washed with 100 ml sat. solution of ammonium chloride and dried by $MgSO_4$. The residue was purified by flash column chromatography resulting in 14 % of **2.9** (0.5 g, 1.79 mmol).

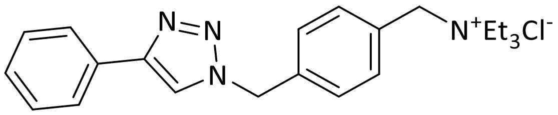
^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.83 – 7.78 (m, 2H), 7.67 (s, 1H), 7.44 – 7.39 (m, 4H), 7.35 – 7.29 (m, 3H), 5.59 (s, 2H), 4.58 (s, 2H)

^{13}C NMR (126 MHz, Chloroform-*d*) δ 138.2, 134.9, 130.4, 129.4, 128.8, 128.4, 128.3, 125.7, 53.8, 45.5

MS (ESI (m/z) $[C_{16}H_{15}ClN_3 + H]^+$) calculated: m/z = 284.0676; found: 284.1

Known compound[127]

N,N-diethyl-N-(4-((4-phenyl-1*H*-1,2,3-triazol-1-yl)methyl)benzyl)ethanaminium chloride (**2.10**)
MD-P2-11



3.27 g of triazole **2.9** (11.5 mmol, 1eq.) and 24 ml of triethylamine (17,5 g, 172 mmol, 15 eq.) were dissolved in 150 ml methanol and heated at reflux for 24 h. Followed by the addition of EtOAc to facilitate a precipitation of the product. The solution was filtered, and the precipitation rinsed in methanol. Removing of the solvent yielding in 99 % of the product (4.5 g, 11.5 mmol) as yellow solid.

^{1}H NMR (500 MHz, DMSO-d_6) δ 8.81 (s, 1H), 7.89 – 7.82 (m, 2H), 7.56 (d, *J* = 8.1 Hz, 2H), 7.53 – 7.42 (m, 4H), 7.39 – 7.30 (m, 1H), 5.75 (s, 2H), 4.52 (s, 2H), 3.22 – 3.11 (m, 6H), 1.29 (t, *J* = 7.2 Hz, 9H)

^{13}C NMR (126 MHz, DMSO-d_6) δ 146.6, 138.1, 133.1, 130.6, 128.9, 128.4, 127.8, 125.2, 122.0, 58.9, 52.0, 48.6, 7.6.

MS (ESI (m/z) $[C_{22}H_{29}N_4]^+$) calculated: m/z = 349.2387; found: 349.2395

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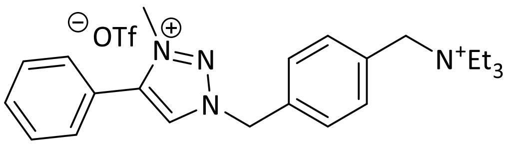
[127] P. Li, L. Wang, *Lett. Org. Chem.*, **2007**, *4*, 23-26.

3-methyl-4-phenyl-1-(4-((triethylammonio)methyl)benzyl)-1*H*-1,2,3-triazol-3-ium chloride trifluoromethanesulfonate (**2.11, L1**)

MD-P2-12



4.5 g of triazole **2.10** (11.7 mmol, 1eq.) was dissolved in 150 ml dry acetonitrile under argon followed by a dropwise addition of 1.92 ml methyltriflate (2.88 g, 17.5 mmol, 1.5 eq.) and stirring overnight at room temperature. The solvent was reduced to approx. 20 ml and 80 ml diethyl ether was added to precipitate the product. The suspension was filtered, and the precipitation rinsed in methanol. Removing of the solvent yielding in 95% of product **L1** (6.11 g, 11.7 mmol) as dark yellow solid.

^{1}H NMR (600 MHz, DMSO-*d*$_6$) δ 9.26 (s, 1H), 7.75 (dd, *J* = 7.6, 2.0 Hz, 2H), 7.69 – 7.64 (m, 5H), 7.61 (d, *J* = 8.0 Hz, 3H), 6.01 (s, 2H), 4.50 (s, 2H), 4.29 (s, 2H), 3.16 (q, *J* = 7.2 Hz, 6H), 1.31 (q, *J* = 6.8 Hz, 9H)

^{13}C NMR (151 MHz, DMSO-*d*$_6$) δ 143.2, 135.2, 133.7, 132.0, 129.8, 129.6, 129.2, 123.0, 122.2, 120.1, 59.3, 56.1, 52.6, 39.4, 7.9

^{19}F NMR (377 MHz, CD_3CN) δ -79.31

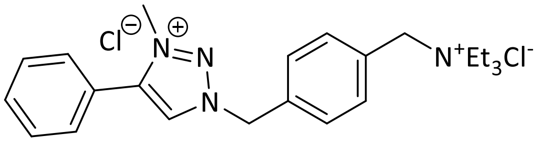
HMBC (^{1}H/^{15}N), (DMSO-*d*$_6$*)*: (9.27, 250.02), (9.27, 240.17), (6.03, 343.09), (6.01, 250.34), (4.32, 343.26), (4.28, 240.52), (1.31, 67.29)

MS (ESI (m/z) [$C_{24}H_{32}N_4SF_3O_3$]$^+$) calculated: m/z = 513.2124; found: 513.2135

MS (ESI (m/z) [$C_{23}H_{32}N_4$]$^{2+}$) calculated: m/z = 182.1308; found: 183.1308

3-methyl-4-phenyl-1-(4-((triethylammonio)methyl)benzyl)-1*H*-1,2,3-triazol-3-ium bischloride (2.13, L2)

MD-P2-12E

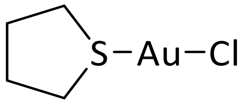


500 ml of the ion exchanger *Amberlite* IRA 900 was suspended in 250 ml methanol followed by the addition of 2.19 g triazole **L1** (3.98 mmol) and stirring for 1 h at room temperature. The solid was separated by filtration subsequently and washed with 30 ml methanol. The solvent was removed from the filtrate resulting in 74% of an orange crystalline solid (1.82 g, 2.96 mmol).

^{1}H NMR (600 MHz, DMSO-*d*$_6$) δ 9.26 (s, 1H), 7.75 (dd, *J* = 7.6, 2.0 Hz, 2H), 7.69 – 7.64 (m, 5H), 7.61 (d, *J* = 8.0 Hz, 3H), 6.01 (s, 2H), 4.50 (s, 2H), 4.29 (s, 2H), 3.16 (q, *J* = 7.2 Hz, 6H), 1.31 (q, *J* = 6.8 Hz, 9H)
^{13}C NMR (151 MHz, DMSO-*d*$_6$) δ 143.2, 135.2, 133.7, 132.0, 129.8, 129.6, 129.2, 123.1, 122.2, 120.1, 59.3, 56.0, 52.6, 39.4, 7.9
^{19}F NMR (377 MHz, CD_3CN) no Fluor could be detected anymore
MS (ESI (m/z) $[C_{23}H_{32}N_4]^{2+}$) calculated: m/z = 182.1308; found: 183.1309

Chloro(tetrahydrothiophene)gold(I) (**2.46**)

MD-P2-20



80 mg of Chloroauric acid (235 µmol, 1 eq.) was dissolved in a mixture of water and ethanol (6:1) followed by the dropwise addition of 43.6 mml tetrahydrothiophene (43.6 mg, 494 µmol, 2.1 eq.) and stirring for 45 min at room temperature. The occurred precipitation was separated by filtration and washed with approx. 20 ml ethanol. The solvent was evaporated from the filtrate and the resulting white solid was dried in vacuo. The desired product could be obtained in 19% yield (14.2 mg, 44.3 µmol).

^{1}H NMR (400 MHz, DMSO-d_6) δ 2.80 (t, *J* = 7.3 Hz, 4H), 1.79 – 1.72 (m, 4H)

^{13}C NMR (101 MHz, DMSO-d_6) δ 30.8, 25.7

Known compound[128]

NBu_4(acac) (**2.47**)

MD-P2-13T

To 7.45 ml of a tetrabutylammonium hydroxide solution (6.48 g, 40% in ethanol, 9.99 mmol, 1 eq.) were dropwise added 3 ml water as well as 1.02 ml acetylacetone (1.00 g, 9.99 mmol, 1 eq.) and stirred for 24 h at room temperature. The solvent was evaporated subsequently, and the remaining residue was resolved in DCM and dried with $MgSO_4$. The solution was reduced by half and the product was precipitated by the addition of 20 ml Et_2O. The precipitate was filtered and rinsed in methanol followed by the removing of the solvent in vacuo resulting in 57% of a white solid (1.95 g, 5.69 mmol).

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[128] C. E. Rezsnyak, J. Autschbach, J. D. Atwood, S. Moncho, *J. Coord. Chem.*, **2013**, *66*, 1153-1165.

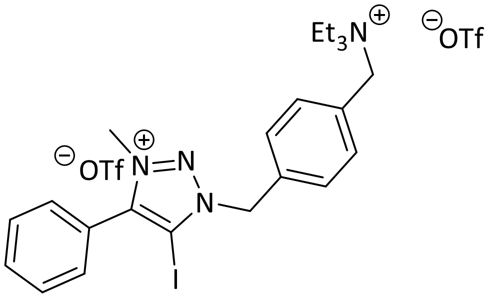
^{1}H NMR (400 MHz, DMSO-d_6) δ 4.93 (s, 1H), 3.24 – 3.12 (m, 8H), 1.60 – 1.53 (m, 4H), 1.31 (h, J = 7.3 Hz, 8H), 0.94 (t, J = 7.3 Hz, 12H)

^{13}C NMR (101 MHz, DMSO-d_6) δ 186.8, 98.0, 57.5, 27.6, 23.1, 19.2, 13.5

Known compound[129]

5-iodo-3-methyl-4-phenyl-1-(4-((triethylammonio)methyl)benzyl)-1*H*-1,2,3-triazol-3-ium bistrifluoromethanesulfonate (**2.48**)

MD-P2-13N



A solution of 60 mg of triazole **L1** (109.3 µmol, 1 eq.) in 50 ml dry acetonitrile under argon was cooled to 0 °C. Then, 49.05 mg KO*t*Bu (437.1 µmol, 4 eq.) was added and the solution was stirred 2.5 h at this temperature followed by the addition of 138.7 mg iodine (546.4 µmol, 5 eq.). The solution could warm up to room temperature subsequent and was stirred for further 12 h. The product was precipitated by the addition of Et_2O (approx. 50 ml). The precipitate was filtered and rinsed in methanol followed by the removing of the solvent in vacuo. A brown solid in a yield of 46% (25.60 mg, 40.5 µmol) could be obtained. The product was used directly in the following gold complexation.

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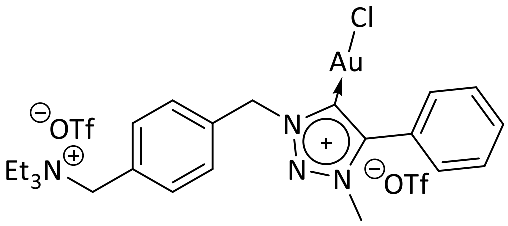
[129] A. Johnson, M. C. Gimeno, *Chem. Commun.*, **2016**, *52*, 9664-9667.

(3-methyl-4-phenyl-1-(4-((triethylammonio)methyl)benzyl)-1*H*-1,2,3-triazol-3-ium-5-yl)gold(II) chloride bis(trifluoromethanesulfonate) (**2.1**, **Cat1**)

MD-P2-13



Transmetalation method: 70 mg triazole **L1** (127 µmol, 1 eq.) was dissolved under argon atmosphere in dry acetonitrile followed by the addition of 19.2 mg silver oxide (82.9 µmol, 0.65 eq.). The solution was then stirred for 24 h at 82 °C with the exclusion of light. After the solution was filtered under inert conditions 37.6 mg chloro(dimethylsulfid)gold(I) (127.49 µmol, 1 eq.) was added and the solution was again stirred for 24 h at 82 °C with the exclusion of light. Subsequent, the product was precipitated by the addition of Et_2O (approx. 40 ml). The precipitate was filtered and rinsed in methanol followed by the removing of the solvent in vacuo. The product could be isolated as yellow solid in a yield of 40% (57.7 mg, 79.1 µmol).

^{1}H NMR (600 MHz, DMSO-d_6) δ 7.76 (ddd, *J* = 21.9, 7.5, 3.7 Hz, 2H), 7.70 – 7.63 (m, 1H), 7.62 – 7.54 (m, 4H), 7.50 – 7.37 (m, 2H), 5.86 – 5.70 (m, 2H), 4.46 (q, *J* = 10.7 Hz, 2H), 4.15 (s, 3H), 3.19 – 3.07 (m, 6H), 1.34 – 1.23 (m, 9H)

^{13}C NMR (151 MHz, DMSO-d_6) δ 156.5, 147.0, 133.7, 133.5, 130.0, 129.9, 129.4, 129.2, 126.9, 125.6, 122.1, 120.0, 59.3, 57.6, 52.5, 49.1, 7.9

^{19}F NMR (565 MHz, DMSO-d_6) δ -77.78

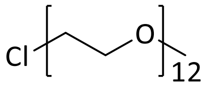
HMBC (^{1}H/^{15}N), (DMSO-d6): (4.25, 346.63), (4.29, 240.46), (3.48, 134.97), (3.43, 125.04), (1.31, 67.61)

MS (ESI (m/z) $[C_{24}H_{32}N_4AuCl]^+$) calculated: m/z = 595.1886; found: 595.3

MS (ESI (m/z) $[C_{48}H_{64}N_8AuS_2C_2O_6F_6]^+$) calculated: m/z = 1222.3865; found: 1221.7

Polyethylene glycol-mono-methyl ether-chloride (~12 entities) (**2.18**)

MD-P25-1

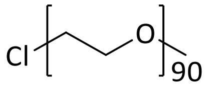


10 g Polyethylene glycol-mono-methyl ether (18.2 mmol, 1 eq.) was dissolved under argon atomosphere in 100 ml dry 1,2-DCE as well as 1.47 ml pyridine (1.44 g, 18.2 mmol, 1 eq.) and 1.32 ml thionyl chloride (2.16 g, 18.2 mmol, 1 eq.). The solution was stirred for 3 h at 84 °C followed by 16 h at room temperature. Afterwards, the reaction was quenched by the addition of 50 ml of a sat. solution of sodium bicarbonate and extracted with DCM (7 x 100 ml). The combined organic phases were dried by $MgSO_4$ and the solvent evaporated resulting in 98% of the desired product as light-yellow liquid (10.08 g, 17.75 mmol).

^{1}H NMR (500 MHz, Chloroform-*d*) δ 3.74 (t, *J* = 5.9 Hz, 2H), 3.64 (d, *J* = 5.7 Hz, 48H), 3.54 (dd, *J* = 5.5, 4.0 Hz, 2H), 3.37 (d, *J* = 1.0 Hz, 3H)
^{13}C NMR (126 MHz, Chloroform-*d*) δ 71.9, 71.4, 70.6, 59.1, 42.8
Known compound[130]

Polyethylene glycol-mono-methyl ether-chloride (~90 entities) (**2.19**)

MD-P25-8



10 g Polyethylene glycol-mono-methyl ether (2.5 mmol, 1 eq.) was dissolved under argon atmosphere in 100 ml dry 1,2-DCE as well as 0.20 ml pyridine (0.2 g, 2.5 mmol, 1 eq.) and 0.18 ml thionyl chloride (0.3 g, 2.5 mmol, 1 eq.). The solution was stirred for 4 h at 84 °C followed by 20 h at room temperature.

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[130] A. Jazayeri, M. Rappas, A. J. Brown, J. Kean, J. C. Errey, N. J. Robertson, C. Fiez-Vandal, S. P. Andrews, M. Congreve, A. Bortolato, *Nature,* **2017**, *546*, 254.

Afterwards, the reaction was quenched by the addition of 50 ml of a sat. solution of sodium bicarbonate and extracted with DCM (7 x 100 ml). The combined organic phases were dried by $MgSO_4$ and the solvent evaporated resulting in 62% of the desired product as white solid (6.26 g, 1.56 mmol).

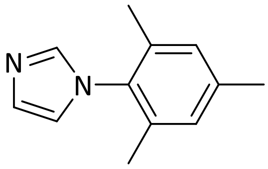
^{1}H NMR (500 MHz, Chloroform-*d*) δ 3.76 (t, *J* = 5.9 Hz, 2H), 3.68 (d, *J* = 5.7 Hz, 352 H), 3.50 (dd, *J* = 5.5, 4.0 Hz, 2H), 3.39 (d, *J* = 1.0 Hz, 3H)

^{13}C NMR (126 MHz, Chloroform-*d*) δ 71.8, 71.2, 70.9, 59.2, 42.6

Known compound[130]

1-mesityl-1*H*-imidazole (2.21)

MD-P8-2

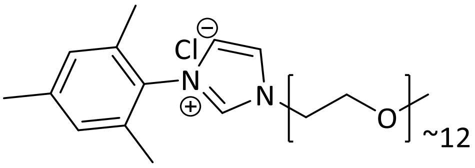


4.16 ml of trimethylaniline (4 g, 29.6 mmol, 1 eq.) and 3.4 ml of a glyoxal solution in water (40%, 1.72 g, 29.6 mmol, 1eq.) were dissolved in methanol and stirred overnight at room temperature. 1.78 g *p*-Formaldehyde (59.2 mmol, 2 eq.) and 3.16 g ammonium chloride (59.2 mmol, 1 eq.) were added subsequently followed by heating the solution at 65 °C for 1 h. Then, 1.54 ml phosphoric acid (2.9 g, 29.6 mmol, 1eq.) was added and the brown solution was heated for additional 2.5 h. Afterwards, the solvent was evaporated, and the residue was adjusted to pH ≤ 9 with a 1 M sodium hydroxide solution. Thereafter, the mixture was extracted with Et_2O (3 x 50 ml). The combined organic phases were washed with 20 ml water as well as 20 ml brine and dried by $MgSO_4$. The solvent was removed, and the residue was purified by flash column chromatography (pentane:Et_2O 2:1) yielding in 45% product as brown solid (2.37 g, 12.7 mmol).

^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.44 (t, *J* = 1.1 Hz, 1H), 7.24 (t, *J* = 1.1 Hz, 1H), 6.97 (h, *J* = 0.7 Hz, 2H), 6.89 (t, *J* = 1.3 Hz, 1H), 2.34 (d, *J* = 0.7 Hz, 3H), 1.99 (d, *J* = 0.7 Hz, 6H)
^{13}C NMR (126 MHz, Chloroform-*d*) δ 139.0, 137.6, 135.6, 129.6, 129.1, 120.2, 21.1, 17.5
Known compound[110]

1-mesityl-3-(PEG-mono-methyl ether (~12 entities))-1*H*-imidazole (**2.22, L3**)

MD-P25-5



In a microwave flask 0.33 g mesityl imidazole (1.76 mmol, 2 eq.) and 0.5 g polyethylene glycol-mono-methyl ether chloride (0.88 mmol, 1 eq.) were dissolved in DMF and heated to 130 °C for 0.5 h by microwave irradiation. Afterwards, the product was precipitated with Et_2O (approx. 40 ml), filtered and rinsed in methanol followed by the removing of the solvent in vacuo yielding in 66% of the product as brown, viscous oil (0.42 g, 0.58 mmol).

^{1}H NMR (500 MHz, Acetonitrile-*d*$_3$) δ 9.02 (s, 1H), 7.78 (s, 1H), 7.63 (d, *J* = 16.2 Hz, 2H), 7.45 (s, 1H), 5.45 (s, 2H), 4.45 (q, *J* = 7.7, 6.2 Hz, 2H), 3.88 (t, *J* = 4.6 Hz, 2H), 3.66 – 3.37 (m, 48H), 3.28 (d, *J* = 2.5 Hz, 3H), 2.35 (s, 3H), 2.10 – 2.01 (m, 6H)
^{13}C NMR (126 MHz, Acetonitrile-*d*$_3$) δ 142.1, 138.5, 135.8, 130.5, 130.4, 124.6, 124.4, 72.6, 71.1, 69.0, 58.9, 55.3, 50.8, 49.8, 21.1, 17.5
MS (ESI (m/z) $[C_{35}H_{71}N_2O_{11}]^+$) calculated: m/z = 695.5052; found: 695.5
Known compound[131]

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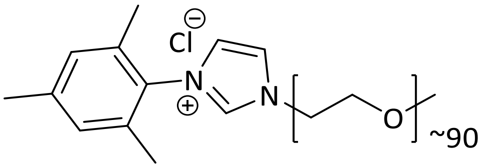
[131] K. Mitsudo, Y. Doi, S. Sakamoto, H. Murakami, H. Mandai, S. Suga, *Chem. Lett.,* **2011**, *40*, 936-938.

1-mesityl-3-(PEG-mono-methyl ether (~90 entities))-1*H*-imidazole (**2.23, L4**)

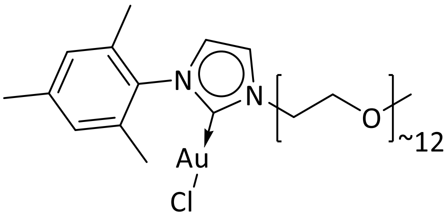
MD-P25-9



In a microwave flask 0.23 g mesityl imidazole (1.24 mmol, 2.5 eq.) and 2 g polyethylene glycol-mono-methyl ether chloride (0.5 mmol, 1 eq.) were dissolved in DMF and heated to 130 °C for 0.5 h by microwave irradiation. Afterwards, the product was precipitated with Et_2O (approx. 40 ml), filtered and rinsed in methanol followed by the removing of the solvent in vacuo. The residue was recrystallised from heptane/toluene (1:12), but the product could not be obtained.

1-mesityl-3-(2-methoxyethyl)-1*H*-imidazol-3-ium-2-yl) gold chloride (~12 entities) (**2.14, Cat2, AuPEG**)

MD-P25-4



Transmetalation method: The imidazolium salt **L3** (0.15 g, 0.19 mmol, 1 eq.) was dissolved under argon atmosphere in a dry solvent followed by the addition of silver oxide. The solution was then stirred for the time specified with the exclusion of light. After the solution was filtered under inert conditions the respective gold species was added and the solution was again stirred for the time specified and at the indicated temperature with the exclusion of light. Subsequent, the product was precipitated by the addition of Et_2O (approx. 40 ml).

The precipitate was filtered and rinsed in methanol followed by the removing of the solvent in vacuo yielding in the product as red brown oil. Table 15 indicates the specified amounts and reaction conditions.

Free carbene method with KO*t*Bu: The imidazolium salt **L3** (0.15 g, 0.19 mmol, 1 eq.) was dissolved under argon atmosphere in a dry solvent followed by the addition of KO*t*Bu and the respective gold species. The solution was then stirred with the exclusion of light for the time specified and at the indicated temperature. Subsequent, the product was precipitated by the addition of Et_2O (approx. 40 ml). The precipitate was filtered and rinsed in methanol followed by the removing of the solvent in vacuo yielding in the product as red brown oil. Table 15 indicates the specified amounts and reaction conditions.

Table 15 Reaction conditions for the complexation with gold

Entry	**Solvent**	**Temp.** **Step 1/2**	**Time** **Step 1/2**	**Base**	**Gold species**	**Result**
1	DCM	rt/rt	24 h/24 h	Ag_2O (0.6 eq.)	$[Au(SMe_2)Cl]$ (1 eq.)	8%
2	1,2-DCE	80 °C/80 °C	24 h/24 h	Ag_2O (1 eq.)	$[Au(SMe_2)Cl]$ (1 eq.)	45%
3	DMF	100 °C/100 °C	24 h/24 h	Ag_2O (1 eq.)	$[Au(SMe_2)Cl]$ (1 eq.)	24%
3	DMF	100 °C/100 °C	48 h/48 h	Ag_2O (1 eq.)	$[Au(SMe_2)Cl]$ (1 eq.)	14%
5	MeCN	82 °C/82 °C	20 h	KO*t*Bu (1 eq.)	$[Au(SMe_2)Cl]$ (1 eq.)	35%

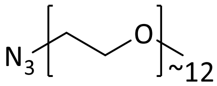
^{1}H NMR (500 MHz, Acetonitrile-d_3) δ 2.03 (s, 6H), 2.37 (s, 3H), 3.32 (s, 3H), 3.49 (m, 2H), 3.58 (m, 57H), 3.64 (m, 2H), 3.92 (t, J = 5.4 Hz, 2H), 4.44 (t, J = 5.4 Hz, 2H), 7.09 (s, 2H), 7.12 (d, J = 2.4 Hz, 1H), 7.53 (d, J = 1.8 Hz, 1H)

^{13}C NMR (126 MHz, Acetonitrile-d_3) δ 140.2, 136.0, 135.8, 129.6, 123.0, 122.8, 72.2, 70.7, 58.5, 51.5, 20.8, 17.5

MS (ESI (m/z) [$C_{28}H_{46}AuN_2O_7Cl$ +H]$^+$) calculated: m/z = 755.2654; found: 755.4716

Polyethylene glycol-mono-methyl ether-azide (~12 entities) (**2.24**)

MD-P25-10



In a microwave flask 0.39 g polyethylene glycol-mono-methyl ether chloride (0.71 mmol, 1 eq.) and 0.09 g sodium azide (1.43 mmol, 2 eq.) were dissolved in DMF and heated to 130 °C for 0.5 h by microwave irradiation. Afterwards, the product was extracted with DCM (3 x 40 ml) and the combined organic phases were dried by $MgSO_4$. After evaporation of the solvent a white solid in 89% yield could be obtained (0.36 g, 0.64 mmol).

^{1}H NMR (500 MHz, Chloroform-*d*) δ 3.70 – 3.60 (m, 42H), 3.54 (dd, *J* = 5.8, 3.6 Hz, 2H), 3.39 (d, *J* = 5.1 Hz, 2H), 3.37 (d, *J* = 0.8 Hz, 3H)

^{13}C NMR (126 MHz, Chloroform-*d*) δ 72.0, 70.7, 70.2, 59.2, 50.8

HMBC (^{1}H/^{15}N), (Chloroform-*d*): (3.69, 69.02), (3.41, 248.23)

Known compound[132]

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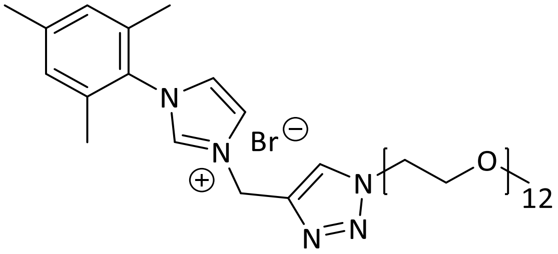
[132] C. Chen, P. Posocco, X. Liu, Q. Cheng, E. Laurini, J. Zhou, C. Liu, Y. Wang, J. Tang, V. D. Col, *Small,* **2016**, *12*, 3667-3676.

1-mesityl-3-((1-(PEG-mono methyl ether)-1*H*-1,2,3-triazol-4-yl)methyl)-1*H*-imidazol-3-ium bromide (~12 entities) (**2.26, L5)**

MD-P26-3



In a microwave flask 0.16 g mesityl imidazole **2.21** (0.83 mmol, 0.8 eq.) and 0.23 ml of a propargyl bromide solution in toluene (80%, 0.31 g, 2.09 mmol, 2 eq.) were dissolved in DMF and heated for 20 min at 120 °C. The interstage was precipitated with Et_2O, filtered, rinsed with methanol and the solvent finally evaporated. The residue was dissolved in a THF:water (1:1) mixture and 0.04 g copper sulphate (0.16 mmol, 0.15 eq.), 0.04 g sodium ascorbate (0.21 mmol, 0.2 eq.), 0.11 g sodium bicarbonate (1.04 mmol, 1 eq.) as well as 0.6 g polyethylene glycol-mono-methyl ether-azide **2.24** (1.04 mmol, 1 eq.) were added. The mixture was stirred for 18 h at room temperature followed by a reduction of the solvent by half and the addition of 50 ml of 1 M Ethylenediaminetetraacetic acid (EDTA) solution in water. The mixture was extracted (7 x 50 ml) subsequently and the combined organic phases dried by $MgSO_4$. The removing of the solvent yields in a brown solid in 69% yield (0.61 g, 0.72 mmol).

^1H NMR (500 MHz, Chloroform-*d*) δ 10.24 (s, 1H), 8.57 (s, 1H), 8.00 (s, 1H), 7.12 (s, 1H), 7.00 (s, 2H), 6.17 – 6.07 (m, 2H), 4.56 (t, *J* = 5.2 Hz, 2H), 3.90 (t, *J* = 5.2 Hz, 2H), 3.71 – 3.57 (m, 41H), 3.54 (t, *J* = 4.7 Hz, 3H), 3.37 (s, 3H), 2.34 (s, 3H), 2.05 (s, 6H)

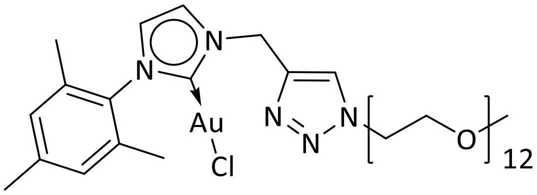
^{13}C NMR (126 MHz, Chloroform-*d*) δ 141.5, 137.6, 134.2, 130.7, 129.9, 123.4, 122.9, 121.6, 100.0, 71.9, 70.5 59.1, 50.8, 21.1, 17.7

HMBC ($^1H/^{15}N$), (Chloroform-*d*): (8.03, 182.79), (7.14, 185.96), (3.91, 246.12), (3.65, 75.21), (3.40, 248.00)

MS (ESI (m/z) $[C_{32}H_{52}BrN_5NaO_8]^+$) calculated: m/z = 735.2891; found: 735.5

1-mesityl-3-((1-(PEG-mono methyl ether)-1*H*-1,2,3-triazol-4-yl)methyl-1*H*-imidazol-3-ium-2-yl)gold chloride (~12 entities) (**2.15, Cat3, AuPEGTriazole**)

MD-P26-4



Transmetalation method: The imidazolium salt **L5** (0.2 g, 0.22 mmol, 1 eq.) was dissolved under argon atmosphere in a dry solvent followed by the addition of silver oxide. Then, the solution was stirred for the time specified with the exclusion of light. After the solution was filtered under inert conditions the respective gold species was added and the solution was again stirred for the time specified and at the indicated temperature with the exclusion of light. Subsequent, the product was precipitated by the addition of Et_2O (approx. 40 ml). The precipitate was filtered and rinsed in methanol followed by the removing of the solvent in vacuo yielding in the product as red brown oil. Table 16 indicates the specified amounts and reaction conditions.

Free carbene method with KO*t*Bu: The imidazolium salt **L5** (0.2 g, 0.22 mmol, 1 eq.) was dissolved under argon atmosphere in a dry solvent followed by the addition of KO*t*Bu and the respective gold species. Then, the solution was stirred with the exclusion of light for the time specified and at the indicated temperature. Subsequent, the product was precipitated by the addition of Et_2O (approx. 40 ml). The precipitate was filtered and rinsed in methanol followed by the removing of the solvent in vacuo yielding in the product as red brown oil. Table 16 indicates the specified amounts and reaction conditions.

Table 16 Reaction conditions for the complexation with gold

Entry	Solvent	Temp. Step 1/2	Time Step 1/2	Base	Gold species	Result
1	DCM	rt/rt	24 h/24 h	Ag_2O (0.6 eq.)	$[Au(SMe_2)Cl]$ (1 eq.)	7%
2	1,2-DCE	80 °C/80 °C	20 h/20 h	Ag_2O (1 eq.)	$[Au(SMe_2)Cl]$ (1 eq.)	21%
3	MeCN	82 °C/82 °C	20 h/20 h	Ag_2O (1 eq.)	$[Au(SMe_2)Cl]$ (1 eq.)	27%
4	MeCN	82 °C/82 °C	20 h	KO*t*Bu (1.2 eq.)	$[Au(SMe_2)Cl]$ (1 eq.)	42%

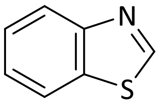
^{1}H NMR (400 MHz, DMSO-*d*$_6$) δ 8.07 (s, 1H), 7.74 (d, *J* = 4.9 Hz, 1H), 7.51 – 7.42 (m, 1H), 6.93 (s, 2H), 5.46 (s, 2H), 4.53 (dt, *J* = 10.2, 5.1 Hz, 2H), 3.79 (t, *J* = 5.2 Hz, 2H), 3.56 – 3.37 (m, 64H), 3.23 (s, 3H), 2.33 (d, *J* = 13.5 Hz, 6H), 1.95 (s, 3H)

^{13}C NMR (126 MHz, Acetone) δ 142.6, 139.1, 134.8, 129.1, 129.0, 128.8, 124.3, 123.2, 71.7, 57.9, 50.1, 38.7, 20.4, 16.8

MS (ESI (m/z) $[C_{34}H_{54}AuN_5O_9]Na+H]^+$) calculated: m/z = 896.3585; found: 894.9545

Benzothiazole (2.33)

MD-P4-2



6.24 g 2-aminothiophenole (48.8 mmol, 1 eq.), 0.4 g ammonium chloride (7.47 mmol, 0.15 eq.) and 9.07 ml triethyl orthoformate (8.12 g, 54.8 mmol, 1.1 eq.) were dissolved in ethanol and heated initially at 78 °C for 1 h and finally stirred for 24 h at room temperature. The solution was extracted with EtOAc (3 x 50 ml), the combined organic phases dried by $MgSO_4$ and the solvent was evaporated. Purification of the residue by flash column chromatography (pentane:Et_2O 5:1) resulting in 90% of a yellow liquid (5.93 g, 43.9 mmol).

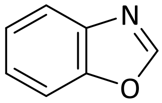
^{1}H NMR (500 MHz, Chloroform-*d*) δ 9.03 (s, 1H), 8.16 (d, *J* = 8.1 Hz, 1H), 7.97 (d, *J* = 8.0 Hz, 1H), 7.57 – 7.49 (m, 1H), 7.45 (t, *J* = 7.6 Hz, 1H)

^{13}C NMR (126 MHz, Chloroform-*d*) δ 154.2, 153.2, 133.8, 126.4, 125.7, 123.7, 122.0

Known compound[133]

Benzoxazole (2.32)

MD-P7-1



10 g 2-aminophenole (91.6 mmol, 1 eq.), 0.74 g ammonium chloride (13.7 mmol, 0.15 eq.) and 16.7 ml triethyl orthoformate (14.94 g, 100.8 mmol, 1.1 eq.) were dissolved in ethanol and heated at 78 °C for 2 h. The solution was extracted with EtOAc (3 x 50 ml), the combined organic phases dried by $MgSO_4$ and the solvent was evaporated. Purification of the residue by Kugelrohr distillation resulting in 86% of a clear liquid (9.43 g, 91.6 mmol)

^{1}H NMR (600 MHz, Chloroform-*d*) δ 8.11 (s, 1H), 7.84 – 7.77 (m, 1H), 7.62 – 7.57 (m, 1H), 7.42 – 7.34 (m, 2H)

^{13}C NMR (151 MHz, Chloroform-*d*) δ 152.7, 150.2, 140.1, 125.8, 124.8, 120.7, 111.1

Known compound[133]

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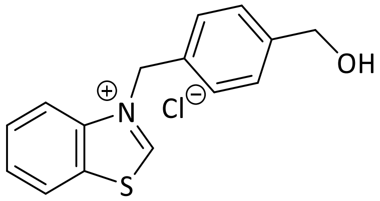
[133] C. Fortenberry, B. Nammalwar, R. A. Bunce, *Org. Prep. Proced. Int.*, **2013**, *45*, 57-65.

3-(4-(hydroxymethyl)benzyl)benzo[d]thiazol-3-ium chloride (**2.34**)

MD-P4-3



1.27 g benzyl alcohol **2.3** (8.14 mmol, 1.1 eq.) and 1 g benzothiazole (7.4 mmol, 1 eq.) were dissolved in acetonitrile and heated at 82 °C for 12 h followed by a precipitation of the product by the addition of Et_2O (approx. 50 ml). The precipitate was filtered and rinsed in methanol followed by the removing of the solvent in vacuo yielding in 15% of the product as brown oil (0.34 g, 1.11 mmol)

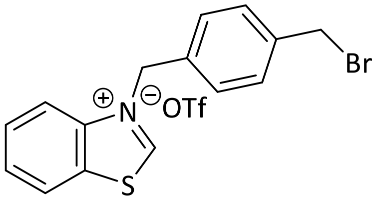
^{1}H NMR (400 MHz, DMSO-*d*$_6$) δ 10.78 (s, 1H), 8.53 (dd, *J* = 8.0, 1.3 Hz, 1H), 8.31 (dd, *J* = 8.0, 1.1 Hz, 1H), 7.96 – 7.77 (m, 2H), 7.53 – 7.45 (m, 2H), 7.37 (d, *J* = 8.0 Hz, 2H), 6.12 (s, 2H), 4.49 (s, 2H)

^{13}C NMR (101 MHz, DMSO-*d*$_6$) δ 144.1, 140.5, 132.4, 130.1, 129.0, 128.7, 127.5, 125.9, 117.9, 68.9, 62.8

MS (ESI (m/z) $[C_{15}H_{14}NOS]^+$) calculated: m/z = 256.0796; found: 256.1

3-(4-(bromomethyl)benzyl)benzo[d]thiazol-3-ium trifluoromethanesulfonate (2.36)

MD-P4-5



0.99 ml trifluoromethanesulfonic anhydride (1.67 g, 5.92 mmol, 1.6 eq.) were dissolved in dry DCM under argon atmosphere at -70°C. Then, a mixture of 0.87 g benzyl alcohol **2.3** (5.55 mmol, 1.5 eq.) and 0.5 ml pyridine (0.5 g, 1.7 eq.) were added slowly using a dropping funnel. The mixture was warmed to -30 °C within 30 min and 0.5 g of benzothiazole **2.33** was added. After 16 h, 50 ml saturated Na_2CO_3 solution was added, the phases separated, and the aqueous phase was extracted with DCM (2 x 50 ml). The solvent was reduced to 5 ml followed by a precipitation of the product by the addition of Et_2O (approx. 50 ml). The precipitate was filtered and rinsed in methanol followed by the removing of the solvent in vacuo yielding in 46% of the product as brown oil (0.53 g, 1.7 mmol)

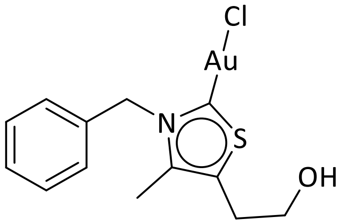
^{1}H NMR (400 MHz, Chloroform-*d*) δ 9.05 (d, *J* = 6.1 Hz, 2H), 8.41 (t, *J* = 7.8 Hz, 1H), 7.99 (t, *J* = 7.0 Hz, 2H), 7.57 – 7.49 (m, 2H), 7.44 (d, *J* = 8.1 Hz, 2H), 5.92 (s, 2H), 4.56 (s, 2H)

^{13}C NMR (101 MHz, Chloroform-*d*) δ 146.5, 144.9, 130.1, 129.7, 129.1, 128.7, 125.5, 122.7, 118.4, 67.7, 32.8

^{19}F NMR (377 MHz, Chloroform-*d*) δ -78.38

(3-benzyl-5-(2-hydroxyethyl)-4-methylthiazol-2-ylidene)gold chloride (**2.29, Cat6**)

MD-P12-11



36.64 mg (135.8 µmol, 1 eq.) thiazole salt **L7** was dissolved in acetonitrile followed by the addition of 15.7 mg (69.9 µmol, 0.5 eq.) silver(I)oxide. Then, the solution was stirred for 12 h with the exclusion of light. After the solution was filtered 40 mg (135.8 µmol, 1 eq.) chloro(dimethyl sulfide)gold(I) was added and the solution was stirred again for 4 h at room temperature with the exclusion of light. Subsequent, the product was precipitated by the addition of Et_2O (approx. 40 ml). The precipitate was filtered and rinsed in methanol followed by the removing of the solvent in vacuo yielding in 14.97 mg (22%) of the desired product as brown solid.

^{1}H NMR (400 MHz, DMSO-d_6) δ 7.47 – 7.33 (m, 3H), 7.26 – 7.21 (m, 2H), 5.80 (s, 2H), 3.60 (t, *J* = 5.8 Hz, 2H), 2.88 (t, *J* = 5.8 Hz, 2H), 2.51 (p, *J* = 1.9 Hz, 2H), 2.25 (s, 3H)

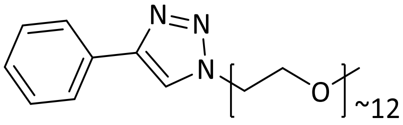
^{13}C NMR (101 MHz, DMSO-d_6) δ 191.2, 141.8, 135.3, 134.7, 129.5, 128.7, 127.0, 60.6, 59.3, 30.4, 12.7

MS (ESI (m/z) $[C_{15}H_{18}N_2AuOS]^+$; $[LAu(MeCN)]^+$) calculated: m/z = 471.0805; found: 471.0801

MS (ESI (m/z) $[C_{26}H_{30}N_2AuO_2S_2]^+$ $[L_2Au]^+$) calculated: m/z = 663.1409; found: 663.1423

1-(PEG-mono methyl ether)-4-phenyl-1*H*-1,2,3-triazol (~12 entities) (**2.43**)

MD-P2-19



1 g PEG-azide **2.24** (1.74 mmol, 1 eq.), 0.29 ml phenylacetylene (0.27 g, 2.61 mmol, 1.5 eq.), 0.09 g copper sulphate (0.35 mmol, 0.2 eq.), 0.09 g sodium ascorbate (0.43 mmol, 0.25 eq.) and 0.18 g sodium bicarbonate (1,74 mmol, 1 eq.) were dissolved in a mixture of THF:water (1:1). After stirring for 24 h 15 ml of a 1 M EDTA-solution was added as well as 20 ml of a sat. sodium chloride solution. The mixture was extracted with DCM (5 x 100 ml) subsequently, the combined organic phases were dried by $MgSO_4$ and the solvent evaporated. The product could be obtained in 80% yield as yellow solid (0.97 g, 1.44 mmol).

^{1}H NMR (600 MHz, Acetonitrile-*d*$_3$) δ 8.17 (s, 1H), 7.89 – 7.82 (m, 2H), 7.45 (t, *J* = 7.7 Hz, 2H), 7.34 (t, *J* = 7.3 Hz, 1H), 4.55 (t, *J* = 5.1 Hz, 2H), 3.89 (t, *J* = 5.1 Hz, 2H), 3.62 – 3.42 (m, 57H), 3.29 (s, 3H)

^{13}C NMR (151 MHz, Acetonitrile-*d*$_3$) δ 147.5, 131.8, 129.4, 128.4, 125.9, 121.9, 117.9, 72.2, 70.7, 69.6, 58.5, 50.6

Known compound[134]

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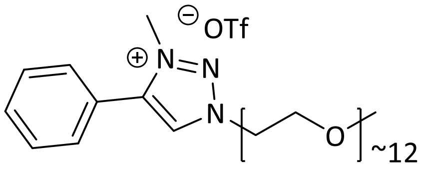
[134] H. B. Nulwala, C. N. Tang, B. W. Kail, K. Damodaran, P. Kaur, S. Wickramanayake, W. Shi, D. R. Luebke, *Green Chem.,* **2011**, *13*, 3345-3349.

1-(PEG-mono methyl ether)-3-methyl-4-phenyl-1*H*-1,2,3-triazol-3-iumtriflate (~12 entities) (2.44, L8)

MD-P2-22



1.3 g of triazole **2.43** (1.92 mmol, 1 eq.) was dissolved in dry acetonitrile under argon atmosphere and 0.31 ml methyltriflate (0.47 g, 2.88 mmol, 1.5 eq.) was added dropwise followed by stirring the solution at room temperature for 24 h. Then, the product was precipitated by the addition of Et_2O (approx. 50 ml). The precipitate was filtered and rinsed in methanol followed by the removing of the solvent in vacuo yielding in 60% of the product as brown oil (0.96 g, 1.15 mmol)

^{1}H NMR (500 MHz, Acetonitrile-d_3) δ 8.63 (d, *J* = 1.6 Hz, 1H), 7.74 – 7.57 (m, 5H), 4.77 (t, *J* = 4.8 Hz, 2H), 4.20 (s, 3H), 3.98 (t, *J* = 4.8 Hz, 2H), 3.76 – 3.41 (m, 46H), 3.32 (d, *J* = 4.4 Hz, 3H), 2.94 (d, *J* = 5.3 Hz, 2H)

^{13}C NMR (126 MHz, Acetonitrile-d_3) δ 144.0, 132.7, 130.7, 130.5, 130.4, 130.2, 130.0, 123.5, 72.3, 70.8, 68.5, 54.8, 39.5

Known compound[134]

3. Allene chemistry with regards to the concept of sustainability

3.1. Allenes

The class of allenes is no longer seen as chemical curiosity, but rather as an interesting building block in modern organic chemistry.[135] In the meantime, allenic motifs could be found in broad variety of natural products (about 150)[136], which represents their importance as a structural element in nature. They are able to undergo a wide range of reactions from C-C bond forming, transformations to intramolecular nucleophilic ring closures. Furthermore, allenes provide the possibility to build up new stereogenic centres due to their exceptional intrinsic axial chirality.[136]

In particular, metal-catalysed cycloisomerisations especially noble metal-based catalysis reactions have arisen as capable tools, as they provide an easy access to complex molecules via the creation of carbon−carbon and carbon−heteroatom bonds.[137] Our group has a special interest in gold-catalysed organic reactions and has reported previously highly efficient and stereoselective syntheses of 2,5-dihydrofurans by gold-catalysed cycloisomerisation of α-hydroxyallenes.[138] In addition, this protocol could be applied to cyclisation reactions of β-hydroxyallenes, α-/β-aminoallenes, as well as α-thioallenes to the corresponding 5- or 6-membered O-, N-, or S-heterocycles.[139] Furthermore, this method could be easily implemented to sustainable reaction conditions.

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[135] S. R. Landor, *The Chemistry of the Allenes: Reactions, Vol. 2*, Academic Pr, **1982**;
H. Schuster, G. Coppola, New York: Wiley, **1984**;
A. Hoffmann-Röder, N. Krause, *Angew. Chem., Int. Ed.,* **2004**, *43*, 1196-1216.

[136] A. Hoffmann-Röder, N. Krause, *Angew. Chem., Int. Ed.,* **2004**, *43*, 1196-1216.

[137] N. Krause, A. Hoffmann-Röder, J. Canisius, *Synthesis,* **2002**, *2002*, 1759-1774.

[138] A. Hoffmann-Röder, N. Krause, *Org. Lett.,* **2001**, *3*, 2537-2538.

[139] A. Hoffmann-Röder, N. Krause, *Org. Lett.,* **2001**, *3*, 2537-2538;
N. Bongers, N. Krause, *Angew. Chem., Int. Ed., Engl.,* **2008**, *47,12*, 2178-2181;
A. Hoffmann-Röder, N. Krause, *Org. Biomol. Chem.,* **2005**, *3*, 387-391;
B. Gockel, N. Krause, *Org. Lett.,* **2006**, *8*, 4485-4488;
N. Morita, N. Krause, *Org. Lett.,* **2004**, *6*, 4121-4123;
N. Morita, N. Krause, *Eur. J. Org. Chem.,* **2006**, *2006*, 4634-4641;
N. Morita, N. Krause, *Angew. Chem., Int. Ed.,* **2006**, *45*, 1897-1899.

Thus, it could be shown that cyclisation of allenes proceed straightforward, inter alia, in water[140], in micellar systems[141] and ionic liquids[142].

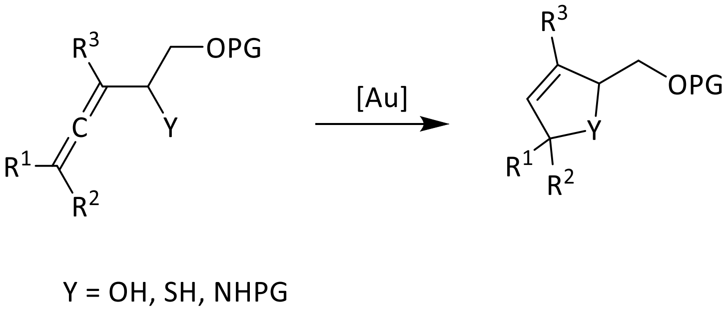

Figure 59 Cycloisomerisation of allenes to their corresponding five-membered rings

The advantage of these isomerisations is their mildness and high tolerance towards functional groups, which they have in common. Therefore, allowing the efficient formation of alkyl-, alkenyl- and aryl-substituted heterocycles at room temperature with complete axis-to-centre chirality transfer.[143] In addition, many of these five-membered rings are biologically active compounds and can be found in antibiotics or mycotoxins.[144]

It is noteworthy that these cycloisomerisations are not limited to gold catalyst but also, inter alia, silver[145], platin[146], palladium[147], ruthenium[148], rhodium[149] or acids[150] can be used.

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[140] K. Belger, N. Krause, *Eur. J. Org. Chem.,* **2015**, *2015*, 220-225;
K. Belger, N. Krause, *Org. Biomol. Chem.,* **2015**, *13*, 8556-8560;
C. Winter, N. Krause, *Green Chem.,* **2009**, *11*, 1309-1312.

[141] S. R. Minkler, N. A. Isley, D. J. Lippincott, N. Krause, B. H. Lipshutz, *Org. Lett.,* **2014**, *16*, 724-726; L. Lempke, A. Ernst, F. Kahl, R. Weberskirch, N. Krause, *Adv. Synth. Catal.,* **2016**, *358*, 1491-1499;
S. R. Minkler, B. H. Lipshutz, N. Krause, *Angew. Chem., Int. Ed.,* **2011**, *50*, 7820-7823.

[142] L. Lempke, T. Fischer, J. Bell, W. Kraus, K. Rurack, N. Krause, *Org. Biomol. Chem.,* **2015**, *13*, 3787-3791;
L. Lempke, H. Sak, M. Kubicki, N. Krause, *Org. Chem. Front.,* **2016**, *3*, 1514-1519;
Ö. Aksin, N. Krause, *Adv. Synth. Catal.,* **2008**, *350*, 1106-1112.

[143] N. Krause, *Nachr. Chem.,* **2012**, *60*, 118-121.

[144] T. L. Boivin, *Tetrahedron,* **1987**, *43*, 3309-3362;
U. Koert, M. Stein, H. Wagner, *Chem. - Eur. J.,* **1997**, *3*, 1170-1180;
M. Ganguli, L. T. Burka, T. M. Harris, *J. Org. Chem.,* **1984**, *49*, 3762-3766;
F. Perron, K. F. Albizati, *Chem. Rev.,* **1989**, *89*, 1617-1661;
A. R. Katritzky, C. W. Rees, E. F. Scriven, *Compr. Heterocycl. Chem. II,*, Pergamon, **1996**;
T. Eicher, S. Hauptmann, A. Speicher, *Structure,* **2003**, *15*, 1;
B. H. Lipshutz, *Chem. Rev.,* **1986**, *86*, 795-819.

[145] J. A. Marshall, C. A. Sehon, *J. Org. Chem.,* **1995**, *60*, 5966-5968.

[146] A. Fürstner, *Chem. Soc. Rev.,* **2009**, *38*, 3208-3221.

[147] S.-K. Kang, T.-G. Baik, A. N. Kulak, *Synlett,* **1999**, *1999*, 324-326;
S. Ma, W. Gao, *J. Org. Chem.,* **2002**, *67*, 6104-6112.

[148] Y. Yamamoto, *Chem. Rev.,* **2012**, *112*, 4736-4769.

[149] C. Aubert, O. Buisine, M. Malacria, *Chem. Rev.,* **2002**, *102*, 813-834.

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

A well-established method for the synthesis of functionalised allenes is the S_N2' reaction of propargylic derivates with organometallic reagents, especially organocuprates, which can be easily generated from their corresponding Grignard compounds and a copper(I) salt.

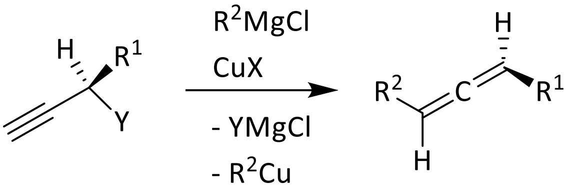

Figure 60

General reaction pattern of the S_N2' reaction to generate allenes

Figure 60 shows the general reaction pattern of this reaction, a readily used leaving group for Y are epoxides, which undergo a ring opening to generate the according hydroxyallene as shown in Figure 61.

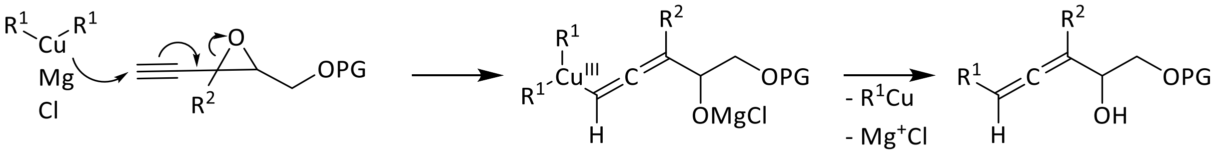

Figure 61 Generation of hydroxyallenes

The reaction yields in absence of any additives in a *syn*/*anti* mixture, this can be prevented by the addition of additives like dimethyl sulphide, alkyl phosphines or alkyl phosphites.[151]

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[151] N. Krause, A. Hoffmann-Röder, *Tetrahedron,* **2004**, *51*, 11671-11694.

3.2. Deep Eutectic Solvents (DESs)

Even though remarkable developments in the field of ionic liquids have been reported in recent years, they often suffer from their toxicity and poor biodegradability.[152] In an effort to fulfil the sustainability criteria imposed by the Twelve Principles of Green Chemistry, a new class of green and biorenewable solvents is desired.[153]

As a promising candidate *Abbott* and co-workers first reported in 2003 that the biomass-derived choline chloride and urea can generate an eutectic liquid, due to strong hydrogen bonds, which have then a lower melting point than their individual constituents.[154] Although eutectic mixtures have been known for decades, these were the first hints that DES could be used as an alternative for ionic liquids.[155]

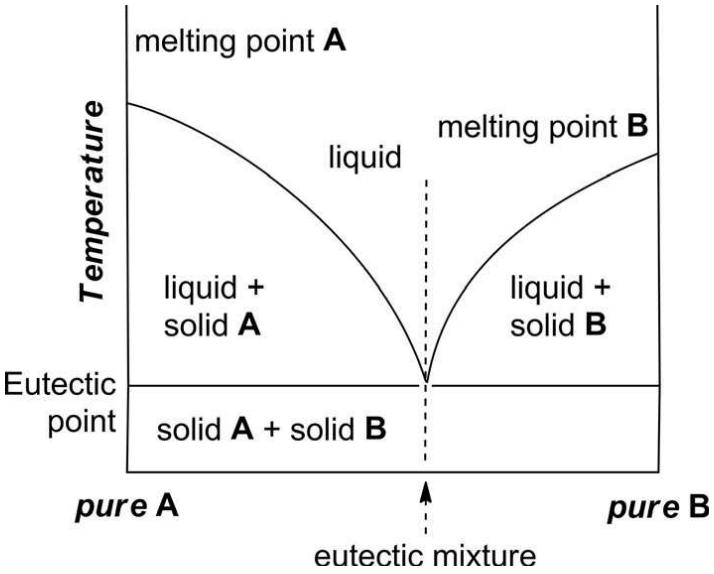

Figure 62 Typical phase diagram of DES[156]

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[152] D. Coleman, N. Gathergood, *Chem. Soc. Rev.,* **2010**, *39*, 600-637;
A. Romero, A. Santos, J. Tojo, A. Rodríguez, *J. Hazard. Mater.,* **2008**, *151*, 268-273;
D. Zhao, Y. Liao, Z. Zhang, *CLEAN – Soil, Air, Water,* **2007**, *35*, 42-48.

[153] J. C. W. P. T. Anastas, *Green Chemistry. Theory and Practice*, Oxford University Press, **1998**.

[154] A. P. Abbott, G. Capper, D. L. Davies, R. K. Rasheed, V. Tambyrajah, *Chem. Commun.,* **2003**, 70-71.

[155] I. Gill, E. Vulfson, *Trends Biotechnol.,* **1994**, *12*, 118-122;
R. Davey, J. Garside, A. Hilton, D. McEwan, J. Morrison, *Nature,* **1995**, *375*, 664;
H. Laitinen, W. Ferguson, R. Osteryoung, *J. Electrochem. Soc.,* **1957**, *104*, 516-520.

[156] Figure from D. A. Alonso, A. Baeza, R. Chinchilla, G. Guillena, I. M. Pastor, D. J. Ramón, *Eur. J. Org. Chem.,* **2016**, *2016*, 612-632.

Figure 62 shows a typical phase diagram of a DES, where **A** (hydrogen bond acceptor (HBA)) and **B** (Hydrogen bond donor (HBD)) are two (or even more) phase-immiscible usually solid components, which can undergo a change of state of aggregation to liquid at the corresponding mixing ratio and temperature, which is usually under 100 °C.[157] The effect is based on the interference with the ability of the initial compounds to crystallise by hydrogen bonds or even van der Waals forces.

Therefore, halide salts can form DESs due to their charge shielding in proximity to a certain HBD.[158] As consequence, the association lowers the entropic difference of the phase transition.[159] The decrease of the freezing point follows a general trend, in fact the freezing point decreases by the hydrogen bonding ability of the HBD and the anion of the salt. As a result, a decrease is observed with a large volume (or buried charge) and asymmetric charge distribution.[160]

DESs can be adjusted to its respective purpose, since the starting materials offer countless combination possibilities[161], e.g. betaine cations, saccharinates, lactates, glycerol, natural carboxylic acids, organic acids or even metal chlorides[162].

One of the most used mixture contains urea as HBA and choline chloride as HBD, because they are both cheap and play an important role in nature and are therefore considered as “edible” constituents for DESs.[163] These and other comparable mixture represent a sub class of DES “natural Deep Eutectic Solvents” (NADESs).

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[157] D. A. Alonso, A. Baeza, R. Chinchilla, G. Guillena, I. M. Pastor, D. J. Ramón, *Eur. J. Org. Chem.,* **2016**, 612-632.

[158] M. Francisco, A. van den Bruinhorst, M. C. Kroon, *Angew. Chem., Int. Ed.,* **2013**, *52*, 3074-3085.

[159] R. C. Harris, *Physical Properties of Alcohol Based Deep Eutectic Solvents,* University of Leicester, **2009**.

[160] M. Francisco, A. van den Bruinhorst, M. C. Kroon, *Angew. Chem., Int. Ed.,* **2013**, *52*, 3074-3085;
C. Ruß, *Conversion of carbohydrates in low melting mixtures and Melanoma Inhibitory Activity (MIA) protein inhibitors for the treatment of malignant melanoma*, Universität Regensburg, **2013**.

[161] M. Francisco, A. van den Bruinhorst, M. C. Kroon, *Angew. Chem., Int. Ed.,* **2013**, *52*, 3074-3085;
C. Ruß, B. König, *Green Chem.,* **2012**, *14*, 2969-2982;
A. P. Abbott, R. C. Harris, K. S. Ryder, C. D'Agostino, L. F. Gladden, M. D. Mantle, *Green Chem.,* **2011**, *13*, 82-90;
A. Paiva, R. Craveiro, I. Aroso, M. Martins, R. L. Reis, A. R. C. Duarte, *ACS Sustainable Chem. Eng.,* **2014**, *2*, 1063-1071.

[162] A. P. Abbott, J. C. Barron, K. S. Ryder, D. Wilson, *Chem. - Eur. J.,* **2007**, *13*, 6495-6501.

[163] A. A. Yates, S. A. Schlicker, C. W. Suitor, *J. Am. Diet. Assoc.,* **1998**, *98*, 699-706;
Y. Fukaya, Y. Iizuka, K. Sekikawa, H. Ohno, *Green Chem.,* **2007**, *9*, 1155-1157.

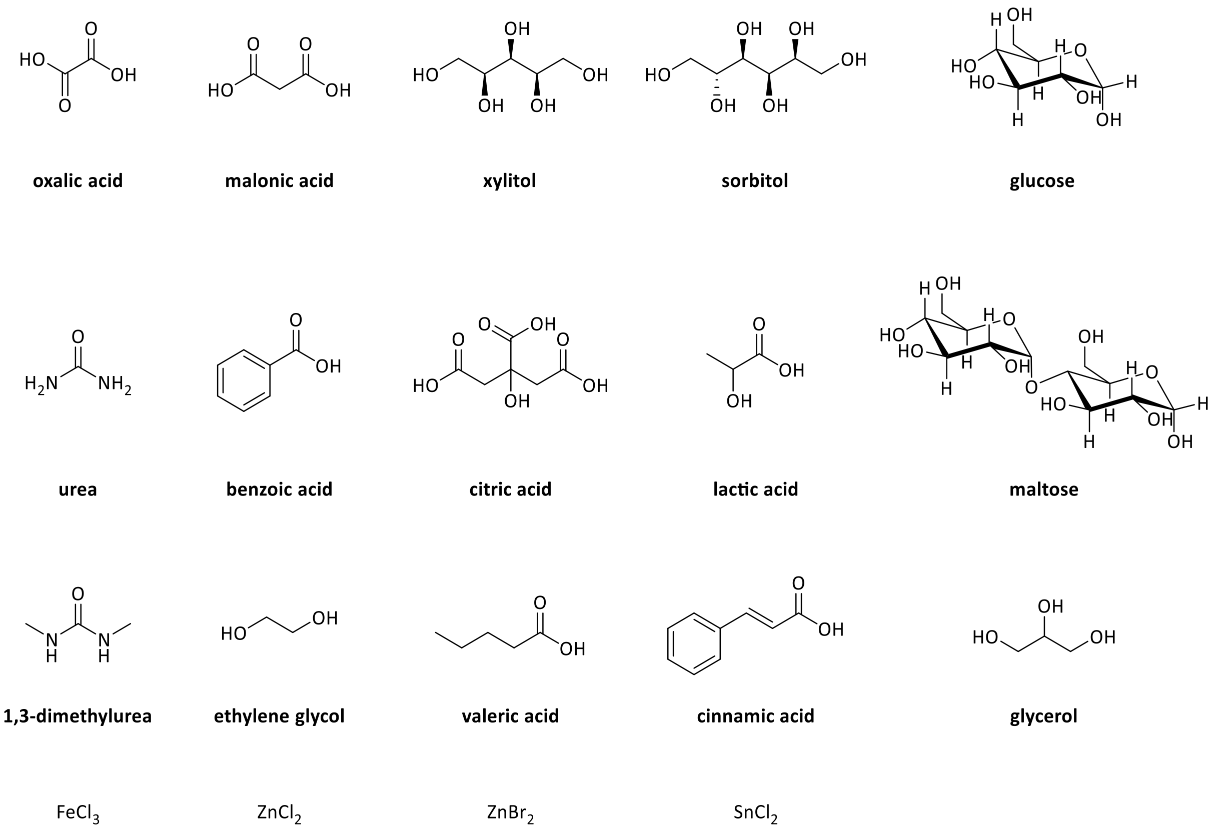

Figure 63 Selected HBDs for the formation of DES

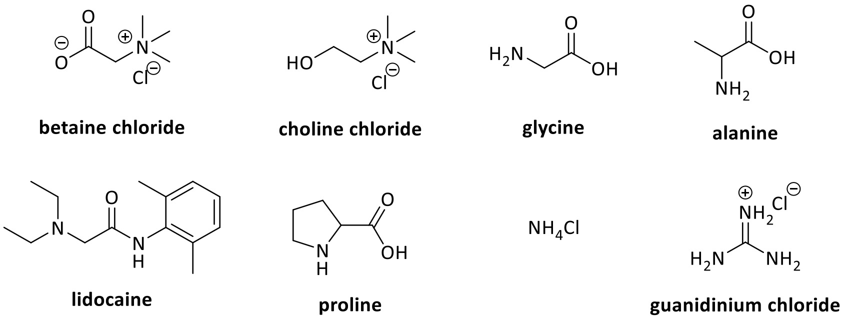

Figure 64 Selected HBAs for the formation of DES

Figure 63 and Figure 64 show selected compounds for the generation of DESs, as can be seen most of them are natural products. Metal salts bear a special interesting feature, they form a Lewis acidic DES, which allows them to be not only the solvent but also the catalyst for the reaction.

However, they lack biodegradability and environmental friendliness even though most DES not only benefit from biorenewability and biodegradability but are also cheap, because they can be straightforwardly prepared from commercially available and renewable raw materials without a purification step.[164]

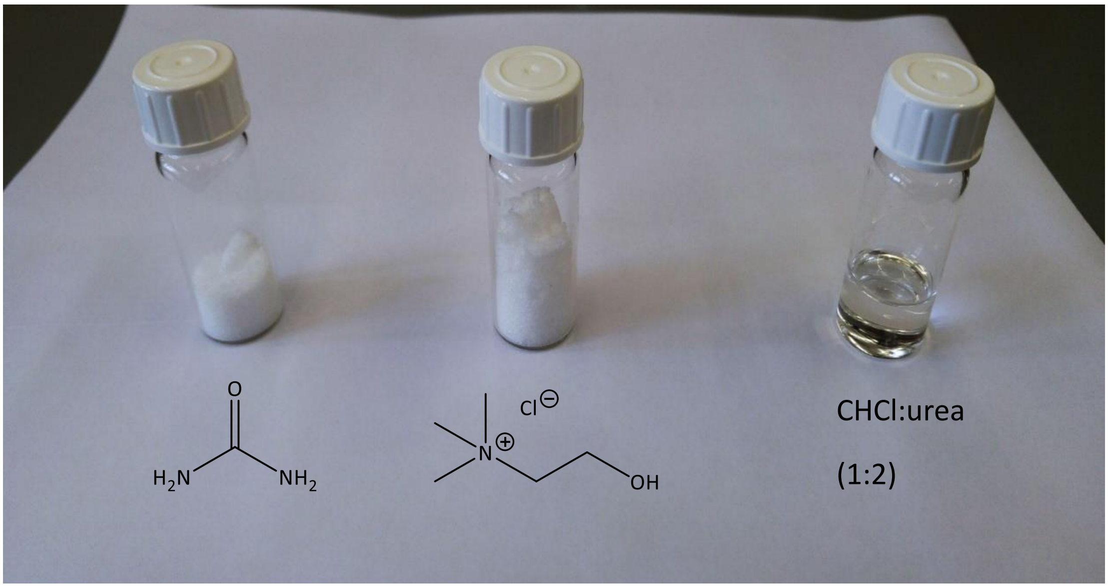

Figure 65 Eutectic mixture of CHCl:urea at room temperature

Although they have been labelled as “the organic reaction medium of the century” in a recent review,[165] they suffer from limited chemical inertness and their high viscosities, which could be a disadvantage for industrial processes.[166] However, a positive impact with regards to the viscosity could be achieved due to the addition of new different components like water or inorganic/organic halides.[167]

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[164] C. K. Z. Andrade, A. R. Dar, *Tetrahedron,* **2016**, *72*, 7375-7391;
M. Petkovic, J. L. Ferguson, H. Q. N. Gunaratne, R. Ferreira, M. C. Leitao, K. R. Seddon, L. P. N. Rebelo, C. S. Pereira, *Green Chem.,* **2010**, *12*, 643-649.

[165] D. A. Alonso, A. Baeza, R. Chinchilla, G. Guillena, I. M. Pastor, D. J. Ramón, *Eur. J. Org. Chem.,* **2016**, *2016*, 612-632.

[166] C. Ruß, B. König, *Green Chem.,* **2012**, *14*, 2969-2982;
A. Yadav, S. Pandey, *J. Chem. Eng. Data,* **2014**, *59*, 2221-2229.

[167] Y. Dai, G.-J. Witkamp, R. Verpoorte, Y. H. Choi, *Food Chem.,* **2015**, *187*, 14-19.

Table 17 shows melting points of selected DESs, but it is noteworthy that some of the DESs are not stirrable at the indicated temperatures although they are melted due to their high viscosity.

Table 17 Melting points of selected DES

DES	**Proportion [mol:mol]**	**Melting point [°C]**
CHCl:glycerol	1:2	-40
CHCl:urea	1:2	12
CHCl:oxalic acid	1:1	34
CHCl:lactic acid	1:2	-20
CHCl:sorbitol	1:1	20
CHCl:dimethylurea	1:2	70
CHCl:D-fructose	1:2	5
urea:$ZnCl_2$	7:2	9
betaineHCl:urea	15:85	27
urea:guanidinium HCl	6:4	60
CHCl:malonic acid	1:1	10

DESs offer manifold implementation possibilities including, among others, in biotechnology, in polymerisation, in extraction and separation processes, in nanotechnology, in biomass valorisation, carbon dioxide capture and particularly (metal-)organic catalysis.[168]

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[168] D. A. Alonso, A. Baeza, R. Chinchilla, G. Guillena, I. M. Pastor, D. J. Ramón, *Eur. J. Org. Chem.,* **2016**, 612-632;
K. Radošević, N. Ćurko, V. Gaurina Srček, M. Cvjetko Bubalo, M. Tomašević, K. Kovačević Ganić, I. Radojčić Redovniković, *LWT--Food Sci. Technol.,* **2016**, *73*, 45-51;
D. Z. Troter, Z. B. Todorović, D. R. Đokić-Stojanović, O. S. Stamenković, V. B. Veljković, *Renewable Sustainable Energy Rev.,* **2016**, *61*, 473-500;
Y. Gu, F. Jerome, *Chem. Soc. Rev.,* **2013**, *42*, 9550-9570.

3.3. Objectives to achieve in this project

The scope of organic reactions, which could be achieved in this green solvent DES are enormous and range from bromination,[169] Perkin reaction,[170] Knoevenagel condensation,[171] reduction,[172] Biginelli reaction[173] and epoxide hydrolysis[174] to metal catalysed reactions like Diels-Alder[175], Suzuki coupling[176], Heck reaction[177], Sonogashira reaction[177], CuAAC[177] and hydrogenation.[176] Despite these remarkable achievements there are only sparsely reports of gold-catalysed reactions in DES. *García-Álvarez* was able to demonstrate gold-catalysed cycloaromatisations of γ-alkynyl acids and amides to their corresponding five-membered rings using iminophosphorane-Au(I) complexes in a mixture of choline chloride and urea.[178] The same group also recently reported gold(I)-catalysed cycloisomerisations of (Z)-enynols to furan derivatives in the eutectic mixture choline chloride:glycerol as well as one-pot tandem cycloisomerisation/Diels–Alder reactions of these enynols and an electron-deficient alkyne as dienophile.[179] However, as far as it is known no cycloisomerisation of allenic compounds were reported in DESs. Therefore, it was intended to utilise the advantages of DESs for this atom economical reaction.

The major part of this project is hence focused on the cycloisomerisation of the well-known and highly functionalised α-hydroxyallenes to their corresponding dihydrofurans as can be seen in Figure 66.

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[169] S. B. Phadtare, G. S. Shankarling, *Green Chem.,* **2010**, *12*, 458-462.

[170] P. M. Pawar, K. J. Jarag, G. S. Shankarling, *Green Chem.,* **2011**, *13*, 2130-2134.

[171] H. N. Harishkumar, K. M. Mahadevan, H. C. K. Kumar, N. D. Satyanarayan, *Org. Commun.,* **2011**, *4*, 26.

[172] N. Azizi, E. Batebi, S. Bagherpour, H. Ghafuri, *RSC Adv.,* **2012**, *2*, 2289-2293.

[173] S. Gore, S. Baskaran, B. Koenig, *Green Chem.,* **2011**, *13*, 1009-1013.

[174] J. T. Gorke, F. Srienc, R. J. Kazlauskas, *Chem. Commun.,* **2008**, 1235-1237.

[175] G. Imperato, E. Eibler, J. Niedermaier, B. König, *Chem. Commun.,* **2005**, 1170-1172;
F. Ilgen, B. König, *Green Chem.,* **2009**, *11*, 848-854.

[176] G. Imperato, S. Höger, D. Lenoir, B. Koenig, *Green Chem.,* **2006**, *8*, 1051-1055.

[177] F. Ilgen, B. König, *Green Chem.,* **2009**, *11*, 848-854.

[178] M. J. Rodríguez-Álvarez, C. Vidal, J. Díez, J. García-Álvarez, *Chem. Commun.,* **2014**, *50*, 12927-12929;
M. J. Rodríguez-Álvarez, C. Vidal, S. Schumacher, J. Borge, J. García-Álvarez, *Chem. - Eur. J.,* **2017**, *23*, 3425-3431.

[179] C. Vidal, L. Merz, J. García-Álvarez, *Green Chem.,* **2015**, *17*, 3870-3878.

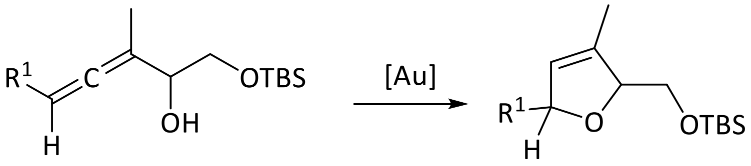

Figure 66 Cycloisomerisation of α-hydroxyallenes

In addition to the above-mentioned gold catalysts and DES, other metal catalysts and solvents, which fulfil the requirements of sustainability should be tested in this project. Another aim was to ensure the recyclability of the catalyst/solvent system and to test the catalysts obtained from chapter 2.3.2.

3.4. Results and discussion

3.4.1. Synthesis of the used allenes

The most used α-hydroxyallenes could be easily synthesised in a well-known three step synthesis introduced by *Krause*[180] starting from (E)-2-en-4-ynol **3.1**, which was epoxidised in the first step (Figure 67).

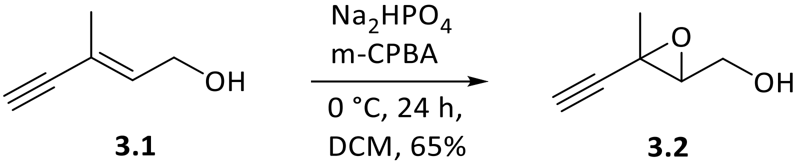

Figure 67 Epoxidation of alkene **3.1**

The epoxidation could be achieved in a moderate yield of 65%. However, the epoxide was pure enough to use it in the next step without purification by column chromatography. The alcohol group had to be protected for the following organometallic reaction, in doing so a TBS-protection was the method of choice as shown in Figure 68.

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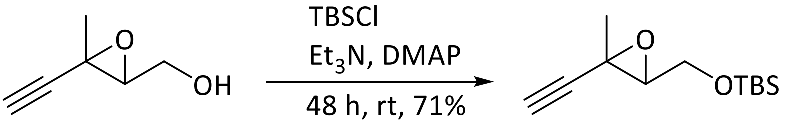
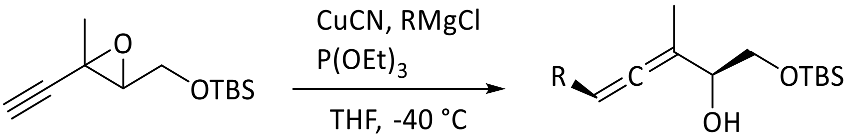
[180] N. Krause, A. Hoffmann-Röder, J. Canisius, *Synthesis,* **2002**, *2002*, 1759-1774;
N. Krause, A. Hoffmann-Röder, *Tetrahedron,* **2004**, *51*, 11671-11694;
F. Volz, N. Krause, *Org. Biomol. Chem.,* **2007**, *5*, 1519-1521;
C. Deutsch, A. Hoffmann-Röder, A. Domke, N. Krause, *Synlett,* **2007**, *2007*, 0737-0740.



3.2 **3.3**

Figure 68 TBS-protection of epoxide **3.2**

The protection proceeded satisfactorily with 71% yield after purification by column chromatography and the product could be characterised by ^{1}H- and ^{13}C-NMR-spectroscopy. The protected epoxide **3.3** was finally used in a S_N2'-reaction with organocuprates to generate the desired allenes as can be seen in Figure 69.



3.3

3.4a (R = *t*Bu) 79%
3.4b (R = Ph) 85%
3.4c (R = *i*Pr) 89%

Figure 69 S_N2'-reaction with organocuprates to generate allenes **3.4a-c**

In doing so, the organocuprate was prepared *in situ* initially by the reaction of one equivalent copper(I) cyanide and two equivalents of the respective commercially available Grignard compound at low temperatures, followed by the addition of the epoxide **3.3**, which then reacts in the mentioned S_N2'-type manner. Triethylphosphite to prevent a copper induced epimerisation.

These reactions gave good yields ranging from 79% to 89% after purification by flash column chromatography. Other used allenes originated from holdings of the Krause group, which were also synthesised by using this method.

Furthermore, it was envisaged to use not only α-hydroxyallenes but also β-hydroxyallenes, which can be synthesised in a two-step synthesis using a Johnson-Claisen-rearrangement.[181]

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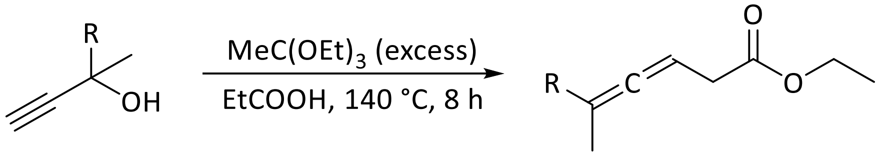
[181] B. Gockel, N. Krause, *Org. Lett.,* **2006**, *8*, 4485-4488;
G. F. Cooper, D. L. Wren, D. Y. Jackson, C. C. Beard, E. Galeazzi, A. R. Van Horn, T. T. Li, *J. Org. Chem.,* **1993**, *58*, 4280-4286;
J. A. Marshall, X. J. Wang, *J. Org. Chem.,* **1992**, *57*, 1242-1252;
M. A. Henderson, C. H. Heathcock, *J. Org. Chem.,* **1988**, *53*, 4736-4745;
R. A. Brawn, J. S. Panek, *Org. Lett.,* **2007**, *9*, 2689-2692.

The commercially available propargyl alcohols were heated with triethylorthoformiate in the presence of an acid to generate the respective allenic ester, as indicated in Figure 70.



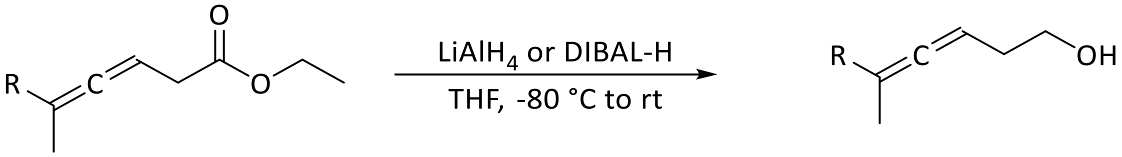
3.5a (R = Me)
3.5b (R = CH_2*i*Pr)

3.6a (R = Me) 75%
3.6b (R = CH_2*i*Pr) 82%

Figure 70 Johnson-Claisen-rearrangement

The reaction was performed in a way that the emerging ethanol would be separated to prevent the reverse reaction, in doing so good yields could be achieved: 75% for the methyl substituent and 82% for the isobutyl substituent.

In a next step, the ester had to be reduced in order to generate an alcohol group, which is required later as nucleophilic species for the planned cycloisomerisation.



3.6a (R = Me)
3.6b (R = CH_2*i*Pr)

3.7a (R = Me) 99%
3.7b (R = CH_2*i*Pr) 65%

Figure 71 Reduction of the allenic esters **3.6a** and **3.6b**

Therefore, the established DIBAL-H or $LiAlH_4$ were used for this reduction, however $LiAlH_4$ proved inferior, since it could achieve a yield of 87%. The reduction by DIBAL-H proceeded in excellent yields up to 99%, a further purification was not required, and the products were identified by NMR-spectroscopy. Table 18 indicates the outcome of the reductions.

Table 18 Outcome of the reductions

Entry	**R**	**Reducing agent**	**Yield**
1	Me	$LiAlH_4$	87%
2	Me	DIBAL-H	99%
3	CH_2*i*Pr	$LiAlH_4$	65%

In addition, β-aminoallenes were planned to be synthesised from the obtained β-hydroxyallene **3.7a**. Therefore, this allene was used in a Mitsunobu-reaction[182] with phthalimide, triphenylphosphine and DIAD resulting in a moderate yield of 66% after flash column chromatography (Figure 72). It is noteworthy that DEAD was used in the initial procedure, which however was substituted by DIAD because of the lower explosion hazard, this could be responsible for the lower yield.

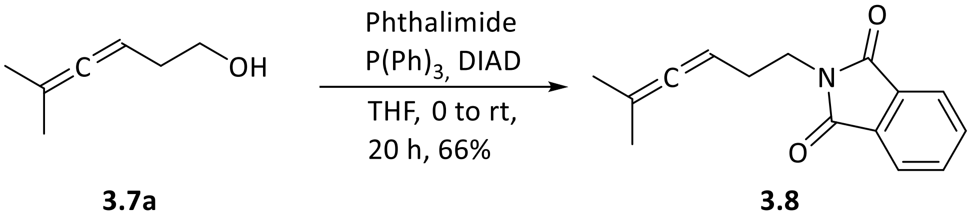


Figure 72 Mitsunobu- reaction of β-hydroxyallene **3.7a**

3.8 was then hydrolysed to the desired aminoallene **3.9** by hydrazine hydrate in ethanol at 78 °C in two hours, **3.9** could be obtained in 70% without further purification in this process (Figure 73).

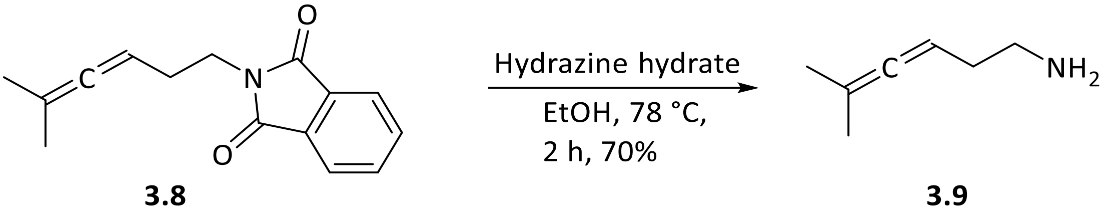


Figure 73 Reduction to the β-aminoallene **3.9**

It is known that the relatively strong Lewis basicity of amines could interfere with gold catalysts[183], therefore in an effort to reduce the basicity a monoprotected β-aminoallene was desired. In doing so, **3.9** was treated with TsCl in the presence of a base with DCM as solvent (Figure 74).

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[182] S. Ma, F. Yu, W. Gao, *J. Org. Chem.,* **2003**, *68*, 5943-5949.

[183] B. Gockel, N. Krause, *Org. Lett.,* **2006**, *8*, 4485-4488;
N. Morita, N. Krause, *Org. Lett.,* **2004**, *6*, 4121-4123;
N. Krause, C. Winter, *Chem. Rev.,* **2011**, *111*, 1994-2009;
R.-X. Zhu, D.-J. Zhang, J.-X. Guo, J.-L. Mu, C.-G. Duan, C.-B. Liu, *J. Phys. Chem. A,* **2010**, *114*, 4689-4696.

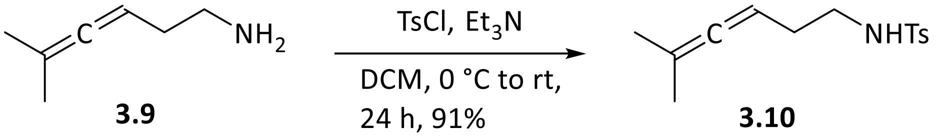


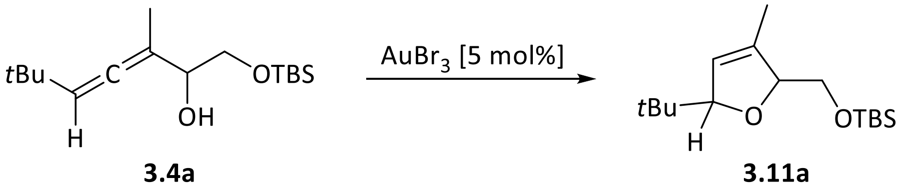
Figure 74 Tosylation of allene **3.9**

The tosylation could be achieved in a very good yield of 91% without the need of a further purification and the product was identified by NMR-spectroscopy.

3.4.2. Cycloisomerisations in green reaction medias

At the outset of this study, the cyclisation of a α-hydroxyallene to the corresponding 2,5-dihydrofuran in two widely used deep eutectic mixtures was investigated, with a common gold catalyst, AuBr$_3$ (5 mol%) at chosen temperatures.

Table 19 Outcome with CHCl:urea (1:2) and CHCl:glycerol(1:2)



Entry	Solvent	Temp.	Time	Yield*
1	CHCl:urea (1:2)	rt	20 h	9%
2	CHCl:glycerol (1:2)	rt	20 h	44%
3	CHCl:urea (1:2)	50 °C	3 h	3%
4	CHCl:glycerol (1:2)	50 °C	3 h	56%
5	CHCl:urea (1:2)	80 °C	3 h	4%
6	CHCl:glycerol (1:2)	80 °C	3 h	30%
7	CHCl:urea (1:2)	80 °C	24 h	24%
8	CHCl:glycerol (1:2)	80 °C	24 h	49%

* Determined by GC with internal standard

Since the two DES choline chloride:urea and choline chloride:glycerol that were used are liquid at room temperature and thus easy to handle, they were used for the first efforts.

Unfortunately, only low yields could be achieved at room temperature (Table 19, entries 1 and 2) and even a warming to 50 °C (Table 19, entries 3 and 4) or 80 °C (Table 19, entries 5 and 6) was not able to increase the yields significantly. In the case of CHCl:urea the yields stayed lower than 10% and in the case of CHCl:glycerol the highest yield of 56% could be obtained at 50 °C but decreased again at 80°C. Even an elongation up to 24 h did not increase the yield particularly (Table 19, entries 7 and 8). It is conceivable that the relatively high Lewis-basicity of urea could inhibit the gold catalyst.

Therefore, a broader range of deep eutectic mixtures, which cannot be stirred at room temperature, was tested as can be seen in Table 20.

Table 20 Additional tested DESs

Entry	**Solvent**	**Temp.**	**Time**	**Yield***
1	CHCl:oxalic acid (1:1)	80 °C	3 h	11% (decompostion)
2	urea:guanidin-HCl (3:2)	80 °C	3 h	6%
3	CHCl:DMU (1:2)	80 °C	3 h	62%
4	CHCl:malonic acid (1:1)	80 °C	3 h	59%
5	CHCl:sorbitol (1:1)	80 °C	3 h	94% (92%)**
6	betaineHCl:urea (15:85)	80 °C	3 h	92% (89%)**

* Determined by GC with internal standard, ** Isolated yield

The first tested alternative CHCl:oxalic acid led to a decomposition, presumably since it is a relatively acidic DESs (Table 20, entry 1). However, the reactions in CHCl:DMU showed moderate yield comparable with CHCl:glycerol as well as the mixture of CHCl:malonic acid and the more basic urea:guanidin-HCl exhibited only low yields (Table 20, entries 2-4).

Fortunately, treatment of **3.4a** in a sugar alcohol system, CHCl:sorbitol and a system with betaine as different hydrogen-bond acceptor betaineHCl:urea delivered the desired 2,5-dihydrofuran **3.11a** after three hours reaction time at 80°C in very high yields (93-94%) (Table 20, entries 5 and 6). It is worth noting that this gold-catalysed cycloisomerisation demonstrated an excellent chemoselectivity, as no by-products in these two eutectic mixtures could be detected. Therefore, betaineHCl:urea was determined as DESs of choice for further reactions in DES due to its lower viscosity compared to CHCl:sorbitol.

Furthermore, other green solvents should be examined, therefore two polymers were tested. Polyethylene glycol (PEG) (~200 g/mol) and polypropylene glycol (PPG) (~3500 g/mol) which are liquid at room temperature as well as propylene carbonate (PC) a cyclic carbonate ester. The outcome is indicated in Table 21.

Table 21 Cycloisomerisation in polymers and carbonate ester

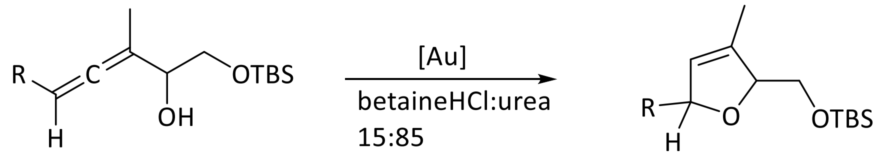
Entry	**Solvent**	**Temp.**	**Time**	**Yield***
1	PPG (~3500 g/mol)	rt	45 min	87%
2	PPG (~3500 g/mol)	rt	10 min	91%
3	propylen carbonate	rt	45 min	21%
4	PEG (~200 g/mol)	rt	45 min	9%
5	PEG (~200 g/mol)	50 °C	45 min	10%

* Determined by GC with internal standard

Delightfully, high yields at room temperature in PPG after 30 min could be obtained (Table 21 entry 1) and even with 10 min reaction time a remarkable yield of 91% could be achieved (Table 21 entry 2). However, it turned out that the major challenge was to remove the solvent afterwards, since it is miscible with nearly every organic solvent. Therefore, the yields could only be determined by GC with internal standard. It is thinkable that the product could be separated by distillation but was not deepened any further. Whereas the other two investigated solvents PEG 200 and propylene carbonate (Table 21 entries 3 and 4) showed only low yields, even after an increase of temperature to 50 °C (Table 21 entry 5).

Inspired by these initial achievements, which indicated the potential of the chosen green and biorenewable solvents for the cycloisomerisation under standard bench experimental techniques, the implication of different gold-catalyst was then examined in the mentioned betaineHCL:urea mixture.

Table 22 Cycloisomerisation catalysed by different gold species (5 mol%)

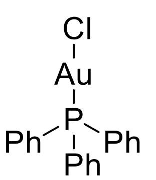


3.4a-b **3.11a-b**

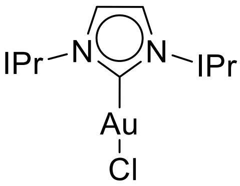
Entry	R =	[Au]	Temp.	Time	Yield*
1	Ph **3.4b**	$AuCl_3$	65 °C	3 h	44%
2	Ph **3.4b**	$HAuCl_4$	65 °C	3 h	51%
3	Ph **3.4b**	$AuBr_3$	65 °C	3 h	56%
4	Ph **3.4b**	$AuBr_3$	80 °C	3 h	93%
5	Ph **3.4b**	**C**	65 °C	3 h	60%
6	Ph **3.4b**	**A****	65 °C	3 h	5%
7	*t*Bu **3.4a**	**B****	80 °C	3 h	1%
8***	*t*Bu **3.4a**	**B****	80 °C	3 h	19%
9	*t*Bu **3.4a**	**C**	80 °C	3 h	19%
10	*t*Bu **3.4a**	$HAuCl_4$	80 °C	3 h	18%
11	*t*Bu **3.4a**	$NaAuCl_4$	80 °C	3 h	23%
12	*t*Bu **3.4a**	AuCl	80 °C	3 h	89% (82%)****

* Determined by GC with internal standard, ** Addition of 5 mol% AgOTf, *** Addition of 10 wt. % methanol, **** Isolated yield

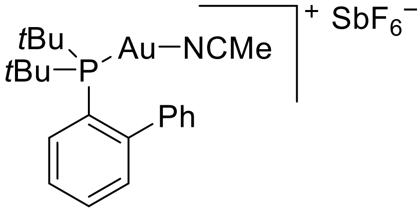
Among the gold(I) and gold(III) catalysts tested, none of them showed a complete conversion to **3.11** under the applied milder conditions (Table 22, entries 1-6). Nonetheless, the impact of the different gold-catalysts could be observed.



A
Triphenylphosphine gold(I) chloride



B
IprAuCl



C
JohnPhos Au(MeCN)SbF$_6$

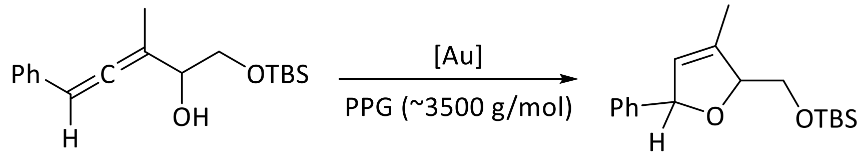
Figure 75 Commercially available gold complexes used in these reactions

Interestingly, the comparatively cheap $AuBr_3$ showed the highest activities with 56% in comparison to the other inorganic gold-catalysts (Table 22, entries 1-3). It is noteworthy that a high yield for the conversion of **3.4b** by using the previous conditions (Table 22, entry 4) could be achieved. Furthermore, two organic gold-complexes were investigated: Whereas the relatively expensive **C** showed a comparatively promising result (Table 22, entry 5), only low yields could be observed for **A** (Table 22, entry 6) even with the addition of AgOTf, which ordinarily gives rise to generation of the active gold-cation. Much the same can be said about the use of the **B** catalyst, which led to no conversion (Table 22, entry 7). Presumably, the active cationic gold species could not be generated in the used DES, even though a silver salt with a non-coordinating anion was added. This finding is supported due to the finding that the addition of 10 wt% methanol showed a better outcome (Table 22, entry 8) likely by a better generation of the gold cation. This also explains the better outcome of the **C** catalyst; hence no addition of a silver salt is required. However, it is also conceivable that the better outcome is caused by a faster protodeauration step by the addition of methanol.

Nonetheless, by using the hotter previous conditions with allene **3.4a**, only 19% could be achieved (Table 22, entry 9), which gives rise to assumption that gold(I) catalysts do not seem to be suitable in this solvent system. Anyhow, chloroauric acid and its sodium salt showed only low yields for the isomerisation (Table 22, entries 10 and 11). Furthermore, gold(I)chloride showed very good yield comparable to $AuBr_3$ (Table 22, entry 12).

In spite of the challenging product separation in PPG, different gold catalyst were tested to examine the difference between gold(I) and gold(III) catalysts (Table 23).

Table 23 Different gold catalysts (5 mol%) in PPG

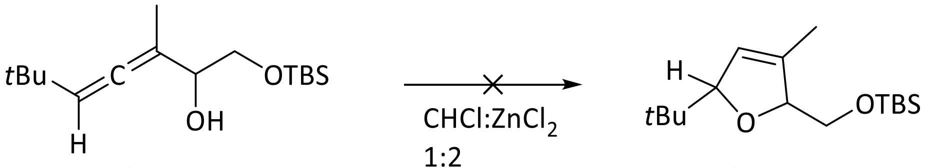


3.4b **3.11b**

Entry	[Au]	Temp.	Time	Yield*
1	$HAuCl_4$	rt	0.5 h	99%
2	**A****	rt	0.5 h	99%
3	$AuBr_3$	rt	0.5 h	99%
4	$AuCl_3$	rt	0.5 h	99%
5	**C**	rt	0.5 h	40%

* Determined by GC with internal standard, ** Addition of 5 mol% AgOTf

Based on the promising experience of the previous experiments with PPG, room temperature was used again, and the reaction time was shortened to half an hour. Even though the solvent system seemed to be so suitable that nearly all accomplished a quantitative yield determined by GC with internal standard (Table 23, entries 1-4). Only the **C** catalyst could only achieve 40% yield (Table 23, entries 5). These findings and empirical values of the *Krause* group[184] suggest that the poor performance of gold(I) catalysts are limited to the used DES system. Furthermore, the Lewis acidic mixture urea:$ZnCl_2$ were tested without a gold catalyst, since the system itself act as solvent and catalyst. Unfortunately, no conversion could be detected (Figure 76).



3.4a **3.11a**

Figure 76 Cycloisomerisation in urea:$ZnCl_2$

Having identified $AuBr_3$ as a suitable catalyst for the cycloisomerisation in DESs the possible substrate scope was next examined (Table 24).

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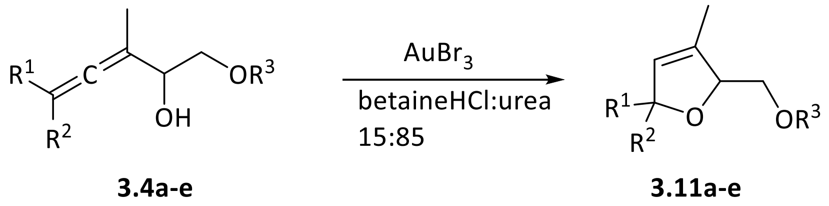
[184] N. Krause, C. Winter, *Chem. Rev.*, **2011**, *111*, 1994-2009.

Table 24 Substrate scope of the solvent/catalyst system



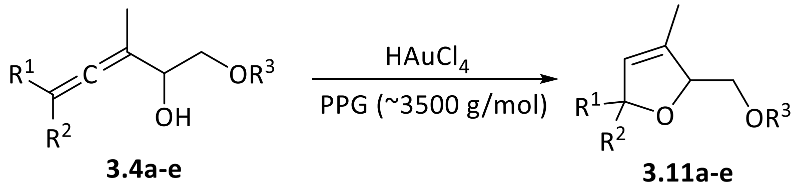
Entry	Allene	R^1 =	R^2 =	R^3 =	Temp.	Time	Product	Yield
1	**3.4b**	Ph	H	TBS	80 °C	3 h	**3.11b**	93%
2	**3.4c**	*i*Pr	H	TBS	80 °C	3 h	**3.11c**	84%
3	**3.4a**	*t*Bu	H	TBS	80 °C	3 h	**3.11a**	92%
4	**3.4d***	*t*Bu	H	Bn	80 °C	3 h	**3.11d**	70%
5	**3.4e***	Me	Me	Me	80 °C	3 h	**3.11e**	81%

*Originated from a former project in the group

Noteworthy, a nearly complete conversion of the used allenes were achieved in most cases and overall good yields could be achieved (Table 24, entries 1-3), which demonstrated the strong potential of these green solvent systems. Only if the protecting group was changed to a benzyl or methyl group the yield decreased slightly (Table 24, entries 4 and 5).

Furthermore, these allenes were also tested in PPG with $HAuCl_4$, which is slightly cheaper than $AuBr_3$ (Table 25).

Table 25 Substrate scope in PPG



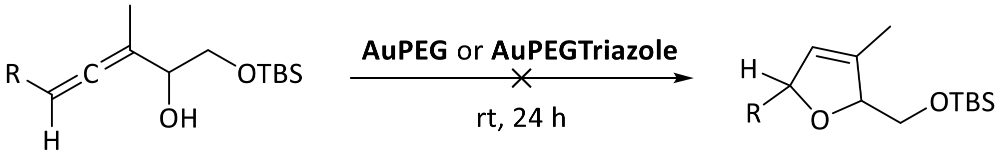
Entry	Allene	R^1 =	R^2 =	R^3 =	Temp.	Time	Product	Yield*
1	**3.4b**	Ph	H	TBS	rt	0.5 h	**3.11b**	98%
2	**3.4c**	*i*Pr	H	TBS	rt	0.5 h	**3.11c**	99%
3	**3.4a**	*t*Bu	H	TBS	rt	0.5 h	**3.11a**	97%
4	**3.4d****	*t*Bu	H	Bn	rt	0.5 h	**3.11d**	95%
5	**3.4e****	Me	Me	Me	rt	0.5 h	**3.11e**	96%

* Determined by GC with internal standard, **Originated from a former project in the group

Once more the PPG systems showed it considerable potential, since full conversion and quantitative yields could be obtained (Table 25, entries 1-5). Nonetheless, the challenging separation is still an overriding issue, which must be solved for the application of this system.

In addition to this, the created NHC-gold catalyst **AuPEG** and **AuPEGTriazole** (see chapter 2.3.2) were tested in these cyclisations (Table 26). Initially, water was used as solvent since the complexes **AuPEG** and **AuPEGTriazole** were envisaged and created as water soluble catalysts. Unfortunately, no conversion could be detected using both catalysts with allene **3.4a** in water without or with the addition of AgOTf as silver salt with a non-coordinating anion. The change to an allene with a phenyl rest **3.4b** as well as the change to methanol did not improve the outcome of this test reaction.

Table 26 Cycloisomerisation catalysed by AuPEG and AuPEGtriazole



3.4a-b **3.11a-b**

Entry	R =	Catalyst	Solvent	Addition of AgOTf	Yield
1	*t*Bu **3.4a**	**AuPEG** (5 mol%)	Water	-	No conversion
2	*t*Bu **3.4a**	**AuPEGTriazole** (5 mol%)	Water	-	No conversion
3	Ph **3.4b**	**AuPEG** (5 mol%)	Water	5 mol %	No conversion
4	Ph **3.4b**	**AuPEGTriazole** (5 mol%)	Water	5 mol %	No conversion
5	Ph **3.4b**	**AuPEG** (5 mol%)	MeOH	5 mol %	No conversion
6	Ph **3.4b**	**AuPEGTriazole** (5 mol%)	MeOH	5 mol %	No conversion

The final step in this project was devoted to the reusability of the introduced reaction system. Initially, $AuBr_3$ in betaineHCL:urea was used since it appeared to be the best catalyst/solvent system. In doing so, the product **3.11a** was separated by an extraction with cyclohexane. After the second run only a yield of 24% could be detected.

Therefore, the system had to be adjusted: a low melting mixture containing betaineHCl:urea:methanol ((m:m:m) 1 : 2.2 : 1) was used instead, which also opens new possibilities because the separation of gold and the chloride anion should be more easily since the amount of free chloride anions coming from the DES mixture is reduced as well as the viscosity of this system.

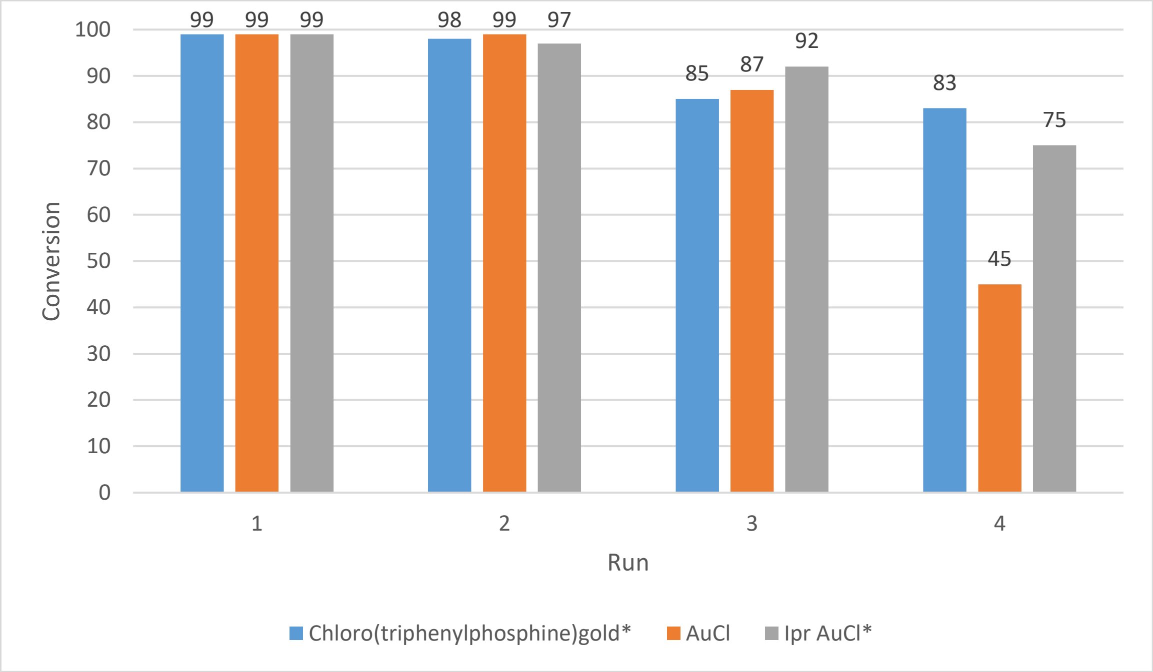
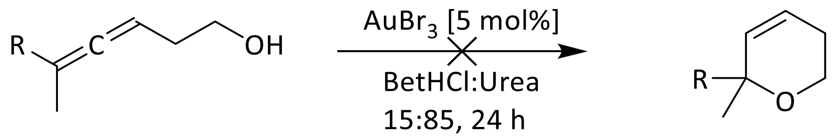


Figure 77 Recycling experiments for the cycloisomerisation of **3.4a** in betaineHCl:urea:Methanol, * Addition of 5 mol% AgOTf

As can be seen in Figure 77, all of the used catalysts (chloro(triphenylphosphine)gold(I) (**A**), gold(I) chloride and chloro[1,3-bis(2,6-diisopropylphenyl)imidazol-2-ylidene]gold(I) (**B**) worked very well in this low melting mixture, which contrasted with the first attempts using those catalysts with an NHC or phosphorous ligand (Table 22). Whereas the first two runs performed with full conversion, the third and fourth run showed a slightly depletion for all catalysts, whereby gold(I) chloride showed the lowest conversion. However, the outcome of the ligand containing catalysts were still reasonable.

Furthermore, the synthesised β-hydroxyallenes were tested in this catalyst solvent system. Even though a small conversion could be observed by TLC and GC the desired products could not be isolated. However, mass spectrometry showed the product **3.12b** in small amounts. On account of the low reactivity the reaction was not deepened further.



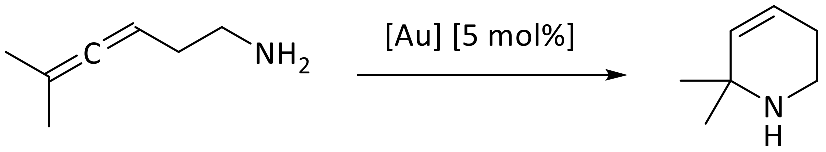
3.7a (R = Me)
3.7b (R = CH_2iPr)

3.12a (R = Me) 0%
3.12b (R = CH_2iPr) traces

Figure 78 Gold-catalysed cyclisation of β-hydroxyallenes

Another interesting and challenging cycloisomerisation, which waited to be tested in this gold/DES catalyst solvent system was the reaction of β-aminoallenes to tetrahydropyridine derivates. Initially, choline-based DES were tested with two gold catalyst, $AuCl_3$ and **A** in combination with silver triflate to abstract the coordinated chloride.

Table 27 Cycloisomerisation of β-aminoallenes[185]



3.9

3.13

Entry	**Catalyst**	**Solvent**	**Temp.**	**Time**	**Yield**
1	$AuCl_3$	CHCl:urea	rt	24 h	0%
2	$AuCl_3$	CHCl:glycerol	rt	24 h	0%
3	**A***	CHCl:urea	rt	24 h	0%
4	**A***	CHCl: glycerol	rt	24 h	0%
5	$AuCl_3$	CHCl:urea	50 °C	20 h	85%
6	$AuCl_3$	CHCl: glycerol	50 °C	20 h	80%
7	**A***	CHCl: glycerol	50 °C	20 h	10%

*Addition of 5 mol% AgOTf

In doing so, no reaction could be observed at room temperature with either of the two catalysts (Table 27, entries 1-4), which is explainable by the proposed mechanism for the cyclisation of α-aminoallenes introduced by Morita and Krause[186] (Figure 79).

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[185] The major work was done in the context of an internship D. Podlesainski, TU Dortmund, Dortmund, **2017**.

[186] N. Morita, N. Krause, *Eur. J. Org. Chem.,* **2006**, 4634-4641.

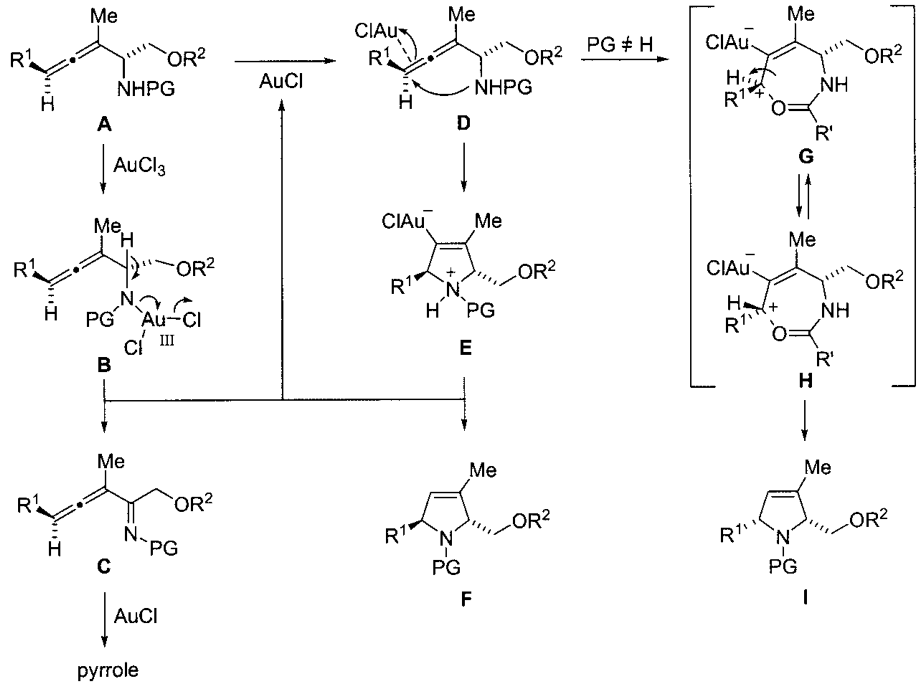


Figure 79 Proposed mechanism of the cyclisation of aminoallenes[186]

The proposed mechanism assumes three possible pathways:

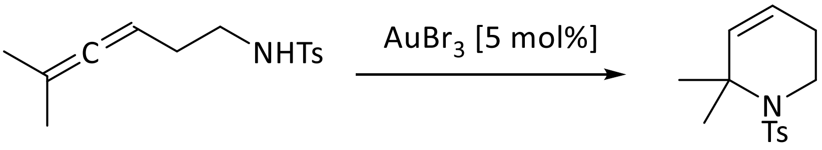
- First, in the case of gold(III) catalysts a strong coordination to the nitrogen atom occurs leading to complex **B**, which is able to react further to the corresponding pyrrole with an imine interstage **C** and gold(I)chloride.
- Second, the gold(I) catalyst can coordinate to the allenic double bond (**D**) facilitating a nucleophilic attack to give intermediate **E**, which is then transformed to product F via protodeauration.
- Third, if the nitrogen atom bears a protection group with oxygen it comes to a stabilisation of the zwitterionic complex **G** and **H** leading to a mixture of the products **F** and **I**.

Although the mechanism is actually proposed for α-aminoallenes, the first pathway is particularly interesting because it shows a strong coordination between the nitrogen and the gold salt, which makes these cycloisomerisations more challenging than their oxygen analogues.

However, an increased temperature of 50 °C and a relatively long reaction time of 20 h led to good yields up to 85% with the gold(III) catalyst $AuCl_3$ (Table 27, entries 5 and 6) whereas the gold(I) catalyst showed again only a low performance in DES (Table 27, entry 7). The product could be characterised by NMR-spectroscopy.

In addition, a tosylated β-aminoallene was tested since the protecting group should decrease the Lewis-basicity of the nitrogen atom and thus promote the cyclisation (Table 28)

Table 28 Cycloisomerisation of tosylated β-Aminoallenes[187]



3.10 **3.13**

Entry	Catalyst	Solvent	Temp.	Time	Yield
1	$AuCl_3$	CHCl:urea	rt	16 h	0%
2	**A***	CHCl:urea	rt	16 h	0%
3	$AuCl_3$	CHCl:urea	50 °C	16 h	0%
4	**A***	CHCl:urea	50 °C	16 h	0%

*Addition of 5 mol% AgOTf

Nevertheless, the outcome differed from the expected result since no conversion could be detected, even at increased temperatures (Table 28 entries 1-4).

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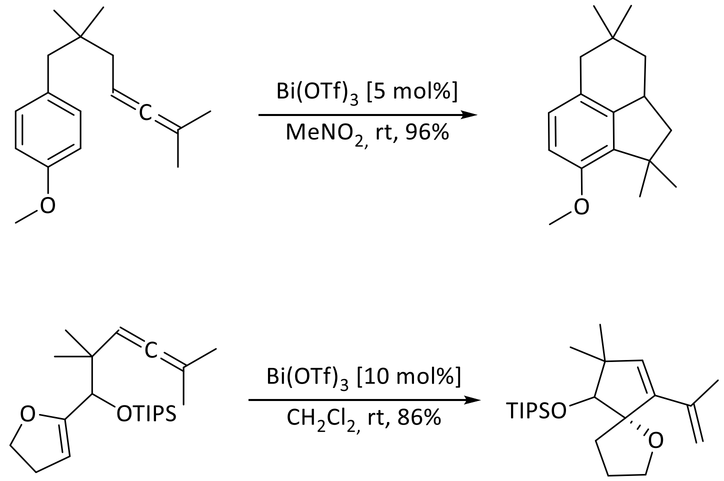
[187] The major work was done in the context of an internship D. Podlesainski, Tu Dortmund, Dortmund, **2017**.

3.5. Excursus: Examination on more cost-efficient alternative catalysts

As stated in chapter 3.1, many transition metals are capable to catalyse allene cyclisations, however the majority of them have a high price and are hazardous. Therefore, the development of new efficient protocols for cycloisomerisations utilising relatively inexpensive, nontoxic, and easily reusable catalysts with low loadings is of significant importance.

Bismuth salts are worth considering as an alternative due to their low toxicity and low cost.[188] Especially bismuth(III) triflate has recently emerged as a suitable and relatively inexpensive catalyst in the wide field of organic transformations including also cycloisomerisations.[189] However, bismuth(III)-catalysed cycloisomerisations involving allenes have been reported only rarely in the literature. Duñach et al. reported in 2012 Bi-catalysed cycloisomerisations of aryl-allenes[190] and three years later cycloisomerisations of allene–enol ethers[191] under Bi-catalysis both under mild reaction conditions with short reaction times (see Figure 80).



TIPS = Triisopropylsilyl ether

Figure 80 Allene cyclisations catalysed by Bi(III) salts[190,191]

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[188] B. Bradley, M. Singleton, A. Po, *J. Clin. Pharm. Ther.,* **1989**, *14*, 423-441;
T. Ollevier, *Org. Biomol. Chem.,* **2013**, *11*, 2740-2755.

[189] J. M. Bothwell, S. W. Krabbe, R. S. Mohan, *Chem. Soc. Rev.,* **2011**, *40*, 4649-4707;
T. Ollevier, *Bismuth-mediated organic reactions, Vol. 311*, Springer Science & Business Media, **2012**;
P. Ondet, G. Lemière, E. Duñach, *Eur. J. Org. Chem.,* **2017**, *2017*, 761-780.

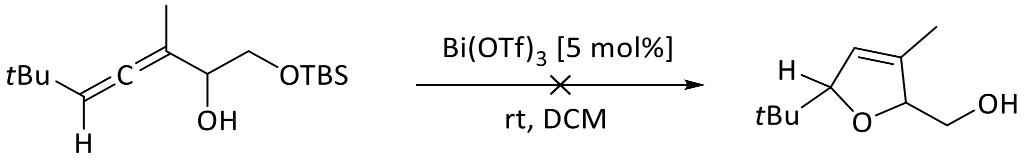
[190] G. Lemiere, B. Cacciuttolo, E. Belhassen, E. Duñach, *Org. Lett.,* **2012**, *14*, 2750-2753.

[191] P. Ondet, A. l. Joffrin, I. Diaf, G. Lemière, E. Duñach, *Org. Lett.,* **2015**, *17*, 1002-1005.

Therefore, the usage of Bi(III)-salts for the well-known cycloisomerisation of α-hydroxyallenes to the corresponding 2,5-dihydrofurans could be promising. Particularly bismuth(III) triflate is of significant importance due to its unique Lewis acidity, which is higher than that of Bi-halides.[192]

Furthermore it is considered that bismuth(III) triflate presents a borderline activity between that of more oxophilic catalysts such as Al(III)- or Mg(II)-triflates and that of more carbophilic ones, such as gold salts.[192] As a consequence bismuth(III) triflate could be a promising approach because it probably could activate the hydroxy group as well as the allenic double bond and should therefore facilitate the generation of the heterocycle.

Initially, it was envisaged in this project to use bismuth salts and other alternatives for the same cycloisomerisations than done before with gold (Chapter 3.4) in a sustainable way.[193] Although, DCM was used for the first test reaction because it is often used for both allene cyclisations as well as bismuth catalysis (Figure 81).



3.4a **3.14a**

Figure 81 Supposed cycloisomerisation catalysed by bismuth

In doing so, TLC control showed very quick a conversion of the used allene, which was supported by GC analysis, as a result an NMR probe was prepared in $CDCl_3$ as a well-known NMR solvent. The NMR-spectroscopy showed the structure of product **3.14a** (Figure 81), the expected dihydrofuran, which underwent a cleavage of the TBS protecting group. Soon, however, it became clear that the observed cyclisation was not caused by the bismuth catalyst but in fact the mild acidic $CDCl_3$ was responsible for the cyclisation, since a made NMR spectrum in C_6D_6 showed only the dihydroxyallene **3.15a**.

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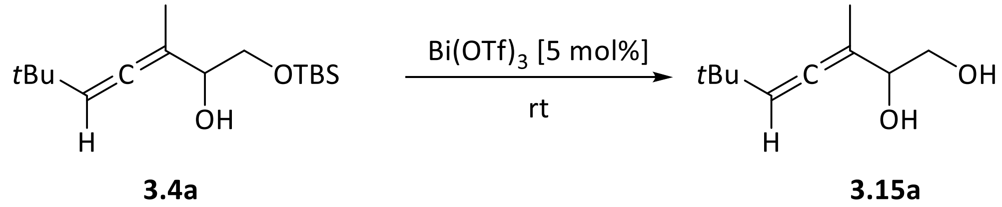
[192] D. V. Partyka, L. Gao, T. S. Teets, J. B. Updegraff III, N. Deligonul, T. G. Gray, *Organometallics,* **2009**, *28*, 6171-6182.

[193] The major work was done in the context of a bachelor thesis
K. Ludwigs, TU Dortmund (Dortmund), **2017**.

Contrary to the expectations, the used bismuth catalyst was only able to perform a deprotection of the TBS group, which is known in the literature using Bi(III)halides[194]. Despite this unpromising finding, the impact of the solvent to the reaction of hydroxyallenes with $Bi(OTf)_3$ [5 mol%] was investigated first (Table 29). It was focused on green solvents.

Table 29 Solvent screening using $Bi(OTf)_3$ as catalyst



Entry	Solvent	Time	Yield
1	DCM	24 h	45%
2	THF	24 h	48%
3	H_2O	24 h	0%
4	MeOH	24 h	99%
5	MeOH	1 h	99%
6	EtOH	24 h	99%
7	EtOH	5 h	99%
8	*i*PrOH	24 h	95%
9	glycerol	24 h	10%
10	propylene carbonate	24 h	0%
11	CHCl:urea (1:2)	24 h	0%
12	CHCl:glycerol	24 h	0%
13	PEG (200 g/mol)	24 h	80%
14	EtOAc	24 h	56%

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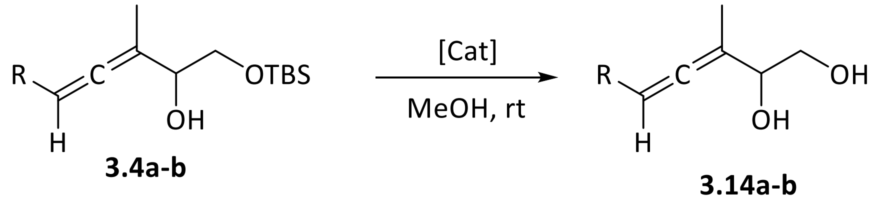
[194] J. S. Bajwa, J. Vivelo, J. Slade, O. Repič, T. Blacklock, *Tetrahedron Lett.,* **2000**, *41*, 6021-6024; G. Sabitha, R. S. Babu, E. V. Reddy, R. Srividya, J. Yadav, *Adv. Synth. Catal.,* **2001**, *343*, 169-170; G. Sabitha, R. S. Babu, E. V. Reddy, J. Yadav, *Chem. Lett.,* **2000**, *29*, 1074-1075; H. Firouzabadi, I. Mohammadpoor-Baltork, S. Kolagar, *Synth. Commun.,* **2001**, *31*, 905-909.

In all tested cases only diol **3.15a** could be observed and no cyclisations at all. At the outset of this study, the common classic solvents DCM and THF were investigated but only moderate yields could be observed (Table 29, entries 1 and 2). As first green solvent water was tested but unfortunately it showed no conversion (Table 29, entries 3). Next, bio renewable, relatively low toxic alcohols were tested (Table 29, entries 4-8). Delightfully, high yields up to 99% with methanol, ethanol and Isopropyl alcohol could be obtained whereas glycerol showed only 10% yield. Interested in an appropriate reaction time, full conversion was observed after one hour in methanol and five hours in ethanol (Table 1, entries 5 and 7). It is worth noting that no by-products in these solvents could be detected at this bismuth-catalysed reaction in alcohols. Furthermore, other green solvents including propylene carbonate, PEG, EtOAc as well as Deep Eutectic Solvents (DESs) were tested with a moderate outcome (Table 29, entries 10-14). Whereas propylene carbonate and two DESs showed no conversion (Table 29, entries 10-12), EtOAc and PEG showed moderate yields of 56% and 80% (Table 29, entries 13 and 14).

In addition to these initial findings, the implication of other catalysts especially metal-based Lewis acids should be examined. Therefore, methanol was determined as alcoholic solvent of choice due to its shortest reaction time, lowest price and “greenness”, further on the allene was partially altered for a better assessment.

Table 30 Catalyst variation of the TBS deprotection



Entry	R =	[mol%]	[Cat]	Time	Yield
1	*t*Bu **3.4a**	10	$InBr_3$	6 h	94%
2	*t*Bu **3.4a**	20	$GaCl_3$	16 h	99%
3	*t*Bu **3.4a**	10	$In(OTf)_3$	3 h	99%
4	Ph **3.4b**	5	$Bi(OTf)_3$	1.5 h	97%
5	*t*Bu **3.4a**	5	$Bi(OTf)_3$	1 h	99%
6	*t*Bu **3.4a**	1	$Bi(OTf)_3$	2.5 h	99%
7	*t*Bu **3.4a**	10	$BiCl_3$	24 h	99%
8	*t*Bu **3.4a**	10	$Bi(NO_3)_3(H_2O)_5$	4.5 h	99%
9	Ph **3.4b**	5	HOTf	24 h	35%
10	Ph **3.4b**	10	HOTf	1 h	79%
11	*t*Bu **3.4a**	10	$(P_2O_5)(WO_3)_{24}(H_2O)_{44}$	0.5 h	99%
12	*t*Bu **3.4a**	5	p-Toluenesulfonic acid·(H_2O)	1 h	99%
13*	*t*Bu **3.4a**	10	$Bi(OTf)_3$	24 h	19%
14	*t*Bu **3.4a**	10	NaOTf	24 h	0%

*Addition of 1 eq. $NaHCO_3$

It is noteworthy that nearly all used catalysts were able to catalyse the deprotection with high yields nonetheless significant differences in the reaction times could be observed. Furthermore, it is important to state that no cyclisation took place. While the full conversion of **3.4** was found to be relatively long with $InBr_3$ (6 h) and $GaCl_3$ (16 h) even with 20 mol% in methanol (Table 30, entries 1 and 2), a shorter reaction time (3 h) until full conversion was obtained using 10 mol% of the triflate salt of indium, $In(OTf)_3$ (Table 30, entry 3). With $Bi(OTf)_3$, the shortest reaction time could be observed with **3.4a** but with **3.4b** a slightly prolongation in reaction time was observed (Table 30, entries 4 and 5). In addition, the catalytic loading could be lowered further to 1 mol% accompanied by a longer reaction time of 2.5 h until full conversion to **3.14a** (Table 30, entry 6).

At this point, it is important to note that quantitative yields for this deprotection process and an excellent selectivity could be obtained, since no by-products were detected by GC or NMR methods.

Moreover, it was interesting to see if the catalytic effect of $Bi(OTf)_3$ is based on a hidden Brønsted acid catalysis, which could be reported for some metal triflates recently.[195] DFT calculation suggest two pathways for the reaction of $Bi(OTf)_3$ with water: hydrolysis or hydration (Figure 82).[196]

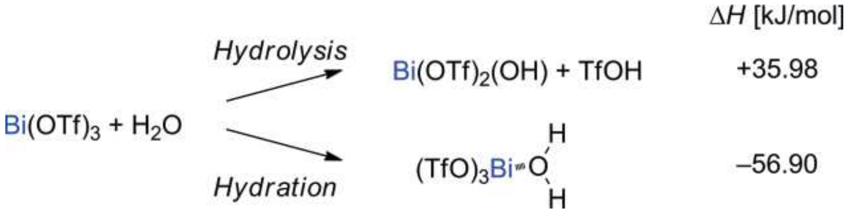


Figure 82 $Bi(OTf)_3$ with water[197]

The hydration pathway was found to be highly favoured against the endothermic hydrolysis. Moreover, the coordinated water molecule possesses a high positive electronic density associated with a high acidity. Therefore, in the case of $Bi(OTf)_3$ there are examples known in which the Bi-cation showed direct activity and also is known that the acidic proton of Bi_3^+-H_2O association is responsible for the activation.[197]

As a consequence, other bismuth salts were tested with the result that the reaction time increased to 24 h with $BiCl_3$, while $Bi(NO_3)_3(H_2O)_5$ could reach full conversion after 4.5 h (Table 30, entries 7 and 8). In the next step, neat triflic acid which can presumably be nascented from $Bi(OTf)_3$ was investigated. Interestingly, with 5 mol% only low yield of **3.14** was obtained after 24 h, whereas an increase to 10 mol% showed higher yields (79%) after 50 min (Table 30, entries 9 and 10). This indicates the relatively inexpensive and easy to use $Bi(OTf)_3$ as the best catalyst for this deprotection reaction (Table 30, entries 9 and 10).

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[195] T. T. Dang, F. Boeck, L. Hintermann, *J. Org. Chem.,* **2011**, *76*, 9353-9361.
[196] J. Godeau, F. Fontaine-Vive, S. Antoniotti, E. Duñach, *Chem. - Eur. J.,* **2012**, *18*, 16815-16822.
[197] P. Ondet, G. Lemière, E. Duñach, *Eur. J. Org. Chem.,* **2017**, *2017*, 761-780.

Furthermore, to unveil the nature of this catalytic bismuth system was interesting, since it is known that the cycloisomerisation of hydroxyallenes could be catalysed by Brønsted acids. However, this could not be substantiate by the use of two solid mainly Brønsted acids $(P_2O_5)(WO_3)_{24}(H_2O)_{44}$ and p-Toluenesulfonic acid at least not in this specific reaction system, since quantitative yields and short reaction times for the deprotection were observed in doing so but no evidence for a cyclisation (Table 30, entries 11 and 12). Therefore, it was intended to trap the potentially nascenting acid by the addition of the non-nucleophilic base $NaHCO_3$ and observed indeed a significant lower yield of 19% after 24 h (Table 30, entry 13). Subsequently, sodium triflate as non-lewis-acid triflate salt was examined and discovered that triflate anion alone is not able to catalyse the reaction (Table 30, entry 14).

In order to clarify the generation of triflic acid out of $Bi(OTf)_3$ ^{19}F-NMR experiments of $Bi(OTf)_3$ were carried out:

- TMSOTf was dissolved in d-methanol
- HOTf was dissolved in d-methanol
- $Bi(OTf)_3$ was stirred in d-methanol for 24 h
- $Bi(OTf)_3$ was dissolved in d-methanol
- $Bi(OTf)_3$ was refluxed for 2 h in d-methanol

It resulted that a generation or a decomposition could not be detected, which leads to the assumption that the triflic acid is not responsible for the catalytic activity (Figure 83). Quite contrary to the case of TMSOTf in methanol where a generation of HOTf can clearly be seen. There is a discussion in the scientific community, as stated before, to the nature of the active species in reactions catalysed by bismuth triflate, regarding the role of triflic acid. As a result of a possible hydrolysis versus hydration of the bismuth triflates, which is in line with the NMR experiments. As the generation of triflic acid was not observed the assumption arise that the acidic proton of the coordinated water is responsible for deprotection, which also would explain the decrease of yield when adding a base.

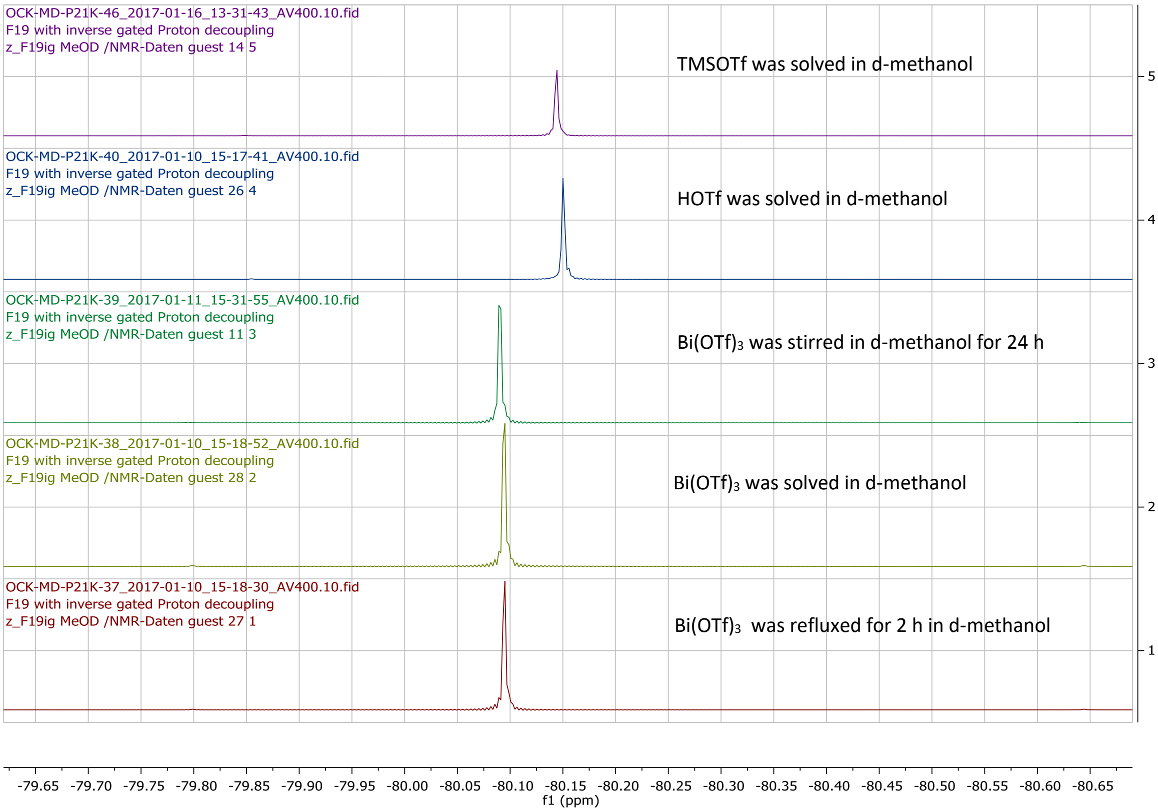


Figure 83 ^{19}F-NMR experiments

Nonetheless, Bi(OTf)$_3$ is a cheap, nontoxic and easy to use and a suitable catalyst for this reaction furthermore, it was possible to reduce the reaction time to 0.5 h by the addition of the chelating ligand salicylaldoxime (Table 31, entry 1), whereas the addition of proline resulting in no conversion(Table 31, entry 2). The use of β-cyclodextrin did also not led to a deviation from the additive free reaction (Table 31, entry 3). However, if triphenylphosphin or diisopropyl tartrate were used, the reaction time decreased to half an hour, too (Table 31, entries 4 and 5).

Table 31 Additive screening for the Bi-catalysed deprotection

Entry	R =	[mol%]	[Cat]	Additive	Time	Yield
1	*t*Bu	10	$Bi(OTf)_3$	Salicylaldoxime (0.4 eq.)	0.5 h	99%
2	*t*Bu	5	$Bi(OTf)_3$	Proline (0.1 eq.)	24 h	0%
3	*t*Bu	5	$Bi(OTf)_3$	β-cyclodextrin (0.1 eq.)	1 h	99%
4	*t*Bu	5	$Bi(OTf)_3$	PPh_3 (0.1 eq.)	0.5 h	97%
5	*t*Bu	5	$Bi(OTf)_3$	Diisopropyl tartrate (0.1 eq.)	0.5 h	98%

With the optimised conditions in hand recycling reactions were tested to paying tribute to sustainability. Initially, 0.05 eq. Bi(III)triflate in MeOH was used without any additives. The product was extracted with cyclohexane after completion; hence methanol and cyclohexane are not miscible (see Figure 84).

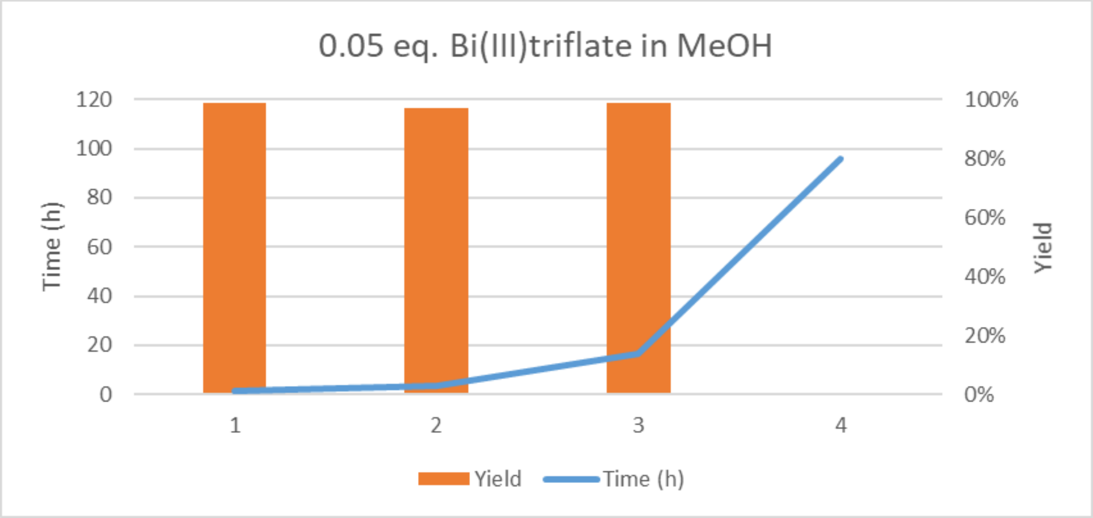


Figure 84 Recycling experiment 0.05 eq. Bi(III)triflate in MeOH

Even though, the first and the second run reached full conversion after a short time, the third run already needed 17 h and no conversion could be detected for the fourth run after 96 h. Furthermore, it was challenging to recognise the phase boundary at the extraction. Therefore, the solvent was altered to a mixture of 1:1 water:methanol (Figure 85)

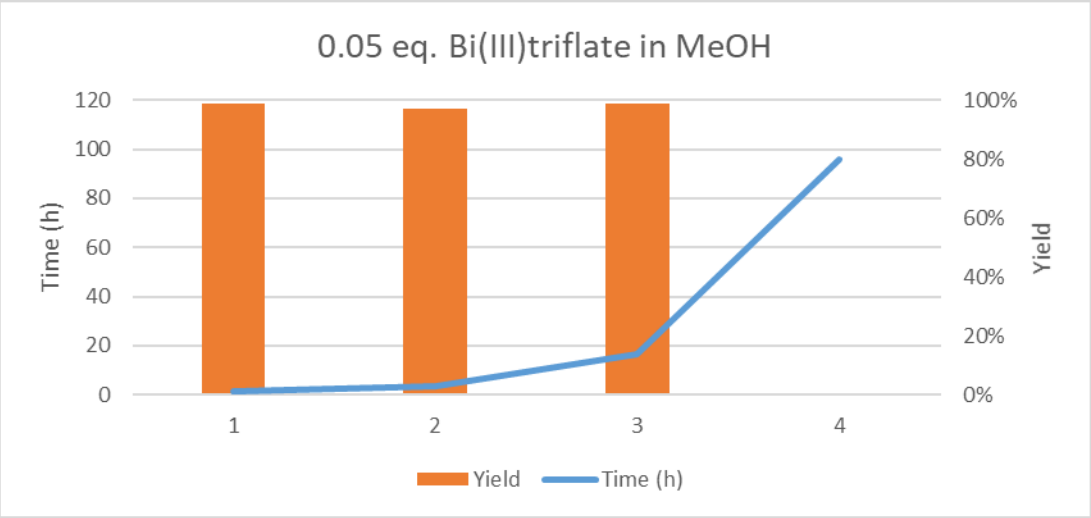


Figure 85 Recycling experiment 0.05 eq. Bi(III)triflate in 1:1 H_2O:MeOH

This led to an improvement not only for the handling but also on the reliability of this system, since full conversion could be detected even at the fourth run, however with the price of a prolonged reaction time.

The last attempt was to avail an additive combined with Bi(III)triflate (Figure 86).

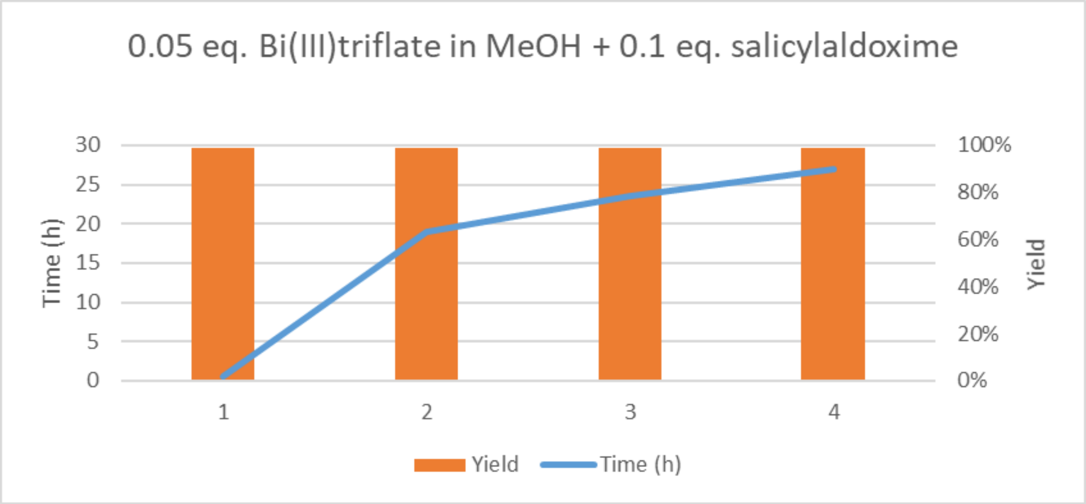


Figure 86 Recycling experiment 0.05 eq. Bi(III)triflate in MeOH + 0.1 eq. Salicylaldoxime

The outcome was very comparable with Figure 85 hence full conversion could be reached in all the four runs with restrictions in the reaction time.

3.6. Conclusion

First examples on the gold-catalysed cycloisomerisation of α- hydroxyallenes respectively, to the corresponding highly functionalised dihydrofurans in green biorenewable Deep Eutectic Solvents and liquid polymers could be achieved in this project.

The used allenes could be synthesised following well-known protocols in the *Krause* group. In the case of the α-hydroxyallenes the corresponding epoxide precursors undergo a nucleophilic attack by an organocuprate resulting in the desired allene via a S_N2'-reaction (see Figure 87). The β-hydroxyallenes could be generated via a Johnson-Claisen-rearrangement and a subsequent reduction (see Figure 87).

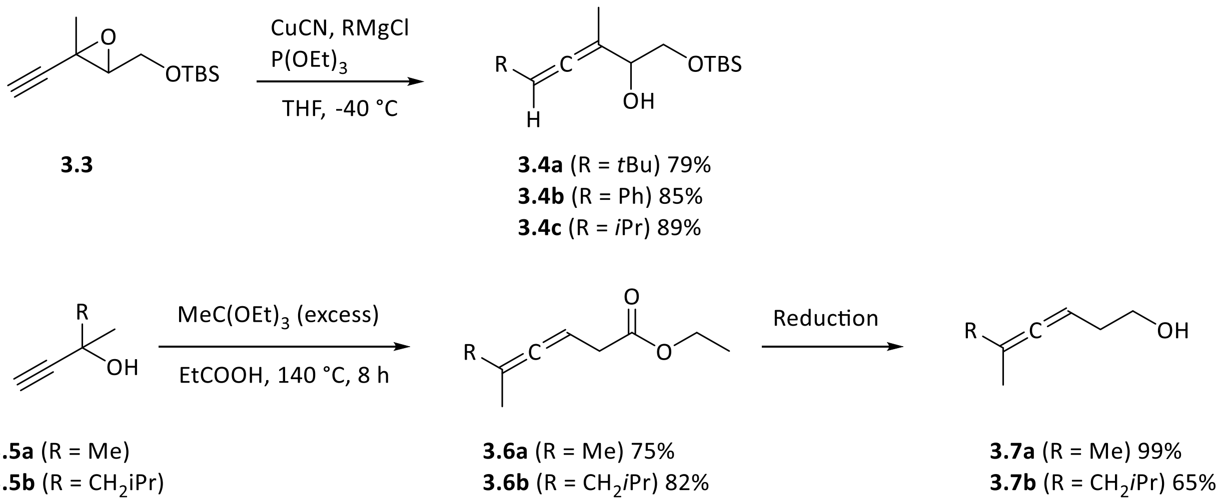
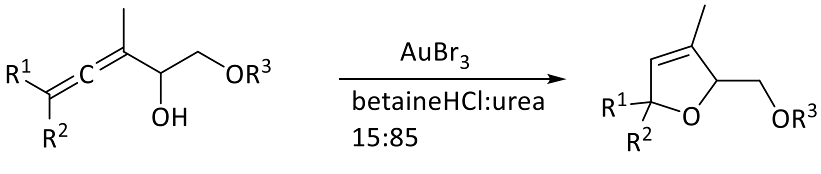


Figure 87 Synthesis of the used allenes

The following cycloisomerisation reactions took place with high yields under mild conditions and were optimised with regard to sustainability and catalyst recycling. The best catalyst DESs system was $AuBr_3$ in betaineHCl:urea, which is air-stable and its relative low viscosity at the reaction temperature of 80 °C makes the catalyst solution very easy to handle and facilitates an extraction of the product. The optimised conditions could be fruitfully applied to a broader scope of allenes as indicated in Table 32.

Table 32 Substrate scope of the solvent/catalyst system



3.4a-e **3.11a-e**

Entry	Allene	R^1 =	R^2 =	R^3 =	Temp.	Time	Product	Yield
1	**3.4b**	Ph	H	TBS	80 °C	3 h	**3.11b**	93%
2	**3.4c**	*i*Pr	H	TBS	80 °C	3 h	**3.11c**	84%
3	**3.4a**	*t*Bu	H	TBS	80 °C	3 h	**3.11a**	92%
4	**3.4d***	*t*Bu	H	Bn	80 °C	3 h	**3.11d**	70%
5	**3.4e***	Me	Me	Me	80 °C	3 h	**3.11e**	81%

*Originated from a former project in the group

In the case of the tested polymers as solvent, $AuBr_3$ in PPG (polypropylene glycol) emerged as the best system with very mild reaction conditions and a considerable low reaction time of 10 min. However, it soon became apparent that the product separation from the solvent is very challenging, although a separation by distillation is also conceivable, this applies for DESs system as well as for polymers.[198]

Furthermore it is noteworthy that a recycling of the catalyst/solvent system could be achieved by altering the DES to another related low melting mixture: betaineHCl:urea:methanol ((m:m:m) 1 : 2.2 : 1). When using this DES, it was also possible to use gold catalysts, where the generation of the active gold cation by a non-coordinating silver salt is mandatory, which failed before. Using Chloro(triphenylphosphine)gold(I) **A** or IprAuCl **B** led to a reasonable outcome and recycling abilities over 4 runs.

Moreover, the two synthesised gold complexes **AuPEG** and **AuPEGTriazole** originating from chapter 2.3.2 were tested in this cyclisations (Table 33). However, neither of the catalysts showed any activity in the cycloisomerisation of α-hydroxyallenes (Table 34). Even the addition of a non-coordinating silver salt like AgOTf, which is a known procedure to generate the active gold cation, could not improve the outcome.

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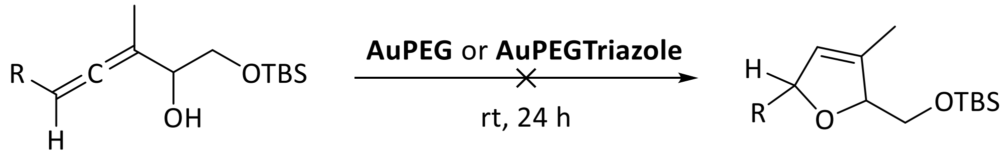
[198] M. Avalos, R. Babiano, P. Cintas, J. L. Jiménez, J. C. Palacios, *Angew. Chem., Int. Ed., Engl.,* **2006**, *45,24*, 3904-308.

Table 33 Cycloisomerisation catalysed by **AuPEG** and **AuPEGTriazole**

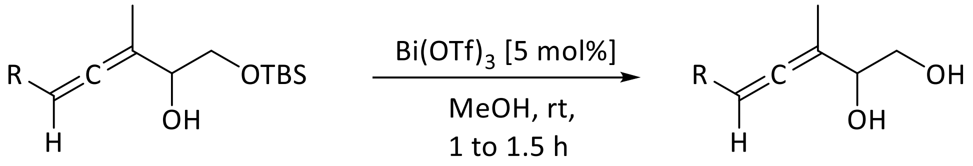


3.4a-b

3.11a-b

Entry	R =	Catalyst	Solvent	Addition of AgOTf	Yield
1	*t*Bu **3.4a**	**AuPEG** (5 mol%)	Water	-	No conversion
2	*t*Bu **3.4a**	**AuPEGTriazole** (5 mol%)	Water	-	No conversion
3	Ph **3.4b**	**AuPEG** (5 mol%)	Water	5 mol %	No conversion
4	Ph **3.4b**	**AuPEGTriazole** (5 mol%)	Water	5 mol %	No conversion
5	Ph **3.4b**	**AuPEG** (5 mol%)	MeOH	5 mol %	No conversion
6	Ph **3.4b**	**AuPEGTriazole** (5 mol%)	MeOH	5 mol %	No conversion

Furthermore, some main group metals were tested on their performance for a cyclisation. However, it became clear that these metals, especially bismuth were suitable and effective catalysts for the cleavage of silyl ether while the allene structure remained untouched (Figure 88).



3.4a (R = *t*Bu)
3.4b (R = Ph)

3.14a (R = *t*Bu) 99%
3.14b (R = Ph) 97%

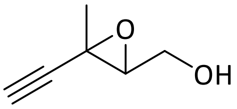
Figure 88 Bismuth catalysed deprotection

In addition, the mechanistic insight was deepened. In doing so the conceivable formation of triflate acid as responsible active species could be excluded by NMR spectroscopy and comparison experiments. Furthermore, the catalyst system could be reused four times, although with an increase in reaction time.

3.7. Experimental

(3-ethynyl-3-methyloxiran-2-yl)methanol (**3.2**)

MD-P1-1

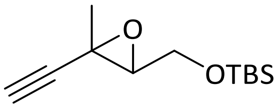


3.3 g of fresh distilled 3-Methylpent-2-en-4-in-1-ol (34.3 mmol, 1 eq.) was dissolved in dry DCM under Argon atmosphere and cooled to 0 °C. Then, 8.24 g Na_2HPO_4 (51.5 mmol, 1.5 eq.) and 12.7 g *m*-CPBA (75%, 51.5 mmol, 1.5 eq.) were added and the solution was stirred for 12 h. 50 ml saturated Na_2CO_3 solution was added to the white suspension subsequently and the mixture was extracted with DCM (5 x 50 ml). The combined organic phases were washed with saturated Na_2CO_3 solution (2 x 20 ml) as well as brine (2 x 20 ml), dried by $MgSO_4$ and the solvent was evaporated resulting in 65 % of product **3.2** (2.43 g, 21.7 mmol) as yellow solid.

^{1}H NMR (500 MHz, Chloroform-*d*) δ 3.85 (ddd, *J* = 12.4, 4.5, 1.5 Hz, 1H), 3.70 (ddd, *J* = 12.3, 6.2, 1.9 Hz, 1H), 3.38 (dd, *J* = 6.1, 4.6 Hz, 1H), 2.33 (s, 1H), 1.55 (d, *J* = 1.3 Hz, 3H)
^{13}C NMR (126 MHz, Chloroform-*d*) δ 83.6, 70.7, 63.7, 60.6, 51.0, 18.5
Known compound[199]

Tert-butyl((3-ethynyl-3-methyloxiran-2-yl)methoxy)dimethylsilane (**3.3**)

MD-P1-2



5.22 g of epoxide **3.2** (46.6 mmol, 1 eq.) were dissolved in dry DCM under argon atmosphere followed by the addition of 8 ml triethylamine (57.4 mmol, 1.2 eq.), 8.44 g tert-butylchlorodimethylsilane (56 mmol, 1.2 eq.) and 0.24 g DMAP (1.96 mmol, 0.05 eq.).

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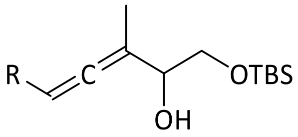
[199] M. E. Piotti, H. Alper, *J. Org. Chem.,* **1997**, *62*, 8484-8489.

The brown solution was stirred for 2 h at room temperature and quenched by the addition of 50 ml of a sat. $NaHCO_3$ solution. The mixture was then extracted with DCM (3 x 100 ml) and the combined organic phases were washed with brine (20 ml). Afterwards, the organic phase was dried by $MgSO_4$, the solvent evaporated, and the residue purified by flash column chromatography (pentane:Et_2O 20:1) resulting in 71% yield of the yellow liquid product **3.3** (7.29 g, 32.2 mmol).

^{1}H NMR (500 MHz, Chloroform-*d*) δ 3.73 (d, *J* = 5.2 Hz, 2H), 3.31 (td, *J* = 5.3, 1.0 Hz, 1H), 2.31 (d, *J* = 1.2 Hz, 0H), 1.52 (d, *J* = 1.0 Hz, 2H), 0.90 (d, *J* = 1.1 Hz, 5H), 0.09 (dd, *J* = 4.7, 1.0 Hz, 3H)
^{13}C NMR (126 MHz, Chloroform-*d*) δ 84.0, 70.4, 64.1, 61.4, 50.5, 26.0, 18.5, -5.1, -5.2
Known compound[200]

General procedure for the synthesis of α-Hydroxyallenes (**3.4a-c**):

Allenes **3.4a-c** were synthesised after a known procedure.[200]



CuCN (1 eq.) was dissolved in dry THF under argon atmosphere and $P(OEt)_3$ (1 eq.) was added slowly and stirred for 0.5 h. Then, the solution was cooled to –40 °C and the respective alkyl magnesium chloride was added dropwise (2 eq.) and stirred for 0.5 h followed by the addition of epoxide **3.3** (1 eq.) at -40 °C. After the solution was stirred for additional 1 h, 50 ml sat. NH_4Cl solution was added carefully and the mixture with Et_2O (3 x 100 ml) extracted. The combined organic phases were dried by $MgSO_4$ and the solvent removed. The residue was purified by flash column chromatography subsequently.

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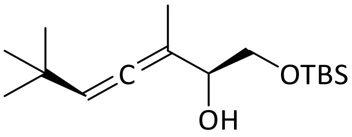
[200] N. Krause, A. Hoffmann-Röder, J. Canisius, *Synthesis,* **2002**, , 1759-1774.

Entry	CuCN	P(OEt)$_3$	RMgCl	Epoxide	Product	Yield
1	1.58 g 17.5 mmol	2.9 g 17.5 mmol	*t*-BuMgCl 4.13 g 33.5 mmol	4 g 33.5 mmol	**3.4a**	3.93 g 79%
2	1.58 g 17.5 mmol	2.9 g 17.5 mmol	PhMgCl 4.8 g 33.5 mmol	4 g 33.5 mmol	**3.4b**	4.25 85%
3	1.58 g 17.5 mmol	2.9 g 17.5 mmol	*i*-PrMgCl 3.5 g 33.5 mmol	4 g 33.5 mmol	**3.4c**	4.18 g 88.5%

1-((tert-butyldimethylsilyl)oxy)-3,6,6-trimethylhepta-3,4-dien-2-ol (**3.4a**)

MD-P1-5



Colourless oil,

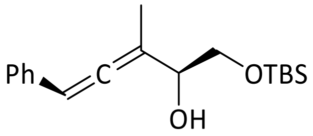
^{1}H NMR (500 MHz, Benzene-d_6) δ 5.32 (p, *J* = 2.8 Hz, 1H), 4.27 (dq, *J* = 6.3, 4.0 Hz, 1H), 3.84 (dd, *J* = 10.1, 3.8 Hz, 1H), 3.74 (dd, *J* = 10.0, 7.2 Hz, 1H), 2.44 (d, *J* = 4.3 Hz, 1H), 1.90 (d, *J* = 3.0 Hz, 3H), 1.14 (d, *J* = 6.6 Hz, 9H), 1.03 (s, 9H), 0.14 (d, *J* = 2.0 Hz, 6H)

^{13}C NMR (126 MHz, Benzene-d_6) δ 198.0, 104.7, 102.0, 72.6, 66.5, 31.9, 30.0, 25.7, 18.2, 15.6, -5.6

Known compound[200]

1-((tert-butyldimethylsilyl)oxy)-3-methyl-5-phenylpenta-3,4-dien-2-ol (**3.4b**)

MD-P1-7



Colourless oil,

^{1}H NMR (500 MHz, Acetonitrile-d_3) δ 7.26 – 7.22 (m, 4H), 7.13 (ddd, *J* = 8.6, 5.4, 3.2 Hz, 1H), 6.15 – 6.11 (m, 1H), 4.09 – 4.03 (m, 1H), 3.66 (dd, *J* = 10.3, 5.1 Hz, 1H), 3.59 (dt, *J* = 10.3, 6.3 Hz, 1H), 3.07 (t, *J* = 5.7 Hz, 1H), 1.74 (d, *J* = 2.9 Hz, 3H), 0.84 (d, *J* = 1.9 Hz, 9H), 0.01 (d, *J* = 5.1 Hz, 6H)

^{13}C NMR (126 MHz, Acetonitrile-d_3) δ 203.8, 136.5, 129.9, 128.1, 127.9, 105.8, 96.0, 74.3, 67.2, 26.6, 19.3, 15.3, -4.9.

Known compound[201]

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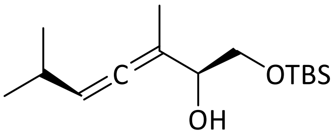
[201] T. Miura, M. Shimada, P. de Mendoza, C. Deutsch, N. Krause, M. Murakami, *J. Org. Chem.,* **2009**, *74*, 6050-6054.

1-((tert-butyldimethylsilyl)oxy)-3,6-dimethylhepta-3,4-dien-2-ol (3.4c)

MD-P1-11



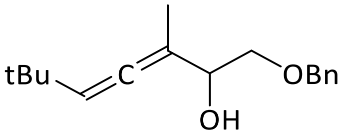
Light-yellow-coloured oil,

^{1}H NMR (400 MHz, Chloroform-*d*) δ 5.13 (dp, *J* = 5.7, 2.9 Hz, 1H), 3.98 (dd, *J* = 6.5, 2.8 Hz, 1H), 3.61 (dd, *J* = 10.1, 3.7 Hz, 1H), 3.48 (dd, *J* = 10.1, 7.5 Hz, 1H), 2.39 (d, *J* = 4.0 Hz, 1H), 2.30 – 2.13 (m, 1H), 1.65 (d, *J* = 2.9 Hz, 3H), 0.92 (d, *J* = 6.8 Hz, 6H), 0.83 (s, 9H), 0.00 (s, 6H)

^{13}C NMR (101 MHz, Chloroform-*d*) δ 198.9, 100.5, 100.3, 72.5, 66.0, 28.0, 25.7, 22.4, 18.1, 15.5, -5.5.

Known compound[202]

1-(benzyloxy)-3,6,6-trimethylhepta-3,4-dien-2-ol (3.4d)



Colourless oil, originated from a former project in the group,

^{1}H NMR (600 MHz, Acetonitrile-*d*$_3$) δ 7.35 (d, *J* = 0.8 Hz, 2H), 7.35 (s, 2H), 7.32 – 7.27 (m, 1H), 5.15 (qd, *J* = 2.9, 2.0 Hz, 1H), 4.53 (s, 2H), 4.13 (dtd, *J* = 6.9, 4.5, 1.9 Hz, 1H), 3.54 (dd, *J* = 9.9, 4.1 Hz, 1H), 3.42 (dd, *J* = 10.0, 7.3 Hz, 1H), 2.97 (d, *J* = 4.9 Hz, 1H), 1.69 – 1.67 (m, 3H), 1.00 (s, 10H)

^{13}C NMR (151 MHz, Acetonitrile-*d*$_3$) δ 198.8, 139.7, 129.2, 128.7, 128.4, 104.9, 103.0, 74.2, 73.6, 72.0, 32.7, 30.4, 16.1

Known compound[203]

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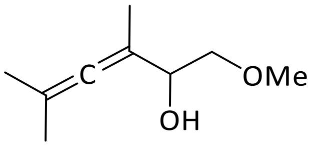
[202] G. Birgit, K. Norbert, *Eur. J. Org. Chem.,* **2010**, 311-316.

[203] S. R. Minkler, B. H. Lipshutz, N. Krause, *Angew. Chem., Int. Ed.,* **2011**, *50*, 7820-7823.

1-methoxy-3,5-dimethylhexa-3,4-dien-2-ol (**3.4e**)



Colourless oil, originated from a former project in the group,

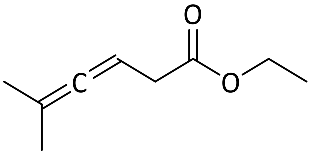
^{1}H NMR (600 MHz, Acetonitrile-d_3) δ 4.03 (dd, *J* = 7.4, 4.2 Hz, 1H), 3.39 – 3.35 (m, 2H), 3.30 (s, 3H), 1.66 (s, 6H), 1.62 (s, 3H)

^{13}C NMR (151 MHz, Acetonitrile-d_3) δ 199.2, 97.2, 76.5, 75.7, 72.3, 58.0, 20.8, 15.8

Known compound[204]

Ethyl 5-methylhexa-3,4-dienoate (**3.6a**)

MD-P1-12



87.7 ml Triethyl orthoacetate (77.14 g, 475.5 mmol, 5 eq.), 9.3 ml 2-methylbut-3-yn-2-ol (8 g, 95.1 mmol, 1 eq.) and 0.7 ml propionic acid (0.7 g, 9.5 mmol, 0.1 eq.) were heated to 140 °C for 4 h with a mounted distillation equipment. Then, 0.7 ml propionic acid (0.7 g, 9.5 mmol, 0.1 eq.) was added again and the mixture was heated for additional 4 h followed by the addition of 100 ml water. The mixture was extracted with EtOAc (3 x 200 ml) afterwards and the combined organic phases were dried by $MgSO_4$ and the solvent was evaporated. The residue was purified by flash column chromatography resulting in 75% yield of the desired product as colourless oil (10.94 g, 90.4 mmol).

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[204] Ö. Aksin, N. Krause, *Adv. Synth. Catal.*, **2008**, *350*, 1106-1112.

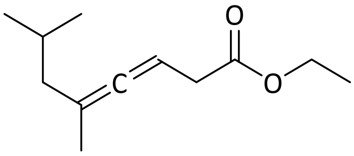
^{1}H NMR (600 MHz, Chloroform-*d*) δ 5.07 (dddd, *J* = 10.0, 7.1, 5.7, 2.8 Hz, 1H), 4.14 (q, *J* = 7.1 Hz, 2H), 2.96 (d, *J* = 7.1 Hz, 2H), 1.68 (d, *J* = 2.9 Hz, 6H), 1.26 (t, *J* = 7.2 Hz, 3H)

^{13}C NMR (151 MHz, Chloroform-*d*) δ 203.1, 172.1, 96.5, 82.1, 60.7, 35.5, 20.6, 14.3

Known compound[205]

Ethyl 5,7-dimethylocta-3,4-dienoate (**3.6b**)

MD-P1-20



34.86 ml Triethyl orthoacetate (30.85 g, 190.2 mmol, 6 eq.), 4.65 ml 3,5-dimethylhex-1-yn-3-ol (4 g, 31.7 mmol, 1 eq.) and 0.17 ml propionic acid (0.16 g, 2.2 mmol, 0.07 eq.) were heated to 140 °C for 4 h with a mounted distillation equipment. Then, 0.17 ml propionic acid (0.16 g, 2.2 mmol, 0.07 eq.) was added again and the mixture was heated for additional 4 h followed by the addition of 100 ml water. The mixture was extracted with EtOAc (3 x 200 ml) afterwards and the combined organic phases were dried by $MgSO_4$ and the solvent was evaporated. The residue was purified by flash column chromatography resulting in 82% yield of the desired product as colourless oil (5.1 g, 26 mmol).

^{1}H NMR (600 MHz, Acetonitrile-*d*$_3$) δ 5.10 (ddt, *J* = 7.1, 5.4, 2.8 Hz, 1H), 4.09 (q, *J* = 7.1 Hz, 2H), 2.93 (d, *J* = 7.1 Hz, 2H), 1.82 (dt, *J* = 6.7, 2.7 Hz, 2H), 1.73 (dt, *J* = 13.5, 6.7 Hz, 1H), 1.64 (d, *J* = 2.9 Hz, 3H), 1.21 (t, *J* = 7.1 Hz, 3H), 0.89 (d, *J* = 6.6 Hz, 6H)

^{13}C NMR (151 MHz, Acetonitrile-*d*$_3$) δ 203.8, 172.4, 100.3, 83.8, 61.3, 44.2, 35.9, 27.0, 22.8, 19.2, 14.5

Known compound[206]

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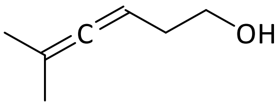
[205] B. M. Trost, A. B. Pinkerton, M. Seidel, *J. Am. Chem. Soc.*, **2001**, *123*, 12466-12476.

[206] J. Bruffaerts, A. Vasseur, S. Singh, A. Masarwa, D. Didier, L. Oskar, L. Perrin, O. Eisenstein, I. Marek, *J. Org. Chem.*, **2018**, *83*, 3497-3515.

5-methylhexa-3,4-dien-1-ol (3.7a)

MD-P1-13



Method 1: 1.41 g ester **3.6a** (9.12 mmol, 1 eq.) was dissolved in 150 ml dry THF under argon atmosphere and cooled to -80 °C followed by the dropwise addition of 27.4 ml DIBAL-H (1 M in *n*-hexane, 27.4 mmol, 3 eq.). The solution was allowed to warm up and stirred for 1.5 h and was then slowly poured to ice water. The organic solvent was evaporated, and the mixture extracted with Et_2O (5 x 50 ml). The combined organic phases were dried by $MgSO_4$ and the solvent removed in vacuo resulting in 99% of product **3.7a** (1.01 g, 9.02 mmol) as colourless liquid.

Method 2: 4.65 g $LiAlH_4$ (122.56 mmol, 2.5 eq.) was dissolved in 150 ml dry THF under argon atmosphere and cooled to -80 °C followed by the addition of 7.56 g ester **3.6a** (49.0 mmol, 1 eq.). The solution was allowed to warm up and stirred for 5 h, was then slowly poured to ice water and the mixture was neutralised to pH 6 with conc. HCl. The organic solvent was evaporated, and the mixture extracted with Et_2O (5 x 50 ml). The combined organic phases were dried by $MgSO_4$ and the solvent removed in vacuo resulting in 87% of product **3.7a** (4.8 g, 9.02 mmol) as colourless liquid.

^1H NMR (500 MHz, Acetonitrile-d_3) δ 4.94 (tt, J = 6.6, 3.1 Hz, 1H), 3.51 (t, J = 6.8 Hz, 2H), 2.18 – 2.02 (m, 2H), 1.65 (d, J = 3.3 Hz, 8H)

^{13}C NMR (126 MHz, Acetonitrile-d_3) δ 203.1, 95.6, 86.3, 62.4, 33.6, 20.8

Known compound[207]

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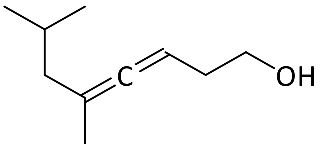
[207] P. Garcia, Y. Harrak, L. Diab, P. Cordier, C. Ollivier, V. Gandon, M. Malacria, L. Fensterbank, C. Aubert, *Org. Lett.,* **2011**, *13*, 2952-2955.

5,7-dimethylocta-3,4-dien-1-ol (**3.7b**)

MD-P1-21

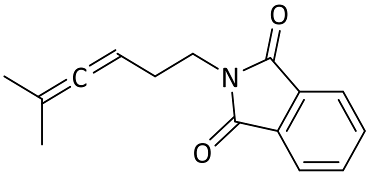


1.16 g $LiAlH_4$ (30.6 mmol, 2 eq.) was dissolved in 100 ml dry THF under argon atmosphere and cooled to -80 °C followed by the addition of 3 g ester **3.6b** (15.3 mmol, 1 eq.). The solution was allowed to warm up and stirred for 12 h at room temperature. The mixture was then slowly poured to ice water and was neutralised to pH 6 with conc. HCl. The organic solvent was evaporated, and the mixture extracted with EtOAc (5 x 50 ml). The combined organic phases were dried by $MgSO_4$ and the solvent removed in vacuo and the residue was purified by flash column chromatography resulting in 65% of product **3.7b** (1.54 g, 9.93 mmol) as colourless liquid.

^{1}H NMR (400 MHz, Chloroform-*d*) δ 4.97 (dddd, *J* = 9.4, 5.6, 3.8, 2.7 Hz, 1H), 3.68 (td, *J* = 6.3, 1.4 Hz, 2H), 2.22 (q, *J* = 6.4 Hz, 2H), 1.82 (dt, *J* = 6.6, 2.5 Hz, 2H), 1.79 – 1.69 (m, 1H), 1.66 (d, *J* = 2.9 Hz, 3H), 0.90 (d, *J* = 6.5 Hz, 6H)
^{13}C NMR (101 MHz, Chloroform-*d*) δ 203.1, 99.0, 85.6, 62.4, 44.0, 32.0, 26.5, 22.7, 22.6, 19.4
Known compound[206]

2-(5-methylhexa-3,4-dien-1-yl)isoindoline-1,3-dione (**3.8**)

MD-P1-14



1.01 g alcohol **3.7a** (9.02 mmol, 1 eq.), 2.65 g phthalimide (18.04 mmol, 2 eq.) and 4.73 g triphenylphosphine (18.04 mmol, 2 eq.) were dissolved in 50 ml THF followed by the dropwise addition of 3.78 ml DIAD (3.89 g, 18.04 mmol 2 eq.). After stirring the solution for 20 h the solvent was removed in vacuo and the residue was purified by flash column chromatography (EtOAc:cyclohexane 1:10) resulting in 66% yield of product **3.8** (1.43 g, 5.94 mmol) as white solid.

^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.84 (dd, J = 5.4, 3.1 Hz, 2H), 7.70 (dd, J = 5.4, 3.0 Hz, 2H), 4.94 – 4.86 (m,1H), 3.75 (t, J = 7.2 Hz, 2H), 2.34 (dd, J = 14.2, 7.0 Hz, 2H), 1.53 (s, 3H), 1.53 (s, 3H)

^{13}C NMR (101 MHz, Chloroform-d) δ 202.8, 168.4, 134.0, 132.3, 123.3, 95.9, 85.1, 77.2, 37.8, 28.4, 20.6

Known compound[208]

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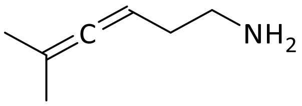
[208] B. Gockel, *Gold-katalysierte Cycloisomerisierung β-funktionalisierter Allene und Anwendung in der Naturstoffsynthese,* TU Dortmund (Dortmund), **2009**.

5-methylhexa-3,4-dien-1-amine (3.9)

MD-P1-18



1.43 g allene **3.8** (5.94 mmol, 1 eq.) and 605 µl hydrazine hydrate (50-60%, 12.47 mmol, 2.1 eq.) were dissolved in ethanol and heated for 2 h at 78 °C. Then, the solvent was removed under reduced pressure and the aqueous mixture was extracted with Et_2O (4 x 40 ml). The combined organic phases were dried by $MgSO_4$ and the solvent was evaporated resulting in 70% yield of product **3.9** (0.46 g, 4.18 mmol) as colourless oil.

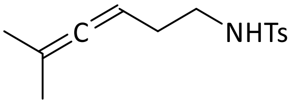
^{1}H NMR (400 MHz, Acetonitrile-d_3) δ 4.98 – 4.89 (m, 1H), 2.63 (t, J = 6.7 Hz, 2H), 1.99 (q, J = 8.2, 4.1 Hz, 2H), 1.67 (s, 3H), 1.66 (s, 3H)

^{13}C NMR (101 MHz, Acetonitrile-d_3) δ 202.6, 95.2, 87.0, 60.5, 42.2, 34.1, 21.8

Known compound[209]

4-methyl-N-(5-methylhexa-3,4-dien-1-yl)benzenesulfonamide (3.10)

MD-P1-19



To a solution of 0.3 g aminoallene **3.9** (2.7 mmol, 1eq.) in 25 ml DCM were added 0.51 g *p*-toluene sulfonyl chloride (2.7 mmol, 1eq.) and 0.41 ml triethylamine (0.3 g, 2.97 mmol, 1.1 eq.) at 0 °C. Then, the solution was stirred for 24 h at room temperature and the solvent was removed subsequently in vacuo. The residue was purified by flash column chromatography (EtOAc:cyclohexane 1:2) resulting in 91% of product **3.10** (0.65 g, 2.46 mmol) as colourless oil.

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[209] J. K. Crandall, T. Reix, *J. Org. Chem.,* **1992**, *57*, 6759-6764.

^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.74 (d, J = 8.2 Hz, 2H), 7.30 (d, J = 8.1 Hz, 2H), 4.82 (m, J = 9.0, 6.0, 2.9 Hz, 1H), 4.50 (t, J = 5.9 Hz, 1H), 3.02 (q, J = 6.4 Hz, 2H), 2.43 (s, 3H), 2.08 (q, J = 6.4 Hz, 2H), 1.65 (s, 3H), 1.64 (s, 3H)

^{13}C NMR (101 MHz, Chloroform-*d*) δ 202.5, 143.5, 137.2, 129.8, 127.2, 96.7, 85.2, 77.2, 42.5, 29.1, 21.7, 20.7

Known compound[207]

General procedure for the preparation of DES:

The respective compounds were filled in a flask and heated in oil bath for about 10-60 min until the mixture was a homogenous liquid. The DESs were used directly without a further purification step.

General procedure for the cycloisomerisation of allenes (3.4a-e and 3.9-3.10)

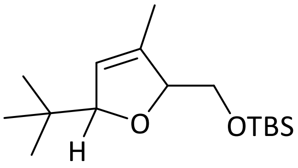
To a mixture of the respective allene (25 mg) and 1 mL of the respective solvent the respective gold catalyst (5 mol%) was added. The solution was stirred at respective temperature and small samples were periodically withdrawn; they were diluted with water and extracted with diethyl ether, and the extract was analysed by TLC and GC. The reaction was continued until no further allene was detected. Upon completion, the mixture was diluted with water (1 ml) and extracted from the reaction mixture with hexane (3 x 2 mL). The combined organic layers were concentrated in vacuo. The crude product was purified by column chromatography on silica gel if necessary.

General procedure for the recycling experiments

In a snap cap Allene **3.4a** (25 mg, 82.10 µmol) and the respective catalysts (0.05 eq.) as well as silver triflate (0.05 eq.) if indicated were dissolved in 5 ml of betaineHCl:urea:methanol ((m:m:m) 1 : 2.2 : 1) and stirred for 3 h at 80 °C. Then the product was removed by extraction with cyclohexane (3 x 2 ml). Allene **3.4a** (25 mg, 82.10 µmol) was added subsequently to the DES followed by a repetition of the procedure.

tert-butyl((5-(tert-butyl)-3-methyl-2,5-dihydrofuran-2-yl)methoxy)dimethylsilane (**3.11a**)

MD-P30



Colourless oil,

^{1}H NMR (600 MHz, Benzene-d_6) δ 5.29 (p, *J* = 1.6 Hz, 1H), 4.63 – 4.59 (m, 1H), 4.54 – 4.49 (m, 1H), 3.70 (dd, *J* = 10.7, 4.4 Hz, 1H), 3.64 (dd, *J* = 10.7, 4.1 Hz, 1H), 1.60 (td, *J* = 1.8, 1.1 Hz, 3H), 0.99 (s, 9H), 0.95 (s, 9H), 0.10 (s, 6H)

^{13}C NMR (151 MHz, Benzene-d_6) δ 138.5, 123.3, 94.1, 89.0, 65.6, 35.9, 26.1, 25.8, 18.5, 12.9, -5.2

Known compound[210]

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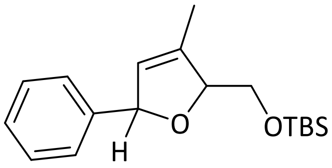
[210] A. Hoffmann-Röder, N. Krause, *Org. Lett.,* **2001**, *3*, 2537-2538.

tert-butyldimethyl((3-methyl-5-phenyl-2,5-dihydrofuran-2-yl)methoxy)silane (**3.11b**)

MD-P30



Colourless oil,

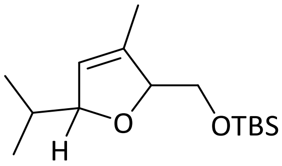
^{1}H NMR (600 MHz, Benzene-*d*$_6$) δ 7.34 – 7.30 (m, 2H), 7.22 – 7.17 (m, 2H), 7.12 – 7.08 (m, 1H), 5.83 (dt, *J* = 5.6, 1.9 Hz, 1H), 5.34 (q, *J* = 1.7 Hz, 1H), 4.81 – 4.75 (m, 1H), 3.82 – 3.75 (m, 1H), 3.73 – 3.64 (m, 1H), 1.57 (td, *J* = 1.8, 1.0 Hz, 3H), 1.00 (s, 9H), 0.11 (d, *J* = 11.7 Hz, 6H)

^{13}C NMR (151 MHz, Benzene-*d*$_6$) δ 143.8, 137.0, 128.6, 127.6, 126.6, 126.5, 89.2, 87.6, 65.2, 26.1, 18.6, 12.6, -5.2

Known compound[211]

tert-butyl((5-isopropyl-3-methyl-2,5-dihydrofuran-2-yl)methoxy)dimethylsilane (**3.11c**)

MD-P30



Colourless oil,

^{1}H NMR (600 MHz, Benzene-*d*$_6$) δ 5.26 (d, *J* = 1.7 Hz, 1H), 4.62 (ddt, *J* = 3.8, 2.9, 1.1 Hz, 2H), 3.75 – 3.69 (m, 1H), 3.68 – 3.61 (m, 1H), 1.73 (pd, *J* = 6.7, 5.1 Hz, 1H), 1.60 (dt, *J* = 1.7, 0.8 Hz, 3H), 0.99 (s, 9H), 0.96 (d, *J* = 6.8 Hz, 3H), 0.93 (d, *J* = 6.8 Hz, 3H), 0.09 (d, *J* = 1.8 Hz, 6H)

^{13}C NMR (151 MHz, Benzene-*d*$_6$) δ 137.9, 124.2, 90.8, 88.7, 65.6, 34.3, 26.1, 18.5, 18.1, 12.9, -5.2

Known compound[204]

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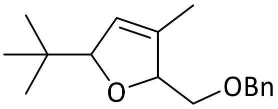
[211] C. Deutsch, A. Hoffmann-Röder, A. Domke, N. Krause, *Synlett*, **2007**, 0737-0740.

2-((benzyloxy)methyl)-5-(tert-butyl)-3-methyl-2,5-dihydrofuran (**3.11d**)

MD-P30



Colourless oil,

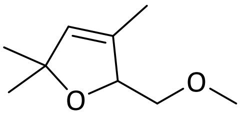
^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.40 – 7.30 (m, 4H), 7.29 – 7.26 (m, 1H), 5.44 (h, *J* = 1.6 Hz, 1H), 4.75 (dtdt, *J* = 5.4, 4.3, 2.2, 1.2 Hz, 1H), 4.61 (s, 1H), 4.41 (ddd, *J* = 4.4, 3.6, 2.1 Hz, 1H), 3.61 (dd, *J* = 10.1, 4.2 Hz, 1H), 3.52 – 3.49 (m, 1H), 1.73 (q, *J* = 1.6 Hz, 3H), 0.86 (s, 9H)

^{13}C NMR (126 MHz, Chloroform-*d*) δ 138.6, 137.6, 128.4, 127.7, 127.6, 123.3, 94.0, 86.7, 73.3, 72.9, 34.4, 26.0, 12.0

Known compound[212]

5-(methoxymethyl)-2,2,4-trimethyl-2,5-dihydrofuran (**3.11e**)

MD-P30



Colourless oil,

^{1}H NMR (500 MHz, Chloroform-*d*) δ 5.44 (p, *J* = 1.7 Hz, 1H), 4.72 (dtt, *J* = 5.5, 2.2, 1.1 Hz, 1H), 3.54 – 3.48 (m, 1H), 3.46 – 3.41 (m, 1H), 3.40 (s, 3H), 1.69 (t, *J* = 1.4 Hz, 3H), 1.32 (s, 3H), 1.27 (s, 3H)

^{13}C NMR (126 MHz, Chloroform-*d*) δ 134.0, 131.4, 87.1, 86.2, 75.2, 59.6, 29.2, 28.2, 12.7

Known compound[204]

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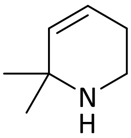
[212] S. R. Minkler, B. H. Lipshutz, N. Krause, *Angew. Chem., Int. Ed.,* **2011**, *50*, 7820-7823.

6,6-dimethyl-1,2,3,6-tetrahydropyridine (**3.13**)

MD-P34



Colourless oil,

^{1}H NMR (400 MHz, Acetonitrile-d_3) δ 5.64 (t, J = 3.7 Hz, 1H), 5.58 (t, J = 2.0 Hz, 1H), 3.15 (dd, J = 12.8, 6.9 Hz, 2H), 2.05 (q, J = 6.9 Hz, 2H), 1.67 (s, 3H), 1.66 (s, 3H)

^{13}C NMR (101 MHz, Acetonitrile-d_3) δ 134.2, 85.6, 77.2, 37.5, 29.1, 22.1, 20.8

Known compound[213]

General procedure for the deprotection of allenes

87.8 µmol of the respective allene and the respective additives were dissolved in 5 ml solvent followed by an addition of the respective catalyst. After the reaction was stirred for the given time, 5 ml water was added, and the mixture was extracted with Et_2O (3 x 4 ml). The combined organic phases were dried by $MgSO_4$ and the solvent evaporated resulting in the respective product.

General procedure for the recycling of the deprotection of allenes

175 µmol of the respective allene and the respective additives were dissolved in 5 ml solvent followed by an addition of the respective catalyst. After the reaction was stirred for given time, the mixture was extracted with cyclohexane (4 x 4 ml) in a microextraction. The combined organic phases were dried by $MgSO_4$ and the solvent evaporated resulting in the respective product. The catalyst phase was directly reused by adding fresh allene.

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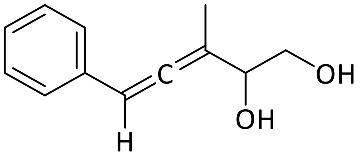
[213] L. Kværnø, P.-O. Norrby, D. Tanner, *Org. Biomol. Chem.,* **2003**, *1*, 1041-1048.

3-methyl-5-phenylpenta-3,4-diene-1,2-diol



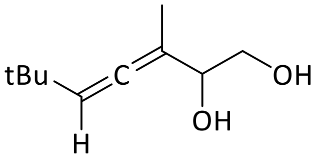
Colourless oil,

^{1}H NMR (500 MHz, Benzene-d_6) δ 7.26 (dt, *J* = 7.2, 1.8 Hz, 2H), 7.15 – 7.10 (m, 2H), 7.03 – 6.98 (m, 1H), 6.14 – 6.09 (m, 1H), 4.12 – 4.01 (m, 1H), 3.61 (dd, *J* = 11.3, 3.7 Hz, 1H), 3.53 – 3.45 (m, 1H), 1.71 – 1.63 (m, 3H)

^{13}C NMR (126 MHz, Benzene-d_6) δ 202.0, 135.2, 129.0, 127.3, 127.1, 104.6, 96.8, 73.2, 66.0, 15.6

MS (ESI (m/z) $[C_{12}H_{14}O_2Na]^+$) calculated: m/z = 213.0801; found: 213.0876

3,6,6-trimethylhepta-3,4-diene-1,2-diol



Colourless oil,

^{1}H NMR (600 MHz, Benzene-d_6) δ 5.19 – 5.10 (m, 1H), 3.95 (s, 1H), 3.56 (d, J = 11.5 Hz, 1H), 3.42 (dd, J = 11.1, 7.1 Hz, 1H), 1.61 (dd, J = 3.0, 0.6 Hz, 3H), 0.98 (s, 9H)

^{13}C NMR (151 MHz, Benzene-d_6) δ 197.3, 169.7, 105.3, 102.1, 72.6, 65.3, 31.8, 29.9, 15.4

MS (ESI (m/z) $[C_{10}H_{18}O_2Na]^+$) calculated: m/z = 193.1204; found: 193.1196

Preparation of the ^{19}F-NMR-experiments

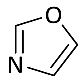
- 5.5 µL TMSOTf was dissolved in *d*-MeOH (0.7 ml) and 1 µL hexafluorobenzene was added, the spectrum was measured around 3 h after.
- 2.6 µL HOTf was dissolved in *d*-MeOH (0.7 ml) and 1 µL hexafluorobenzene was added, the spectrum was measured around 3 h after.
- 20.7 mg $Bi(OTf)_3$ was dissolved in *d*-MeOH (0.7 ml) and stirred for 24 h, afterwards 1 µL hexafluorobenzene was added, the spectrum was measured around 4 h after stirring.
- 20.7 mg $Bi(OTf)_3$ was dissolved in *d*-MeOH (0.7 ml) and 1 µL hexafluorobenzene was added, the spectrum was measured around 3 h after.
- 20.7 mg $Bi(OTf)_3$ was dissolved in *d*-MeOH (0.7 ml) and refluxed for 2 h, afterwards 1 µL hexafluorobenzene was added, the spectrum was measured around 3 h after stirring.

4. Cyclisation reactions of carboxamides in sustainable media; a way station on the road to sustainable oxazoles

4.1. Oxazoles

4.1.1. Properties of oxazoles

Oxazoles (Figure 89) are a vast subclass of the five-membered heterocyclic azoles, which also includes imidazoles, triazoles and thiazoles.



1,3-oxazole

Figure 89 Unsubstituted oxazole

They are very stable aromatic compounds and their first representatives were discovered in the 1800s while the unsubstituted oxazole was only synthesised in 1947.[214] The prevalence of the oxazole core in a wide diversity of biologically active compounds gave rise to a high interest and curiosity in the synthesis of this compound class (Examples in Figure 90).[215]

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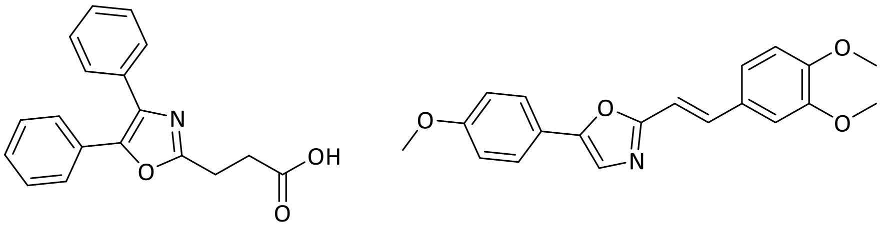
[214] A. Katritzky C. Ramsden E. AAA R. Taylor, *Comprehensive Heterocyclic Chemistry III*, **2008**, Elsevier Science.

[215] Z. Jin, *Nat. Prod. Rep.,* **2011**, *28*, 1143-1191;
J. R. Lewis, *Nat. Prod. Rep.,* **1995**, *12*, 135-163;
P. Wipf, *Chem. Rev.,* **1995**, *95*, 2115-2134.

This is based on their wide-ranging applications, in particular as anti-tumor[216], anti-bacterial[217] especially anti-tubercular[218], anti-fungal[219] and anti-inflammatory activities.[220]



Oxaprozin
NSAID

Annuloline
Fluorescent alkaloid from *Lolium multiflorum*

Figure 90 Examples for oxazole core containing biologically active compounds

In addition to this, oxazoles attracts significant attention as useful precursors in organic synthesis, inter alia in dye chemistry such as fluorescent whitening agents.[221]

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[216] Y. Kato, N. Fusetani, S. Matsunaga, K. Hashimoto, S. Fujita, T. Furuya, *J. Am. Chem. Soc.,* **1986**, *108*, 2780-2781;
S. Carmeli, R. E. Moore, G. M. L. Patterson, T. H. Corbett, F. A. Valeriote, *J. Am. Chem. Soc.,* **1990**, *112*, 8195-8197.

[217] G. Crank, M. Neville, R. Ryden, *J. Med. Chem.,* **1973**, *16*, 1402-1405;
N. R. Stokes, N. Baker, J. M. Bennett, P. K. Chauhan, I. Collins, D. T. Davies, M. Gavade, D. Kumar, P. Lancett, R. Macdonald, L. MacLeod, A. Mahajan, J. P. Mitchell, N. Nayal, Y. N. Nayal, G. R. W. Pitt, M. Singh, A. Yadav, A. Srivastava, L. G. Czaplewski, D. J. Haydon, *Bioorg. Med. Chem. Lett.,* **2014**, *24*, 353-359.

[218] X. Lu, X. Liu, B. Wan, S. G. Franzblau, L. Chen, C. Zhou, Q. You, *Eur. J. Med. Chem.,* **2012**, *49*, 164-171.

[219] C.-K. Ryu, R.-Y. Lee, N. Y. Kim, Y. H. Kim, A. L. Song, *Bioorg. Med. Chem. Lett.,* **2009**, *19*, 5924-5926;
Shamsuzzaman, M. S. Khan, M. Alam, Z. Tabassum, A. Ahmad, A. U. Khan, *Eur. J. Med. Chem.,* **2010**, *45*, 1094-1097.

[220] K. Brown, J. F. Cavalla, D. Green, A. B. Wilson, *Nature,* **1968**, *219*, 164;
E. Fernandes, D. Costa, S. A. Toste, J. L. F. C. Lima, S. Reis, *Free Radicals Biol. Med.,* **2004**, *37*, 1895-1905.

[221] I. H. Leaver, B. Milligan, *Dyes Pigm.,* **1984**, *5*, 109-144.

4.1.2. Synthesis of oxazoles

There are three important classical oxazole syntheses known (Figure 91):

- **Van Leusen reaction:**[222] a reaction of a toluene sulfonylmethyl isocyanide and an aldehyde in the presence of a base forming 4-substituated oxazoles
- **Fischer oxazole synthesis:**[223] A reaction of a cyanohydrin and an aldehyde in the presence of an acid forming 2,5-disubstituted oxazoles
- **Robinson–Gabriel synthesis:**[224] Intramolecular reaction of an amino ketone with the elimination of water forming 2,4,5-trisubstituted oxazoles

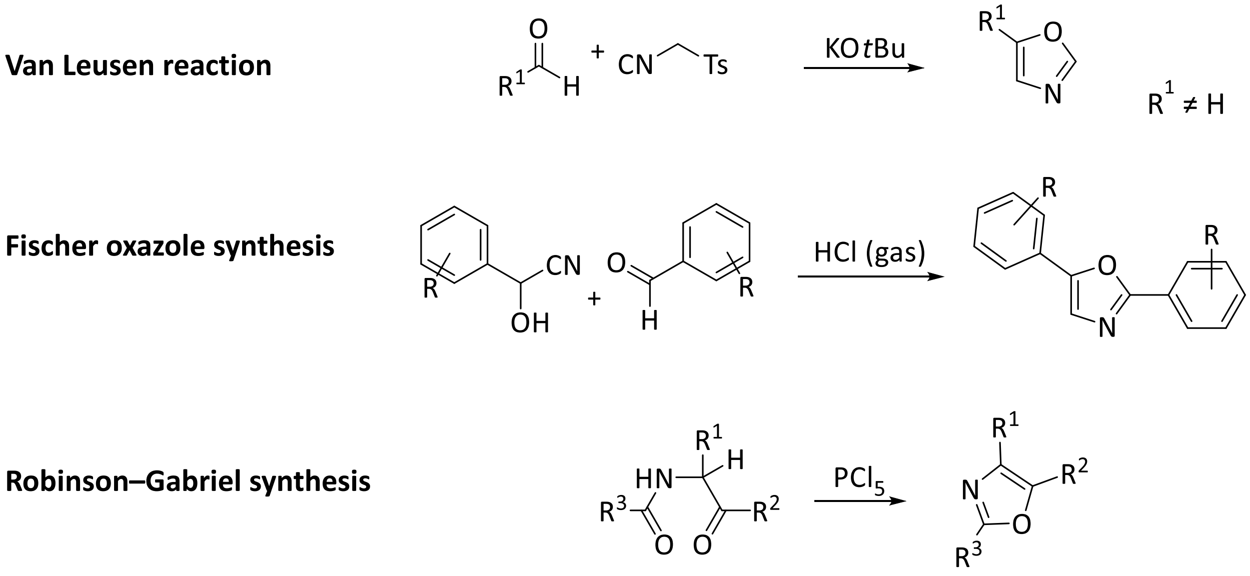

Figure 91 classical oxazole syntheses

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[222] O. H. Oldenziel, D. Van Leusen, A. M. Van Leusen, *J. Org. Chem.,* **1977**, *42*, 3114-3118.

[223] E. Fischer, in *Untersuchungen aus Verschiedenen Gebieten*, Springer, **1924**, pp. 292-300.

[224] R. Robinson, *J. Chem. Soc., Trans.,* **1909**, *95*, 2167-2174;
S. Gabriel, *Ber. Dtsch. Chem. Ges.,* **1910**, *43*, 134-138;
S. Gabriel, *Ber. Dtsch. Chem. Ges.,* **1910**, *43*, 1283-1287.

However, these classical methods suffer from harsh conditions and lack of sustainability. Much experimentation has been done here, and a variety of methods to synthesise oxazole derivates,[225] including intramolecular alkyne additions catalysed by metals, such as mercury,[226] zinc,[227] iron,[227] ruthenium,[228] palladium,[229] silver[230] and gold[231] were reported. In particular, N-propargylamides emerged as a promising building blocks for the synthesis of substituted oxazoles. Especially the gold-catalysed conversion of N-propargyl carboxamides received wide attention in recent years.

In principal, two cyclisation pathways for **4.1** are conceivable: a 5-exo-type cyclization to **4.2** or a 6-endo-type cyclisation to molecule **4.4** (Figure 92).[232]

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[225] P. Wipf, J.-L. Methot, *Org. Lett.,* **2001**, *3*, 1261-1264;
T. R. Kelly, F. Lang, *J. Org. Chem.,* **1996**, *61*, 4623-4633;
P. Wipf, T. H. Graham, *J. Am. Chem. Soc.,* **2004**, *126*, 15346-15347;
A. Tárraga, P. Molina, D. Curiel, M. Desamparados Velasco, *Tetrahedron,* **2001**, *57*, 6765-6774;
M. Lautens, A. Roy, *Org. Lett.,* **2000**, *2*, 555-557;
M. Ohba, H. Kubo, T. Fujii, H. Ishibashi, M. V. Sargent, D. Arbain, *Tetrahedron Lett.,* **1997**, *38*, 6697-6700;
J. Sisko, A. J. Kassick, M. Mellinger, J. J. Filan, A. Allen, M. A. Olsen, *J. Org. Chem.,* **2000**, *65*, 1516-1524.

[226] J. C. Lee, I.-G. Song, *Tetrahedron Lett.,* **2000**, *41*, 5891-5894.

[227] P. Knochel, A. K. Steib, *Synfacts,* **2012**, *8*, 1362-1362.

[228] M. D. Milton, Y. Inada, Y. Nishibayashi, S. Uemura, *Chem. Commun.,* **2004**, 2712-2713.

[229] A. Arcadi, S. Cacchi, L. Cascia, G. Fabrizi, F. Marinelli, *Org. Lett.,* **2001**, *3*, 2501-2504;
J. K. Mali, B. S. Takale, V. N. Telvekar, *RSC Adv.,* **2017**, *7*, 2231-2235.

[230] D. J. Ritson, C. Spiteri, J. E. Moses, *J. Org. Chem.,* **2011**, *76*, 3519-3522;
Y. Hu, R. Yi, F. Wu, B. Wan, *J. Org. Chem.,* **2013**, *78*, 7714-7726.

[231] A. S. K. Hashmi, J. P. Weyrauch, W. Frey, J. W. Bats, *Org. Lett.,* **2004**, *6*, 4391-4394;
W. J. P., H. A. S. K., S. Andreas, H. Tobias, S. Stefanie, L. Anna, R. Matthias, H. Melissa, V. Jorge, R. Frank, F. Wolfgang, B. J. W., *Chem. - Eur. J.,* **2010**, *16*, 956-963;
H. A. S. K., R. Matthias, S. Stefan, V. Jorge, F. Wolfgang, *Eur. J. Org. Chem.,* **2006**, , 4905-4909;
D. P. W., C. Alex, D. Lidia, *Angew. Chem., Int. Ed.,* **2011**, *50*, 8931-8935.

[232] H. A. S. K., R. Matthias, S. Stefan, V. Jorge, F. Wolfgang, *Eur. J. Org. Chem.,* **2006**, 4905-4909.

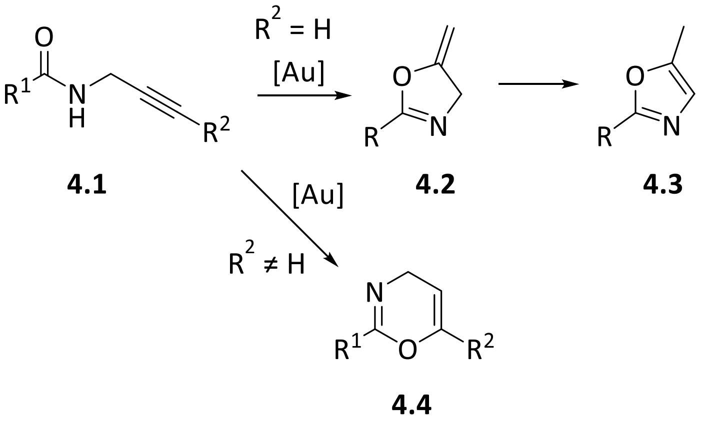

Figure 92 Gold-catalysed cycloisomerisation of propargylamides

Investigations indicate that the 5-exo-type cyclisation occurs in general for terminal alkynes while substituted alkynes undergo in general a 6-endo-type cyclisation due to the different stability of the vinylgold intermediates.[233] It is noteworthy that the intermediate methylene-3-oxazoline **4.2** could be directly observed in this mild reaction, a rarely occurring species in metal catalysis.[234] Olefin **4.2** resulting from the 5-exo-type cyclisation could be proved by NMR spectroscopy during the reaction, this finding is supported by quantum mechanical calculations, which also show that the following aromatisation is favoured by about 15 kcal/mol.[235] As a result, *Hashmi* et al. proposed the following reaction mechanism (Figure 93).235

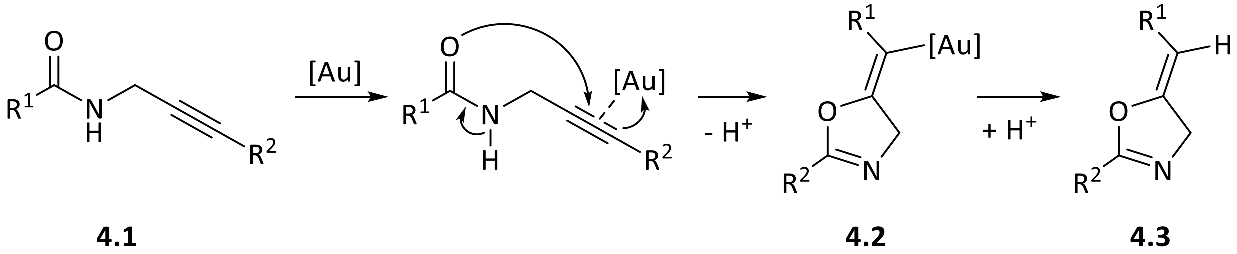

Figure 93 Proposed reaction mechanism235

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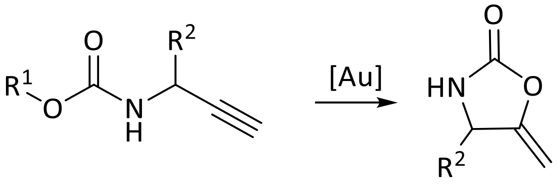
[233] A. S. K. Hashmi, A. M. Schuster, F. Rominger, *Angew. Chem., Int. Ed.,* **2009**, *48*, 8247-8249.

[234] J. J. Kennedy-Smith, S. T. Staben, F. D. Toste, *J. Am. Chem. Soc.,* **2004**, *126*, 4526-4527;
M. Tiecco, L. Testaferri, M. Tingoli, F. Marini, *J. Org. Chem.,* **1993**, *58*, 1349-1354;
G. Capozzi, C. Caristi, M. Gattuso, G. S. d'Alcontres, *Tetrahedron Lett.,* **1981**, *22*, 3325-3328.

[235] A. S. K. Hashmi, J. P. Weyrauch, W. Frey, J. W. Bats, *Org. Lett.,* **2004**, *6*, 4391-4394.

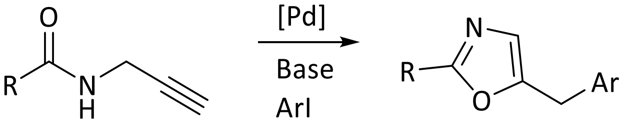
Furthermore, a similar gold-catalysed protocol can be used for the cyclisation of carbamates to the corresponding oxazolidinones, however this type of cyclisation goes hand in hand with the loss of the R¹ substituent (Figure 94).[236]



4.4 **4.5**

Figure 94 Gold-catalysed formation of oxazolidinones

As stated previously, the cyclisation of propargylamides can also be catalysed by other metals than gold, in doing so Pd catalysts occupy a special position due to their ability to catalyse a coupling step followed by the in-situ cyclisation (Figure 95).[237]



4.1 **4.6**

Figure 95 Formation of disubstituted oxazoles catalysed by palladium

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[236] A. Buzas, F. Gagosz, *Synlett,* **2006**, *2006*, 2727-2730; E.-S. Lee, H.-S. Yeom, J.-H. Hwang, S. Shin, *Eur. J. Org. Chem.,* **2007**, *2007*, 3503-3507.

[237] A. Arcadi, S. Cacchi, L. Cascia, G. Fabrizi, F. Marinelli, *Org. Lett.,* **2001**, *3*, 2501-2504.

4.2. Problem statement

Despite, there have been some reports on new approaches to fulfil the sustainability benchmark, like using greener solvents,[238] metal free reactions[239] or utilisation of ultrasound.[240] These cyclisations are mostly carried out in classical VOCs. One of the most promising approaches is the use of Deep Eutectic Solvents (DES). All the previously reported synthesis of oxazole notwithstanding, gold-catalysed cycloisomerisation of N-Propargyl carboxamides have not been performed in green low melting mixtures, as far as it is known. With the advantages of DESs in one hand and the well-established gold-catalysis in the other a sustainable synthesis of oxazole derivates seems to be tangibly near. Therefore, it is envisaged to use the cycloisomerisation of N-propargyl carboxamides with terminal alkynes to the corresponding functionalised oxazoles as tool for a greener synthesis.

Furthermore, the reaction scope should be expanded to a variety of different substituents as well as to other catalysts. In addition, the optimised reaction system will happen to be recyclable in order to avoid waste and reduce the environmental impact to a minimum.

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[238] N. Azizi, Z. Rahimi, M. Alipour, *C. R. Chim.,* **2015**, *18*, 626-629.

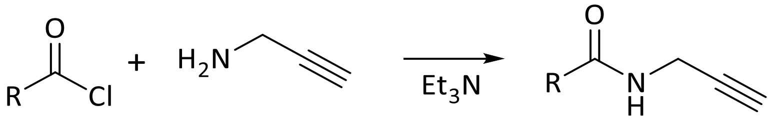
[239] W. Zhou, C. Xie, J. Han, Y. Pan, *Org. Lett.,* **2012**, *14*, 4766-4769;
Y.-m. Pan, F.-j. Zheng, H.-x. Lin, Z.-p. Zhan, *J. Org. Chem.,* **2009**, *74*, 3148-3151.

[240] B. S. Singh, H. R. Lobo, D. V. Pinjari, K. J. Jarag, A. B. Pandit, G. S. Shankarling, *Ultrason. Sonochem.,* **2013**, *20*, 287-293.

4.3. Results and discussion

4.3.1. Synthesis of the propargylamides

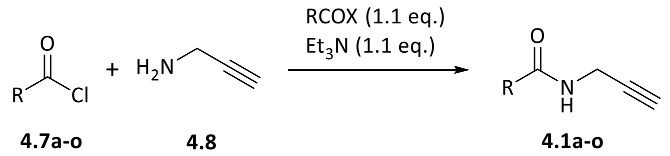
The majority of the propargylamides were synthesised in a straightforward manner by mixing the respective acyl halides with a propargyl amine in presence of a base at reduced temperatures (Figure 96). DCM was mostly used as solvent, but EtOAc as greener alternative could also be used with comparable yields.

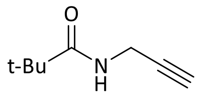


4.7 **4.8** **4.1**

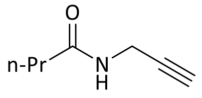
Figure 96 Synthesis of substituted propargylamides

In the most cases the reaction resulted in good yields without the need of further purification. The following propargylamides were synthesised using this protocol (see Figure 97):

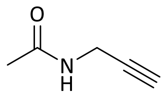




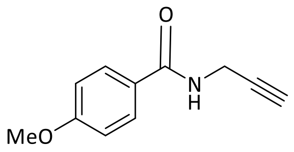
4.1a (X = Cl)
95%



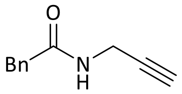
4.1b (X = Cl)
98%



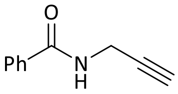
4.1c (X = Cl)
97%



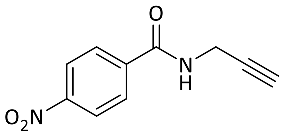
4.1d (X = Cl)
79%



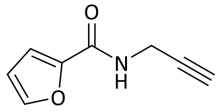
4.1e (X = Cl)
93%



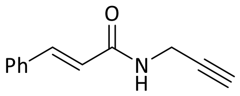
4.1f (X = Cl)
85%



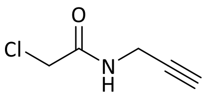
4.1g (X = Cl)
22%



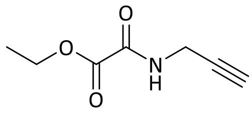
4.1h (X = Cl)
69%



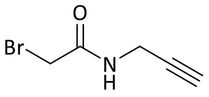
4.1i (X = Cl)
78%



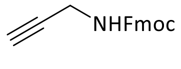
4.1j (X = Cl)
82%



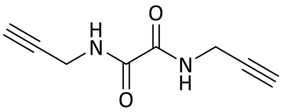
4.1k (X = Cl)
98%



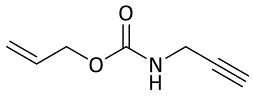
4.1l (X = Br)
53%



4.1m (X = Cl)
76%



4.1n (X = Cl)
0%



4.1o (X = Cl)
75%

Figure 97 Synthesised propargylamides

Despite the overall good yields, some acyl halides did not react well. Especially electron-withdrawing substituents like bromide or nitrophenyl resulted in moderate or poor yields. Furthermore, the dipropargylamide **4.1n** prepared from oxalyl chloride was not isolable, even at -78 °C due to the high reactivity of oxalyl chloride.

In addition, a propargylamide bearing a trifluoromethyl group was synthesised in a good yield of 82% from ethyl-trifluoroacetate and propargyl amine.

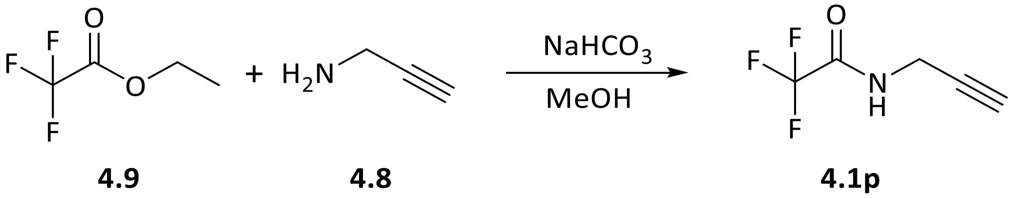
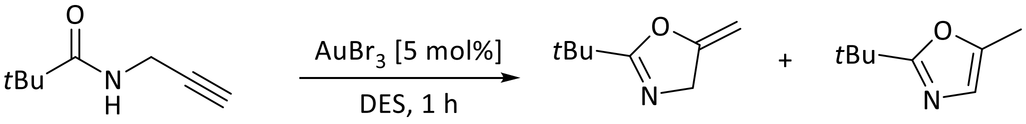


Figure 98 Synthesis of fluorinated propargylamides

4.3.2. Cyclisation reactions

Initially, the solvent was tailored, in particular the choice of DES in the reaction of oxazole **4.1a** with $AuBr_3$ [5 mol%] at chosen temperatures (Table 34).

Table 34 Cycloisomerisation of N-Propargyl carboxamides **4.1a** catalysed by gold bromide in different DESs



4.1a **4.2a** **4.3a**

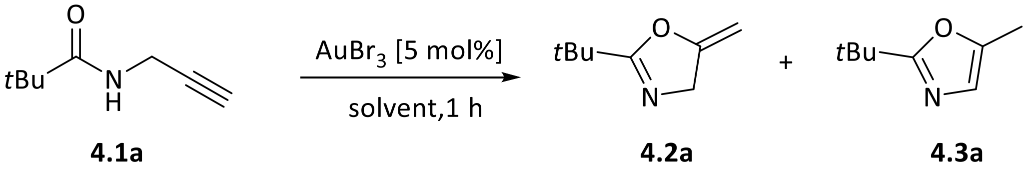
Entry	**Solvent (mol:mol)**	**Temp.**	**Overall Yield***
1	CHCl:urea (1:2)	20 °C	99%
2	CHCl:urea (1:2)	80 °C	99%
3	CHCl:glycerol (1:2)	20 °C	36%
4	CHCl:glycerol (1:2)	40 °C	68%
5	betaineHCl:glycerol (1:2)	40 °C	74%
6	CHCl:fructose (1:2)	80 °C	73%
7	CHCl:dimethylurea (1:2)	80 °C	65%
8	urea:guanidinium HCl (6:4)	80 °C	0%
9	CHCl:sorbitol (1:1)	80 °C	56%
10	CHCl:DMU (1:2)	80 °C	65%
11	CHCl:sorbitol:glycerol	80 °C	49%
12	CHCl:valeriansäure	40 °C	66%
13	betaineHCl:glycerol (1:2)	40 °C	74%
14	betaine:lactic acid (1:2)	40 °C	22%
15	betaineHCl:urea (15:85)	80 °C	93% (99%)**
16	lactic acid:proline (2:1)	80 °C	99%
17	CHCl:malonic acid (1:1)	80 °C	99% (96%)**

* Determined by GC with internal standard, ** isolated yield

Two well-established DES combinations were investigated at the outset of this study (Table 34, entries 1-4). They are liquid at room temperature and showed promising results at mild temperatures. In particular the combination of CHCl:urea showed a quantitative overall yield but unfortunately this solvent system was very unreliable and as a result proved to be unsuitable. Because of this drawback, the view was extended to DESs with high viscosities at room temperature (Table 34, entries 5-17). Therefore, the reaction mixtures must be heated up to 40 or 80 °C to enable a sufficient stirability. However, the mostly used mixtures could only achieve low or moderate yields up to 74% (Table 34, entries 5-14) or even no conversion (Table 34, entry 8). Only after using three further mixtures the desired products could be obtained in good to quantitative overall yields (Table 34, entries 15-17). In the case of betaineHCl:urea (Table 34, entry 15), lactic acid:proline (Table 34, entry 16) and CHCl:malonic acid (1:1) (Table 34, entry 17) quantitative yields determined by GC as well as isolated yields could be achieved. Given the fact that betaineHCl:urea and CHCl:malonic acid were easier to handle, these solvent systems were used as method of choice in further optimisations.

In addition, other green solvents were tested (Table 35).

Table 35 Cycloisomerisation of N-Propargyl carboxamides **4.1a** catalysed by gold bromide in different solvents



Entry	Solvent	Time	Temp.	Overall Yield*
1	PEG (~2000 g/mol)	0.5 h	80 °C	16%
2	PPG (~3500 g/mol)	0.5 h	20 °C	99%
3	propylene carbonate	1 h	20 °C	95%

* Determined by GC with internal standard

The first tested polymer PEG (polyethylene glycol) with an average molecular weight of 2000 g/mol did not perform well in this reaction even at 80 °C, which was also necessary for the stirability (Table 35, entry 1). Quantitative yields could be achieved by using the less polar polymer PPG (polypropylene glycol), which is liquid at room temperature (Table 35, entry 2) and with propylene carbonate, a cyclic carbonate ester (Table 35, entry 3).
Even though these two systems demonstrated an astonishing performance, they failed in terms of easy separation of the product since both solvents are miscible with the most organic solvents, which makes an extraction almost impossible. As a result, these systems were not examined further.

In the next step the selectivity between the aromatic oxazole **4.2a** and the non-aromatic product **4.3a** was examined. As mentioned before, this reaction is well-known and it could be shown that gold(III) catalysts favour an aromatisation of the methylene-3-oxazoline to the aromatic product, whereas gold(I) catalysts afforded mainly the non-aromatic product.[241] Also higher temperatures should favour the formation of the aromatic product, due to the superior thermodynamic stability.

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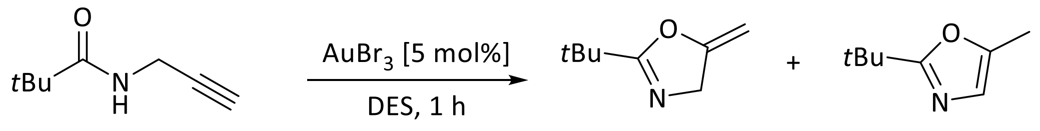
[241] A. S. K. Hashmi, J. P. Weyrauch, W. Frey, J. W. Bats, *Org. Lett.,* **2004**, *6*, 4391-4394;
H. A. S. K., R. Matthias, S. Stefan, V. Jorge, F. Wolfgang, *Eur. J. Org. Chem.,* **2006**, *2006*, 4905-4909;
A. S. K. Hashmi, A. M. Schuster, S. Gaillard, L. Cavallo, A. Poater, S. P. Nolan, *Organometallics,* **2011**, *30*, 6328-6337.

Table 36 Selectivity determination of the cycloisomerisation of N-Propargyl carboxamides catalysed by gold bromide in different DESs

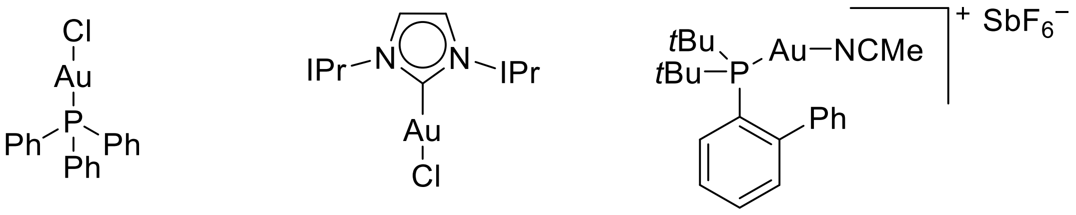


4.1a **4.2a** **4.3a**

Entry	DES (mol:mol)	Temp.	Overall Yield*	Selectivity* 2/3
1	CHCl:glycerol (1:2)	20 °C	36%	>99:1
2	CHCl:glycerol (1:2)	60 °C	68%	>99:1
3	CHCl:malonic acid (1:1)	20 °C	82%	>99:1
4	CHCl:malonic acid (1:1)	40 °C	99%	<1:99
5	CHCl:malonic acid (1:1)	60 °C	99%	<1:99
6	CHCl:malonic acid (1:1)	80 °C	99%	<1:99
7	CHCl:urea (1:2)	20 °C	99%	>99:1
8	CHCl:urea (1:2)	80 °C	99%	<1:99
9	CHCl:DMU (1:2)	80 °C	75%	80:20
10	CHCl:sorbitol:glycerol (2:1:1)	40°C	49%	>99:1

* Determined by GC with internal standard

Remarkably, the formation of **4.2a** even with a gold(III) catalyst in the solvent systems CHCl:glycerol (Table 36, entry 1), CHCl:malonic acid (Table 36, entry 3) and CHCl:urea (Table 36, entry 7) could be observed. Even at higher temperature of 60 °C in CHCl:glycerol the reaction afforded exclusively **4.2a** (Table 36, entry 2). Product **4.2a** was stable under these conditions and aromatisation did not take place. However, as predicted, higher temperatures in CHCl:malonic acid and CHCl:urea (Table 36, entry 4-6 and entry 8) favour the formation of the thermodynamically more stable product **4.3a**. In the case of CHCl:dimethylurea(DMU) and CHCl:sorbitol:glycerol (Table 36, entry 9 and 10) only moderate yields but high selectivity could be achieved.



A Triphenylphosphine gold(I) chloride

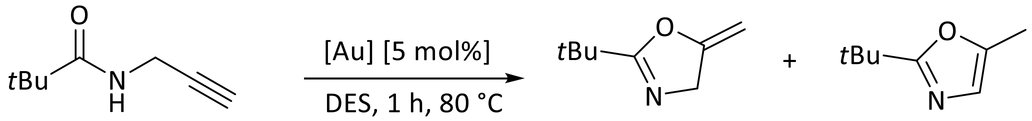
B IprAuCl

C JohnPhos Au(MeCN)SbF_6

Figure 99 Commercially available gold complexes

Inspired by these results, it was interesting to see how other gold catalysts (Figure 99) work in this reaction at higher temperatures, especially if they can change the selectivity even at 80 °C.

Table 37 Cycloisomerisation of N-Propargyl carboxamides with different gold catalysts



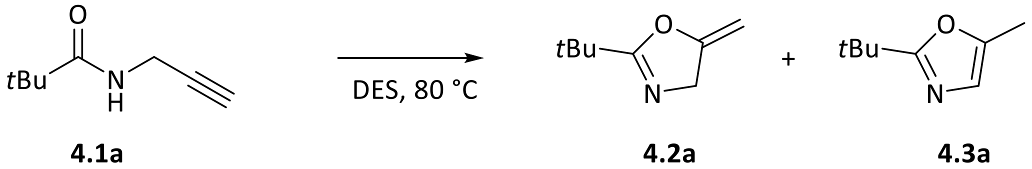
4.1a **4.2a** **4.3a**

Entry	Catalyst	DES (mol:mol)	Overall Yield*	Selectivity* 2/3
1	AuCl	betaineHCl:urea (15:85)	36%	<1:99
2	$HAuCl_4$	betaineHCl:urea (15:85)	99%	<1:99
3	AuI	betaineHCl:urea (15:85)	86%	<1:99
4	**A***	betaineHCl:urea (15:85)	7%	<1:99
5	**C**	betaineHCl:urea (15:85)	47%	<1:99

* Determined by GC with internal standard, **Addition of 5 mol% AgOTf

Unfortunately, the selectivity could not be influenced anymore at this high temperature, so only the aromatic product **4.3** could be observed. However, ligand-free gold catalysts result in good or quantitative yields (Table 37, entries 1-3). Whereas gold catalyst bearing phosphine ligands showed low yields (Table 37, entries 4 and 5). This observation seems to be a general characteristic for DES systems, since gold catalyst bearing phosphine ligands showed also a low performance in the cyclisation of allenes in chapter 3.4.2. Additionally, metal-containing DESs were used, which may have a "Janus-faced" character, being both solvent and catalyst.

Table 38 Cycloisomerisation of N-Propargyl carboxamides with metal containing DES



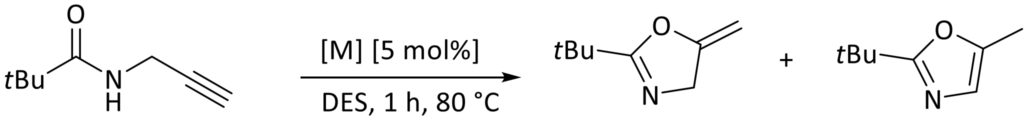
Entry	DES (mol:mol)	Time	Overall Yield*	Selectivity* 2/3
1	CHCl:$FeCl_3$ (1:2)	1 h	99%	<1:99
2	urea:$ZnCl_2$ (7:2)	1 h	82%	<1:99
3	urea:$ZnCl_2$ (7:2)	0.5 h	20%	<1:99
4	urea:$ZnBr_2$ (7:2)	1 h	99% (98%)**	<1:99
5	urea:$ZnBr_2$ (7:2)	0.5 h	47%	<1:99
6	CHCl:$ZnCl_2$ (1:2)	1 h	99% (96%)**	<1:99
7	CHCl:$ZnBr_2$ (1:2)	1 h	77%	<1:99

* Determined by GC with internal standard, ** Isolated yield

In doing so, remarkable yields could be obtained in the most cases. The first tested DES containing $FeCl_3$ achieved quantitative yield but showed a challenging workup (Table 38, entry 1). Next, two mixtures of zinc halides and urea were tested at different reaction times (Table 38, entries 2-5). Both mixtures could achieve good yields after 1 h (Table 38, entries 2 and 4). However, the mixture with $ZnBr_2$ was slightly better than the mixture with $ZnCl_2$ (82% compared to 99%). This became particularly clear at shorter reaction times (20% versus 47%) (Table 38, entries 3 and 5).

Furthermore, two other zinc halide containing mixtures with CHCl were tested, with also promising yields (Table 38, entries 6 and 7), admittedly the handling was more difficult. Other main group catalysts were also tested in this reaction with little success (Table 39).

Table 39 Cycloisomerisation of N-Propargyl carboxamides with different main group catalysts



4.1a **4.2a** **4.3a**

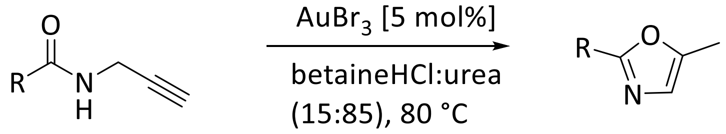
Entry	Catalyst	Solvent (mol:mol)	Overall Yield*	Selectivity 2/3
1	$Ga(OTf)_3$	betaineHCl:urea (15:85)	10%	<1:99
2	$Bi(OTf)_3$	betaineHCl:urea (15:85)	0%	-
3	$BiCl_3$	betaineHCl:urea (15:85)	0%	-
4	$Bi(NO_3)_3$	betaineHCl:urea (15:85)	0%	-

* Determined by GC with internal standard

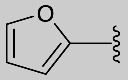
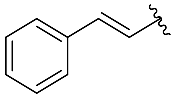
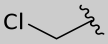
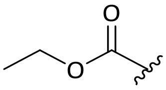
Only $Ga(OTf)_3$ was capable to catalyse this reaction, but only achieved a yield of 10% (Table 39, entry 1). All other used catalysts failed in this reaction system (Table 39, entries 2-4).

Furthermore, it was interesting to see how other substrates would perform in this reaction, therefore the most promising reaction system betaineHCl:urea with gold(III) bromide as catalyst was used.

Table 40 Gold-catalysed cyclisations with different substrates



4.1b-k,o,p **4.3b-k,o,p**

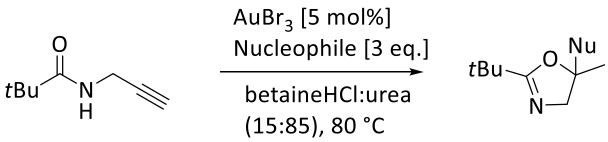
Entry	R =	Product	Time	Yield
1	n-Pr	**4.3b**	24 h	62%
2	Me	**4.3c**	2 h	99%
3	4-methoxyphenyl	**4.3d**	2 h	95%
4	benzyl	**4.3e**	2 h	77%
5	phenyl	**4.3f**	2 h	99%
6	4-nitrophenyl	**4.3g**	2 h	85%
7	CF_3	**4.3p**	24 h	0%
8		**4.3h**	2 h	96%
9		**4.3i**	2 h	88%
10		**4.3j**	2 h	0%
11		**4.3k**	2 h	0%
12	Alloc	**4.3o**	2 h	0%

The substrate having a methyl group reacted smoothly to the corresponding oxazole, whereas a longer alkyl chain gave a lower yield at longer reaction time (Table 40, entries 1 and 2). In addition, electron-rich and electron-deficient aryl groups were well suitable, giving good to excellent yields (Table 40, entries 3-6). Nonetheless, substrate **4.1p** containing a trifluoromethyl substituent turned out to be challenging and showed no conversion (Table 40, entry 7).

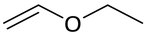
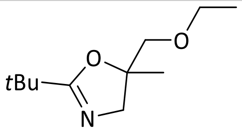
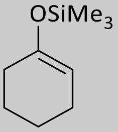
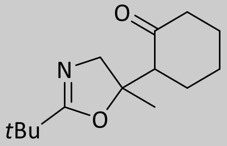
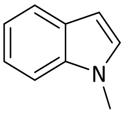
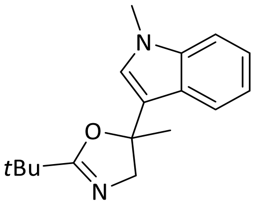
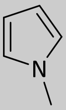
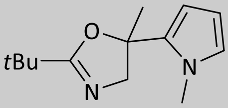
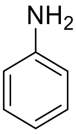
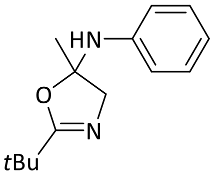
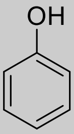
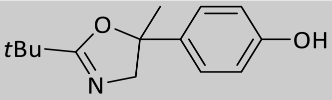
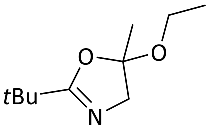
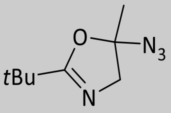
Moreover, substrates bearing a heterocycle or adjacent alkene groups reacted seamless in **4.1h** and **4.1i** (Table 40, entries 8 and 9), whereas more challenging substrates like **4.3j** and **4.3k** (Table 40, entries 10 and 11) and a carbamate substrate were not feasible for this cyclisation (Table 40, entry 12). All in all, it was mostly possible to implement the catalyst solvent system to a broad variant of substrates.

In addition, it was tested if the non-aromatic product could be scavenged by a nucleophile since the olefin **4.2**a should be relatively electrophilic.

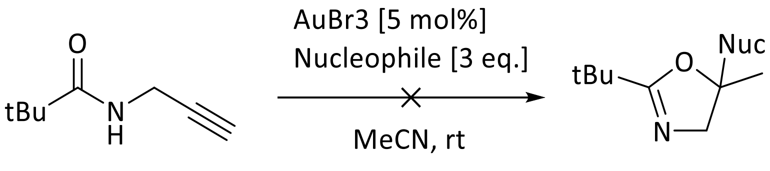
Table 41 Cyclisation reaction in the presence of nucleophiles



4.1a **4.10I-VII**

Entry	Nucleophile		Product	
1		**4.11**		**4.10I**
2		**4.12**		**4.10II**
3		**4.13**		**4.10III**
4		**4.14**		**4.10IV**
5		**4.15**		**4.10V**
6		**4.16**		**4.10VI**
7	EtOH	**4.17**		**4.10VII**
8	NaN$_3$	**4.18**		**4.10VIII**

Unfortunately, none of the desired products could be observed, even though a broad range of nucleophiles were used (Table 41, entries 1-8). The reactions were repeated in acetonitrile, which is known to stabilise the non-aromatic product at room temperature but again no nucleophilic attack could be observed (Figure 100).[243]

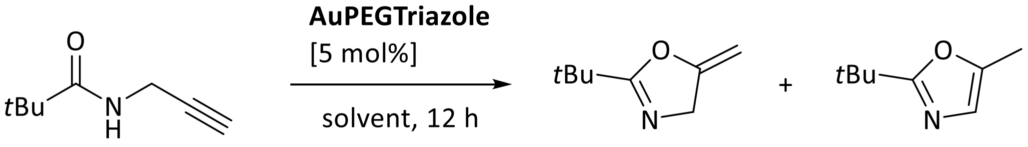


4.1a **4.10**

Figure 100 Cyclisation reaction in the presence of nucleophiles in MeCN

Furthermore, catalyst **AuPEGTriazole** (see chapter 2.3.2) was tested for this cyclisation reaction in different solvents (Table 42).

Table 42 Cycloisomerisation of N-Propargylcarboxamides with catalyst **AuPEGTriazole**



4.1a **4.2a** **4.3a**

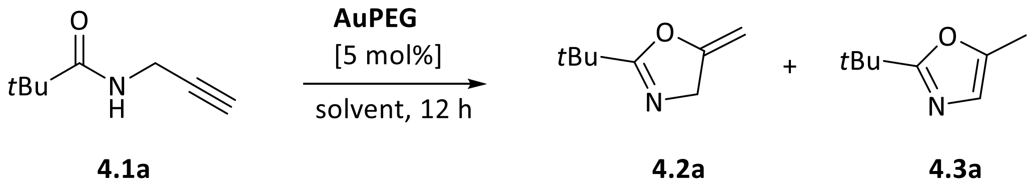
Entry	Solvent (mol:mol)	Additive	Temp.	Overall Yield*	Selectivity 2/3*
1	propylene carbonate	-	20 °C	27%	44:56
2	CHCl:glycerol (1:2)	-	20 °C	10%	<1:99
3	CHCl:urea (1:2)	-	20 °C	12%	<1:99
4	CHCl:glycerol (1:2)	-	80 °C	17%	31:69
5	CHCl:urea (1:2)	-	80 °C	90% (85%)**	11:89
6	propylene carbonate	0.05 eq. AgOTf	20 °C	0%	-
7	CHCl:glycerol (1:2)	0.05 eq. AgOTf	20 °C	0%	-
8	CHCl:urea (1:2)	0.05 eq. AgOTf	20 °C	23%	<1:99
9	CHCl:glycerol (1:2)	0.05 eq. AgOTf	80 °C	25%	<1:99
10	CHCl:urea (1:2)	0.05 eq. AgOTf	80 °C	69% (65%)**	<1:99
11	methanol	0.05 eq. AgOTf	65 °C	48% (50%)**	>99:1

* Determined by GC with internal standard, ** Isolated yield

At the outset of this study propylene carbonate and two eutectic mixtures were tested at room temperature, albeit only moderate yields (Table 42, entries 1-3). Only an increase in temperature could raise the yield up to 90% in the case of CHCl:urea (Table 42, entry 5), while only a marginal increased yield could be observed for CHCl:glycerol (Table 42, entry 4). The selectivity was, as expected, strongly shifted to the aromatic product. In a next step, silver(I) triflate was added to ensure the formation of the active gold cation (Table 42, entries 6-10). However, the addition did not lead to an increase in yield but, on the contrary to decreased yields in all cases. Finally, the green solvent methanol was used resulting in a moderate yield of 48%, but an astonishing selectivity could be observed since only product **4.2a** could be detected. This is remarkable because at this high temperature only product **4.3** could be observed in previous reactions (see Table 36).

The second synthesised PEG-NHC gold complex originating from chapter 2.3.2 was also tested in this reaction but no conversion could be achieved with this catalyst, even with the addition of silver(I) triflate (Table 43).

Table 43 Cycloisomerisation of N-Propargylcarboxamides with catalyst **AuPEG**



Entry	Solvent (mol:mol)	Additive	Temp.	Overall Yield*	Selectivity 2/3*
1	propylene carbonate	-	20 °C	0%	-
2	CHCl:glycerol (1:2)	-	20 °C	0%	-
3	CHCl:urea (1:2)	-	20 °C	0%	-
4	methanol	-	20 °C	0%	-
5	water	-	20 °C	0%	-
6	propylene carbonate	0.05 eq. AgOTf	20 °C	0%	-
7	CHCl:glycerol (1:2)	0.05 eq. AgOTf	20 °C	0%	-
8	CHCl:urea (1:2)	0.05 eq. AgOTf	20 °C	0%	-
9	methanol	0.05 eq. AgOTf	20 °C	0%	-
10	water	0.05 eq. AgOTf	20 °C	0%	-

* Determined by GC with internal standard

Finally, the recyclability of this catalyst system was examined, therefore urea:$ZnBr_2$ and **4.1a** were used and the product was separated by Kugelrohr distillation before using the mixture again (Figure 101).

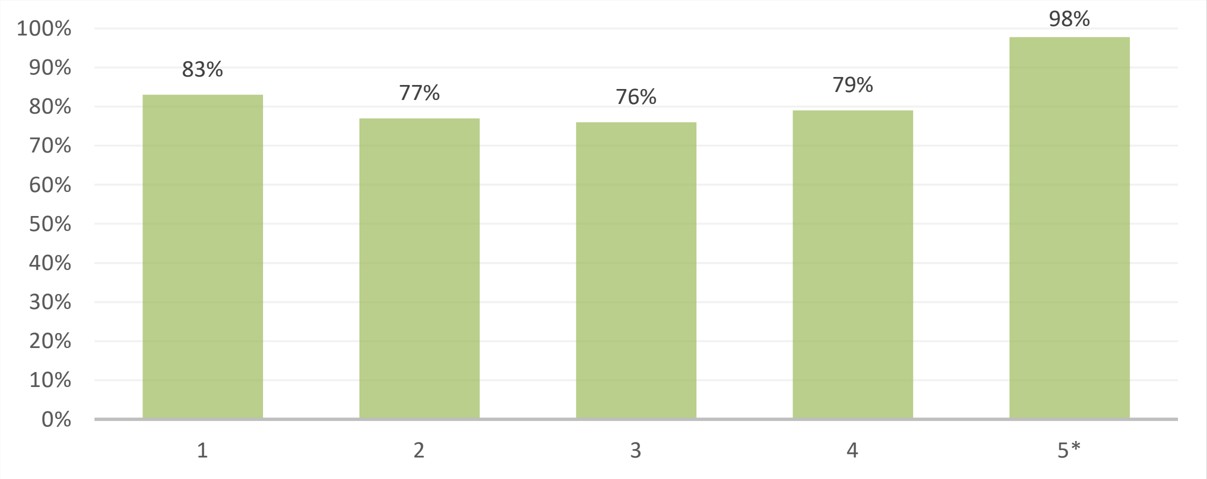


Figure 101 Recyclability of this catalyst system using urea:$ZnBr_2$ and **4.1a**

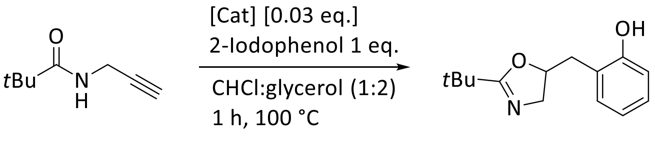
*Extraction with Et_2O

This reaction system showed an impressive recycling capacity, it could be reused five times without a depletion of its reactivity. In the fifth run the product was extracted and a quantitative yield could be obtained, showing that the lower yields in the first four runs were caused by losses during the distillation.

4.3.3. Twofold catalysed cyclisations

Another interesting approach for the synthesis of substituted oxazoles is the use of palladium catalysts due to their ability to catalyse not only the cyclisation but also a cross-coupling between the terminal alkyne and an aryl halide. At first, different reaction conditions were tested for the reaction of the standard N-propargyl carboxamide **4.1a** and 2-iodophenol (Table 44).

Table 44 Pd catalysed cyclisation and cross coupling



4.1a **4.6l**

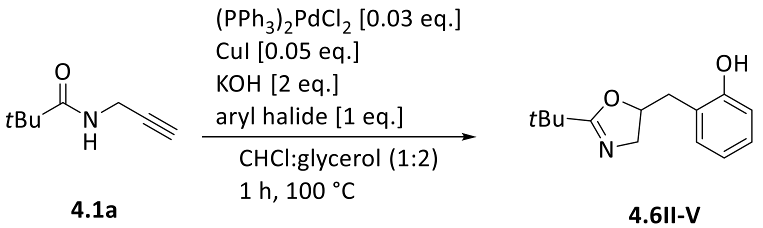
Entry	Catalyst	Additive	Base	Yield*
1	$(C_6H_5CN)_2PdCl_2$	CuI (0.05 eq.)	Et_3N (1 eq.)	0%
2	$(PPh_3)_2PdCl_2$	CuI (0.05 eq.)	Et_3N (1 eq.)	86% (90%)**
3	$(PPh_3)_2PdCl_2$	-	Et_3N (3 eq.)	30%
4	-	CuI (0.05 eq.)	Et_3N (3 eq.)	0%
5	$(PPh_3)_2PdCl_2$	CuI (0.05 eq.)	DABCO (1 eq.)	78%
6	$(PPh_3)_2PdCl_2$	CuI (0.05 eq.)	diisopropylamine (1 eq.)	0%
7	$(PPh_3)_2PdCl_2$	CuI (0.05 eq.)	K_2CO_3 (1 eq.)	79%
8	$(PPh_3)_2PdCl_2$	CuI (0.05 eq.)	K_2CO_3 (2 eq.)	83% (79%)**
9	$(PPh_3)_2PdCl_2$	CuI (0.05 eq.)	KOH (1 eq.)	96% (91%)**
10	$(PPh_3)_2PdCl_2$	CuI (0.05 eq.)	KOH (2 eq.)	98% (95%)**
11	$(PPh_3)_2PdCl_2$	$InOTf_3$ (0.05 eq.)	KOH (2 eq.)	92%
12	$(PPh_3)_2PdCl_2$	$BiOTf_3$ (0.05 eq.)	KOH (2 eq.)	86%

* Determined by GC with internal standard, ** Isolated yield

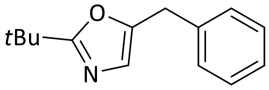
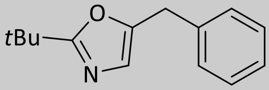
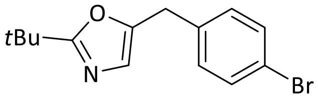
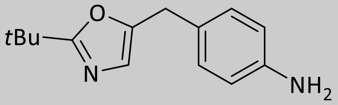
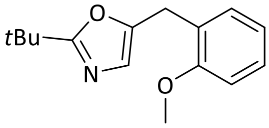
Initially, two different Pd catalysts were tested with triethylamine as a standard base in the practicable eutectic mixture CHCl:glycerol. Copper(I)iodide was used as co-catalysts and the electron-rich iodophenol as aryl halide. The first used catalysts $(C_6H_5CN)_2PdCl_2$ turned out to be unsuitable under these reaction conditions (Table 44, entry 1), whereas $(PPh_3)_2PdCl_2$ showed a very promising result of 86% after 1 h at 100 °C (Table 44, entry 2). In a next step, the influence of the palladium catalysts and the copper co-catalyst was tested. The absence of the co-catalyst led to a significant decrease of the yield (Table 44, entry 3), but without a palladium species no conversion could be observed anymore (Table 44, entry 4). After this, different bases were tested starting with two amine bases DABCO and diisopropylamine.

While DABCO led to comparable results as triethylamine (Table 44, entry 5), no conversion could be detected with the use of diisopropylamine (Table 44, entry 6). Next, the much greener and cheaper bases K_2CO_3 and KOH were tested in this reaction, with a remarkable outcome: The use of K_2CO_3 showed good results up to 83% when two equivalents were used (Table 44, entries 7 and 8) and when KOH was used quantitative yields could be obtained (Table 44, entries 9 and 10). Finally, the co-catalyst was altered to either $InOTf_3$ or $BiOTf_3$ resulting in a slightly lower yield compared to CuI (Table 44, entries 11 and 12). The optimised protocol was then applied to different aryl halides as indicated in Table 45.

Table 45 Pd catalysed cyclisation and cross coupling with different aryl halides



4.1a **4.6II-V**

Entry	Aryl halide	Product		Yield
1	brombenzene **4.19**		**4.6II**	78%
2	iodbenzene **4.20**		**4.6II**	99%
3	1-bromo-4-iodobenzene **4.21**		**4.6III**	95%
4	4-iodoaniline **4.22**		**4.6IV**	0%*
5	1-iodo-2-methoxybenzene **4.23**		**4.6V**	85%

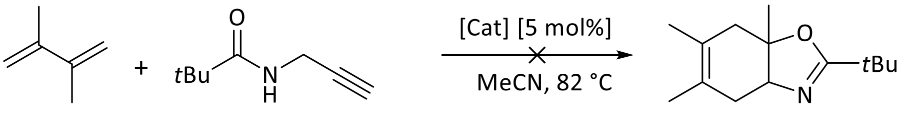
* Formation of **4.3a**

As shown, the majority of the used aryl halides reacted slightly to the desired oxazole derivates. Furthermore, it could be demonstrated that also aryl bromides are suitable for this reaction (Table 45, entry 1).

However, in direct comparison iodoarenes are more reactive than their bromo analogues (Table 45, entry 2). In fact, if both are available the reaction proceeds very selectively to product **4.6III** (Table 45, entry 3). Nonetheless, 4-iodoaniline resulted only in product **4.3a** (Table 45, entry 4) but using 1-iodo-2-methoxybenzene a good yield of 85% could be obtained (Table 45, entry 5).

Furthermore, it was tested if the known cyclisation of propargylamides can be combined with a Diels-Alder-reaction, since the educt **4.1** and the products **4.2** and **4.3** bearing dienophilic groups.

Table 46 Outcome of the tested Diels-Alder-reaction



4.24 **4.1a** **4.25**

Entry	Catalyst	Yield
1	$AuBr_3$	Only **4.3a**
2	$ZnBr_2$	Only **4.3a**

The formation of the proposed product **4.25** could not be detected, only the formation of the oxazole **4.3a** could be observed. This applies to both used catalysts $AuBr_3$ and $ZnBr_2$, which are well-known Lewis acids for Diels-Alder-reactions[242].

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[242] U. Pindur, G. Lutz, C. Otto, *Chem. Rev.,* **1993**, *93*, 741-761;
A. P. Abbott, G. Capper, D. L. Davies, R. K. Rasheed, V. Tambyrajah, *Green Chem.,* **2002**, *4*, 24-26;
K. A. Jørgensen, *Angew. Chem., Int. Ed.,* **2000**, *39*, 3558-3588;
S. Otto, F. Bertoncin, J. B. Engberts, *J. Am. Chem. Soc.,* **1996**, *118*, 7702-7707.

4.4. Conclusion

An efficient synthesis of substituted oxazoles by a cyclisation of propargyl carboxamides catalysed by gold or zinc salts in green mostly biorenewable Deep Eutectic Solvents could be achieved.

Furthermore, the majority of the used propargylamides could be synthesised straightforwardly and in good yields by mixing the respective acyl halides with a propargyl amine in presence of a base at reduced temperatures (see Figure 102).

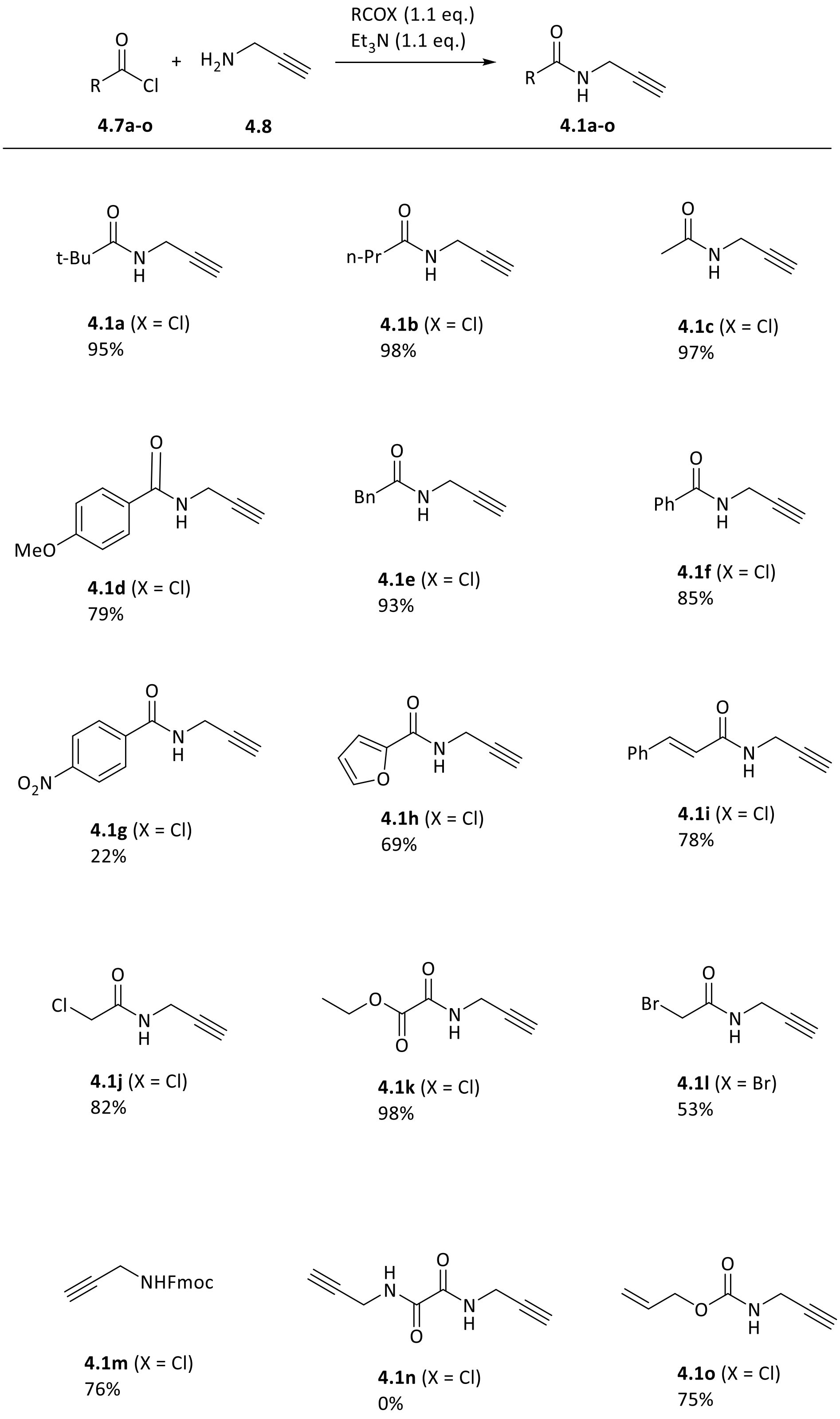
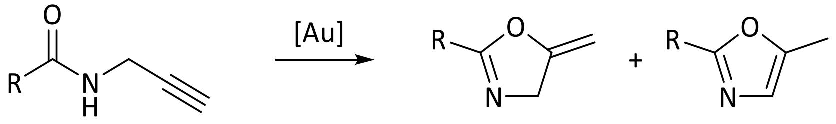


Figure 102 Synthesised propargylamides

The following cyclisation reactions took place with high yield in DESs as green and sustainable solvent system. Furthermore, it was possible to control the selectivity between the two possible products **4.2** and **4.3**.

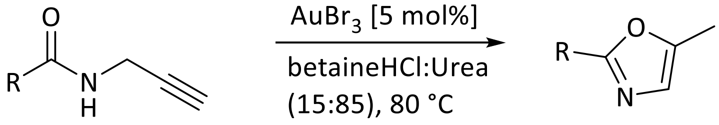


4.1 **4.2** **4.3**

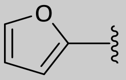
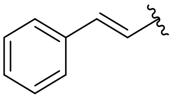
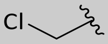
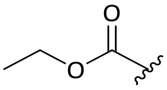
Figure 103 Gold-catalysed cyclisation of propargylamides

After an optimisation of the catalysts and the DES mixture it became clear that the best catalyst DES system was $AuBr_3$ in betaineHCl:urea, which is air-stable and relatively easy to handle regarding viscosity. Therefore, an extraction of the product was straightforward. Furthermore, the method was applicable for a wide range of substituents in good yields (see Table 47).

Table 47 Gold-catalysed cyclisation with different substituents



4.1b-k,o,p **4.3b-k,o,p**

Entry	**R =**	**Product**	**Time**	**Yield**
1	n-Pr	**4.3b**	24 h	62%
2	Me	**4.3c**	2 h	99%
3	4-methoxyphenyl	**4.3d**	2 h	95%
4	benzyl	**4.3e**	2 h	77%
5	phenyl	**4.3f**	2 h	99%
6	4-nitrophenyl	**4.3g**	2 h	85%
7	CF_3	**4.3p**	24 h	0%
8		**4.3h**	2 h	96%
9		**4.3i**	2 h	88%
10		**4.3j**	2 h	0%
11		**4.3k**	2 h	0%
12	Alloc	**4.3o**	2 h	0%

It was also possible to perform recycling experiments, in doing so another DES, urea:$ZnBr_2$ was used, which showed on the one hand a good recycling capacity and on the other hand that gold is not necessarily needed for this reaction but also other metals can be used (Figure 104).

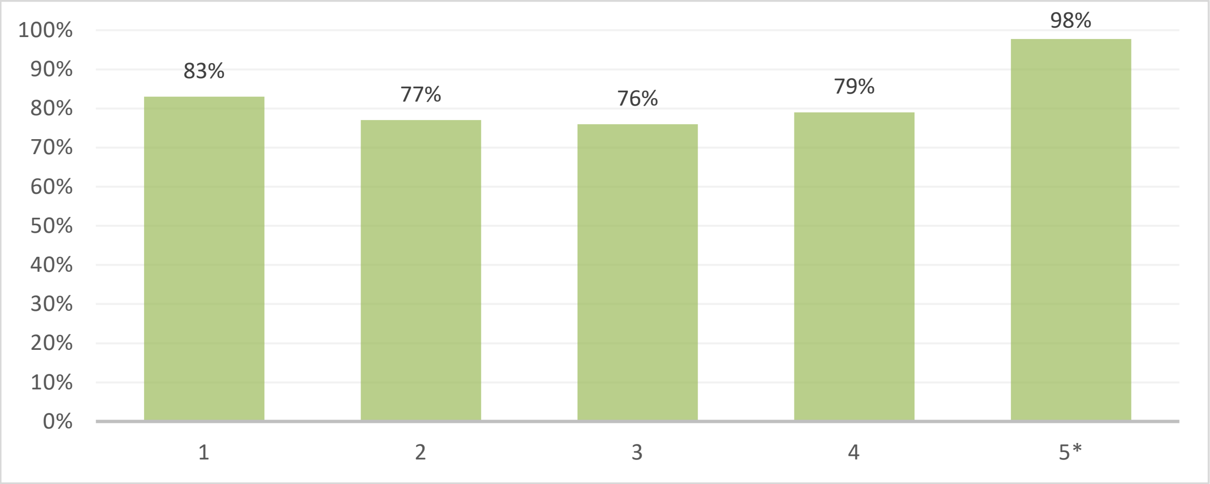
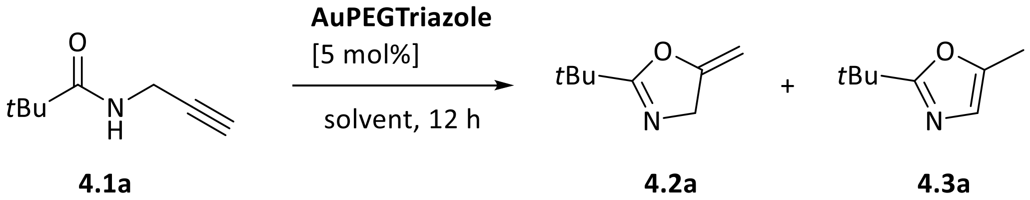


Figure 104 Recyclability of this catalyst system using urea:$ZnBr_2$ and **4.1a**

*Extraction with Et_2O

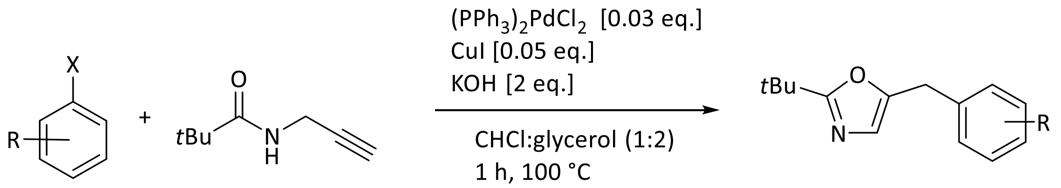
Moreover, the two gold complexes **AuPEG** and **AuPEGTriazole** originating from chapter 2.3.2 were tested in this cyclisation (Table 48). Whereas gold complex AuPEG showed no activity, gold complex AuPEGtriazol was able to catalyse this reaction up to 90% yield as a matter of fact it showed an excellent selectivity in methanol, since the catalyst was able to generate only the non-aromatic product, which undergoes normally a very fast conversion to **4.3** at higher temperatures (Table 48, entries 5 and 11).

Table 48 Cyclisation of N-Propargylcarboxamides with catalyst **AuPEGTriazole**

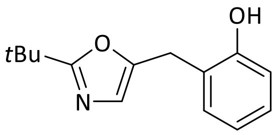


Entry	Solvent (mol:mol)	Additive	Temp.	Overall Yield*	Selectivity 2/3*
1	propylene carbonate	-	20 °C	27%	44:56
2	CHCl:glycerol (1:2)	-	20 °C	10%	<1:99
3	CHCl:urea (1:2)	-	20 °C	12%	<1:99
4	CHCl:glycerol (1:2)	-	80 °C	17%	31:69
5	CHCl:urea (1:2)	-	80 °C	90% (85%)**	11:89
6	propylene carbonate	0.05 eq. AgOTf	20 °C	0%	-
7	CHCl:glycerol (1:2)	0.05 eq. AgOTf	20 °C	0%	-
8	CHCl:urea (1:2)	0.05 eq. AgOTf	20 °C	23%	<1:99
9	CHCl:glycerol (1:2)	0.05 eq. AgOTf	80 °C	25%	<1:99
10	CHCl:urea (1:2)	0.05 eq. AgOTf	80 °C	69% (65%)**	<1:99
11	methanol	0.05 eq. AgOTf	65 °C	48% (50%)**	>99:1

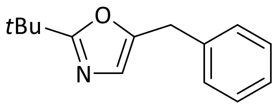
In addition to these results, the use of palladium catalysts was tested and optimised due to their ability to catalyse not only the cyclisation but also a cross-coupling between the terminal alkyne **4.1** and different aryl halides. The optimised protocol could be successfully applied to miscellaneous aryl halides indicated in Figure 105.



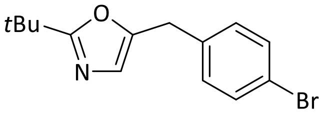
4.19-23 **4.1a** **4.6I-V**



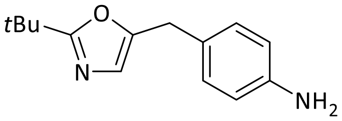
4.6I (X = I) 95%



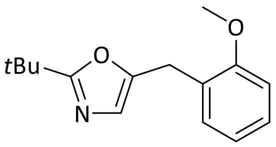
4.6II (X = Br) 78%
4.6II (X = I) 95%



4.6III (X = I) 95%



4.6IV (X = I) 0%



4.6V (X = I) 85%

Figure 105 Outcome of the twofold reaction between alkyne **4.1a** and different aryl halides

Furthermore, the ability of alkyne **4.1a** to undergo a cyclisation and a Diels-Alder-reaction was tested resulting in no conversion with either $AuBr_3$ or $ZnBr_2$.

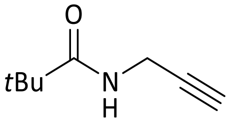
4.5. Experimental

General procedure for the synthesis of N-Propargylamides:

Propargyl amine (1 eq.) and triethylamine (1.1 eq.) were dissolved in EtOAc at 0 °C. Then, the respective acid chloride (1.1 eq.) was added dropwise, and the solution was warmed up to room temperature. After 12 h the reaction was quenched by saturated solution of Ammonium chloride, the phases were separated, and the aqueous phase was extracted two times with EtOAc. The combined organic phases were dried over $MgSO_4$, filtered and the solvent was evaporated yielding in the respective *N*-Propargylamide.

N-(prop-2-yn-1-yl)pivalamide (**4.1a**)

MD-P31-1



Propargyl amine	**Et_3N**	**Acid halide**	**Yield**
2 g (2.32 ml)	4.04 g (5.57 ml)	pivaloyl chloride	4.79 g
36.31 mmol	39.94 mmol	4.82 g (4.91 ml)	34.46 mmol
		39.9 mmol	95%

Light yellow-coloured solid,

^{1}H-NMR: (400 MHz, Chloroform-d) δ 3.97 (dd, J = 5.1, 2.6 Hz, 2H), 2.16 (t, J = 2.6 Hz, 1H), 1.14 (s, 9H)

^{13}C NMR (101 MHz, Chloroform-*d*) δ 178.0, 79.8, 71.6, 38.7, 29.5, 27.5

Known compound[243]

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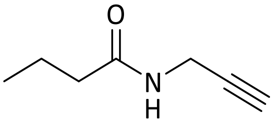
[243] P. Wipf, Y. Aoyama, T. E. Benedum, *Org. Lett.*, **2004**, *6*, 3593-3595.

N-(prop-2-yn-1-yl)pentanamide (4.b)

MD-P31-221



Propargyl amine	Et_3N	Acid halide	Yield
1 g (1.16 ml)	2.02 g (2.78 ml)	butyryl chloride	2.51 g
18.2 mmol	20 mmol	2.13 g (2.07 ml)	17.8 mmol
		20 mmol	98%

Brown liquid,

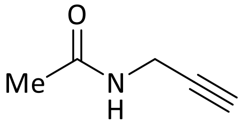
^{1}H NMR (600 MHz, Chloroform-*d*) δ 6.06 (s, 1H), 4.02 (dd, *J* = 5.0, 2.4 Hz, 2H), 2.20 (t, *J* = 2.5 Hz, 1H), 2.17 (t, *J* = 7.5 Hz, 2H), 1.65 (h, *J* = 7.4 Hz, 2H), 0.93 (t, *J* = 7.4 Hz, 3H)

^{13}C NMR (151 MHz, Chloroform-*d*) δ 172.9, 79.7, 71.4, 38.3, 29.1, 19.0, 13.7

Known compound[244]

N-(prop-2-yn-1-yl)acetamide (4.1c)

MD-P31-222



Propargyl amine	Et_3N	Acid halide	Yield
1 g (1.16 ml)	2.02 g (2.78 ml)	acetyl chloride	1.7 g
18.2 mmol	20 mmol	1.57 g (1.43 ml)	17.6 mmol
		20 mmol	97%

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[244] M. Kögler, B. Vanderhoydonck, S. De Jonghe, J. Rozenski, K. Van Belle, J. Herman, T. Louat, A. Parchina, C. Sibley, E. Lescrinier, P. Herdewijn, *J. Med. Chem.*, **2011**, *54*, 4847-4862.

Light tan-coloured solid,

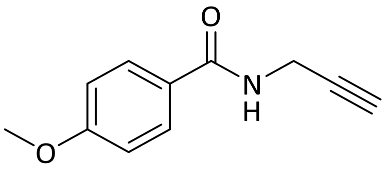
^{1}H NMR (600 MHz, Chloroform-*d*) δ 5.93 (s, 1H), 4.07 (s, 2H), 3.39 (s, 0H), 2.25 (d, *J* = 2.2 Hz, 1H), 2.04 (s, 3H)

^{13}C NMR (151 MHz, Chloroform-*d*) δ 169.9, 79.5, 71.7, 29.4, 23.2

Known compound[245]

4-methoxy-N-(prop-2-yn-1-yl)benzamide (**4.1d**)

MD-P31-93



Propargyl amine	**Et$_3$N**	**Acid halide**	**Yield**
1 g (1.16 ml) 18.2 mmol	2.02 g (2.78 ml) 20 mmol	4-methoxybenzoyl chloride 3.41 g (2.7 ml) 20 mmol	2.70 g 14.3 mmol 79%

Tan-coloured solid,

^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.73 – 7.65 (m, 2H), 6.88 – 6.82 (m, 2H), 4.17 (dd, *J* = 5.2, 2.6 Hz, 2H), 3.78 (s, 3H), 2.20 (t, *J* = 2.6 Hz, 1H)

^{13}C NMR (101 MHz, Chloroform-*d*) δ 166.6, 162.4, 128.9, 126.0, 113.81 79.7, 71.8, 55.4, 29.7

Known compound[246]

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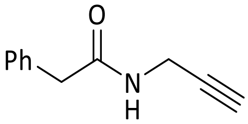
[245] A. S. K. Hashmi, J. P. Weyrauch, W. Frey, J. W. Bats, *Org. Lett.*, **2004**, *6*, 4391-4394.

[246] E. M. Beccalli, E. Borsini, G. Broggini, G. Palmisano, S. Sottocornola, *J. Org. Chem.*, **2008**, *73*, 4746-4749.

2-phenyl-N-(prop-2-yn-1-yl)acetamide (**4.1e**)

MD-31-89



Propargyl amine	**Et$_3$N**	**Acid halide**	**Yield**
1 g (1.16 ml) 18.2 mmol	2.02 g (2.78 ml) 20 mmol	phenylacetyl chloride 3.04 g (2.6 ml) 20 mmol	3.07 g 17.4 mmol 93%

Yellow-coloured solid,

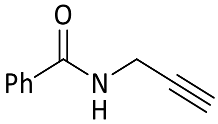
^{1}H NMR (700 MHz, Chloroform-*d*) δ 7.33 (t, J = 7.5 Hz, 2H), 7.27 (t, J = 7.3 Hz, 1H), 7.23 (d, J = 6.4 Hz, 2H), 3.97 (dd, J = 5.1, 2.3 Hz, 2H), 3.56 (s, 2H), 2.14 (q, J = 3.6, 2.7 Hz, 1H)

^{13}C NMR (151 MHz, Chloroform-*d*) δ 170.5, 134.3, 129.5, 129.1, 127.5, 79.3, 71.6, 43.6, 29.4

Known compound[246]

N-(prop-2-yn-1-yl)benzamide (**4.1f**)

MD-P31-14



Propargyl amine	**Et$_3$N**	**Acid halide**	**Yield**
2 g (2.33 ml) 36.3 mmol	4.04 g (5.57 ml) 39.9 mmol	benzoyl chloride 5.61 g (5.73 ml) 39.9 mmol	4.94 g 30.9 mmol 85%

Colourless solid,

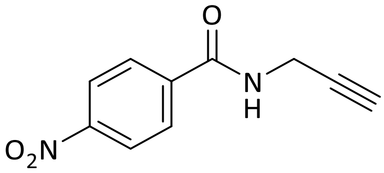
^{1}H NMR (600 MHz, Chloroform-*d*) δ 7.81 – 7.76 (m, 2H), 7.55 – 7.49 (m, 1H), 7.48 – 7.42 (m, 2H), 6.28 (s, 1H), 4.27 (dd, *J* = 5.2, 2.6 Hz, 2H), 2.29 (t, *J* = 2.6 Hz, 1H)

^{13}C NMR (151 MHz, Chloroform-*d*) δ 167.2, 133.9, 132.0, 128.8, 127.1, 79.6, 72.1, 30.0

Known compound[243]

4-nitro-N-(prop-2-yn-1-yl)benzamide (**4.1g**)

MD-P31-235



Propargyl amine	**Et$_3$N**	**Acid halide**	**Yield**
1 g (1.16 ml) 18.2 mmol	2.02 g (2.78 ml) 20 mmol	4-Nitrobenzoyl chloride 3.71 g 20 mmol	0.81 g 4 mmol 22%

Tan-coloured solid,

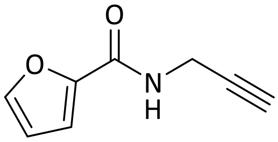
^{1}H NMR (700 MHz, Chloroform-*d*) δ 8.30 – 8.21 (m, 2H), 8.10 – 8.05 (m, 2H), 4.24 (dd, *J* = 5.1, 2.5 Hz, 2H), 2.25 (t, *J* = 2.5 Hz, 1H)

^{13}C NMR (176 MHz, Chloroform-*d*) δ 165.1, 149.7, 139.4, 128.7, 123.7, 79.4, 71.6, 29.8

Known compound[243]

N-(prop-2-yn-1-yl)furan-2-carboxamide (**4.1h**)

MD-P31-237



Propargylamine	**Et_3N**	**Acid halide**	**Yield**
1 g (1.16 ml)	2.02 g (2.78 ml)	2-furoyl chloride	1.87 g
18.2 mmol	20 mmol	2.61 g (1.97 ml)	12.5 mmol
		20 mmol	69%

Tan-coloured solid,

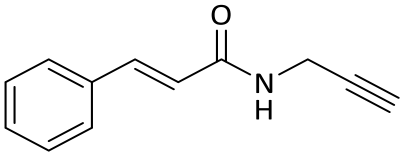
^{1}H NMR (700 MHz, Chloroform-*d*) δ 7.42 (dd, *J* = 1.7, 0.7 Hz, 1H), 7.11 (dd, *J* = 3.5, 0.7 Hz, 1H), 6.60 (d, *J* = 19.0 Hz, 1H), 6.47 (dd, *J* = 3.5, 1.7 Hz, 1H), 4.19 (dd, *J* = 5.2, 2.5 Hz, 2H), 2.24 (t, *J* = 2.6 Hz, 1H)

^{13}C NMR (176 MHz, Chloroform-*d*) δ 157.9, 147.4, 144.2, 114.7, 112.2, 79.3, 71.8, 28.8

Known compound[243]

N-(prop-2-yn-1-yl)cinnamamide (**4.1i**)

MD-P31-236



Propargyl amine	**Et_3N**	**Acid halide**	**Yield**
1 g (1.16 ml)	2.02 g (2.78 ml)	cinnamoyl chloride	2.61 g
18.2 mmol	20 mmol	3.33 g	14.2 mmol
		20 mmol	78%

Tan-coloured solid,

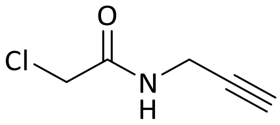
^{1}H NMR (700 MHz, Chloroform-*d*) δ 7.66 (d, *J* = 15.6 Hz, 1H), 7.51 – 7.49 (m, 2H), 7.36 (dd, *J* = 4.9, 2.3 Hz, 3H), 6.43 (d, *J* = 15.6 Hz, 1H), 4.22 – 4.16 (m, 2H), 2.25 (t, *J* = 2.5 Hz, 1H)

^{13}C NMR (176 MHz, Chloroform-*d*) δ 165.5, 141.9, 134.6, 129.9, 128.8, 127.9, 119.8, 79.5, 71.7, 29.4

Known compound[245]

2-chloro-N-(prop-2-yn-1-yl)acetamide (**4.1j**)

MD-P31-242



Propargyl amine	**Et₃N**	**Acid halide**	**Yield**
1 g (1.16 ml)	2.02 g (2.78 ml)	chloroacetyl chloride	1.96 g
18.2 mmol	20 mmol	2.26 g (1.59 ml)	14.9 mmol
		20 mmol	82%

Yellow-coloured solid,

^{1}H NMR (500 MHz, Chloroform-*d*) δ 6.83 (s, 1H), 4.09 (dd, *J* = 5.4, 2.5 Hz, 2H), 4.07 (s, 2H), 2.28 (t, *J* = 2.5 Hz, 1H)

^{13}C NMR (126 MHz, Chloroform-*d*) δ 165.7, 78.5, 72.2, 42.4, 29.9

Known compound[247]

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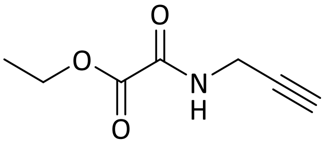
[247] J. Martinelli, B. Balali-Mood, R. Panizzo, M. F. Lythgoe, A. J. P. White, P. Ferretti, J. H. G. Steinke, R. Vilar, *Dalton Trans.,* **2010**, *39*, 10056-10067.

Ethyl 2-oxo-2-(prop-2-yn-1-ylamino)acetate (**4.1k**)

MD-P31-85



Propargyl amine	**Et$_3$N**	**Acid halide**	**Yield**
2 g (2.3 ml) 36.3 mmol	4.05 g (5.6 ml) 40 mmol	ethylchlorooxo acetate 5.44 g (4.5 ml) 40 mmol	5.57 g 35.8 mmol 98%

Tan-coloured solid,

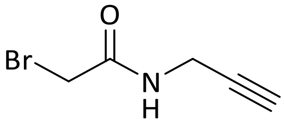
^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.30 (s, 1H), 4.35 (q, *J* = 7.1 Hz, 2H), 4.13 (dd, *J* = 5.5, 2.5 Hz, 2H), 2.28 (t, *J* = 2.5 Hz, 1H), 1.37 (t, *J* = 7.1 Hz, 3H)

^{13}C NMR (101 MHz, Chloroform-*d*) δ 160.1, 156.2, 77.9, 72.6, 63.4, 29.6, 14.0

Known compound[245]

2-Bromo-N-(prop-2-yn-1-yl)acetamide (**4.1l**)

MD-P31-88



Propargyl amine	**Et$_3$N**	**Acid halide**	**Yield**
1 g (1.16 ml) 18.2 mmol	2.02 g (2.78 ml) 20 mmol	bromoacetyl chloride 4.03 g (1.75 ml) 20 mmol	1.75 g 10 mmol 53%

Tan-coloured solid,

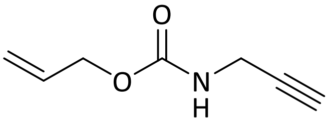
^{1}H NMR (500 MHz, Chloroform-*d*) δ 6.74 (s, 1H), 4.08 (dd, *J* = 5.3, 2.5 Hz, 2H), 3.89 (s, 2H), 2.28 (t, *J* = 2.5 Hz, 1H)

^{13}C NMR (126 MHz, Chloroform-*d*) δ 165.3, 78.6, 72.4, 30.1, 28.8

Known compound[248]

Allyl prop-2-yn-1-ylcarbamate (**4.1o**)

MD-P31-94



Different from the general procedure the mixture was cooled to -78 °C here.

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[248] F. Liu, P. Tang, R. Ding, L. Liao, L. Wang, M. Wang, J. Wang, *Dalton Trans.*, **2017**, *46*, 7515-7522.

Propargyl amine	Et_3N	Acid halide	Yield
2.06 g (2.4 ml)	4.06 g (5.6 ml)	allyl chloroformate	5.3 g
37.5 mmol	40.1 mmol	6.97 g (5.2 ml)	28.1 mmol
		40.8 mmol	75%

Colourless solid,

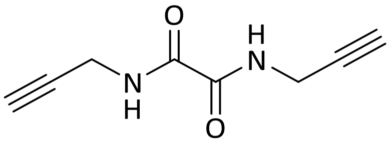
^{1}H NMR (400 MHz, Chloroform-*d*) δ 5.88 (ddt, *J* = 16.3, 10.8, 5.6 Hz, 1H), 5.28 (d, *J* = 17.3 Hz, 1H), 5.19 (d, *J* = 10.4 Hz, 1H), 4.56 (d, *J* = 4.8 Hz, 2H), 3.95 (d, *J* = 4.4 Hz, 2H), 2.23 (t, *J* = 2.5 Hz, 1H)

^{13}C NMR (101 MHz, Chloroform-*d*) δ 155.8, 132.6, 117.9, 79.7, 71.5, 65.9, 30.8

Known compound[249]

N^1,N^2-di(prop-2-yn-1-yl)oxalamide (**4.1n**)

MD-P31-77



1.74 ml Propargyl amine (1.5 g, 27.2 mmol, 1 eq.) and 3.8 ml triethylamine (2.76 g, 27.2 mmol, 1.1 eq.) were dissolved in dry DCM at -78 °C under argon atmosphere.

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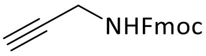
[249] P. Baumhof, N. Griesang, M. Bächle, C. Richert, *J. Org. Chem.*, **2006**, *71*, 1060-1067.

Then, 1.28 ml oxalyl chloride (1.9 g, 15 mmol, 1.1 eq.) was dissolved in 20 ml DCM and added dropwise. The solution was warmed up to room temperature. After 12 h the reaction was quenched by saturated solution of Ammonium chloride, the phases were separated, and the aqueous phase was extracted two times with EtOAc (50 ml). The combined organic phases were dried over $MgSO_4$, filtered and the solvent was evaporated but the desired product could not be isolated.

(9H-fluoren-9-yl)methyl prop-2-yn-1-ylcarbamate (**4.1m**)

MD-P31-92



2.57 g Fluorenylmethyloxycarbonyl chloride (10.5 mmol, 1.05 eq.) was dissolved in dry DCM under argon atmosphere and cooled to – 90 °C followed by the addition of 0.64 ml propargyl amine (0.55 g, 10 mmol, 1 eq.) and 1.5 ml triethylamine (1.11 g, 11 mmol, 1.1 eq.). After stirring for 36 h the mixture was diluted with 40 ml DCM and 40 ml of a sat. NH_4Cl solution were added. The phases were separated, and the mixture was extracted with DCM (2 x 30 ml), then the combined organic phases were washed with sat. $NaHCO_3$ solution (30 ml) and water (30 ml) and dried by $MgSO_4$. The solvent was removed resulting in 76% of the desired product (2.1 g, 7.6 mmol) as white solid.

^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.77 (d, *J* = 7.5 Hz, 2H), 7.59 (d, *J* = 7.5 Hz, 2H), 7.41 (t, *J* = 7.4 Hz, 2H), 7.32 (td, *J* = 7.5, 1.1 Hz, 2H), 4.43 (d, *J* = 7.0 Hz, 2H), 4.23 (t, *J* = 7.0 Hz, 1H), 4.01 (dd, *J* = 5.8, 2.5 Hz, 2H), 2.26 (t, *J* = 2.5 Hz, 1H)

^{13}C NMR (126 MHz, Chloroform-*d*) δ 143.8, 141.3, 128.8, 127.8, 127.1, 125.0, 120.0, 79.6, 71.7, 67.1, 47.1, 30.9

Known compound[250]

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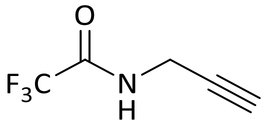
[250] S. Mourtas, M. Canovi, C. Zona, D. Aurilia, A. Niarakis, B. La Ferla, M. Salmona, F. Nicotra, M. Gobbi, S. G. Antimisiaris, *Biomaterials,* **2011**, *32*, 1635-1645.

2,2,2-trifluoro-N-(prop-2-yn-1-yl)acetamide (**4.1p**)

MD-P31-229



1.59 g $NaHCO_3$ (18.9 mmol, 1.3 eq.), 1.73 ml ethyl trifluoracetate (2.06 g, 14.5 mmol, 1 eq.) and 0.93 ml propargyl amine (0.8 g, 14.5 mmol, 1 eq.) were dissolved in 5 ml methanol in a microwave flask. The mixture was heated to 100 °C for 1 h by microwave irradiation and subsequent diluted with 10 ml of a sat. $NaHCO_3$ solution followed by an extraction with DCM (3 x 30 ml). The combined organic phases were dried by $MgSO_4$ and the solvent evaporated resulting in 82% of the desired product (1.79 g, 11.9 mmol) as clear liquid.

Colourless liquid,
^{1}H NMR (400 MHz, Chloroform-*d*) δ 4.18 – 4.11 (m, 2H), 2.33 (t, *J* = 2.6 Hz, 1H)
^{13}C NMR (101 MHz, Chloroform-*d*) δ 156.9 (q, *J* = 37.8 Hz), 115.6 (q, *J* = 287.5 Hz), 73.2, 65.8, 29.7
^{19}F NMR (377 MHz, Chloroform-*d*) δ -75.92
Known compound[251]

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[251] Y. Miclo, P. Garcia, Y. Evanno, P. George, M. Sevrin, M. Malacria, V. Gandon, C. Aubert, *Synlett,* **2010**, *2010*, 2314-2318.

General procedure for the preparation of DES:

The respective compounds were filled in a flask and heated in oil bath for about 10-60 min until the mixture was a homogenous liquid. The DESs were used directly without a further purification step.

General procedure for the cyclisations of *N*-Propargylamides:

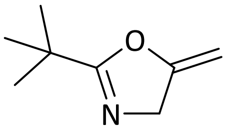
The catalyst (0.05 eq.) was dissolved in 2 ml of the respective DES and stirred for 10 min in a snap-cap jar. Then, 25 mg of the respective *N*-Propargylamide (1 eq.) was dissolved and stirred for the respective time and temperature. After this, 2 ml of water was added, and the mixture was extracted with Et_2O (3 x 2 ml). The combined organic phases were dried over $MgSO_4$ and the solvent was evaporated. Followed by a purification by column chromatography if necessary.

General procedure for the recycling reactions:

In a flask N-(prop-2-yn-1-yl)pivalamide **1a** (250 mg) were dissolved in 10 ml of urea:$ZnBr_2$ (1:2) and stirred for 2 h at 80 °C. Then the product was removed by Kugelrohr distillation at 80 °C in vacuo. N-(prop-2-yn-1-yl)pivalamide **1a** was added subsequently to the DES followed a repetition of the procedure. After the fifth run, 10 ml of water were added, and the mixture was extracted with Et_2O (3 x 10 ml). The combined organic phases were dried over $MgSO_4$ and the solvent was evaporated.

2-(tert-butyl)-5-methylene-4,5-dihydrooxazole (**4.2a**)

MD-P31-4



Colourless oil, purified by flash column chromatography (pentane:Et_2O 10:1)

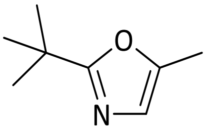
^1H NMR (500 MHz, Acetonitrile-d_3) δ 4.59 (q, *J* = 2.9 Hz, 1H), 4.38 (t, *J* = 2.8 Hz, 2H), 4.28 (q, *J* = 2.5 Hz, 1H), 1.23 (s, 9H)

^{13}C NMR (126 MHz, Acetonitrile-d_3) δ 173.2, 160.6, 82.2, 57.5, 30.2, 27.1

Known compound[252]

2-(tert-butyl)-5-methyloxazole (**4.3a**)

MD-P31-4



Colourless oil, purified by flash column chromatography (pentane:Et_2O 10:1)

^1H NMR (500 MHz, Chloroform-*d*) δ 6.62 – 6.53 (m, 1H), 2.26 (d, *J* = 1.1 Hz, 3H), 1.35 (s, 9H)

^{13}C NMR (126 MHz, Chloroform-*d*) δ 170.1, 148.0, 121.8, 33.6, 28.6, 10.9

Known compound[252]

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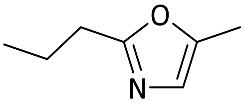
[252] W. J. P., H. A. S. K., S. Andreas, H. Tobias, S. Stefanie, L. Anna, R. Matthias, H. Melissa, V. Jorge, R. Frank, F. Wolfgang, B. J. W., *Chem. - Eur. J.*, **2010**, *16*, 956-963.

5-methyl-2-propyloxazole (**4.3b**)

MD-P31-249



Colourless oil, purified by flash column chromatography (pentane:Et_2O 10:1)

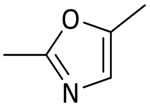
^{1}H NMR (400 MHz, Chloroform-*d*) δ 6.66 – 6.56 (m, 1H), 2.70 (t, *J* = 7.5 Hz, 2H), 2.26 (d, *J* = 1.2 Hz, 3H), 1.75 (h, *J* = 7.4 Hz, 2H), 0.96 (t, *J* = 7.4 Hz, 3H)

^{13}C NMR (101 MHz, Chloroform-*d*) δ 164.0, 148.3, 121.9, 30.0, 20.5, 13.7, 10.8

Known compound[253]

2,5-dimethyloxazole (**4.3c**)

MD-P31-223



Colourless oil, purified by flash column chromatography (pentane:Et_2O 10:1)

^{1}H NMR (600 MHz, Chloroform-*d*) δ 6.56 (s, 1H), 2.37 – 2.33 (m, 6H)

^{13}C NMR (151 MHz, Chloroform-*d*) δ 169.1, 134.8, 124.5, 14.3, 9.8

Known compound[245]

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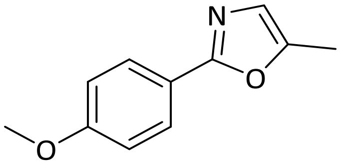
[253] V. O. G., W. P., *J. Food Sci.,* **1974**, *39*, 1210-1215.

2-(4-methoxyphenyl)-5-methyloxazole (**4.3d**)

MD-P31-230



Tan-coloured oil,

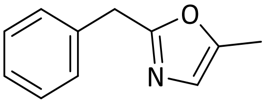
^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.85 (d, *J* = 8.8 Hz, 2H), 6.87 (d, *J* = 8.8 Hz, 2H), 6.72 (s, 1H), 3.77 (s, 3H), 2.33 – 2.24 (m, 3H)

^{13}C NMR (126 MHz, Chloroform-*d*) δ 160.9, 160.7, 148.2, 127.5, 123.7, 120.4, 114.0, 55.2, 10.9

Known compound[254]

2-benzyl-5-methyloxazole (**4.3e**)

MD-P31-136



Yellow-coloured oil,

^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.33 – 7.15 (m, 5H), 6.59 (s, 1H), 4.01 (s, 2H), 2.20 (d, *J* = 0.9 Hz, 3H)

^{13}C NMR (101 MHz, Chloroform-*d*) δ 148.9, 135.8, 128.8, 128.7, 127.0, 122.7, 34.7, 10.9

Known compound[254]

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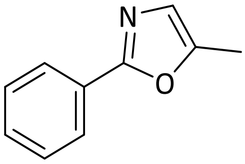
[254] J. K. Mali, B. S. Takale, V. N. Telvekar, *RSC Adv.,* **2017**, *7*, 2231-2235.

5-methyl-2-phenyloxazole (**4.3f**)

MD-P31-53



Light-yellow oil,

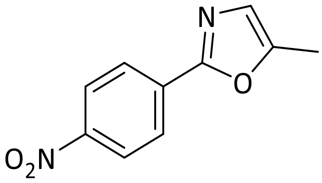
^{1}H NMR (500 MHz, Chloroform-*d*) δ 8.05 – 7.95 (m, 2H), 7.43 (q, *J* = 6.2 Hz, 3H), 6.85 (s, 1H), 2.39 (s, 3H)

^{13}C NMR (126 MHz, Chloroform-*d*) δ 160.7, 148.9, 130.0, 128.7, 127.6, 126.0, 124.0, 11.1

Known compound[245]

5-methyl-2-(4-nitrophenyl)oxazole (**4.3g**)

MD-P31-238



Tan-coloured solid,

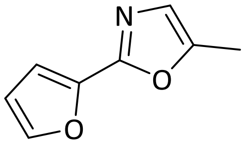
^{1}H NMR (600 MHz, Chloroform-*d*) δ 8.31 – 8.25 (m, 2H), 8.16 – 8.10 (m, 2H), 6.96 – 6.89 (m, 1H), 2.43 (d, *J* = 1.0 Hz, 3H)

^{13}C NMR (151 MHz, Chloroform-*d*) δ 156.7, 148.9, 146.4, 131.2, 124.7, 123.4, 122.3, 9.2

Known compound[254]

2-(furan-2-yl)-5-methyloxazole (**4.3h**)

MD-P31-240



Tan-coloured oil,

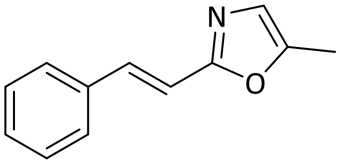
^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.51 (dd, *J* = 1.8, 0.8 Hz, 1H), 6.94 (dd, *J* = 3.4, 0.8 Hz, 1H), 6.81 (q, *J* = 1.2 Hz, 1H), 6.50 (dd, *J* = 3.5, 1.8 Hz, 1H), 2.36 (d, *J* = 1.2 Hz, 3H)

^{13}C NMR (101 MHz, Chloroform-*d*) δ 153.6, 148.5, 143.9, 143.2, 123.9, 111.7, 110.5, 10.9

Known compound[254]

(E)-5-methyl-2-styryloxazole (**4.3i**)

MD-P31-239



Tan-coloured solid,

^{1}H NMR (600 MHz, Chloroform-*d*) δ 7.49 (d, *J* = 7.4 Hz, 2H), 7.40 (d, *J* = 16.4 Hz, 1H), 7.35 (t, *J* = 7.5 Hz, 2H), 7.29 (t, *J* = 7.3 Hz, 1H), 6.88 (d, *J* = 16.4 Hz, 1H), 6.77 (s, 1H), 2.34 (s, 3H)

^{13}C NMR (151 MHz, Chloroform-*d*) δ 168.8, 158.7, 146.8, 133.9, 132.9, 127.1, 127.0, 125.2, 122.6, 112.4, 9.2

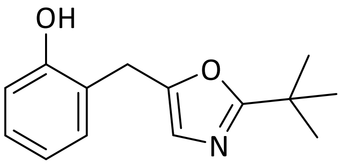
Known compound[254]

General procedure for the palladium catalysed cyclisations of *N*-Propargylamides:

The catalyst (0.03 eq.), the co-catalyst (0.05 eq.), the base and 25 mg of the respective *N*-propargylamide (1 eq.) were dissolved in 2 ml of the respective DES. The DES was previously degassed under vacuum for 15 min. The mixture was stirred for the respective time at 100 °C. After this, 2 ml of water were added, and the mixture was extracted with Et_2O (3 x 2 ml). The combined organic phases were dried over $MgSO_4$ and the solvent was evaporated, followed by a purification by column chromatography if necessary.

2-((2-(tert-butyl)oxazol-5-yl)methyl)phenol (4.6l)

MD-P31-272



Dark-brown oil,

^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.52 (dt, *J* = 7.6, 0.9 Hz, 1H), 7.44 (dq, *J* = 8.1, 0.9 Hz, 1H), 7.29 – 7.24 (m, 1H), 7.21 (td, *J* = 7.4, 1.1 Hz, 1H), 6.59 (d, *J* = 0.9 Hz, 1H), 6.10 (s, 1H), 4.58 (dd, *J* = 5.5, 0.9 Hz, 2H), 1.23 (s, 9H)

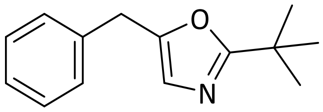
^{13}C NMR (126 MHz, Chloroform-*d*) δ 178.5, 155.0, 154.4, 128.4, 124.3, 123.0, 121.1, 111.2, 104.2, 39.0, 37.3, 27.7

HSQC (^{1}H/^{13}C), (Chloroform-*d)*: (7.55, 121.0), (7.46, 111.1), (7.24, 122.9), (7.11, 128.5), (6.61, 104.0), (4.60, 37.1), (1.26, 27.6)

MS (ESI (m/z) $[C_{14}H_{16}NO_2Na + H]^+$) calculated: m/z = 254.1073; found: 254.1149

5-benzyl-2-(tert-butyl)oxazole (4.6II)

MD-P31-319



Brown oil, purified by flash column chromatography (pentane:Et_2O 10:1)

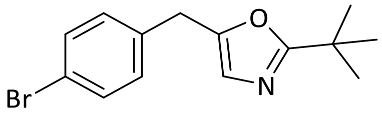
^{1}H NMR (600 MHz, Chloroform-*d*) δ 7.65 – 7.60 (m, 2H), 7.28 – 7.22 (m, 2H), 7.05 – 7.00 (m, 3H), 6.93 (d, *J* = 7.3 Hz, 1H), 4.20 (d, *J* = 4.9 Hz, 2H), 1.16 (s, 9H)

^{13}C NMR (151 MHz, Chloroform-*d*) δ 177.0, 166.2, 136.5, 130.7, 129.2, 127.3, 126.4, 30.9, 28.7, 21.7

MS (ESI (m/z) [$C_{14}H_{17}NO$ +H]$^+$) calculated: m/z = 216.1310; found: 216.1367

5-(4-bromobenzyl)-2-(tert-butyl)oxazole (4.6III)

MD-P31-315



Brown oil, purified by flash column chromatography (pentane:Et_2O 5:1)

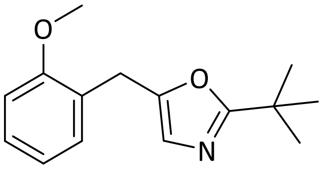
^{1}H NMR (600 MHz, Chloroform-*d*) δ 7.44 (d, *J* = 8.4 Hz, 2H), 7.28 (d, *J* = 8.5 Hz, 2H), 4.25 (d, *J* = 5.0 Hz, 2H), 1.23 (s, 9H)

^{13}C NMR (151 MHz, Chloroform-*d*) δ 178.1, 171.9, 133.3, 132.1, 130.2, 122.3, 30.4, 29.8, 27.6

MS (ESI (m/z) [$C_{14}H_{16}BrNO$ +H]$^+$) calculated: m/z = 295.1920; found: 295.1585

2-(tert-butyl)-5-(2-methoxybenzyl)oxazole (4.6V)

MD-P31-320



Dark-brown oil, purified by flash column chromatography (pentane:Et_2O 5:1)

^{1}H NMR (600 MHz, Chloroform-*d*) δ 7.78 (dd, *J* = 7.7, 1.6 Hz, 1H), 7.32 (ddd, *J* = 8.2, 7.3, 1.6 Hz, 1H), 6.84 (dd, *J* = 8.2, 1.3 Hz, 2H), 6.72 (td, *J* = 7.6, 1.4 Hz, 1H), 3.89 (s, 2H), 1.27 (s, 9H)

^{13}C NMR (151 MHz, Chloroform-*d*) δ 157.0, 138.5, 129.4, 128.5, 126.5, 125.9, 125.3, 121.5, 110.0, 55.2, 30.9, 28.7, 28.4

MS (ESI (m/z) $[C_{15}H_{19}NO_2 + H]^+$) calculated: m/z = 246.3220; found: 246.1478

5. Excursus: Main group metal-catalysed S_N1-reactions

5.1. Introduction

The functionalisation of arenes has traditionally been important for chemical synthesis, especially in pharmaceuticals, agrochemicals and fine chemicals.[255] Therefore, there are many classical reactions known for this purpose for example Friedel-Crafts reactions. However, these classical methods often suffer from harsh reaction conditions and large amounts of waste production. As a result, more straightforward and milder protocols are desired. While doing so the frequently used S_N1-type reactions could be an alternative solution. The generation and the characteristics of carbocations formed from benzylic or benzhydrylic halides is well known and understood by now, especially by the work of *Mayr* et. Al..[256]

The emerging stabilised, but nonetheless reactive carbocations can easily undergo reactions with nucleophiles. It is noteworthy that even the solvent can react as a nucleophile like in a Ritter-type reaction. In doing so a nitrile group attacks the carbocation resulting in a nitrilium ion which is then hydrolysed by water to an amide (Figure 106).[257]

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[255] M. Rueping, B. J. Nachtsheim, W. Ieawsuwan, *Adv. Synth. Catal.,* **2006**, *348*, 1033-1037.

[256] H. Mayr, S. Minegishi, *Angew. Chem., Int. Ed.,* **2002**, *41*, 4493-4495;
S. Minegishi, R. Loos, S. Kobayashi, H. Mayr, *J. Am. Chem. Soc.,* **2005**, *127*, 2641-2649;
S. Minegishi, S. Kobayashi, H. Mayr, *J. Am. Chem. Soc.,* **2004**, *126*, 5174-5181;
T. B. Phan, C. Nolte, S. Kobayashi, A. R. Ofial, H. Mayr, *J. Am. Chem. Soc.,* **2009**, *131*, 11392-11401;
N. Streidl, A. Antipova, H. Mayr, *J. Org. Chem.,* **2009**, *74*, 7328-7334;
G. A. Olah, W. S. Tolgyesi, S. J. Kuhn, M. E. Moffatt, I. J. Bastien, E. B. Baker, *J. Am. Chem. Soc.,* **1963**, *85*, 1328-1334;
H. Mayr, M. Patz, *Angew. Chem., Int. Ed., Engl.,* **1994**, *33*, 938-957;
H. Mayr, T. Bug, M. F. Gotta, N. Hering, B. Irrgang, B. Janker, B. Kempf, R. Loos, A. R. Ofial, G. Remennikov, H. Schimmel, *J. Am. Chem. Soc.,* **2001**, *123*, 9500-9512;
R. A. McClelland, *Tetrahedron,* **1996**, *52*, 6823-6858;J. P. Richard, T. L. Amyes, M. M. Toteva, *Acc. Chem. Res.,* **2001**, *34*, 981-988.

[257] L. I. Krimen, Donald J. Cota, *The Ritter Reaction*; Wiley, **1969**
R. Bishop, in *Comprehensive Organic Synthesis* (Eds.: B. M. Trost, I. Fleming), Pergamon, Oxford, **1991**, pp. 261-300;
A. Guérinot, S. Reymond, J. Cossy, *Eur. J. Org. Chem.,* **2012**, *2012*, 19-28.

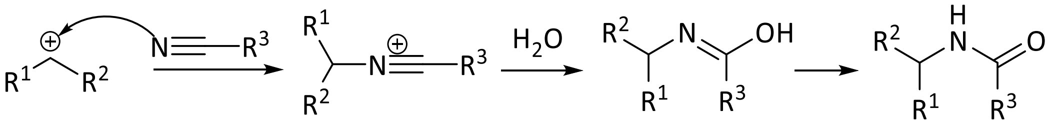
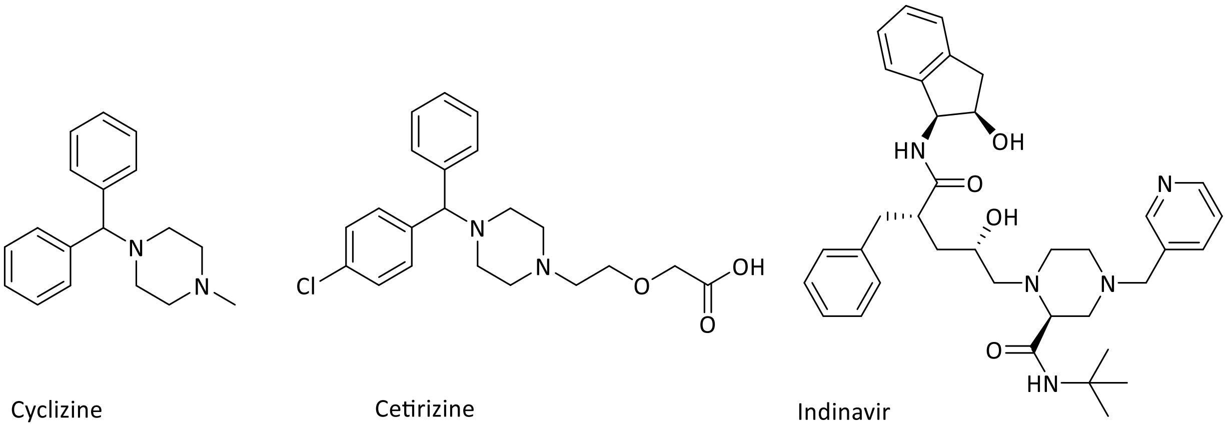


Figure 106 Ritter-reaction

As stated before, the products emerging from these reactions are often biologically active and have many applications. Especially the functionalised benzhydryl group can be found in many pharmaceuticals like modern second-generation antihistamines as Cetirizine (Figure 107).



Cyclizine
Motion sickness treatment

Cetirizine
Histamine H1 receptor antagonist

Indinavir
Protease inhibitor for antiretroviral therapy

Figure 107 Applications for the resulting products

In the following, the corresponding carbocations are generated from benzhydryl halides or benzhydrol followed by a nucleophilic trapping under green and mild reaction conditions.[258]

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[258] The most work was done in the context of a bachelor thesis H. Busen, Tu Dortmund (Dortmund), **2018**.

Therefore, a suitable catalyst is needed and even though there have been numerous reports on the use of different kinds of catalysts ranging from H-bond donor catalysts,[259] halogen and chalcogen-bond donor catalysts,[260] proline derivates,[261] Lewis-acidic Deep Eutectic Solvents,[262] phosphotungstic Acid[263] to active metals[264] they often lack sustainable characteristics.

5.2. Results and discussion

Initially, the Ritter reaction between a benzhydryl halide in acetonitrile, which is solvent and reactant at the same time, was examined at room temperature. In doing so, different metals were tested (Table 49).

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[259] A. R. Brown, W.-H. Kuo, E. N. Jacobsen, *J. Am. Chem. Soc.,* **2010**, *132*, 9286-9288.

[260] S. M. Walter, F. Kniep, E. Herdtweck, S. M. Huber, *Angew. Chem., Int. Ed.,* **2011**, *50*, 7187-7191; P. Wonner, L. Vogel, M. Düser, L. Gomes, F. Kniep, B. Mallick, D. B. Werz, S. M. Huber, *Angew. Chem., Int. Ed.,* **2017**, *56*, 12009-12012.

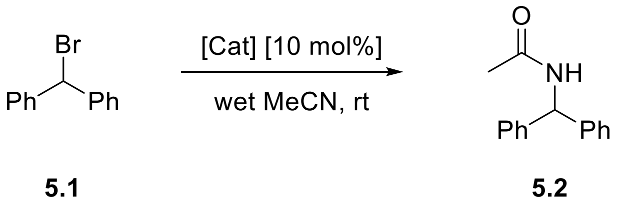
[261] P. G. Cozzi, F. Benfatti, L. Zoli, *Angew. Chem., Int. Ed.,* **2009**, *48*, 1313-1316.

[262] H. T. Nguyen, P. H. Tran, *RSC Adv.,* **2016**, *6*, 98365-98368.

[263] G. W. Wang, Y. B. Shen, X. L. Wu, *Eur. J. Org. Chem.,* **2008**, *2008*, 4367-4371.

[264] D. Posevins, K. Suta, M. Turks, *Eur. J. Org. Chem.,* **2016**, *2016*, 1414-1419; N. Ibrahim, A. S. K. Hashmi, F. Rominger, *Adv. Synth. Catal.,* **2011**, *353*, 461-468; E. Emer, R. Sinisi, M. G. Capdevila, D. Petruzziello, F. De Vincentiis, P. G. Cozzi, *Eur. J. Org. Chem.,* **2011**, *2011*, 647-666; P. Rubenbauer, T. Bach, *Tetrahedron Lett.,* **2008**, *49*, 1305-1309.

Table 49 Catalyst screening for the Ritter-reaction



Entry	**Catalyst**	**Yield***
1	$Bi(NO_3)_3$	20%
2	$Bi(OTf)_3$	57% (48%)**
3	$GaCl_3$	34%
4	$InBr_3$	7%
5	$In(OTf)_3$	43% (45%)**
6	$AuCl_3$	29%
7	PPh_3AuCl***	18%
8	AgOTf	17%
9	HOTf	10%
10	-	5%

* Determined by GC with internal standard, ** Isolated yield, ***Addition of 0.1 eq. AgOTf

Different main group and transition metal salts were tested in this reaction with moderate yields. In general, the generation of benzhydrol and dimerization products could always be detected as side products. However, especially the triflate salts of bismuth and indium catalysed this reaction best with 57% and 43% yield (Table 49, entries 2 and 5). That leads to the question of whether the reaction is catalysed by the generation of HOTf. This could be excluded since the addition of HOTf gives a yield of just 10% (Table 49, entry 9). Furthermore, it is noteworthy that only low conversion was detected in the absence of any catalyst (Table 49, entry 10).

In a next step the influence of the catalyst loading of the best catalyst $Bi(OTf)_3$ was determined (Figure 108).

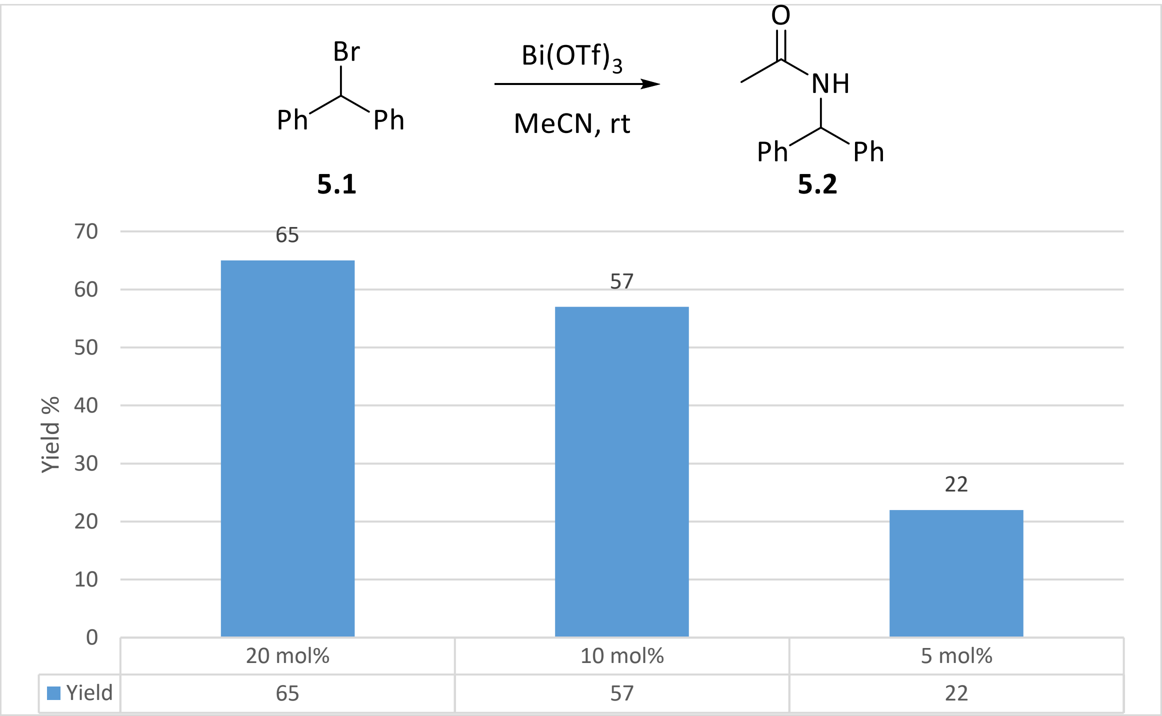


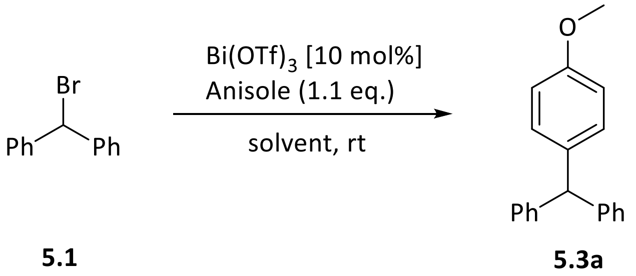
Figure 108 Different catalyst loadings for the Ritter-reaction

* Determined by GC with internal standard

The results showed that a doubling of the catalyst loading leads only to a minor increase of yield, while halving the catalysts loading showed a significant decline of yield to 22%.

In the following, it was envisaged to use stronger nucleophiles than acetonitrile and the already mentioned mostly green solvent class DES as well as other green solvents. Anisole was chosen as a benchmark nucleophile because of its high nucleophilicity and low toxicity.

Table 50 S_N1 substitution with different solvents at room temperature

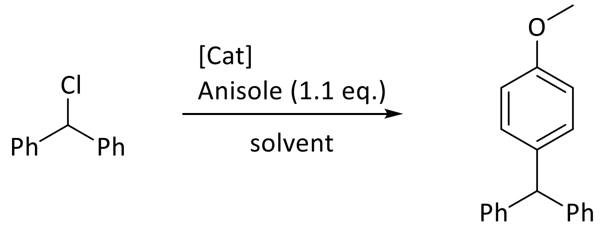


Entry	**Solvent**	**Yield**
1	PEG (~200 g/mol)	5%
2	EtOAc	4%
3	water	11%
4	water + 2 wt% TPGS-750-M	12%
5	propylene carbonate	29%
6	CHCl:glycerol (1:2)	24%
7	CHCl:urea (1:2)	31%

* Determined by GC with internal standard

In doing so, different solvents were tested at room temperature. It has been found that the solvents PEG and EtOAc are not suitable for this reaction since only very low yields could be obtained (Table 50, entries 1 and 2). Furthermore, water was used, which led only to low yields for the substitution product. Instead a large amount of benzhydrol as side product could be observed (Table 50, entry 3). Even with the addition of TPGS-750-M (tocopheryl polyethylene glycol succinate), a surfactant, the same result was observed (Table 50, entry 4). Next, propylene carbonate and two DESs were used and led to yields about 30% (Table 50, entries 5-7), which were not satisfactory. As a consequence, a broad range of DESs were tested at increased temperatures and the educt was changed to the cheaper and more atom economical benzhydryl chloride (Table 51).

Table 51 S_N1 substitution in different DESs



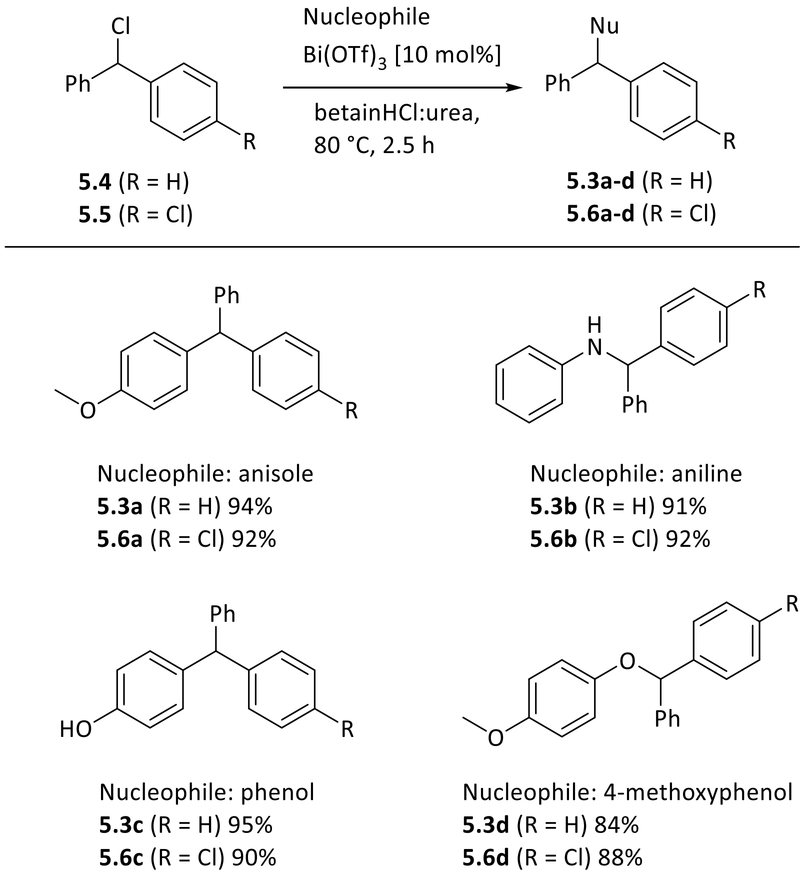
5.4 **5.3a**

Entry	Solvent (mol:mol)	Catalyst	Temperature	Yield
1	CHCl:urea (1:2)	$Bi(OTf)_3$ [10 mol%]	80 °C	80% (77%)**
2	CHCl:glycerol (1:2)	$Bi(OTf)_3$ [10 mol%]	80 °C	27%
3	CHCl:sorbitol:glycerol (2:1:1)	$Bi(OTf)_3$ [10 mol%]	80 °C	79%
4	CHCl:DMU (1:2)	$Bi(OTf)_3$ [10 mol%]	80 °C	82%
5	CHCl:oxalic acid (1:1)	$Bi(OTf)_3$ [10 mol%]	80 °C	71%
6	betaineHCl:urea (15:85)	$Bi(OTf)_3$ [10 mol%]	80 °C	94% (91%)**
7	betaineHCl:glycerol (1:2)	$Bi(OTf)_3$ [10 mol%]	80 °C	92%
8	CHCl:sorbitol (1:1)	$Bi(OTf)_3$ [10 mol%]	80 °C	93%
9	urea:guanidiniumHCl	$Bi(OTf)_3$ [10 mol%]	80 °C	95%
10	betaineHCl:urea (15:85)	-	80 °C	0%

* Determined by GC with internal standard, ** Isolated yield

While an increased temperature of 80 °C could increase the yield up to 80% in CHCl:urea, CHCl:glycerol failed to lead to an increased yield and remained at about 30% (Table 51, entries 1 and 2). The eutectic mixtures CHCl:sorbitol:glycerol, CHCl:DMU and CHCl:oxalic acid led to good but still extendable results between 71% and 82% (Table 51, entries 3-5). Very good results could be obtained in the mixtures betaineHCl:urea, betaineHCl:glycerol, CHCl:sorbitol and urea:guanidiniumHCl up to 95% yield (Table 51, entries 6-9). It is noteworthy that without the bismuth salt no conversion could be determined (Table 51, entry 10).

After these promising results it was interesting to see if the optimised conditions could be applied to a broader range of nucleophiles as well as to another aromatic halide like 4-chlorobenzhydryl chloride, Figure 109 indicates the outcome.



5.4 (R = H)
5.5 (R = Cl)

5.3a-d (R = H)
5.6a-d (R = Cl)

Nucleophile: anisole
5.3a (R = H) 94%
5.6a (R = Cl) 92%

Nucleophile: aniline
5.3b (R = H) 91%
5.6b (R = Cl) 92%

Nucleophile: phenol
5.3c (R = H) 95%
5.6c (R = Cl) 90%

Nucleophile: 4-methoxyphenol
5.3d (R = H) 84%
5.6d (R = Cl) 88%

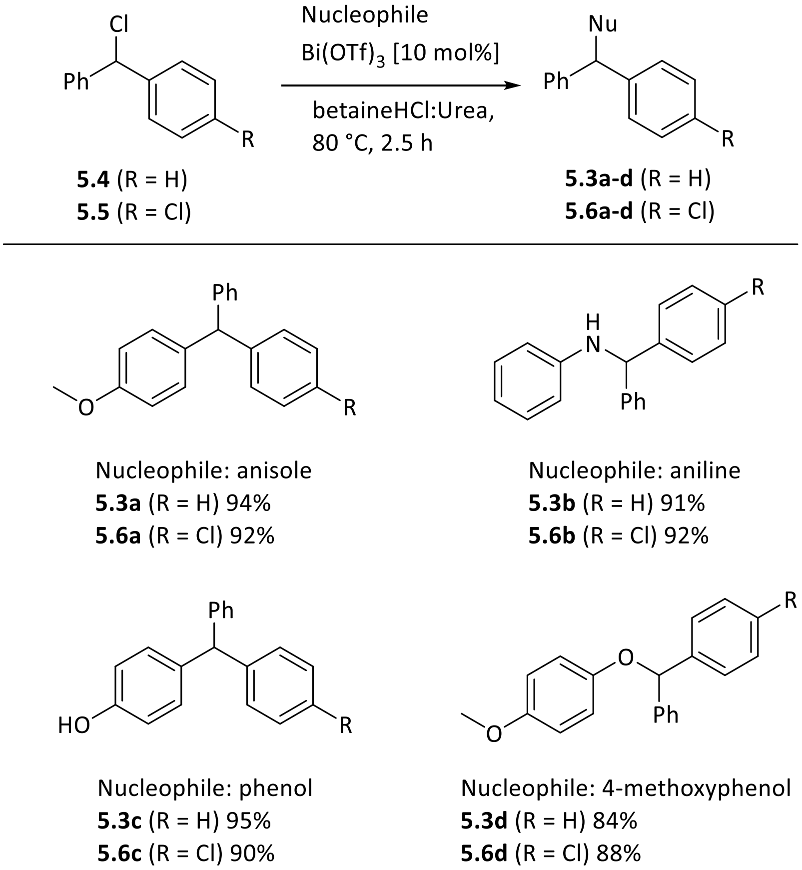
Figure 109 Outcome with different nucleophiles and two aromatic chlorides

As can be seen it was possible to use alcohols, amines and aromatic nucleophiles for this reaction with very good yields. Between benzhydryl chloride and 4-chlorobenzhydryl chloride there was only a minor difference regarding the yield.

5.3. Conclusion

In the context of this project, a more sustainable and easy protocol was tested for the functionalisation of benzhydryl derivates in DESs. In doing so, a benzhydryl halide underwent a nucleophilic attack in in a S_N1-reaction catalysed by main group metals.

The reactions were optimised with regards to the DESs mixture as well as the catalysts. The result of this process was the promising reaction system bismuth(III)triflate in betaineHCl:urea, which could be used to introduce different nucleophiles like alcohols, amines and aromatic compounds (Figure 110).



5.4 (R = H)
5.5 (R = Cl)

5.3a-d (R = H)
5.6a-d (R = Cl)

Nucleophile: anisole
5.3a (R = H) 94%
5.6a (R = Cl) 92%

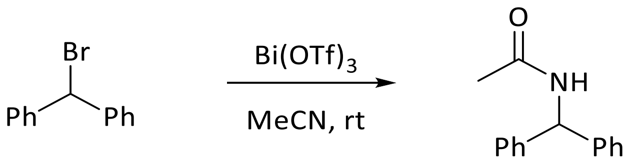
Nucleophile: aniline
5.3b (R = H) 91%
5.6b (R = Cl) 92%

Nucleophile: phenol
5.3c (R = H) 95%
5.6c (R = Cl) 90%

Nucleophile: 4-methoxyphenol
5.3d (R = H) 84%
5.6d (R = Cl) 88%

Figure 110 Outcome with different nucleophiles and two aromatic chlorides

Furthermore, it could be shown that a Ritter-type reaction can also be catalysed by bismuth(III)triflate with acetonitrile as both solvent and nucleophile (Figure 111).



5.1 **5.2**

Figure 111 Ritter-type-reaction catalysed by bismuth(III)triflate

5.4. Experimental

General procedure for the preparation of DES:

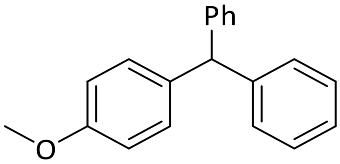
The respective compounds were filled in a flask and heated in oil bath for about 10-60 min until the mixture was a homogenous liquid. The DESs were used directly without a further purification step.

General procedure for the S_N1-reaction:

The catalyst (0.1 eq.) was dissolved in 2 ml of the respective DES and stirred for 10 min in a snap-cap jar. Then, 50 mg of the respective aromatic halide (1 eq.) and the nucleophile (1.1 eq.) were dissolved and stirred for the respective time and temperature. After this, 2 ml of water was added, and the mixture was extracted with Et_2O (3 x 2 ml). The combined organic phases were dried over $MgSO_4$ and the solvent was evaporated. Followed by a purification by column chromatography if necessary.

((4-methoxyphenyl)methylene)dibenzene (**5.3a**)

MD-P33-106



Light yellow solid, purified by flash column chromatography (pentane:Et_2O 20:1)

^1H NMR (600 MHz, Acetonitrile-d_3) δ 7.29 (t, J = 7.5 Hz, 4H), 7.21 (t, J = 7.3 Hz, 2H), 7.14 (d, J = 7.5 Hz, 4H), 7.05 (d, J = 8.7 Hz, 2H), 6.85 (d, J = 8.7 Hz, 2H), 5.54 (s, 1H), 3.74 (s, 3H)

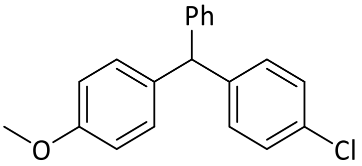
^{13}C NMR (151 MHz, Acetonitrile-d_3) δ 159.1, 145.4, 137.0, 131.1, 130.2, 130.1, 129.3, 129.2, 127.2, 118.3, 114.6, 56.6, 55.8

HSQC (^1H/^{13}C), (Acetonitrile-d_3): (7.29, 129.32), (7.21, 127.23), (7.14, 130.12), (7.05, 131.16), (6.86, 114.67), (5.54, 56.67), (3.74, 55.84)

Known compound[265]

1-chloro-4-((4-methoxyphenyl)(phenyl)methyl)benzene (**5.6a**)

MD-P31-341



Light yellow solid, purified by flash column chromatography (pentane:Et_2O 20:1)

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[265] J. Zhang, A. Bellomo, A. D. Creamer, S. D. Dreher, P. J. Walsh, *J. Am. Chem. Soc.,* **2012**, *134*, 13765-13772.

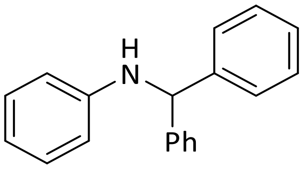
^{1}H NMR (600 MHz, Acetonitrile-d_3) δ 7.27 (s, 4H), 7.14 – 7.00 (m, 7H), 6.85 (d, J = 8.8 Hz, 2H), 5.52 (s, 1H), 3.74 (s, 3H)

^{13}C NMR (151 MHz, Acetonitrile-d_3) δ 145.0, 144.4, 136.6, 131.7, 131.1, 130.1, 129.4, 129.3, 127.4, 118.3, 114.8, 55.9, 55.9

MS (ESI (m/z) $[C_{20}H_{16}ClO]^+$) calculated: m/z = 307.8050; found: 307.2617

N-benzhydrylaniline (**5.3b**)

MD-P33-421



Brown solid, purified by flash column chromatography (pentane:Et_2O 5:1)

^{1}H NMR (600 MHz, Acetonitrile-d_3) δ 7.43 (d, J = 7.9 Hz, 4H), 7.34 (t, J = 7.7 Hz, 5H), 7.26 (t, J = 7.4 Hz, 2H), 7.08 (t, J = 7.7 Hz, 2H), 6.65 – 6.60 (m, 3H), 5.64 (s, 1H)

^{13}C NMR (151 MHz, Acetonitrile-d_3) δ 148.7, 144.4, 129.9, 129.6, 128.2, 128.1, 114.5, 62.9

HSQC (^{1}H/^{13}C), (Acetonitrile-d_3): (7.43, 128.23), (7.34, 129.59), (7.26, 128.13), (7.08, 129.87), (6.65 – 6.60, 114.46), (5.64, 62.87)

HMBC (^{1}H/^{15}N), (Acetonitrile-d_3): (6.65 – 6.60, 78.50), (5.64, 78.50)

Known compound[266]

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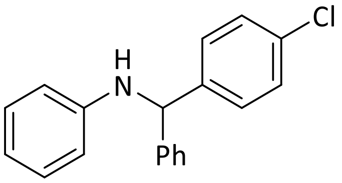
[266] J. S. Samec, J. E. Bäckvall, *Chem. - Eur. J.,* **2002**, *8*, 2955-2961.

N-((4-chlorophenyl)(phenyl)methyl)aniline (**5.6b**)

MD-P33-420



Brown solid, purified by flash column chromatography (pentane:Et_2O 5:1)

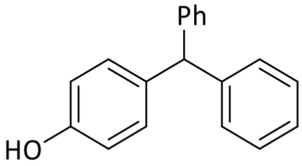
^{1}H NMR (600 MHz, Acetonitrile-*d*$_3$) δ 7.41 – 7.37 (m, 4H), 7.34 (t, J = 7.7 Hz, 4H), 7.26 (t, J = 7.3 Hz, 1H), 7.07 (dd, J = 8.5, 7.4 Hz, 2H), 6.61 (d, J = 8.6 Hz, 2H), 5.62 (s, 1H)

^{13}C NMR (151 MHz, Acetonitrile-*d*$_3$) δ 148.4, 143.9, 143.2, 133.2, 129.9, 129.9, 129.7, 129.5, 128.3, 128.3, 118.3, 114.5, 62.1

Known compound[267]

4-benzhydrylphenol (**5.3c**)

MD-P33-377



Light yellow solid, purified by flash column chromatography (pentane:Et_2O 8:1)

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[267] A. Yu, Y. Wu, B. Cheng, K. Wei, J. Li, *Adv. Synth. Catal.,* **2009**, *351*, 767-771.

^{1}H NMR (600 MHz, Acetonitrile-d_3) δ 7.30 (t, J = 7.5 Hz, 4H), 7.21 (t, J = 7.4 Hz, 2H), 7.13 (d, J = 7.4 Hz, 4H), 6.95 (d, J = 8.5 Hz, 2H), 6.83 (s, 1H), 6.74 (d, J = 8.6 Hz, 2H), 5.51 (s, 1H)

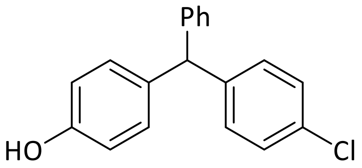
^{13}C NMR (151 MHz, Acetonitrile-d_3) δ 156.2, 145.5, 136.2, 131.1, 130.1, 130.0, 129.2, 129.2, 127.1, 118.3, 115.8, 56.5, 1.3

HSQC (^{1}H/^{13}C), (Acetonitrile-d_3): (7.29, 129.27), (7.21, 127.15), (7.13, 130.08), (6.96, 131.19), (6.75, 115.99), (5.51, 56.63)

Known compound[265]

4-((4-chlorophenyl)(phenyl)methyl)phenol (**5.6c**)

MD-P33-427



Light yellow solid, purified by flash column chromatography (pentane:Et$_2$O 8:1)

^{1}H NMR (600 MHz, Acetonitrile-d_3) δ 7.27 (d, J = 8.4 Hz, 4H), 7.21 (t, J = 7.3 Hz, 1H), 7.10 (dd, J = 12.9, 8.0 Hz, 4H), 6.95 (d, J = 8.5 Hz, 2H), 6.90 (s, 1H), 6.79 (dd, J = 7.2, 6.6 Hz, 2H), 5.49 (s, 1H)

^{13}C NMR (151 MHz, Acetonitrile-d_3) δ 156.4, 145.0, 144.4, 135.8, 132.4, 131.7, 131.2, 130.0, 129.4, 129.2, 127.3, 118.3, 116.1, 55.9

Known compound[268]

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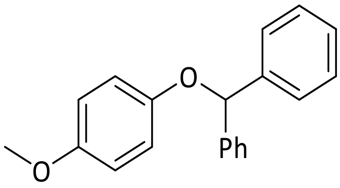
[268] Lapkin, *Zh. Org. Khim.*, *9*, 1690-1692.

((4-methoxyphenoxy)methylene)dibenzene (**5.3d**)

MD-P33-433



Light yellow solid, purified by flash column chromatography (pentane:Et_2O 8:1)

^1H NMR (600 MHz, Acetonitrile-d_3) δ 7.30 (t, *J* = 7.6 Hz, 5H), 7.23 (t, *J* = 7.4 Hz, 2H), 7.14 (d, *J* = 7.9 Hz, 4H), 6.80 (d, *J* = 8.7 Hz, 1H), 6.69 (dd, *J* = 8.7, 1.5 Hz, 1H), 6.58 (s, 1H), 6.39 (s, 1H), 5.86 (s, 1H), 3.60 (s, 3H)

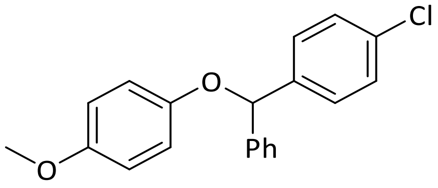
^{13}C NMR (151 MHz, Acetonitrile-d_3) δ 154.0, 149.1, 144.6, 132.5, 130.2, 129.2, 127.2, 118.3, 117.6, 116.6, 112.6, 56.0, 50.8

HSQC ($^1H/^{13}C$), (Acetonitrile-d_3): (7.30, 129.22), (7.23, 127.18), (7.14, 132.49), (6.80, 116.58), (6.69, 112.63), (6.39,117.63), (5.86, 50.79), (3.60, 56.03)

Known compound[269]

1-chloro-4-((4-methoxyphenoxy)(phenyl)methyl)benzene (**5.6d**)

MD-P33-434



Light yellow solid, purified by flash column chromatography (pentane:Et_2O 8:1)

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[269] K. T. Howard, B. C. Duffy, M. R. Linaburg, J. D. Chisholm, *Org. Biomol. Chem.*, **2016**, *14*, 1623-1628.

^{1}H NMR (600 MHz, Acetonitrile-d_3) δ 7.29 (t, J = 7.9 Hz, 5H), 7.22 (t, J = 7.3 Hz, 1H), 7.09 (dd, J = 11.4, 8.1 Hz, 4H), 6.78 (d, J = 8.7 Hz, 1H), 6.68 (dd, J = 8.7, 3.1 Hz, 1H), 6.60 (s, 1H), 6.33 (d, J = 3.0 Hz, 1H), 5.81 (s, 1H), 3.59 (s, 3H)

^{13}C NMR (151 MHz, Acetonitrile-d_3) δ 154.0, 149.0, 144.1, 143.6, 132.4, 132.0, 131.8, 130.1, 129.3, 129.1, 127.3, 118.3, 117.4, 116.6, 112.9, 56.0, 50.2

MS (ESI (m/z) [$C_{20}H_{17}ClONa$]$^+$) calculated: m/z = 331.7948; found: 331.2844

6. Summary

In the last years, the limitation of the natural resources on our earth has become more omnipresent than ever. Mankind’s lifestyle is far beyond the borders of regenerative capacity of earth and the biosphere. Therefore, the development of sustainable processes in the spirit of Green Chemistry is more important than ever before. The concept of Green Chemistry was introduced by Anastas, Warner, Sheldon and Trost in the early 1990s and is defined as: „Green Chemistry efficiently utilises (preferably renewable) raw materials, eliminates waste and avoids the use of toxic and/or hazardous reagents and solvents in the manufacture and application of chemical products.“ Many of the criteria of Green Chemistry could be satisfied by the development and utilisation of highly active, selective and recyclable catalysts in combination with separation processes, lastly, and importantly the application of green solvents since the usage of solvents is a significant factor due to their ubiquitous role in chemistry. However, the majority of the used solvents are still volatile organic compounds (VOCs), as a consequence there is a compelling need of alternative solvents which can provide the demanded specifications on the one hand and are able to overcome the known drawbacks of classic organic solvents on the other hand.

As a promising candidate *Abbott* and co-workers first reported in 2003 that the biomass-derived choline chloride and urea can generate an eutectic liquid, due to strong hydrogen bonds, which have lower melting points than their individual constituents. These so-called DESs (Deep Eutectic Solvents) can be adjusted to their respective purpose since the starting materials offer countless combinations, e.g. betaine cations, saccharinates, lactates, glycerol, natural carboxylic acids, organic acids or even with metal chlorides.

The main goal of this work is divided into two parts, on the one hand the synthesis of highly polar, water soluble and therefore easy separable NHC-gold catalysts and their application in gold-catalysed cyclisation reactions in which an intramolecular nucleophilic attack takes place. On the other hand, the development and application of green solvent systems for gold-catalysed reactions.

6.1. First steps into sustainability: Synthesis of recyclable NHC-catalysts

In doing so, the first part dealt with the synthesis of water-soluble ligands which can be categorised into two classes: NHC and mesoionic carbenes (MICs). Initially, a triazole-based ligand bearing quaternary ammonium salt group **L1** was envisioned, which could be synthesised very straightforwardly, indicated by Figure 112.

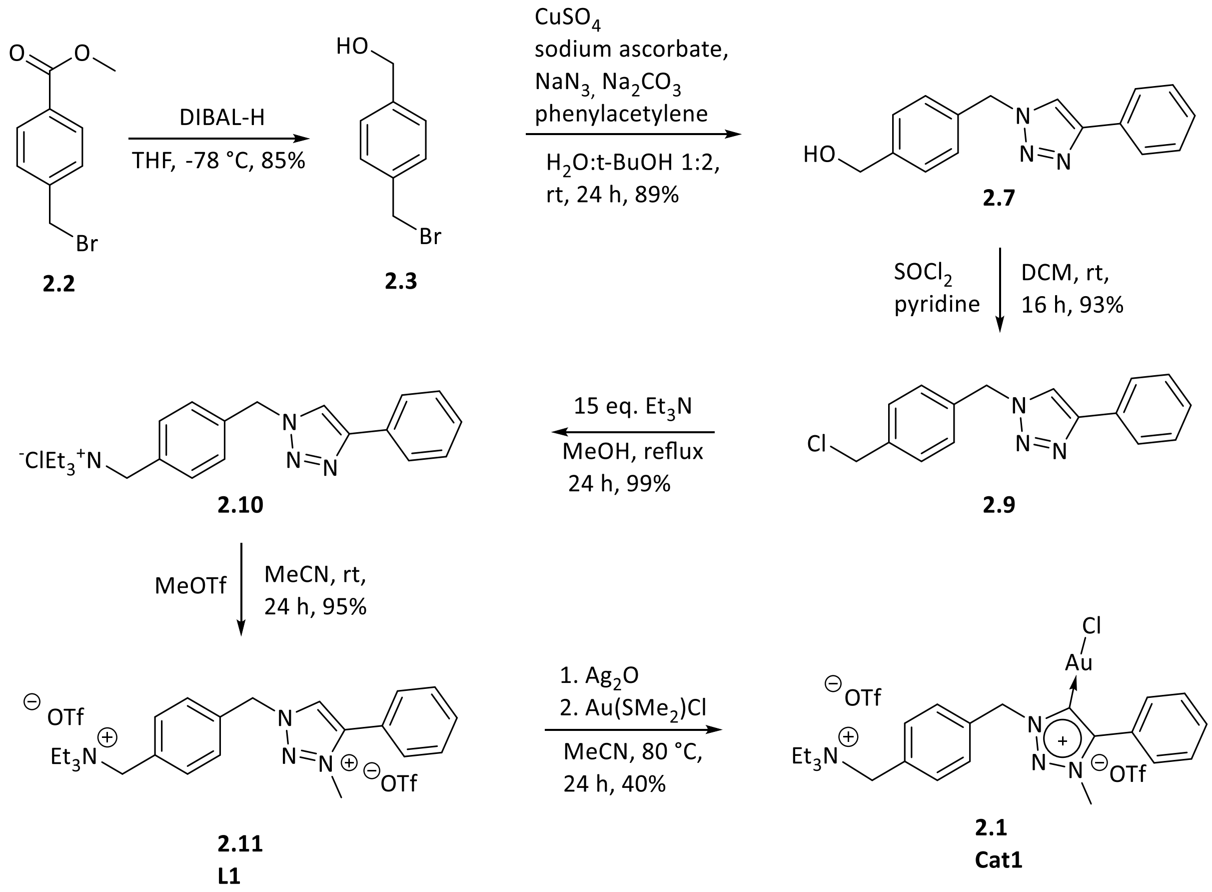


Figure 112 Synthesis of gold complex **Cat1**

Ligand **L1** could be synthesised with a remarkable total yield of 66% in five steps, however the introduction of gold turned out to be very challenging. In fact, the synthesis of gold complex **Cat1** proceeded only once using a transmetalation step of an *in situ* generated silver complex to the desired gold complex. Despite numerous efforts to reproduce the initial findings, it was not possible to synthesise **Cat1** again.

Therefore, another ligand was envisaged based on an imidazolium core bearing a polyethylene glycol group, which is a well-established possibility to add hydrophilicity to a ligand. The respective gold complex could be synthesised efficiently in a four-step synthesis with a total yield of 16% as indicated in Figure 113. Initially, two different length of the PEG-monomethyl ether chains were used, one with an average 12 entities and an average molecular weight of 550 g/mol and the second with an average chain length of 90 and a corresponding weight of 4000 g/mol. However, it became clear that the shorter one was more suitable for these reactions, since a much better yield could be obtained. Once again, the introduction of the gold moiety was challenging due to the poor reactivity of the polymeric ligands, therefore only a reproduceable yield of 45% could be obtained using the known transmetalation method.

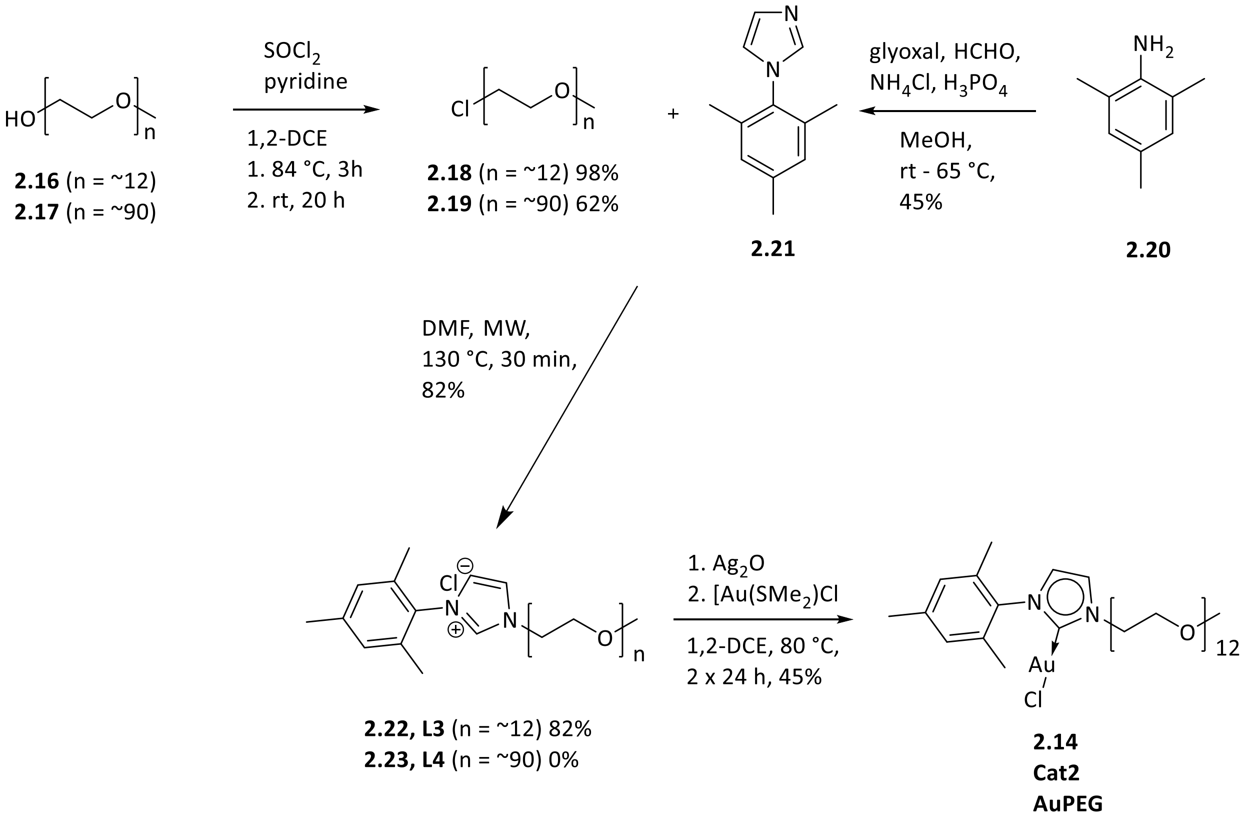


Figure 113 Synthesis of gold complex **AuPEG**

The second PEG-containing gold complex could be synthesised in a similar way as indicated in Figure 114.

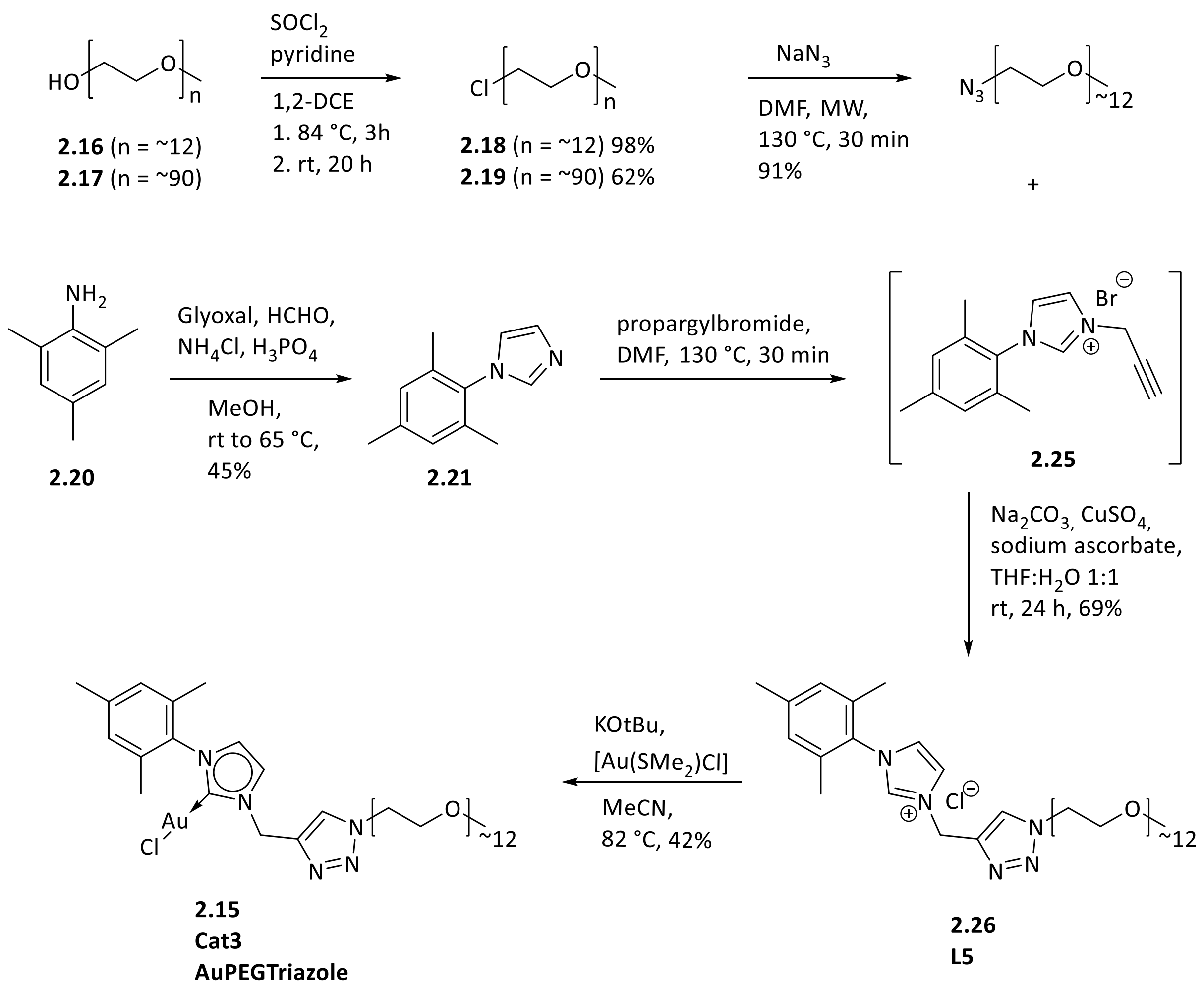
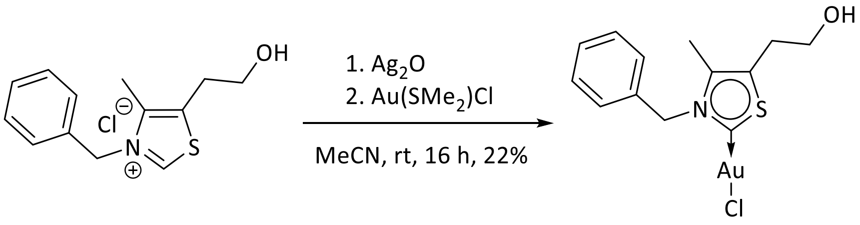


Figure 114 Synthesis of gold complex **AuPEGTriazole**

Gold complex **AuPEGTriazole** could be synthesised in a good overall yield, although the introduction of the gold turned out to be the bottleneck here again and could be achieved in a yield of 42%, using the free carbene method in this case. This includes the generation of the free carbene by the strong base KO*t*Bu followed by the addition of the gold species.

Furthermore, thiazole-based ligands were envisaged, which however could not be realised due to their poor stability. Nonetheless, one water-soluble vitamin B1-derived ligand was tested, and gold could be introduced to the ligand via the transmetalation method (Figure 115). This case was similar to gold complex **Cat1**, the reaction only proceeded once.



2.38
L7

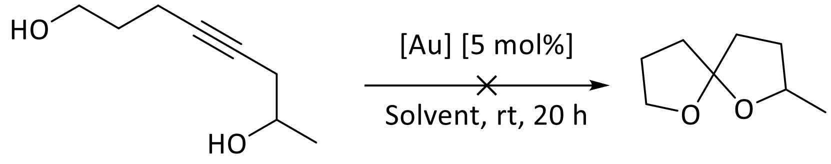
2.29
Cat6

Figure 115 Generation of the gold complex **Cat6**

Finally, both gold complexes **AuPEG** and **AuPEGTriazol** were tested in different gold-catalysed reactions, including cyclisation reactions of alkynediols, α-hydroxyallenes and N-propargylamides, which builds a bridge to the second part of this work.

The gold-catalysed cyclisations of alkynediols and α-hydroxyallenes are well-known in the *Krause* group. Therefore, these reactions seemed to be an ideal test for the generated gold complexes. The used educts could be obtained efficiently or originated from previous projects.

Table 52 Outcome of the cycloisomerisation of an alkynediol



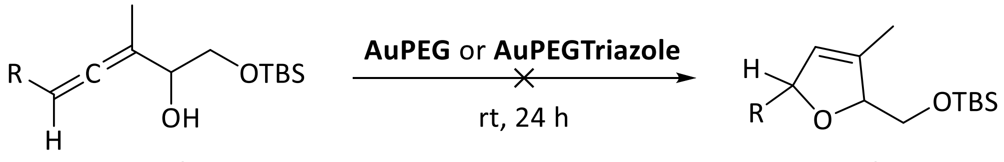
2.46

2.47

Entry	Solvent	Catalyst	Additive	Yield
1	H_2O	**AuPEG**	-	No conversion
2	H_2O	**AuPEGTriazol**	-	No conversion
3	H_2O	**AuPEG**	AgOTf [5 mol%]	No conversion
4	H_2O	**AuPEGTriazol**	AgOTf [5 mol%]	No conversion
5	DCM	**AuPEG**	AgOTf [5 mol%]	No conversion
6	DCM	**AuPEGTriazol**	AgOTf [5 mol%]	No conversion

However, neither in the cyclisation of an alkynediol nor in the cycloisomerisation of α-hydroxyallenes any conversion could be observed using both complexes in different green reaction media (Table 52 and Table 53). Even the addition of a non-coordinating silver salt like AgOTf, which is a known procedure to generate the active gold cationic species, could not improve the outcome.

Table 53 Cycloisomerisation catalysed by **AuPEG** and **AuPEGTriazole**

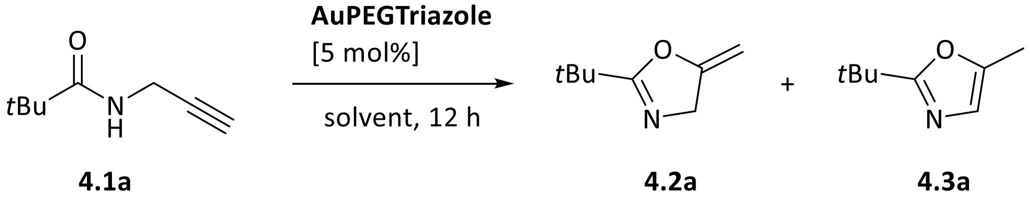


3.4a-b **3.11a-b**

Entry	R =	Catalyst	Solvent	Addition of AgOTf	Yield
1	*t*Bu **3.4a**	**AuPEG** (5 mol%)	Water	-	No conversion
2	*t*Bu **3.4a**	**AuPEGTriazole** (5 mol%)	Water	-	No conversion
3	Ph **3.4b**	**AuPEG** (5 mol%)	Water	5 mol %	No conversion
4	Ph **3.4b**	**AuPEGTriazole** (5 mol%)	Water	5 mol %	No conversion
5	Ph **3.4b**	**AuPEG** (5 mol%)	MeOH	5 mol %	No conversion
6	Ph **3.4b**	**AuPEGTriazole** (5 mol%)	MeOH	5 mol %	No conversion

The third test reaction was the cyclisation of N-propargylamides to their corresponding oxazole derivates. The *Hashmi* group has reported an in-depth examination of this reaction. Two products, a non-aromatic and an aromatic oxazole derivate are possible in this reaction, however the non-aromatic product is not thermodynamically stable and is converted into the more stable aromatic product.

Table 54 Cyclisation of N-Propargylcarboxamides with catalyst **AuPEGTriazole**



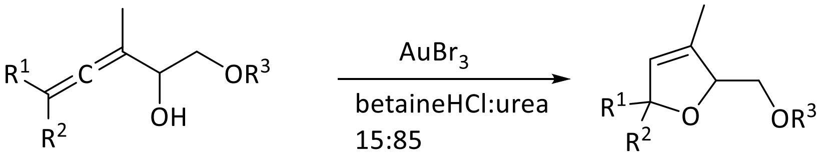
Entry	Solvent (mol:mol)	Additive	Temp.	Overall Yield*	Selectivity 2/3*
1	propylene carbonate	-	20 °C	27%	44:56
2	CHCl:glycerol (1:2)	-	20 °C	10%	<1:99
3	CHCl:urea (1:2)	-	20 °C	12%	<1:99
4	CHCl:glycerol (1:2)	-	80 °C	17%	31:69
5	CHCl:urea (1:2)	-	80 °C	90% (85%)**	11:89
6	propylene carbonate	0.05 eq. AgOTf	20 °C	0%	-
7	CHCl:glycerol (1:2)	0.05 eq. AgOTf	20 °C	0%	-
8	CHCl:urea (1:2)	0.05 eq. AgOTf	20 °C	23%	<1:99
9	CHCl:glycerol (1:2)	0.05 eq. AgOTf	80 °C	25%	<1:99
10	CHCl:urea (1:2)	0.05 eq. AgOTf	80 °C	69% (65%)**	<1:99
11	methanol	0.05 eq. AgOTf	65 °C	48% (50%)**	>99:1

Whereas gold complex **AuPEG** showed no activity, gold complex **AuPEGtriazol** was able to catalyse this reaction with up to 90% yield. As a matter of fact it showed an excellent selectivity in methanol, since the catalyst was able to generate only the non-aromatic product, which undergoes normally a very fast conversion to **4.3** at higher temperatures (Table 54, entries 5 and 11).

6.2. Allene chemistry in the face of sustainability

Furthermore, it was interesting to see how the DESs systems behave with simple gold salts. At the outset of the study the cycloisomerisation of α-hydroxyallenes in different deep eutectic mixtures was tested with different commercially available gold catalysts. Having identified $AuBr_3$ in betaineHCl:urea as the most suitable catalyst/solvent system for this cycloisomerisation, the possible substrate scope was next examined (see Table 55).

Table 55 Substrate scope of the solvent/catalyst system



3.4a-e **3.11a-e**

Entry	**Allene**	**R¹ =**	**R² =**	**R³ =**	**Temp.**	**Time**	**Product**	**Yield**
1	**3.4b**	Ph	H	TBS	80 °C	3 h	**3.11b**	93%
2	**3.4c**	*i*Pr	H	TBS	80 °C	3 h	**3.11c**	84%
3	**3.4a**	*t*Bu	H	TBS	80 °C	3 h	**3.11a**	92%
4	**3.4d***	*t*Bu	H	Bn	80 °C	3 h	**3.11d**	70%
5	**3.4e***	Me	Me	Me	80 °C	3 h	**3.11e**	81%

*Originated from a former project in the group

Noteworthy, a nearly complete conversion of the allenes was achieved in the most cases and overall good yields could be obtained (Table 55, entries 1-3), which demonstrated the strong potential of this green solvent system. Only if the protecting group was changed to a benzyl or methyl group the yield decreased slightly (Table 55, entries 4 and 5).

In a next step, the recyclability of the system was tested. However, the system had to be adjusted since after the second run only a yield of 24% could be detected. A low melting mixture containing betaineHCl:urea:methanol ((m:m:m) 1 : 2.2 : 1) was used instead.

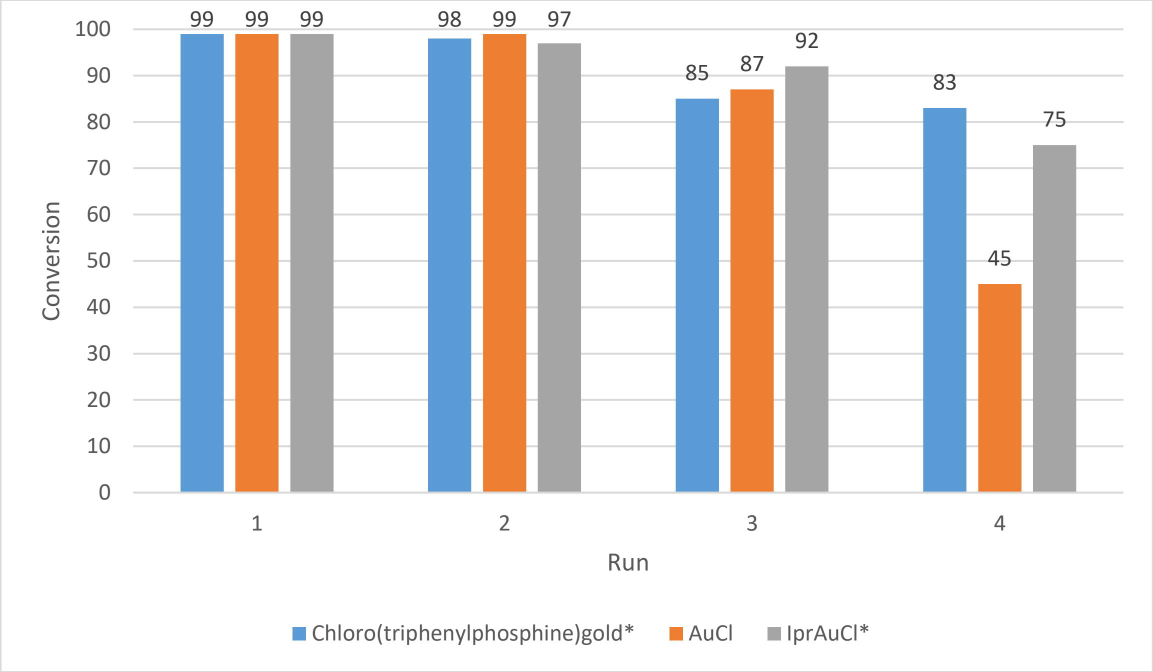


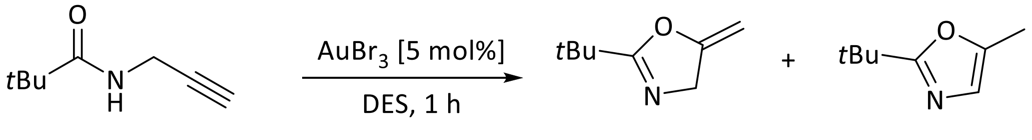
Figure 116 Recycling experiments for the cycloisomerisation of **3.4a** in betaineHCl:urea:Methanol, * Addition of 5 mol% AgOTf

As can be seen in Figure 116, all of the used catalysts (chloro(triphenylphosphine)gold(I), gold (I) chloride and chloro[1,3-bis(2,6-diisopropylphenyl)imidazol-2-ylidene]gold(I)) worked very well in this low melting mixture. Whereas the first two runs performed with full conversion, the third and fourth run showed a slightly deactivation for all catalysts, whereby gold(I) chloride showed the lowest conversion.

6.3. Cyclisation reactions of carboxamide, a way station on the road to sustainable oxazoles

The cyclisation of N-propargylamides was examined similarly, the solvent was tailored, in particular the choice of DES in the reaction to oxazole **4.3**. Furthermore, the selectivity of the two possible products was also investigated with $AuBr_3$ as catalyst. On the one hand it could be demonstrated that in the case of betaineHCl:urea and CHCl:malonic acid (1:1) quantitative yields could be achieved. Given the fact that betaineHCl:urea and CHCl:malonic acid are easy to handle and showed the best activity, these solvent systems were used as method of choice in further optimisations. On the other hand, it could be shown that the selectivity is adjustable by the choice of solvent and temperature, obviously higher temperatures favour the formation of the aromatic product, due to the superior thermodynamic stability (Table 56).

Table 56 Selectivity determination of the cycloisomerisation of N-Propargylcarboxamides catalysed by gold(III) bromide in different DESs



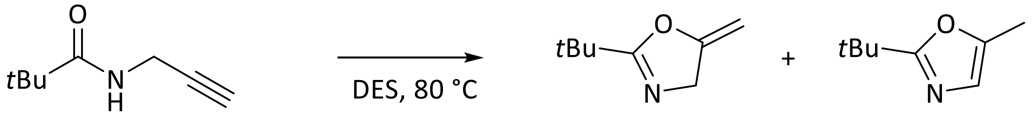
4.1a **4.2a** **4.3a**

Entry	**DES (mol:mol)**	**Temp.**	**Overall Yield***	**Selectivity 4.2/4.3**
1	CHCl:glycerol (1:2)	20 °C	36%	>99:1
2	CHCl:glycerol (1:2)	60 °C	68%	>99:1
3	CHCl:malonic acid (1:1)	20 °C	82%	>99:1
4	CHCl:malonic acid (1:1)	40 °C	99%	<1:99
5	CHCl:malonic acid (1:1)	60 °C	99%	<1:99
6	CHCl:malonic acid (1:1)	80 °C	99%	<1:99
7	CHCl:urea (1:2)	20 °C	99%	>99:1
8	CHCl:urea (1:2)	80 °C	99%	<1:99
9	CHCl:DMU (1:2)	80 °C	75%	80:20
10	CHCl:sorbitol:glycerol (2:1:1)	40°C	49%	>99:1

* Determined by GC with internal standard

Additionally, a metal-containing DES was used, which has a “Janus-faced” character, being both solvent and catalyst, which performed very well in the most cases (Table 56). In contrast, other main group metals like gallium and bismuth failed to catalyse this reaction.

Table 57 Cycloisomerisation of N-Propargylcarboxamides with metal containing DES



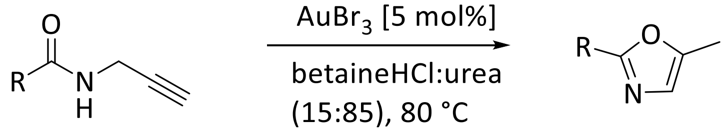
4.1a **4.2a** **4.3a**

Entry	DES (mol:mol)	Time	Overall Yield*	Selectivity 2/3
1	CHCl:$FeCl_3$ (1:2)	1 h	99%	<1:99
2	urea:$ZnCl_2$ (7:2)	1 h	82%	<1:99
3	urea:$ZnCl_2$ (7:2)	0.5 h	20%	<1:99
4	urea:$ZnBr_2$ (7:2)	1 h	99% (98%)**	<1:99
5	urea:$ZnBr_2$ (7:2)	0.5 h	47%	<1:99
6	CHCl:$ZnCl_2$ (1:2)	1 h	99% (96%)**	<1:99
7	CHCl:$ZnBr_2$ (1:2)	1 h	77%	<1:99

* Determined by GC with internal standard, ** Isolated yield

With the optimised reaction conditions in hand it was interesting to see how other substrates perform in this reaction (Table 57).

Table 58 Gold-catalysed cyclisations with different substrates



4.1b-k,o,p **4.3b-k,o,p**

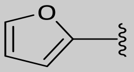
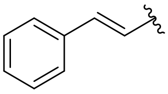
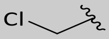
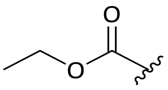
Entry	R =	Product	Time	Yield
1	n-Pr	**4.3b**	24 h	62%
2	Me	**4.3c**	2 h	99%
3	4-methoxyphenyl	**4.3d**	2 h	95%
4	benzyl	**4.3e**	2 h	77%
5	phenyl	**4.3f**	2 h	99%
6	4-nitrophenyl	**4.3g**	2 h	85%
7	CF_3	**4.3p**	24 h	0%
8		**4.3h**	2 h	96%
9		**4.3i**	2 h	88%
10		**4.3j**	2 h	0%
11		**4.3k**	2 h	0%
12	Alloc	**4.3o**	2 h	0%

Table 58 indicates that the method was applicable for a wide range of substituents in good yield with a few exceptions like a CF_3- substituent.

It was also possible to achieve recycling experiments, in doing so urea:$ZnBr_2$ and **4.1a** were used and the products were separated by Kugelrohr distillation. This reaction system showed an impressive recycling capacity, it could be reused five times without a loss of reactivity (Figure 117). In the fifth run the product was extracted and a quantitative yield could be obtained, showing that the lower yields in the first four runs caused from losses by the distillation.

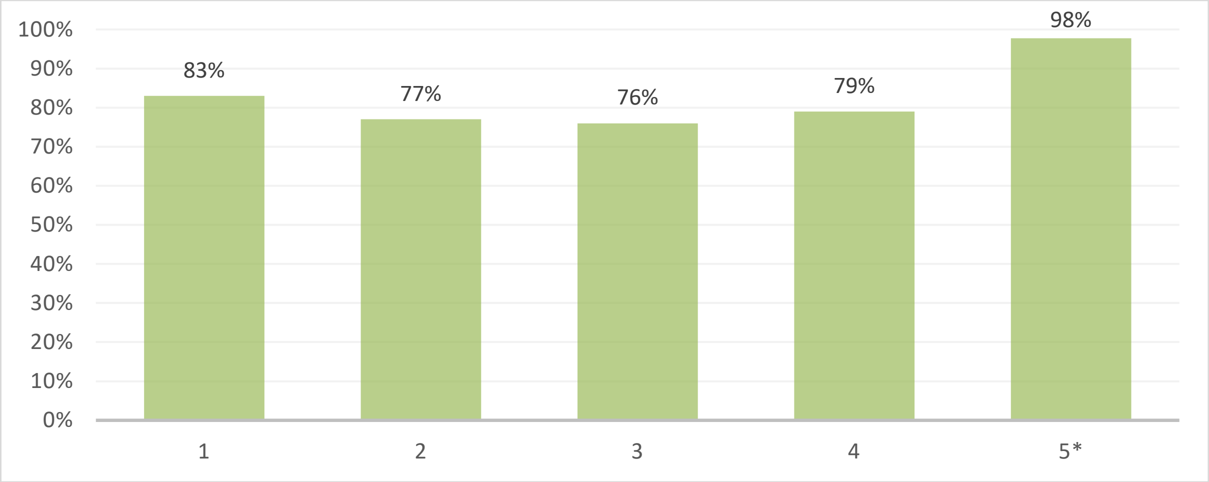
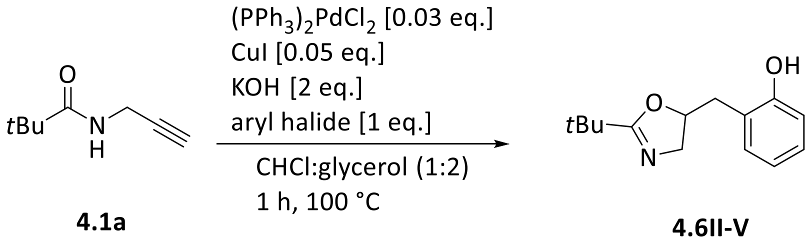


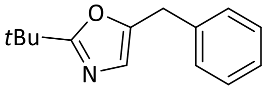
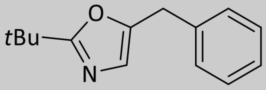
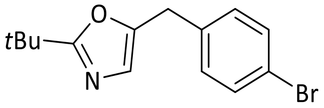
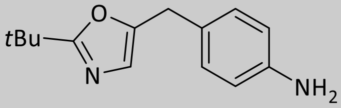
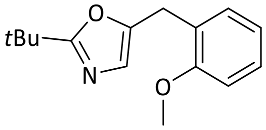
Figure 117 Recyclability of this catalyst system using urea:$ZnBr_2$ and **4.1a**

Another interesting approach for the synthesis of substituted oxazoles is the use of palladium catalysts due to their ability to catalyse not only the cyclisation but also a cross-coupling between the terminal alkyne and an aryl halide. Therefore, the solvent and the base were optimised in this reaction and applied to different aryl halides (Table 59).

Table 59 Pd catalysed cyclisation and cross coupling with different aryl halides



4.1a **4.6II-V**

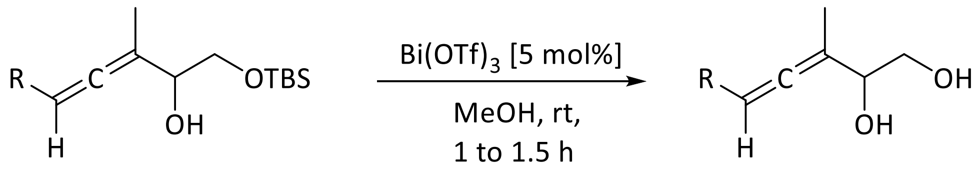
Entry	Aryl halide	Product		Yield
1	Brombenzene **4.19**		**4.6II**	78%
2	Iodbenzene **4.20**		**4.6II**	99%
3	1-Bromo-4-iodobenzene **4.21**		**4.6III**	95%
4	4-iodoaniline **4.22**		**4.6IV**	0%*
5	1-iodo-2-methoxybenzene **4.23**		**4.6V**	85%

* Formation of **4.3a**

As shown, the majority of the used aryl halides reacted efficiently to the desired oxazole derivates. Furthermore, it could be demonstrated that also aryl bromides are suitable for this reaction.

6.4. Excursuses: Examination on more cost-efficient alternative catalysts / Main group metal catalysed S$_N$1-reactions

This work included two digressions: on the one hand the use of primary main group metals to catalyse a cycloisomerisation of an TBS-protected α-hydroxyallenes. However, the reaction proceeded not in the desired cyclisation but in a rapid deprotection of the TBS-group (Figure 118). Nevertheless, the reaction conditions could be optimised resulting in the best outcome for $Bi(OTf)_3$ in methanol and a recycling of the system could be achieved, too.

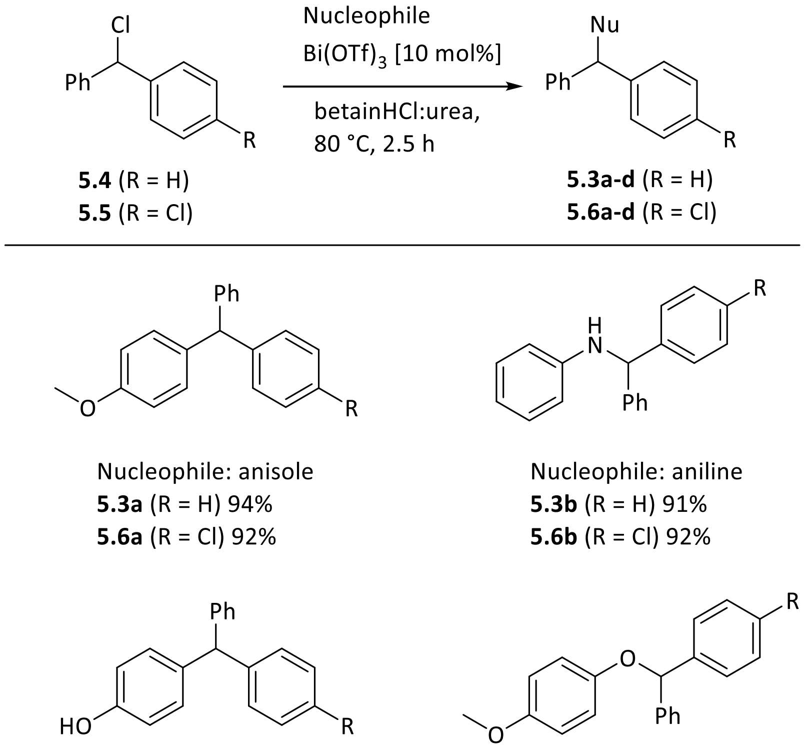


3.4a (R = *t*Bu)
3.4b (R = Ph)

3.14a (R = *t*Bu) 99%
3.14b (R = Ph) 97%

Figure 118 Bismuth catalysed deprotection

On the other hand, a sustainable and easy protocol was tested for the functionalisation of benzhydryl derivates in DES. In doing so, a benzhydryl halide underwent a nucleophilic attack in a S_N1-reaction catalysed by main group metals. The reactions were optimised with regards to the DESs mixture and the catalysts. The result of this process was the promising reaction system bismuth(III)triflate in betaineHCl:urea, which could be used to introduce different nucleophiles like alcohols, amines and aromatic compounds (Figure 119).



5.4 (R = H)
5.5 (R = Cl)

5.3a-d (R = H)
5.6a-d (R = Cl)

Nucleophile: anisole
5.3a (R = H) 94%
5.6a (R = Cl) 92%

Nucleophile: aniline
5.3b (R = H) 91%
5.6b (R = Cl) 92%

Nucleophile: phenol
5.3c (R = H) 95%
5.6c (R = Cl) 90%

Nucleophile: 4-methoxyphenol
5.3d (R = H) 84%
5.6d (R = Cl) 88%

Figure 119 Outcome with different nucleophiles and two aromatic chlorides

7. Annexe

2.13, L2

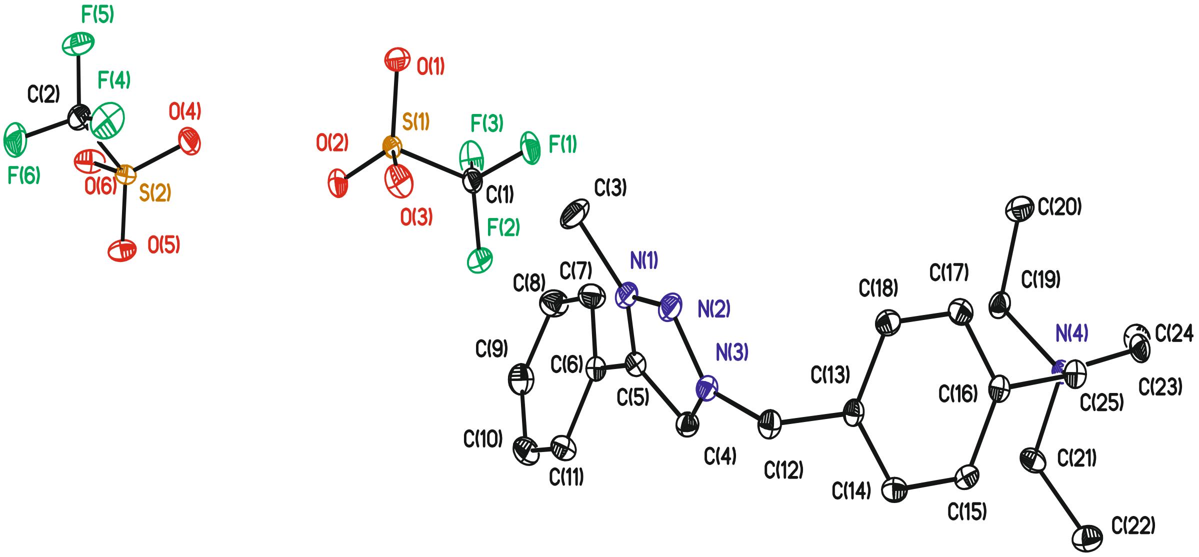


Table 1. Crystal data and structure refinement for 3557_End.

Identification code	3557
Empirical formula	C25 H32 F6 N4 O6 S2
Formula weight	662.66
Temperature	173(2) K
Wavelength	0.71073 A
Crystal system, space group	Orthorhombic, Pbca
Unit cell dimensions	a = 14.7462(3) A alpha = 90 deg. b = 13.8262(3) A beta = 90 deg. c = 28.7480(6) A gamma = 90 deg.
Volume	5861.2(2) A^3
Z, Calculated density	8, 1.502 Mg/m^3
Absorption coefficient	0.267 mm^-1
F(000)	2752
Crystal size	0.240 x 0.220 x 0.180 mm
Theta range for data collection	2.140 to 31.120 deg.
Limiting indices	-21<=h<=21, -18<=k<=19,-41<=l<=41

Reflections collected / unique	59227 / 8851 [R(int) = 0.0337]
Completeness to theta = 27.000	100.0 %
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	1.00000 and 0.90529
Refinement method	Full-matrix least-squareson F^2
Data / restraints / parameters	8851 / 0 / 392
Goodness-of-fit on F^2	1.033
Final R indices [I>2sigma(I)]	R1 = 0.0369, wR2 = 0.0909
R indices (all data)	R1 = 0.0463, wR2 = 0.0963
Extinction coefficient	n/a
Largest diff. peak and hole	0.480 and -0.393 e.A^-3

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters (A^2 x 10^3) for 3557_End.
U(eq) is defined as one third of the trace of the orthogonalized Uij tensor.

	x	y	z	U(eq)
S(1)	150(1)	4593(1)	2340(1)	15(1)
O(1)	-825(1)	4635(1)	2371(1)	24(1)
O(2)	539(1)	5058(1)	1935(1)	22(1)
O(3)	550(1)	3675(1)	2457(1)	25(1)
C(1)	507(1)	5376(1)	2817(1)	17(1)
F(1)	151(1)	5089(1)	3223(1)	23(1)
F(2)	1407(1)	5371(1)	2868(1)	28(1)
F(3)	244(1)	6286(1)	2749(1)	27(1)
S(2)	360(1)	7729(1)	156(1)	15(1)
O(4)	-50(1)	7932(1)	599(1)	30(1)
O(5)	1280(1)	7388(1)	172(1)	24(1)
O(6)	176(1)	8440(1)	-200(1)	26(1)
C(2)	-292(1)	6684(1)	-46(1)	20(1)
F(4)	-217(1)	5944(1)	251(1)	34(1)
F(5)	-1172(1)	6896(1)	-81(1)	31(1)
F(6)	-17(1)	6371(1)	-459(1)	32(1)
N(1)	1766(1)	332(1)	4064(1)	16(1)
N(3)	2662(1)	-244(1)	4550(1)	14(1)
N(2)	1878(1)	-415(1)	4345(1)	17(1)
C(3)	965(1)	337(1)	3761(1)	24(1)
N(4)	2557(1)	2278(1)	6614(1)	12(1)
C(4)	3048(1)	590(1)	4410(1)	14(1)
C(5)	2463(1)	980(1)	4090(1)	14(1)
C(6)	2532(1)	1866(1)	3812(1)	15(1)
C(7)	1793(1)	2483(1)	3756(1)	21(1)
C(8)	1874(1)	3300(1)	3478(1)	24(1)
C(9)	2691(1)	3503(1)	3257(1)	22(1)
C(10)	3434(1)	2903(1)	3323(1)	21(1)
C(11)	3360(1)	2089(1)	3602(1)	18(1)
C(12)	2978(1)	-906(1)	4919(1)	15(1)
C(13)	2883(1)	-403(1)	5383(1)	12(1)
C(14)	3640(1)	-37(1)	5611(1)	15(1)
C(15)	3539(1)	472(1)	6025(1)	14(1)
C(16)	2681(1)	628(1)	6214(1)	13(1)
C(17)	1925(1)	236(1)	5989(1)	15(1)
C(18)	2025(1)	-274(1)	5576(1)	15(1)
C(19)	1880(1)	2614(1)	6250(1)	16(1)
C(20)	892(1)	2443(1)	6368(1)	21(1)
C(21)	3480(1)	2643(1)	6451(1)	16(1)
C(22)	4265(1)	2418(1)	6770(1)	22(1)
C(23)	2322(1)	2668(1)	7093(1)	16(1)
C(24)	2248(1)	3761(1)	7119(1)	20(1)
C(25)	2550(1)	1177(1)	6662(1)	14(1)

Table 3. Bond lengths [A] and angles [deg] for 3557_End.

S(1)-O(3)	1.4397(10)
S(1)-O(1)	1.4414(10)
S(1)-O(2)	1.4469(10)
S(1)-C(1)	1.8256(13)
C(1)-F(3)	1.3311(15)
C(1)-F(2)	1.3349(15)
C(1)-F(1)	1.3388(14)
S(2)-O(4)	1.4376(11)
S(2)-O(5)	1.4376(10)
S(2)-O(6)	1.4432(10)
S(2)-C(2)	1.8301(14)
C(2)-F(6)	1.3261(16)
C(2)-F(5)	1.3354(16)
C(2)-F(4)	1.3373(16)
N(1)-N(2)	1.3205(15)
N(1)-C(5)	1.3656(16)
N(1)-C(3)	1.4691(16)
N(3)-N(2)	1.3181(14)
N(3)-C(4)	1.3481(15)
N(3)-C(12)	1.4780(15)
C(3)-H(3B)	0.9800
C(3)-H(3C)	0.9800
C(3)-H(3D)	0.9800
N(4)-C(23)	1.5182(15)
N(4)-C(19)	1.5186(15)
N(4)-C(21)	1.5254(15)
N(4)-C(25)	1.5290(15)
C(4)-C(5)	1.3725(17)
C(4)-H(4B)	0.9500
C(5)-C(6)	1.4664(17)
C(6)-C(7)	1.3940(17)
C(6)-C(11)	1.3965(17)
C(7)-C(8)	1.3893(19)
C(7)-H(7A)	0.9500
C(8)-C(9)	1.3905(19)
C(8)-H(8A)	0.9500
C(9)-C(10)	1.3871(19)
C(9)-H(9A)	0.9500
C(10)-C(11)	1.3852(18)
C(10)-H(10A)	0.9500
C(11)-H(11A)	0.9500
C(12)-C(13)	1.5099(16)
C(12)-H(12A)	0.9900
C(12)-H(12B)	0.9900
C(13)-C(14)	1.3906(16)
C(13)-C(18)	1.3937(16)
C(14)-C(15)	1.3914(17)
C(14)-H(14A)	0.9500
C(15)-C(16)	1.3940(16)

C(15)-H(15A)	0.9500
C(16)-C(17)	1.3995(16)
C(16)-C(25)	1.5070(16)
C(17)-C(18)	1.3885(17)
C(17)-H(17A)	0.9500
C(18)-H(18A)	0.9500
C(19)-C(20)	1.5155(18)
C(19)-H(19A)	0.9900
C(19)-H(19B)	0.9900
C(20)-H(20A)	0.9800
C(20)-H(20B)	0.9800
C(20)-H(20C)	0.9800
C(21)-C(22)	1.5088(18)
C(21)-H(21A)	0.9900
C(21)-H(21B)	0.9900
C(22)-H(22A)	0.9800
C(22)-H(22B)	0.9800
C(22)-H(22C)	0.9800
C(23)-C(24)	1.5163(17)
C(23)-H(23A)	0.9900
C(23)-H(23B)	0.9900
C(24)-H(24A)	0.9800
C(24)-H(24B)	0.9800
C(24)-H(24C)	0.9800
C(25)-H(25A)	0.9900
C(25)-H(25B)	0.9900
O(3)-S(1)-O(1)	115.44(7)
O(3)-S(1)-O(2)	114.65(6)
O(1)-S(1)-O(2)	115.31(6)
O(3)-S(1)-C(1)	103.18(6)
O(1)-S(1)-C(1)	102.54(6)
O(2)-S(1)-C(1)	103.12(6)
F(3)-C(1)-F(2)	108.04(11)
F(3)-C(1)-F(1)	107.07(10)
F(2)-C(1)-F(1)	107.04(10)
F(3)-C(1)-S(1)	111.48(9)
F(2)-C(1)-S(1)	111.45(9)
F(1)-C(1)-S(1)	111.53(9)
O(4)-S(2)-O(5)	115.55(7)
O(4)-S(2)-O(6)	114.55(7)
O(5)-S(2)-O(6)	115.11(6)
O(4)-S(2)-C(2)	102.41(6)
O(5)-S(2)-C(2)	104.31(6)
O(6)-S(2)-C(2)	102.36(6)
F(6)-C(2)-F(5)	107.62(11)
F(6)-C(2)-F(4)	107.29(11)
F(5)-C(2)-F(4)	107.19(11)
F(6)-C(2)-S(2)	112.38(10)
F(5)-C(2)-S(2)	111.12(9)
F(4)-C(2)-S(2)	111.00(9)
N(2)-N(1)-C(5)	112.74(10)
N(2)-N(1)-C(3)	117.90(11)
C(5)-N(1)-C(3)	129.29(11)
N(2)-N(3)-C(4)	113.05(10)
N(2)-N(3)-C(12)	119.14(10)
C(4)-N(3)-C(12)	127.59(10)

N(3)-N(2)-N(1)	104.01(10)
N(1)-C(3)-H(3B)	109.5
N(1)-C(3)-H(3C)	109.5
H(3B)-C(3)-H(3C)	109.5
N(1)-C(3)-H(3D)	109.5
H(3B)-C(3)-H(3D)	109.5
H(3C)-C(3)-H(3D)	109.5
C(23)-N(4)-C(19)	111.46(9)
C(23)-N(4)-C(21)	111.36(9)
C(19)-N(4)-C(21)	105.90(9)
C(23)-N(4)-C(25)	105.66(9)
C(19)-N(4)-C(25)	111.25(9)
C(21)-N(4)-C(25)	111.31(9)
N(3)-C(4)-C(5)	105.63(10)
N(3)-C(4)-H(4B)	127.2
C(5)-C(4)-H(4B)	127.2
N(1)-C(5)-C(4)	104.57(11)
N(1)-C(5)-C(6)	124.88(11)
C(4)-C(5)-C(6)	130.52(11)
C(7)-C(6)-C(11)	119.97(12)
C(7)-C(6)-C(5)	121.30(11)
C(11)-C(6)-C(5)	118.74(11)
C(8)-C(7)-C(6)	119.72(12)
C(8)-C(7)-H(7A)	120.1
C(6)-C(7)-H(7A)	120.1
C(7)-C(8)-C(9)	120.14(13)
C(7)-C(8)-H(8A)	119.9
C(9)-C(8)-H(8A)	119.9
C(10)-C(9)-C(8)	120.04(12)
C(10)-C(9)-H(9A)	120.0
C(8)-C(9)-H(9A)	120.0
C(11)-C(10)-C(9)	120.22(12)
C(11)-C(10)-H(10A)	119.9
C(9)-C(10)-H(10A)	119.9
C(10)-C(11)-C(6)	119.85(12)
C(10)-C(11)-H(11A)	120.1
C(6)-C(11)-H(11A)	120.1
N(3)-C(12)-C(13)	108.68(9)
N(3)-C(12)-H(12A)	110.0
C(13)-C(12)-H(12A)	110.0
N(3)-C(12)-H(12B)	110.0
C(13)-C(12)-H(12B)	110.0
H(12A)-C(12)-H(12B)	108.3
C(14)-C(13)-C(18)	119.68(11)
C(14)-C(13)-C(12)	120.65(11)
C(18)-C(13)-C(12)	119.64(10)
C(13)-C(14)-C(15)	120.13(11)
C(13)-C(14)-H(14A)	119.9
C(15)-C(14)-H(14A)	119.9
C(14)-C(15)-C(16)	120.62(11)
C(14)-C(15)-H(15A)	119.7
C(16)-C(15)-H(15A)	119.7
C(15)-C(16)-C(17)	118.86(11)
C(15)-C(16)-C(25)	121.82(11)
C(17)-C(16)-C(25)	119.29(11)
C(18)-C(17)-C(16)	120.58(11)

C(18)-C(17)-H(17A)	119.7
C(16)-C(17)-H(17A)	119.7
C(17)-C(18)-C(13)	120.09(11)
C(17)-C(18)-H(18A)	120.0
C(13)-C(18)-H(18A)	120.0
C(20)-C(19)-N(4)	115.50(10)
C(20)-C(19)-H(19A)	108.4
N(4)-C(19)-H(19A)	108.4
C(20)-C(19)-H(19B)	108.4
N(4)-C(19)-H(19B)	108.4
H(19A)-C(19)-H(19B)	107.5
C(19)-C(20)-H(20A)	109.5
C(19)-C(20)-H(20B)	109.5
H(20A)-C(20)-H(20B)	109.5
C(19)-C(20)-H(20C)	109.5
H(20A)-C(20)-H(20C)	109.5
H(20B)-C(20)-H(20C)	109.5
C(22)-C(21)-N(4)	115.48(10)
C(22)-C(21)-H(21A)	108.4
N(4)-C(21)-H(21A)	108.4
C(22)-C(21)-H(21B)	108.4
N(4)-C(21)-H(21B)	108.4
H(21A)-C(21)-H(21B)	107.5
C(21)-C(22)-H(22A)	109.5
C(21)-C(22)-H(22B)	109.5
H(22A)-C(22)-H(22B)	109.5
C(21)-C(22)-H(22C)	109.5
H(22A)-C(22)-H(22C)	109.5
H(22B)-C(22)-H(22C)	109.5
C(24)-C(23)-N(4)	114.54(10)
C(24)-C(23)-H(23A)	108.6
N(4)-C(23)-H(23A)	108.6
C(24)-C(23)-H(23B)	108.6
N(4)-C(23)-H(23B)	108.6
H(23A)-C(23)-H(23B)	107.6
C(23)-C(24)-H(24A)	109.5
C(23)-C(24)-H(24B)	109.5
H(24A)-C(24)-H(24B)	109.5
C(23)-C(24)-H(24C)	109.5
H(24A)-C(24)-H(24C)	109.5
H(24B)-C(24)-H(24C)	109.5
C(16)-C(25)-N(4)	114.97(9)
C(16)-C(25)-H(25A)	108.5
N(4)-C(25)-H(25A)	108.5
C(16)-C(25)-H(25B)	108.5
N(4)-C(25)-H(25B)	108.5
H(25A)-C(25)-H(25B)	107.5

Symmetry transformations used to generate equivalent atoms:

Table 4. Anisotropic displacement parameters (A^2 x 10^3) for 3557_End.
The anisotropic displacement factor exponent takes the form:
-2 pi^2 [h^2 a*^2 U11 + ... + 2 h k a* b* U12]

	U11	U22	U33	U23	U13	U12
S(1)	14(1)	17(1)	14(1)	-4(1)	0(1)	2(1)
O(1)	14(1)	32(1)	26(1)	-10(1)	-1(1)	0(1)
O(2)	22(1)	29(1)	13(1)	0(1)	1(1)	2(1)
O(3)	29(1)	18(1)	28(1)	-2(1)	5(1)	7(1)
C(1)	18(1)	18(1)	14(1)	0(1)	2(1)	-2(1)
F(1)	30(1)	26(1)	13(1)	0(1)	5(1)	-5(1)
F(2)	18(1)	43(1)	24(1)	-4(1)	-3(1)	-7(1)
F(3)	42(1)	14(1)	23(1)	-2(1)	3(1)	0(1)
S(2)	12(1)	15(1)	18(1)	2(1)	1(1)	0(1)
O(4)	25(1)	42(1)	23(1)	-10(1)	7(1)	-11(1)
O(5)	15(1)	24(1)	32(1)	2(1)	-4(1)	4(1)
O(6)	18(1)	21(1)	38(1)	13(1)	-1(1)	1(1)
C(2)	20(1)	18(1)	22(1)	1(1)	-3(1)	1(1)
F(4)	41(1)	20(1)	42(1)	11(1)	-7(1)	-9(1)
F(5)	16(1)	30(1)	48(1)	-9(1)	-5(1)	-2(1)
F(6)	36(1)	33(1)	27(1)	-12(1)	-2(1)	4(1)
N(1)	14(1)	21(1)	14(1)	1(1)	-2(1)	-3(1)
N(3)	14(1)	15(1)	13(1)	-2(1)	-1(1)	0(1)
N(2)	16(1)	20(1)	15(1)	0(1)	-3(1)	-3(1)
C(3)	19(1)	31(1)	23(1)	3(1)	-10(1)	-6(1)
N(4)	13(1)	11(1)	12(1)	1(1)	1(1)	0(1)
C(4)	14(1)	15(1)	15(1)	0(1)	0(1)	-1(1)
C(5)	13(1)	17(1)	13(1)	-1(1)	1(1)	0(1)
C(6)	14(1)	18(1)	12(1)	0(1)	0(1)	0(1)
C(7)	15(1)	25(1)	23(1)	4(1)	2(1)	2(1)
C(8)	19(1)	25(1)	27(1)	7(1)	0(1)	5(1)
C(9)	24(1)	21(1)	21(1)	6(1)	0(1)	0(1)
C(10)	20(1)	21(1)	22(1)	3(1)	5(1)	-2(1)
C(11)	15(1)	19(1)	20(1)	1(1)	3(1)	2(1)
C(12)	17(1)	13(1)	14(1)	0(1)	-1(1)	2(1)
C(13)	15(1)	10(1)	12(1)	1(1)	-1(1)	1(1)
C(14)	13(1)	15(1)	18(1)	0(1)	0(1)	2(1)
C(15)	13(1)	14(1)	16(1)	-1(1)	-3(1)	1(1)
C(16)	16(1)	9(1)	13(1)	2(1)	0(1)	0(1)
C(17)	14(1)	13(1)	17(1)	0(1)	2(1)	-1(1)
C(18)	14(1)	14(1)	17(1)	0(1)	-1(1)	-2(1)
C(19)	17(1)	16(1)	14(1)	2(1)	-2(1)	3(1)
C(20)	15(1)	24(1)	25(1)	-4(1)	-3(1)	3(1)
C(21)	14(1)	13(1)	21(1)	2(1)	4(1)	-1(1)
C(22)	16(1)	21(1)	28(1)	-4(1)	-2(1)	-1(1)
C(23)	20(1)	16(1)	12(1)	-3(1)	2(1)	-2(1)
C(24)	22(1)	16(1)	22(1)	-6(1)	1(1)	-1(1)
C(25)	18(1)	9(1)	14(1)	1(1)	0(1)	-1(1)

Table 5. Hydrogen coordinates (x 10^4) and isotropic displacement parameters (A^2 x 10^3) for 3557_End.

	x	y	z	U(eq)
H(3B)	1143	535	3446	37
H(3C)	516	794	3883	37
H(3D)	701	-313	3750	37
H(4B)	3609	854	4513	17
H(7A)	1235	2346	3908	25
H(8A)	1371	3721	3438	28
H(9A)	2740	4052	3060	26
H(10A)	3995	3051	3177	25
H(11A)	3871	1683	3649	21
H(12A)	3620	-1082	4865	18
H(12B)	2612	-1506	4917	18
H(14A)	4228	-135	5484	18
H(15A)	4060	716	6181	17
H(17A)	1338	320	6119	18
H(18A)	1507	-535	5425	18
H(19A)	1971	3315	6198	19
H(19B)	2017	2279	5954	19
H(20A)	511	2668	6110	32
H(20B)	736	2800	6651	32
H(20C)	789	1751	6419	32
H(21A)	3610	2359	6142	19
H(21B)	3445	3353	6411	19
H(22A)	4831	2639	6626	32
H(22B)	4296	1718	6823	32
H(22C)	4178	2750	7068	32
H(23A)	1738	2384	7192	19
H(23B)	2792	2452	7316	19
H(24A)	2091	3953	7437	30
H(24B)	1776	3984	6904	30
H(24C)	2830	4052	7032	30
H(25A)	3036	986	6882	16
H(25B)	1964	979	6801	16

Table 6. Torsion angles [deg] for 3557_End.

O(3)-S(1)-C(1)-F(3)	175.74(9)
O(1)-S(1)-C(1)-F(3)	-64.00(10)
O(2)-S(1)-C(1)-F(3)	56.11(10)
O(3)-S(1)-C(1)-F(2)	54.93(10)
O(1)-S(1)-C(1)-F(2)	175.20(9)
O(2)-S(1)-C(1)-F(2)	-64.70(10)
O(3)-S(1)-C(1)-F(1)	-64.64(10)
O(1)-S(1)-C(1)-F(1)	55.63(10)
O(2)-S(1)-C(1)-F(1)	175.73(9)
O(4)-S(2)-C(2)-F(6)	-179.90(10)
O(5)-S(2)-C(2)-F(6)	-59.11(11)
O(6)-S(2)-C(2)-F(6)	61.17(11)
O(4)-S(2)-C(2)-F(5)	59.44(11)
O(5)-S(2)-C(2)-F(5)	-179.77(10)
O(6)-S(2)-C(2)-F(5)	-59.49(11)
O(4)-S(2)-C(2)-F(4)	-59.74(11)
O(5)-S(2)-C(2)-F(4)	61.04(11)
O(6)-S(2)-C(2)-F(4)	-178.68(10)
C(4)-N(3)-N(2)-N(1)	0.44(13)
C(12)-N(3)-N(2)-N(1)	175.41(10)
C(5)-N(1)-N(2)-N(3)	-0.49(14)
C(3)-N(1)-N(2)-N(3)	176.66(11)
N(2)-N(3)-C(4)-C(5)	-0.24(14)
C(12)-N(3)-C(4)-C(5)	-174.70(11)
N(2)-N(1)-C(5)-C(4)	0.35(14)
C(3)-N(1)-C(5)-C(4)	-176.39(13)
N(2)-N(1)-C(5)-C(6)	178.69(11)
C(3)-N(1)-C(5)-C(6)	1.9(2)
N(3)-C(4)-C(5)-N(1)	-0.06(13)
N(3)-C(4)-C(5)-C(6)	-178.27(12)
N(1)-C(5)-C(6)-C(7)	45.61(18)
C(4)-C(5)-C(6)-C(7)	-136.51(14)
N(1)-C(5)-C(6)-C(11)	-134.57(13)
C(4)-C(5)-C(6)-C(11)	43.31(19)
C(11)-C(6)-C(7)-C(8)	2.3(2)
C(5)-C(6)-C(7)-C(8)	-177.84(13)
C(6)-C(7)-C(8)-C(9)	-0.3(2)
C(7)-C(8)-C(9)-C(10)	-1.6(2)
C(8)-C(9)-C(10)-C(11)	1.4(2)
C(9)-C(10)-C(11)-C(6)	0.7(2)
C(7)-C(6)-C(11)-C(10)	-2.6(2)
C(5)-C(6)-C(11)-C(10)	177.62(12)
N(2)-N(3)-C(12)-C(13)	-106.76(12)
C(4)-N(3)-C(12)-C(13)	67.39(15)
N(3)-C(12)-C(13)-C(14)	-104.57(12)
N(3)-C(12)-C(13)-C(18)	73.19(14)
C(18)-C(13)-C(14)-C(15)	-1.33(18)
C(12)-C(13)-C(14)-C(15)	176.43(11)
C(13)-C(14)-C(15)-C(16)	-0.46(18)
C(14)-C(15)-C(16)-C(17)	2.11(18)
C(14)-C(15)-C(16)-C(25)	179.96(11)

C(15)-C(16)-C(17)-C(18)	-2.00(18)
C(25)-C(16)-C(17)-C(18)	-179.90(11)
C(16)-C(17)-C(18)-C(13)	0.23(18)
C(14)-C(13)-C(18)-C(17)	1.44(18)
C(12)-C(13)-C(18)-C(17)	-176.34(11)
C(23)-N(4)-C(19)-C(20)	-51.36(14)
C(21)-N(4)-C(19)-C(20)	-172.61(10)
C(25)-N(4)-C(19)-C(20)	66.30(13)
C(23)-N(4)-C(21)-C(22)	56.94(13)
C(19)-N(4)-C(21)-C(22)	178.26(10)
C(25)-N(4)-C(21)-C(22)	-60.69(13)
C(19)-N(4)-C(23)-C(24)	-56.31(14)
C(21)-N(4)-C(23)-C(24)	61.71(13)
C(25)-N(4)-C(23)-C(24)	-177.29(10)
C(15)-C(16)-C(25)-N(4)	81.77(14)
C(17)-C(16)-C(25)-N(4)	-100.40(13)
C(23)-N(4)-C(25)-C(16)	174.48(10)
C(19)-N(4)-C(25)-C(16)	53.37(13)
C(21)-N(4)-C(25)-C(16)	-64.50(13)

Symmetry transformations used to generate equivalent atoms:

Eidesstattliche Erklärung

Hiermit erkläre ich des Eides statt, dass ich die vorliegende Dissertation mit dem Titel: *„Metal-catalysed cyclisation reactions in sustainable reaction media“* selbständig und ohne unzulässige Hilfe angefertigt habe. Ich habe keine anderen als die angegebenen Quellen und Hilfsmittel benutzt, sowie wörtliche und sinngemäße Zitate kenntlich gemacht.

Die Arbeit hat in gleicher oder ähnlicher Form noch keiner Prüfungsbehörde vorgelegen. Es haben bisher keine Promotionsverfahren stattgefunden.

Dortmund, den