universität wien

MASTERARBEIT / MASTER'S THESIS

Titel der Masterarbeit / Title of the Master's Thesis

„Part I: A Gold(I)-Catalysed Domino Coupling of Alcohols with Allenes Enables the Synthesis of Highly Substituted Indenes

Part II: Synthetic Studies on the Asymmetric Synthesis of Allenes“

verfasst von / submitted by

Alexander Preinfalk, BSc

angestrebter akademischer Grad / in partial fulfilment of the requirements for the degree of

Master of Science (MSc)

Wien, 2016 / Vienna, 2016

Studienkennzahl lt. Studienblatt / degree programme code as it appears on the student record sheet:	A 066862
Studienrichtung lt. Studienblatt / degree programme as it appears on the student record sheet:	Masterstudium Chemie
Betreut von / Supervisor:	Univ.-Prof. Dr. Nuno Maulide

Acknowledgements

First and foremost, I would like to thank Prof. Dr. Nuno Maulide for the opportunity to be part of his group and for his guidance and support during my master thesis. I am grateful for my interesting projects, the encouraging conversations and the many fruitful ideas which all help me to develop as a chemist.

I also want to thank Dr. Antonio Misale for the countless discussions and explanations especially at the early stage of my work.

Additionally, I am thankful to the whole Maulide Group, especially my lab colleagues Juliette Sabbatani and Martina Drescher, and my office colleagues Dr. Paul Aillard, Daniel Kaiser and Dr. Catarina Rodrigues for an exceptionally productive and humorous atmosphere. Special thanks go to Immo Klose, Rik Oost and Dr. Alberto Oppedisano for the amicable hours of fun and discussions about both, chemical and personal things.

Furthermore, I want to thank my parents and my sister, Valentina, for all the love they have shown me at every day since I was born.

Lastly, I want to thank Verena, my partner, for all the support she has given me over the last years and for always being there for me, even in the hard days of our common life.

Table of Contents

Acknowledgements I

Abstracts IV

English Abstract IV

Deutsche Zusammenfassung V

Abbreviations VI

Part I: A Gold(I)-Catalysed Domino Coupling of Alcohols with Allenes Enables the Synthesis of Highly Substituted Indenes 1

I.1 Gold Catalysis 1

I.1.1 General reactivity: 3

I.1.2 Gold Catalysis for the Activation of Unsaturated Alcohols 5

I.2 Indenes 7

I.3 Results and Discussion 14

I.3.1 Gold-Catalysed Synthesis of 1,3-Disubstituted Indenes 14

I.3.2 Attempts towards the C–C coupling of a vinyl-gold intermediate 17

I.4 Conclusion 31

I.5 References 32

I.6 Experimental 34

I.6.1 General Information 34

I.6.2 General Procedures 35

I.6.3 Synthesis of the acetates 38

I.6.4 Synthesis of Allenes I.3.1a-I.3.1l 46

I.6.5 Synthesis of Allylation Products I.3.18a-I.3.18m 51

I.6.6 Synthesis of Benzylation Products I.3.26a-I.3.26g 59

I.6.7 Characterisation Data for Products I.3.2a-I.3.2d 62

1.6.8 References: 64

Part II: Studies on the Asymmetric Synthesis of Allenes 65

II.1 Allenes 65

II.2 Synthesis of Allenes 66

II.2.1 Synthesis of Chiral Allenes using Enantiomerically Enriched Substrates 66

II.2.2 Synthesis of Chiral Allenes using Asymmetric Catalysis 69

II.3 Results and Discussion 72

II.3.1 Further Investigations on Nucleophiles 72

II.3.2 Dialkylzinc Nucleophiles 76

II.3.3 Conclusions and Outlook 78

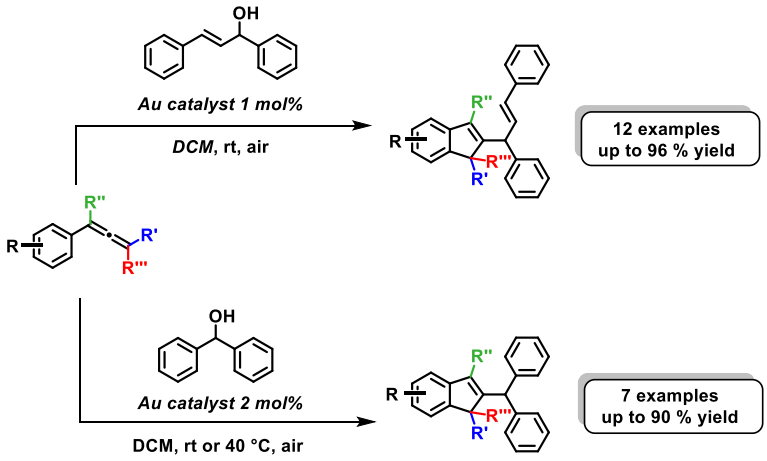
II.4 References 79
II.5 Experimental 80
II.5.1 General Information 80
II.5.2 Preparation of LG 2 80
II.5.3 Typical Procedure for the Asymmetric Aynthesis of Allenes 81
II.5.4 References: 82

Abstracts

English Abstract

This work is divided into two sections: In the first section, we present a gold(I)-catalysed cascade cyclisation of aryl-substituted allenes and alcohols, leading to densely substituted indenes. Several different approaches to achieve such a transformation are described, culminating in the successful development of a novel synthetic method.

Using this method, the corresponding indene products were obtained in good yields, under mild conditions and with low catalyst loading. During this domino transformation, two C–C bonds are formed with water as the only by-product.



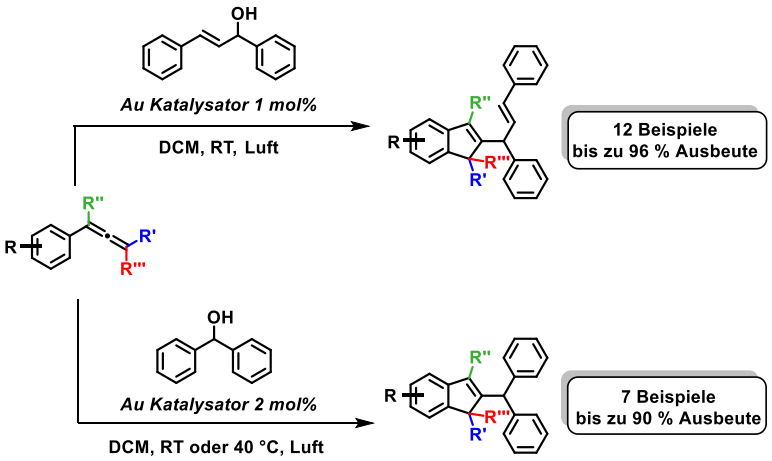
In the second section, we present our synthetic efforts towards the palladium-catalysed synthesis of chiral, trisubstituted allenes. The described methodology relies on the deracemisation of racemic propargylic substrates using suitable nucleophiles under asymmetric palladium catalysis.

This section covers the successful screening of nucleophiles, followed by an investigation of the dependence of enantiomeric excess on the reaction conditions. With the first steps already taken for this project, subsequent studies are currently ongoing in our laboratories.

Deutsche Zusammenfassung

Diese Arbeit gliedert sich in zwei Teile: Im ersten Teil beschreiben wir eine Gold(I)-katalysierte Kaskadenzyklisierung von Aryl-substituierten Allenen mit Alkoholen, welche hochsubstituierte Indene liefert. Um eine solche Transformation zu ermöglichen wurden verschiedene Ansätze verfolgt, welche schließlich in der erfolgreichen Entwicklung einer neuen synthetischen Methode gipfeln.

Die mittels dieser Methode leicht zugänglichen Inden-Produkte wurden in guten Ausbeuten, unter milden Bedingungen und niedriger Katalysatorbeladung erhalten. Während dieser Dominoreaktion werden zwei C–C Bindungen gebildet, mit Wasser als einziges Abfallprodukt.



Im zweiten Teil beschreiben wir unsere synthetischen Untersuchungen hinsichtlich einer Palladium-katalysierten Synthese von dreifach substituierten, chiralen Allenen. Diese Methode beruht auf der Deracemisierung von propargylischen Substraten mittels passenden Nukleophilen unter asymmetrischer Palladiumkatalyse.

Dieser Teil beschäftigt sich im Wesentlichen mit einer erfolgreichen Untersuchung verschiedener Nukleophile, gefolgt von der Überprüfung des Einflusses der Reaktionsbedingungen auf die asymmetrische Induktion. Mit diesen ersten Erkenntnissen endet diese Arbeit, wobei weiterführende Forschungen an diesem Projekt bereits in unseren Labors fortschreiten.

Abbreviations

Ac	acetyl
AcOH	acetic acid
app	apparent (NMR)
aq	aqueous
ATR	attenuated total reflection
br	broadened (NMR)
brsm	based on recovered starting material
Bu	butyl
c	concentration
cat.	Catalyst
Cy	Cyclohexyl
d	days
d	doublet
δ	chemical shift (NMR)
DCE	1,2-dichloroethane
DCM	dichloromethane
decomp.	decomposition
DIPA	diisopropylamine
DMF	N,N-dimethylformamide
dppm	1,1-Bis(diphenylphosphino)methane
EI	electron ionisation
ESI	electrospray ionisation
Et	ethyl
EtOAc	ethyl acetate
EtOH	ethanol
equiv	equivalent
FC	Friedel-Crafts
FTIR	Fourier transform infrared spectroscopy
h	hours

HRMS	high resolution mass spectroscopy
IR	infrared
LDA	lithium diisopropylamide
LG	leaving group
m	multiplet
M	molar
Me	methyl
MeCN	acetonitrile
MeOH	methanol
mmol	millimole
µmol	micromole
MS	mass spectroscopy
MS	molecular sieves
NBS	N-bromosuccinimide
NHC	N-heterocyclic carbene
NIS	N-iodosuccinimide
n.d.	not determined
NMR	nuclear magnetic resonance
Ph	phenyl
ppm	parts per million
p-TsOH	*para*-toluenesulfonic acid
quant.	quantitative
quin	quintet
RCM	ring-closing metathesis
s	singlet
SM	starting material
solv.	solvent
t	triplet
t-Bu	tert-butyl
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TLC	thin-layer chromatography

TMS	trimethylsilyl
TMSCl	trimethylsilyl chloride
UV	ultraviolet
X	halogen

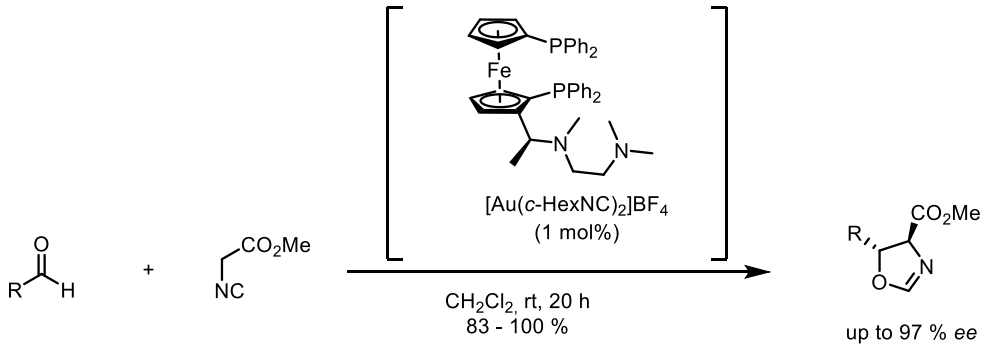
Part I: A Gold(I)-Catalysed Domino Coupling of Alcohols with Allenes Enables the Synthesis of Highly Substituted Indenes

I.1 Gold Catalysis

The element gold can look back on a long history and has found many applications in society, most prominently for jewellery. Considering this long history it is surprising that, compared to other elements like palladium, the use of gold for homogeneous catalysis is a relatively young research area. This phenomenon is attributed to the high redox potential between Au^{I} and Au^{III}, hindering typical oxidative addition / reductive elimination pathways.[1] These pathways, which are responsible for the remarkable cross-coupling reactivity of other metals like palladium,[2] nickel[3] and copper,[4] became standards in homogeneous catalysis. Since this cross-coupling reactivity is not at all characteristic of gold, it is less surprising that considerable time elapsed before other fascinating reactivity patterns could introduce this metal into the field of homogeneous catalysis. Noteworthy, very recent work demonstrated that cross coupling with gold is indeed possible under suitable conditions.[5]

The first report of homogeneous gold catalysis dates back to 1986, when Hayashi and co-workers discovered that a chiral ferrocenylphosphine-gold(I) complex can catalyse the asymmetric aldol reaction of aldehydes with isocyanoacetate (Scheme 1).[6] The next breakthrough was the discovery that gold can effectively catalyse the addition of nucleophiles to alkynes by activation of the triple bond.[7] This mode of π-activation was then further extended towards other types of unsaturations, such as allenes and alkenes. And indeed, the

electrophilic activation of C–C unsaturated systems to facilitate the addition of a nucleophile is the predominant role of gold in homogeneous catalysis.



Scheme 1: Hayashi's gold-catalysed asymmetric aldol reaction.[6]

These initial results led to new discoveries, such as the activation of unsaturated alcohols,[8] carbenoid-,[9] as well as the previously mentioned cross-coupling reactivity. The current extensive use of gold is mostly attributed to the tolerance to water and oxygen, the high functional group compatibility and the unique regioselectivity, which is often complementary to other methods. This authentic "gold rush" in catalysis can be graphically illustrated by the number of publications involving the term "gold catalysis" since its initial development in the 1980s (Figure 1).

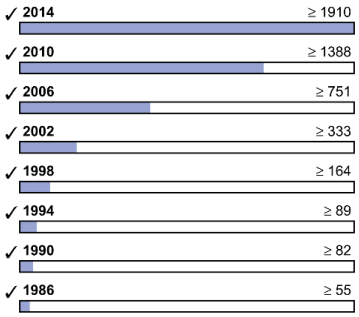
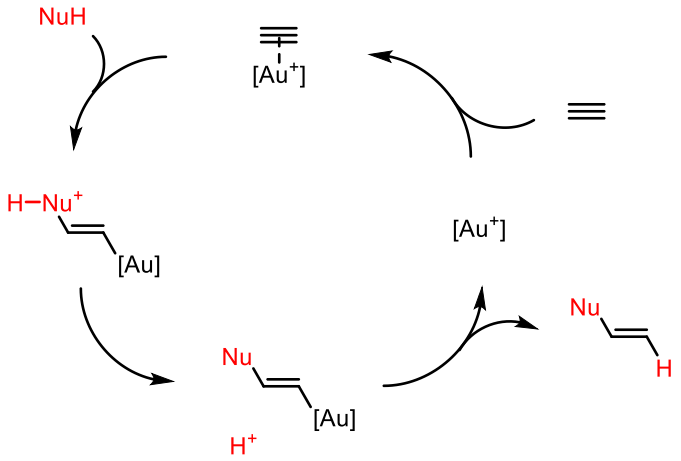


Figure 1: Number of publications involving the term "gold catalysis".[10]

I.1.1 General reactivity:

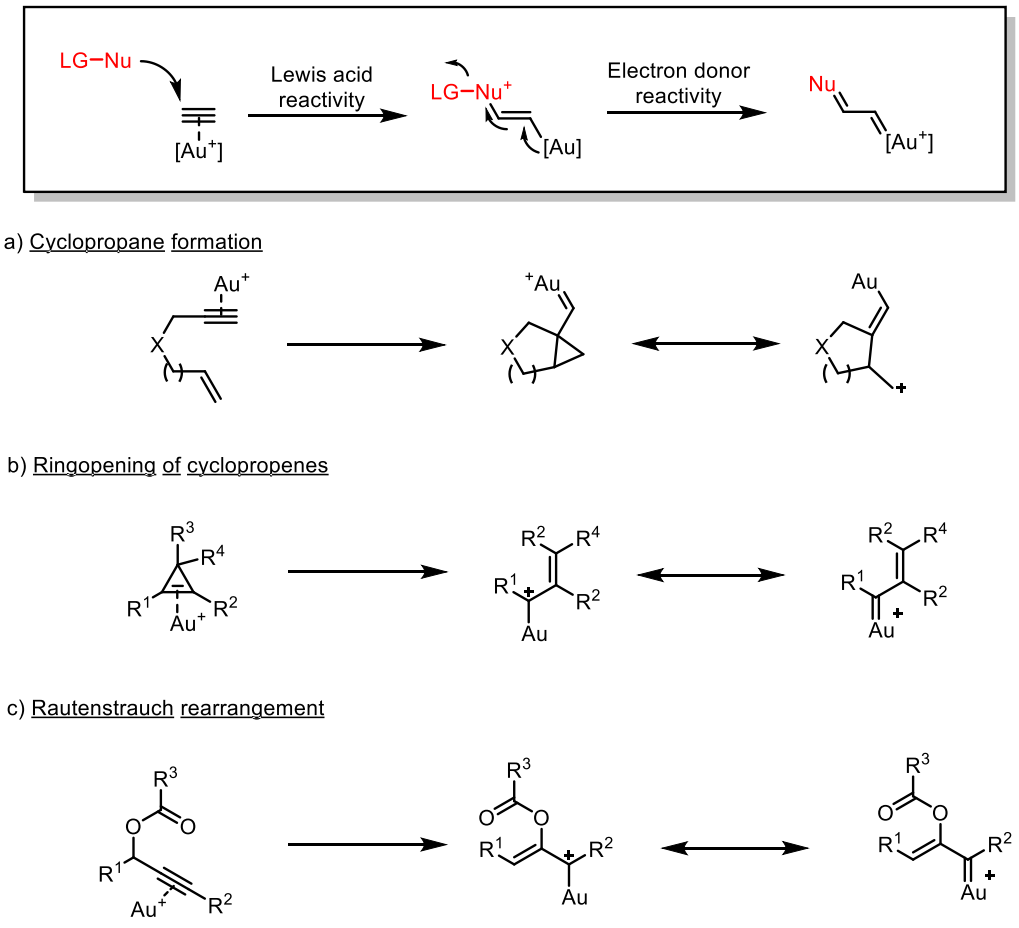
From the various possible oxidation states of gold, ranging from -1 to +5, the most important for catalysis are 0, +1 and +3.[1] Although the activation of aldehydes and ketones by Au(III) is known,[11] the classical reactivity of gold catalysed reactions is based on the activation of π-systems by the electrophilic gold complex and subsequent attack of a nucleophile (Scheme 2). This is usually either a carbon-, oxygen-, nitrogen-, or sulfur-nucleophile.[12] After the nucleophilic attack, the resulting organogold species can undergo various reaction pathways. For the vast majority of reactions, the nucleophilic attack is followed by a proton loss / protodeauration event which forms the product and regenerates the electrophilic gold catalyst.



Scheme 2: General catalytic cycle of gold-catalysed alkyne activation.

The high π-acidity of gold catalysts, which is superior to the other elements of group 11 (Ag and Cu) can be explained by relativistic effects.[13] These effects lead to the contraction of the 6s orbital, which has a shielding effect on the nucleus, resulting in a weaker attraction of the 5d electrons. Due to this, the 5d orbitals of the gold are expanded and the electrons are more delocalised. This highly delocalised electron cloud is the reason for the “soft”-character of gold, allowing it to efficiently interact with π-systems and also stabilise cationic intermediates by electron donation.

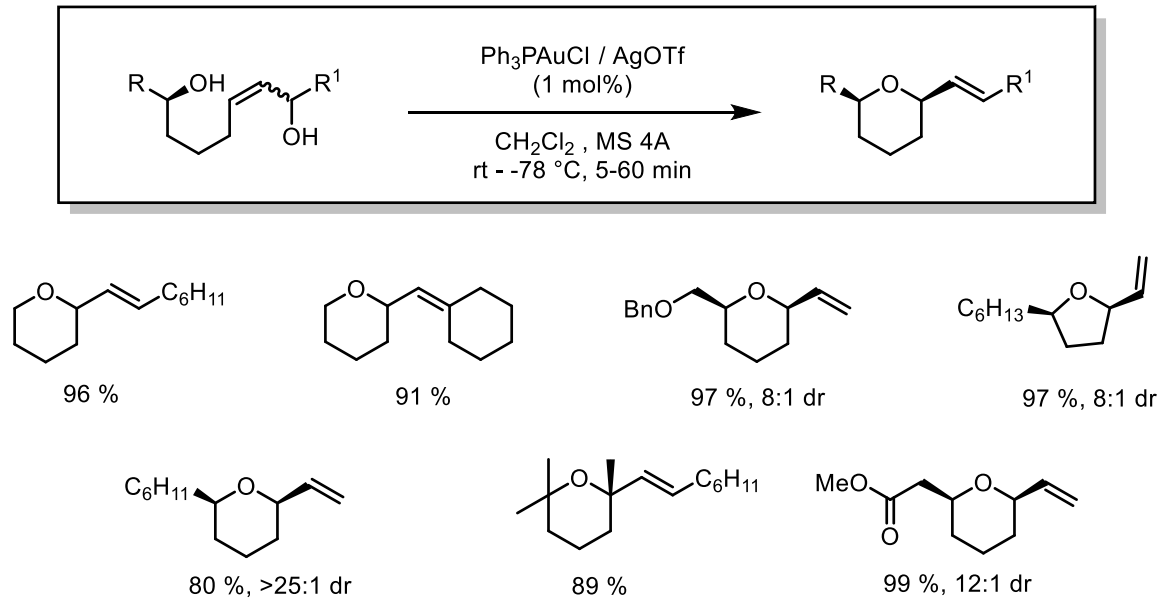
This electron donating effect allows the gold catalysts to stabilise carbocationic or even carbenoid species, depending on the nature of catalyst (oxidation state, ligands) and substrate.[14] The dual Lewis acid / electron donor reactivity has enabled a series of fascinating new transformations. The general reactivity of these reaction pathways is based on the initial activation of a C–C unsaturated system followed by the attack of a nucleophile bearing a leaving group. The metal can then donate electrons into the π-system, triggering the elimination of the leaving group, to form the carbenoid intermediate which can further react (Scheme 3). This strategy has been successfully applied for a series of transformations, including cyclopropane formation (Scheme 3a), opening of cyclopropenes (Scheme 3b) and the well-known Rautenstrauch rearrangement (Scheme 3c).[9]



Scheme 3: Carbenoid-reactivity of gold.

I.1.2 Gold Catalysis for the Activation of Unsaturated Alcohols

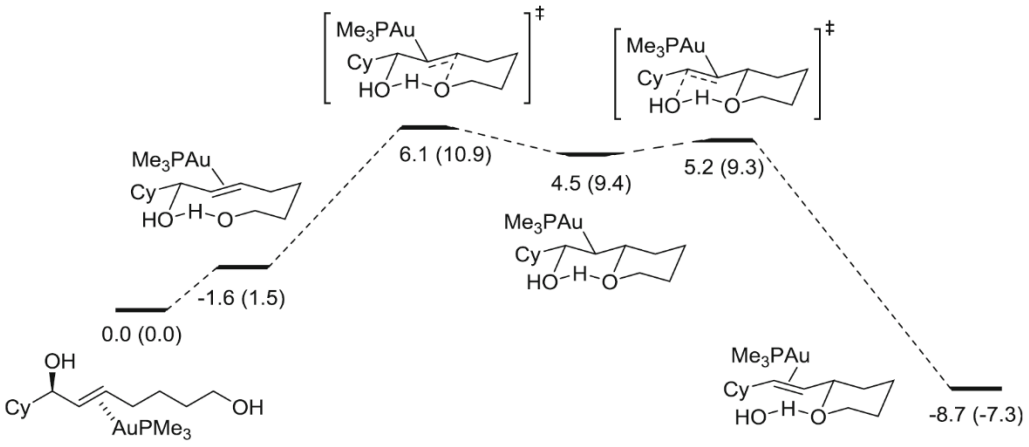
The activation of π-systems by a suitable gold catalyst followed by the attack of a nucleophile is well known. In this context it seems surprising that gold can activate something we might also consider as a nucleophile towards the attack of a nucleophile.[8, 15] This very interesting reactivity was first discovered by the Aponick group, enabling the gold catalysed formal S_N2' reaction of allylic alcohols (Scheme 4).[16] Although this reactivity is also accessible with other metal catalysts as well as Lewis- or Brønsted acids,[17] gold has several significant advantages for these transformations, including low catalyst loading, mild conditions and insensitivity of the catalyst towards water and air.



Scheme 4: Gold-catalysed activation of allylic alcohols.[16]

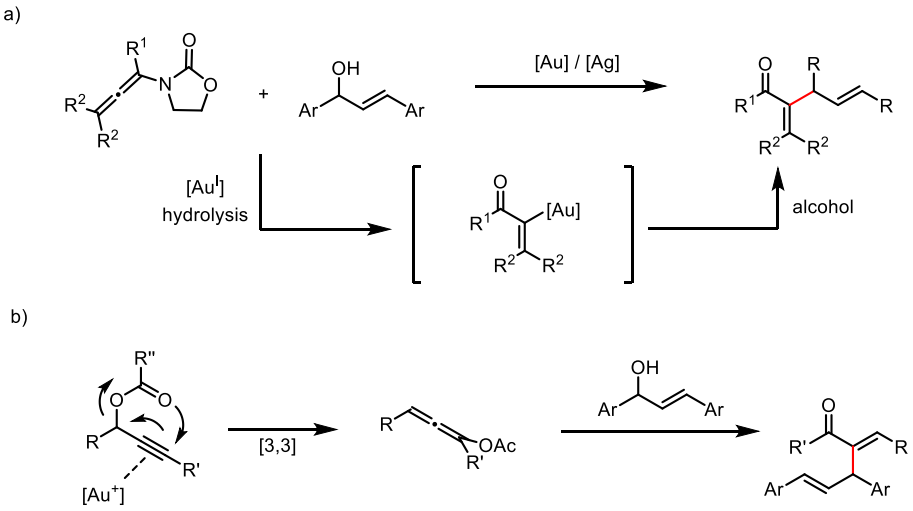
For a system similar to that described in Scheme 4, a stepwise *anti*-addition, *anti*-elimination mechanism was proposed supported by experimental and computational evidence.[18] *Syn*-addition, *syn*-elimination as well as concerted S_N2' mechanisms were also considered, but found to be significantly higher in energy. In the proposed mechanism the catalyst first activates the double bond followed by *anti*-addition of the alcohol moiety (Scheme 5). Upon *anti*-elimination of water and catalyst, the product is formed. The computational studies also

reveal that hydrogen bonding plays an important role in the stereochemical outcome by templating the intermediates.



Scheme 5: Calculated mechanism for the formal S_N2' reaction of allylic alcohols.[18]

Recently, Bandini and co-workers found that allenamides can also react with aryl substituted allylic alcohols to form α-allylated enals and enols (Scheme 6a).[19] This methodology was then further extended by the same group exploiting the well-known [3,3]-sigmatropic rearrangement of propargylic carboxylates, leading to substituted allenoates (Scheme 6b).[20] These intermediates can undergo electrophilic trapping with the allylic alcohol to form dienones. Notably both transformations need aryl substituted allylic alcohols to proceed. Interestingly the use of non-symmetric allylic alcohols (Ar ≠ Ar) resulted in a mixture of regioisomers, indicating a carbocationic intermediate. Apparently, reactions of aryl-substituted allylic alcohols proceed by S_N1-type mechanisms, whereas alcohols which do not give highly stabilized carbocations upon activation, undergo formal S_N2- or S_N2' mechanisms. At this point it is not clear what activates the allylic alcohol substrates. Both activation by silver salts[19] and Brønsted acid activation[20] have been considered by the Bandini group. However, alcohol activation directly by the gold catalyst, which seems to be the mode of action for the gold-catalysed synthesis of unsymmetrical ethers from benzylic alcohols,[21] could also be a possibility and will be discussed later.

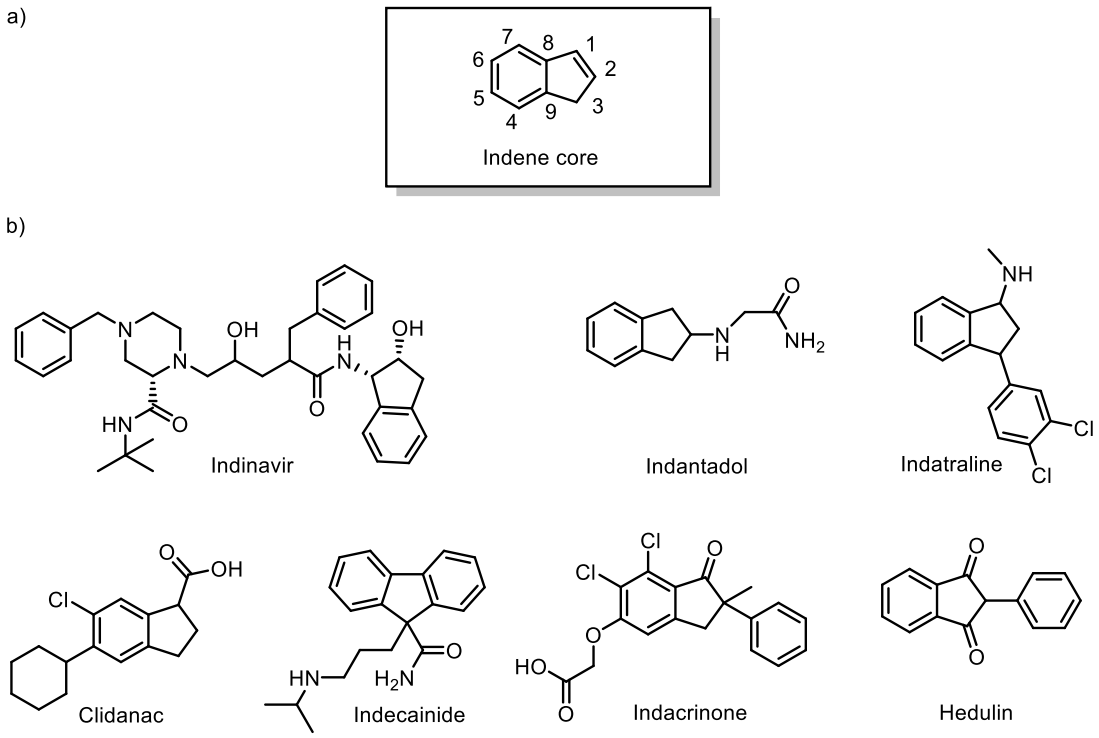


Scheme 6: a) Working hypothesis of the formal α-allylation of enones and enals.[19] b) Working hypothesis of the propargylic rearrangement / allylation cascade.[20]

I.2 Indenes

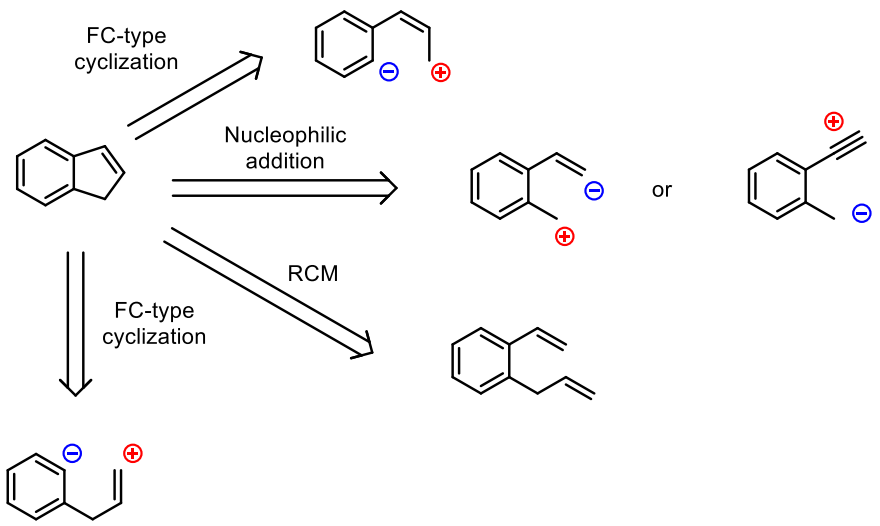
Indenes (benzocyclopentadienes) are important bicyclic hydrocarbon derivatives (Scheme 7a). They form the core of many biologically active substances. In particular indanes, their reduced counterparts, display biological activity on a wide variety of targets.[22] This renders them privileged structures in medicinal chemistry. Many of these compounds have already found application as drugs in medicine.[23] Examples of marketed drugs containing the indane core are indinavir, an HIV-1 protease inhibitor,[24] the MAO-inhibitor indantadol,[25] indatraline, an amine uptake inhibitor,[26] the anti-inflammatory clidanac,[27] antiarrhythmic agent indecainide,[28] diuretic indacrinone,[29] and the anticoagulant hedulin (Scheme 7b). Furthermore, several indenes are known to posses herbicidal, fungicidal and antimicrobial activities.[30]

Indenes are also important ligands for transition metal catalysis owing to the well-known ring-slippage properties.[31] They are also used as building blocks for polymers in materials science. A very recent and important discovery in this field is the use of indene-containing fullerenes and azuliporphyrins for solar cells.[32]



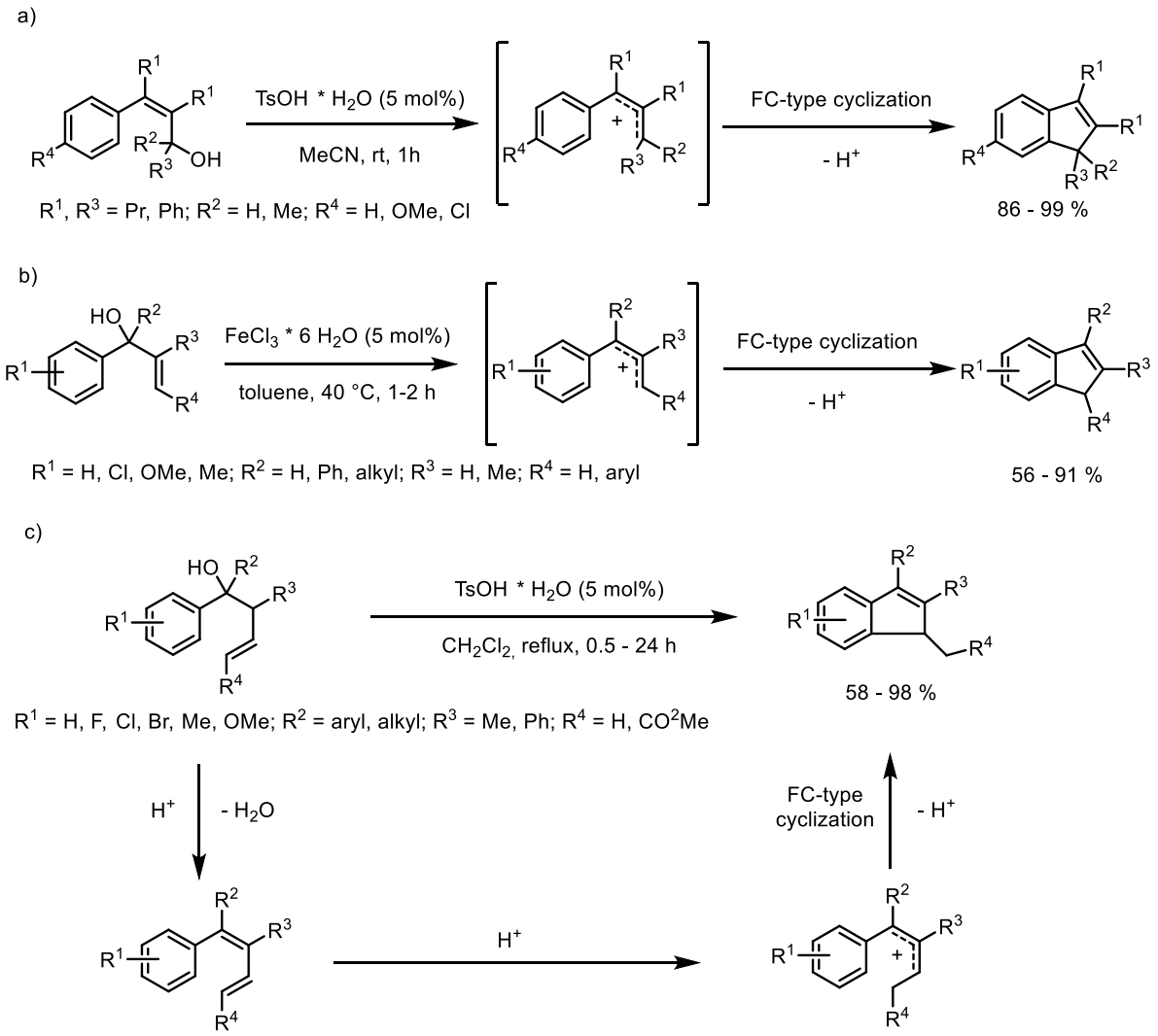
Scheme 7: a) Indene core structure. b) Examples of marketed drugs containing the indane core.

Among the many methods described for the synthesis of indenes, most are based on intramolecular Friedel-Crafts (FC) type cyclisations of an electron-rich aromatic system with a suitable electrophilic functional group (Scheme 8).[22] Apart from FC-type reactions, the addition of several nucleophiles to electrophiles forming the 5-membered ring is known. Furthermore, many other methods, involving ring contraction or –expansion, functionalisation of a cyclic precursor and metal-catalysed processes are described in the literature.[33] In the next chapter, representative examples for some classical approaches will be presented.[34]



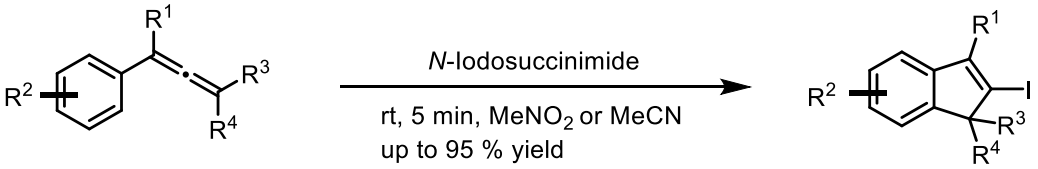
Scheme 8: Selected disconnections for the synthesis of indenes.

One of the most exploited approaches is based on the generation of an allylic carbocation, followed by a FC-type cyclisation (Scheme 9). This allylic carbocation is generated from a suitable precursor, which can be an allylic alcohol, upon treatment with a Lewis- or Brønsted acid.[35] Also the use of a homoallylic alcohol has been described.[36] All of these substrates form, by activation of the alcohol, the same intermediate allylic carbocation, which undergoes nucleophilic attack by the aromatic ring to form the 5-membered ring. This general methodology can even be extended to propargylic alcohols which can, in a similar sequence, also undergo carbocation formation, FC–Cyclisation.[37]



Scheme 9: a) FC–Cyclisation of allylic alcohols using Brønsted acid catalysis.[35a] b) FC–Cyclisation using Lewis-acid catalysis.[35b] C) FC–Cyclisation using Brønsted acid activation of a homoallylic alcohol.[36]

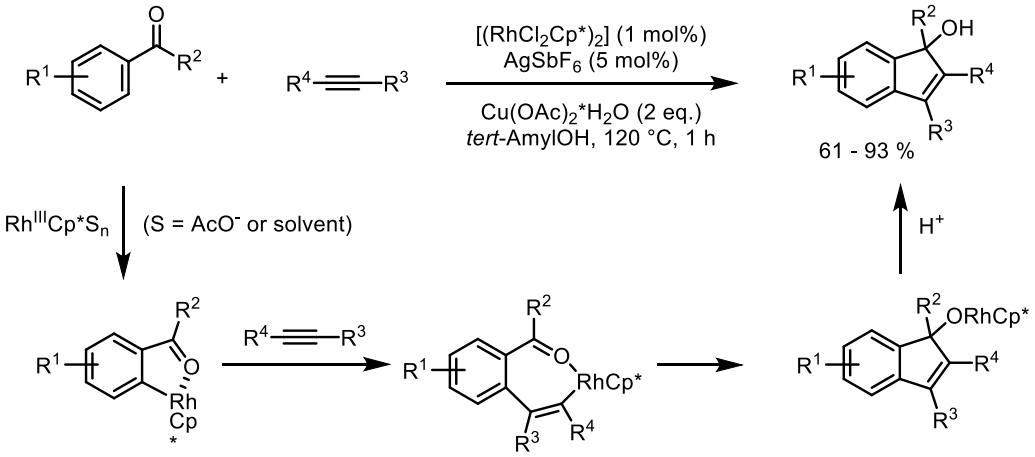
However, carbocation formation can also be achieved from other substrates than alcohols. Dienes and allenes can also, upon electrophilic activation, generate carbocations suitable for cyclisation.[38] In a recent example,[38d] Toullec and co-workers showed that aryl-substituted allenes can, when treated with NIS, undergo a 5-*endo* iodocarbocyclisation to form the corresponding 2-iodoindenes in moderate to good yields and short reaction time (Scheme 10). The advantage of this methodology is to have a functional group introduced in the product, allowing further modifications on the 2-position of the indene. Nevertheless, this and the previously described approaches suffer from competing side reactions with other nucleophilic functional groups leading to a narrow substrate scope.



R^1 = $C_4H_8OTBDMS$, $C_3H_6OTBDMS$, $C_2H_4OTBDMS$, C_4H_9, *c*-hexyl;
R^2 = H, F, Br;
R^3 = Me, H;
R^4 = H, Me, $C3H_7$, *c*-propyl, Ph

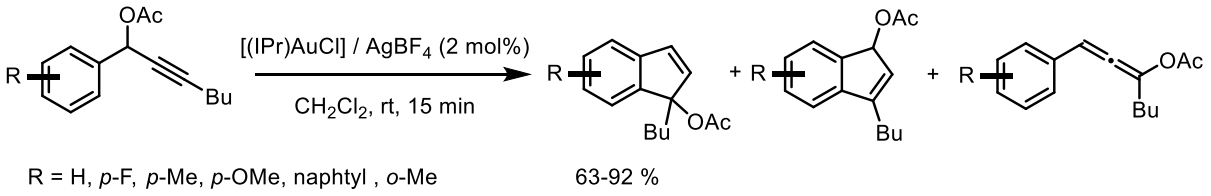
Scheme 10: NIS-induced iodocarbocyclisation by Toullec.[38d]

Another approach for the synthesis of indenes is the use of transition metal catalysis. Very interesting examples for this strategy are based on rhodium-catalysed C–H activation.[39] In a pioneering work in that field,[39a] Cheng and co-workers achieved the synthesis of indenols in an intermolecular fashion starting from readily available substrates (Scheme 11). Mechanistically, this reaction proceeds *via* coordination of the substrate to the active catalyst leading to a rhodacycle. Regioselective insertion of the alkyne, followed by intramolecular insertion of the C=O group into the rhodium-carbon bond leads to an intermediate rhodium indenolato complex, which, after protonolysis, gives the product. As the catalytic activity of the system increases with the amount of silver / rhodium ratio, the most plausible role of silver in this transformation is the activation of the rhodium catalyst by removal of the chlorine ligands to generate the active species. During their work, the authors noticed that, although there should not be a redox cycle involved, either substrates or solvent appeared to reduce the active Rh^{III}-catalyst, thus hampering turnover. Therefore, excess of a Cu^{II}-salt as oxidant to regenerate the catalyst is required to achieve good yields.



Scheme 11: Indenol synthesis by Cheng *via* Rh-catalysed C–H-activation.[39a]

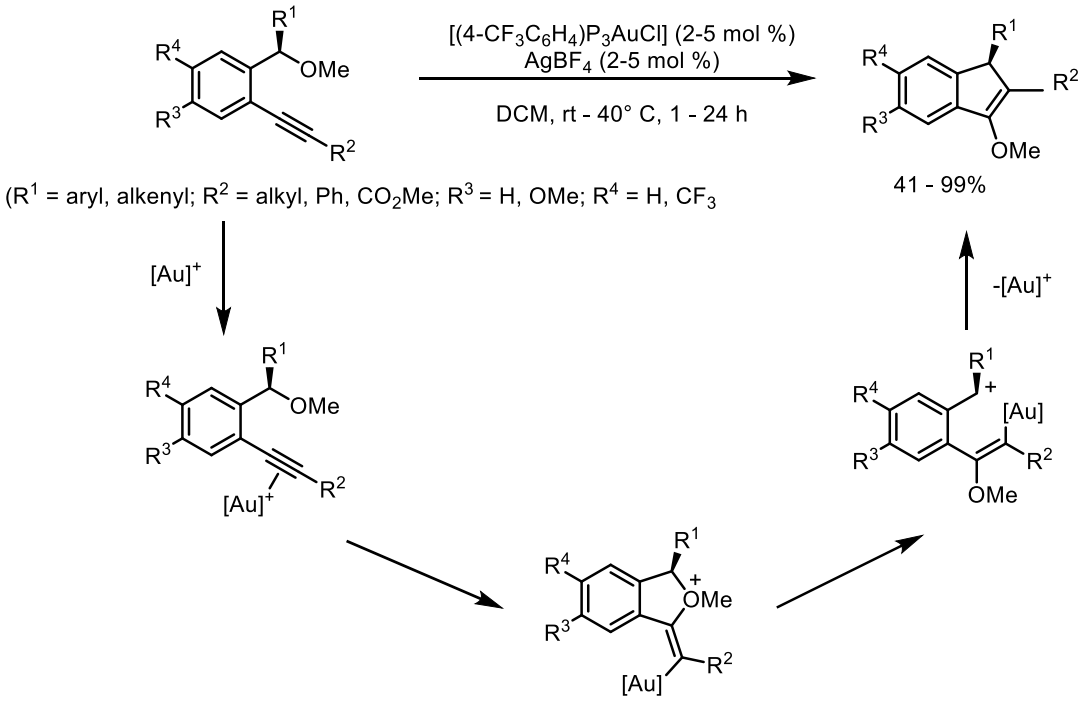
Also gold catalysis has been successfully employed for the synthesis of indenes. To our knowledge, the first synthesis of indenes was reported by the group of Nolan in 2006 using an NHC-gold catalyst (Scheme 12).[40] This work exploits the gold- or silver-catalysed[41] [3,3]-sigmatropic rearrangement of propargylic acetates to form an allenoate (*vide supra*), which can also be isolated as side product of the reaction. This intermediate can then again be activated by the gold-catalyst to form the desired product. As a side reaction, the alkyne moiety of the substrate can also directly undergo a gold-promoted 5-*endo*-*dig* cyclisation / protodeauration sequence leading to side products, in ratios strongly depending on the substrate. This high substrate-dependence can be considered as the main drawback of an otherwise highly elegant and mild transformation.



Scheme 12: First gold-catalysed synthesis of indenes by Nolan.[40]

Another example for gold-catalysed indene synthesis is the synthesis of indenyl ethers as originally described by the Toste group (Scheme 13).[42] In this transformation, the alkyne is activated by the cationic gold catalyst to undergo a 5-exo-dig cyclisation forming a vinyl-gold

intermediate. This intermediate can then rearrange to form a benzylic carbocation. Intramolecular addition of the vinyl-gold species to the carbocation leads to the product. Notably, the last step follows a concerted pathway, similar to the mechanism described for protodeauration and formation of bis(gold) vinyl intermidates from vinyl gold species,[43] allowing the reaction to proceed with good to excellent levels of chirality transfer starting from enantiomerically enriched substrates.



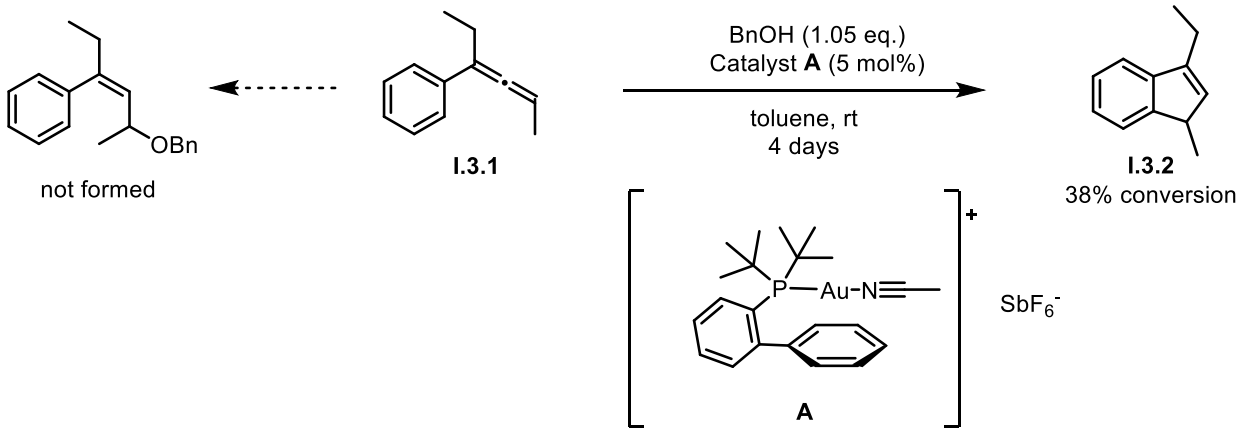
Scheme 13: Gold-catalysed stereospecific synthesis of indenyl ethers as described by Toste.[42]

Due to the aforementioned importance of indenes as core substructures, expanding the toolbox for the synthesis of densely substituted indenes is a topic of interest. In particular gold catalysis is well suited for this endeavour since the conditions are usually mild and offer a high functional group tolerance. In the following chapters we will describe the development of a novel gold-catalysed approach for the synthesis of highly substituted indenes from aryl-substituted allenes.

I.3 Results and Discussion

I.3.1 Gold-Catalysed Synthesis of 1,3-Disubstituted Indenes

During our work on derivatisations of allenes, we investigated the well-known hydroalkoxylation reactions of allenes with alcohols.[44] Based on a previous report by Widenhoefer and co-workers, we envisioned a synthetic route, in which a suitable alcohol reacts with allene **I.3.1** to form the hydroalkoxylation product under gold catalysis (Scheme 14).[45] However, the applied conditions did not lead to the desired hydroalkoxylation-product. Instead, indene **I.3.2** was formed. This serendipitous finding caught our attention since this transformation would be a mild and simple approach for the synthesis of 1,3-disubstituted indenes.

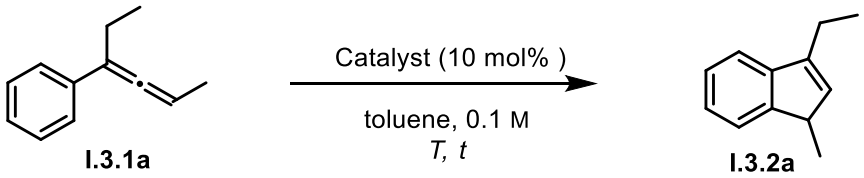


Scheme 14: Carbocyclisation of aryl-substituted allenes to form 1,3-disubstituted indenes.

We therefore started a screening of different reaction conditions. A combination of XPhosAuCl and AgOTf as additive led to a poor conversion of **I.3.1a** (Table 1, entry 1). Raising the temperature to 50 °C resulted in a better conversion of 10 % after 19 hours reaction time (Table 1, entry 2). $AuCl_3$ as catalyst led to a slightly higher conversion (Table 1, entry 3), whereas Ph_3PAuCl (Table 1, entry 4), in the absence of an additive does not induce any reactivity at all. A subsequent screening of different monomeric and a dimeric phosphine (Table 1, entries 5-7), as well as a phosphite gold catalyst (entry 8) in combination with a silver salt to activate the catalyst always led to a full conversion of allene **I.3.1a**, but with a complex

and sluggish reaction profile. Attaching an NHC-ligand to the gold-center resulted in **I.3.2a** in 74 % isolated yield (Table 1, entry 9). However, best results were obtained with a pre-activated catalyst bearing a JohnPhos ligand giving the product in 90 % isolated yield after 19 hours reaction time (Table 1, entry 10). Changing the solvent to dichloromethane allowed the reaction to proceed already at room temperature, but with a significantly less clean reaction profile (Table 1, entry 11). Therefore, the conditions of entry 10 were selected as standard conditions for further reactions. It should be noted that the addition of a Brønsted acid led to decomposition (Table 1, entry 12).

Table 1: Optimisation of the reaction conditions for the carbocyclisation.

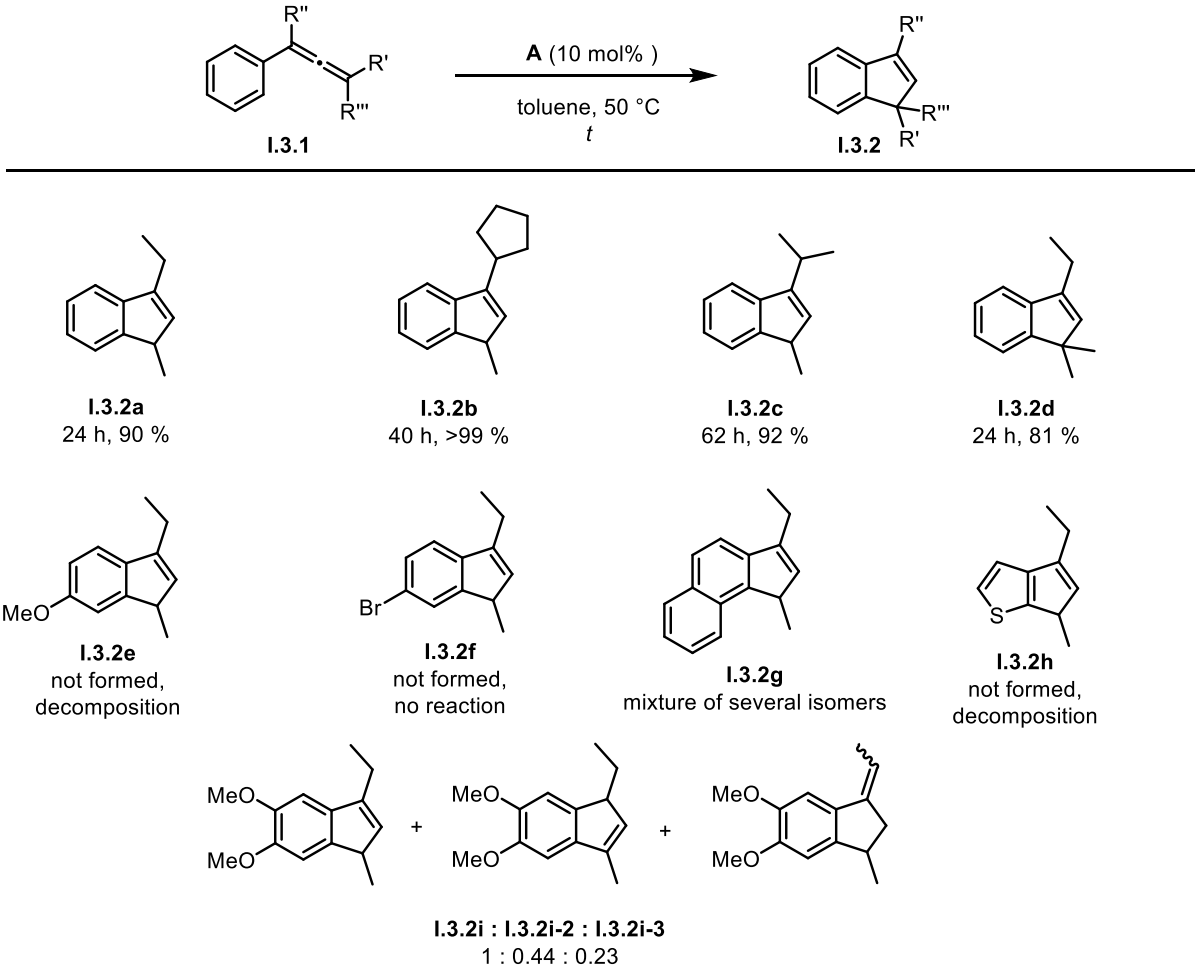


I.3.1a **I.3.2a**

Entry	Catalyst	Additive	Temperature	Time [h]	Conversion of Allene [%][b]
1	XPhosAuCl	AgOTf	rt	38	2 %
2	XPhosAuCl	AgOTf	50° C	19	10 %
3	$AuCl_3$	-	50° C	24	18 %
4	Ph_3PAuCl	-	50° C	24	n.r.
5	Ph_3PAuCl	AgOTf	50° C	19	100[c]
6	Cy_3PAuCl	AgOTf	50° C	19	100[c]
7	$(dppm)Au_2Cl_2$	AgOTf	50° C	19	100[c]
8	(1,3-di-tert-butyl-phenyl)$_3$-phosphite-AuCl	AgOTf	50° C	19	100[c]
9	[IPrAuCl]	AgOTf	50° C	19	100 (74[d])
10	$[JohnPhosAu(MeCN)]SbF_6$	-	50° C	19	100 / (90[d])
11[e]	$[JohnPhosAu(MeCN)]SbF_6$	-	rt	14	77 / (31[d])
12	TfOH (1 equiv.)	-	rt	5	Decomposition

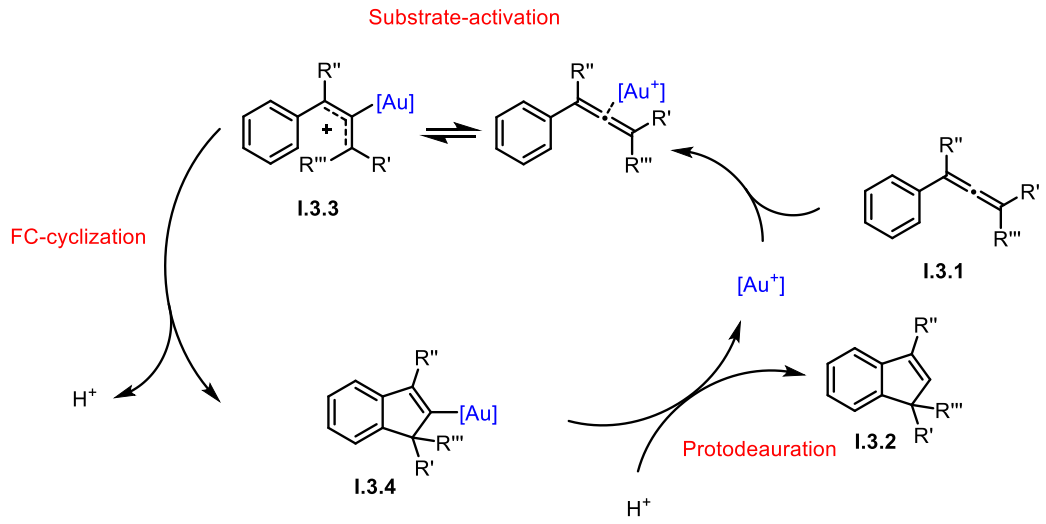
[a] Reactions were carried out under anhydrous conditions. [b] Determined by ^{1}H-NMR spectroscopic analysis of the crude reaction mixture [c] Complex mixture [d] Isolated yield [%]. [e] Reaction performed in DCM.

With the optimised conditions in hand, we went on to investigate the scope of this transformation (Scheme 15). Subjecting model-allene **I.3.1a** to the optimized conditions resulted in a very clean reaction and gave indene **I.3.2a** in 90 % isolated yield. Changing the nature of the substituent at the α-carbon of the allene (R'' on the Scheme) led to longer reaction times, but afforded products **I.3.2b** and **I.3.2c** in excellent yields. Disubstitution on the terminal position of the allene showed almost no effect on the reaction time and indene **I.3.2d** was obtained in 81 % yield. However, the reaction seemed to be sensitive towards a change of substituents on the aromatic ring either leading to decomposition, no reaction or a mixture of different isomers.



Scheme 15: Gold-catalysed cyclisation of allenes to indenes.

Mechanistically, this reaction probably proceeds *via* an activation / cyclisation sequence (Scheme 16). The catalytic cycle starts with activation of the substrate by the electrophilic gold catalyst. Cationic intermediate **I.3.3** can then undergo a FC-type cyclisation with rearomatisation *via* the loss of a proton to form vinyl gold complex **I.3.4**. Protodeauration then leads to the product and regenerates the catalyst.

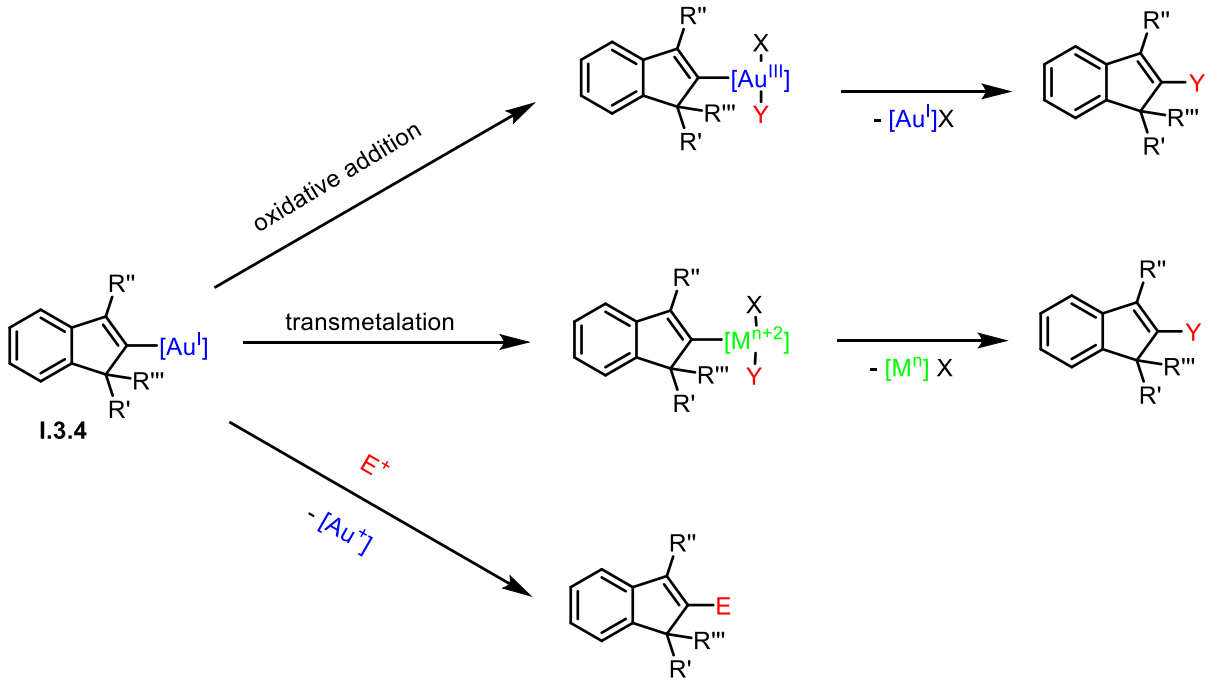


Scheme 16: Proposed mechanism for the indene formation.

I.3.2 Attempts towards the C–C coupling of a vinyl-gold intermediate

To further extend the gold-catalysed allene-activation indene-formation methodology, we became interested in vinyl-gold species **I.3.4** (Scheme 17). As an appealing postulate, the identification of suitable conditions to suppress protodeauration might allow this intermediate in the catalytic cycle to be intercepted enabling further modification on the indene product. This would enable the synthesis of highly substituted indenes in one step from readily available allenes. In the following section we will describe different approaches to achieve this transformation, culminating in the development of a novel cascade reaction for the mild and efficient synthesis of highly substituted indenes.

For the interception of vinyl-gold intermediate **I.3.4**, three different approaches were tested. One possibility was the oxidation of Au^{I} to Au^{III} followed by reductive elimination to form the desired product. Transmetalation of **I.3.4** to palladium to unlock more classical palladium-catalysed cross-coupling reactivity also seemed appealing to us. Finally, vinyl-gold intermediate **I.3.4** could also react with a suitable electrophile to furnish functionalised products.



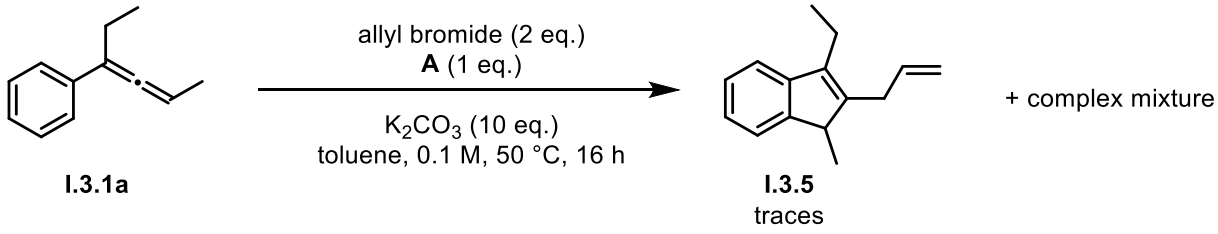
Scheme 17: Different envisaged approaches for the further modification of **I.3.4**.

I.3.2.1 Oxidative-Addition Approach

The first approach investigated for the C–C bond domino coupling was the oxidative addition manifold. In this strategy, **I.3.4** should be oxidized either directly by oxidative addition of an alkyl-, alkenyl- or aryl-halide or by an external oxidant. By oxidising Au^{I} to Au^{III}, the metal center can increase its coordination sphere from two to four. Reductive elimination should then give the product.

It already has been shown by the Toste group that allyl bromide can, under suitable conditions, undergo oxidative addition to gold(I) intermediates.[46] Inspired by this work, we attempted to

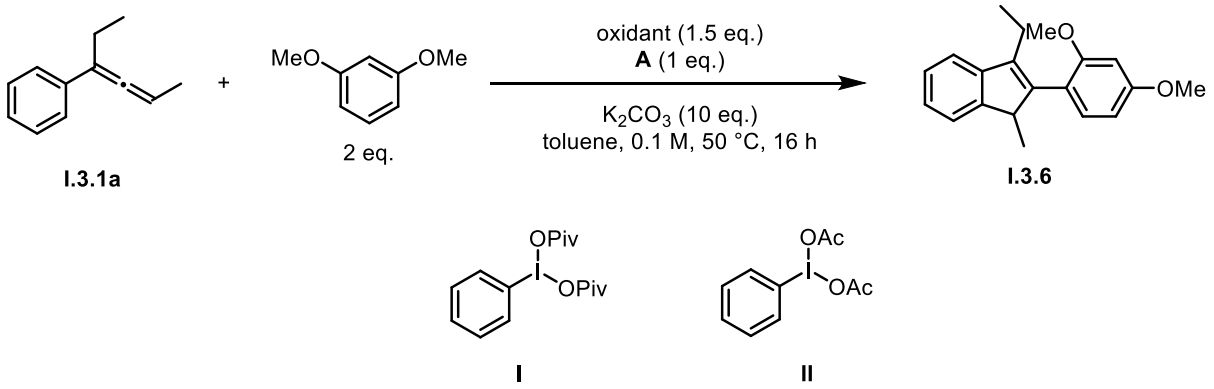
use allyl bromide, hoping to form allylated indene **I.3.5**. However, although traces of product were identified via GC-MS analysis, most of the reaction mixture decomposed or underwent homo-coupling.



Scheme 18: Attempts at oxidative addition of allyl bromide.

We then investigated the use of an external oxidant. First attempts focused on a C–H activation strategy (Table 2).[47] For this system, we started with 1,3-dimethoxybenzene as substrate for C–H activation and screened several oxidants. To avoid turnover problems, we used a full equivalent of gold-catalyst for the initial screenings. An excess of potassium carbonate was used to prevent deleterious protodeauration. The first attempt using selectfluor as oxidant resulted in a slow conversion of allene, indene **I.3.2a** as by-product and only small traces of desired product, as confirmed by HRMS of the crude reaction mixture (Table 2, entry 1). Using hypervalent iodine reagents led to decomposition or no reaction (Table 2, entries 2 and 3).

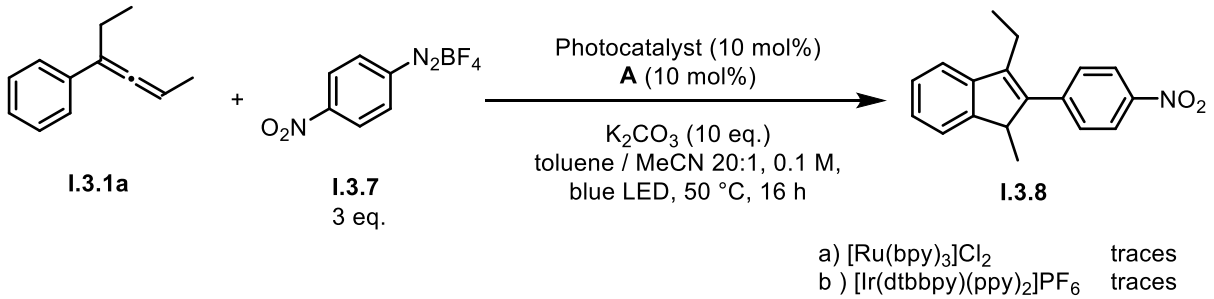
Table 2: Attempted gold-catalysed C–H activation



Entry	Oxidant	**I.3.1a : I.3.2 a : I.3.6**[a]
1	Selectfluor	1 : 0.3 : traces[b]
2	**I**	Decomposition
3	**II**	1 : 0 : 0

a) Determined by ^{1}H-NMR analysis of the crude reaction mixture. b) Determined by HRMS-analysis

We then investigated photocatalytic oxidation using aryl diazonium salts as trapping reagents (Scheme 19). To test this approach, we started with diazonium salt **I.3.7** and two transition metal photocatalysts which, under blue light irradiation, could furnish product **I.3.8**. However, the applied conditions just led to trace amounts of product with the rest being decomposition and homo-coupling products.

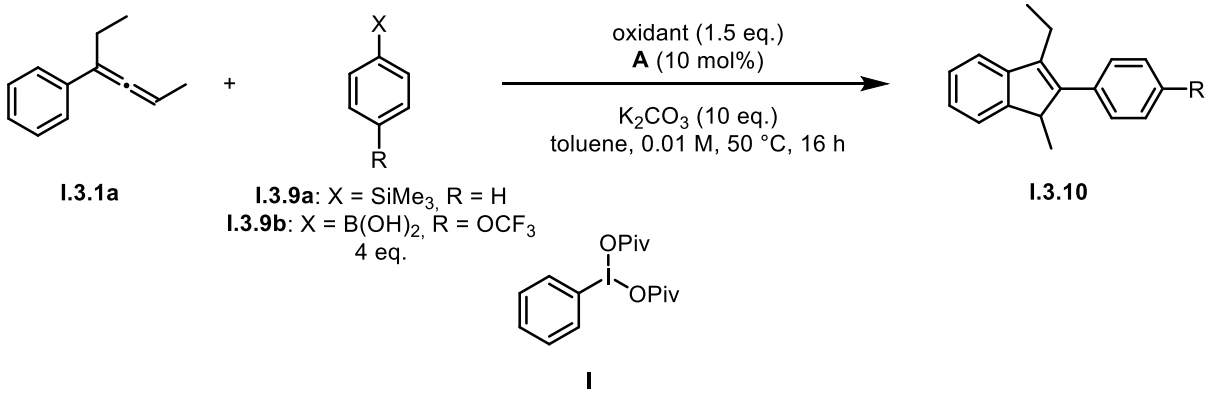


Scheme 19: Photocatalytic oxidation of the gold-catalyst.

Furthermore, we tested various reagents which might add to the Au^{III}-intermediate to, upon reductive elimination, afford the desired product. To prove this approach, we used two different metalloid reagents based on boron (**I.3.9b**) or silicon (**I.3.9a**) in combination with

either a fluorine- or iodine-based oxidant. To reduce the amount of indene-homocoupling we worked under more dilute conditions. Since the observed homocoupling products most likely result from a gold-to-gold transmetalation, the reactions were performed with lower catalyst loading and higher excess of **I.3.9**. However, all the conditions either led to no reaction (Table 3, entries 1 and 2) or slow conversion into the 1,3-substituted indene **I.3.2a**, indicating that a slowed protodeauration was brought about by the added base.

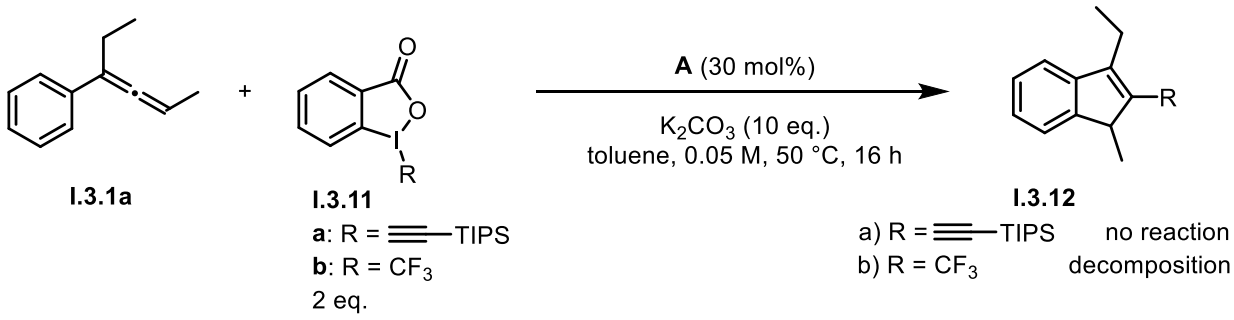
Table 3: C–C coupling attempts using transmetalating reagents.



Entry	Reagent	Oxidant	**I.3.1a : I.3.2a : I.3.10**[a]
1	**I.3.9a**	Selectfluor	1 : 0 : 0
2	**I.3.9a**	**I**	1 : 0 : 0
3	**I.3.9b**	Selectfluor	1 : 0.3 : 0
4	**I.3.9b**	**I**	1 : 2.7 : 0

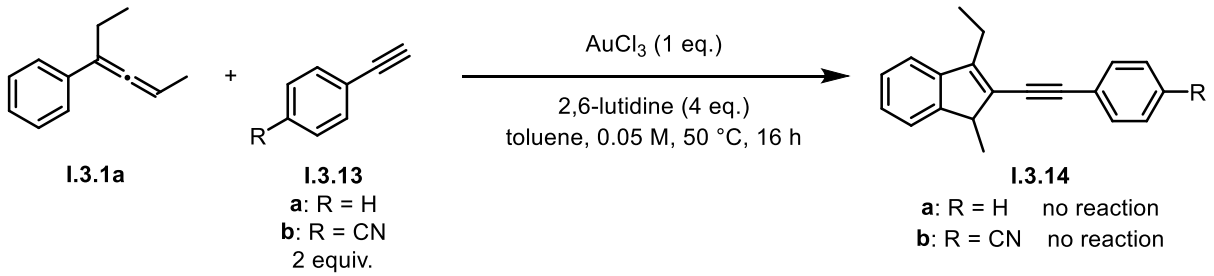
a) Determined by 1H-NMR analysis of the crude reaction mixture.

To avoid possible transmetalation problems, we tested two hypervalent iodine reagents (**I.3.11a** and **I.3.11b**), which can directly transfer an organic ligand to the gold during oxidative addition (Scheme 20). However, **I.3.11a** did not induce any reaction, whereas Togni's reagent **I.3.11b** led to decomposition of the reaction mixture.



Scheme 20: C–C coupling attempts using substituted hypervalent iodine reagents.

Since the initial screening of reaction conditions for the allene-cyclisation revealed that Au^{III} can also catalyse this reaction (Table 1, entry 3), we directly tested a Au^{III}-catalyst to achieve further C–C coupling (Scheme 21). As model system, we chose a gold-catalysed Sonogashira-type coupling, in which the gold activates both allene and alkyne to, upon deprotonation by the base and reductive elimination, give the product. For this transformation, ethynylbenzene (**I.3.13a**) and its derivative **I.3.13b** were chosen as substrates. 2,6-lutidine was chosen as a base, because of its ability to also coordinate to the gold-center and stabilise possible reaction intermediates. However, both conditions did not lead to the product **I.3.14**.



Scheme 21: Attempts at a gold-catalysed Sonogashira coupling.

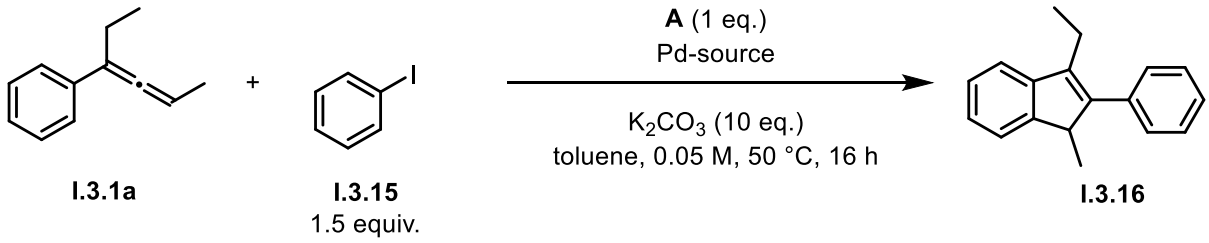
I.3.2.2 Transmetalation approach

It has already been shown by the pioneering groups of Blum and Hashmi, that transmetalation from gold to other metals like palladium is feasible.[5a, 48] This result might seem surprising, since transmetalation from the more noble metal to the less noble metal seems thermodynamically unfavoured. An extensive experimental and computational study on the

thermodynamics of this kind of reactions revealed that the strength of the gold-halide bond, which is formed upon transmetalation, is the thermodynamic driving force for this transformation.[49]

Inspired by these results, we were eager to access classical cross-coupling reactivity in our system. To probe this hypothesis, we performed several standard experiments using iodobenzene as reagent and different palladium sources (Table 4). Since with this experimental setup, turnover of the gold catalyst is not possible, a stoichiometric amount of gold was used. Using $(Ph_3P)_2PdCl_2$ as catalyst resulted in a slow conversion without formation of the desired product (Table 4, entry 1). $Pd(Ph_3P)_4$ led to traces of product (Table 4, entry 2), whereas the use of $Pd_2(dba)_3$ resulted in decomposition of the reaction mixture (Table 4, entry 3).

Table 4: Gold to palladium transmetalation experiments.



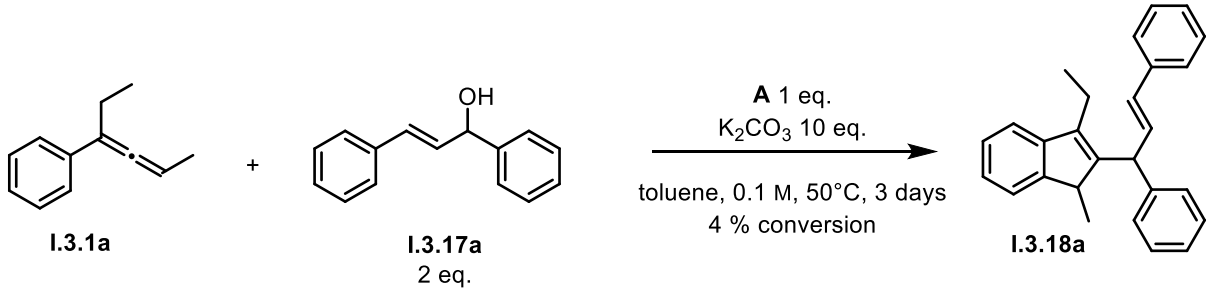
Entry	Pd-source	**I.3.1a : I.3.2a : I.3.16**[a]
1	$(Ph_3P)_2PdCl_2$	1 : 0.18 : 0
2	$Pd(PPh_3)_4$	1 : 0.02 : traces[b]
3	$Pd_2(dba)_3$	decomposition

a) Confirmed by 1H-NMR analysis of the crude reaction mixture. b) Confirmed by HRMS analysis.

I.3.2.3 Addition of an Electrophile

The last approach was the addition of an electrophile to vinyl gold species **I.3.4**. Inspired by the results of Bandini and co-workers on the electrophilic trapping with allylic alcohols (cf. Section I.1.2), we envisioned a mechanistic manifold in which **I.3.4** is trapped by a suitable allylic alcohol to form highly substituted indenes in a domino C–C bond formation sequence.

An initial experiment using allylic alcohol **I.3.17a** and potassium carbonate as base to prevent deleterious protodeauration prior to C–C coupling, led to the desired product in a poor, but encouraging 4 % NMR-yield (Scheme 22).

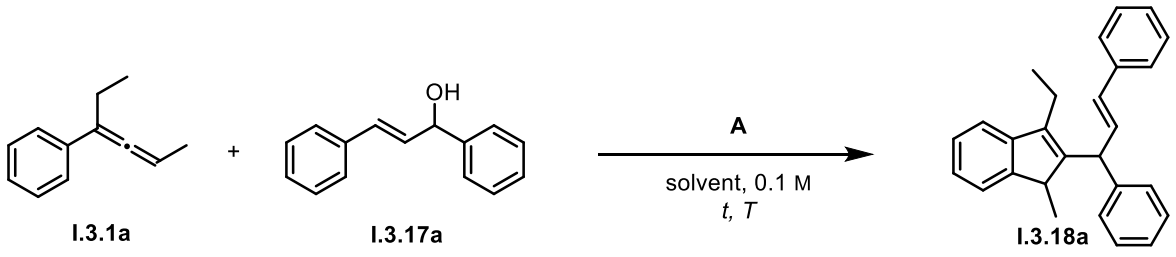


Scheme 22: Initial experiment for the electrophilic trapping.

Encouraged by this result, an optimisation of reaction conditions was performed. A screening of various solvents proved dichloromethane to be the best (Table 5, entries 2-8). To investigate a potential role of silver salts in this transformation, $AgNTf_2$ was added to the reaction mixture. This always led to decomposition, essentially mandating the use of a silver-free system (Table 5, entries 9 and 10). Interestingly, the reaction proceeded much faster and was cleaner in absence of a base, giving the product quantitatively already after five minutes at room temperature (Table 5, entry 11). Lowering the amount of allylic alcohol and catalyst loading showed almost no effect on the reaction outcome (Table 5, entries 12 and 13). Therefore the conditions of entry 13 were adopted as standard conditions for this transformation.

It should be noted that the use of *p*-TsOH alone led to only 9 % NMR-yield of desired product, alongside extensive decomposition (Table 5, entry 14). Pt^{II} and Pt^{IV} can also catalyse this transformation, but with longer reaction times, higher catalyst loadings and a less clean reaction profile (Table 5, entries 15 and 16).

Table 5: Optimisation of reaction conditions for the allylation-cyclisation sequence.

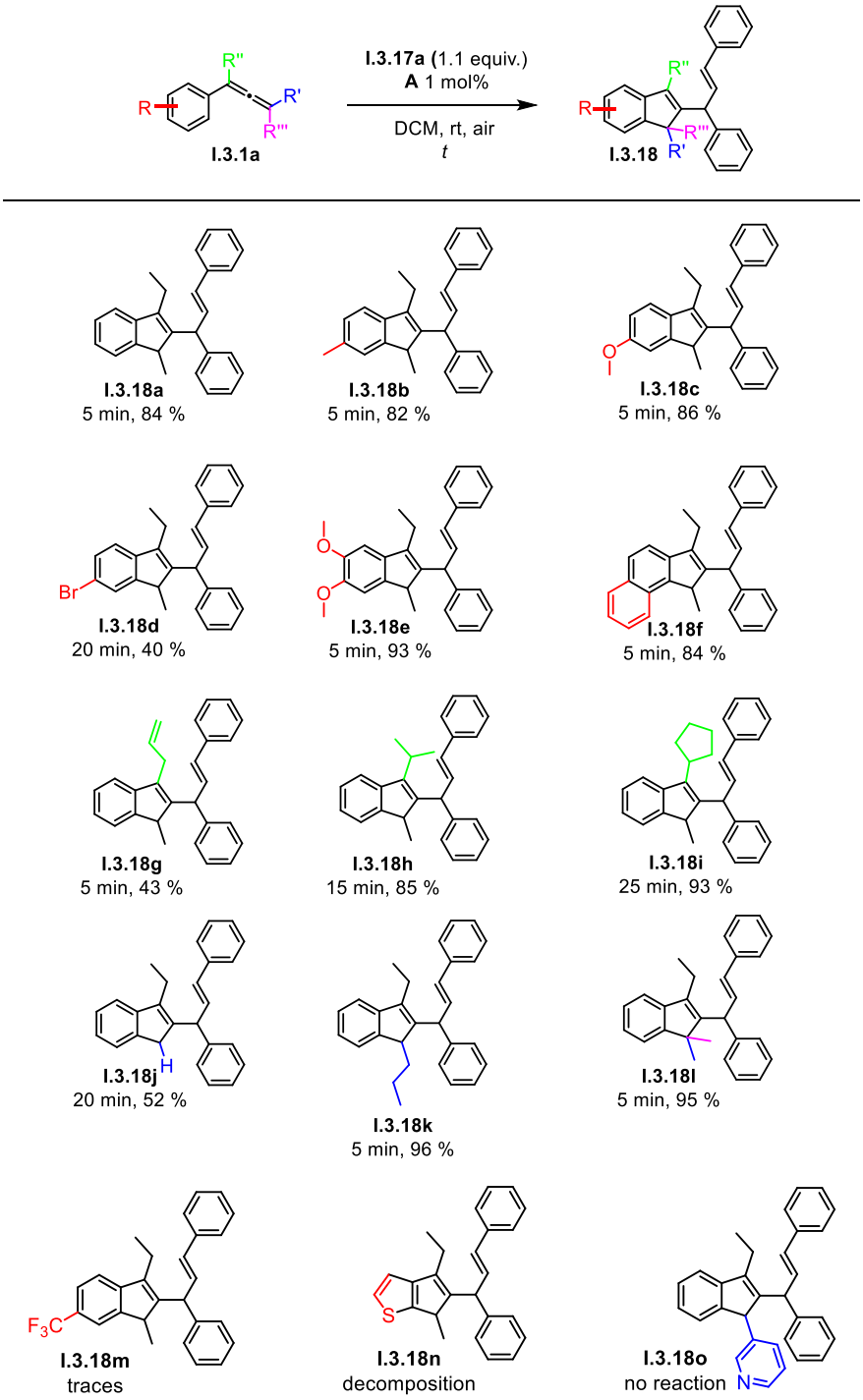


Entry	Catalyst	Solvent	Base	T [°C], t	Conversion [%][b]	NMR-Yield [%][c]
1	**A**	toluene	K_2CO_3	110 / 60 h	9	4
2	**A**	THF	K_2CO_3	50 / 15 h	16	15
3	**A**	1,2-DCE	K_2CO_3	50 / 15 h	66	65
4	**A**	acetonitrile	K_2CO_3	50 / 15 h	100	-[h]
5	**A**	MeNO2	K_2CO_3	50 / 15 h	100	-
6	**A**	1,2-DCE	K_2CO_3	84 / 15 h	54	51
7	**A**	$CHCl_3$	K_2CO_3	61 / 15 h	71	58
8	**A**	DCM	K_2CO_3	40 / 15 h	100	65
9	**A**/$AgNTf_2$	toluene	K_2CO_3	50 / 60 h	100	-
10[d]	$AgNTf_2$	DCM	K_2CO_3	40 / 16 h	100	-
11[e]	**A**	DCM	-	23 / 5 min	100	>99
12[e,f]	**A**	DCM	-	23 / 5 min	100	99
13[e,g]	**A**	DCM	-	23 / 5 min	100	95 (84[i])
14	*p*-TsOH	DCM	-	23 / 10 min	100	9
15	$PtCl_2$	DCM	-	23 / 13 h	100	81
16	$PtCl_4$	DCM	-	23 / 30 min	100	85

[a] Reactions were carried out under anhydrous conditions (**1a**/**2**/catalyst 1 : 2 : 0.01). [b] Determined by ^{1}H-NMR spectroscopic analysis of the crude reaction mixture [c] Determined by ^{1}H-NMR spectroscopic analysis of the crude reaction mixture using 1,3,5-trimethylbenzene as internal standard. [d] Performed in absence of a gold catalyst. [e] Reaction was carried out under ambient conditions. [f] Reaction was carried out using 1.1 equivalents of alcohol [g] Reaction was carried out using 1.1 equivalents of alcohol and 1 mol% catalyst . [h] Decomposition. [i] Isolated yield after purification.

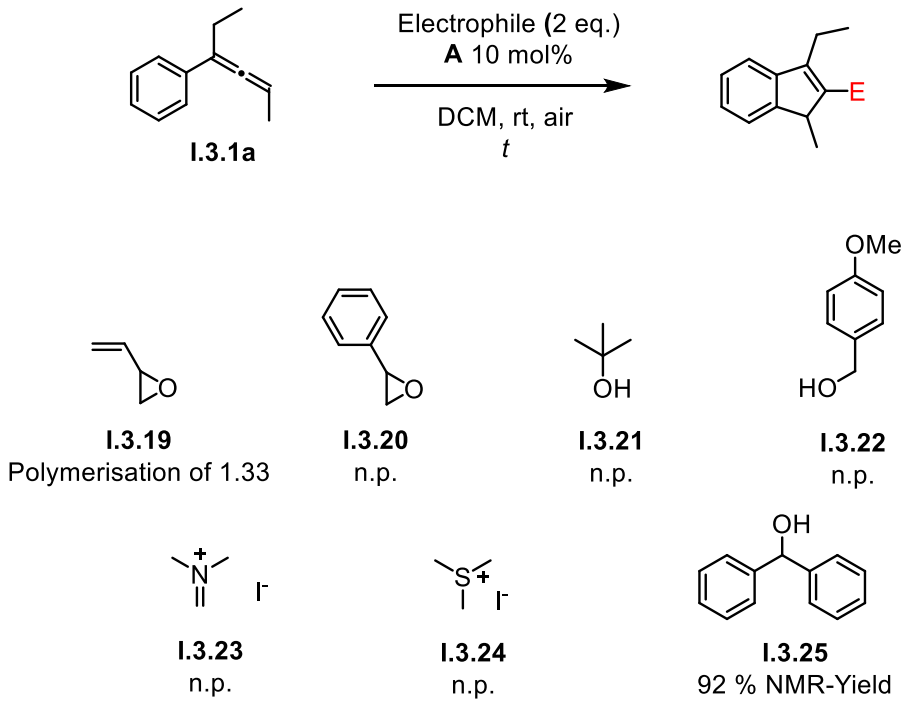
With the optimized conditions in hand, we investigated the scope of this transformation. The reaction proceeded smoothly with a variety of different allenes. Notably, all reactions were run open to air and without pre-drying of the solvent. We first studied the influence of the substituent on the aromatic ring. Electron-neutral to –rich aromatic systems afforded the desired products in good to excellent yields (**I.3.18a**-**I.3.18f**). Pleasingly, the reactions of **I.3.18e** and **I.3.18f** afforded selectively only one regioisomer, **I.3.18e** and **I.3.18f**, respectively, with the FC–Cyclisation occurring exclusively at the most nucleophilic position. Electron-poor aromatic system **I.3.18m** led only to traces of desired product along decomposition. This coupling also tolerates allyl (**I.3.18g**), as well as linear (**I.3.18a**), branched (**I.3.18h**) and cyclic (**I.3.18i**) aliphatic substituents on the α-position of the allene. On the γ-position, mono- and disubstituted allenes gave the corresponding products in excellent yields (**I.3.18k** and **I.3.18l**). Terminal allene **I.3.1j** also led to the desired product **I.3.18j** in moderate yield and after a slightly longer reaction time compared to the corresponding mono- and disubstituted

derivatives **I.3.18a** and **I.3.18l**. The use of thiophene as an aromatic substituent on the allene led to decomposition (**I.3.18n**), and a *meta*-pyridyl ring on the terminal position of the allene completely shut down reactivity (**I.3.18o**).



Scheme 23: Substrate scope of the C–C domino coupling reaction.

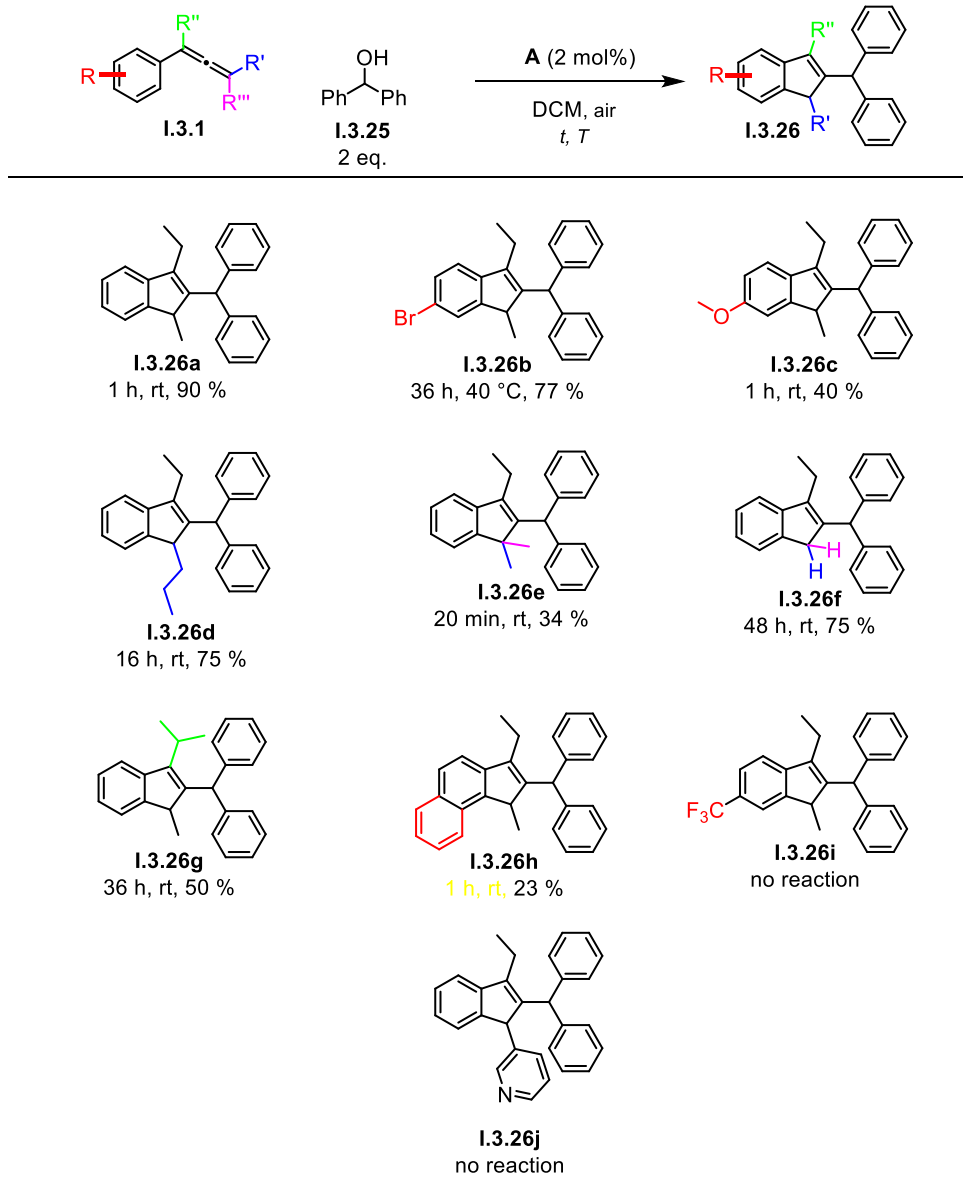
Additionally, we examined other possible electrophiles for this transformation. The epoxides **I.3.19** and **I.3.20** did not lead to the formation of the desired product, but the formation of indene **I.3.2a** (E = H) and epoxide-derived polymerisation by-products. Alcohols **I.3.21** and **I.3.22**, which could also act as a source of a stabilized carbocation, just led to simpler indene **I.3.2a**, as did electrophiles **I.3.23** and **I.3.24**. Pleasingly, reacting benzhydrol (**I.3.25**) with allene **I.3.1a** resulted in a clean transformation into the desired product in 92 % NMR-yield.



Scheme 24: Screening of electrophiles.

Thus, we then investigated the scope of this benzylation (Scheme 25). The reaction proceeded smoothly with our model substrate, giving **I.3.26a** in excellent yield. However, this transformation appears less facile than the one involving the allylic alcohol **I..3.17a**, as reflected by longer reaction times and slightly lower yields. Less activated substrates gave products **I.3.26b** and **I.3.26f** in good yields. A longer aliphatic chain at the γ-position of the allene led to a clean reaction and **I.3.26d** was obtained in 75 % yield. Interestingly, more electron-rich allenes gave the desired products (**I.3.26c**, **I.3.26e** and **I.3.26g**) in moderate yields, with the main by-product being the simple indene resulting from gold-catalysed cyclisation (*vide supra*). Naphtyl-substituted allene led to product **I.3.26h** in low yield.

Electron-poor aromatic system **I.3.26i** as well as pyridyl-substitution on the γ-position of the allene blocked the reaction.

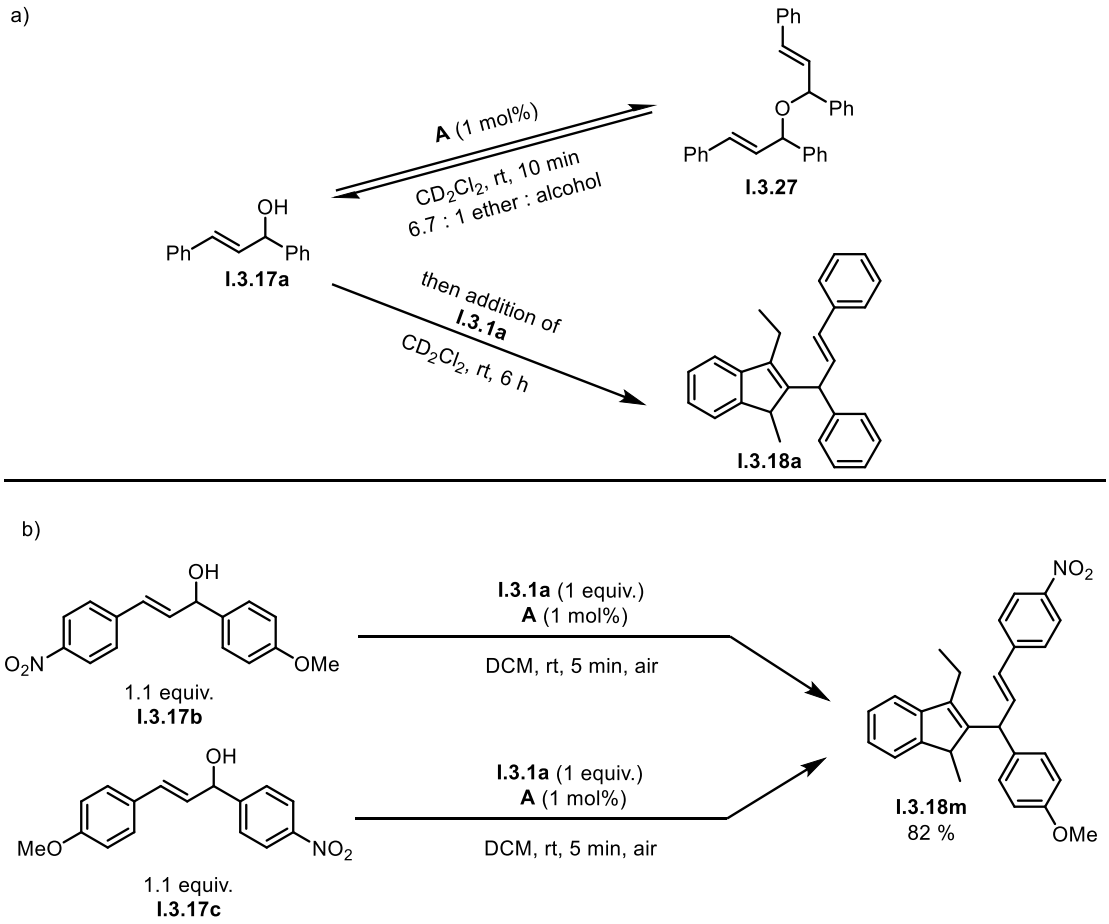


Scheme 25: Substrate scope for the domino C–C coupling of differently substituted allenes with benzhydrol.

At this stage, we carried out some preliminary mechanistic experiments. First, we wanted to clarify the role of allylic ether **I.3.27**, which is a typical by-product of gold-catalysed allylation reactions, as also observed by the Bandini group (*vide supra*).[19-20] Premixing of allylic alcohol **I.3.17a** and gold catalyst **A** in CD_2Cl_2 resulted in an equilibrium ratio of alcohol **I.3.17a** : ether **I.3.27** of 1:6.7. Adding allene **I.3.1a** to this mixture gave the corresponding product **I.3.18a** in the same yield as the original reaction (*vide supra*), but with a significantly longer reaction

time (Scheme 5a). This strongly suggests that ether **I.3.27** is not an intermediate of the catalytic cycle, but rather a reversibly formed off-cycle by-product of the reaction.

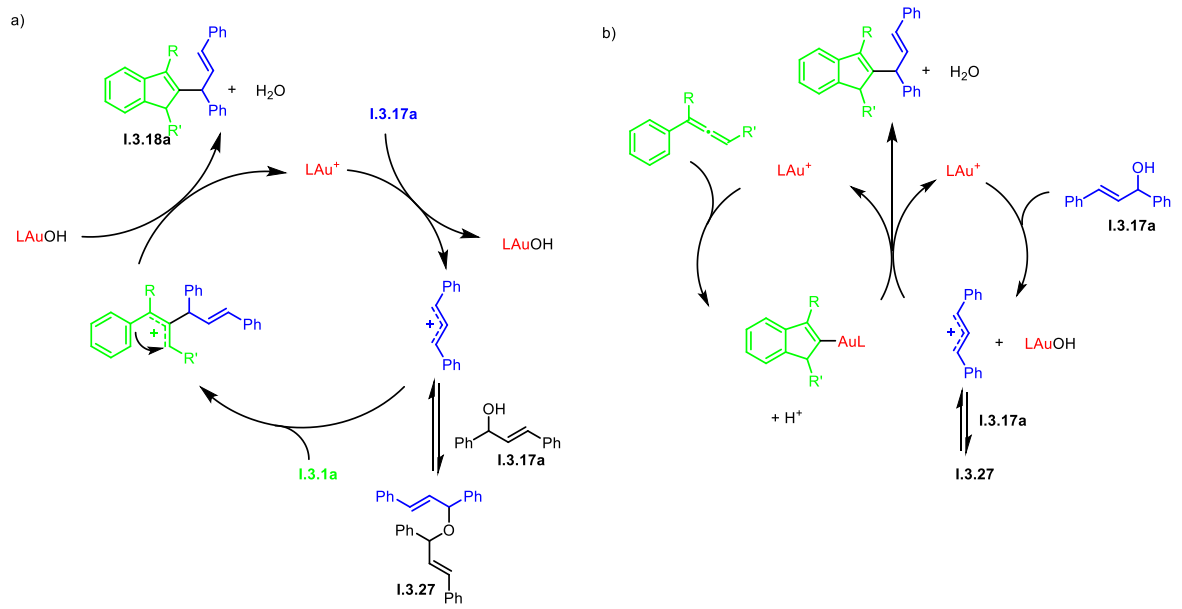
We then prepared allylic alcohols **I.3.17b** and **I.3.17c**, which, upon reaction with allene **I.3.1a**, both led to the same product **I.3.18m**, as confirmed by NOESY (Scheme 5b). Since C–C bond formation occurs at the position of what would be the best-stabilized benzylic carbocation, this result is suggestive of a cationic pathway.



Scheme 26: Preliminary mechanistic investigations.

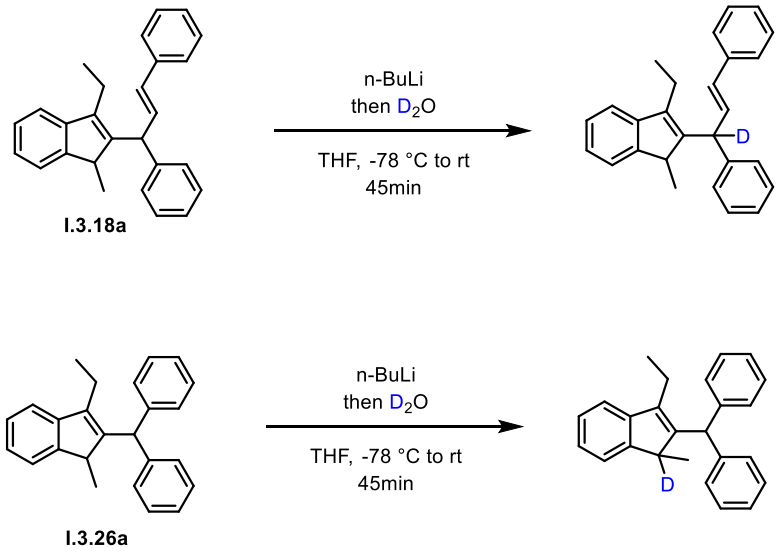
We can rationalise these observations according to two possible pathways, both relying on the formation of an allylic carbocation (Scheme 27). One possible pathway is the direct capture of the carbocation by the allene, which, in this case, would act as the nucleophile, forming another allylic carbocation. Friedel-Crafts cyclisation then leads to the final product (Scheme 27, Pathway a). The second possibility would be a synergistic catalytic transformation with two cycles. Gold-catalysed activation of the allylic alcohol to form the carbocation intermediate is accompanied by allene activation which, upon cyclisation, forms an

intermediate vinyl gold species. Combination of the latter species with the carbocationic intermediate then forms the product (Scheme 27, Pathway b). At this point it is not possible to rule out any of the two pathways. However, the failure of simple Brønsted acids to efficiently promote the reaction would appear to favour pathway b.



Scheme 27. Plausible mechanistic scenarios.

Finally, we were interested in evaluating the relative acidity of products **I.3.18a** and **I.3.26a**. Thus, we performed a standard deprotonation/deuterium labeling experiment using *n*-BuLi as the base. In the case of allylation product **I.3.18a**, the allylic/benzylic position was shown to be the most acidic. Interestingly, deprotonation of **I.3.26a** under the same condition led to deprotonation at the benzylic position of the indene core.



Scheme 28: Deuterium labeling experiments

I.4 Conclusion

In summary, we have presented synthetic studies on a new gold-catalysed domino C–C coupling of aryl substituted allenes. To achieve such a transformation, various approaches were systematically tested, with best results obtained when activated alcohols were used as electrophiles. The corresponding substituted indenes were obtained in good yields, with low catalyst loadings and under mild conditions. Notably, these reactions proceed without a need for exclusion of air or pre-drying of the solvent. The cyclisation of aryl-substituted allenes using gold catalysis was also achieved, and preliminary mechanistic evidence in favour of carbocationic intermediates was obtained.

I.5 References

[1] S. r. Kramer, G. Fabien, in *Gold Catalysis, Vol. Volume 13*, IMPERIAL COLLEGE PRESS, **2011**, pp. 1-49.

[2] a) R. Jana, T. P. Pathak, M. S. Sigman, *Chem. Rev.* **2011**, *111*, 1417-1492; b) Á. Molnár, *Chem. Rev.* **2011**, *111*, 2251-2320; c) A. Roglans, A. Pla-Quintana, M. Moreno-Mañas, *Chem. Rev.* **2006**, *106*, 4622-4643; d) N. Miyaura, A. Suzuki, *Chem. Rev.* **1995**, *95*, 2457-2483.

[3] B. M. Rosen, K. W. Quasdorf, D. A. Wilson, N. Zhang, A.-M. Resmerita, N. K. Garg, V. Percec, *Chem. Rev.* **2011**, *111*, 1346-1416.

[4] G. Evano, N. Blanchard, M. Toumi, *Chem. Rev.* **2008**, *108*, 3054-3131.

[5] a) J. J. Hirner, Y. Shi, S. A. Blum, *Acc. Chem. Res.* **2011**, *44*, 603-613; b) M. N. Hopkinson, A. D. Gee, V. Gouverneur, *Chem. Eur. J.* **2011**, *17*, 8248-8262; c) P. Garcia, M. Malacria, C. Aubert, V. Gandon, L. Fensterbank, *ChemCatChem* **2010**, *2*, 493-497.

[6] Y. Ito, M. Sawamura, T. Hayashi, *J. Am. Chem. Soc.* **1986**, *108*, 6405-6406.

[7] Y. Fukuda, K. Utimoto, *J. Org. Chem.* **1991**, *56*, 3729-3731.

[8] P. H. S. Paioti, A. Aponick, in *Homogeneous Gold Catalysis* (Ed.: M. L. Slaughter), Springer International Publishing, Cham, **2015**, pp. 63-94.

[9] S. Shin, in *Homogeneous Gold Catalysis* (Ed.: M. L. Slaughter), Springer International Publishing, Cham, **2015**, pp. 25-62.

[10] Number of publications determined by a SciFinder search for articles containing the concept "gold catalysis".

[11] A. W. Sromek, M. Rubina, V. Gevorgyan, *J. Am. Chem. Soc.* **2005**, *127*, 10500-10501.

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

[13] D. J. Gorin, F. D. Toste, *Nature* **2007**, *446*, 395-403.

[14] D. Benitez, N. D. Shapiro, E. Tkatchouk, Y. Wang, W. A. Goddard, F. D. Toste, *Nat Chem* **2009**, *1*, 482-486.

[15] a) B. Biannic, A. Aponick, *Eur. J. Org. Chem.* **2011**, *2011*, 6605-6617; b) M. Bandini, *Chemical Society Reviews* **2011**, *40*, 1358-1367; c) A. Quintavalla, M. Bandini, *ChemCatChem* **2016**, *8*, 1437-1453; dJ. Muzart, *Tetrahedron* **2008**, *64*, 5815-5849.

[16] A. Aponick, C.-Y. Li, B. Biannic, *Org. Lett.* **2008**, *10*, 669-671.

[17] J. M. Ketcham, A. Aponick, in *Synthesis of Heterocycles via Metal-Catalyzed Reactions that Generate One or More Carbon-Heteroatom Bonds* (Ed.: P. J. Wolfe), Springer Berlin Heidelberg, Berlin, Heidelberg, **2013**, pp. 157-186.

[18] T. Ghebreghiorgis, B. Biannic, B. H. Kirk, D. H. Ess, A. Aponick, *J. Am. Chem. Soc.* **2012**, *134*, 16307-16318.

[19] M. M. Mastandrea, N. Mellonie, P. Giacinto, A. Collado, S. P. Nolan, G. P. Miscione, A. Bottoni, M. Bandini, *Angew. Chem. Int. Ed.* **2015**, *54*, 14885-14889.

[20] E. Manoni, M. Daka, M. M. Mastandrea, A. D. Nisi, M. Monari, M. Bandini, *Adv. Synth. Catal.* **2016**, *358*, 1404-1409.

[21] Y. Liu, X. Wang, Y. Wang, C. Du, H. Shi, S. Jin, C. Jiang, J. Xiao, M. Cheng, *Adv. Synth. Catal.* **2015**, *357*, 1029-1036.

[22] B. Gabriele, R. Mancuso, L. Veltri, *Chem. Eur. J.* **2016**, *22*, 5056-5094.

[23] M. Vilums, J. Heuberger, L. H. Heitman, A. P. Ijzerman, *Med. Chem. Rev.* **2015**, *35*, 1097-1126.

[24] B. D. Dorsey, R. B. Levin, S. L. McDaniel, J. P. Vacca, J. P. Guare, P. L. Darke, J. A. Zugay, E. A. Emini, W. A. Schleif, *J. Med. Chem.* **1994**, *37*, 3443-3451.

[25] G. Villetti, G. Bregola, F. Bassani, M. Bergamaschi, I. Rondelli, C. Pietra, M. Simonato, *Neuropharmacol.* **2001**, *40*, 866-878.

[26] H. Yu, I. J. Kim, J. E. Folk, X. Tian, R. B. Rothman, M. H. Baumann, C. M. Dersch, J. L. Flippen-Anderson, D. Parrish, A. E. Jacobson, K. C. Rice, *J. Med. Chem.* **2004**, *47*, 2624-2634.

[27] S. Tamura, S. Kuzuna, K. Kawai, *J. Pharm. Pharmacol.* **1981**, *33*, 29-32.

[28] P. F. Nestico, J. Morganroth, L. N. Horowitz, C. Mulhern, *Am. J. Cardiol.* **1987**, *59*, 1332-1336.
[29] O. W. Woltersdorf, S. J. DeSolms, G. E. Stokker, E. J. Cragoe, *J. Med. Chem.* **1984**, *27*, 840-845.
[30] J. W. Huffman, L. W. Padgett, *Curr. Med. Chem.* **2005**, *12*, 1395-1411.
[31] aM. Stradiotto*, M. J. McGlinchey*, *Coord. Chem. Rev.* **2001**, *219–221*, 311-378; bJ. M. O'Connor, C. P. Casey, *Chem. Rev.* **1987**, *87*, 307-318.
[32] a) Y. Li, *Acc. Chem. Res.* **2012**, *45*, 723-733; b) T. D. Lash, *Acc. Chem. Res.* **2016**, *49*, 471-482.
[33] E. Markus, W. B. Robert, *Curr. Org. Chem.* **2006**, *10*, 937-953.
[34] For a more exhaustive summary, see the reviews cited above.
[35] a) S. Guo, Y. Liu, *Org. Biomol. Chem.* **2008**, *6*, 2064-2070; b) J. Wang, L. Zhang, Y. Jing, W. Huang, X. Zhou, *Tetrahedron Lett.* **2009**, *50*, 4978-4982; c) P. Shanmugam, P. Rajasingh, *Chem Lett.* **2005**, *34*, 1494-1495.
[36] X. Zhang, W. T. Teo, W. Rao, D.-L. Ma, C.-H. Leung, P. W. H. Chan, *Tetrahedron Lett.* **2014**, *55*, 3881-3884.
[37] a) B. V. S. Reddy, B. B. Reddy, K. V. R. Rao, J. S. Yadav, *Tetrahedron Lett.* **2010**, *51*, 5697-5700; b) C. M. Sousa, J. Berthet, S. Delbaere, P. J. Coelho, *J. Org. Chem.* **2014**, *79*, 5781-5786; c) M. Egi, K. Shimizu, M. Kamiya, Y. Ota, S. Akai, *Chem. Commun.* **2015**, *51*, 380-383.
[38] a) D. Eom, S. Park, Y. Park, T. Ryu, P. H. Lee, *Org. Lett.* **2012**, *14*, 5392-5395; b) X. Sun, K.-J. Izumi, C.-Q. Hu, G.-Q. Lin, *Chin. J. Chem.* **2006**, *24*, 430-434; c) S. Yamazaki, Y. Yamamoto, Y. Fukushima, M. Takebayashi, T. Ukai, Y. Mikata, *J. Org. Chem.* **2010**, *75*, 5216-5222; d) C. Grandclaudon, V. Michelet, P. Y. Toullec, *Org. Lett.* **2016**, *18*, 676-679.
[39] a) K. Muralirajan, K. Parthasarathy, C.-H. Cheng, *Angew. Chem. Int. Ed.* **2011**, *50*, 4169-4172; b) X.-Y. Shi, C.-J. Li, *Org. Lett.* **2013**, *15*, 1476-1479; c) X.-C. Huang, X.-H. Yang, R.-J. Song, J.-H. Li, *J. Org. Chem.* **2014**, *79*, 1025-1031.
[40] N. Marion, S. Díez-González, P. de Frémont, A. R. Noble, S. P. Nolan, *Angew. Chem. Int. Ed.* **2006**, *45*, 3647-3650.
[41] H. Schlossarczyk, W. Sieber, M. Hesse, H.-J. Hansen, H. Schmid, *Helv. Chim. Acta* **1973**, *56*, 875-944.
[42] P. Dubé, F. D. Toste, *J. Am. Chem. Soc.* **2006**, *128*, 12062-12063.
[43] T. J. Brown, D. Weber, M. R. Gagné, R. A. Widenhoefer, *J. Am. Chem. Soc.* **2012**, *134*, 9134-9137.
[44] J. H. Teles, in *Modern Gold Catalyzed Synthesis*, Wiley-VCH Verlag GmbH & Co. KGaA, **2012**, pp. 201-235.
[45] Z. Zhang, R. A. Widenhoefer, *Org. Lett.* **2008**, *10*, 2079-2081.
[46] M. D. Levin, F. D. Toste, *Angew. Chem. Int. Ed.* **2014**, *53*, 6211-6215.
[47] X. C. Cambeiro, N. Ahlsten, I. Larrosa, *J. Am. Chem. Soc.* **2015**, *137*, 15636-15639.
[48] A. S. K. Hashmi, C. Lothschütz, R. Döpp, M. Rudolph, T. D. Ramamurthi, F. Rominger, *Angew. Chem. Int. Ed.* **2009**, *48*, 8243-8246.
[49] M. M. Hansmann, M. Pernpointner, R. Döpp, A. S. K. Hashmi, *Chem. Eur. J.* **2013**, *19*, 15290-15303.

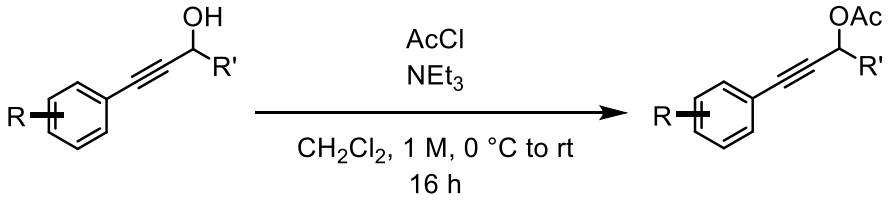
I.6 Experimental

I.6.1 General Information

For the starting material synthesis and the gold-catalysed cyclisation, all glassware was flame-dried before use and the reactions were performed under an atmosphere of argon. The alcohol-activation cyclisation reactions were carried out without any pre-drying and under ambient conditions. All dry solvents were bought from Acros and used as recieved. JohnPhosAu(MeCN)SbF_6[1], $(Ph_3P)_2PdCl_2$,[2] **I.3.9a**,[3] **I.3.17b** and **I.3.17c**[4] were prepared according to literature procedures. All other reagents were used as received from commercial suppliers. Reaction progress was monitored by thin layer chromatography (TLC) performed on aluminum plates coated with silica gel F254 with 0.2 mm thickness or LC-MS analysis. Chromatograms were visualized by fluorescence quenching with UV light at 254 nm or by staining using potassium permanganate. Column chromatography was performed using silica gel 60 (230-400 mesh, Merck and co.). Preparative HPLC was performed on a Waters XBridge Prep C18 5 µm OBD 30×150 mm system, using isocratic acetonitrile / (water + 1% formic acid) 95:5. Neat infra-red spectra were recorded using a Perkin-Elmer Spectrum 100 FT-IR spectrometer. Wavenumbers (= 1/λ) are reported in cm^{-1}. Mass spectra were obtained using a Finnigan MAT 8200 or (70 eV) or an Agilent 5973 (70 eV) spectrometer, using electrospray ionisation (ESI), or Finnigan MAT 95 Q using electron impact ionisation (EI). All ^1H NMR and ^{13}C NMR spectra were recorded using a Bruker AV-400 or AV-600 spectrometer at 300K. Chemical shifts were given in parts per million (ppm, δ), referenced to the solvent peak of $CDCl_3$, defined at δ = 7.26 ppm (^1H NMR) and δ = 77.16 (^{13}C NMR). Coupling constants are quoted in Hz (J). ^1H NMR splitting patterns were designated as singlet(s), doublet (d), triplet (t), quartet (q), pentet (p). Splitting patterns that could not be interpreted or easily visualized were designated as multiplet (m).

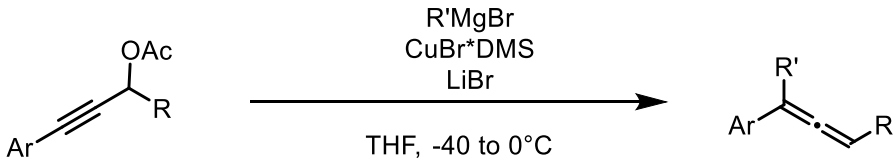
I.6.2 General Procedures

General procedure A: Preparation of Acetates



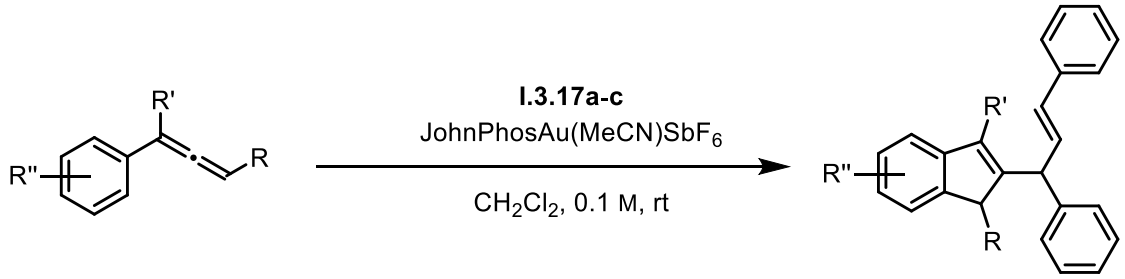
To a stirred solution of propargylic alcohol (1 eq.) and NEt_3 (2 eq.) in DCM (1 M) at 0°C was slowly added acetyl chloride (2 eq.). The reaction mixture was warmed to rt.., stirred for 16 h and quenched with 1M HCl. The biphasic mixture was extracted with DCM, washed with sat. $NaHCO_3$ and brine, dried and concentrated. Flash column chromatography affords the propargylic alcohols.

General Procedure B: Preparation of Allenes



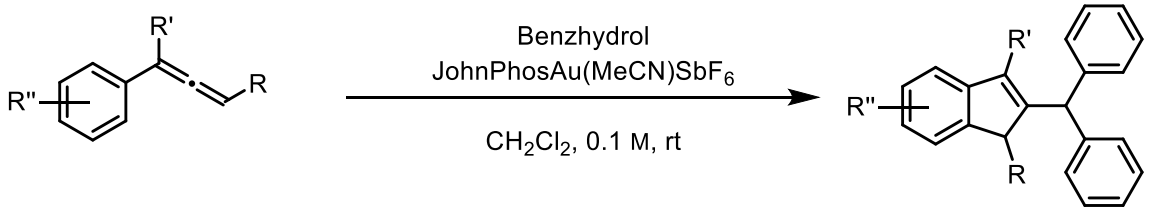
CuBr·DMS (3 mmol, 2 eq.) and Lithium Bromide (3 mmol, 2 eq.) were suspended in THF (6 mL) and cooled to -40 °C. R'MgBr (3 mmol, 1 M solution in THF, 2 eq.) was added and the resulting mixture was stirred at this temperature for 40 minutes. After addition of the alkyne (1.5 mmol, 1 eq.), the reaction mixture was allowed to warm to 0° C and stirred at this temperature for the given time. After completion, the reaction mixture was quenched with sat. aq. NH_4Cl, extracted with diethyl ether, washed with sat. aq. NH_4Cl and brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was purified by column chromatography.

General Procedure C: Gold-Catalysed Allylation



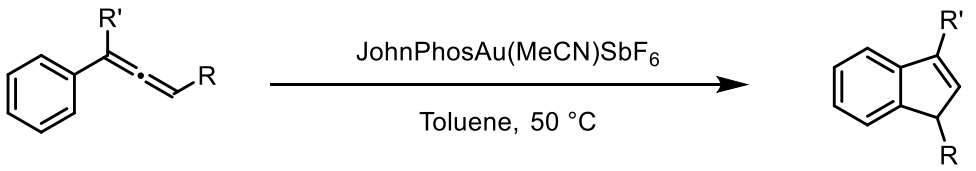
JohnPhosAu(MeCN)SbF_6 (1 mol%) was added to a solution of allene and allylic alcohol (1.1 eq.) in DCM. The reaction mixture was stirred at room temperature for the given time, filtered over a short pad of silica and concentrated under reduced pressure. The crude product was then purified either by silica gel chromatography or preparative HPLC using isocratic acetonitrile / (water + 1% formic acid) 95:5.

General Procedure D: Gold-Catalysed Benzylation



JohnPhosAu(MeCN)SbF_6 (2 mol%) was added to a solution of allene and benzhydrol (2 eq.) in DCM. The reaction mixture was stirred at room temperature for the given time, filtered over a short pad of silica and concentrated under reduced pressure. The crude product was then purified either by silica gel chromatography or preparative HPLC using isocratic acetonitrile / (water + 1% formic acid) 95:5.

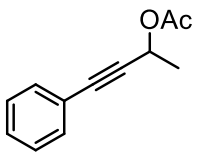
General Procedure E: Gold-Catalysed Cyclisation



Allene (0.2 mmol) and catalyst (0.02 mmol, 10 mol%) were dissolved in toluene (2 mL) and stirred at 50 °C for the given time. The reaction mixture was filtered over a short pad of silica and concentrated under reduced pressure. The crude product was purified by column chromatography or directly used for further analysis.

I.6.3 Synthesis of the acetates

Prepatation of 4-phenylbut-3-yn-2-yl acetate (**I.3.1a-Ac**)

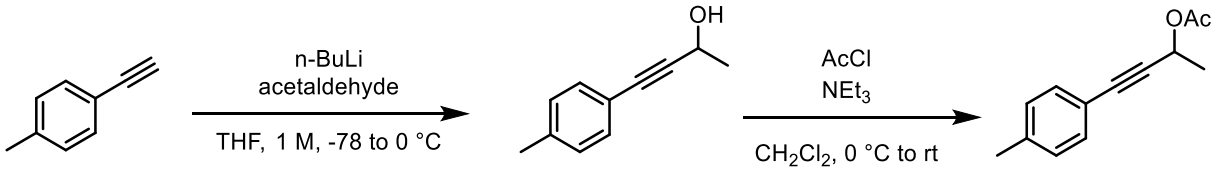


I.3.1a-Ac

Following the general procedure A, compound **I.3.1a-Ac** was prepared from 4-phenylbut-3-yn-2-ol in 86 % yield (average over four runs) after flash column chromatography (heptane / EtOAc 20:1) and obtained as colorless oil.

The spectroscopic properties were in accordance to those reported in the literature.[5]

Preparation of 4-(p-tolyl)but-3-yn-2-yl acetate (**I.3.1b-Ac**)

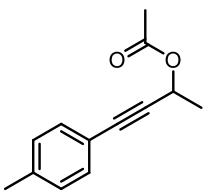


I.3.1b-Ac

To a solution of 1-ethynyl-4-methylbenzene (8.61 mmol) in dry THF, cooled to -78°C, was added *n*-BuLi (1.6 M in hexanes, 8.64 mmol, 1.01 equiv.). The mixture was stirred for 15 min at -78°C, followed by addition of acetaldehyde (8.64 mmol, 1.01 equiv.) over 5 minutes. The solution was allowed to warm to 0°C for 1 h and saturated ammonium chloride was added. The resultant biphasic mixture was separated and extracted twice with ethyl acetate. The combined organic phase was washed with brine, dried (Na_2SO_4), filtered and concentrated *in vacuo*. The crude product was subjected to flash chromatography (heptane : EtOAc 7:3) to give the product as yellow oil (8.4 mmol, 98 %).

The spectral properties were in accordance with those reported in the literature.[6]

Following general procedure A, compound **I.3.1b-Ac** was then prepared in 76 % yield (6.4 mmol) after flash column chromatography (heptane : EtOAc 9:1) as colorless oil.



I.3.1b-Ac

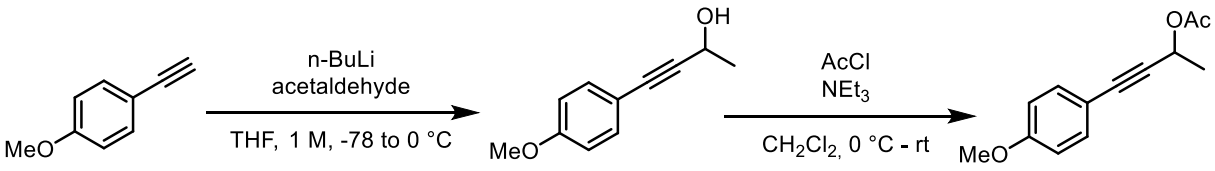
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33 (d, J = 8.1 Hz, 2H, H4), 7.11 (d, J = 8.2 Hz, 2H, H3), 5.68, (q, J = 6.7 Hz, 1H, H8), 2.34 (s, 3H, H1), 2.10 (s, 3H, H11), 1.57 (d, J = 6.7 Hz, 3H, H9)

^{13}C NMR (100 MHz, $CDCl_3$) δ 170.1, 138.9, 131.9, 129.1, 119.3, 86.9, 84.9, 61.1, 21.7, 21.6, 21.3

IR (neat): 3030, 2989, 2936, 2870, 2231, 1738, 1510, 1370, 1225, 1084, 1031, 950, 816, 543 cm^{-1}

HRMS (ESI): [M+Na]$^+$ calculated for $C_{13}H_{14}O_2Na^+$ 225.0891; found 225.0883.

Preparation of 4-(4-methoxyphenyl)but-3-yn-2-yl acetate (**I.3.1c-Ac**)



I.3.1c-Ac

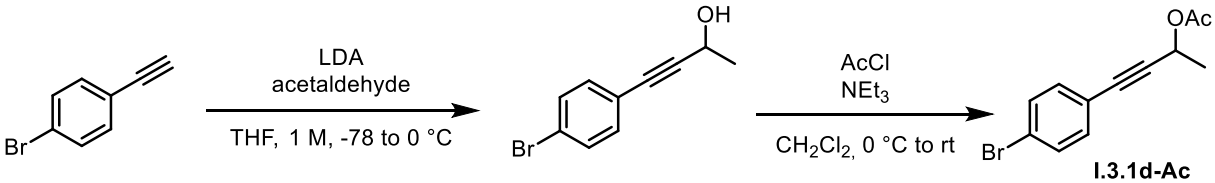
To a solution of 4-ethynylanisole (8.61 mmol) in dry THF, cooled to -78°C, was added *n*-BuLi (1.6 M in hexanes, 8.64 mmol, 1.01 equiv.). The mixture was stirred for 15 min at -78°C, followed by addition of acetaldehyde (8.64 mmol, 1.01 equiv.) over 5 minutes. The solution was allowed to warm to 0°C for 1 h and saturated ammonium chloride was added. The resultant biphasic mixture was separated and extracted twice with ethyl acetate. The combined organic phase was washed with brine, dried (Na_2SO_4), filtered and concentrated *in vacuo*. The crude product was subjected to flash chromatography (heptane : EtOAc 7:3) to give the product as white solid (8.14 mmol, 95 %).

The spectral properties were in accordance with those reported in the literature.[7]

Following general procedure A, compound **I.3.1c-Ac** was then prepared in 79 % yield (6.4 mmol) after flash column chromatography (heptane : EtOAc 9:1) as colorless oil.

The spectral properties were in accordance with those reported in the literature.[8]

Preparation of 4-(4-bromophenyl)but-3-yn-2-yl acetate (**I.3.1d-Ac**)



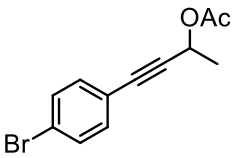
I.3.1d-Ac

To diisopropylamine (3.6 mmol) in 9 mL THF at -78°C was added *n*-BuLi (1.6 M in hexanes, 3.3 mmol) and the mixture stirred 1 min at -78°C. Then a solution of 1-bromo-4-ethynylbenzene (3 mmol) in 6 mL THF was added *via* cannula needle and the mixture was stirred for 15 min at -78°C. Acetaldehyde (3.6 mmol, 1.2 equiv.) was added dropwise over 5 minutes. The solution

was allowed to warm to 0°C for 1 h, then saturated ammonium chloride was added. The resulting biphasic mixture was separated and extracted twice with ethyl acetate. The combined organic phase was washed with brine, dried over Na_2SO_4, filtered and concentrated *in vacuo*. The crude product was subjected to flash chromatography (heptane : EtOAc 8:2) to give the product as white solid (2.76 mmol, 92 %).

The spectral properties were in accordance with those reported in the literature.[9]

Following general procedure A, compound **I.3.1d-Ac** was then prepared in 87 % yield (1.74 mmol) after flash column chromatography (heptane : EtOAc 9:1) as colorless oil.



I.3.1d-Ac

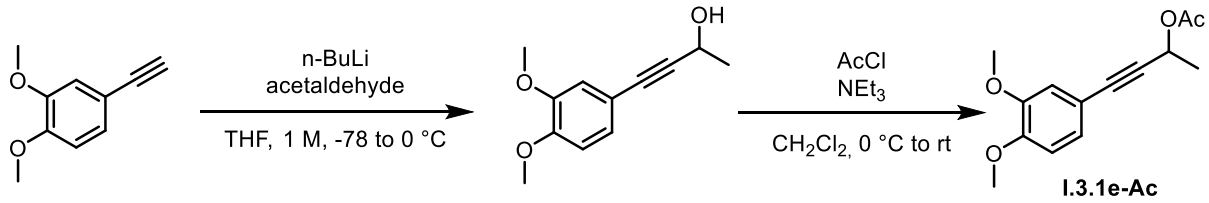
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.48 – 7.41 (m, 2H), 7.35 – 7.27 (m, 2H), 5.66 (q, *J* = 6.7 Hz, 1H), 2.10 (s, 3H), 1.58 (d, *J* = 6.7 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 169.9, 133.4, 131.6, 123.0, 121.3, 88.7, 83.6, 60.7, 21.4, 21.1.

IR (neat): 2989, 2937, 1744, 1486, 1370, 1229, 1086, 1070, 1033, 1010 cm^{-1}

HRMS (ESI): [M+Na]$^+$ calculated for $C_{12}H_{11}O_2BrNa^+$ 288.9835, found 288.9824

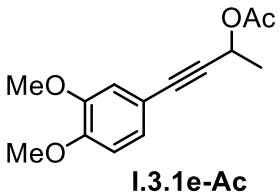
Preparation of 4-(3,4-dimethoxyphenyl)but-3-yn-2-yl acetate (**I.3.1e-Ac**)



I.3.1e-Ac

To a solution of 4-ethynyl-1,2-dimethoxybenzene (3.08 mmol) in dry THF, cooled to -78°C, was added *n*-BuLi (1.6 M in hexanes, 3.1 mmol, 1.01 equiv.). The mixture was stirred for 15 min at -78°C, followed by addition of acetaldehyde (3.1 mmol, 1.01 equiv.) over 5 minutes. The solution was allowed to warm to 0°C for 1 h and saturated ammonium chloride was added. The resultant biphasic mixture was separated and extracted twice with ethyl acetate. The combined organic phase was washed with brine, dried (Na_2SO_4), filtered and concentrated *in vacuo*. The crude product was subjected to flash chromatography (heptane : EtOAc 7:3) to give the product as yellow oil (quantitative yield).

Following general procedure A, compound **I.3.1d-Ac** was then prepared in 80 % yield (1.6 mmol) after flash column chromatography (heptane : EtOAc 9:1) as colorless oil.



I.3.1e-Ac

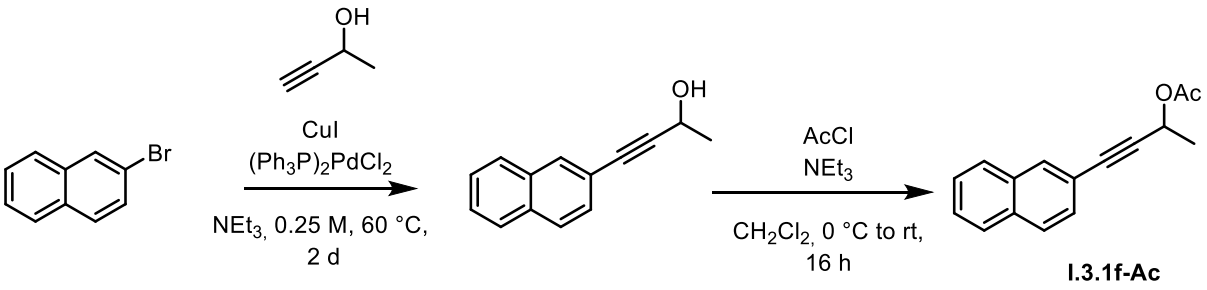
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.05 (dd, *J* = 8.3, 1.9 Hz, 1H), 6.94 (d, *J* = 1.9 Hz, 1H), 6.79 (d, *J* = 8.3 Hz, 1H), 5.68 (q, *J* = 6.7 Hz, 1H), 3.87 (d, *J* = 4.5 Hz, 6H), 2.10 (s, 3H), 1.58 (d, *J* = 6.7 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 170.1, 149.9, 148.7, 125.4, 114.8, 114.6, 111.1, 86.1, 84.8, 61.1, 56.1, 56.0, 21.8, 21.3.

IR (neat): 2988, 2936, 2836, 1736, 1512, 1442, 1370, 1266, 1228, 1208, 1170, 1137, 1085, 1022 cm^{-1}

HRMS (ESI): $[M+Na]^+$ calculated for $C_{14}H_{16}O_4Na^+$ 271.0941, found 271.0935

Preparation of 4-(naphthalen-2-yl)but-3-yn-2-yl acetate (**I.3.1f-Ac**)

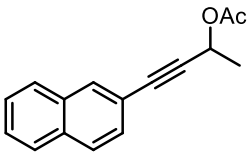


I.3.1f-Ac

$(Ph_3P)_2PdCl_2$ (0.05 mmol) and CuI (0.1 mmol) were suspended in NEt_3. 2-Bromonaphtalene (5 mmol) was added, followed by propargyl alcohol (5.5 mmol), and the reaction was stirred at 60 °C for 2 days. The reaction mixture was quenched with 1 M HCl, extracted with EtOAc, washed three times with 1 M HCl and brine, dried and the solvent was removed under reduced pressure. The crude product was purified using flash column chromatography (heptane : EtOAc 8:2) giving a slightly white to yellow solid (3.2 mmol, 64 % yield).

The spectral properties were in accordance with the literature.[10]

Following general procedure A, compound **I.3.1d-Ac** was then prepared in 85 % yield (2.7 mmol) after flash column chromatography (heptane : EtOAc 20 :1) as white solid.



I.3.1f-Ac

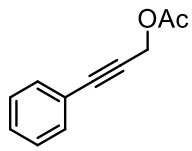
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.98 (s, 1H), 7.79 (m, 3H), 7.60 – 7.39 (m, 3H), 5.74 (d, *J* = 6.7 Hz, 1H), 2.13 (s, 3H), 1.62 (d, *J* = 6.7 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 170.1, 133.1, 133.0, 132.1, 128.6, 128.1, 127.9, 127.9, 126.9, 126.7, 119.7, 87.9, 85.1, 61.0, 21.7, 21.3.

IR (neat): 3058, 2989, 2937, 2229, 1737, 1597, 1502, 1369, 1346, 1230, 1188, 1132, 1084, 1033 cm^{-1}

HRMS (ESI): $[M+Na]^+$ calculated for $C_{16}H_{14}O_2Na^+$ 261.0891, found 261.0884

3-phenylprop-2-yn-1-yl acetate (**I.3.1j-Ac**)

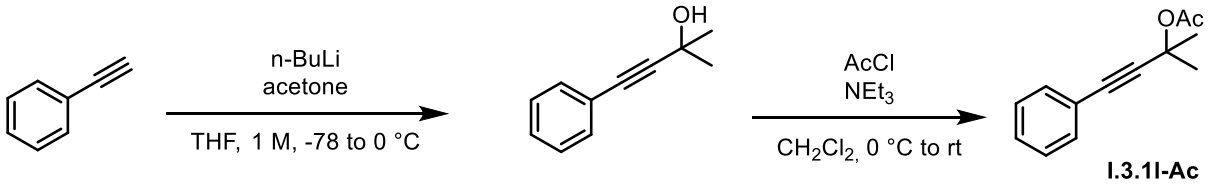


I.3.1j-Ac

Following general procedure A, compound **I.3.1j-Ac** was prepared from 3-phenylprop-2-yn-1-ol in 96 % yield (4.8 mmol) after flash column chromatography (heptane : EtOAc 20 :1) as colorless oil.

The spectral properties were in accordance with the literature.[11]

2-methyl-4-phenylbut-3-yn-2-yl acetate (**I.31l-Ac**)



I.3.1l-Ac

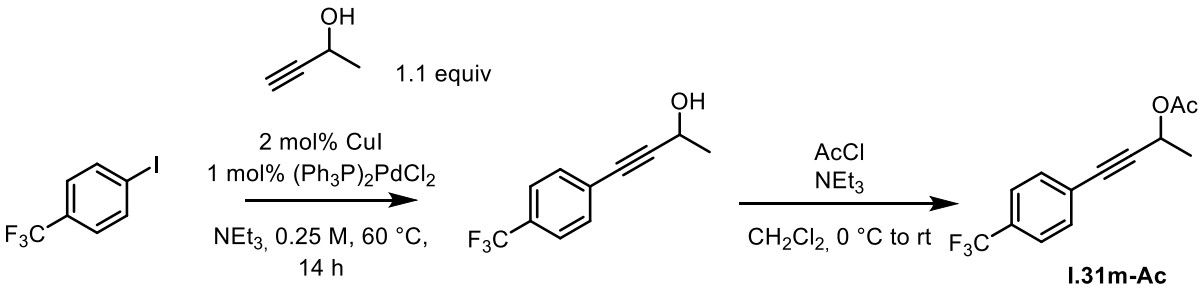
To a solution of ethynylbenzene (9.79 mmol) in dry THF, cooled to -78°C, was added *n*-BuLi (1.6 M in hexanes, 9.89 mmol, 1.01 equiv.). The mixture was stirred for 15 min at -78°C, followed by addition of acetone (29 mmol, 3 equiv.) over 5 minutes. The solution was allowed to warm to 0°C for 1 h and saturated ammonium chloride was added. The resultant biphasic mixture was separated and extracted twice with ethyl acetate. The combined organic phase was washed with brine, dried (Na_2SO_4), filtered and concentrated *in vacuo*. The crude product was subjected to flash chromatography (heptane : EtOAc 9:1) to give the product as coloress oil (quantitative yield).

The spectral properties were in accordance with the literature.[12]

Following general procedure A, compound **I.3.1l-Ac** was then prepared in 37 % yield (3.6 mmol) after flash column chromatography (heptane : EtOAc 20 :1) as colorless oil.

The spectral properties were in accordance with the literature.[12]

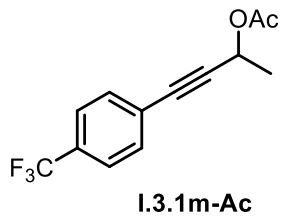
4-(4-(trifluoromethyl)phenyl)but-3-yn-2-yl acetate (**I.3.1m-Ac**)



$(Ph_3P)_2PdCl_2$ (0.05 mmol) and CuI (0.1 mmol) were suspended in NEt_3. 1-iodo-4-(trifluoromethyl)benzene (5 mmol) was added, followed by but-3-yn-2-ol (5.5 mmol), and the reaction was stirred at room temperature for 14 h. The reaction mixture was quenched with 1 M HCl, extracted with EtOAc, washed three times with 1 M HCl and brine, dried and the solvent was removed under reduced pressure. The crude product was purified using flash column chromatography (Heptane : EtOAc 1:1) giving the product as brown oil (5 mmol, quantitative yield).

The spectral properties were in accordance with the literature.[13]

Following general procedure A, compound **I.3.1m-Ac** was then prepared in 86 % yield (4.3 mmol) after flash column chromatography (heptane : EtOAc 20 :1) as colorless oil.



I.3.1m-Ac

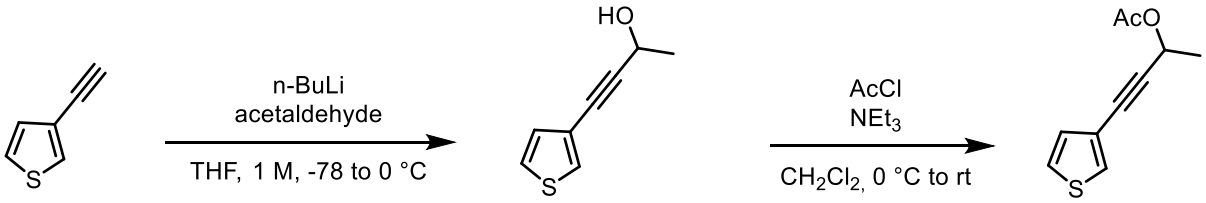
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.67 – 7.43 (m, 4H), 5.68 (q, *J* = 6.7 Hz, 1H), 2.11 (s, 3H), 1.59 (d, *J* = 6.7 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 170.0 (s), 132.3 (s), 130.5 (d, *J* = 32.7 Hz), 126.3 (s), 125.4 (q, *J* = 3.8 Hz), 122.6 (s), 90.0 (s), 83.3 (s), 60.7 (s), 21.5 (s), 21.2 (s).

HRMS (ESI): [M+Na]$^+$ calculated for $C_{13}H_{11}O_2F_3Na^+$ 279.0603, found 279.0604

IR (neat): 2993, 2941, 1744, 1615, 1405, 1372, 1320, 1226, 1166, 1123, 1105, 1088, 1064, 1033, 1016 cm^{-1}

4-(thiophen-3-yl)but-3-yn-2-yl acetate (I.3.1n-Ac)

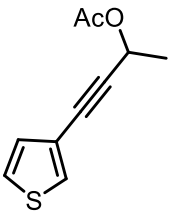


I.3.1n-Ac

To a solution of 3-ethynylthiophene (3.08 mmol) in dry THF, cooled to -78°C, was added *n*-BuLi (1.6 M in hexanes, 3.1 mmol, 1.01 equiv.). The mixture was stirred for 15 min at -78°C, followed by addition of acetaldehyde (3.1 mmol, 1.01 equiv.) over 5 minutes. The solution was allowed to warm to 0°C for 1 h and saturated ammonium chloride was added. The resultant biphasic mixture was separated and extracted twice with ethyl acetate. The combined organic phase was washed with brine, dried (Na_2SO_4), filtered and concentrated *in vacuo*. The crude product was subjected to flash chromatography (heptane : EtOAc 7:3) to give the product as yellow oil (2.4 mmol, 63 %).

The spectral properties were in accordance with the literature.[13]

Following general procedure A, compound **I.3.1n-Ac** was then prepared in 84 % yield (1.51 mmol) after flash column chromatography (heptane : EtOAc 4:1) as yellow oil.



I.3.1n-Ac

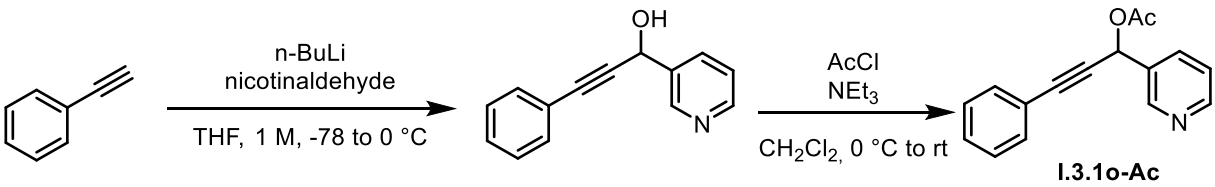
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.49 (dd, *J* = 3.0, 1.1 Hz, 1H), 7.33 – 7.24 (m, 1H), 7.13 (dd, *J* = 5.0, 1.2 Hz, 1H), 5.69 (q, *J* = 6.7 Hz, 1H), 2.12 (s, 3H), 1.59 (t, *J* = 4.8 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 170.1, 130.1, 129.6, 125.4, 121.5, 87.2, 79.9, 61.0, 21.6, 21.3.

IR (neat): 3108, 2989, 2937, 1737, 1369, 1225, 1085, 1033 cm^{-1}

HRMS (ESI): $[M+Na]^+$ calculated for $C_{10}H_{10}O_2SNa^+$ 217.0294, found 217.0288

Preparation of 3-phenyl-1-(pyridin-3-yl)prop-2-yn-1-yl acetate (**I.3.1o-Ac**)



I.3.1o-Ac

To a solution of ethynylbenzene (5.98 mmol) in dry THF, cooled to -78°C, was added *n*-BuLi (1.6 M in hexanes, 6 mmol, 1.01 equiv.). The mixture was stirred for 15 min at -78°C, followed by addition of nicotinaldehyde (3.1 mmol, 1.01 equiv.) over 5 minutes. The solution was allowed to warm to 0°C for 1 h and saturated ammonium chloride was added. The resultant biphasic mixture was separated and extracted twice with ethyl acetate. The combined organic phase was washed with brine, dried (Na_2SO_4), filtered and concentrated *in vacuo*. The crude product was subjected to flash chromatography (heptane : EtOAc 7:3) to give the product as brown oil (5.6 mmol, 95 %).

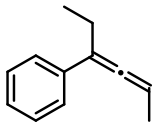
The spectral properties were in accordance with the literature.[14]

Following general procedure A, compound **I.3.1o-Ac** was then prepared in 20 % yield (0.3 mmol) after flash column chromatography (heptane : EtOAc 2:3) as brown oil.

The spectral properties were in accordance with the literature.[15]

I.6.4 Synthesis of Allenes I.3.1a-I.3.1l

Hexa-3,4-dien-3-ylbenzene (I.3.1a)

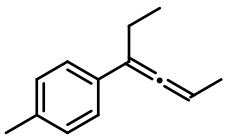


I.3.1a

Following the general procedure B, compound **I.3.1a** was prepared after 3 hours reaction time and after column chromatography (100% pentane) in 83% yield as colorless oil. The spectroscopic properties were in accordance with those reported in the literature.[16]

1-(hexa-3,4-dien-3-yl)-4-methylbenzene (I.3.1b)

Following the general procedure B, compound **I.3.1b** was prepared after 5 hours reaction time and after column chromatography (100% pentane) in 88% yield as yellow oil.



I.3.1b

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31–7.28 (m, 2H), 7.13–7.11 (m, 2H), 5.53–5.45 (m, 1H), 2.45–2.37 (m, 2H), 2.34 (s, 3H), 1.77 (d, *J* = 7.0 Hz, 3H), 1.13 (t, *J* = 7.3 Hz, 3H)

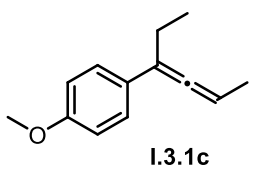
^{13}C NMR (100 MHz, $CDCl_3$) δ 204.3, 136.1, 134.8, 129.1, 126.0, 106.8, 89.5, 23.1, 21.2, 14.7, 12.8

IR (neat): ν_{max} = 3023, 2965, 2921, 2862, 1945, 1510, 1443, 1370, 897, 820, 799, 766, 596, 569 cm^{-1}

MS (EI): $[M+H]^+$ calculated for $C_{13}H_{17}^+$, 173.1325; found 173.1328

1-(hexa-3,4-dien-3-yl)-4-methoxybenzene (I.3.1c)

Following the general procedure B, compound **I.3.1c** was prepared after 5 hours reaction time and after column chromatography (heptane / ethyl acetate 9:1) in 86% yield as slightly yellow oil.



I.3.1c

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34–7.30 (m, 2H), 6.88–6.84 (m, 2H), 5.51–5.46 (m, 1H), 3.81 (s, 3H), 2.42–2.36 (m, 2H), 1.77 (d, *J* = 7.0 Hz, 3H), 1.13 (t, *J* = 7.3 Hz, 3H)

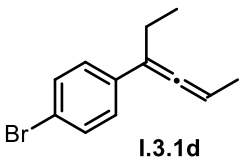
^{13}C NMR (100 MHz, $CDCl_3$) δ 204.0, 158.5, 130.1, 127.1, 113.9, 106.5, 89.5, 55.4, 23.2, 14.7, 12.7

IR (neat): ν_{max} = 2964, 2931, 2834, 1945, 1606, 1508, 1459, 1441, 1293, 1243, 1176, 1036, 831, 769, 598 cm^{-1}

HRMS (ESI): $[M+H]^+$ calculated for $C_{13}H_{17}O^+$, 189.1274; found 189.1273

1-bromo-4-(hexa-3,4-dien-3-yl)benzene (I.3.1d)

Following the general procedure B, compound **I.3.1d** was prepared after 3 hours reaction time and after column chromatography (100% heptane) in 74% yield as colorless oil



I.3.1d

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32-7.16 (m, 2H), 7.16-7.12 (m, 2H), 5.44-5.27 (m, 1H), 2.32-2.20 (m, 2H), 1.66 (d, *J* = 7.0 Hz, 3H), 1.02 (t, *J* = 7.3 Hz, 3H)

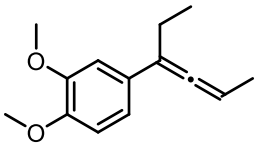
^{13}C NMR (100 MHz, $CDCl_3$) δ 204.5, 136.8, 131.4, 127.6, 120.2, 106.3, 90.2, 22.9, 14.4, 12.6

IR (neat): ν_{max} = 2974, 2937, 2879, 1948, 1721, 1688, 1586, 1486, 1396, 1217, 1101, 1071, 1009 cm^{-1}

HRMS (EI): $[M]^{\cdot+}$ calculated for $C_{12}H_{13}Br^{\cdot+}$, 236.0195; found 236.0188

4-(hexa-3,4-dien-3-yl)-1,2-dimethoxybenzene (I.3.1e)

Following the general procedure B, compound **I.3.1e** was prepared after 16 hours reaction time and after column chromatography (heptane / ethyl acetate 9:1) in 73% yield as yellow oil.



I.3.1e

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.99 (d, *J* = 2.0 Hz, 1H), 6.94 (dd, *J* = 2.0, 8.4 Hz, 1H), 6.82 (d, *J* = 8.4 Hz, 1H), 5.56-5.49 (m, 1H), 3.89 (s, 3H), 3.87 (s, 3H), 2.49-2.36 (m, 2H), 1.79 (d, *J* = 7.0 Hz, 3H), 1.16 (t, *J* = 7.3 Hz, 3H)

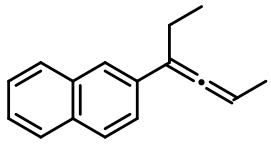
^{13}C NMR (100 MHz, $CDCl_3$) δ 203.9, 148.8, 147.9, 130.3, 117.8, 111.0, 109.7, 106.6, 89.5, 55.8, 55.7, 23.0, 14.5, 12.6

IR (neat): ν_{max} = 2965, 2935, 2836, 1946, 1585, 1514, 1463, 1416, 1324, 1261, 1244, 1212, 1166, 1143 cm^{-1}

HRMS (ESI): $[M+H]^+$ calculated for $C_{14}H_{19}O_2^+$, 219.1380; found 219.1370

2-(hexa-3,4-dien-3-yl)naphthalene (I.3.1f)

Following the general procedure B, compound **I.3.1f** was prepared after 16 hours reaction time and after column chromatography (100% heptane) in 71% yield as slightly yellow oil.



I.3.1f

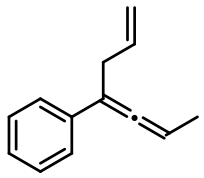
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.81-7.74 (m, 4H), 7.61 (dd, *J* = 1.7, 8.7 Hz, 1H), 7.47-7.39 (m, 2H), 5.63-5.57 (m, 1H), 2.62-2.48 (m, 2H), 1.83 (d, *J* = 7 Hz, 3H), 1.21 (t, *J* =7.3 Hz, 3H)

^{13}C NMR (100 MHz, $CDCl_3$) δ 205.3, 135.2, 133.8, 132.5, 128.1, 127.7, 127.7, 126.1, 125.7, 125.6, 123.4, 107.3, 90.0, 23.0, 14.6, 12.8

IR (neat): ν_{max} = 3056, 2967, 2933, 1946, 1739, 1685, 1370, 1187, 1078 cm^{-1}

HRMS (EI): $[M]^{\cdot+}$ calculated for $C_{16}H_{16}^{\cdot+}$, 208.124; found 208.1247

Hepta-1,4,5-trien-4-ylbenzene (I.3.1g)



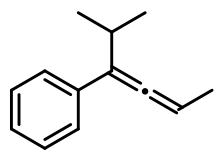
1g

Following the general procedure B, compound **I.3.1g** was prepared after 16 hours reaction time and after column chromatography (100% heptane) in 4.1% yield as colorless oil.

The spectroscopic properties were in accordance with those reported in the literature.[17]

(2-methylhexa-3,4-dien-3-yl)benzene (I.3.1h)

Following the general procedure B, compound **I.3.1h** was prepared after 16 hours reaction time and after column chromatography (100% heptane) in 85% yield as colorless oil.



I.3.1h

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44 – 7.36 (m, 2H), 7.36 – 7.23 (m, 2H), 7.21-7.16 (m, 1H), 5.50 (qd, *J* = 6.9, 2.3 Hz, 1H), 2.87-2.76 (m, 1H), 1.77 (d, *J* = 7.0 Hz, 3H), 1.13 (t, *J* = 6.7 Hz, 6H)

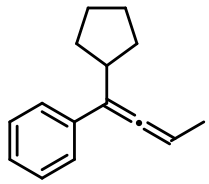
^{13}C NMR (100 MHz, $CDCl_3$) δ 203.9, 137.6, 128.4, 126.7, 126.4, 112.6, 89.9, 28.1, 22.7, 22.4, 14.7

IR (neat): ν_{max} = 3026, 2962, 2925, 2868, 1942, 1596, 1493, 1458, 1381, 1294, 1078, 1032 cm^{-1}

HRMS (EI): $[M]^{\cdot+}$ calculated for $C_{13}H_{16}^{\cdot+}$, 172.1247; found 172.0880; **$[M\text{-}C_3H_4]^{\cdot+}$** calculated for $C_{10}H_{12}^{\cdot+}$, 132.0934; found 132.0922

(1-cyclopentylbuta-1,2-dien-1-yl)benzene (I.3.1i)

Following the general procedure B, compound **I.3.1i** was prepared after 5 hours reaction time and after column chromatography (100% heptane) in 55% yield as colorless oil.



I.3.1i

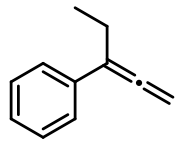
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.50 – 7.36 (m, 2H), 7.30 (appt, *J* = 7.7 Hz, 2H), 7.17 (appt, *J* = 7.3 Hz, 1H), 5.48 (qd, *J* = 6.9, 2.7 Hz, 1H), 2.96 (pd, *J* = 7.4, 2.6 Hz, 1H), 2.02 – 1.87 (m, 2H), 1.76 (d, *J* = 7.0 Hz, 3H), 1.72 – 1.44 (m, 6H)

^{13}C NMR (150 MHz, $CDCl_3$) δ 203.6, 138.1, 128.3, 126.7, 126.4, 110.4, 89.8, 39.3, 32.8, 32.5, 25.3, 25.2, 14.6

IR (neat): ν_{max} = 3025, 2948, 2864, 1943, 1684, 1596, 1492, 1447, 1368, 1074 cm^{-1}

HRMS (EI): $[M]^{\cdot+}$ calculated for $C_{15}H_{18}^{\cdot+}$, 198.1403; found 198.1403

Penta-1,2-dien-3-ylbenzene (I.3.1j)



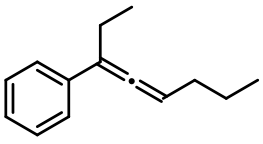
I.3.1j

Following the general procedure B, compound **I.3.1j** was prepared after 4 hours reaction time and after column chromatography (100% pentane) in 60% yield as colorless oil.

The spectroscopic properties were in accordance with those reported in the literature.[18]

Octa-3,4-dien-3-ylbenzene (I.3.1k)

Following the general procedure B, compound **I.3.1k** was prepared after 3 hours reaction time and after column chromatography (100% pentane) in 59% yield as colorless oil.



I.3.1k

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44–7.41 (m, 2H), 7.33–7.28 (m, 2H), 7.20–7.16 (m, 1H), 5.58–5.53 (m, 1H), 2.47–2.40 (m, 2H), 2.14–2.09 (m, 2H), 1.55–1.49 (m, 2H), 1.16 (*t*, J = 7.3 Hz, 3H), 0.98 (t, *J* = 7.4 Hz, 3H)

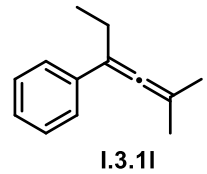
^{13}C NMR (100 MHz, $CDCl_3$) δ 203.8, 137.8, 128.4, 126.4, 126.0, 107.4, 95.1, 31.5, 23.0, 22.8, 14.0, 12.8

IR (neat): ν_{max} = 3424 (bs), 2961, 2933, 2873, 1950, 1720, 1687, 1598, 1493, 1450, 1378, 1263, 1220, 1126, 1076, 951, 748, 698 cm^{-1}

MS (ESI): $[M+OH]^+$ calculated for $C_{14}H_{19}O^+$, 203.1430; found 203.1426

(5-methylhexa-3,4-dien-3-yl)benzene (I.3.1l)

Following the general procedure B, compound **I.3.1l** was prepared after 5 hours reaction time and after column chromatography (100% heptane) in 87% yield as colorless oil.



I.3.1l

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38 (dt, *J* = 8.2, 1.6 Hz, 2H), 7.33 – 7.26 (m, 2H), 7.21 – 7.14 (m, 1H), 2.40 (q, *J* = 7.3 Hz, 2H), 1.82 (s, 6H), 1.11 (t, *J* = 7.3 Hz, 3H)

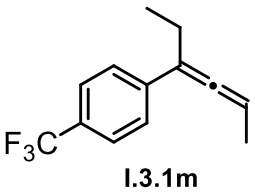
^{13}C NMR (100 MHz, $CDCl_3$) δ 201.7, 138.7, 128.3, 126.2, 126.1, 105.4, 99.1, 23.3, 20.6, 12.8

IR (neat): ν_{max} = 3082, 3026, 2965, 2931, 2905, 2853, 1951, 1597, 1491, 1445, 1386, 1183 cm^{-1}

HRMS (EI): $[M]^{\cdot+}$ calculated for $C_{13}H_{16}^{\cdot+}$, 172.1247; found 172.1248

1-(hexa-3,4-dien-3-yl)-4-(trifluoromethyl)benzene (I.3.1m)

Following the general procedure B, compound **I.3.1m** was prepared after 4 hours reaction time and after column chromatography (100% heptane) in 65% yield as colorless oil.



I.3.1m

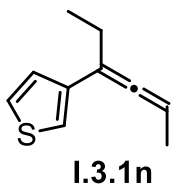
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.54 (d, *J* = 8.3 Hz, 2H), 7.48 (d, *J* = 8.4 Hz, 2H), 5.76 – 5.45 (m, 1H), 2.58 – 2.30 (m, 2H), 1.79 (d, *J* = 7.0 Hz, 3H), 1.14 (t, *J* = 7.3 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 205.32 (s), 141.72 (s), 128.95 (s), 128.55 (s), 126.18 (s), 126.1 (s), 125.89 (s), 125.29 (dd, *J* = 7.6, 3.8 Hz), 106.35 (s), 90.38 (s), 22.91 (s), 14.34 (s), 12.62 (s).

HRMS (EI): $[M]^{\cdot+}$ calculated for $C_{13}H_{13}F_3^{\cdot+}$, 226.0964; found 226.0966

3-(hexa-3,4-dien-3-yl)thiophene (I.3.1n)

Following the general procedure C, compound **I.3.1n** was prepared after 4 hours reaction time and after column chromatography (100% heptane) in 72% yield (0.72 mmol) as yellow oil.



I.3.1n

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.13 (dd, *J* = 5.0, 2.9 Hz, 1H), 7.01 (dd, *J* = 5.0, 1.3 Hz, 1H), 6.96 – 6.87 (m, 1H), 5.42 – 5.32 (m, 1H), 2.36 – 2.20 (m, 3H), 1.66 (d, *J* = 7.0 Hz, 4H), 1.04 (t, *J* = 7.4 Hz, 4H).

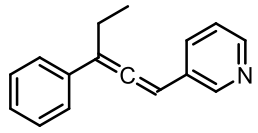
^{13}C NMR (101 MHz, $CDCl_3$) δ 204.4, 139.7, 127.1, 125.1, 118.3, 103.3, 89.3, 23.7, 14.7, 12.5.

HRMS (EI): $[M]^{\bullet+}$ calculated for $C_{10}H_{12}S^{\bullet+}$, 164.0654; found 164.0651

IR (neat): ν_{max} = 3106, 2966, 2931, 2873, 1948, 1456, 1371, 1237, 1080 cm^{-1}

3-(3-phenylpenta-1,2-dien-1-yl)pyridine (I.3.1o)

Following the general procedure B, compound **I.3.1n** was prepared after 4 hours reaction time and after column chromatography (heptane : EtOAc 1:1) in 54% yield (0.54 mmol) as yellow oil.



I.3.1o

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.50 (d, J = 1.8 Hz, 1H), 8.36 (dd, *J* = 1.6 + 4.8 Hz, 1H,), 7.56–7.53 (m, 1H), 7.37–7.34 (m, 2H), 7.27–7.23 (m, 2H), 7.18–7.12 (m, 2H), 6.48–6.46 (m, 1H), 2.61–2.45 (m, 2H), 1.12 (t, *J* = 7.3 Hz, 3H)

^{13}C NMR (100 MHz, $CDCl_3$) δ 206.9, 148.4), 148.3, 135.8, 133.5, 130.9, 128.7, 127.5, 126.2, 123.7, 112.7, 95.4, 23.3, 12.7

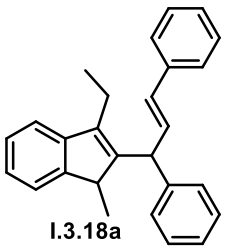
HRMS (ESI): $[M+H]^+$ calculated for $C_{16}H_{16}N^+$ 222.1277, found 222.1277

IR (neat): ν_{max} = 3055, 3028, 2965, 2931, 2874, 1934, 1571, 1493, 1479, 1454, 1426, 1025, 831, 751, 706, 693, 631 cm^{-1}

I.6.5 Synthesis of Allylation Products I.3.18a-I.3.18m

(E)-2-(1,3-diphenylallyl)-3-ethyl-1-methyl-1H-indene (I.3.18a)

Following the general procedure C, compound **I.3.18a** was prepared after 5 minutes reaction time and after column chromatography (100% heptane) in 84% yield (0.17 mmol) as colorless oil (1:1 diastereomeric mixture).


I.3.18a

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43 – 6.96 (m, 28H), 6.65-6.59 (m, 2H), 6.42-6.37 (m, 2H), 4.88-4.80 (m, 2H), 3.39 (q, *J* = 7.5 Hz, 1H), 3.20 (q, *J* = 7.4 Hz,

1H), 2.54 (q, *J* = 7.5 Hz, 2H), 2.47 (q, *J* = 7.5 Hz, 2H), 1.24 (d, *J* = 7.5 Hz, 3H), 1.09-1-02 (m, 9H)

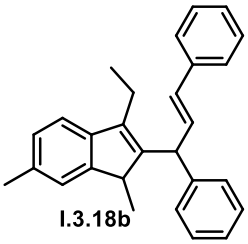
^{13}C NMR (100 MHz, $CDCl_3$) δ 149.0, 146.6, 146.4, 144.7, 144.6, 143.4, 142.9, 140.5, 139.9, 137.6, 137.5, 131.6, 131.5, 131.4, 130.8, 128.7, 128.5, 128.5, 128.4, 128.2, 127.5, 127.4, 126.5, 126.4, 126.4, 126.4, 124.6, 124.5, 122.5, 119.0, 118.9, 47.5, 47.4, 46.0, 45.5, 19.3, 19.2, 16.9, 13.5, 13.4

IR (neat): ν_{max} = 3025, 2965, 2930, 2871, 1734, 1701, 1599, 1492, 1449, 1373, 1177, 1156, 1070, 1045 cm^{-1}

HRMS (EI): $[M]^{\cdot+}$ calculated for $C_{27}H_{26}^{\cdot+}$, 350.2029; found 350.2027

(E)-2-(1,3-diphenylallyl)-3-ethyl-1,6-dimethyl-1H-indene (I.3.18b)

Following the general procedure C, compound **I.3.18b** was prepared after 5 minutes reaction time and after column chromatography (heptane / ethyl acetate 9:1) in 82 % yield (0.123 mmol) as colorless oil (1:1 diastereomeric mixture).


I.3.18b

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33-7.29 (m, 4H), 7.26-6.99 (m, 22H), 6.65-6.59 (m, 2H), 6.42-6.36 (m, 2H), 4.87-4.78 (m, 2H), 3.36 (q, *J* = 7.5 Hz, 1H), 3.18 (q, *J* = 7.5 Hz, 1H), 2.53 (q, *J* = 7.5 Hz, 2H), 2.45 (q, *J* = 7.5 Hz, 2H), 2.31 (s, 3H), 2.30 (s, 3H), 1.24 (d, *J* = 7.5 Hz, 3H), 1.08-1.02 (m, 9H)

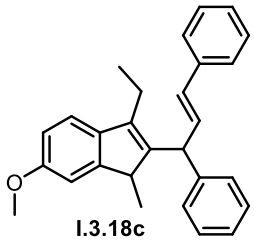
^{13}C NMR (100 MHz, $CDCl_3$) δ 149.3, 145.5, 145.3, 143.5, 143.0, 142.1, 142.0, 140.3, 139.7, 137.7, 137.6, 134.3, 134.2, 131.7, 131.5, 131.3, 130.9, 128.7, 128.5, 128.4, 128.3, 128.2, 127.4, 127.4, 127.1, 127.1, 126.4, 126.3, 123.5, 118.7, 47.5, 47.4, 45.8, 45.3, 21.6, 19.4, 19.2, 17.0, 16.9, 13.5, 13.4

IR (neat): ν_{max} = 3026, 2965, 2929, 2871, 1701, 1600, 1492, 1450, 1374, 1070 cm^{-1}

HRMS (EI): $[M]^{\cdot+}$ calculated for $C_{28}H_{28}^{\cdot+}$, 364.2186; found 364.2184

(E)-2-(1,3-diphenylallyl)-3-ethyl-6-methoxy-1-methyl-1H-indene (I.3.18c)

Following the general procedure C, compound **I.3.18c** was prepared after 5 minutes reaction time and after preparative HPLC in 86 % yield (0.172 mmol) as colorless oil (1.9:1 diastereomeric mixture).


I.3.18c

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.47-7.42 (m, 3.1H), 7.38-7.24 (m, 13.8H), 6.99 (d, *J* = 2.3 Hz, 1H), 6.96 (d, *J* = 2.3 Hz, 0.54H), 6.90-6.86 (m, 1.54H), 6.78-6.72 (m, 1.54H), 6.55-6.50 (m, 1.54H), 4.98 (d, *J* = 7.3 Hz, 0.54H), 4.91 (d, *J* = 8.1 Hz, 1H), 3.87 (s, 3H), 3.86 (s, 1.62H), 3.49 (q, *J* = 7.5 Hz, 1H), 3.30 (q, *J* =7.4 Hz, 0.54H), 2.65 (q, *J* = 7.5 Hz, 2H), 2.58 (q, *J* = 7.5 Hz, 1.1H), 1.37 (d, 7.5 Hz, 1.62H), 2.21-1.16 (m, 7.62H)

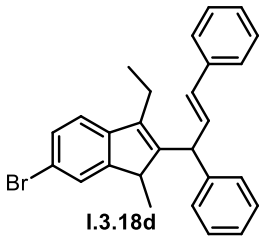
^{13}C NMR (100 MHz, $CDCl_3$) δ 158.0, 150.8, 144.3, 144.2, 143.5, 143.1, 140.0, 139.4, 137.8, 137.7, 137.7, 137.6, 131.7, 131.5, 131.3, 131.0, 128.7, 128.5, 128.4, 128.3, 128.2, 127.4, 127.3, 126.4, 126.4, 119.3, 111.6, 111.5, 109.6, 55.8, 47.5, 47.4, 45.9, 45.5, 19.4, 19.2, 17.2, 17.1, 13.5, 13.4

IR (neat): ν_{max} = 3025, 2964, 2932, 2871, 2834, 1701, 1602, 1582, 1481, 1451, 1430, 1355, 1285, 1238, 1154, 1141, 1127, 1091, 1064 cm^{-1}

HRMS (EI): $[M]^{\bullet+}$ calculated for $C_{28}H_{28}O^{\bullet+}$, 380.2135; found 380.2143

(E)-6-bromo-2-(1,3-diphenylallyl)-3-ethyl-1-methyl-1H-indene (I.3.18d)

Following the general procedure C, compound **I.3.18d** was prepared after 20 minutes reaction time and after preparative TLC (heptane / ethyl acetate 100:1) in 40 % yield (0.06 mmol) as colorless oil (1.3:1 diastereomeric mixture).


I.3.18d

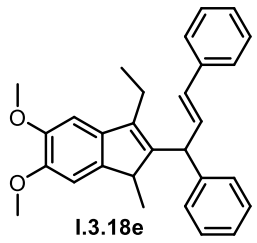
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.48-7.17 (m, 22.8H), 6.74-6.68 (m, 1.75H), 6.53-6.48 (m, 1.75H), 4.97 (d, *J* = 7.4 Hz, 0.75H), 4.90 (d, *J* = 8.1 Hz, 1H), 3.49 (q, *J* = 7.5 Hz, 1H), 3.31 (q, *J* = 7.4 Hz, 0.75H), 2.63 (q, *J* = 7.4 Hz, 2H), 2.55 (q, *J* = 7.4 Hz, 1.5H), 1.35 (d, *J* = 7.5 Hz, 2.25H), 1.19-1.11 (m, 8.25H)

^{13}C NMR (100 MHz, $CDCl_3$) δ 151.1, 147.1, 146.9, 143.7, 143.6, 143.1, 142.5, 139.9, 139.4, 137.5, 137.4, 131.8, 131.6, 131.1, 130.4, 129.5, 129.4, 128.8, 128.6, 128.5, 128.3, 128.1, 127.6, 127.5, 126.6, 126.4, 126.4, 125.9, 120.3, 118.6, 47.5, 47.4, 46.00, 45.6, 19.2, 19.1, 16.8, 13.4, 13.3

IR (neat): ν_{max} = 3026, 2966, 2929, 2873, 1702, 1598, 1493, 1459, 1408, 1374, 1269, 1156, 1059, 1030 cm^{-1}

HRMS (EI): $[M]^{\cdot+}$ calculated for $C_{27}H_{25}Br^{\cdot+}$, 428.1134; found 428.1122

(E)-2-(1,3-diphenylallyl)-3-ethyl-5,6-dimethoxy-1-methyl-1H-indene (I.3.18e)


I.3.18e

Following the general procedure C, compound **I.3.18e** was prepared after 5 minutes reaction time and after preparative HPLC in 93 % yield (0.14 mmol) as slightly yellow oil (2.5:1 diastereomeric mixture).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42-7.38 (m, 2.81H), 7.34-7.20 (m, 11.26H), 6.95 (s, 1H), 6.92 (s, 0.41H), 6.89 (s, 1H), 6.87 (s, 0.41H), 6.73-6.67 (m, 1.41H), 6.51-6.45 (m, 1.41H), 4.93 (d, *J* = 7.3 Hz, 0.41H), 4.87 (d, *J* =8.1 Hz, 1H), 3.94 (s, 3H), 3.93 (s, 1.23H), 3.90 (s, 3H), 3.89 (s, 1.23H), 3.42 (q, *J* =7.5 Hz, 1H), 3.24 (q, *J* =7.4 Hz, 0.41H), 2.61 (q, *J* =7.5 Hz, 2H), 2.53 (q, *J* = 7.5 Hz, 0.82H), 1.32 (d, *J* = 7.5 Hz, 1.23H), 1.17-1-12 (m, 7.23H)

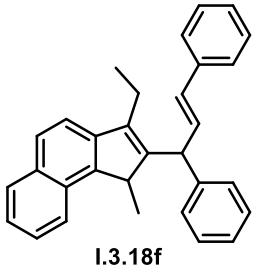
^{13}C NMR (100 MHz, $CDCl_3$) δ 148.5, 147.3, 145.3, 145.1, 143.6, 143.1, 141.5, 140.0, 139.4, 137.6, 137.6, 137.4, 137.3, 131.7, 131.5, 131.3, 131.0, 128.7, 128.5, 128.4, 128.3, 128.2, 127.4, 127.4, 126.4, 126.3, 107.3, 103.2, 56.6, 56.5, 47.6, 47.5, 45.9, 45.4, 19.4, 19.2, 17.2, 13.6, 13.5

IR (neat): ν_{max} = 2967, 2935, 2872, 2834, 1701, 1601, 1494, 1452, 1366, 1207, 1175, 1135, 1083 cm^{-1}

HRMS (ESI): $[M+Na]^+$ calculated for $C_{29}H_{30}O_2Na^+$, 433.2138; found 433.2140

(E)-2-(1,3-diphenylallyl)-3-ethyl-1-methyl-1H-cyclopenta[a]naphthalene (I.3.18f)

Following the general procedure C, compound **I.3.18f** was prepared after 5 minutes reaction time and after preparative HPLC in 84 % yield (0.125 mmol) as white solid (2.6:1 diastereomeric mixture, 3.3:1 after preparative HPLC).


I.3.18f

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.84-7.77 (m, 2.6H), 7.72 (d, *J* = 8.4 Hz, 1H), 7.71 (d, *J* = 8.3 Hz, 0.3H), 7.47-7.43 (m, 1.3H), 7.39-7.11 (m, 15.6H), 6.73-6.63 (m, 1.3H), 6.47-6.39 (m, 1.3H), 4.93 (d, *J* = 7.6 Hz, 0.3H), 4.87 (d, *J* = 8 Hz, 1H), 3.76 (q, *J* = 7.4 Hz, 1H), 3.72 (q, *J* = 7.4 Hz, 0.3H), 2.63 (q, *J* = 7.5 Hz, 2H), 2.51 (qd, *J* = 7.6, 2.6 Hz, 0.6H), 1.43 (d, *J* = 7.4 Hz, 0.9H), 1.28 (d, *J* = 7.4 Hz, 3H), 1.09-1.04 (m, 3.9H)

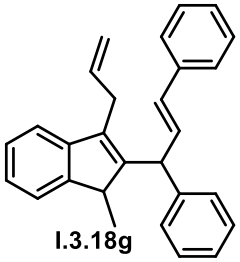
^{13}C NMR (100 MHz, $CDCl_3$) δ 147.5, 147.3, 144.3, 144.3, 143.6, 143.1, 142.1, 141.9, 140.6, 140.0, 137.6, 132.0, 131.9, 131.4, 131.2, 129.3, 129.3, 128.8, 128.5, 128.4, 128.3, 127.5, 126.5, 126.4, 126.4, 126.0, 126.0, 124.2, 123.7, 123.6, 118.8, 47.9, 47.7, 46.0, 45.5, 19.6, 19.4, 18.3, 18.2, 13.6, 13.5

IR (neat): ν_{max} = 3080, 3055, 3025, 2967, 2931, 2871, 1599, 1583, 1516, 1493, 1449, 1372, 1310, 1264, 1240, 1210, 1180, 1153, 1074, 1060, 1029 cm^{-1}

HRMS (EI): $[M]^{\cdot+}$ calculated for $C_{31}H_{28}^{\cdot+}$, 400.2186; found 400.2183

<u>(E)-3-allyl-2-(1,3-diphenylallyl)-1-methyl-1H-indene (I.3.18g)</u>

Following the general procedure C, compound **I.3.18g** was prepared after 5 minutes reaction time and after preparative TLC (heptane / ethyl acetate 75:1) in 43 % yield (0.013 mmol) as colorless oil (1:1 diastereomeric mixture).



^{1}H NMR (600 MHz, $CDCl_3$) δ 7.40-7.15 (m, 28H), 6.72-6.67 (m, 2H), 6.49-6.43 (m, 2H), 5.94-5.85 (m, 2H), 5.10-5.02 (m, 4H), 4.97 (d, *J* = 7.4 Hz, 1H), 4.90 (d, *J* = 8.2 Hz, 1H), 3.50 (q, *J* = 7.5 Hz, 1H), 3.39-3.29 (m, 5H), 1.34 (d, *J* = 7.5 Hz, 3H), 1.19 (d, *J* = 7.6 Hz, 3H)

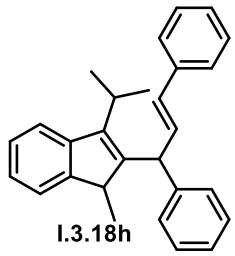
^{13}C NMR (150 MHz, $CDCl_3$) δ 148.7, 148.5, 148.4, 144.8, 144.7, 143.2, 142.6, 137.5, 137.5, 136.1, 135.5, 135.4, 135.4, 131.7, 131.6, 131.4, 130.5, 128.7, 128.5, 128.5, 128.4, 128.2, 127.5, 127.4, 126.5, 126.5, 126.4, 126.4, 126.4, 124.7, 124.7, 122.4, 119.4, 119.4, 116.2, 47.6, 47.4, 46.1, 45.7, 30.5, 30.4, 17.00, 16.9

IR (neat): ν_{max} = 3026, 2963, 2927, 2869, 1728, 1703, 1639, 1600, 1493, 1450, 1411, 1372, 1261, 1205, 1181, 1156, 1092, 1020 cm^{-1}

HRMS (EI): $[M]^{\cdot+}$ calculated for $C_{28}H_{26}^{\cdot+}$, 362.2029; found 362.2015

(E)-2-(1,3-diphenylallyl)-3-isopropyl-1-methyl-1H-indene (I.3.18h)

Following the general procedure C, compound **I.3.18h** was prepared after 15 minutes reaction time and after preparative HPLC in 85 % yield (0.127 mmol) as colorless oil (1:1 diastereomeric mixture).


I.3.18h

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.55-7.52 (m, 2H), 7.43-7.14 (m, 26H), 6.73-6.66 (m, 2H), 6.51 (d, *J* = 15.6 Hz, 2H), 7.98-7.93 (m, 2H), 3.52 (q, *J* =7.5 Hz, 1H), 3.26 (q, *J* =7.5 Hz, 1H), 3.21-3.10 (m, 2H), 1.42-1.38 (m, 6H), 1.34 (d, *J* = 7.5 Hz, 3H), 1.28 (d, *J* = 7.0 Hz, 3H), 1.23-1.20 (m, 6H)

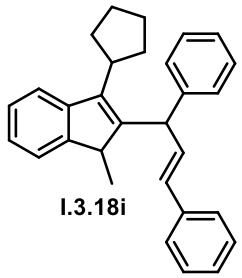
^{13}C NMR (100 MHz, $CDCl_3$) δ 149.7, 149.7, 145.9, 145.7, 143.9, 143.6, 143.4, 143.3, 143.3, 143.0, 137.6, 137.6, 132.0, 131.5, 131.3, 130.6, 128.8, 128.4, 128.4, 128.3, 128.0, 127.5, 127.4, 126.4, 126.3, 126.1, 124.2, 124.2, 122.8, 122.8, 121.4, 121.3, 47.2, 47.1, 46.2, 45.5, 27.5, 27.4, 21.1, 21.1, 20.4, 17.0, 16.8

IR (neat): ν_{max} = 3081, 3058, 3024, 2961, 2928, 2870, 1599, 1492, 1463, 1448, 1383, 1364, 1308, 1265, 1181, 1155, 1119, 1103, 1073, 1028 cm^{-1}

HRMS (EI): $[M]^{\cdot+}$ calculated for $C_{28}H_{28}^{\cdot+}$, 364.2186; found 364.2172

(E)-3-cyclopentyl-2-(1,3-diphenylallyl)-1-methyl-1H-indene (I.3.18i)

Following the general procedure C, compound **I.3.18i** was prepared after 25 minutes reaction time and after preparative HPLC in 93 % yield (0.052 mmol) as colorless oil (1:1 diastereomeric mixture).


I.3.18i

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.54 – 7.09 (m, 28H), 6.70 (dt, *J* = 15.8, 7.2 Hz, 2H), 6.58 – 6.43 (m, 2H), 4.97-4.94 (m, 2H), 3.53 (q, *J* = 7.5 Hz, 1H), 3.37 – 3.09 (m, 3H), 2.13 – 1.77 (m, 10H), 1.77 – 1.51 (m, 6H), 1.34 (d, *J* = 7.5 Hz, 3H), 1.21 (d, *J* = 7.5 Hz, 3H)

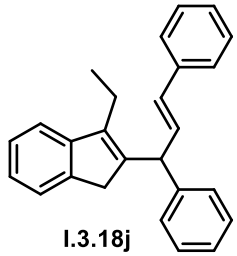
^{13}C NMR (100 MHz, $CDCl_3$) δ 149.7, 149.6, 147.2, 147.0, 143.5, 143.2, 143.0, 141.6, 141.2, 137.6, 137.6, 132.0, 131.4, 131.4, 131.0, 128.8, 128.4, 128.4, 128.3, 128.0, 127.5, 127.4, 126.4, 126.4, 126.3, 126.0, 124.2, 122.9, 122.8, 120.8, 120.8, 47.2, 47.1, 46.2, 45.6, 38.7, 30.8, 30.2, 30.2, 27.0, 27.0, 26.9, 16.9, 16.8

IR (neat): ν_{max} = 3080, 3058, 3024, 2954, 2868, 1559, 1492, 1448, 1264, 1028, 955 cm^{-1}

HRMS (EI): $[M]^{\cdot+}$ calculated for $C_{30}H_{30}^{\cdot+}$, 390.2342; found 390.2334

(E)-2-(1,3-diphenylallyl)-3-ethyl-1H-indene (I.3.18j)

Following the general procedure C, compound **I.3.18j** was prepared after 20 minutes reaction time and after preparative HPLC in 52 % yield (0.052 mmol) as colorless oil.


I.3.18j

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45 – 7.19 (m, 13H), 7.15 (td, *J* = 7.4, 1.1 Hz, 1H), 6.65 (dd, *J* = 15.8, 7.0 Hz, 1H), 6.45 (d, *J* =15.8 Hz, 1H), 5.00 (d, *J* = 7.0 Hz, 1H), 3.42 (d, *J* = 22.6 Hz, 1H), 3.13 (d, *J* = 22.6 Hz, 1H), 2.70 (q, *J* = 7.6 Hz, 1H), 1.22 (t, *J* = 7.6 Hz, 1H)

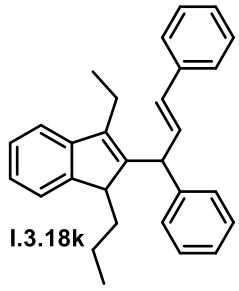
^{13}C NMR (100 MHz, $CDCl_3$) δ 146.0, 143.6, 143.4, 142.2, 140.7, 137.5, 131.6, 131.4, 128.7, 128.6, 128.3, 127.5, 126.6, 126.4, 126.3, 124.3, 123.7, 119.0, 47.4, 38.4, 18.9, 13.8

IR (neat): ν_{max} = 3024, 2966, 2931, 2872, 1599, 1493, 1462, 1449, 1394, 1029 cm^{-1}

HRMS (EI): $[M]^{\cdot+}$ calculated for $C_{26}H_{24}^{\cdot+}$, 336.1873; found 336.1871

(E)-2-(1,3-diphenylallyl)-3-ethyl-1-propyl-1H-indene (I.3.18k)

Following the general procedure C, compound **I.3.18k** was prepared after 5 minutes reaction time and after preparative HPLC in 96 % yield (0.144 mmol) as slightly yellow oil (1.2:1 diastereomeric mixture).


I.3.18k

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31-7.03 (m, 25.66H), 6.67-6.57 (m, 1.83H), 6.43 (d, *J* = 15.8 Hz, 1H), 6.34 (d, *J* = 15.8 Hz, 0.83H), 4.85 (d, *J* = 8.0 Hz, 1H), 4.72 (d, *J* = 7.9 Hz, 0.83H), 3.41-3.38 (m, 0.83H), 3.33-3.30 (m, 1H), 2.63-2.52 (m, 1.66 H), 2.50-2.38 (m, 2H), 1.96-1.77 (m, 1.83H), 1.67-1.45 (m, 1.83H), 1.20-0.77 (m, 9.15H), 0.78 (t, *J* = 7.3 Hz, 3H), 0.61 (t, *J* = 7.3 Hz, 2.49H)

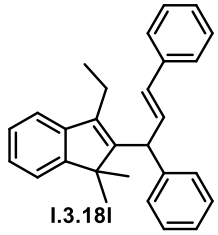
^{13}C NMR (150 MHz, $CDCl_3$) δ 147.5, 147.4, 145.7, 145.5, 144.9, 144.7, 143.3, 142.9, 141.1, 140.6, 137.6, 131.8, 131.3, 131.1, 130.7, 128.7, 128.5, 128.5, 128.3, 128.3, 127.4, 127.4, 126.5, 126.4, 126.4, 126.3, 124.3, 124.3, 122.8, 122.8, 118.9, 118.9, 51.1, 50.4, 48.0, 47.8, 32.7, 32.6, 19.6, 19.3, 18.4, 18.0, 14.4, 14.4, 13.5, 13.4

IR (neat): ν_{max} = 3024, 2957, 2930, 2870, 1599, 1492, 1463, 1449, 1376, 1074 cm^{-1}

HRMS (EI): $[M]^{\cdot+}$ calculated for $C_{29}H_{30}^{\cdot+}$, 378.2342; found 378.2348

(E)-2-(1,3-diphenylallyl)-3-ethyl-1,1-dimethyl-1H-indene (I.3.18l)

Following the general procedure C, compound **I.3.18l** was prepared after 5 minutes reaction time and after preparative HPLC in 95 % yield (0.19 mmol) as white solid.



^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43 – 7.00 (m, 14H), 6.53 (dd, *J* = 15.8, 7.7 Hz, 1H), 6.36 (d, *J* = 15.8 Hz, 1H), 4.58 (d, *J* = 7.7 Hz, 1H), 2.33 (q, *J* = 7.5 Hz, 2H), 1.25 (s, 3H), 1.25 (s, 3H), 0.85 (t, *J* = 7.5 Hz, 3H)

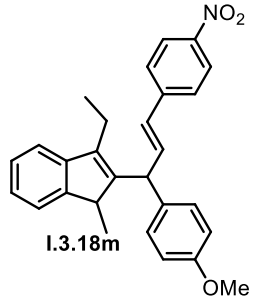
^{13}C NMR (150 MHz, $CDCl_3$) δ 153.3, 150.0, 143.6, 143.0, 138.6, 137.6, 131.6, 131.0, 128.7, 128.4, 128.3, 127.4, 126.5, 126.3, 124.8, 121.3, 119.3, 51.0, 45.7, 25.0, 24.6, 20.1, 12.5

IR (neat): ν_{max} = 3080, 3024, 2960, 2927, 2873, 2860, 1599, 1492, 1469, 1449, 1378, 1358, 1265, 1156, 1073, 1029 cm^{-1}

HRMS (EI): $[M]^{\cdot+}$ calculated for $C_{28}H_{28}^{\cdot+}$, 364.2186; found 364.2187

(E)-3-ethyl-2-(1-(4-methoxyphenyl)-3-(4-nitrophenyl)allyl)-1-methyl-1H-indene (I.3.18m)

Following the general procedure C, compound **I.3.18m** was prepared after 5 minutes reaction time and after preparative HPLC in 82 % yield (0.082 mmol) as yellow oil (1:1 diastereomeric mixture).



^{1}H NMR (400 MHz, $CDCl_3$) δ 8.20-8.16 (m, 4H), 7.51 (apptt, 8.5, 2 Hz, 4H), 7.36-7.27 (m, 6H), 7.24-7.17 (m, 6H), 6.94-6.85 (m, 6H), 6.55-6.48 (m, 6H), 4.95 (d, *J* = 7.2 Hz, 1H), 4.89 (d, *J* = 7.9 Hz, 1H), 3.82 (s, 3H), 3.80 (s, 3H), 3.44 (q, *J* = 7.5 Hz, 1H), 3.31 (q, *J* = 7.5 Hz, 1H), 2.66-2.54 (m, 4H), 1.32 (d, *J* = 7.5 Hz, 3H), 1.20 (d, *J* = 7.5 Hz, 3H), 1.17-1.12 (m, 6H)

^{13}C NMR (100 MHz, $CDCl_3$) δ 158.5, 158.5, 148.8, 146.9, 146.9, 145.8, 145.6, 144.5, 144.4, 144.1, 144.0, 140.9, 140.2, 137.3, 136.6, 134.4, 133.9, 129.3, 129.3, 129.2, 129.2, 126.8, 126.8, 126.6, 124.8, 124.8, 124.2, 122.6, 122.6, 119.1, 114.0, 55.4, 47.0, 46.8, 45.8, 45.7, 19.4, 19.3, 17.0, 16.9, 13.6, 13.5

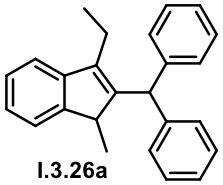
IR (neat): ν_{max} = 2964, 2931, 2871, 2836, 1642, 1596, 1510, 1462, 1339, 1301, 1247, 1177, 1109, 1035 cm^{-1}

HRMS (ESI): $[M+Na]^+$ calculated for $C_{28}H_{27}NO_3Na^+$, 448.1889; found 448.1890

I.6.6 Synthesis of Benzylation Products I.3.26a-I.3.26g

2-benzhydryl-3-ethyl-1-methyl-1H-indene (I.3.26a)

Following the general procedure D, compound **I.3.26a** was prepared after 1 hour reaction time and after preparative TLC (100% heptane) in 90 % yield (0.135 mmol) as colorless oil.


I.3.26a

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45 – 7.16 (m, 14H), 5.54 (s, 1H), 3.37 (q, *J* = 7.5 Hz, 1H), 2.56 – 2.26 (m, 2H), 1.26 (d, *J* = 7.5 Hz, 3H), 0.92 (t, *J* = 7.5 Hz, 3H)

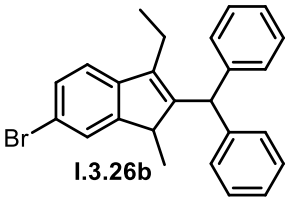
^{13}C NMR (150 MHz, $CDCl_3$) δ 149.0, 146.9, 144.9, 143.5, 142.7, 140.7, 129.6, 129.4, 128.4, 128.4, 126.4, 126.4, 126.4, 124.6, 122.5, 119.0, 50.4, 46.6, 19.3, 17.0, 12.7

IR (neat): ν_{max} = 3032, 2964, 2929, 2870, 1600, 1493, 1450, 1372, 1076, 1031, 1018 cm^{-1}

HRMS (EI): $[M]^{\cdot+}$ calculated for $C_{25}H_{24}^{\cdot+}$, 324.1873; found 324.1878

2-benzhydryl-6-bromo-3-ethyl-1-methyl-1H-indene (I.3.26b)

Following the general procedure D, compound **I.3.26b** was prepared after 48 hours reaction time at 40 °C and after preparative HPLC in 77 % yield (0.116 mmol) as colorless oil.



I.3.26b

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42 (d, *J* = 1.8 Hz, 1H), 7.39 (dd, *J* = 8.0, 1.5 Hz, 1H), 7.32 – 7.12 (m, 11H), 5.45 (s, 1H), 3.30 (q, *J* = 7.4 Hz, 1H), 2.42 – 2.20 (m, 2H), 1.18 (d, *J* = 7.5 Hz, 3H), 0.83 (t, *J* = 7.5 Hz, 3H)

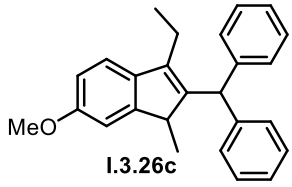
^{13}C NMR (100 MHz, $CDCl_3$) δ 151.1, 147.5, 143.8, 143.1, 142.4, 140.2, 129.5, 129.4, 129.3, 128.5, 128.4, 126.6, 126.6, 125.9, 120.3, 118.6, 50.4, 46.6, 19.2, 16.9, 12.6

IR (neat): ν_{max} = 3083, 3060, 3024, 2966, 2929, 2873, 1599, 1493, 1454, 1408, 1373, 1271, 1141, 1076, 1059, 1031 cm^{-1}

HRMS (EI): $[M]^{\cdot+}$ calculated for $C_{25}H_{23}Br^{\cdot+}$, 402.0978; found 402.0944

2-benzhydryl-3-ethyl-6-methoxy-1-methyl-1H-indene (I.3.26c)

Following the general procedure D, compound **I.3.26c** was prepared after 1 hour reaction time and after preparative HPLC in 40 % yield (0.04 mmol) as colorless oil.



I.3.26c

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32 – 7.16 (m, 13H), 6.91 (d, *J* = 2.3 Hz, 1H), 6.82 (dd, *J* = 8.2, 2.4 Hz, 1H), 5.45 (s, 1H), 3.82 (s, 3H), 3.28 (q, *J* = 7.4 Hz, 1H), 2.41 – 2.17 (m, 2H), 1.19 (d, *J* = 7.5 Hz, 3H), 0.86 (t, *J* = 7.5 Hz, 3H)

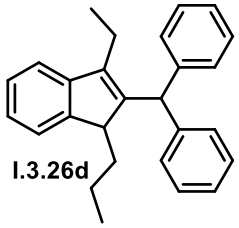
^{13}C NMR (100 MHz, $CDCl_3$) δ 158.0, 150.9, 144.8, 143.6, 142.9, 140.2, 137.9, 129.6, 129.4, 128.3, 128.3, 126.4, 126.4, 119.4, 111.6, 109.5, 55.8, 50.4, 46.5, 19.4, 17.3, 12.7

IR (neat): ν_{max} = 3082, 3059, 3024, 2962, 2929, 2870, 2833, 1604, 1581, 1480, 1452, 1430, 1372, 1356, 1286, 1238, 1180, 1149, 1090, 1076, 1032 cm^{-1}

HRMS (EI): $[M\text{-}OCH_3]^{\cdot+}$ calculated for $C_{25}H_{23}^{\cdot+}$, 323.1794; found 323.1371

2-benzhydryl-3-ethyl-1-propyl-1H-indene (I.3.26d)

Following the general procedure D, compound **I.3.26d** was prepared after 16 hours reaction time and after preparative HPLC in 75 % yield (0.113 mmol) as colorless oil.


I.3.26d

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.60 – 7.08 (m, 14H), 5.47 (s, 1H), 3.44 (dd, *J* = 6.2, 4.3 Hz, 1H), 2.44 – 2.16 (m, 2H), 2.04 – 1.86 (m, 1H), 1.59 – 1.46 (m, 1H), 1.29 – 1.20 (m, 1H), 1.12 – 0.91 (m, 1H), 0.87 (t, *J* = 7.5 Hz, 3H), 0.76 (t, *J* = 7.3 Hz, 3H)

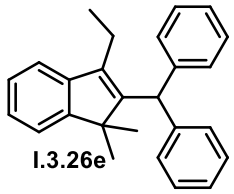
^{13}C NMR (150 MHz, $CDCl_3$) δ 147.5, 145.8, 145.4, 143.5, 143.0, 141.2, 129.5, 129.5, 128.5, 128.3, 126.5, 126.4, 126.3, 124.3, 122.8, 119.0, 51.7, 50.8, 32.7, 19.3, 18.5, 14.4, 12.6

IR (neat): ν_{max} = 3023, 2957, 2929, 2869, 1599, 1493, 1450, 1375, 1076, 1030 cm^{-1}

HRMS (EI): $[M]^{\cdot+}$ calculated for $C_{27}H_{28}^{\cdot+}$, 352.2186; found 352.2188

2-benzhydryl-3-ethyl-1,1-dimethyl-1H-indene (I.3.26e)

Following the general procedure D, compound **I.3.26e** was prepared after 20 minutes reaction time and after preparative HPLC in 34 % yield (0.068 mmol) as colorless oil.


I.3.26e

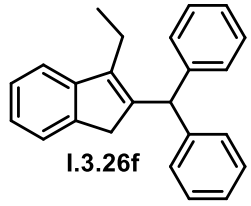
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37 – 7.07 (m, 14H), 5.27 (s, 1H), 2.26 (q, *J* = 7.5 Hz, 2H), 1.27 (s, 6H), 0.53 (t, *J* = 7.5 Hz, 3H)

^{13}C NMR (100 MHz, $CDCl_3$) δ 153.1, 151.1, 143.9, 143.3, 139.0, 129.5, 128.3, 126.5, 126.3, 124.8, 121.3, 119.3, 51.1, 48.5, 25.1, 20.2, 11.3

IR (neat): ν_{max} = 3025, 2959, 2926, 2874, 1600, 1493, 1452, 1378, 1358, 1076, 1031 cm^{-1}

HRMS (EI): $[M]^{\cdot+}$ calculated for $C_{26}H_{26}^{\cdot+}$, 338.2029; found 338.2030

2-benzhydryl-3-ethyl-1H-indene (I.3.26f)


I.3.26f

Following the general procedure D, compound **I.3.26f** was prepared after 48 hours reaction time using 10mol% catalyst and after preparative HPLC in 75 % yield (0.075 mmol) as white solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38 – 6.96 (m, 14H), 5.45 (s, 1H), 3.12 (s, 2H), 2.54 (q, *J* = 7.6 Hz, 2H), 1.04 (t, *J* = 7.6 Hz, 3H)

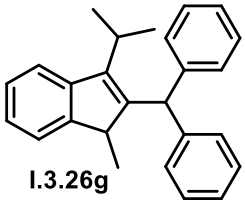
^{13}C NMR (100 MHz, $CDCl_3$) δ 145.9, 144.0, 143.5, 142.5, 141.3, 129.2, 128.4, 126.4, 126.3, 124.3, 123.6, 119.1, 50.0, 39.5, 19.0, 13.6

IR (neat): ν_{max} = 3059, 3023, 2965, 2930, 2872, 1559, 1493, 1461, 1449, 1395, 1075, 1030 cm^{-1}

HRMS (EI): $[M]^{\cdot+}$ calculated for $C_{24}H_{22}^{\cdot+}$, 310.1716; found 310.1723

2-benzhydryl-3-isopropyl-1-methyl-1H-indene (I.3.26g)

Following the general procedure D, compound **I.3.26g** was prepared after 38 hours reaction time and after preparative HPLC in 50 % yield (0.075 mmol) as colorless oil.


I.3.26g

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.52 (d, *J* = 7.6 Hz, 1H), 7.39 – 7.10 (m, 13H), 5.54 (s, 1H), 3.27 (q, *J* = 7.5 Hz, 1H), 2.94 (hept, *J* = 7.1 Hz, 1H), 1.24 – 1.11 (m, 9H)

^{13}C NMR (100 MHz, $CDCl_3$) δ 149.9, 146.2, 144.2, 143.5, 143.2, 142.7, 129.5, 129.4, 128.3, 126.4, 126.4, 126.0, 124.2, 122.7, 121.5, 50.3, 46.4, 27.3, 20.5, 20.4, 17.1

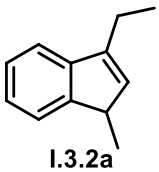
IR (neat): ν_{max} = 3083, 3060, 3023, 2963, 2870, 1600, 1493, 1465, 1450, 1383, 1365, 1155, 1076, 1030 cm^{-1}

HRMS (EI): $[M]^{\cdot+}$ calculated for $C_{26}H_{26}^{\cdot+}$, 338.2029; found 338.2030

I.6.7 Characterisation Data for Products I.3.2a-I.3.2d

3-ethyl-1-methyl-1H-indene (I.3.2a)

Following the general procedure E, compound **I.3.2a** was prepared after 24 hours reaction time and after column chromatography (100% pentane) in 90 % yield (0.18 mmol) as colorless oil.



I.3.2a

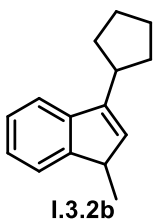
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43 – 7.38 (m, 1H), 7.33 – 7.26 (m, 2H), 7.21 (apptd, *J* = 7.2, 1.5 Hz, 1H), 6.14 (dd, *J* = 3.4, 1.7 Hz, 1H), 3.54 – 3.36 (m, 1H), 2.71 – 2.46 (m, 2H), 1.35 – 1.22 (m, 6H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 150.2, 144.8, 144.5, 134.2, 126.3, 124.8, 122.7, 119.0, 43.7, 20.7, 16.5, 12.5

IR (neat): ν_{max} = 3063, 3016, 2963, 2925, 2869, 2853, 1611, 1460, 1371, 1271, 1078, 1019, 823, 747 cm^{-1}

MS (EI): $[M+H]^+$ calculated for $C_{12}H_{15}^{+}$, 159.1168; found 159.1171

3-cyclopentyl-1-methyl-1H-indene (I.3.2b)



I.3.2b

Following the general procedure E, compound **I.3.2b** was prepared after 40 hours reaction time and used without further purification giving the title compound in >99 % yield as colorless oil.

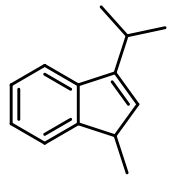
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44 – 7.36 (m, 2H), 7.33 – 7.27 (m, 1H), 7.22 (apptd, *J* = 7.3, 1.1 Hz, 1H), 6.19 – 6.10 (m, 1H), 3.51 – 3.35 (m, 1H), 3.18 – 2.98 (m, 1H), 2.20 – 2.03 (m, 2H), 1.88 – 1.60 (m, 6H), 1.31 (d, *J* = 7.5 Hz, 3H)

^{13}C NMR (100 MHz, $CDCl_3$) δ 150.4, 146.9, 144.9, 132.9, 126.2, 124.7, 122.7, 119.8, 43.6, 38.5, 31.9, 25.4, 16.6

IR (neat): ν_{max} = 3059, 3014, 2953, 2866, 1605, 1458, 1392, 1368, 1327, 1304, 1261, 1171, 1080, 1019 cm^{-1}

HRMS (EI): $[M]^{\cdot+}$ calculated for $C_{15}H_{18}^{\cdot+}$, 198.1403; found 198.1401

3-isopropyl-1-methyl-1H-indene (I.3.2c)



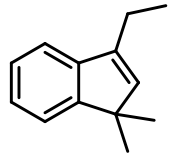
I.3.2c

Following the general procedure E, compound **I.3.2c** was prepared after 62 hours reaction time and after column chromatography (100% pentane) in 92 % yield (0.184 mmol) as colorless oil.

The spectroscopic properties were in accordance with those reported in the literature.[19]

3-ethyl-1,1-dimethyl-1H-indene (6d)

Following the general procedure D, compound **6d** was prepared after 24 hours reaction time and after column chromatography (100% pentane) in 81 % yield (0.162 mmol) as colorless oil.



6d

The spectroscopic properties were in accordance with those reported in the literature.[20]

1.6.8 References:

[1] C. Nieto-Oberhuber, M. P. Muñoz, S. López, E. Jiménez-Núñez, C. Nevado, E. Herrero-Gómez, M. Raducan, A. M. Echavarren, *Chem. Eur. J.* **2006**, *12*, 1677-1693.

[2] A.-M. Lord, M. F. Mahon, M. D. Lloyd, M. D. Threadgill, *J. Med. Chem.* **2009**, *52*, 868-877.

[3] D. W. Slocum, T. K. Reinscheld, N. D. Austin, D. Kusmic, P. E. Whitley, *Synthesis* **2012**, *44*, 2531-2536.

[4] a) P. Kottala Vijaya, S. Murugesan, A. Siva, *Tetrahedron Lett.* **2015**, *56*, 5209-5212; b) M. Zhuang, H. Du, *Org. Biomol. Chem.* **2014**, *12*, 4590-4593.

[5] S. Wang, L. Zhang, *J. Am. Chem. Soc.* **2006**, *128*, 8414-8415.

[6] S. Ma, H. Ren, Q. Wei*, J J. Am. Chem. Soc.* **2003**, *125*, 4817

[7] X. Zhang, Z. Lu, C. Fu, S. Ma, *Org. Biomol. Chem.* **2009**, *7*, 3258

[8] I. Cikotiene, *Org. Lett.* **2014,** *16*, 2260

[9] K. L. Butler, M. Tragni, R. A. Widenhoefer, *Angew. Chem. Int. Ed.* **2012**, *51*, 5175-5178.

[10] T. Saravanan, S. Jana, A. Chadha, *Org. Biomol. Chem.* **2014**, *12*, 4682-4690.

[11] H. Imagawa, Y. Asai, H. Takano, H. Hamagaki, M. Nishizawa, *Org. Lett.* **2006**, *8*, 447-450.

[12] Y. Qian, C. S. Shanahan, M. P. Doyle, *Eur. J. Org. Chem.* **2013**, *2013*, 6032-6037.

[13] J. Panteleev, R. Y. Huang, E. K. J. Lui, M. Lautens, *Org. Lett.* **2011**, *13*, 5314-5317.

[14] N. Sakai, R. Kanada, M. Hirasawa, T. Konakahara, *Tetrahedron*, **2005**, *61*, 9298

[15] Q. Li, J. Jeng, H.Gau, *Eur. J. Org. Chem.* **2014**, *35*, 7916

[16] J. G. Duboudin, B. Jousseaume, A. Saux, *J. Organomet. Chem.* **1979**, *168*, 1-11.

[17] H. T. Dao, U. Schneider, S. Kobayashi, *Chem. Commun.* **2011**, *47*, 692-694.

[18] K. Kobayashi, H. Naka, A. E. H. Wheatley, Y. Kondo, *Org. Lett.* **2008**, *10*, 3375-3377.

[19] E. Bappert, P. Muller, G. C. Fu, *Chem. Commun.* **2006**, 2604-2606.

[20] P. N. Chatterjee, S. Roy, *J. Org. Chem.* **2010**, *75*, 4413-4423.

Part II: Studies on the Asymmetric Synthesis of Allenes

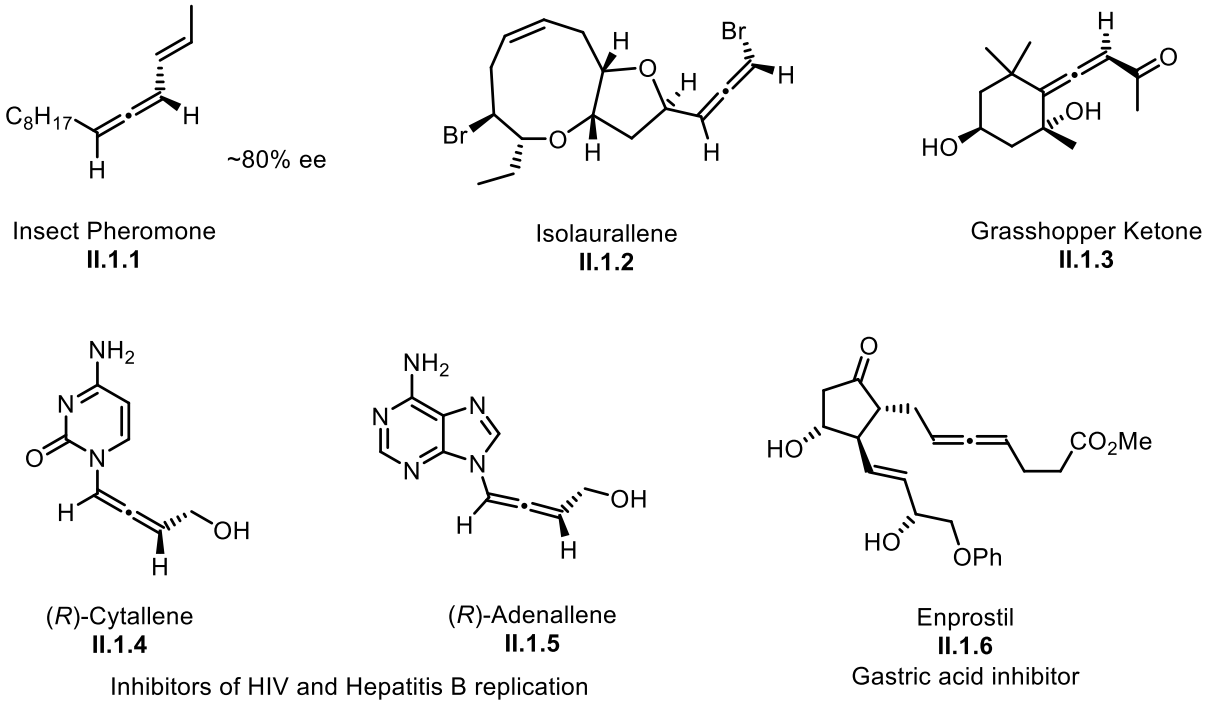
II.1 Allenes

Allenes, characterised by two cumulative double bonds, are important synthetic intermediates, as well as building blocks of bioactive compounds and drugs.[1] Around 150 natural products containing an allenic or cumulenic functionality are known.[2] Most of these natural compunds can be classified into three groups: linear allenes, bromoallenes and allenic terpenoids and carotenoids.[2] A classical example for linear allenes is insect pheromone **II.1.1**, which constitutes an interesting target for crop protection.[3] Isolaurallene (**II.1.2**), a bromoallene with a synthetically challenging nine-membered ring, is a metabolite generated by a type of red algae.[4] Probably the most famous allenic natural product is the well-known grasshopper ketone (**II.1.3**), an allenic carotinoid.[5]

Allenes are also present in the pharmaceutical industry.[2] Classical examples are the cytotoxic and antiviral allenic nucleoside analogues cytallene (**II.1.4**) and adenallene (**II.1.5**), which respectively inhibit HIV and Hepatitis B replication.[6] Enprostil (**II.1.6**), an allenic prostaglandin, is a marketed drug used as gastric acid inhibitor.[7]

All of the mentioned compounds bear a chiral allene moiety, arising through the orthogonal bonding of the cumulative diene system. The axial chirality is the reason why 1,3-disubstituted allenes have a mirror plane and can therefore exist as two enantiomers. However, although all of these compounds are chiral, not all of them were isolated in enantiomerically pure form. An example is the grasshopper ketone, which was isolated with just 80% ee. Moreover, whereas Enprostil is usually administered as a racemic mixture of the two enantiomeric allenes,[2] only the (R)-enantiomer of cytallene and adenallene is biologically active.[8]

For this reason, the development of methods for the asymmetric synthesis of allenes is a contemporary synthetic challenge and will be discussed within the next chapters.



Insect Pheromone
II.1.1

Isolaurallene
II.1.2

Grasshopper Ketone
II.1.3

(*R*)-Cytallene
II.1.4

(*R*)-Adenallene
II.1.5

Enprostil
II.1.6
Gastric acid inhibitor

Inhibitors of HIV and Hepatitis B replication

Scheme 1: Examples of naturally occuring and biologically active allenes.

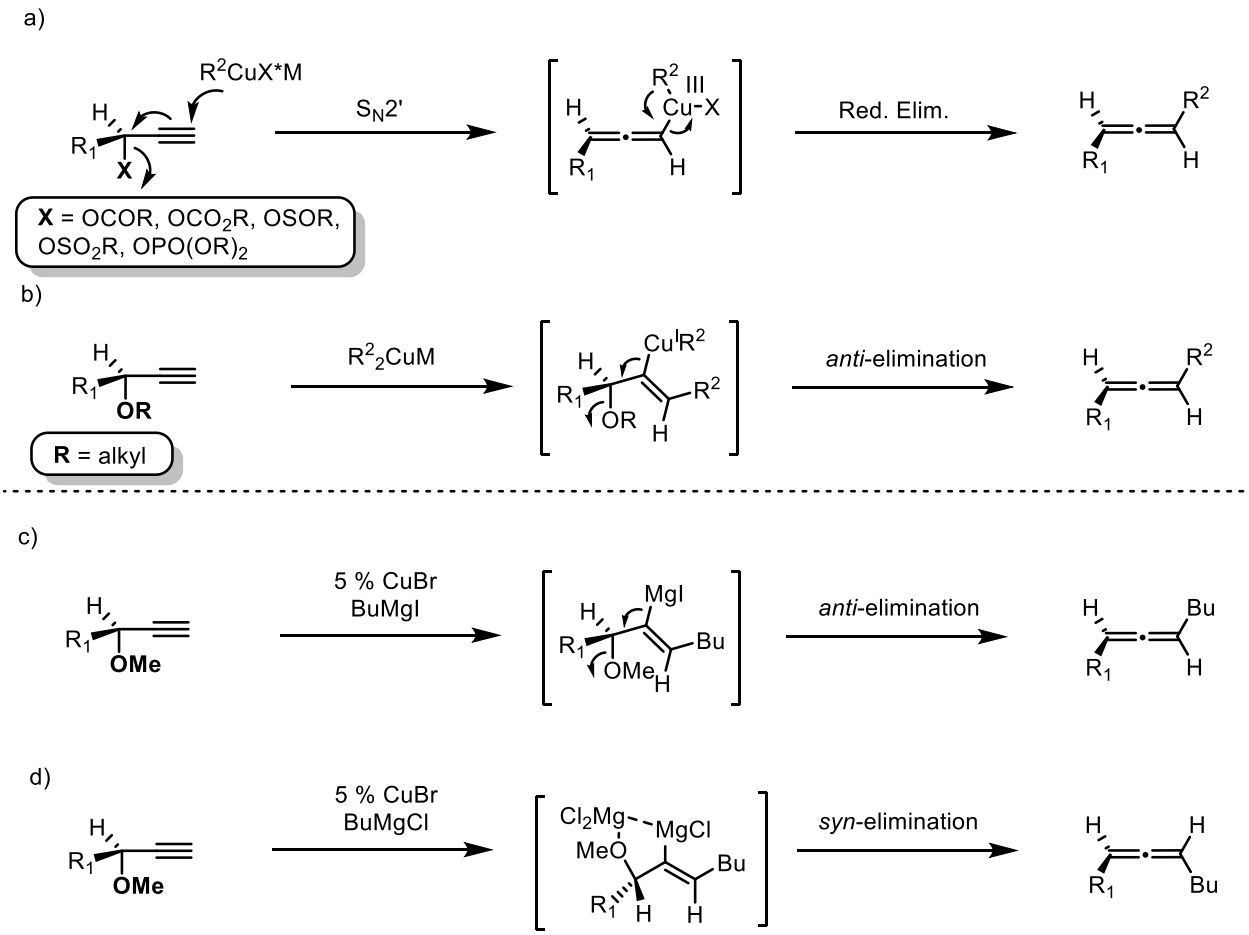
II.2 Synthesis of Allenes

II.2.1 Synthesis of Chiral Allenes using Enantiomerically Enriched Substrates

Among the many methods reported for the synthesis of chiral allenes,[9] the addition of an organocopper-species to a propargylic system is the most exploited approach. Interestingly, this transformation proceeds *via* an *anti*-S_N2' displacement allowing the synthesis of chiral allenes from enantiomerically enriched propargylic electrophiles. Mechanistically, however, different transition states arise depending on reagent and leaving group employed. The combination of a propargylic system bearing a good leaving group (typically a mesylate) and an organocopper(I)-reagent of type RCuX·M,[10] results in an S_N2'-addition of the reagent followed by reductive elimination of the intermediate Cu^{III}-species (Scheme2, pathway a).[11] Due to a better orbital overlap between the π-system of the substrate and the d-orbital of the copper-reagent, the S_N2'-displacement proceeds preferentially in an anti-fashion, thereby

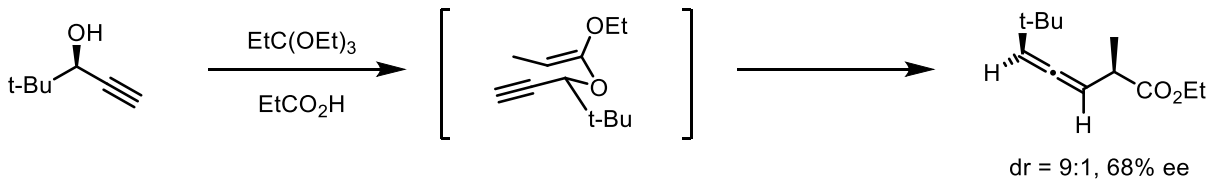
allowing high levels of chirality transfer.[12] Changing the substrate to a propargylic ether resulted in the same stereochemical outcome, but a different mechanistic pathway is involved (Scheme 2, pathway b).[13] The key step is the *anti*-β-elimination of the Cu^{I}-intermediate formed upon carbocupration of the alkyne functionality of the substrate.

Interestingly, when the amount of copper was lowered from stoichiometric to catalytic, a dependence of the stereochemical outcome on the counterion was observed (Scheme 2, pathways c and d).[14] When a Grignard reagent of type RMgI was used, the β-elimination event proceeded in an *anti*-fashion, whereas the use of RMgCl resulted in a *syn*-elimination. The higher electronegativity of chlorine compared with iodine leads to a more polarised intermediate, which, along with the smaller size of chlorine might allow the reaction to proceed *via* a cyclic transition state involving the coordination of the formed $MgCl_2$ (Scheme 2, pathway d). The greater Lewis acidity of $MgCl_2$ is another factor in favour of the cyclic intermediate. Conversely, the larger size of iodine hinders the formation of a such an intermediate leading to predominant *anti*-elimination (Scheme 2, pathway c).



Scheme 2: Mechanistic pathways for the addition of an organocopper reagent to a propargylic substrate

Another important approach for the synthesis of chiral allenes is the rearrangement of propargyl alcohols. The first report for this concept was by Henderson and Heathcock in 1988,[15] where an orthoester Claisen-rearrangement takes place from an optically pure propargyl alcohol *via* a chair-like transition state. A clear dependence of the diastereoselectivity on the steric bulk of the aliphatic substituent α-to the alcohol was observed.

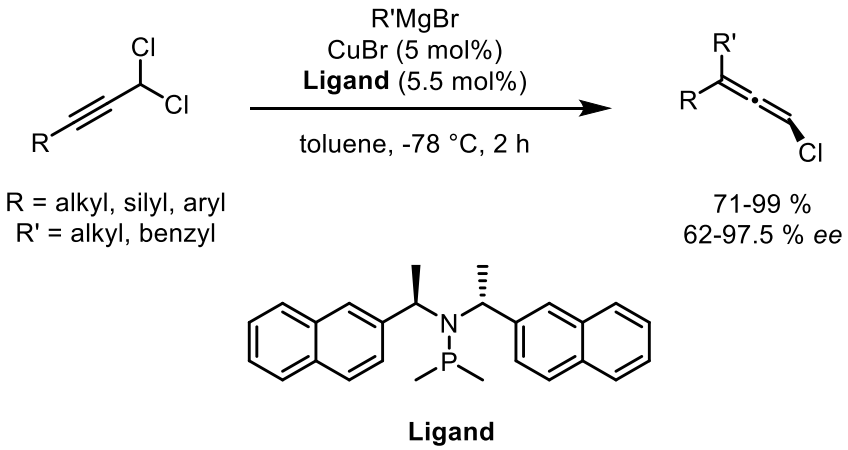


Scheme 3: Synthesis of chiral allenes using an orthoester Claisen rearrangement.[15]

II.2.2 Synthesis of Chiral Allenes using Asymmetric Catalysis

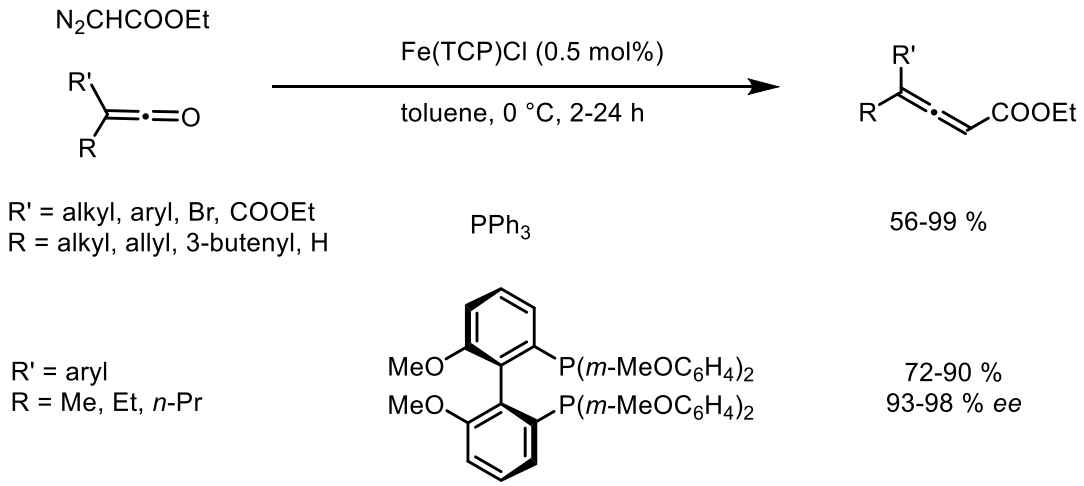
The synthesis of chiral allenes using chirality transfer strategies is well established in the literature.[9] However, there are surprisingly few reports on the catalytic enantioselective synthesis of allenes.

One approach is the S_N2' displacement by a Grignard reagent in combination with a chiral copper catalyst.[16] In this context,[16a] Alexakis and co-workers show the propargylic substitution of achiral dichloro-substrates to form substituted chloroallenes. The reaction displays a good tolerance for a variety of substrates including alkyl, aryl, benzyl and silyl groups with moderate to excellent enantioselectivity using SimplePhos as chiral ligand. However, further modification of the chloroallenes led to a significant loss of optical purity.



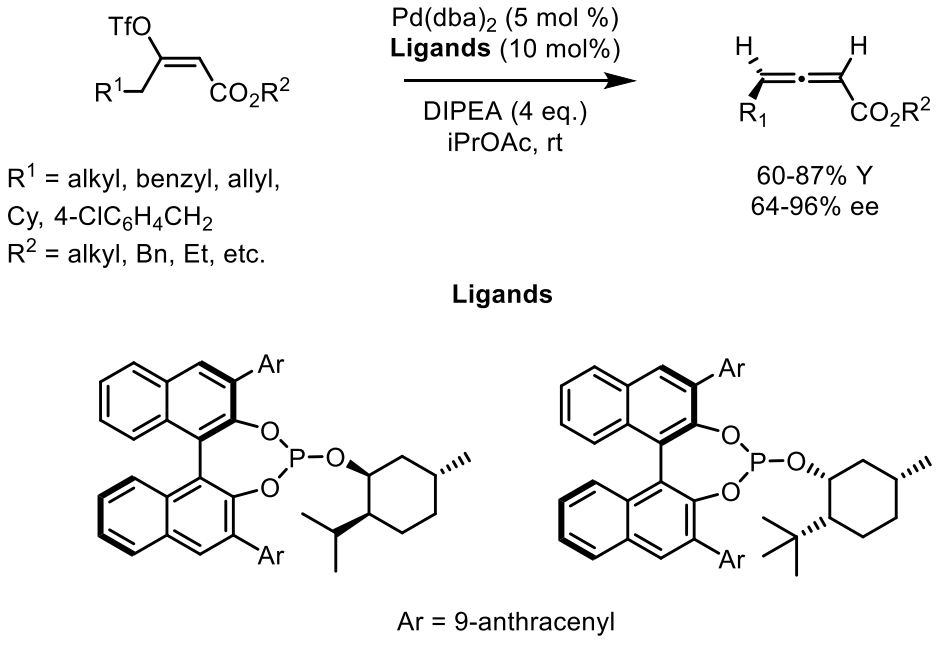
Scheme 4: Asymmetric synthesis of chloroallenes by Alexakis.[16a]

An alternative approach relies upon iron catalysis for the asymmetric synthesis of allenyl esters.[17] This reaction is based on the iron-catalysed Wittig-type olefination of ketenes with diazoacetates. The racemic variant appears to be very flexible and leads to the desired products in moderate to excellent yields. However, the asymmetric version, using stoichiometric amounts of a chiral BIPHEP-type phosphine and Fe(TCP)Cl as catalyst was highly enantioselective by somewhat narrow in scope.



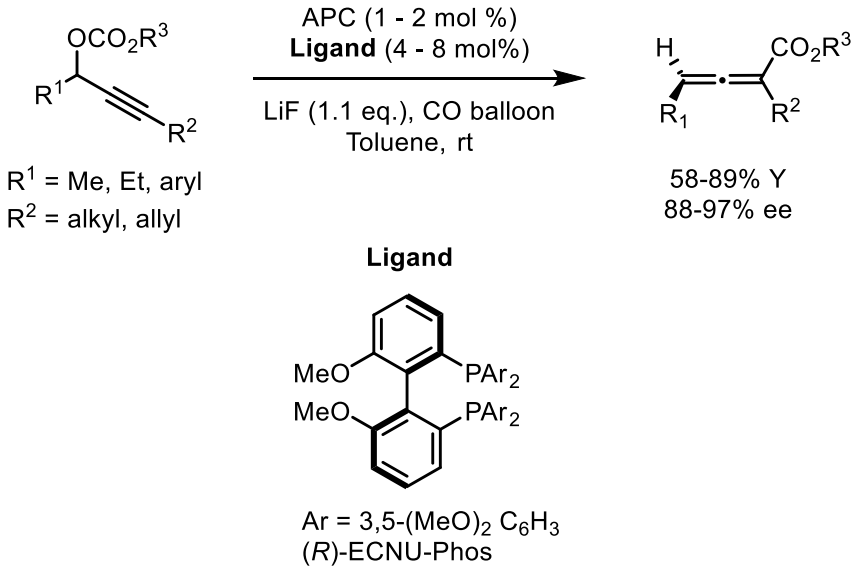
Scheme 5: Synthesis of allenyl esters using an iron-porphyrin catalyst.[17]

Palladium catalysis has also been successfully investigated for the synthesis of allenes.[18] One example is the work of Frantz and co-workers, based on the enantioselective β-hydride elimination of enol triflates to form enantiomerically enriched allenyl esters in moderate to good yields and good enantioselectivities. The best levels of enantioselectivity were obtained with a phosphite ligand bearing BINOL and neomenthol substituents. Depending on the stereoconfiguration of the neomenthol portion, either the (-)- or the (+)-enantiomer could be obtained.



Scheme 6: Synthesis of allenyl esters from enol triflates by Frantz.[18b]

Another asymmetric synthesis of allenyl esters was introduced by Ma and co-workers (Scheme 7). This approach is based on the deracemisation of propargylic carbonates using a palladium catalyst and a chiral ECNU-Phos ligand. The reaction, employing CO (1 atm) at room temperature, leads to excellent enantioselectivities and a broad substrate scope. As reported, the 3,5-dimethoxy groups on the aromatic rings of the ligand are crucial to achieve these high levels of asymmetric induction.

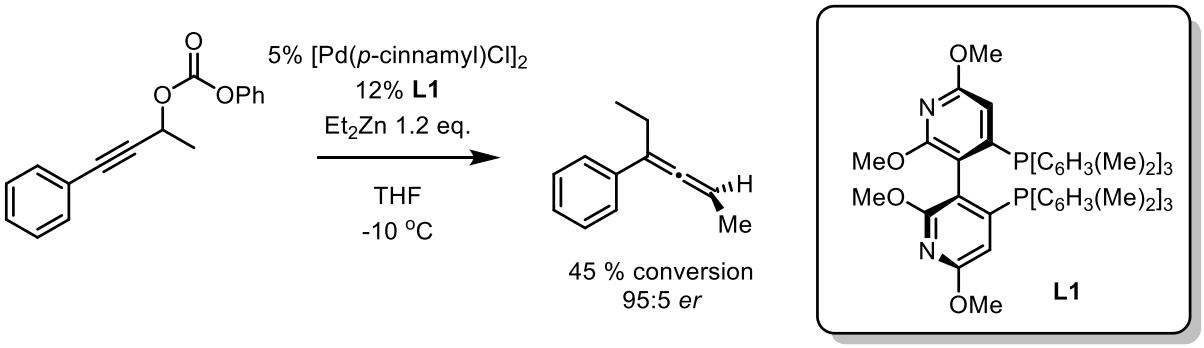


Scheme 7: Ma's synthesis of allenyl esters from propargylic substrates.[18c]

Although few methods exist for the asymmetric synthesis of allenes, most of the work in this field has focused on allenyl esters, which are thermodynamically more stable than their propargylic counterparts.[1] The challenging direct asymmetric synthesis of aryl- and alkyl-substituted chiral allenes from racemic propargylic substrates has been, to our knowledge, unpreceded in literature. In the following chapters we will present our efforts towards this endeavour.

II.3 Results and Discussion

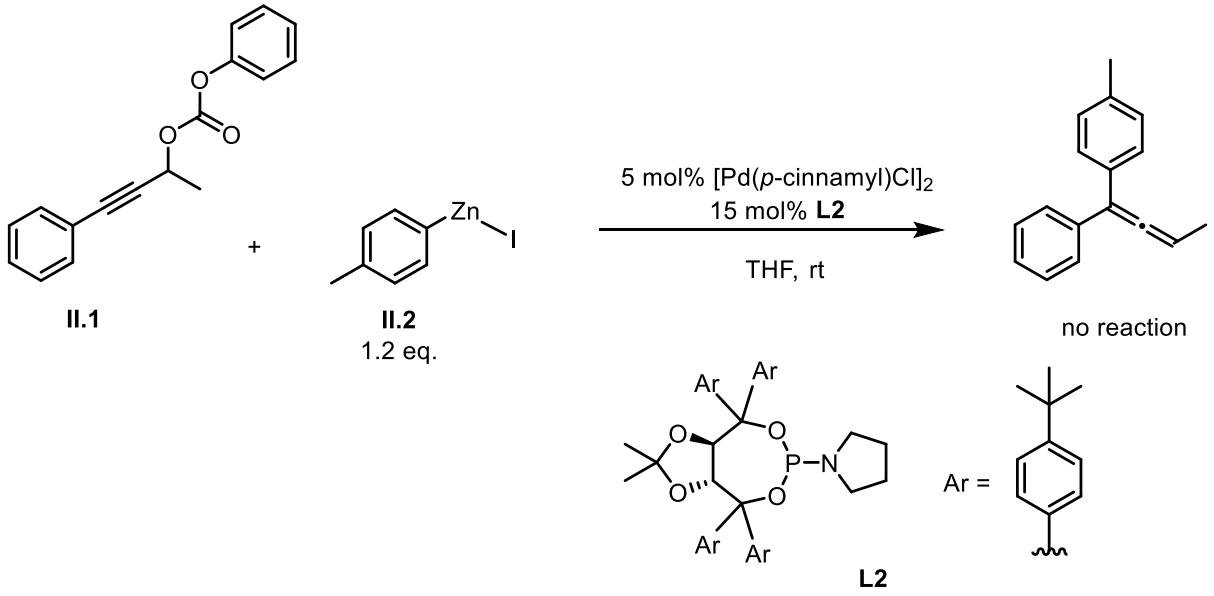
Previous work on this project, including ligand, catalyst and a preliminary solvent screening, has been carried out by Dr. Antonio Misale and the best results are shown in Scheme 8. Although the optical purity of the product is excellent, the obtained conversion factor is low.



Scheme 8: Preliminary results on the asymmetric synthesis of trisubstituted allenes.

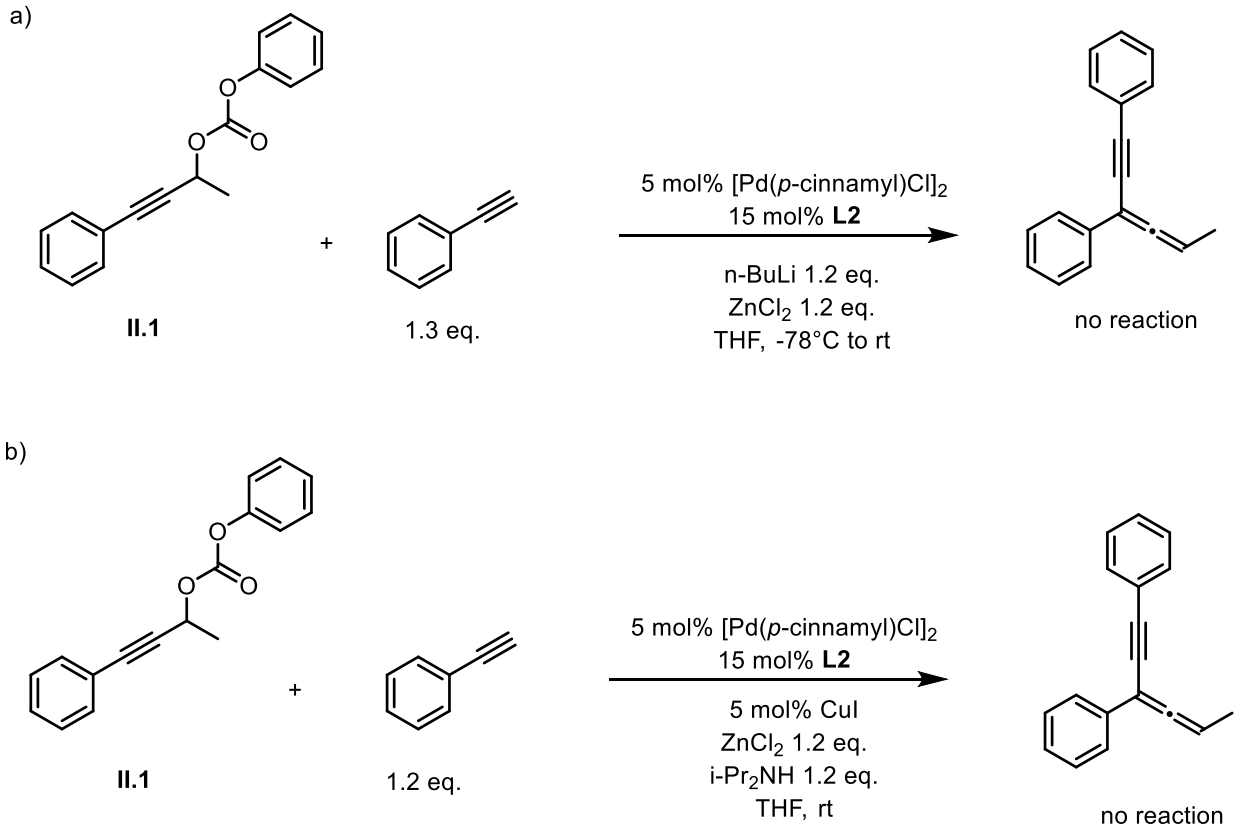
II.3.1 Further Investigations on Nucleophiles

At the onset, we investigated other nucleophiles. Our first investigations focused on the use of monoorganozinc reagents. Reacting propargylic substrate **II.1** with monoarylzinc reagent **II.2** using phosphoramidite ligand **L2**, which showed good catalytic activity in previous experiments carried out by Dr. Antonio Misale, did not induce any reactivity (Scheme 9).



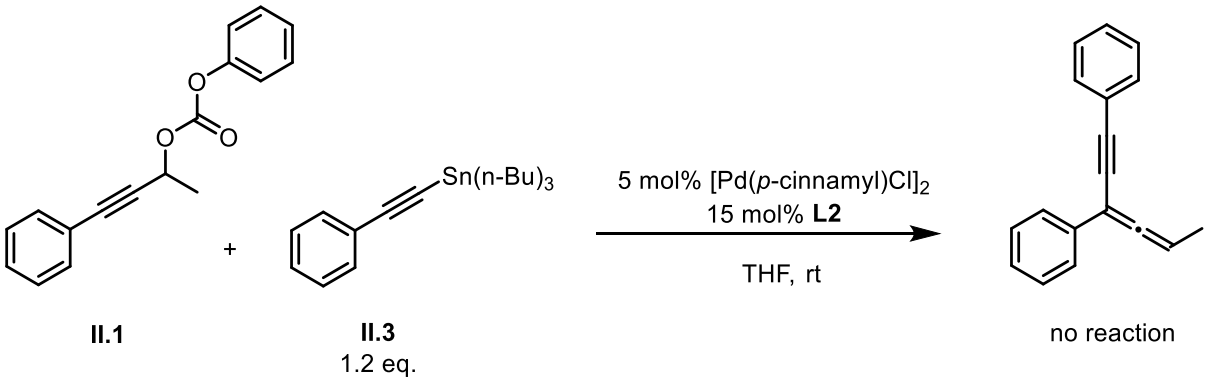
Scheme 9: Attempt for the allene synthesis using a monoorganozinc reagent.

We then investigated monoalkynylzinc reagents, prepared by deprotonation of ethynylbenzene with *n*-BuLi and transmetalation to $ZnCl_2$ (Scheme 10a). However, the use of these reagents did not lead to any reaction. We also tested a Sonogashira-type approach (Scheme 10b). In this reaction, an alkynyl copper species is formed, which can then be transmetalated to $ZnCl_2$. Unfortunately, these conditions also did not lead to observable reactivity.



Scheme 10: a) Attempted allene synthesis using a monoalkynylzinc reagent. b) Attempted allene synthesis using a Sonogashira-type approach.

Furthermore, we tested an alkynyltin reagent. However, reacting Tributyl(phenylethynyl)stannane (**II.3**) under standard conditions did not lead to the formation of any desired product (Scheme 11).

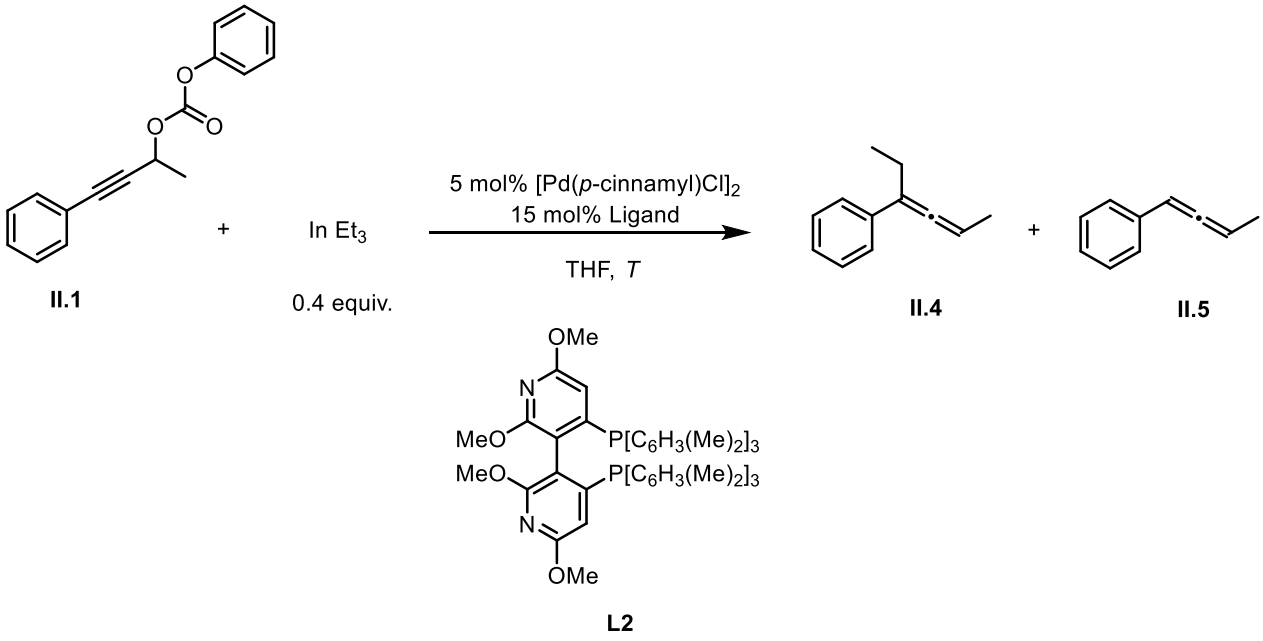


Scheme 11: Attempted allene synthesis using a tin-nucleophile.

Further studies then focused on the use of trialkylindium reagents. Initial attempts using triethylindium under standard conditions led to the desired product **II.4** in moderate yield as

a racemic mixture (Table 1, entry 1). Lowering the temperature to -10 °C led to a 2:1 mixture of product and the reduced product **II.5** (Table 1, entry 2). Changing the ligand to P-Phos ligand **L1** resulted in slow conversion to the racemic, alkyl-substituted allene (Table 1 entry 3). Introducing a longer aliphatic chain on the nucleophile led only to traces of the corresponding racemic products (Table 1, entry 4).

Table 1: Allene synthesis using indium nucleophiles



Entry	Conditions	Yield	*er*
1	**L2**, rt	60 %	47:53
2	**L2**, -10 °C	Mixture	-
3	**L1**, -10 °C	20 % (25 % Conversion)	47:53
4	$InBu_3$, **L1**, -10 °C	traces	50:50

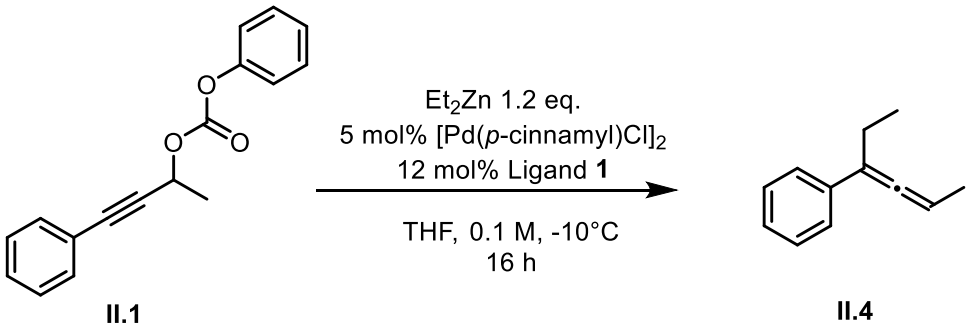
Since it was not possible to achieve enantioselectivity with indium-based nucleophiles in these preliminary studies, subsequent work focused on the use of dialkyl zinc reagents.

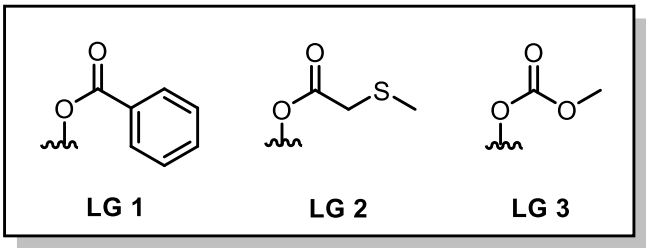
II.3.2 Dialkylzinc Nucleophiles

With the intent of reproducing the results previously reported, we obtained a yield of 70 %, but with an *er* of 63:37 (Table 2, entry 1). The best *er* obtained was 72:28 using standard conditions, but using a ligand purchased from a different supplier (Table 2, entry 2).[19] Increasing the reaction time to 4 days then led to the same *er*, but with low conversion. (Table 2, entry 3). Further increasing the amount of nucleophile and the catalyst loading led to a slight reduction of *er* but better conversion in case of entry 5 (Table 2, entry 4 and 5). Addition of LiCl as additive shut down the reaction entirely and any change of ligand led to a racemic allene (Table 2, entries 5 and 6). In order to push the conversion, we attempted several modifications of the reaction setup, including: degassing of solvent, increased catalyst loading and use of freshly opened bottles of all chemicals, but this did not lead to better reactivity (Table 2, entries 7 and 8).

Additionally, further investigation of the temperature dependence was carried out. Performing the reaction at -20 °C did not lead to any reactivity (Table 2, entry 9). Since also at -15 °C no reactivity was observed, the reaction mixture was warmed up to -10 °C, which did not lead to a better *er*. Performing the reaction at -5 °C did not improve the yield and led to traces of desired product with similar *er* (Table 2, entry 12). Furthermore, we also changed palladium source and leaving groups, but without any significant improvement (Table 2, entries 13 and 14).

Table 2: Asymmetric synthesis of allenes.





Entry	Deviations from Standard Conditions	Yield	*er*
1	-	70%	37:63
2	-	Traces	28:72
3	4 days	Traces	28:72
4	3 eq. Et_2Zn	Traces	45:55
5	3 eq. Et_2Zn, 10 mol% cat.	30% Conversion	33:67
6	LiCl	-	-
7	Ligand **2**	Traces	53:47
8	10 mol% cat., degased THF	Traces	-
9	freshly opened bottles	Traces	-
10	-20° C	-	-
11	-15 to -10°C	Traces	45:55
12	-5° C	Traces	39:61
13	$[Pd(allyl)Cl]_2$	Traces	-
14	**LG 1-3**, $[Pd(allyl)Cl]_2$	Traces	-

II.3.3 Conclusions and Outlook

In summary, we have presented a new approach for the synthesis of chiral, trisubstituted allenes. Different nucleophiles were tested to achieve such a transformation with best results obtained when using dialkylzink reagents and readily available propargylic substrates. Due to reproducibility issues, many different reaction conditions, including small experimental changes not mentioned in this work, were tested to identify the pivotal factor for these problems. Although it seems like catalyst turnover is somehow hampered, it is by now not completely clear what the actual cause is.

Due to time constraints it was not possible to perform further experiments on this topic, but subsequent studies on this project are currently ongoing in our laboratories.

II.4 References

[1] A. S. K. Hashmi, in *Modern Allene Chemistry*, Wiley-VCH Verlag GmbH, **2008**, pp. 2-50.

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

[3] D. F. Horler, *Journal of the Chemical Society C: Organic* **1970**, 859-862.

[4] K. Kurata, A. Furusaki, K. Suehiro, C. Katayama, T. Suzuki, *Chem Lett.* **1982**, *11*, 1031-1034.

[5] J. Meinwald, K. Erickson, M. Hartshorn, Y. C. Meinwald, T. Eisner, *Tetrahedron Lett.* **1968**, *9*, 2959-2962.

[6] a) S. Hayashi, S. Phadtare, J. Zemlicka, M. Matsukura, H. Mitsuya, S. Broder, *Proc. Natl. Acad. Sci. USA* **1988**, *85*, 6127-6131; b) S. Phadtare, J. Zemlicka, *J. Am. Chem. Soc.* **1989**, *111*, 5925-5931; c) S. Phadtare, D. Kessel, T. H. Corbett, H. E. Renis, B. E. Court, J. Zemlicka, *J. Med. Chem.* **1991**, *34*, 421-429.

[7] a) P. W. Collins, S. W. Djuric, *Chem. Rev.* **1993**, *93*, 1533-1564; b) A. P. Roszkowski, G. L. Garay, S. Baker, M. Schuler, H. Carter, *J. Pharm. Exp. Ther.* **1986**, *239*, 382-389; c) R. P. Rosenkranz, P. E. Fisher, M. L. Turke, M. R. Perry, A. G. Wong, D. L. Wren, G. F. Cooper, W. L. Smith, *Arzneimittel-Forschung* **1989**, *39*, 1568-1571; d) C. K. Ching, S. K. Lam, *J. Gastroenterology* **1995**, *30*, 607-614; e) N. Omura, H. Kashiwagi, T. Aoki, K. Omura, Y. Fukuchi, *J. Gastroenterology* **1997**, *32*, 740-746.

[8] a) B. C. N. M. Jones, J. V. Silverton, C. Simons, S. Megati, H. Nishimura, Y. Maeda, H. Mitsuya, J. Zemlicka, *J. Med. Chem.* **1995**, *38*, 1397-1405; b) S. Megati, Z. Goren, J. V. Silverton, J. Orlina, H. Nishimura, T. Shirasaki, H. Mitsuya, J. Zemlicka, *J. Med. Chem.* **1992**, *35*, 4098-4104; c) S. Megati, Z. Goren, J. V. Silverton, J. Orlina, H. Nishimura, T. Shirasaki, H. Mitsuya, J. Zemlicka, *J. Med. Chem.* **1993**, *36*, 634-634.

[9] H. Ohno, Y. Nagaoka, K. Tomioka, in *Modern Allene Chemistry*, Wiley-VCH Verlag GmbH, **2008**, pp. 141-181.

[10] A. Claesson, L.-I. Olsson, *J. Chem. Soc., Chem. Commun.* **1979**, 524-525.

[11] C. J. Elsevier, P. Vermeer, *J. Org. Chem.* **1989**, *54*, 3726-3730.

[12] E. J. Corey, N. W. Boaz, *Tetrahedron Lett.* **1984**, *25*, 3063-3066.

[13] I. Marek, P. Mangeney, A. Alexakis, J. F. Normant, *Tetrahedron Lett.* **1986**, *27*, 5499-5502.

[14] A. Alexakis, I. Marek, P. Mangeney, J. F. Normant, *J. Am. Chem. Soc.* **1990**, *112*, 8042-8047.

[15] M. A. Henderson, C. H. Heathcock, *J. Org. Chem.* **1988**, *53*, 4736-4745.

[16] a) H. Li, D. Grassi, L. Guénée, T. Bürgi, A. Alexakis, *Chem. Eur. J.* **2014**, *20*, 16694-16706; b) M. Wang, Z.-L. Liu, X. Zhang, P.-P. Tian, Y.-H. Xu, T.-P. Loh, *J. Am. Chem. Soc.* **2015**, *137*, 14830-14833.

[17] C.-Y. Li, X.-B. Wang, X.-L. Sun, Y. Tang, J.-C. Zheng, Z.-H. Xu, Y.-G. Zhou, L.-X. Dai, *J. Am. Chem. Soc.* **2007**, *129*, 1494-1495.

[18] a) M. Ogasawara, T. Nagano, T. Hayashi, *J. Org. Chem.* **2005**, *70*, 5764-5767; b) I. T. Crouch, R. K. Neff, D. E. Frantz, *J. Am. Chem. Soc.* **2013**, *135*, 4970-4973; c) Y. Wang, W. Zhang, S. Ma, *J. Am. Chem. Soc.* **2013**, *135*, 11517-11520.

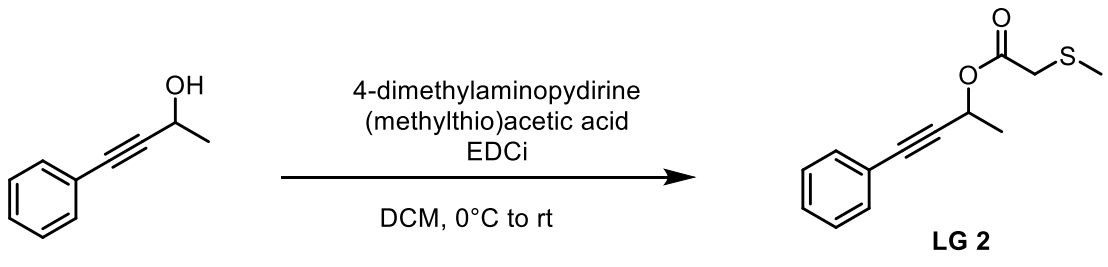
[19] Chiral Ligands were bought either from Sigma Aldrich (Table 2, entry 1) or Strem (Table 2, entry 2).

II.5 Experimental

II.5.1 General Information

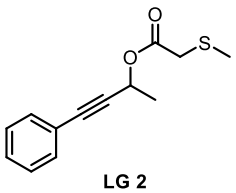
All glassware was flame-dried before use and the reactions were performed under argon atmosphere. **II.1**,[1] **LG1**,[2] **LG3**[3] were prepared according to literature procedures. Racemic allenes were prepared according to the procedure described in part I. All other reagents were used as received from commercial suppliers. Reaction progress was monitored by thin layer chromatography (TLC) performed on aluminium plates coated with silica gel F254 with 0.2 mm thickness or LC-MS analysis. Chromatograms were visualised by fluorescence quenching with UV light at 254 nm or by staining with potassium permanganate. Column chromatography was performed using silica gel 60 (230-400 mesh, Merck and co.). Neat infra-red spectra were recorded using a Perkin-Elmer Spectrum 100 FT-IR spectrometer. Wavenumbers (= 1/λ) are reported in cm^{-1}. Mass spectra were obtained using a Finnigan MAT 8200 or (70 eV) or an Agilent 5973 (70 eV) spectrometer, using electrospray ionisation (ESI), or Finnigan MAT 95 Q using electron impact ionisation (EI). All ^{1}H NMR and ^{13}C NMR spectra were recorded using a Bruker AV-400 or AV-600 spectrometer at 300K. Chemical shifts were given in parts per million (ppm, δ), referenced to the solvent peak of $CDCl_3$, defined at δ = 7.26 ppm (^{1}H NMR) and δ = 77.16 (^{13}C NMR). Coupling constants are quoted in Hz (J). ^{1}H NMR splitting patterns were designated as singlet(s), doublet (d), triplet (t), quartet (q), pentet (p). Splitting patterns that could not be interpreted or easily visualized were designated as multiplet (m).

II.5.2 Preparation of LG 2



LG 2

(Methylthio)acetic acid (1.71 mmol, 2.5 eq.) was dissolved in DCM (1.5 M) and cooled to 0° C. DMAP (1.37 mmol, 2 eq.) and then EDCi (1.71 mmol, 2.5 eq.) were added. The resulting yellow solution was stirred for 15 min, after which the propargylic alcohol (0.68 mmol, 1 eq.) was added. The reaction mixture was allowed to warm to rt and stirred for 16 h, quenched with 1 M HCl (mL), extracted with ethyl acetate (3 x mL), washed with brine, dried over Na_2SO_4, filtered and the solvent was removed *in vacuo*. The crude product was purified by column chromatography (heptane / ethyl acetate 20:1) giving compound **6** as slightly yellow oil in 49% yield.



LG 2

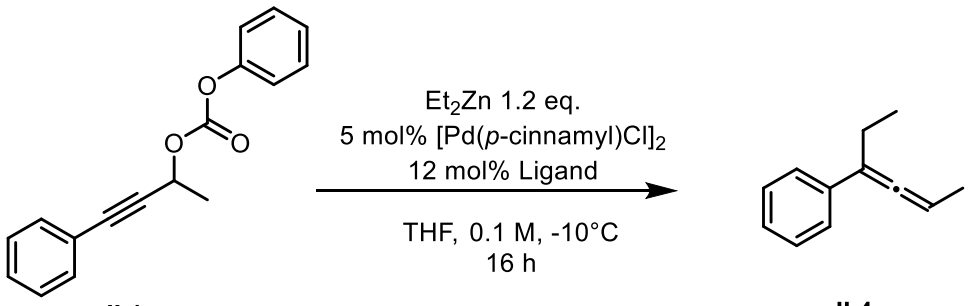
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.46–7.44 (m, 2H), 7.34–7.29 (m, 3H), 5.75 (q, J = 6.7 Hz, 1H), 3.25 (s, 2H), 2.25 (s, 3H), 1.63 (d, J = 6.7 Hz, 3H)

^{13}C NMR (100 MHz, $CDCl_3$) δ 169.4, 132.0, 128.8, 128.4, 122.3, 87.1, 85.1, 61.9, 35.8, 21.6, 16.4

IR (neat): ν_{max} = 2987, 2919, 2234, 1731, 1490, 1442, 1313, 1263, 1126, 1083, 1022, 989, 952, 756, 690, 544 cm^{-1}

HRMS (ESI): calculated for $[M+Na]^+$ 257.0612, found 257.0604

II.5.3 Typical Procedure for the Asymmetric Aynthesis of Allenes



II.1 II.4

[Pd(p-cinnamyl)Cl]$_2$ (0.002 mmol, 5 mol%) and **L1** (0.0048 mmol, 12 mol%) were dissolved in THF (0.4 mL) and stirred at rt for 40 minutes. The solution was cooled to -10 °C and **II.1** (0.04 mmol, 1 eq.) was added followed by dropwise addition of Et_2Zn (0.048 mmol, 1.2 eq., 1 M in hexanes). The reaction mixture was stirred at this temperature for 16 h and quenched with 1

M aq. HCl. The biphasic mixture was separated and extracted with EtOAc (3 x mL). The combined organic layers were washed with brine, dried over Na2SO4 and the solvent was removed *in vacuo*.

The crude product was purified by flash column chromatography (100 % pentane) giving the product as colourless oil. The spectral properties of **II.4** can be found in the experimental section of part I.

II.5.4 References:

[1] T. Schwier, M. Rubin, V. Gevorgyan, *Org. Lett.* **2004**, *6*, 1999-2001.
[2] B. T. Ramanjaneyulu, V. Reddy, P. Arde, S. Mahesh, R. V. Anand, *Chem. Asian J.* **2013**, *8*, 1489-1496.
[3] M. Kalek, T. Johansson, M. Jezowska, J. Stawinski, *Org. Lett.* **2010**, *12*, 4702-4704.