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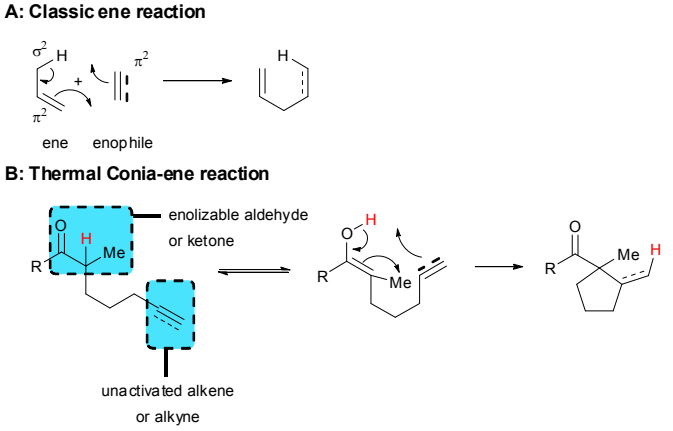
Since its initial inception, the Conia-ene reaction, known as the intramolecular addition of enols to alkynes or alkenes, has experienced a tremendous development and appealing catalytic protocols have emerged. This review fathoms the underlying mechanistic principles rationalizing how substrate design, substrate activation and the nature of the catalyst work hand in hand for the efficient synthesis of carbocycles and heterocycles at mild reaction conditions. Nowadays, Conia-ene reactions can be found as part of tandem reactions, and the road for asymmetric versions has already been paved. Based on their broad applicability, Conia-ene reactions have turned into a highly appreciated synthetic tool with impressive examples in natural product synthesis reported in recent years.

1. Introduction

The exploitation of novel chemical reactions and their improvement to minimize waste and circumvent previously known limitations are the focus of ongoing research. Especially reactions that occur under high atom economy, with the majority of the involved atoms being converted into the final product, are of paramount importance in terms of ecology and economy.[1] In this context, pericyclic ene reactions have always been an appealing class of reactions for carbon-carbon bond formation, because most ene reactions progress through a concerted mechanism with potentially 100% atom economy.[2]
In general, ene reactions refer to an intra- or intermolecular reaction between an alkene bearing an allylic hydrogen (the ene component) and an alkene or alkyne (the enophile) by migration of the double bond with a concurrent [1,5]-hydrogen shift (Scheme 1, A).[2]



Scheme 1 Similarities between the classic ene reaction and the thermal Conia-ene reaction.

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Marcus Blümel was born in Hoyerswerda, Germany in 1989. In 2011 he received his B.Sc. and in 2013 his M.Sc. from the Dresden University of Technology under the supervision of Prof. P. Metz. Thereafter he joined the research group of Prof. D. Enders at the RWTH Aachen University for his doctoral studies. His current research interests include the development of organocatalytic domino reactions and organo-metal co-catalysis for the synthesis of various carbon- and heterocycles.

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From a theoretical point of view, the intramolecular version of this reaction can, according to the Woodward Hofmann rules, be well understood as a thermally allowed all suprafacial $[\pi^2+\pi^2+\sigma^2]$ sigmatropic rearrangement.[4]

One special type of ene reaction, which will be covered in this review, is the Conia-ene reaction (CER). As described by Conia and Le Perchec in their in-depth review in 1975, the original version of this reaction refers to the thermal intramolecular cyclization of enolizable carbonyl compounds with a tethered alkyne or alkene moiety leading to valuable five- or six-membered carbocycles (Scheme 1, B).[5,6] Proceeding *via* a similar mechanism as the ene reaction, the only difference of a CER is the replacement of the traditional ene component with an enol, which can be generated from a ketone or aldehyde. However, without any extra stabilization provided for the enol tautomer and the low acidity of aldehydes and ketones, the amount of enol is insignificantly low. This makes conversion unfeasible at room temperature, so that a temperature higher than 300 °C is necessary for the reaction to occur. The restrictive reaction conditions impose one major drawback, as many functional groups, being prone to pyrolysis, are incompatible under the applied reaction conditions. To overcome this shortfall of the original set-up, all synthetic efforts were directed towards the development of alternatives with milder reaction conditions. Nevertheless, up to the late nineties most protocols relied on other harsh conditions employing strong acids or bases or photochemical activation. It was not until the advent of the millennium that Lewis acidic metals emerged as efficient catalysts for the Conia-ene reaction, allowing for milder reaction conditions and a broader applicability range.

As a result, the Conia-ene reaction has become a noteworthy contestant for the formation of carbon-carbon bonds and the synthesis of valuable carbo- and heterocycles. Recent endeavours include impressive examples in natural product synthesis, the formation of larger carbocycles and asymmetric versions of this reaction.

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Although strictly speaking the original Conia-ene reaction demands for the presence of an enol, many reactions have been reported in which the nucleophilic activation of the carbonyl compound occurs through the formation of a metal enolate.[7] These examples will also be included in this review if the reaction proceeds under sub-stoichiometric amounts of metals and bases, and we suggest referring to these reactions as Conia-ene-type or Conia-ene-related reactions for better clarity.[8]

This review is divided into four sections. In the first we address the common features of the reactions including typical substrates, regio- and diastereoselectivity during the cyclization and different activation modes for the reaction. Section two then discusses the different activation modes presenting different metal systems and their development throughout the years. Section three focuses on various strategies for asymmetric Conia-ene reactions, while section four deals with recent applications in natural product synthesis.

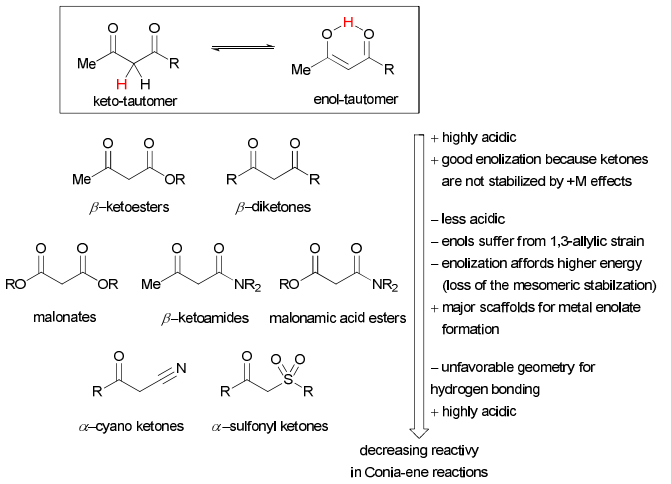
2. Reaction Features

2.1. Carbonyl compounds and their reactivity

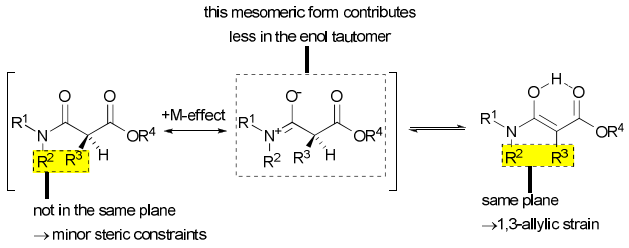
The key to overcome the initial limitations imposed on thermal Conia-ene reactions is to rely on activated carbonyl compounds possessing an inherently more favourable enolization rate.[9] The originally used aldehydes and ketones are not acidic enough (pK_a for acetone in DMSO is 26.5) and the enol tautomer lacks sufficient extra stabilization. In contrast, carbonyl compounds providing an extra stabilizing group in the β-position offer various advantages (Scheme 2): (1) The presence of an extra electron-withdrawing group in β-position is beneficial for the acidity and enolization rate (pK_a in DMSO is around 10-18).[8] (2) Concurrent stabilization of the enol by hydrogen-bonding between the OH of the enol and the basic oxygen of the β-functionality. (3) The β-carbonyl compounds act as efficient chelate ligands for hard Lewis acids. Upon coordination, the substrates experience an increase in acidity thus facilitating deprotonation and metal enolate formation.

For catalytic Conia-ene reactions the most typical substrates include β-ketoesters, β-diketones, β-ketoamides, malonates, malonamic esters and, less commonly, cyano esters and sulfonyl esters. Although there is no big difference in terms of acidity, enolization is generally more favourable for β-keto carbonyl compounds. The presence of a strong +M-effect, provided by oxygen, nitrogen or aryl groups, hampers the enolization of amides, esters and electron-rich aryl ketones, because the extra mesomeric stabilization granted for the carbonyl tautomer will be diminished when the corresponding enol is formed (Scheme 3). In addition, enols derived from esters and amides normally suffer from 1,3-allylic strain making enolization less likely.

It should be noted that although α-cyano esters and sulfonyl esters are slightly more acidic, enolization is not as efficient, because of the unfavourable geometry for hydrogen bonding to take place. Thus, it is not surprising that β-ketoesters are the most common substrates used for Conia-ene reactions, even if β-diketones possess a comparable reactivity. From a practical point of view though, the ketoesters are more suitable, because the ester moiety, needed to promote the reaction, can be easily cleaved off *via* Krapcho decarboxylation. In contrast, malonates are commonly used when the formation of metal enolates is involved, although they are, similar to β-ketoamides and malonamic esters in terms of reactivity.



Scheme 2 Overview on β-carbonyl compounds and their reactivity in Conia-ene reactions.

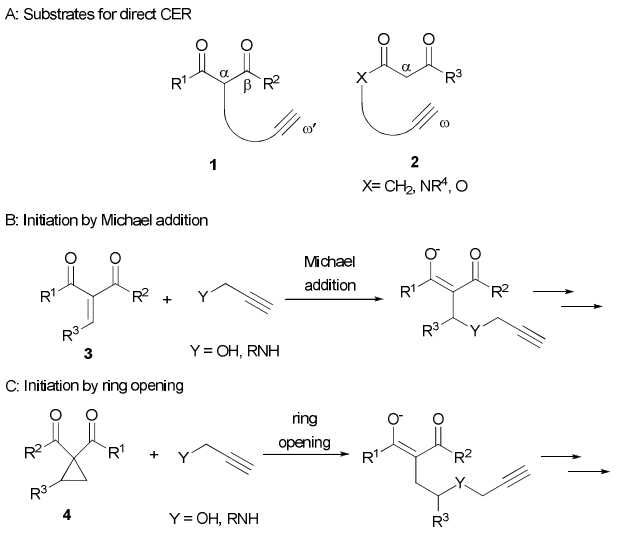


Scheme 3 Electronic and steric effects on carbonyl tautomerization.

2.2. Reaction initiation

Frequently used substrates for direct Conia-ene reactions are alkyne- or alkene-tethered β-dicarbonyl compounds, which can be acyclic or cyclic (Scheme 4). Depending on the position of the alkyne/alkene branch, $\alpha(\omega$'-alkynyl/alkenyl)- and ω-alkynyl/alkenyl β-dicarbonyl compounds **1** and **2** can be distinguished (ω denotes a terminal alkyne or alkene). These substrates provide both moieties necessary for a Conia-ene reaction, and the substrates normally undergo straight cyclization when exposed to a suitable catalyst. In addition, the synthesis of heterocycles is also feasible with ω-alkynyl/alkenyl β-dicarbonyl compounds if the alkyne/alkene is tethered by an amide or ester (X =NR, O).

Sometimes, the enolization or the formation of a metal enolate is difficult to achieve, as is the case for malonates. Therefore a sequential approach is often easier, using an alkyne-tethered nucleophile and an electrophilic substrate with a *β*-dicarbonyl scaffold (Scheme 4, B/C). Initially the nucleophile adds to the electrophile, thereby generating an enolate anion/metal enolate that then can participate in the subsequent cyclization reaction. Typical nucleophiles include *N*-protected propargylamines or propargyl alcohols while alkylidene *β*-dicarbonyls **3** (Michael addition) and donor-acceptor-substituted cyclopropanes **4** (ring opening reactions) are used as electrophiles. Because the nucleophiles are heteroatoms such as oxygen or nitrogen, heterocycles will be obtained after the cyclization.

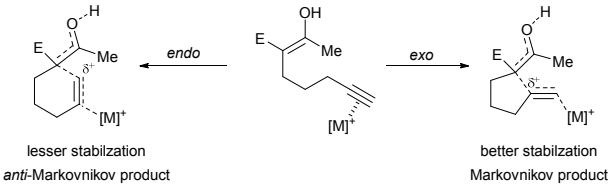


Scheme 4 Common substrates and initiations for Conia-ene reactions.

2.3. About alkynes, alkenes and Baldwin rules

As described by Baldwin, cyclization reactions are influenced by stereo-electronic effects, which have a tremendous impact on the reaction rate and the outcome of the reaction.[10] Based on these guidelines, the presence of alkynes allows for diverse *dig* cyclization modes with the exception of 3- and 4-*exo-dig* while for alkenes the formation of small rings *via* 3-, 4- and 5-*endo-trig* cyclization is in general unfavourable (Scheme 5).

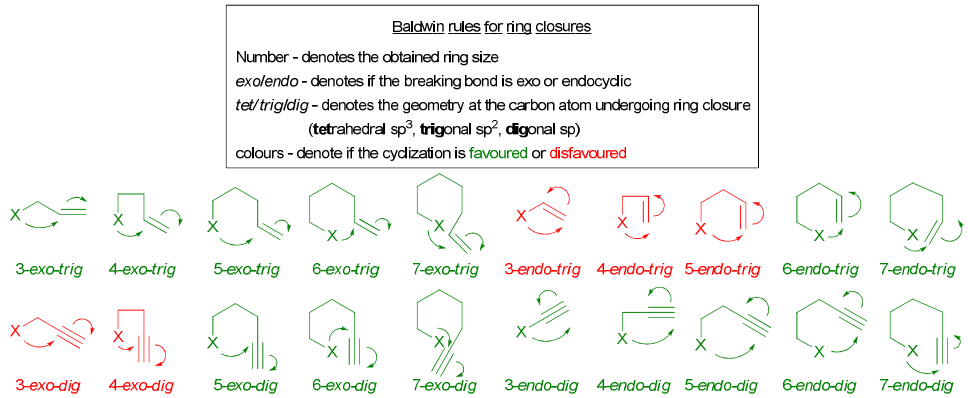
For terminal alkynes the Conia-ene reaction proceeds selectively, with a general bias towards the *exo* cyclization. Thus, 5-*exo* is preferred over 6-*endo*, 6-*exo* over 7-*endo* and the same tendency continues for the formation of larger rings. In contrast, for substrates allowing for 4-*exo* or 5-*endo* cyclization, normally the latter occurs. The strong bias towards *exo* cyclizations is not surprising, because the addition to the internal site of the alkyne benefits from the extra stabilization provided by the additional internal substituent (Markovnikov's addition; Scheme 6). For the formation of larger rings, unfavourable transannular interactions as well as high entropy contributions have to be addressed.



Scheme 6 Electronic effects on the cyclization mode.

The situation becomes more difficult and challenging when internal alkynes are employed, because the electronic differentiation of the two alkyne sides is attenuated and steric constraints between the additional substituent, the catalyst, and the carbonyl moiety have a bigger impact on the outcome of the reaction. Therefore, thorough adjustment of the substituents is of utmost importance in order to achieve a selective cyclization. However, in some cases the formation of regioisomers cannot be avoided.

The use of alkenes for Conia-ene reactions has been explored less, and among the various possible cyclization modes, only 5-*exo*, 5-*endo* and 6-*exo* have been reported. Regrettably, the reactions seem to be limited to terminal alkenes.



Scheme 5 Baldwin rules for ring closing reactions.

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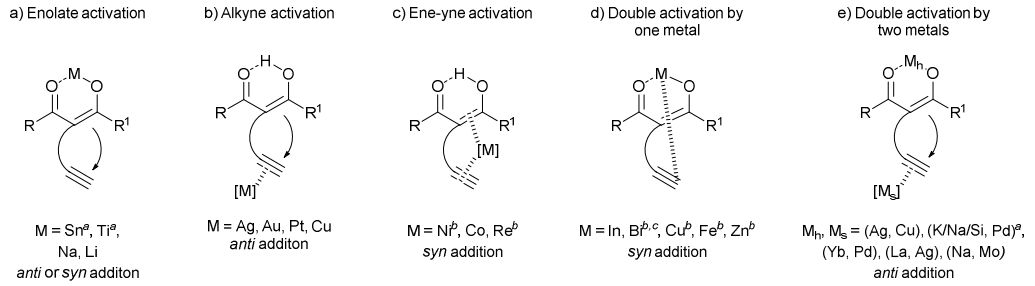


Scheme 7 Different activation modes found for Conia-ene and Conia-ene-related reactions. [a] Stoichiometric amounts of the catalyst or the co-catalyst needed. [b] Mechanism not completely verified. [c] No full account given, meaning no broad scope was investigated.

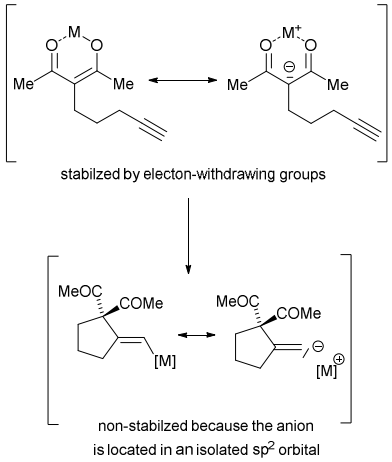
2.4. Activation modes[10]

As suggested by Nakamura and co-workers, Conia-ene and Conia-ene-type reactions can be categorized into five distinct modes of activation (Scheme 7).[11] In genral, commonly employed substrates provide two different sites for activation: the enol, originating from the carbonyl compounds, for nucleophilic and the alkyne or alkene for electrophilic activation. Enols can be converted into enolates or metal enolates by hard Lewis acids and inorganic or organic bases, while the eletrophilicity of alkynes can be enhanced upon coordination to carbophilic Lewis acids. As these two possibilities provide an orthogonal type of activation, there are various examples in literature in which only one activation is sufficient to trigger the outcome of the reaction, but also several examples in which both activations occur hand in hand in a cooperative fashion.

2.4.1. Addition of a metal enolate to unactivated alkynes or alkenes

Examples of Conia-ene-related reactions in which metal enolates add to unactivated alkynes or alkenes are scarce, mainly because the involved carbocyclization is an unfavourable endothermic process. This can be rationalized by the fact that the initially stabilized enolate anion derived from an active methylene compound will be converted to an unstable carbanion at a sp^2 or sp^3 carbon (Scheme 8).

The unfavourable thermodynamic profile can be overcome by different strategies, such as: 1) The presence of an additional metal that can activate the alkyne and assist the *trans* addition of the lithium, potassium, or sodium enolates. However, this reaction strategy then belongs to dual activation by two different metals (**2.4.5.**). 2) The application of Lewis acids which after the carbocyclization generate an intermediate stabilized by intramolecular coordination to the functional groups in close proximity. Popular examples include Ti(IV) and Sn(IV) enolates which add in a *cis*-selective fashion to the alkyne.[12,13] But, as a major drawback, an excess amount of Lewis acids and triethylamine has to be employed. Thus these examples will not be covered in this review. 3) A few strong bases including NaH or *n*BuLi can promote the cyclization if they are used in sub-stoichiometric amounts. Interestingly, the addition then occurs in an *anti* fashion.



Scheme 8 Anion stabilization before and after the cyclization.

2.4.2. Addition of enols to activated alkynes or alkenes

The intramolecular addition of enols to alkynes and alkenes is the domain of the late transition metals, which are often referred to as soft carbophilic Lewis acids, such as Pt, Au, and in fewer cases also Ag and Cu.[14] Upon coordination to the alkyne, an electrophilic activation by the depletion of electron density due to the dominating σ-donation of the olefinic ligand occurs. The coordination can be explained by the Dewar-Chatt-Duncanson model.[15] Conia-ene reactions which occur *via* this mode of activation normally proceed through a *trans* addition of the enol to the activated alkyne generating a vinylmetal intermediate. This intermediate is prone to protodemetallation leading to the final cyclized product by regeneration of the active catalytic species; thus, most reactions of this type can be performed with a sub-stoichiometric amount of metal.

2.4.3. Ene-yne activation

The simultaneous activation of the enol-alkene and the alkyne is normally found for transition metals that are associated with [2+2+2] cycloadditions such as cobalt and nickel. Compared to the other activation modes, ene-yne activation may involve the

change of the oxidation state of the metal. Although the products appear to be derived from a simple Conia-ene reaction, the reaction actually proceeds *via* typical metal organic elementary reactions including oxidative addition, *β*-hydride elimination and reductive elimination.

2.4.4. Dual activation by a single metal

The challenge to find metals which can activate both the enol and the alkyne has attracted considerable attention over the last years. It is indeed difficult to find a judicious catalyst that also concurrently acts as a π-acid for the alkyne activation. For some examples the acidification provided by the chelation of the metal is not sufficient to cause enolization, so that the external organic bases or harsh reaction conditions (microwave irradiation, high temperatures) are still necessary. Due to geometrical constraints these reactions always proceed *via syn* addition of the metal enolate. Interestingly, most metals suitable for this dual activation are not particularly well known for their capability to activate alkynes.[16] But even if the electronic activation of the alkyne is negligible, the reaction still profits from the lower entropy energy contribution, due to the precoordination of the alkyne to the metal centre. Regrettably, from the reported metals including In(III), Zn(II), Fe(III), and Cu(I), only the reaction with indium has been fully understood.

2.4.5. Dual activation by two different metals

Basically, this activation mode is the merger of the enol activation (**2.4.1.**) and the alkyne/alkene activation (**2.4.2.**). In general, the enol activation normally demands for hard metal ions (early transition metals) with high oxygen affinity, which can promote chelation-assisted enolization/deprotonation of the carbonyl compound, while softer carbophilic Lewis acids (late transition metals) are needed for the activation of triple or double bonds.

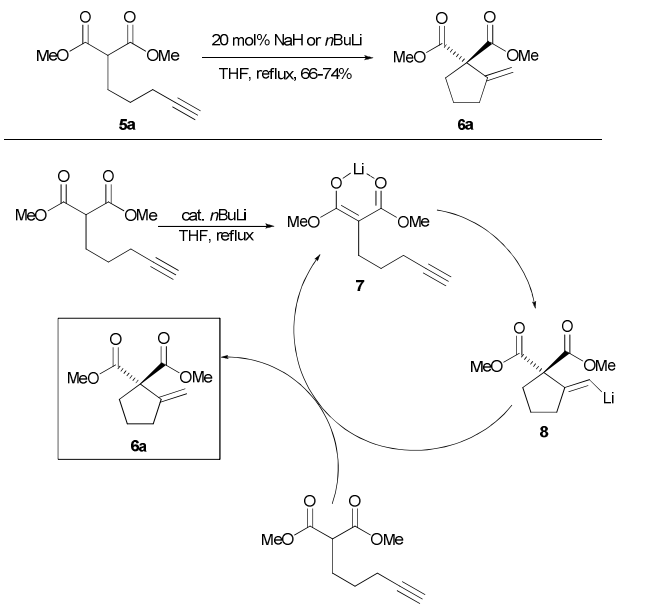
These reactions will usually proceed *via anti* addition, similar to reactions that involve pure alkyne activation. Interestingly, it has turned out that in general it is more challenging to find suitable reaction conditions for which only sub-stoichiometric amounts of the harder Lewis acids are required. However, while there are many protocols where stoichiometric amounts of the harder metal are necessary, this strategy provides the possibility for asymmetric reactions because the harder metals allow for an easy coordination of chiral ligands.

3. Seminal Publications

3.1. Enolate activation

One rare example of a catalytic pure enolate activation was reported by Taguchi and co-workers.[17] They demonstrated that the alkyne-tethered malonate **5** underwent clean cyclization to the corresponding cyclopentane **6** in excellent yields in the presence of sub-stoichiometric amounts of NaH or *n*BuLi in THF at reflux (Scheme 9). Since stoichiometric amounts of the catalysts provided strongly diminished yields, the authors proposed that using sub-stoichiometric amounts of the catalysts was pivotal for their reactivity. Indeed, the observed carbolithiation of **7** is an unfavourable process, but the irreversible protonation of the generated non-stabilized vinyl anion **8** by the remaining acidic starting material addresses this problem by attenuating the initial critical thermodynamics. In consequence, this protonation is virtually impossible when the starting material is fully converted into its corresponding enolate with stoichiometric amounts of the bases. This rationale was further confirmed when the assisting presence of an additional proton source, in this case simple dimethylmalonate, led to a slight increase in yield. Interestingly, KO*t*Bu is not a suitable catalyst for this transformation and the presence of an additional metal for further activation is necessary (see double activation by two metals, Scheme 7e).

Under the optimized reaction conditions, a range of different carbonyl compounds **5** underwent clean cyclization with moderate to excellent yields, including highly acidic cyano esters, sulfonyl esters and phosphonoesters (Scheme 10). It was also shown, that *ω*-alkynyl *β*-ketoesters were amenable to cyclization, giving the corresponding cyclopentanone **9** in moderate yield. Noteworthy, the cyclization of the *in situ* generated substrate **10** suggested that the cycloaddition proceeds *via* a *trans* addition of the enolate, due to **11** being obtained as *Z*-diastereomer.



Scheme 9 Alkali metal-catalyzed Conia-ene-related reaction.

3.2. Reactions with pure alkyne activation

Cationic gold(I) complexes are considered to be among the most important and influential catalysts for Conia-ene reactions under exceptionally mild reaction conditions. After the seminal publication of Teles and co-workers reporting on the intermolecular addition of water to alkynes, the field of homogeneous gold catalysis experienced a tremendous growth in the last decade,.[18] Before 1998 gold was more or less

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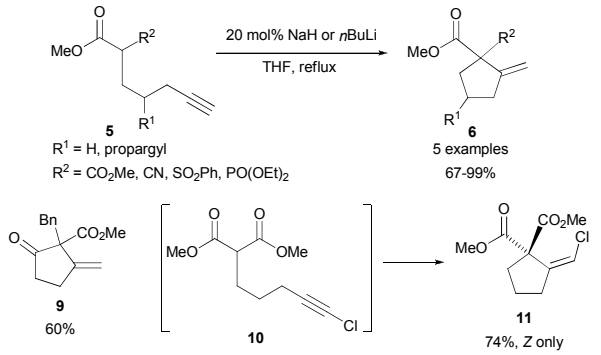
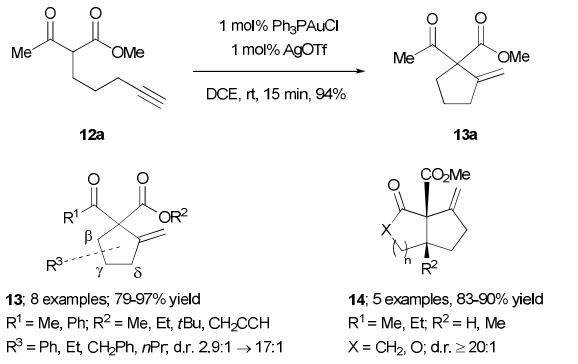
considered to be catalytically not active, but soon thereafter a myriad of publications appeared, reporting on the gold-catalyzed addition of heteroatom and carbon nucleophiles to alkynes in which gold acted as carbophilic π-acid.[19]



Scheme 10 Scope of alkali metal-catalyzed Conia-ene-related reaction.

The first entry on gold-catalyzed Conia-ene reactions dates back to early 2004, when Toste and co-workers discovered the cyclization of α-(ω-acetylenic)β-ketoesters **12a** to *exo*-methylene cyclopentanes **13a** (Scheme 11).[20] After fruitless attempts to drive the reaction using silver salts and the observation that $AuCl_3$ mainly led to fast decomposition of the starting material, the presence of only 1 mol% of $[Ph_3PAu]OTf$ enabled the full conversion of the starting material within 15 minutes at room temperature in dichloroethane. The active gold species was generated in situ by either anion metathesis using Ph_3PAuCl and AgOTf or by protonation of $[(Ph_3PAu)_3O]BF_4$ in the presence of triflic acid.



Scheme 11 Gold-catalyzed 5-*exo-dig* cyclization of β-ketoesters.

Under the optimized conditions, the conversion of a variety of diversely substituted β-ketoesters **12** was possible. Good to excellent yields were obtained in all cases, tolerating different substituents on the ketone (R^1), ester (R^2) and alkyl substituents in the β-, γ-, δ-position, with the latter generating a diastereomic mixture. In the case of cyclopentanones as starting materials, *cis*-fused 5,5-bicyclic ketones **14** were obtained in good results as single diastereomers, respectively. Following this strategy, it was also possible to synthesize 6,5- and 7,5-bicyclic ring structures with comparable results.

For the majority of examples, the cyclization proceeds *via* a 5-*exo-dig* cyclization, although the corresponding 6-*endo*-dig cyclization would also be feasible in principle. The strong bias towards 5-*exo* might arise from electronic and steric reasons. As the positive charge that builds up during the transition state is more stabilized on the internal side of the alkyne enol, addition will be favoured there (Markonikov addition). Also the vinylgold intermediate **16,** arising from a 6-*endo-dig* cyclization, would suffer from steric strain because the gold catalyst and the ester or ketone moiety would end up in closer proximity to each other (Figure 1).

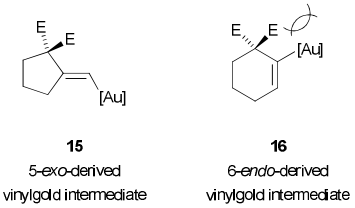
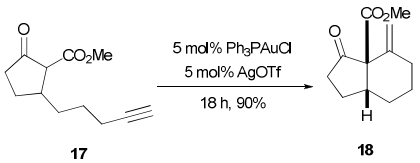


Figure 1 Steric constraints for *exo* and *endo* cyclizations.

Interestingly, by introducing a further methylene group between the β-ketoester and the alkyne, product **18**, derived from the 6-*exo-dig* cyclization of **17** , was obtained in excellent yield (Scheme 12). However, even with an increased catalyst loading of 5 mol% the reaction was rather slow in comparison to the previously mentioned examples, thus indicating that the activation energy for 5-*exo* cyclizations seems to be lower in general.

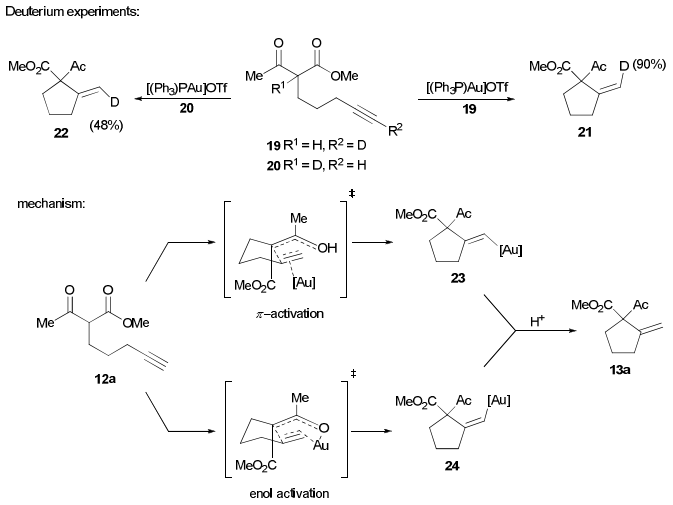


Scheme 12 Observed 6-*exo* cyclization.

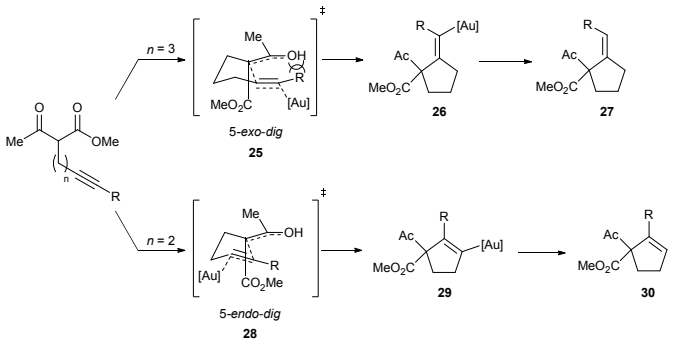
Toste and co-workers proposed that the observed Conia-ene reaction proceeds *via* the *anti* addition of the enol to the activated alkyne (Scheme 13, upper pathway). To rule out the possibility that the cyclization occurs *via* nucleophilic activation of the enol by the formation of a gold enolate (Scheme 13, lower pathway), deuterium-labeled substrates **19** and **20** were exposed to similar reaction conditions. It turned out that D in product **21** (from substrate **19**) was *syn* in respect to the ketoesters, while in product **22** it was found to be *anti*. These results clearly favour the upper mechanistic pathway, which also accounts for the poor reactivity of malonates and β-ketoamides. For those substrates the enol formation is hampered due to the 1,3-allylic strain of the enol tautomers.

As the substrates were restricted to terminal alkynes only, Toste and co-workers wondered if it was possible to extend the scope of the gold-catalyzed Conia-ene reaction to internal alkynes. However, the corresponding 5-*exo-dig* cyclizations would suffer from 1,3-allylic strain in the transition state **25** making cyclizations energetically unfavourable (Scheme 14).

Because reports on 5-*endo* cyclization of carbon nucleophiles were scarce at the time, they envisioned to circumvent the steric constraints by using internal alkynes suitable for 5-*endo* cyclization instead. In theory, 1,3-allylic strain should not occur in those substrates, thus allowing for selective cyclization under mild reaction conditions (Scheme 14, lower part).



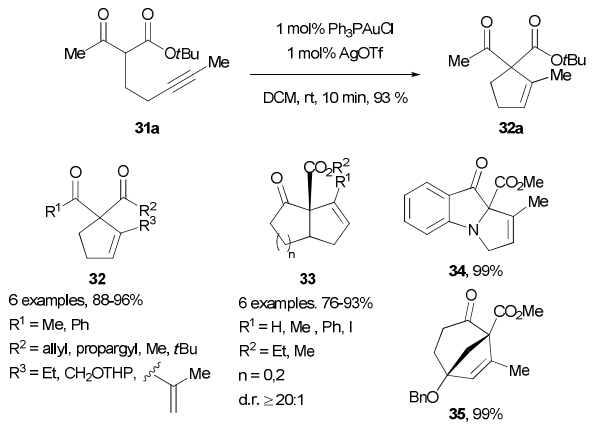
Scheme 13 Deuterium labelling experiments and proposed reaction mechanism for the gold-catalyzed 5-*exo* cyclization.



Scheme 14 Steric constraints of internal alkynes for 5-*exo* and 5-*endo* cyclizations.

Indeed, in their seminal publication in late 2004 they were able to demonstrate that the *β*-ketoester **31a** underwent clean cyclization *via* 5-*endo*-dig to the corresponding cyclopentene **32a** in the presence of 1 mol% $[Ph_3PAu]OTf$ as catalyst (Scheme 15).[21]

Under the same reaction conditions a broad scope of substrates underwent cyclization including aliphatic and cyclic *β*-ketoesters with different substituents on the alkyne, ketone, and ester moiety. Due to the exceptionally mild reaction conditions, acid-labile groups including *tert*-butyl esters and tetrahydropyranyl ethers were also tolerated. All cyclopentene products **32** were obtained in good to excellent yields and the competing 4-*exo*-derived products were never observed for all conducted experiments. However, a longer reaction time was required for sterically more demanding substrates such as aryl ketones (R^1 = Ar) or cyclopentanones (**33**, n = 2). Remarkably, no 5-*exo-dig* cyclization was observed with a propargyl ester-derived product (**32**, R^1, R^3 = Me, R^2 = propargyl). As previously demonstrated, cyclic substrates led to bicyclic scaffolds **33** with excellent diastereoselectivity. In addition to the more complex cyclized products **34** and **35**, diketones also represented suitable nucleophiles for the presented cyclization mentioned earlier.



Scheme 15 Optimization and scope for the gold-catalzyed 6-*endo* cyclization.

Shortly thereafter, Gagosz and co-workers demonstrated that $[Ph_3PAu]NTf_2$ is also a suitable catalyst for Conia-ene reactions.[22] Silver salts used for the activation of gold catalysts are highly hygroscopic, which makes weighing troublesome and which can lead to the generation of acids, e.g. TfOH. Considering the acid incompatibility of many substrates and that the presence of water can lead to disfavoured hydration of the alkyne, Gagosz and co-workers focused on the synthesis of $[Ph_3PAu]NTf_2$ catalyst in order to circumvent the initial shortfalls of other gold catalysts.[23] The catalytic salt is air stable, non-hygroscopic, and more stable than salts with fluorine-based counter anions.[24] The absence of silver during the catalyzed reaction can also have a serious impact on the reactivity as shown by Shi and co-workers.[25] The catalytic activity was demonstrated on *α*-(*ω*-acetylenic) *β*-ketoester **12a** (the same substrate used for his initial studies by Toste 2004, Scheme 11) and the cyclized product **13a** was obtained in 96% yield after 30 min with 1 mol% of catalyst or within 60 min in 93% yield with 0.1 mol% catalyst loading. In conclusion, the newly developed $[Ph_3PAu]NTf_2$ provides a higher TON and TOF (93000; 25.8 s^{-1}) than $[Ph_3PAu]OTf$ (9400; 10.4 s^{-1}) and can therefore be used as good alternative for gold-catalyzed Conia-ene reactions.

As the initial reports on gold-catalyzed reactions were mainly restricted to 5-*exo* and 5-*endo* cyclizations, Sawamura and co-workers focused on the development of efficient catalysts for 6-*exo* cyclizations.[26] In general, 6-*exo* cyclizations of *β*-ketoesters containing a terminal alkyne have always been challenging, because the substrates possess too many rotational degrees of freedom, which leads to a higher activation entropy

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and a poor overall conversion. For this purpose they designed gold catalysts containing novel triethynylphosphines **A** and **B** (Figure 2).

These phosphines provide minimum steric demand around the phosphor centre, while bulky substituents on the outer sphere protect the internal alkynes of the ligand from metal co-

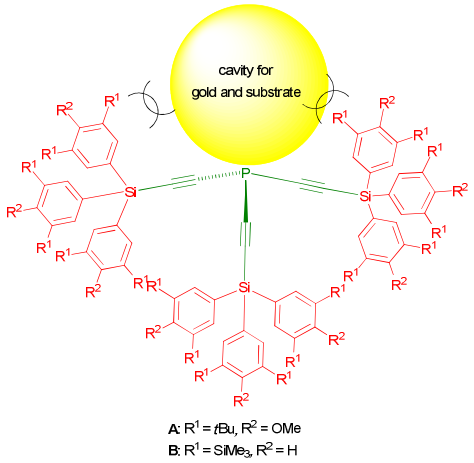
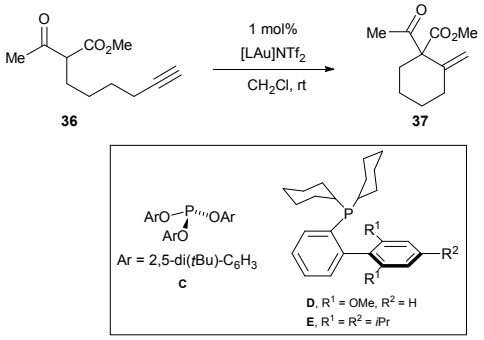


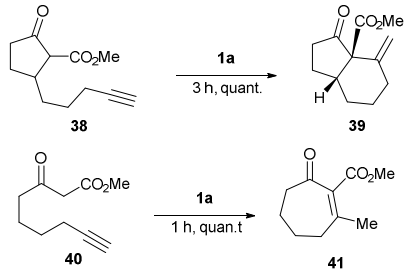
Figure 2 Triethynylphosphines as ligands in gold catalysis.

ordination. Thus, these phosphines can be used as η^1-ligands for gold catalysis. Sawamura and co-workers anticipated that the small cavity created by the outer sphere substituents would force the enol into a closer proximity to the activated alkyne, thus overcoming the initial entropy barrier. Indeed, at room temperature and in the presence of 1 mol% of [**A**Au]NTf_2 the *β*-ketoester **36** underwent fast cyclization to the 6-*endo*-derived product **37** in 90 minutes with full conversion as indicated by ^{1}H NMR spectroscopy (Scheme 16).



Scheme 16 6-*exo* cyclization catalyzed by novel triethynylphosphine catalysts.

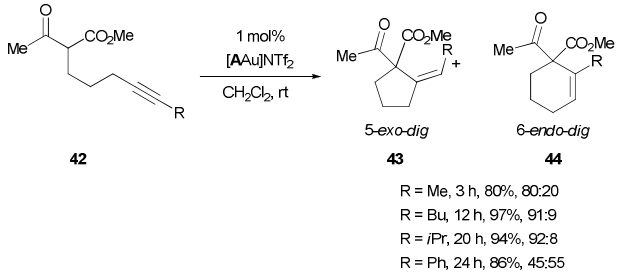
In contrast, [Ph_3PAu]NTf_2 gave only 3% conversion in the same reaction time, while triarylphosphite [**C**Au]NTf_2 complexes seemed more active with up to 30% conversion and other gold catalysts, such as the Echavarren-type biphenyl catalysts [**D**Au]NTf_2 and [**E**Au]NTf_2, even failed to promote the reaction. In addition, triethynylphosphines with less bulky substituents led to lower conversion indicating that the bulkiness of the ligand has an effect on the reaction rate. However, the difference in catalytic activity between [Ph_3PAu]NTf_2 and **A** was less pronounced in the case of the cyclic ketoester **38** and cyclization to **39** occurred with 80% and 100% in three hours, respectively (Scheme 17). This is in accordance with the catalysts' design, because cyclic substrates possess fewer degrees of freedom, so that the entropy barrier should therefore be smaller for such substrates in general. Interestingly, it was also possible to achieve a 7-*exo* cyclization of the ketoester **40** to form the cycloheptenone derivative **41** with quantitative yield; however, isomerization of the double occurred under the applied reaction conditions. For the latter reaction, triethynylphosphines were again superior to PPh_3.



Scheme 17 6-*exo* and 7-*exo* cyclization of *β*-ketoesters **38** and **40**.

Inspired by their initial results and given that reactions with triethynylphosphine ligands were scarce at that time, Sawamura and co-workers exploited further applications of these ligands for Conia-ene reactions. They started focusing on the cyclization of *β*-ketoesters **42** with tethered internal alkynes, which can either undergo 5-*exo*-*dig* or 6-*endo*-*dig* cyclization to sterically congested five- and six-membered rings (Scheme 18).[27]

With only 1 mol% of [**A**Au]NTf_2, it was possible to obtain a mixture of **43** and **44** in dichloromethane at room temperature within 3-24 hours. The ratio of products was strongly dependent on the steric bulk of the substituent R, but for the majority of cases higher amounts of the *exo*-product were obtained. As a tendency, the reaction time and the amount of 5-*exo* product increased with growing bulkiness of R (Me < Bu < *i*Pr). While full conversion was generally observed for gold complexes with **A**, PPh_3, $P(OPh)_3$, and less bulky triethynylphosphines either failed to promote the reaction or gave only limited conversions below 23%. It is noteworthy though that PPh_3 leads to a more favourable ratio of *exo*/*endo* products, with slightly better ratios for the *exo*-derived products.



Scheme 18 Competing 5-*exo* and 6-*endo* cyclization of internal alkyne-tethered ketoesters.

The authors compared the different transition states to account for the observed bias towards the 5-*exo-dig* cyclization. In both transition states two predominant steric repulsions are present: the repulsion between the incoming nucleophile and the substituent on the alkyne and the repulsion between the substituent R and the gold catalyst. They suggest that the latter is small in the 5-*exo* transition state **45**, because gold and R are in geminal position to each other, while this repulsion becomes more dominant for the corresponding 6-*endo* cyclization **46**. Thus, for bulky substituents R 5-*exo* cyclization is more favourable.

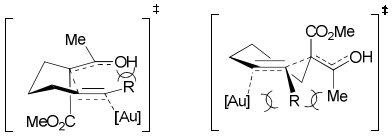


Figure 3 Evaluation of the steric influences on the 5-*exo* and 6-*endo* transition states.

As can be clearly seen from the previous examples, phosphines have been proven to be valuable ligands for gold catalysis. However, while generally the phosphine gold catalysts are stable compounds, the synthesis of novel phosphines often turns out to be cumbersome due to their air and moisture susceptibility. Therefore, Yang and co-workers shifted their attention to thiourea catalysts, which had been applied for other transition metals with great success.[28] Using the same substrate **12a** as Toste and co-workers in 2004, they demonstrated that the activated preformed gold thiourea catalyst [**F**Au]OTf gave the best results. Among the different catalysts tested, 1 mol% of the gold catalyst [**F**Au]OTf gave the cyclized product **13a** in a comparable yield of 93% at room temperature in CH_2Cl_2, but the reaction was significantly slower (4.5 hours vs. 15 min for [Ph_3PAu]OTf).

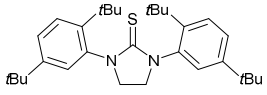
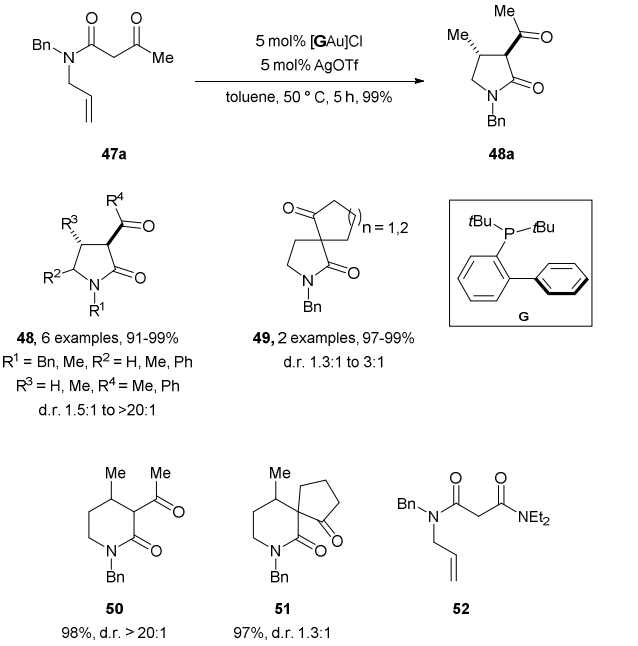


Figure 4 The most promising thiourea ligand for gold-catalyzed reactions.

While the newly developed thiourea gold catalysts provided no remarkable advantage at first glance, it turned out that these catalysts excelled at challenging substrates including ketoamides, lactams and diketones, which underwent no cyclization in the presence of [Ph_3PAu]OTf. Also, sterically more congested substrates such as lactones and *β*-ketoaryl esters were obtained with higher reaction rates. However, for less challenging substrates present in the scope of Toste and co-workers, the thiourea gold catalysts only demanded for a longer reaction time without any crucial change in terms of yield.

While the first reported examples of gold-catalyzed Conia-ene reactions have always relied on alkyne activation, Che and co-workers tried to apply alkene-tethered *β*-ketoamides for the synthesis of pyrrolidines.[29] At that time, only palladium-catalyzed intramolecular hydroalkylations of alkenes with *β*-diketones had been known, however, these cyclizations are limited to 6-*endo-trig*-derived products.[30]

They demonstrated that the *β*-ketoamide **47a** underwent clean cyclization to the corresponding pyrrolidinone **48a** in the presence of different gold catalysts (Scheme 19). Among the different catalysts tested, Ph_3PAuCl afforded the lactam **48a** in 87% at 90 °C after 10 hours. In contrast, the use of bulky biphenyl-phosphine-derived gold catalysts, developed by Echavarren and co-workers, allowed for milder reaction conditions giving higher yields (97%) at 50 °C after 5 hours.[31]



Scheme 19 Gold-catalyzed Conia-ene reaction for the synthesis of pyrrolidines.

In the presence of 5 mol% of [**G**Au]OTf a variety of substrates was tested, giving the corresponding products in excellent yields (91-99%) without any traces of 6-*endo-trig*-derived products. In general, acyclic *β*-ketoamides afforded the lactams as a single diastereomer, while cyclic substrates underwent cyclization with only moderate diastereoselectivity (1.3:1 to 3:1). In addition, further substituents on the *α*-position of the allyl-moiety (R^2) did not have a noticeable effect on the reaction; however, substituents R^3 on the alkene led to a deteriorated reaction rate and higher temperature had to be applied for the conversion. Substrates having an additional methylene group and are therefore able to undergo either 6-*exo-trig* or 7-*endo-trig*, gave the corresponding 6-*exo-trig*-derived piperidinones **50** and **51** in excellent yields. This proposed mechanism closely resembles the one discussed above by Toste and co-workers (Scheme 14), where the replacement of the alkyne by the alkene is the major difference. Apart from that, the reaction proceeds *via* familiar steps: enolization, alkene activation, cyclization, and subsequent protodeauration. The mechanism was further supported by mass spectrometry

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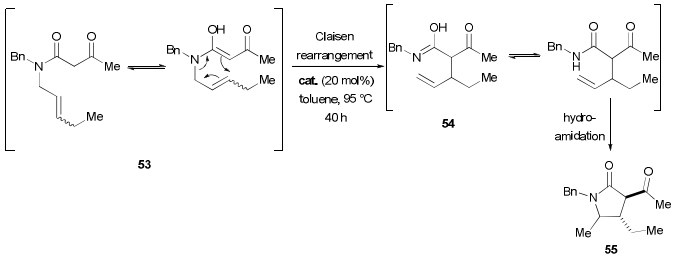
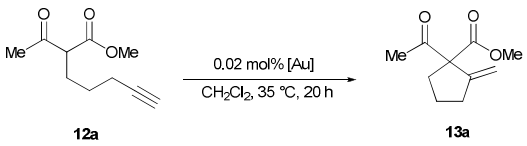
experiments with substrates that offer an alkene moiety for the catalyst coordination, but for which enolization was hampered, so that no cyclization could occur (diamides and amide esters). Thus, a complex consisting of an unreactive alkene-tethered amide ester **52** and [**G**Au]$^+$ could be detected by MALDI-TOF experiments. Interestingly, experiments with internal alkenes indicated that a different mechanism must be operating for those substrates, because the same diastereomer was obtained irrespective of the geometry of the alkene **53** (*Z* and *E*). Therefore it was concluded that the reaction proceeds *via* a Claisen rearrangement to the intermediate **54**, followed by a subsequent gold-catalyzed hydroamination (Scheme 20). Indeed, using the intermediate **54** as starting material led *via* hydroamination to the desired product **55** in the presence of the gold catalyst, further supporting this proposed mechanism.



Scheme 20 Proposed reaction mechanism for substrates with internal alkenes.

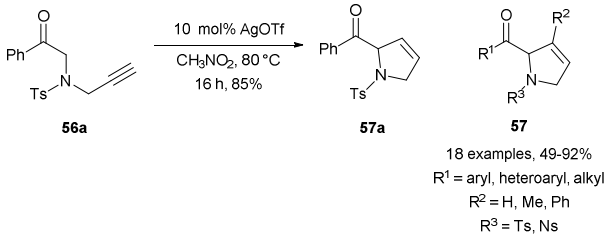
Recently, Corma and co-workers have demonstrated that gold clusters consisting of 3-6 atoms can also act as efficient catalysts for different carbon-carbon and carbon-heteroatom bond-forming reactions.[32] Opposite to gold nanoparticles, small gold clusters still have defined HOMO and LUMO frontier orbitals, which for example enable the activation of alkynes or alkenes. In the presence of 0.2 mol% TfOH, Au_5-clusters were generated from 0.2 mol% of $AuCl_3$ or AuCl, as indicated by fluorescence analysis and MALDI-TOF experiments. Their catalytic behaviour was tested for the typical gold-catalyzed cyclization of *β*-ketoester **12a**, and the product was obtained with 76% yield under mild reaction conditions (Scheme 21). In contrast, other commonly applied gold catalysts failed to promote the reaction at such a low catalyst loading. Unfortunately, no further examples for CERs are given in this seminal publication, but other examples for gold-catalyzed reactions confirm the general applicability of gold clusters.



$[PPh_3Au]Cl+AgOTf$	0% (> 99% for 3 mol%)
AuCl or $AuCl_3$	0% (~30% for 10 mol%)
TfOH (0.2 mol%)	0%
$AuCl_3$+TfOH (0.2 mol%)	52%
AuCl+TfOH (0.2 mol%)	76%

Scheme 21 Gold cluster-catalyzed Conia-ene reaction.

In 2013 Wang and co-workers demonstrated that it is not always necessary to activate terminal alkynes with gold(I) complexes which are generated *in situ* from gold(I) halides and silver(I) salts as explained earlier.[33] They used various silver salts for the conversion of *β*-ketopropargylamines **56** to substituted 3-pyrrolines **57** *via* a 5-*endo* Conia-ene reaction (Scheme 22).



Scheme 22 Silver-catalyzed Conia-ene reaction.

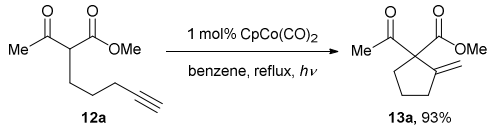
It is noteworthy that in this heterocycle-focused approach, most other metal sources including Cu(I), In(III), Sc(III), Zn(II), and Fe(III) as well as triflic acid failed to promote the reaction even at elevated temperatures, while Au(I) catalysts led to the complete hydration of the alkyne in dichloroethane at room temperature. Among various silver salts, it turned out that 10 mol% of AgOTf in nitromethane at 80 °C gave the desired product **57a** in 85% yield after 16 hours. The reaction occurred without isomerization of the double-bond formed and seemed to be completely selective since no traces of the 4-*exo* product were observed.

With these optimized conditions in hand, different *β*-ketopropargylamines **56** were tested to demonstrate the general applicability of the reaction. Irrespective of the nature of the ketone employed, good results were obtained for different aryl, heteroaryl and alkyl groups. In addition, internal alkynes were also converted to the corresponding 3-pyrrolines, albeit with moderate to good yields. Interestingly, the reaction seems to be restricted to sulfonamides (R^3 = Ts and Ns), as tertiary amines (R^3 = Me, Ph) and amides (R^3 = Ac) did not react. The obtained 3-pyrrolines find broad application in biology and chemistry and can be converted further into the corresponding pyrroles by base-mediated desulfonylation.

From a mechanistic point of view, a 5-*endo-dig* cyclization from the generated enol to the activated alkyne was proposed, followed by protodemetallation similar to a gold(I) cycle. This reaction is the first in which simple ketones were used in catalytic Conia-ene reactions. It is remarkable that the reaction proceeds under such mild conditions considering the unfavourable enolization of ketones. Possibly, tautomerization to the enol is favoured due to the presence of the strongly electron-withdrawing sulfonamide nitrogen atom. This could explain why the reaction with more electron rich nitrogen derivatives (tertiary amines and amides) did not work. The fact that small amounts of triflic acid are formed throughout the reaction might be beneficial for the faster equilibration of the different tautomers.

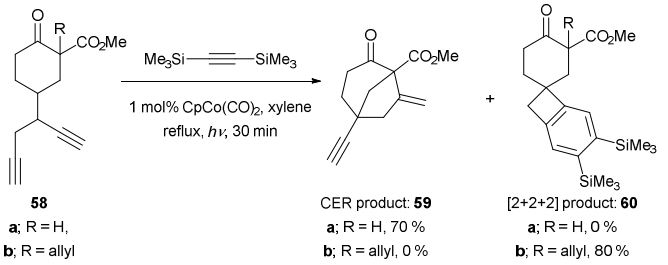
3.3. Ene-yne activation

The most elaborate system to date is the selective 5-*exo*-*dig* cyclization of acetylenic-β-ketoesters in the presence of the η^5-(cyclopentadienyl)-cobalt dicarbonyl half sandwich complex. In their seminal publication from 1994, Stammler and Malacria demonstrated that the α-(ω-acetylenic)β-ketoester **12a**, the bench-mark substrate for Conia-ene reactions, underwent clean cycloisomerization to the corresponding methylene cyclopentane derivative **13a** in 93% yield in the presence of 1 mol% $CpCo(CO)_2$ under irradiation in boiling toluene after one hour (Scheme 23).[34]



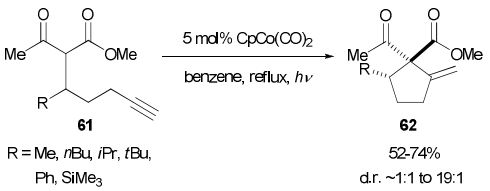
Scheme 23 Cobalt-catalyzed Conia-ene reaction.

The reaction can be performed at higher temperature in solvents like xylene with an increased reaction rate, but simultaneous isomerization of the double bond occurs. For substrate **58a**, which could, in principle also undergo a competing [2+2+2]-cycloaddition in the presence of (bistrimethylsilyl) ethyne, only the ene-derived biycyclo[3.2.1]octane **59a** was obtained in 70% yield (Scheme 24). The [2+2+2] product **60b** was only obtained if the generation of the enol was not possible (R = allyl) indicating that the reaction is highly chemoselective.



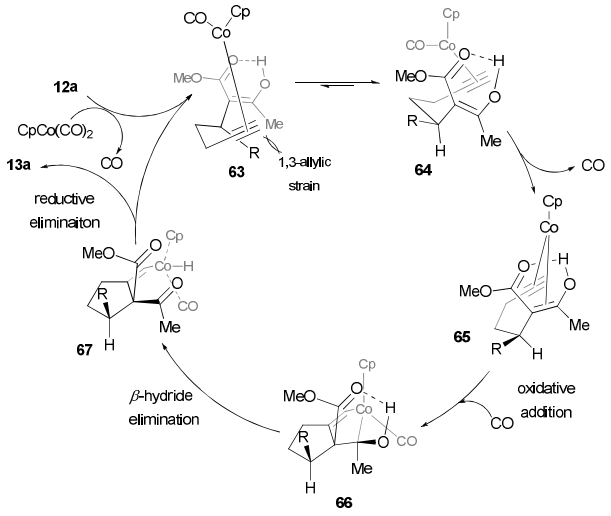
Scheme 24 Exploitation of the chemoselectivity provided by Co-catalyzed Conia-ene reactions.

Based on these experiments, Malacria and co-workers considered using β'-substituted acetylenic β-ketoesters.[35] They anticipated that the presence of a substituent in the β'-position would enable the stereocontrol on the two contiguous stereogenic centres in the product. With an increased catalyst loading of 5 mol%, they were able to obtain the 5-*exo*-derived products **62** in moderate to good yields with a moderate to high level of diastereoselectivity (Scheme 25). Apparently, the increasing size of the β'-substituents leads to more favourable diastereomeric ratios (Me < *n*Bu < *i*Pr < *t*Bu), which is in accordance with the proposed mechanism.



Scheme 25 Cyclization of β'-substituted β-carbonyl substrates.

The mechanism starts with an irradiation-assisted dissociation of one of the two carbonyl ligands from the stable 18 valence electron complex, thus creating a vacant binding site on the cobalt catalyst (Scheme 26). After the alkyne coordination, another CO ligand can dissociate allowing for the coordination of the alkene (enol). Subsequent oxidative addition leads to the cobalt complex **66** that undergoes β-hydride elimination to the cobalt vinyl intermediate **67**. Finally, reductive elimination generates product **13a** with retention of the *E*-configuration, which can dissociate from the cobalt complex and the catalyst can enter the next catalytic cycle. In addition, they observed that the diastereoselectivity can be reasonably explained by this model. For the two different rotamers **63** and **64**, that are formed after the complexation of the alkyne, the 1,3-allylic strain, which is imposed by the conformational rigidity of the enol-yne cobalt(I) complex, is higher for rotamer **63**. Thus, the reaction proceeds preferably *via* rotamer **64**. Only in the case of CH_2SiMe_3, an antagonistic 1,2-steric interaction seemed to lower the diastereoselectivity.



Scheme 26. Mechanism of the Co-catalyzed Conia-ene reaction.

In 1999 Malacria and co-workers tried to expand their previous work by using δ'-substituted β-ketoesters **68**. They envisioned the synthesis of triquinane derivatives by combining the cobalt-catalyzed Conia-ene-type reaction with a subsequent cobalt-catalyzed Pauson-Khand reaction.[36] For the first step of this sequence, the 5-*exo*-*dig* derived products **69** were obtained in good to excellent yields under the typical reaction conditions (5 mol% $CpCo(CO)_2$, toluene at reflux, irradiation), albeit with low diastereoselectivity (Scheme 27). The low selectivity is not

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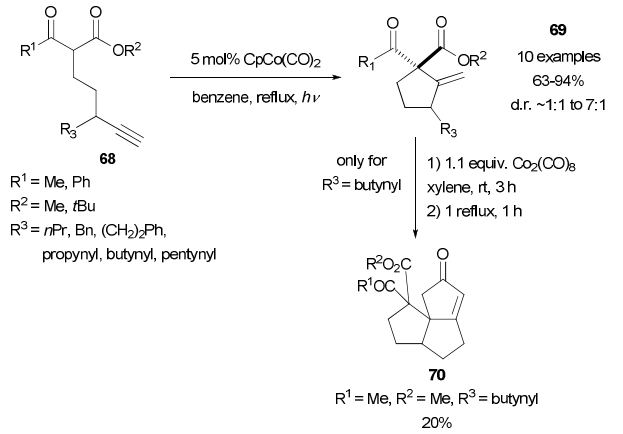
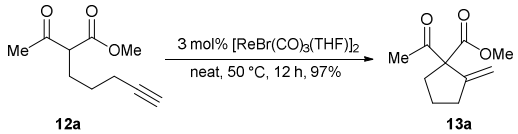
suprising, considering the lack of a differentiating 1,3-allylic strain for the two rotamers prior the cyclization. Unfortunately, the subsequent Pauson-Khand reaction turned out to be quite challenging, and the desired product **70** was obtained in only one case with 20% yield in the presence of stoichiometric amounts of $Co_2(CO)_8$ in benzene at reflux.

In summary, this cobalt-catalyzed Conia-ene reaction demonstrates an early example of a transition metal-catalyzed Conia-ene reaction. Although the catalyst loading was acceptable at that time, the reaction proceeded only under harsh reaction conditions, thus limiting the scope of the reaction. In addition, the catalyst is highly air sensitive and the reaction has to be performed with dry solvents under an argon atmosphere. Ultimately, the catalyst does not provide any significant advantage in terms of scope, yield or selectivity, therefore other catalysts that allow for milder reaction conditions can be used for similar reactions.



Scheme 27 Co-catalyzed Conia-ene and Pauson-Khand reaction.

Despite the obvious initial potential of the cobalt catalysis, not much effort was directed towards the ene-yne-activating systems.[37] In 2005 Kuninobu and co-workers showed that the dimeric $[ReBr(CO)_3(THF)]_2$ complex can function as a catalyst for the intermolecular addition of acetylacetone to acetylene derivatives under mild reaction conditions. Although the main focus was directed towards the intermolecular reaction, they also reported one example with the common *β*-ketoester **12a**, which underwent clean cyclization to the product **13a** in 97% in the presence of 3 mol% catalyst (Scheme 28). Complete verification of the reaction mechanism has not been undertaken, but a mechanism similar to Co(I) was proposed.



Scheme 28 Re-catalyzed Conia-ene reaction of ketoester **12a**.

Yang and co-workers reported that a bimetallic system of $Ni(acac)_2$ and $Yb(OTf)_3$ also enabled the cyclization of the *β*-ketoester **12a**.[38] Initial experiments revealed that the cyclized product could be obtained with 83% yield in the presence of 10 mol% $Ni(acac)_2$ and 20 mol% $Yb(OTf)_3$ in THF at 50 °C after 12 hours. Notably, this reaction also proceeded without the presence of the Yb co-catalyst, but with a deteriorated reaction rate. Because excess amounts of $Yb(OTf)_3$ only led to drastically diminished yields, the authors envisioned, that $Yb(OTf)_3$ might not be involved in the actual cyclization, but in the generation of the more active $Ni(OTf)_2$.

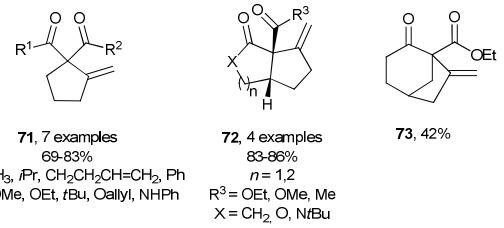


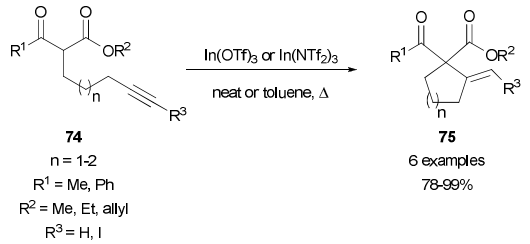
Figure 5 Scope of the Ni-catalyzed Conia-ene reaction.

In contrast to the Co(I)-catalyzed cyclizations, the milder reaction conditions associated with Ni(II) allow for a broader applicability tolerating various *β*-ketoesters, diketones, and also such challenging substrates like *β*-ketoamides. However, generally longer reaction times were required for bulky substrates. The reaction was also amenable to cyclic substrates **72** including lactons and lactams generating bicyclic key structures in good yields.

Mechanistic experiments were undertaken, but although deuterium labelling experiments clearly indicated *syn* addition, the progression of the reaction remained unclear. Ni(II) is isoelectronic to Co(I), thus a similar activation mechanism *via* ene-yne activation can be proposed being in accordance with the observed stereoselectivity.

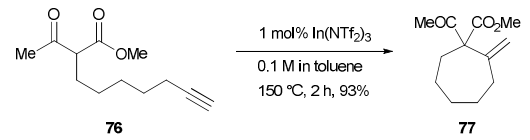
3.4. Double activation by one metal

Initially, in the early 2000s Nakamura and co-workers used $In(OTf)_3$ for the intermolecular addition of malonates and *β*-ketoesters to alkynes.[39] But it was not until late 2007 that they considered the application of indium salts for the corresponding intramolecular reaction. They demonstrated that $In(OTf)_3$ or $In(NTf_2)_3$ were efficient catalysts for the cyclization of *α*(*ω*'-alkynyl)-*β*-ketoesters **74** yielding 5-*exo* or 6-*exo*-derived products **75** (Scheme 29).[11] For the formation of five-membered rings an extremely low catalyst loading of 0.01 mol% was sufficient in order to obtain the desired products in good to excellent yields (78-99%) under neat conditions at 60 °C within 24 to 72 hours. For higher catalyst loading, isomerization of the *exo* double bond to an internal alkene occurred, possibly due to the generation of HOTf or $HNTf_2$. Similar results were obtained for *β*-ketoesters which undergo cyclization to cyclohexanes (n = 2), but higher catalyst loadings had to be employed in that case. Notably, an iodo-alkyne-tethered substrate (R^3 = I) gave the expected alkenyl iodide product with exclusive *E* geometry indicating that addition of a possible indium enolate to the alkyne occurs in a *cis* fashion.



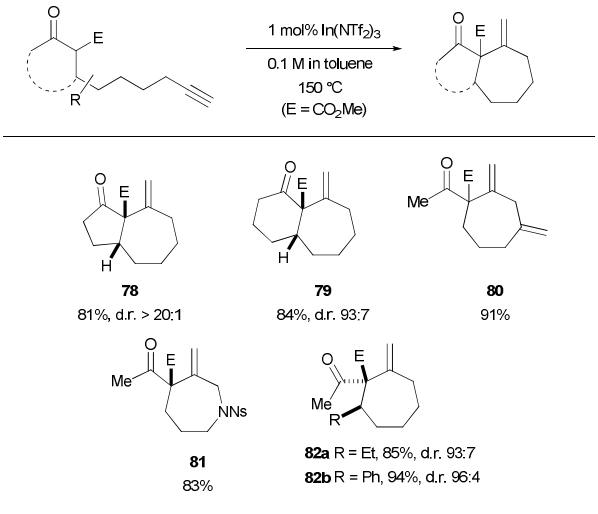
Scheme 29 Indium-catalyzed 5-*exo* and 6-*exo* cyclization of *β*-ketoesters.

Based on these results, Nakamura and co-workers tried to extend the scope of their reaction to substrates, which can undergo a cyclization to seven-membered rings. However, the cyclization of the *β*-ketoester **76** using $In(OTf)_3$ under similar conditions gave the desired product **77** in only 40% yield. The initial shortcomings could be circumvented though by application of $In(NTf_2)_3$ yielding **77** in 93% yield after 2 hours at 150 °C in toluene (Scheme 30). Possibly, the increased steric bulkiness of the NTf_2 anion prevents the deactivation of the active indium cation.



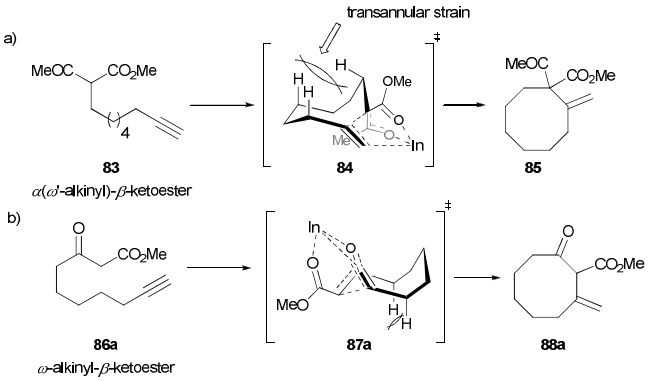
Scheme 30 Indium-catalyzed 7-*exo* cyclization.

With the optimized conditions in hand, differently substituted cycloheptanes were synthesized in good yields and diastereoselectivity, including the bicyclo[5.3.0]decanone **78**, the bicyclo[5.4.0]undecanone **79** and the azepane **81** (Scheme 31). The relative configuration of those products was assigned by NOE analysis. Cycloheptanes **82a** and **82b** derived from aliphatic *β*-ketoesters were also obtained in good yields and diastereoselectivities.



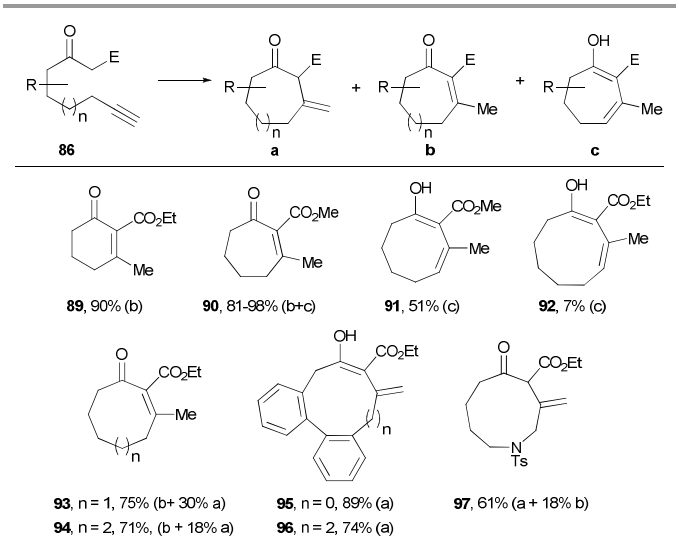
Scheme 31 Scope of the indium-catalyzed Conia-ene-related reaction.

Although $In(NTf_2)_3$ allowed for an easy cyclization of *β*-ketoesters, no reaction occurred for ester **83**, which could in principle undergo an 8-*exo* cyclization to cyclooctane **85**. Nakamura and co-workers argued that because of the energetically unfavourable transannular strain in **84** steric interactions are the main reason for the lack of reactivity (Scheme 32, a). Thus, they envisaged to replace *α*(*ω*'-alkynl)-*β*-ketoesters **83** with *ω*-alkynl-*β*-ketoesters **86a**.[40] Because the ketone will be incorporated in the ring system of the product **88a**, an additional sp^2-carbon is present during the cyclization decreasing the disfavouring steric interactions in the transition state **87a** (Scheme 32, b).



Scheme 32 The effect of transannular strain on cyclization.

As anticipated, a series of *ω*-alkynl-*β*-ketoesters **86** underwent cyclization to medium and larger ring carbocycles in good to excellent yield for most cases in the presence of 0.1-1 mol%) $In(NTf_2)_3$ in toluene at elevated temperatures (100-150 °C) (Scheme 33). Although *exo* cyclization occurred for most of the substrates, the direct cyclization product could not be isolated, due to isomerization of the external double bond to the products of the structure **b** and **c**.



Scheme 33 Scope of the indium-catalyzed large-ring formation.

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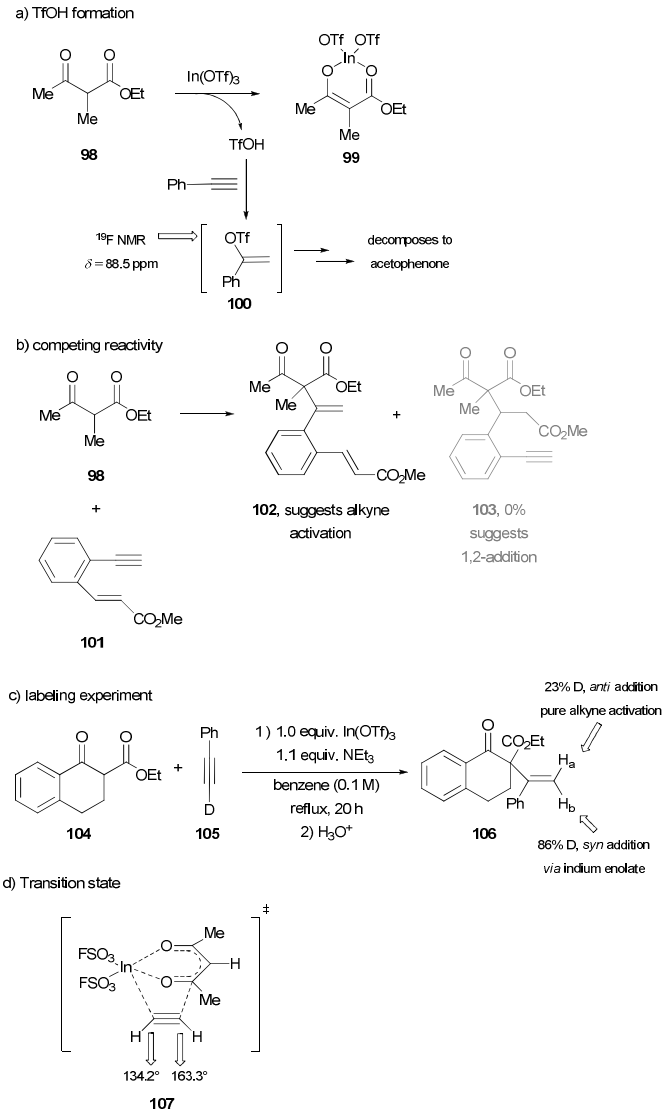
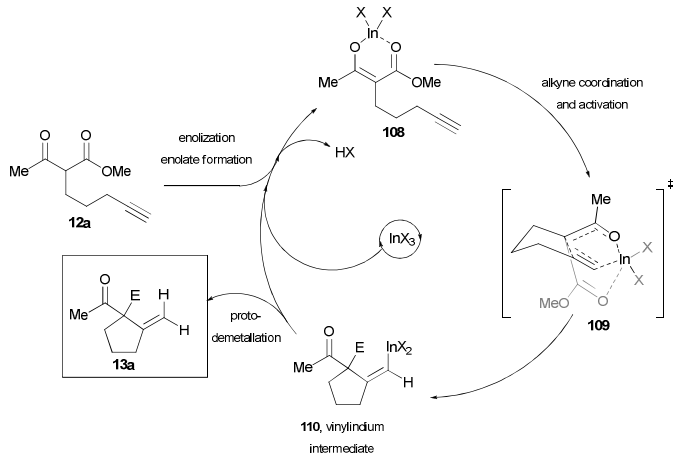
Although the amount of mechanistic studies conducted for the intramolecular case is limited, a good deal of insight has been gained for the intermolecular indium-catalzyed Conia-ene reaction (Scheme 34).[39] The reaction requires a base to remove the acidic proton from the *β*-ketoesters. For $In(OTf)_3$ it has been shown that the triflate anion acts as the base leading to the formation of TfOH, which adds to the alkyne (Scheme 34, a). The formation of styryl triflate **100** has been verified by ^{19}F NMR studies. 2) For the intermolecular case, alkyne **101** with a tethered acrylic ester underwent clear addition to the alkyne yielding **102** (Scheme 34, b). This indicates that the reaction must proceed *via* alkyne activation by the Lewis acidic metal. If that had not been the case and the reaction had proceeded *via* a simple 1,2-addition, the addition to the electronically more activated acryl ester **103** should have occurred.



Scheme 34 Mechanistic investigations.

3) The indium salt generates an indium enolate which adds in a *cis* fashion to the alkyne as suggested by labeling experiments (Scheme 34, c) 4) Finally, a transition state was obtained for the proposed addition by theoretical calculations. In the transition state **107** the C-In bond formation and the rehybridization of the terminal alkyne carbon is rather advanced as compared to the C-C-bond formation and the rehybridization of the internal alkyne carbon (Scheme 34, d). Therefore, a strong interaction between the alkyne and the indium metal must be present prior to the cyclization. In addition, the alkyne moiety adopts a position just above the pseudo-C_2 symmetry plane of the ketoester for maximum orbital interaction.

Thus, the following mechanism can be deduced for the intramolecular mechanism. At first $In(X)_3$ supports the enolization of the *β*-ketoester **12a** with subsequent formation of the indium enolate **108**. This leads to the regeneration of HX, which can be neutralized by an additional base or which reacts with the alkyne. Afterwards, the alkyne can be coordinated by the indium metal for electrophilic activation. Simultaneously, the preorientation of the alkyne leads to a significant reduction of the entropy barrier enabling the *syn* addition of the indium enolate *via* **109** to generate the vinylindium intermediate **110**. This intermediate undergoes fast protodemetallation releasing the product **13a** and the catalyst, which is then available for the next catalytic cycle.

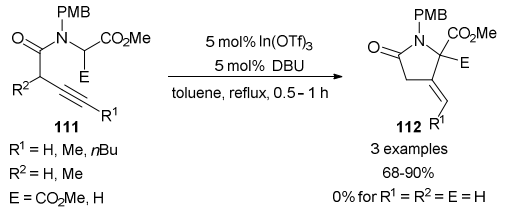


Scheme 35 Catalytic cycle for indium-catalyzed Conia-ene-related reactions.

A more heterocycle-oriented approach was pursued by Hatakeyama and co-workers in 2008.[41] They focused on the synthesis of pyrrolidinones and other heterocycles using nitrogen- and oxygen-tethered acetylenic malonates. Initial experiments for the 5-*exo* cyclization of malonates **111** to pyrrolidinones **112** revealed that $[Ph_3PAu]OTf$ did not promote the reaction while a binary system of $[Ni(acac)_2]$ and $Yb(OTf)_3$ afforded the product **112a** ($R^1 = R^2 = H$, $E = CO_2Me$) in 19% yield in THF at 50 °C (Scheme 36). Surprisingly, 5 mol% of $In(OTf)_3$ and DBU were sufficient to obtain the same product in 90% in toluene at reflux after 30 minutes. The reaction also worked without the addition of the additional base, albeit slower and lower yielding. This might indicate that the enolization is more challenging for malonates (1,3-allylic strain

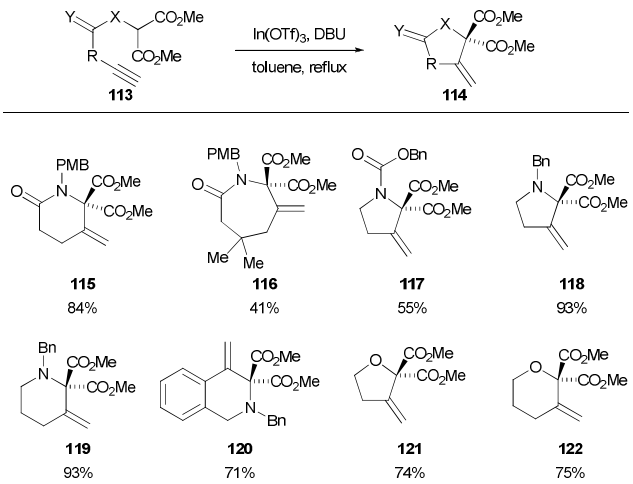
for the enol tautomer) as compared to ketoesters, and that the formation of an indium ester enolate is significantly slower than the formation of a ketoester-derived indium enolate, since the $In(OTf)_3$-catalyzed 5-*exo* cyclization of ketoesters proceeded under milder reaction conditions, without the addition of a base, at 0.01 mol% catalyst loading. The reaction was not limited to terminal alkynes, as substrates with aliphatic substituents also underwent a clean cyclization (R^1 = Me, Bu), however, the malonyl moiety was essential for the reactivity. Accordingly, a simple ester (E = H) was not converted under the applied reaction conditions, because of the lacking acidity and unfavourable enolization.

Using similar conditions with varying catalyst loading, a broad scope of heterocycles, including piperidinone **115**, pyr-



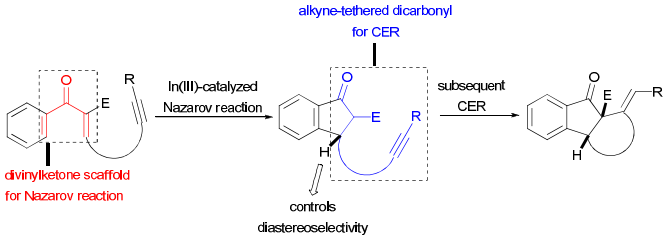
Scheme 36 In-catalyzed 5-*exo* cyclization of heteroatom alkyne-tethered malonates.

rolidines **117** and **118**, piperidine **119**, tetrahydroiso-quinoline **120**, tetrahydrofuran **121** and tetrahydopyran **122**, was obtained in moderate to excellent yields (Scheme 37). Only the cyclization to the azepanone **116** proved to be difficult and a higher catalyst loading of 15 mol% had to be employed because of the higher entropy barrier. Noteworthy, substrates containing a basic tertiary amine gave the desired heterocycles in excellent yields indicating that $In(OTf)_3$ is not deactivated by basic amines. This is a significant advantage, as for example gold(I) catalysts would be deactivated under similar conditions. Because of their general applicability, indium-catalyzed Conia-ene reactions have emerged as useful tools in the synthesis of several natural products (see section 5).



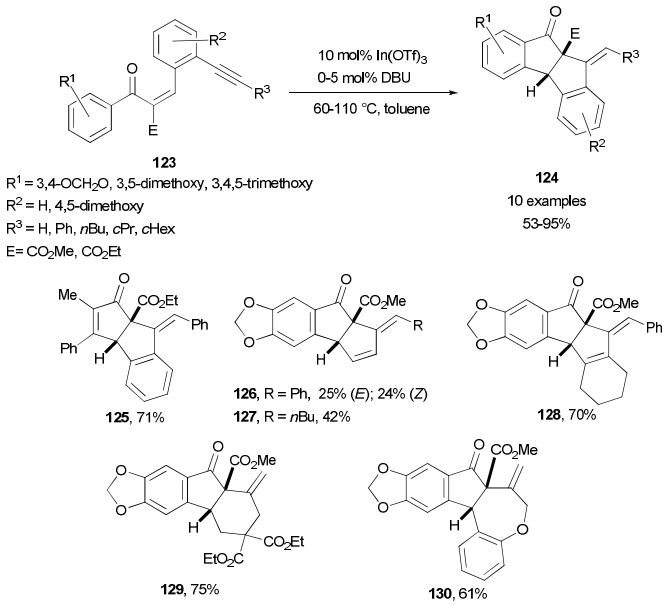
Scheme 37 In-catalyzed formation of heterocycles.

Remarkably, the catalytic efficiency of indium can also be exploited in the context of tandem reactions as demonstrated by Zhang and co-workers in 2010.[42] They envisioned the diastereoselective synthesis of tricyclic scaffolds *via* an indium(III)-catalyzed Nazarov cyclization and a Conia-ene reaction (Scheme 38). The substrates employed provide both necessary scaffolds: a divinyl ketone for the Nazarov cyclization and an alkyne-tethered *β*-ketoester for the subsequent Conia-ene reaction.



Scheme 38 General strategy for the sequential Nazarov cyclization/Conia-ene-related reaction.

Starting from the alkyne enones **123** and using 10 mol% of $In(OTf)_3$ along with 5 mol% DBU - for some cases no additional base was required - the targeted products **124** were obtained in good yields (up to 95%) in toluene at elevated temperature (Scheme 39). The products were isolated as a single diastereomer with *cis* configuration and an *E*-configurated *exo* double bond. The reaction proceeded especially well for electron-rich aryl substituents, which have a beneficial effect on the Nazarov cyclization, but good yields were also obtained for unsubstituted aryl moieties.



Scheme 39 Scope of the sequential indium-catalyzed Nazarov/Conia-ene related reaction.

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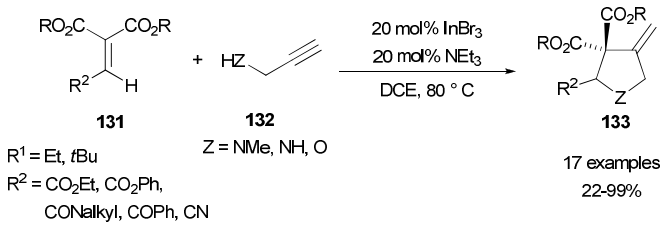
Terminal as well as internal alkynes were tolerated; however, for some substrates bearing internal alkynes with alkyl substituents a mixture of *E*/*Z* isomers was obtained. Most intriguingly, the substitution did not have an impact on the size of the generated ring, as for all examples only *exo* cyclization was observed. In addition, the linking phenyl group between the enone and alkyne moieties could be replaced by simple alkenes with moderate to good yields and the same protocol was applicable for the synthesis of the 6-*exo*- and 7-*exo*-derived products **129** and **130**. Later on, a one-pot reaction was developed, in which the substrates were generated *in situ* by a Knoevenagel condensation of the malonates with the corresponding alkyne-tethered aldehydes catalyzed by piperidinium acetate.

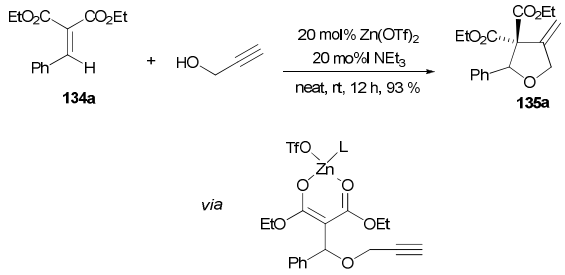
A different sequential reaction was presented by Kakiuchi and co-workers.[43] They combined an indium-catalyzed Michael addition of propargylamines and propargylalcohols **132** to ethenetricarboxylates **131**, followed by a subsequent 5-*exo* cyclization to afford the corresponding methylenepyrrolidines and tetrahydrofurans **133** (Scheme 40). While the reaction also worked in the presence of stoichiometric amounts of $ZnBr_2$, lowering the catalyst loading down to 20 mol% was only possible for the binary system of $InBr_3$ and NEt_3. The desired heterocyclic products were obtained in moderate to good yields in dichloroethane at 80 °C. Interestingly, for propargylalcohols the addition of NEt_3 was not necessary.



Scheme 40 Michael/Conia-ene sequence for the generation of heterocycles.

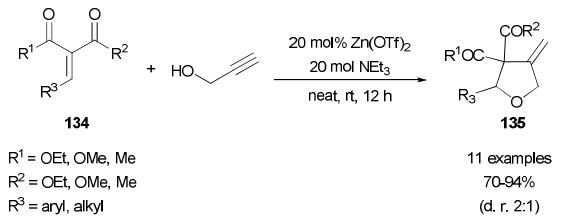
Another popular transition metal, which probably involves double activation of the substrate, is zinc. Many different approaches using ZnX_2 catalysts have been reported and a diversity of substrates including heterocycles is accessible. However, when compared with indium, the mechanistic progress of the reaction is less thoroughly investigated and verification is still necessary.

The first Zn-catalyzed Conia-ene-related reaction dates back to 2004. Nakamura and co-workes applied a one-pot 1,4-addition/cyclization sequence between propargyl alcohol and alkylidene malonates **134**.[44] For their model compound **134a**, the corresponding tetrahydrofuran **135a** was formed in the presence of 20 mol% $Zn(OTf)_2$ and NEt_3 at room temperature in 93% yield (Scheme 41). This approach is slightly different from the previously described Conia-ene reactions, as the nucleophilic zinc enolate for the actual 5-*exo* cyclization is not obtained directly from an alkyne-tethered malonate by chelation/deprotonation. Instead it is triggered by a Michael addition which will generate the zinc enolate directly, thus avoiding common problems associated with the formation of enols or metal enolates from malonates (allylic strain and unfavourable enolization ratio). The reaction can be performed under neat conditions with a huge excess of alcohol, which can be reisolated after the reaction.



Scheme 41 Zinc-catalyzed Michael addition/Conia-ene-related reaction of propargyl alcohol and malonate **134a**.

Under the mild reaction conditions, a variety of benzylidene and alkylidene malonates **135** afforded the methylene-tetrahydrofurans **135** in good to excellent yields, irrespective of the steric or electronic nature of the substrate (Scheme 42). This also includes methyl esters, which did not undergo a trans-esterification. In addition, alkylidene *β*-ketoesters (R^3 = alkyl) were also applicable and gave the corresponding products in good yields, but with low diastereoselectivity. Only the use of alkylidene diketones ($R^1 = R^2$ = Me) proved to be troublesome and higher reaction temperatures had to be applied.

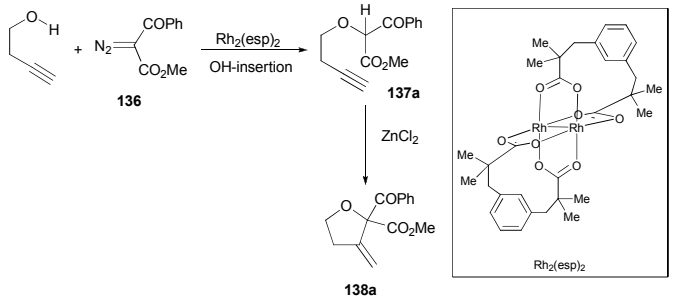


Scheme 42 Scope of the zinc-catalyzed Michael addition/Conia-ene-related reaction.

The authors propose a mechanism, in which a zinc alkoxide is formed acting as a nucleophile for the 1,4-addition. After the Michael addition, a zinc enolate is formed enabling the subsequent 5-*exo* cyclization. A more detailed description for the Zn-catalyzed Conia-ene reaction will be given later.

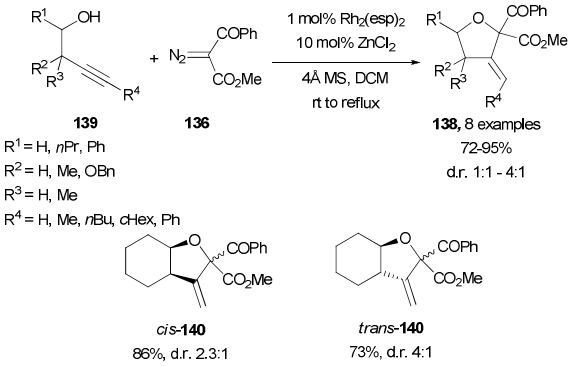
Intriguingly, tetrahydrofurans **138** are also accessible *via* a formal [4+1] cycloaddition, including a Rh(II)-catalyzed insertion of a diazo-*β*-ketoester **136** into alkyne-tethered alcohols, followed by a Zn-catalyzed Conia-ene reaction, as shown by Hatakeyama and co-workers (Scheme 43).[45] In one of their previous works, they demonstrated that the insertion had proceeded efficiently with 1 mol% of the $Rh(esp)_2$ catalyst in CH_2Cl_2 at room temperature. For the experiments presented in this paper, the additional presence of 10 mol% $ZnCl_2$ enabled the subsequent 5-*exo* cyclization to the corresponding tetrahydrofurans **138**. Initially, it was found that $In(OTf)_3$ was more suitable for this transformation, however it turned out that this catalyst was gravely limiting the substrate scope. Essential

for the suppression of unwanted side reactions, e.g. transesterification, was the careful selection of a judicious *β*-ketocarbonyl derivative such as **136**.



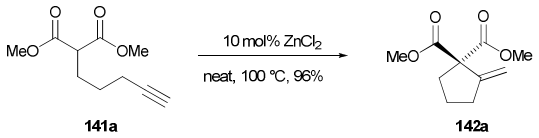
Scheme 43 Rh(II)-catalyzed formal [4+1]-cycloaddition of homo propargylalcohol and azo-*β*-ketoester **136**.

Applying these conditions, it was possible to use different alcohols **139** with additional substituents affording the tetrahydrofurans in good to excellent yields and moderate diastereoselectivity (Scheme 44). Alcohols with internal alkynes bearing alkyl groups were also suitable and proceeded with high *exo* selectivity, but elevated temperatures were required for the conversion. In contrast, it was not possible to obtain tetrahydropyrans (from 6-*exo*) or oxetans (from 4-*exo*) from suitable substrates and the reaction of *α*,*α*-disubstituted alcohols was seriously hampered and gave rise to a complex mixture.



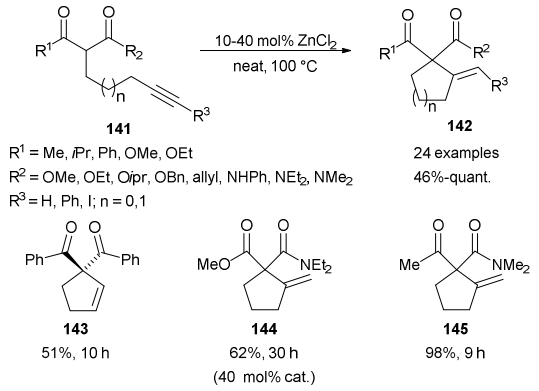
Scheme 44 Scope of the Rh(II)-catalyzed reaction.

A more direct approach towards Zn-catalyzed Conia-ene reactions was pursued by Li and co-workers applying alkyne-tethered malonates for 5-*exo*-*dig* cyclizations.[46] It was revealed that among several zinc catalysts, 10 mol% of $ZnCl_2$ was the most suitable choice for the cyclization of malonate **141a** giving the corresponding cyclopentane **142a** in excellent yield at 100 °C (Scheme 45). Remarkably, zinc(II) seems to promote the enolization of malonates and the formation of a zinc enolate seems to be feasible with the given reaction conditions. In contrast, other Lewis acidic metals with high oxygen affinity, including Fe(III), Al(III) and Sn(IV), did not promote the reaction at all or gave the desired product in low yields.



Scheme 45 Zn-catalyzed direct Conia-ene-related cyclization of malonates.

Based on these reaction conditions, a broad scope of substrates **141** was applicable for the CER-related cyclizations including alkyne-tethered *β*-ketoesters, diketones, and malonates (Scheme 46). Only *t*-butyl ketoesters showed limited compatibility under the applied conditions, giving a 5-*exo*-derived decarboxylated cyclopentane derivative. For all other cases, the corresponding cyclopentanes and cyclohexanes **142** were isolated in good to excellent yields and only the *exo* cyclization occurred (5 or 6), even for substrates with internal alkynes. Interestingly, a 5-*endo*-derived cyclopentene **143** was isolated, albeit with only moderate yield.[47] In addition, challenging substrates such as *β*-ketoamides and amide esters underwent cyclization to the corresponding products **144** and **145**, with a higher catalyst loading necessary for the latter.



Scheme 46 Scope of the Zn-catalyzed cyclization.

A similar strategy was proposed by Burton and Hess using alkynyl-*α*-aminomalonates **146** and alkynyl-*α*-amidomalonates **151** for the generation of nitrogen-containing heterocycles (Scheme 47, 48).[48] As anticipated, the benzyl-protected substrates underwent clean 5-*exo* cyclization to the corresponding pyrrolidines **147** (X = H_2) and pyrrolidinones **147** (X = O) in the presence of 10 mol% $ZnCl_2$ in dichloroethane at reflux in good yields. Other protecting groups at the nitrogen atom led to diminished yields, while the application of a free amine led to a deteriorated conversion. Although the cyclization clearly favoured *syn* addition of the zinc-enolate generating *E*-configurated olefins, minor amounts of the *Z* product were obtained for the majority of substrates. The origin of this deviation remains unclear, and it is possible that a competing reaction mechanism is operating. Nonetheless, under the applied conditions the synthesis of larger nitrogen-containing heterocycles, including piperidine **148**, piperidinone **149** and azepane **150**, was feasible with moderate to excellent yields.

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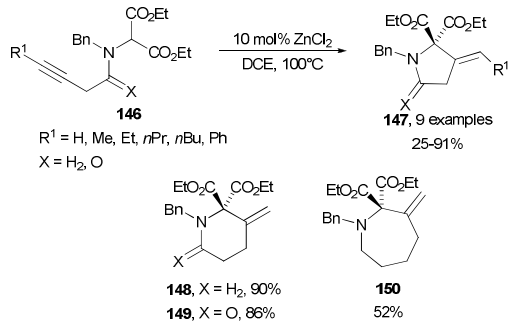
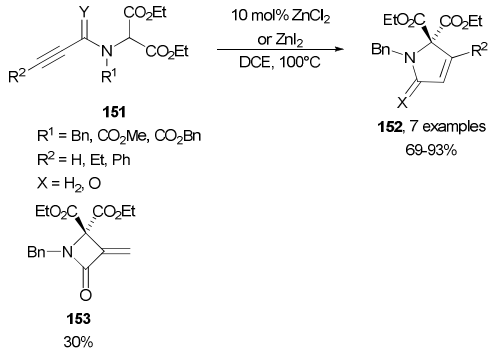


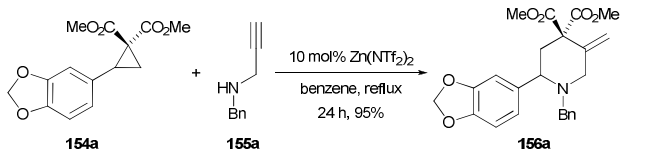
Scheme 47 Scope of the Zn-catalyzed *exo* cyclization for the synthesis of *N*-containing heterocycles.

Furthermore, the cyclization could be turned into a 5-*endo-dig* cyclization by employing substrates **151** with shorter alkyne-linker (Scheme 48). Using either $ZnCl_2$ or ZnI_2, the corresponding pyrrolines **152** (X = H_2) and pyrrolinones (X = O) were obtained in satisfactory to excellent yields. As a contrast though, for one of the substrates a competing 4-*exo* cyclization was observed, and the resulting *β*-lactam **153** was isolated with 30% in addition to the expected product.



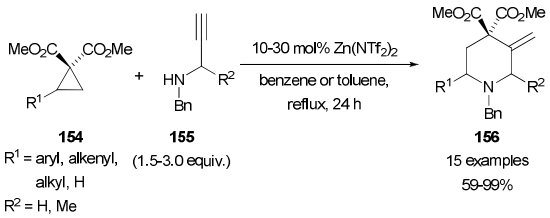
Scheme 48 Scope of the Zn-catalyzed *endo* cyclization for the synthesis of *N*-containing heterocycles.

Another approach for the efficient generation of a reactive zinc enolate was presented by Kerr and co-workers.[49] They proposed that donor-acceptor-substituted cyclopropanes **154** would undergo Lewis acid-assisted ring-opening by nucleophilic propargyl amines **155**. Thereby a metal enolate would be generated, which can participate in a subsequent Conia-ene reaction. However, the identification of a judicious catalyst which can catalyze both steps is challenging, as the chelation-assisted ring-opening requires a hard oxophilic acid while the alkyne-activation normally demands for a soft carbophilic Lewis acid. Gratifyingly, the 1,1-cyclopropane diester **154a** and the benzyl-protected propargyl amine **155a** underwent ring-opening and a subsequent clean 6-*exo* cyclization to afford piperidine **156a** in 95% in the presence of 10 mol% $Zn(OTf)_2$ in benzene at reflux after 24 hours (Scheme 49). Zn(II)-salts turned out to be superior choices for this tandem reaction, catalyzing both reactions steps in contrast to $In(OTf)_3$, which failed to promote the ring opening. Interestingly, among the different amines tested, only the benzyl-protected secondary amine worked, while primary amines or less nucleophilic carbamates (NBoc) and sulfonamides (NTos) did not participate in the nucleophilic ring-opening.



Scheme 49 Zn-catalyzed ring-opening of cyclopropanes with a subsequent Conia-ene-related cyclization.

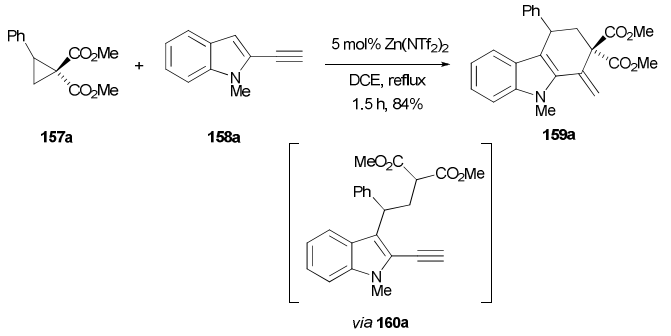
When the general practicability was probed it turned out that the reaction was applicable to various cyclopropanes **154** and the corresponding piperidines **156** were obtained in moderate to good yields (Scheme 50). However, as one would expect from their general reactivity, cyclopropanes with strong electron-withdrawing aryl groups (R^1 = 4-CN- or 4-MeO_2C-C_6H_4) or lacking a +I-donor capability (R^1 = H, Me) required a higher catalyst loading for the ring-opening to occur. In addition, it was also possible to use chiral cyclopropanes and amines without a significant loss of enantiomeric excess.



Scheme 50 Scope of the Zn-catalyzed domino reaction.

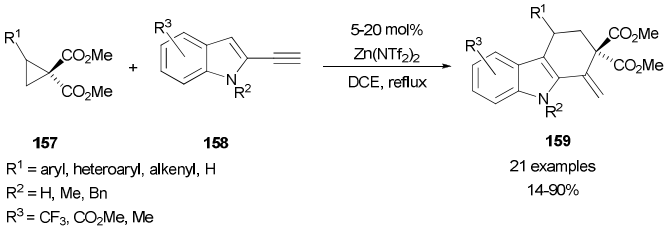
Based on this approach, Kerr and co-workers argued that the alkyne-tethered propargyl amine can be replaced by a 2-alkynyl-indole **158**.[50] Indole has a distinct nucleophilic site at the C3-position and can therefore participate in a Friedel-Crafts-type nucleophilic ring opening of donor-acceptor-substituted cyclopropanes. Next, the opened cyclopropane can, similar to the previously described project, undergo addition to the metal-activated alkyne leading to tetrahydrocarbazoles. The formal [3,3]-annulation was first tested with the indole derivative **158a** and cyclopropane **157a** affording the corresponding tetrahydrocarbazole **159a** in 84% in the presence of 5 mol% $Zn(NTf_2)_2$ in dichloroethane at reflux after 1.5 hours (Scheme 51). With these optimized reaction conditions the reaction worked for a broad range of substrates (Scheme 52). As expected, the substituent on the cyclopropanes did indeed have a pivotal effect on the outcome of the reaction, with good yields for +M-substituents. In general, methyl-protected indoles gave superior yields as compared to unprotected or benzyl-protected indoles. In addition, electron-donating and electron-withdrawing groups on the indole backbone were also tolerated. Disappointingly, internal alkynes were not suitable substrates for this tandem reaction, because only the ring-opening reaction was observed. The only exception was an internal alkyne with

an ester substituent, however this substrate may only undergo cyclization *via* an electronically driven 1,2-addition.



Scheme 51 Zn-catalyzed ring-opening of cyclopropanes by alkyne-tethered indoles with a subsequent Conia-ene-related cyclization.

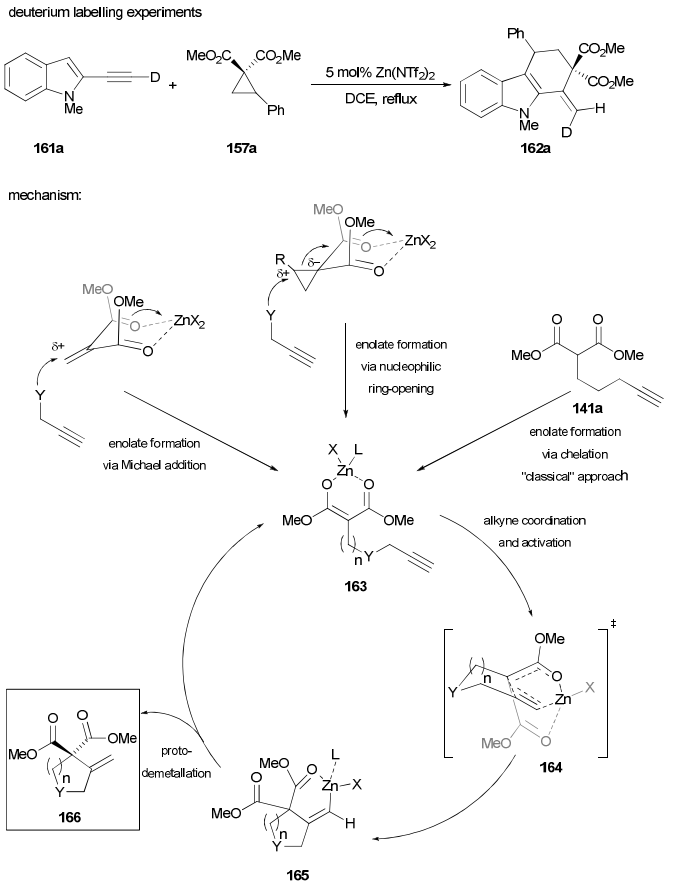
In order to shed some light on the mechanism of the zinc-catalyzed Conia-ene-type reaction, studies with the deuterium-labeled substrate **161a** were undertaken (Scheme 53). The studies revealed that the addition occurred in a *syn* fashion to **162a**, thus supporting the formation of a zinc ester enolate. Hence the following mechanism can be proposed: the crucial step is the formation of the zinc ester enolate **163**.



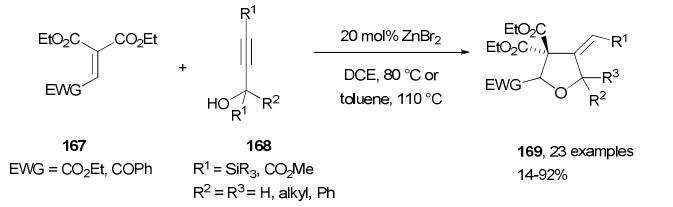
Scheme 52 Scope of the Zn-catalyzed domino-reaction.

Up to now, we have seen three different main approaches: 1) Direct enolization and chelation of alkyne-tethered malonates. 2) Formation *via* nucleophilic ring-opening of cyclopropanes by alkyne-tethered nucleophiles 3) Formation *via* Michael addition of alkyne-tethered nucleophiles to alkylidene malonates. Although zinc complexes are not as well-known as the softer gold complexes for alkyne activation, precedence exists where Zn^{2+}-alkyne activation is clearly involved.[51] Thus, double activation seems feasible, especially since the Zn-vinyl intermediate **165** can be additionally stabilized by coordination to the oxygen. Protonation releases the product **166**, and the catalyst can enter the next catalytic cycle.

Based on their In-catalyzed tandem reaction, Kakiuchi and co-workers envisioned to replace the terminal alkynes **132** with propargylalcohols bearing internal alkynes **168** for the synthesis of tetrahydrofurans **170** (Scheme 54).[52] However, common terminal propargyl alcohols were not applicable and electronically more activating substituents had to be employed instead. For propargyl alcohols with *γ*-silyl or *γ*-ester groups, 10 mol% of $ZnBr_2$ was suitable to promote the sequential Michael



Scheme 53 Mechanistic experiments and the proposed catalytic cycle for Zn-catalyzed Conia-ene-related cyclizations.



Scheme 54 Zn-catalyzed Michael addition with a subsequent Conia-ene-related cyclization.

Using 2-*tert*-butyl ethenetricarboxylate **170** and 2(trimethylsilylethynyl)anilines **171**, Yamazaki and co-workers were able to synthesize bridged quinoline derivatives **172** in moderate and good yields in the presence of 20 mol% $Zn(OTf)_2$ in 1,2-dichloroethane at 80 °C (Scheme 55).[53] While different substituents were tolerated at the aromatic ring, the reaction seemed to be limited to *tert*-butyl-esters and trimethylsilyl-substituted alkynes, as other substituents normally led to a complex mixture of products. The reaction mechanism was not completely unraveled, but one possible mechanism, which would be in accordance with control experiments, was proposed. The sequence is initiated by an aza-Michael addition, followed by a zinc-catalyzed 6-*exo* cyclization. At some unknown point of the reaction, desilylation and cleavage of the

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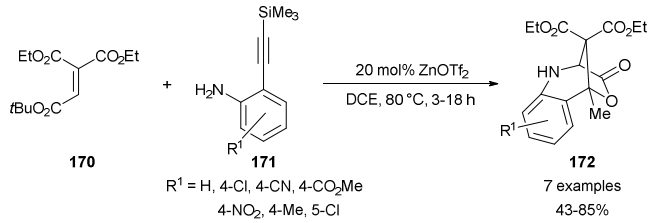
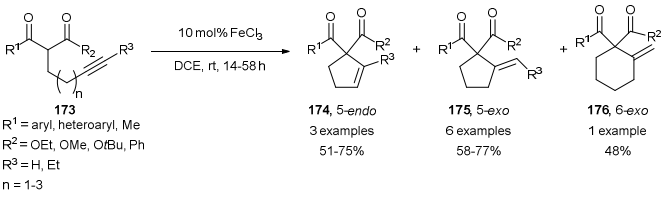
tert-butyl-alcoholate takes place, which allows for a subsequent Zn-catalzyed hydrocarboxylation of the alkene.



Scheme 55 Zn-catalyzed synthesis of quinoline derivatives.

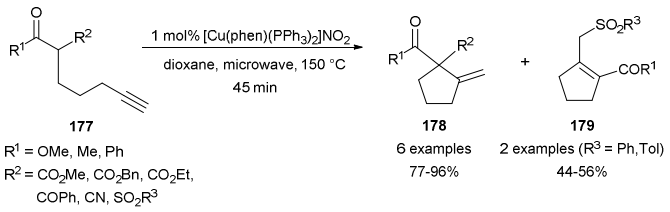
Recently, the application of iron salts has been probed for Conia-ene-related reaction by Lee and co-workers.[54] They found that the conversion of the typical model substrate **12a** to the 5-*exo* product **13a** was promoted by various Fe(II) and Fe(III) salts, and $FeCl_3$ turned out to be the most efficient one. The desired product was obtained in the presence of 10 mol% $FeCl_3$ in 1,2-dichloroethane at room temperature after 90 minutes in 76% yield. Interestingly, at higher catalyst loading isomerization of the double bond took place. Demonstrating the general applicability of this reaction, *β*-ketoesters **173** with different substituents were tested generally leading to the desired products **174** in good yields, irrespective of the steric and electronic nature of the substituents. However, diketones turned out to be less reactive and although the cyclization did occur, minor amounts of the starting material remained even after a prolonged reaction time. In exchange, the exploitation of 5-*endo* and 6-*exo* cyclization modes was feasible to form the cyclopentanes **175** and the cyclohexane **176** by varying the distance between the ketone moiety and the alkyne, but the 6-*exo* products normally suffered from double bond migration (Scheme 56).



Scheme 56 Iron-catalyzed Conia-ene-related reactions with different cyclization modes.

Although the reaction was intended to proceed *via* ene-yne activation, it is more likely that iron acts in a similar fashion to zinc and indium because of the high oxygen affinity. This has also been suggested by White and co-workers recently in their asymmetric iron-catalzyed Conia-ene-related reaction.[55]

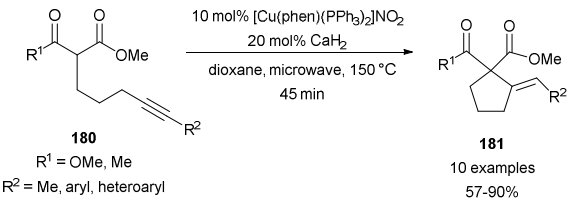
Another suitable metal for Conia-ene-type reactions is Cu(I) or Cu(II). Similar to iron salts, the application of copper salts is highly desirable, because copper is an inexpensive alternative to the more expensive transition metals such as Au, Ag, and Pd. After initial experiments on Cu/Li-catalyzed CER-type reactions, Balme and co-workers tried to avoid the use of BuLi by using more elaborate copper catalysts under microwave irradiation.[56] Following this approach, cyclization of the more challenging alkyne-tethered malonates **177** to the corresponding 5-*exo* cyclopentanes **178** succeeded in the presence of 1 mol% $[Cu(phen)(PPh_3)_2]NO_2$ in dioxane under microwave irradiation at 150 °C. However, no conversion of the starting material was observed for other solvents, under conventional heating or with a more simple catalyst such as CuI. Gratifyingly, the reaction also tolerates *β*-ketoester, diketones, and substrates with lower acidity and a more unfavourable keto/enol ratio including *β*-cyanoesters and sulfonylesters (Scheme 57).



Scheme 57 Cu-catalyzed Conia-ene-related reactions of malonates, ketoesters, and analogues.

Except for the latter, which undergo a thermal 1,3-rearrangement to the products **179** in moderate yields, the cyclopentanes **178** were obtained in good to excellent yields.

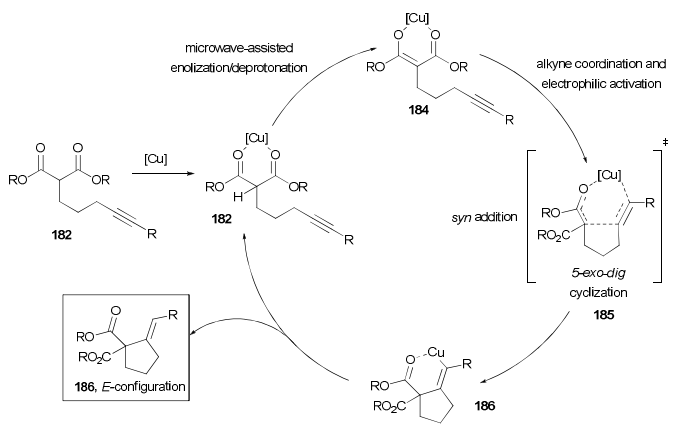
As internal alkynes are rarely used for Conia-ene reactions, because of the competitive 5-*exo*/6-*endo* cyclization, Balme and co-workers tried to enable the cyclization for those substrates. However, cyclization occurred only at higher catalyst loadings and in the presence of 20 mol% CaH_2. Under these conditions various malonates and *β*-ketoesters **180** bearing aliphatic and aromatic alkynes underwent selective cyclization to the 5-*exo*-derived cyclopentanes **181** with complete *E*-selectivity, except for the piperonyl case, for which small amounts of the corresponding 6-*endo* monoester were obtained (Scheme 58).



Scheme 58 Cu-catalyzed cyclizations of internal alkynes.

Compared to other metals, the full elucidation of the reaction mechanism involving copper catalysis is problematic, mainly because copper can act through different activation modes. Later in the section about double activation by two metals (3.5.) a binary system of Li/Cu will be described, in which copper is involved in alkyne activation only, thus addition of the lithium enolate occurring in an *anti* fashion. In the case of the microwave-assisted approach, copper acts as a single catalyst and judging from the configuration of the products (*E*-isomers), addition must proceed in a *syn* fashion. This suggests the formation of a copper enolate **184** and subsequent activation of the alkyne **185** as shown in Scheme 59 and as calculated by Dixon and co-workers, similar to indium

and zinc.[57] However, in contrast to those metals, copper-promoted enolization of malonates appears to be slow, because conversion only takes place under microwave irradiation or with the help of an additional catalyst promoting the enolization/deprotonation. Moreover, the effect of CaH_2 is not fully understood. Based on the configuration of the products, the formation of a calcium enolate can be ruled out, because a Ca/Cu system like a Li/Cu system should give products with the opposite configuration.



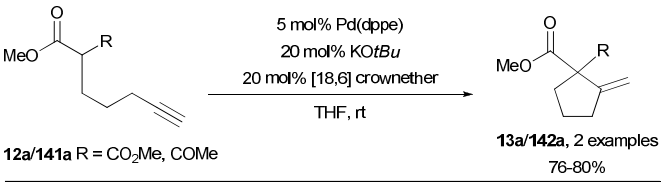
Scheme 59 Proposed mechanism for Cu(I)-catalyzed Conia-ene-related cyclizations.

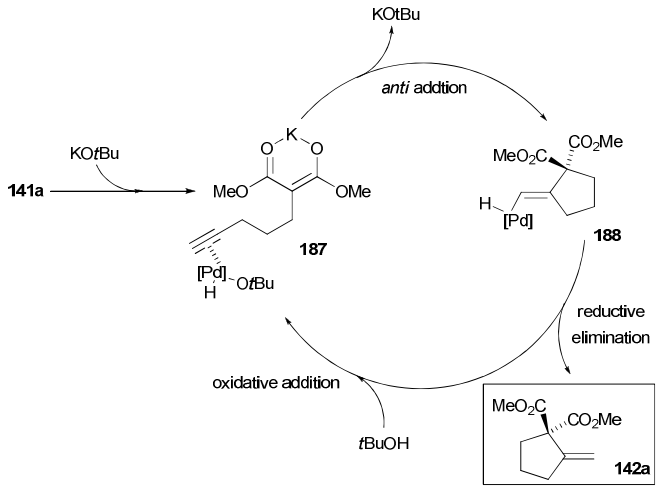
3.5. Double activation by two metals

Initially Balme and co-workers demonstrated that a bicatalytic system of Pd(0) and *t*BuOK promoted the cyclization of acetylenic malonates and *β*-ketoesters in good yields.[58] The scope of the reaction was limited though, and cyclization proceeded only in the presence of 18-crown-6 ethers. They also reported the formation of cyclohexanes *via* 6-exo cyclization, but stoichiometric amounts of *t*BuOK had to be employed. Mechanistically, they suggested that Pd(0) underwent oxidative addition to *t*BuOH, generating a Pd(II)-hydride species (Scheme 60).[59]

The latter activates the alkyne, thereby enabling the addition of the enolate and the formation of the product after reductive elimination of the vinyl-Pd(II)-hydride intermediate **188**.

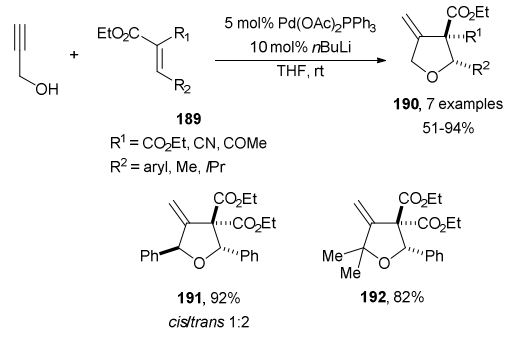
This concept was later expanded to the synthesis of heterocycles using a sequential Michael addition/Conia-ene approach. In 1997 Balme *et al*. reported the formation of 3-methylene-tetrahydrofurans **190** *via* a Michael addition of propargylalcohol to alkylidene or arylidene malonates **189**, followed by a subsequent Pd/Li-catalyzed Conia-ene-type reaction (Scheme 61).[60] Preliminary studies revealed that 10 mol% *n*BuLi and 5 mol% $Pd(OAc)_2PPh_3$ were the most suitable catalysts in THF at room temperature, and the protocol was applicable to differently substituted electrophiles and nucleophiles. As a general tendency, arylidene malonates and ketoesters gave the tetrahydrofuran derivatives in better yields as compared to alkylidene malonates or cyanoesters. As anticipated the products **191** and **192** derived from substituted propargylalcohols were obtained in good to excellent yields, although **191** was obtained as a mixture of diastereomers.





Scheme 60. Pd/K-catalyzed Conia-ene-related cyclization of ketoesters and malonates.

The authors envisioned a mechanism, in which the lithium alcoholate attacks the Michael acceptor, followed by a cyclization similar to the previously reported methodology.



Scheme 61 Pd/Li-catalyzed synthesis of tetrahydrofurans.

Soon thereafter the group turned their focus to heterobimetallic systems using Cu(I)-salts as soft Lewis acids for alkyne activation.[61] Initially it was demonstrated that a bicatalytic system consisting of 15 mol% KO*t*Bu and 10% CuI was appropriate for the cyclization of common CER-substrates including malonates and *β*-ketoesters in THF at 30 °C (Scheme 62), but internal alkynes required stoichiometric amounts of the catalysts.

Further evaluation of this catalytic system showed that *n*BuLi performed better as a base, especially in the context of heterocycle synthesis. Thus, in 1999 the sequential reaction

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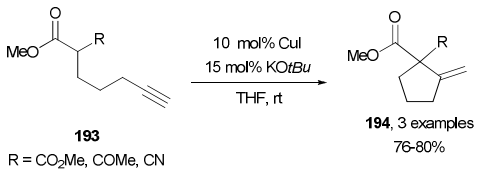
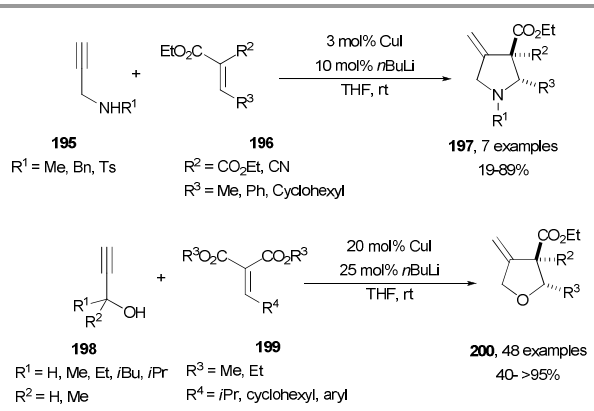
between propargylamines **195** and alkylidene and arylidene malonates and analogues **196** was exploited for the formation of 3-methylene pyrrolidines **197** (Scheme 63).[62]



Scheme 62 Cu/K-catalyzed Conia-ene-related reactions.

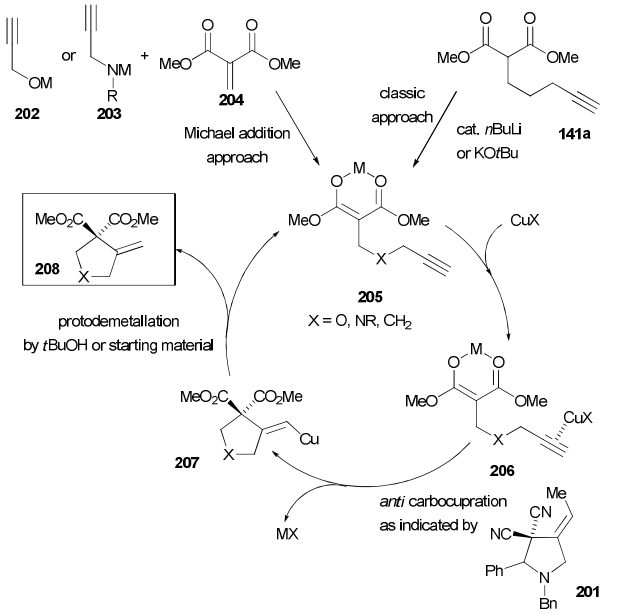
Remarkably, the addition between *N*-methyl propargylamine and diethyl benzylidene malonate proceeded smoothly under their previously reported conditions with Pd/Li activation, however, these conditions were not applicable for propargyl amines with other protection groups. Changing the catalytic system to 3 mol% CuI and 10 mol% *n*BuLi circumvented this problem, tolerating benzyl and tosyl-protected propargyl amines and more challenging electrophiles such as alkylidene malonates. Likewise, propargylalcohols **198** could be used instead of amines leading to tetrahydrofuran derivatives, though higher catalyst loading had to be employed.[63] The reaction was amenable to a broad scope of alcohols and Michael acceptors, demonstrating the general applicability of this protocol.



Scheme 63 Syntheses of heterocycles *via* Cu/Li-catalyzed Conia-ene-related reactions.

Mechanistically, it could be shown that the application of a substrate with an internal alkyne led to the formation of only one stereoisomer with *Z*-configuration **201**. In accordance with other heterobimetallic systems, the copper-catalyzed reaction proceeds *via anti* carbocupration of the corresponding potassium or lithium enolate **205** to the activated alkyne. In contrast to Pd though, there is no evidence that copper is involved in an oxidative addition prior to the coordination to the alkyne. Thus, the oxidation state of copper is maintained throughout the catalytic cycle, and the reaction is terminated by hydrolysis of the vinylcopper species **207**.

In contrast to the previous reports, Li and co-workers focused on the application of linear acetylenic *β*-ketoesters **209**.[64] Using a bicatalytic system of 10 mol% $Cu(OTf)_2$ and 10 mol% $AgSbF_6$, the 6-*endo* cyclization of **209a** was feasible in dichloroethane at 95 °C with good overall yield. Although no competing 5-*exo*-*dig* cyclization was observed, isomerization of the double bond to **210a** occurred and small amounts of the decarboxylated product **211a** were observed (Scheme 65). As could be expected, the decarboxlyation was more dominant at higher temperatures. When *β*-ketoesters with different substituents on the internal alkyne were probed, it turned out that in most cases a mixture of cyclized and decarboxylated products was obtained in moderate yields. Generally, cleaner reactions were observed for electron- donating and electron-neutral aryl groups while electron-withdrawing groups led to sluggish reactions.

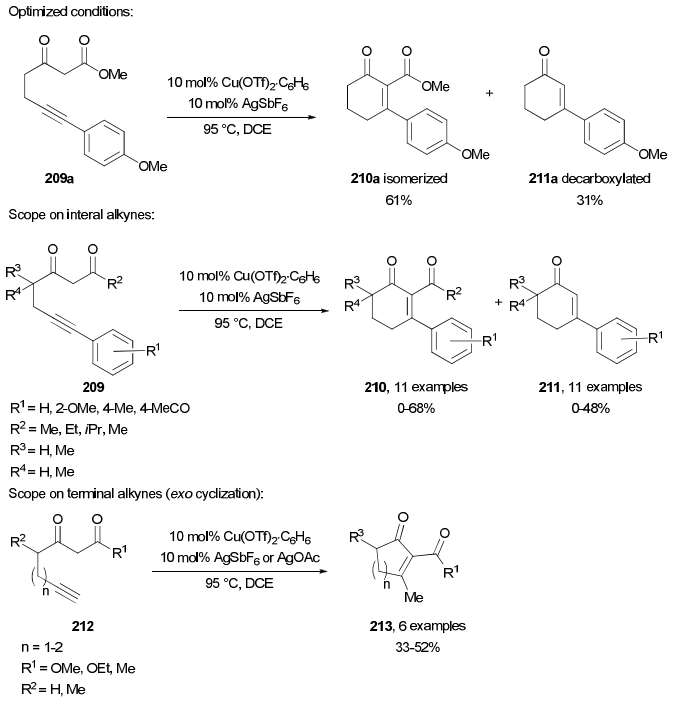


Scheme 64 Proposed catalytic cycle for Pd/Li-catalyzed Conia-ene-related reactions.

The reaction was amenable to different ester groups and also allowed for the application of diketones with comparable results. Interestingly, terminal-alkyne-tethered substrates gave products derived from 5-*exo* or 6-*exo* cyclizations in moderate yields. Only one internal alkyne with a methyl group afforded a mixture of *exo*/*endo*-derived products indicating that the cyclization mode depends on steric and electronic effects provided by the substituent on the alkyne.

Although not fully verified, the authors believed that the reaction proceeds *via* an orthogonal activation of the enol and the alkyne moiety. Considering other studies, it can be proposed that Cu(II) is involved in the formation of a copper enolate, while the less oxophilic Ag(I) enhances the electrophilicity of the alkyne. Therefore the addition should occur in an *anti* fashion, generating a vinylsilver intermediate which undergoes fast protodeargentation. Encouraged by their initial findings, Li and co-workers speculated that the more common (*ω*'-alkynyl) *β*-ketoesters **214** might also be applicable for the cooperative Cu/Ag-catalysis.[65] As anticipated, *β*-ketoester **12a** underwent a smooth cyclization to cyclopentane **13a** in quantitative yields in the presence of 10 mol% $Cu(OTf)_2$

and $AgBF_4$ at 100 °C in dichloroethane without a subsequent decarboxylation or isomerization (Scheme 66).

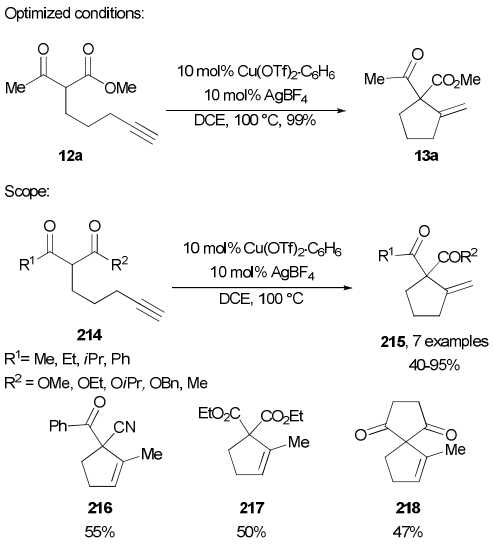


Scheme 65 Cooperative Cu/Ag-catalyzed Conia-ene-reactions.

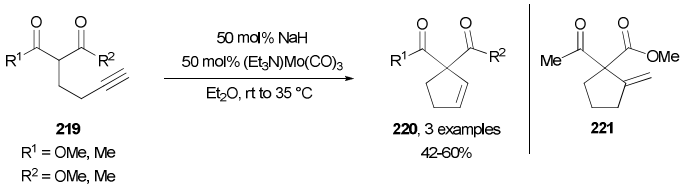
While the reaction afforded cyclopentanes with good to excellent yields from various *β*-ketoesters and diketones with different esters, alkyl and aryl groups, malonates and cycloketones demanded for a higher catalyst loading of 20 mol%. Still, the yield of **216** and **217** were only moderate and the isomerization of the double bond occurred due to the presence of the strong electron-withdrawing groups. A similar tendency was observed for a cyclic diketone due to the unfavourable 1,3-allylic strain, but the corresponding product **218** was observed in moderate yield at 20 mol% catalyst loading.

An exception to the previously described biheterometallic systems is the Mo/Na combination. As shown in 1997 by McDonald and co-workers, the 5-*endo* cyclization of ketoesters and malonates **219** to the corresponding cyclopentenes **220** is feasible in the presence of 50 mol% NaH and 50 mol% $(Et_3N)Mo(CO)_5$ at room temperature in diethyl ether with moderate yields.[66] The same reaction conditions allowed for the synthesis of **221** in good yields *via* a 5-*exo* cyclization (Scheme 67).

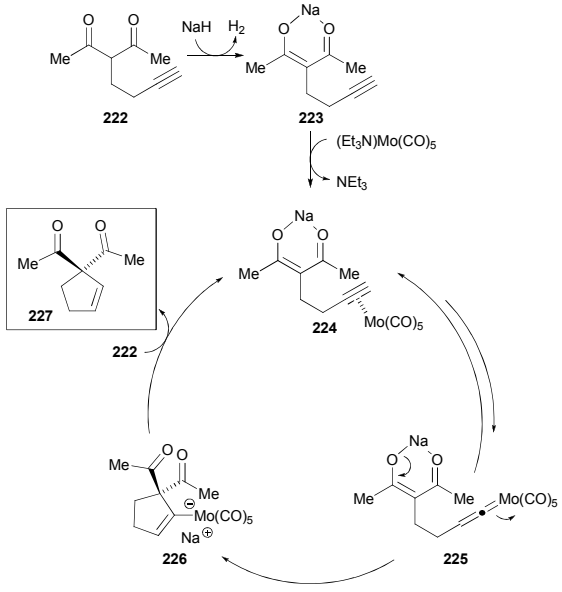
Based on their previous experiences, the authors suggested the formation of a sodium enolate **223** which can add to the activated alkyne. In contrast to other cooperative metal systems, the alkyne activation is achieved by a rearrangement to an electrophilic Mo-vinylidene intermediate **225**.[67] This can be attacked by the sodium enolate, and after the protonation of the Mo-vinyl intermediate **226** the product can be obtained (Scheme 68).



Scheme 66 Cooperative Cu/Ag-catalyzed Conia-ene-reactions.



Scheme 67 Mo-catalyzed 5-*endo* cyclization.



Scheme 68 Proposed catalytic cycle for the Mo-catalyzed cyclization.

3.6. Miscellaneous

When Dixon and co-workers attempted an aryl boronic acid-catalyzed transesterification of **228** (R^1 = Me, R^2 = OBn) with an alcohol, the desired ester could not be isolated.[68] Instead, the corresponding 5-*exo*-*dig*-derived product **229** was isolated

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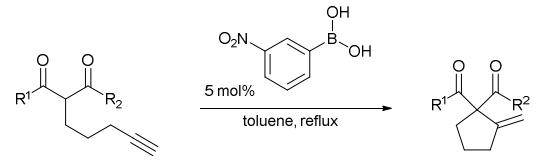
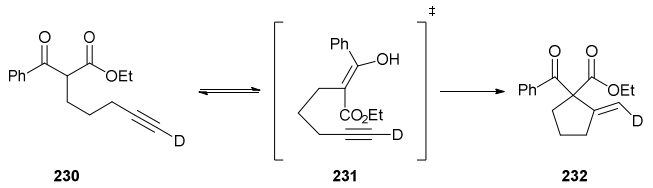
(Scheme 69). This unexpected result led to further investigations revealing that aryl boronic acids with electron withdrawing substitutents were suitable catalysts for this transformation. The best results were achieved by using 5 mol% of nitrobenzene boronic acid yielding the cyclized product with 90% yield in toluene at reflux after 16 hours. The reaction was applicable to a range of α-pentynyl-β-ketoesters, irrespective of their electronic nature. Only arylketones with electron donating groups in *para*-position required a prolonged reaction time while there was no tremendous influence of the ester group. In addition, the reaction was amenable to alkyne-tethered ketones (R^1 = Ph, R^2 = Me) and β-ketoamides (R^1 = Ph, R^2 = NHPh).



Scheme 69 Conia-ene reaction catalyzed by boronic acids.

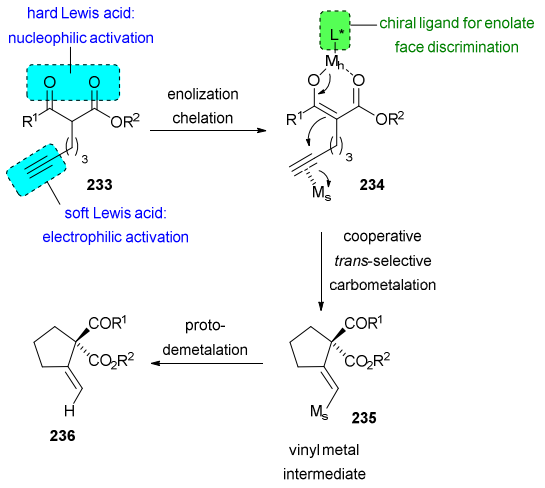
Deuterium labelling experiments of the substrate **230** led to the exclusive formation of *E*-**232** indicating that the addition of the enol must occur in a *syn* fashion as shown in the transition state **231** (Scheme 70). Among various possible mechanistic pathways, the authors suggest that boronic acids catalyze the enolization of the carbonyl compounds with subsequent 5-*exo*-cyclization to the corresponding cyclopentene derivatives.



Scheme 70 Deuterium labelling experiment with proposed transition state.

4. Stereoselective Conia-ene Reactions

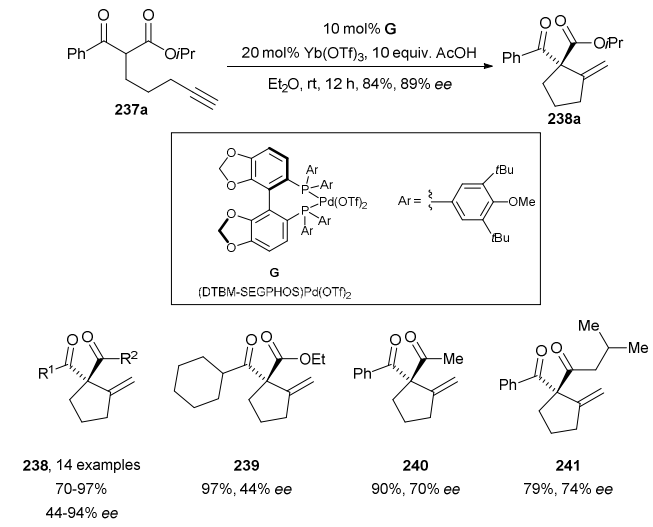
More than three decades have passed from the inception to the first stereoselective protocol of the Conia-ene reaction. The majority of the developed protocols exploit cooperative catalysis with most of the examples employing a biheterometallic system, in which the orthogonal activation of the substrate is achieved (**233**) by the concomitant presence of a hard and soft Lewis acid (Scheme 71). Typically, the hard metal is coordinated by a chiral enantiopure ligand, thus enabling face discrimination of the generated prochiral metal enolate, so that the subsequent *trans*-selective carbometalation can proceed in an asymmetric fashion (**234**). This affords metalvinyl intermediates **235** that are generally prone to hydrolysis, and the desired products **236** can be obtained with concurrent release of the catalyst.



Scheme 71 Common cooperative strategy for asymmetric Conia-ene reactions.

4.1. Enantioselective Conia-ene reactions

The first example of an enantioselective version of the Conia-ene reaction dates back to 2005 when Toste and co-workers focused on the asymmetric synthesis of cyclopentanes **238** *via* an enantioselective 5-*exo*-*dig* cyclization of acetylenic β-ketoesters **237**.[69] After testing several chiral Au(I), Cu(II), Ni(II), and Pt(II) complexes with limited success, they found that the Pd(II) DTBM-SEGPHOS complex **G** afforded the corresponding Conia-ene adduct with a moderate enantiomeric excess of 68%, albeit with only 18% yield after 72 hours in CH_2Cl_2 at room temperature. Gratifyingly, the addition of several equivalents of acetic acid had a beneficial effect on the yield, without diminishing the enantioselectivity. The authors suggested that the acid suppresses the competitive alkyne dimerization but in the context of the other protocols, it is also possible that the presence of the acid facilitates the protodemetalation after the initial cycloaddition.[70] In exchange, the use of 20 mol% $Yb(OTf)_3$ in the presence of an excess of acetic acid enhanced the reaction rate, generating the desired product in 84% yield and 89% ee after 12 hours in diethyl ether (Scheme 72). This protocol is applicable to a broad range of aromatic β-ketoesters with only minor impact on the outcome of the reaction. For instance, excellent results were obtained for electron-rich aryl ketoesters and bulky 1- and 2-naphthyl ketones, and electron-withdrawing groups on the aryl moiety were tolerated as well. While *iso*-propyl or allyl esters gave good enantioselectivities of 89% and 90% ee, respectively, the introduction of a bulky *tert*-butyl ester lowered the enantio-selectivity to 80% ee. In contrast, the use of a cyclic aliphatic ketone resulted in only 44% ee of **239**, indicating that π-π stacking interactions between the substrate and the catalyst might be crucial for a good asymmetric induction. Diketones with aromatic and aliphatic substituents were also



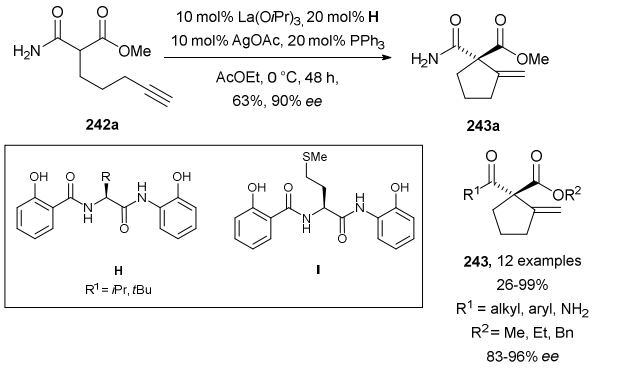
Scheme 72 Asymmetric Conia-ene-related cyclization catalyzed by Pd/Yb.

used, leading the corresponding cyclopentanes **240** and **241** with high yields and good enantiomeric excesses between 70% and 74% ee. Employing a suitable substrate, a 6-*endo-dig* cyclization was possible, but unfortunately the product was isolated after seven days as a racemic mixture.

The mechanism was not fully elucidated and the role of Pd and Yb still remains unclear. Studies with deuterium-labeled substrates revealed that the addition occurs in a *trans* fashion, thus the only suitable activation modes are either a pure alkyne activation or a dual activation by two metals. There is precedence on the formation of Pd-enolates and the coordination of Pd(II) to alkynes, however, based on previous studies[71-73], the authors have ruled out the possibility that Pd(II) acts as soft-Lewis acids. Nonetheless, Balme and co-workers demonstrated that alkali metal enolates add to Pd(II)-activated alkynes. Because the reaction also takes place in the absence of $Yb(OTf)_3$, it could be envisioned that the mode of activation changes when the second metal is present. Still, the assignment as to which metal is involved in the enolate formation and which in the alkyne activation cannot be deduced unequivocally.

Following this cooperative strategy, Shibasaki and co-workers reported on the asymmetric 5-e*xo* cyclization of the alkyne-tethered malonamic acid ester **242a** to the corresponding cyclopentane **243a** in 2011.[74] After initial attempts to promote the reaction by using a previously applied ternary system of $La(NO_3)_3$, an amide based ligand **H**, and an amino ester, together with softer transition metals, such as Ni(II), Rh(I), Cu(I), and Pd(II), to no avail, conversion of the starting was achieved when either Ag(I) or Au(I) was employed.[75] However, the yields and selectivity were only moderate under the applied reaction conditions, since concomitant hydration of the alkyne occurred, especially for the stronger activating Au(I) complex.

Nethertheless, this initial shortfall could be circumvented, by the careful evaluation of the catalytic system consisting of four major components: 1) 10 mol% of $La(OiPr)_3$ as the most suitable rare earth metal complex for the generation of the corresponding metal enolate. 2) 20 mol% of the chiral amide-based ligand **H**, which allows for the prochiral face discrimination 3) 10 mol% of AgOAc as optimized soft Lewis acid for the activation of the alkyne 4) 20 mol% of PPh_3 to avoid the degradation of the silver catalyst by precipitation. This cooperative catalysis yielded the desired product in excellent yield and enantioselectivity in ethyl acetate at 0 °C after two days (Scheme 73).



Scheme 73 Asymmetric cooperative Conia-ene-related reaction catalyzed by Ag/La.

Aside from the malonamic acid ester **242a** the reaction was applicable to various *β*-ketoesters with different ester and ketone functionalities. Whereas the results differed for various ester substituents marginally, the nature of the aryl ketone had a serious impact on the outcome of reaction. Especially, strong electron-donating substituents led to decreased reaction rates and low yields, possibly due to a more unfavorable enolization of the substrates. In contrast, the reaction proceeded smoothly for unsubstituted or electron-withdrawing aryl ketones and alkyl ketones giving the corresponding products **243** in good to excellent yields and enantioselectivities. Remarkably, the high reactivity provided by aliphatic *β*-ketoesters allowed for a decreased catalyst loading to as low as 0.5 mol%.

The cooperative nature of the catalyst system was confirmed by control experiments, as no reaction occurred when the components were tested independently. Since the ^{31}P NMR spectrum of the entire catalytic system showed no apparent difference compared to the spectrum of $AgOAc/PPh_3$, it was concluded that there was no direct interaction between the soft and hard metal systems. Thus, the cyclization should proceed in a *trans*-selective fashion. Interestingly, the employment of the amide-based ligand **I** led to the products as opposite enantiomers. Most likely this inversion is caused by an interaction between the two metal systems with the thioether group of the ligand as mediator.

In 2012 an asymmetric protocol for the rare 5-*endo-dig* cyclization of *β*-dicarbonyl compounds **244** bearing an internal alkyne moiety was provided by Shibata and co-workers.[76] The use of a highly elaborate cooperative catalytic system consisting of Box-Ph **J**/Zn^{II}/$Yb(OTf)_3$/ HFIP (hexafluoro *iso*-propyl alcohol) enabled the smooth cyclization of the *β*-

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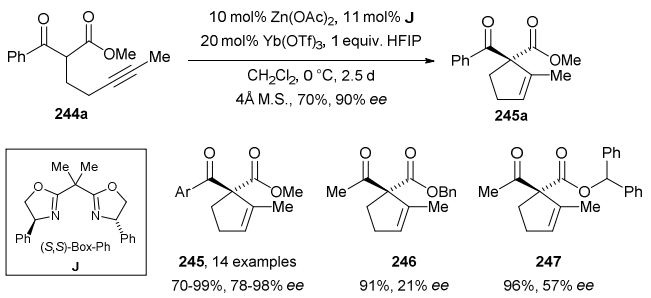
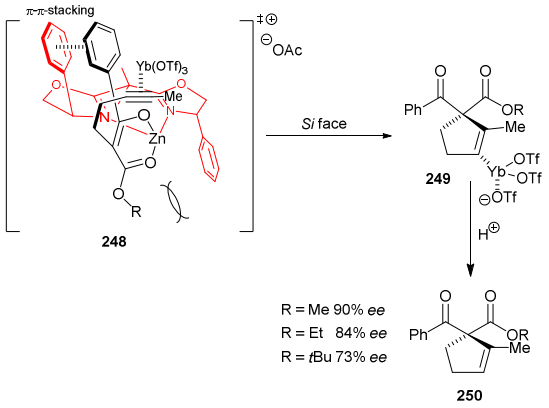


Scheme 74 Zn/Yb-catalyzed asymmetric Concia-ene-related cyclization.

ketoester **245a** in 70% yield and 90% ee in CH_2Cl_2 at 0 °C after 2.5 days (Scheme 74).

This newly established reaction could be applied to a wide range of aryl *β*-ketoesters, tolerating electron-donating- as well as electron-withdrawing-substituted aryl groups, irrespective of the bulkiness or substitution pattern (*ortho*, *meta*, *para*). Even the larger aromatic 1- or 2-naphthyl substrates underwent the cyclization with high yields and enantioselectivities. However, when an aliphatic *β*-ketoester was probed, cyclized **246** was still obtained in excellent yields, but the selectivity broke down to only 21% ee. The bad selectivity could be attenuated to some degree, when bulkier ester groups were applied, as shown by product **247**, but as a general tendency, the reaction seemed to be limited to aryl ketones.

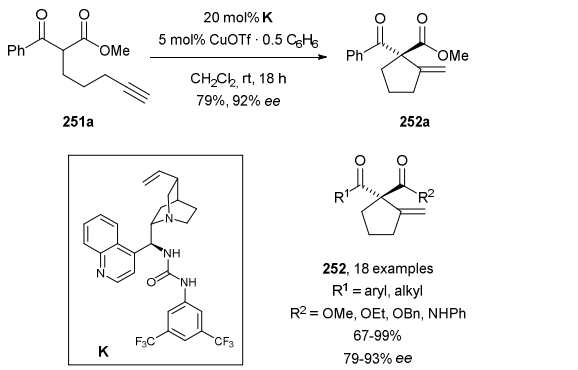
The reason for the diminished enantioselectivity in the case of aliphatic ketones can be found in the proposed transition state **248**. For aromatic substrates there seems to be a beneficial π-π stacking of the pseudo-axial aryl group provided by the substrate with the pseudo-equatorial phenyl group of the bisoxazoline ligand (Scheme 75).



Scheme 75 Proposed model to explain the enantioselectivity.

This interaction is not present for aliphatic groups, thus allowing for a higher flexibility in the transition state, which accounts for the less effective facial discrimination. With the Zn ion being in an almost tetrahedral geometry, intramolecular nucleophilic *trans* attack seems feasible, possibly leading to an $Yb(OTf)_3$/alkyne complex that is subsequentially protonated to release the product **250**. It should be noted though that the proposed intermediate **249** could not be detected by mass spectrometry. Therefore, although there is precedence in the literature on the alkyne activation by rare earth metals, e.g. for hydroaminations[77], the role of $Yb(OTf)_3$ remains somewhat ambiguous. Based on this assumption, the authors concluded that the beneficial effect of HFIP originates from the fast protonation of the intermediate **249** by the highly acidic fluorinated alcohol. Not surprisingly, alcohols with similar acidity, such as phenols, can be used instead.

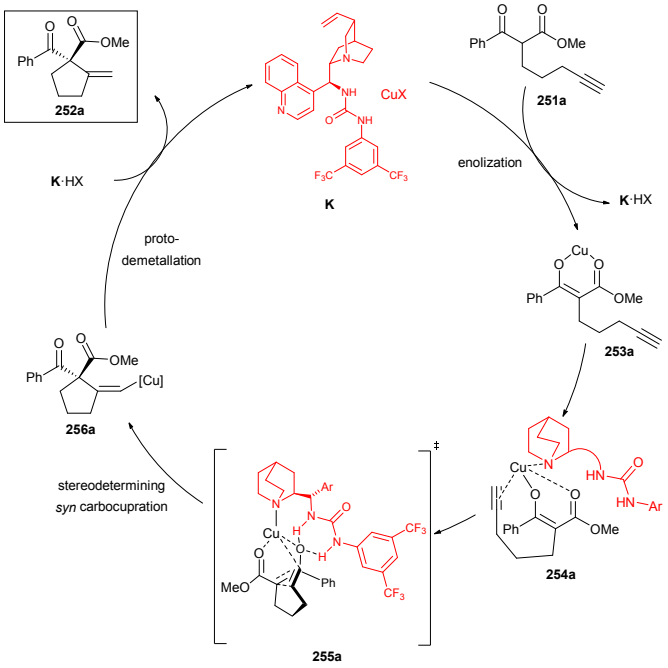
In 2009 Dixon and co-workers reported on an asymmetric Conia-ene-related reaction by employing a cooperative system consisting of a carbophilic Lewis acid and a Brønsted base.[78] Among the different combinations tested, it was found that the bicatalytic system of 5 mol% Cu(OTf) and 20 mol% of the cinchonidine-derived urea **K** was the most suitable combination for the enantioselective 5-*exo*-*dig* cyclization of the *β*-ketoester **251a** to the cyclopentane derivative **252a** yielding the desired product in 79% yield and 92% ee after 18 hours at room temperature in CH_2Cl_2 (Scheme 76). In stark contrast, other metals, including Au(I) and Ag(I), which have previously been proven as efficient catalysts for the π-activation of alkynes, failed to promote this reaction. Only metals which are not limited to pure alkyne activation, such as Ni(II) and Zn(II), were suitable, however, the reaction proceeded with low enantioselectivity. Most astonishingly, the sole presence of the catalytic copper salt was not sufficient for the cyclization to occur, indicating that the role of the bifunctional urea was not limited to acting as a chiral ligand.



Scheme 76 Asymmetric Conia-ene-related reaction by Cu/thiourea catalysis.

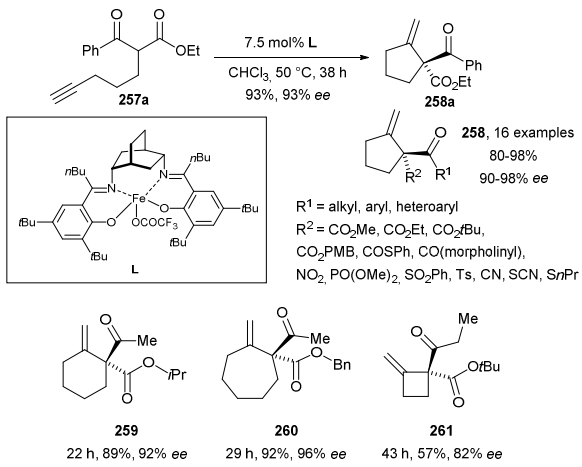
With the optimal reaction conditions established, it was shown that the reaction is applicable to a broad range of *β*–ketoesters and it turned out that the corresponding cyclopentanes **252** were obtained in good to excellent yields and enantioselectivites, irrespective of the steric or electronic nature of the substrates. As a tendency though, the cyclization proceeded with slightly higher enantioselectivity for bulky aryl ketoesters and the authors assumed that there was a general correlation between the acidity of the substrates and the reaction rates indicating that the enolization/deprotonation was the rate-determining step. Thus, smooth cyclization of a *β*–ketoamide (R^1 = Ph, R^2 = NHPh) occurred in 85% yield and 83% ee after five days.

Further investigations were undertaken to unravel the mechanism of the reaction.[57] Essentially, the authors could verify that the rate determining step is associated with the deprotonation of the *β*-ketoester and that the bifunctional character of the employed urea catalyst is pivotal for the reactivity. While the urea moiety is crucial for the acidification of the substrate through hydrogen bonding, the tertiary amine incorporated in the quinuclidine ring serves as Brønsted base, thus facilitating the formation of a copper enolate (Scheme 77). Supported by quantum mechanical calculations and deuterium labelling experiments, the authors suggested that the formed copper enolate **254a** concurrently coordinates to the alkyne, thereby activating the alkyne for the subsequent *syn* carbocupration. The observed enantioselectivity originates from the coordination of the urea catalyst to the copper enolate. As indicated in the transition structure **255a**, the quinuclidine moiety directly coordinates to the copper centre, while the urea moiety can interact with the additional oxygen provided by the ketone group.



Scheme 77 Proposed mechanism for the Cu/thiourea catalyzed Conia-ene-related reaction.

In 2014 White and co-workers pursued a more distinct approach by relying on the single metal activation provided by novel metal salen complexes.[55] After employing different catalysts for the asymmetric 5-*exo-dig* cyclization of the *β*-ketoester **257a**, it turned out that the novel Fe(III)-salen catalyst **L** was the most suitable to give the cyclized product **258a** in excellent yields and enantioselectivities in chloroform at 50 °C after 38 hours (Scheme 78). The modification of the frequently used C_2-symmetrical salen ligand was vital for the high asymmetric induction, and derivatives in which the aldimine



Scheme 78 Asymmetric iron-catalyzed Conia-ene-related reaction.

scaffold was replaced by bulky alkyl ketimines led to a tremendous increase in enantioselectivity.

Interestingly, there was no severe limitation on the reaction scope as excellent yields and enantioselectivities were obtained for all *β*-carbonyl compounds tested. In contrast to previously reported protocols, no diminished enantiomeric excess was observed for less bulky alkyl ketones and under the optimized reaction conditions, even substrates with an unfavorable enolization rate underwent clean cyclization. In addition, the reaction was also suitable for 6-*exo* and 7-*exo* cyclizations, yielding the corresponding cyclohexane **259** and cycloheptane **260** with comparable results. Most enthralling, a 4-*exo*-derived cyclobutane **261** was obtained in moderate yield in spite of the unfavourable thermodynamics.

The proposed transition state shows the 5-*exo-dig* cyclization at the *Si*-face of the prochiral iron enolate (Figure 6). The metal ion works in two distinctive ways, as it activates the alkyne and forms the *Z*-enolate. This explains why this protocol is so efficient, as this feature eliminates the need for a dual catalyst system. The alkyl substituent attached to the imine carbon blocks the *Re*-face, thus favoring the *Si*-face attack of the enolate.

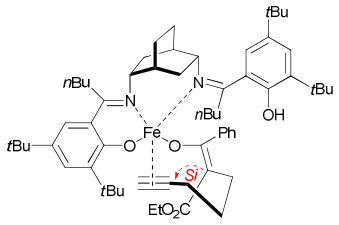


Figure 6 Transition state for the iron-catalyzed Conia-ene-related cyclization.

All examples discussed so far, dealt with the cyclization of alkyne-tethered carbonyl compounds. Surprisingly, there have been no extensive studies on the asymmetric Conia-ene reactions of substrates containing alkenes. Apart from controlling the enantioselectivity, the addition to alkenes is a new challenge, because the generation of an additional stereocentre leads to the formation of diastereomers. There is

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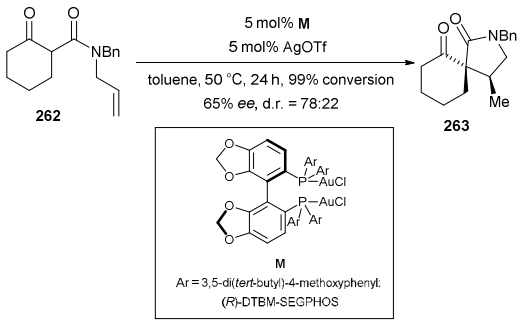
only one example provided by Gandon and co-workers, in which an asymmetric high yielding gold-catalyzed cyclization of **262** to **263** was observed, albeit with only moderate stereoselectivity (Scheme 79).[23]



Scheme 79 Example of an asymmetric Conia-ene-type reaction of alkenes.

5. Applications in Natural Product Syntheses

In the first part of this section the formation of interesting cyclic skeletons will be discussed, whereas various impressive examples of total syntheses relying on a Conia-ene or a Conia-ene-related reaction as a key step will be presented in the second part.

Up to now we have not included examples, in which silyl enol ethers have been employed. However, for most of the complex natural products presented, these Conia-ene-related reactions are more elegant. For many cases only ketones are needed as the structural moiety, but catalytic Conia-ene reactions of ketones are too challenging, because of their unfavourable enol ratio. In contrast to ketones, *β*-ketoesters allow for catalytic methods, but the cleavage of the ester group after cyclization is often troublesome, as the majority of substrates does not tolerate the reaction conditions needed for a Krapcho decarboxylation. Therefore, the conversion of a ketone into the corresponding silyl enol ether and subsequent Conia-ene-related reaction is the best applicable approach.

5.1. Syntheses of cyclic backbones

5.1.1. The tricyclic furanochromanone skeleton

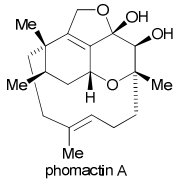
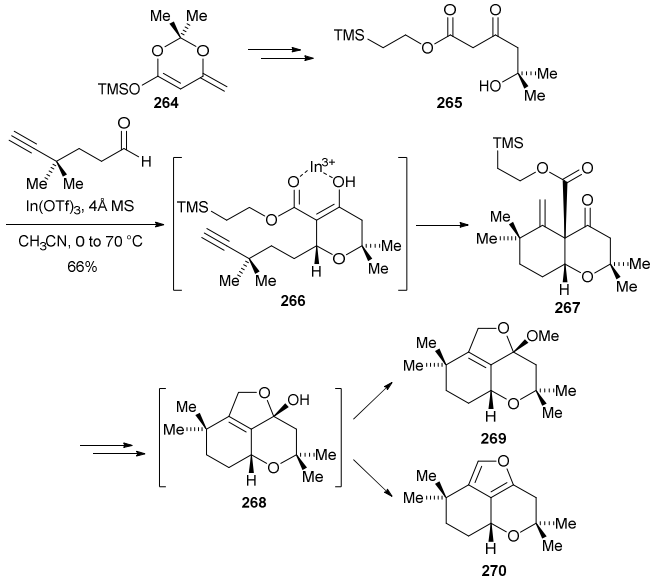


Figure 7 Structure of Phomactin A.

Phomactin A belongs to a new class of antagonists for platelet activating factors (PAF). (Figure 7).[79] It represents the structurally most challenging phomactin compound and has attracted much synthetic interest. Beside the three known total syntheses, Lee and co-workers have developed a Prins/Conia-ene cascade to diastereoselectively generate the tricyclic backbone of phomactin A.[80]

At first a Mukaiyama aldol reaction between the readily available silyl enol ether **264** and acetone, followed by a subsequent transesterification afforded the intermediate **265**, which was the starting point for the cascade reaction (Scheme 80). The $In(OTf)_3$-catalyzed Prins/Conia-ene cascade opened access to the bicyclic structure **267** bearing the correct substitution pattern in 66% yield as a single diastereomer. Interestingly, previous experiments without the presence of molecular sieves gave the dealkoxycarbonylated products. However, electrophilic epoxidation of the exocyclic double bond using *m*CPBA and subsequent cleavage of the TMS group led to the model compounds **269** and **270** by a methylation or an elimination reaction that occurred on silica gel during column chromatography.



Scheme 80 Synthesis of the tricyclic core of phomactin A.

5.1.2. The 6,6,5,7-tetracyclic backbone of daphnilongeranin B

The daphniphyllum alkaloids represent a group of bioactive polycyclic natural products with more than 250 members known up to now.[81] Therefore, a fast and efficient access to their tetracyclic core is of utmost importance (Figure 8).

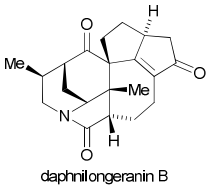
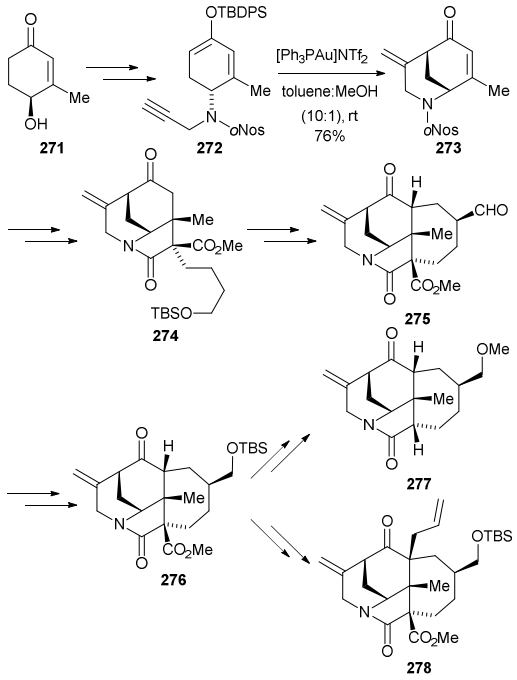


Figure 8 Structure of daphnilongeranin B, daphniphyllum alkaloid.

In 2014 Li and Shao published an elegant synthesis of this complex structure using a gold-catalyzed Conia-ene reaction and two diastereoselective Michael reactions as key steps.[82] By

pursuing this strategy they could generate highly complex compounds bearing two different substitution patterns (Scheme 81).

They commenced their synthesis with the introduction of a propargylamide moiety *via* a Mitsunobu substitution, followed by the formation of a TBDPS enol ether. Structure **273** was then obtained in 76% yield by a selective, $[Ph_3PAu]NTf_2$-catalyzed Conia-ene-type reaction. An *in situ* mixture of $[Ph_3PAu]Cl$ and AgOTf exhibited significantly lower catalytic activity. After the cleavage of the nosyl substituent, subsequent amidation, and the first diastereoselective Michael addition the tricyclic structure **274** was obtained. In order to prepare **275** in the second Michael addition, an exocyclic methylene group was introduced in the α-position to the carbonyl group and the oxidation pattern on the alkyl chain was corrected. Reduction of the Michael adduct **275** and subsequent protection as a TBS ether yielded the precursor for two different target structures that could be achieved by means of an *O*-allylation followed by thermal Claisen rearrangement or hydrogenation, protection group exchange, and a Krapcho demethoxycarbonylation sequence.



Scheme 81 Synthesis of potential daphnilongeranin alkaloid precursors.

5.1.3. Large macrolide cycles

Fürstner and co-workers have demonstrated the generation of macrolides *via* an elegant alkyne metathesis and Conia-ene reaction sequence approach.[83] Instead of closing the macrocycle by intramolecular esterification of the aromatic acid, they first cyclized a β-ketoester bearing two alkyne groups *via* metathesis and afterwards formed the benzene ring by means of a Conia-ene reaction and subsequent dehydrogenation. This structural

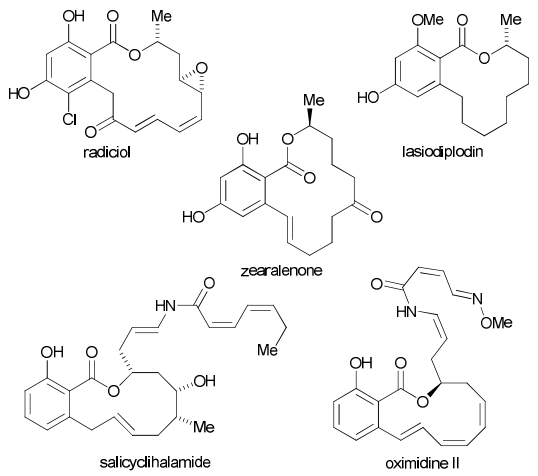
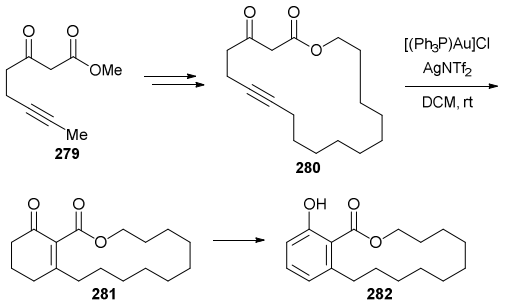


Figure 9 Interesting natural products with a macrolide moiety.

motif is part of the salicylic and resorcylic acid macrolide family. Prominent members of this subgroup of natural products are depicted in Figure 9.

Starting from the β-ketoester **279**, they synthesized the internal alkyne **280** by transesterification with an alkynol and a subsequent alkyne metathesis using a molybdenum alkylidyne catalyst. The following Conia-ene reaction furnished the 6-*endo*-cyclized product that gave the enone **281** upon isomerization (Scheme 82). Finally, the model compound **282** was gained through DDQ oxidation and aromatization-driven tautomerization of the carbonyl functionality.



Scheme 82 Synthesis of a model macrolide compound by Fürstner and co-workers.

5.1.4. The tetracyclic diterpene backbone

The diterpenes of the kauran and phyllocladane family are synthetically extremely difficult because of their complex cyclic structure including a [3.2.1]-bicyclic moiety with a quaternary bridgehead carbon atom (Figure 10). Therefore, the elegant synthesis of the phyllocladane skeleton by Malacria and co-workers represents an impressive milestone.[84-86]

As cyclization precursor they chose the triyne **284** that can be readily synthesized from β-ketoester **283**. A Knoevenagel condensation, followed by a Michael addition, and a final TBAF-promoted deprotection yielded **284** in 66% yield in three

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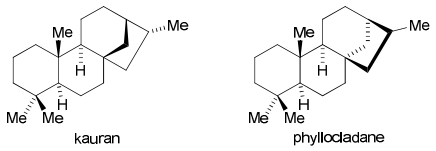
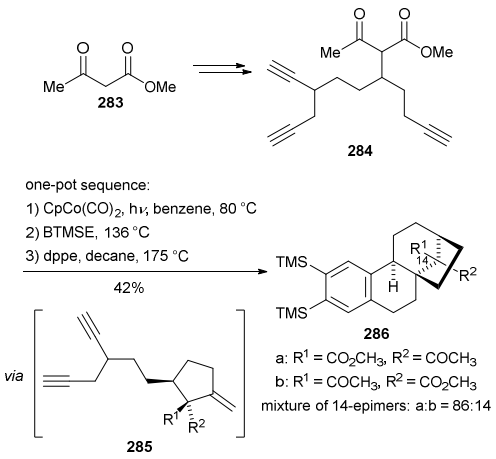


Figure 10 The structure of kauran and phyllocladane.

steps. With the triyne **284** in hand, Malacria and co-workers performed a triple one-pot reaction sequence. Firstly, a cobalt(I)-catalyzed 5-*exo*-selective Conia-ene reaction furnished the five-membered ring with an exocyclic methylene group (Scheme 83). Secondly, a dihydrocyclobutabenzene motif is formed *via* alkyne trimerization. An electrocyclic ring opening *in situ* furnished the reactive diene motif for the final Diels-Alder cycloaddition that leads to the tetracyclic phyllocladane-type structure **286** in remarkable 42% yield. Avoiding the steric interaction of the *gem*-dicarbonyl moiety with the aromatic hydrogens in the transition state, the intramolecular Diels-Alder reaction selectively gave the phyllocladane instead of the kauran diastereomers.



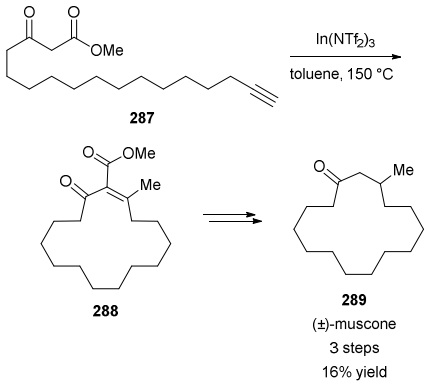
Scheme 83 Synthesis of the tetracyclic phyllocladane skeleton *via* a one-pot Conia-ene/[2+2+2]-cycloaddition/IMDA reaction. BTMSE = bis(trimethylsilyl)ethyne; dppe = 1,2-bis(diphenylphosphino)ethane.

5.2. Total syntheses

5.2.1. (±)-Muscone

In their publication on indium-catalyzed cycloisomerization reactions of *ω*-alkynyl-*β*-ketoesters Nakamura and co-workers reported on a three-step protocol to (±)-muscone, which is the primary contributor to the odor of musk.[40]

At first they used their previously developed $In(NTf_2)_3$-catalyzed Conia-ene reaction to generate the fifteen-membered *exo*-selective product that immediately underwent isomerization to the enone **288** (Scheme 84) The natural product was then obtained by a heterogeneous hydrogenation on Pd/C and a Krapcho demethoxycarbonylation in 16% overall yield in three steps.

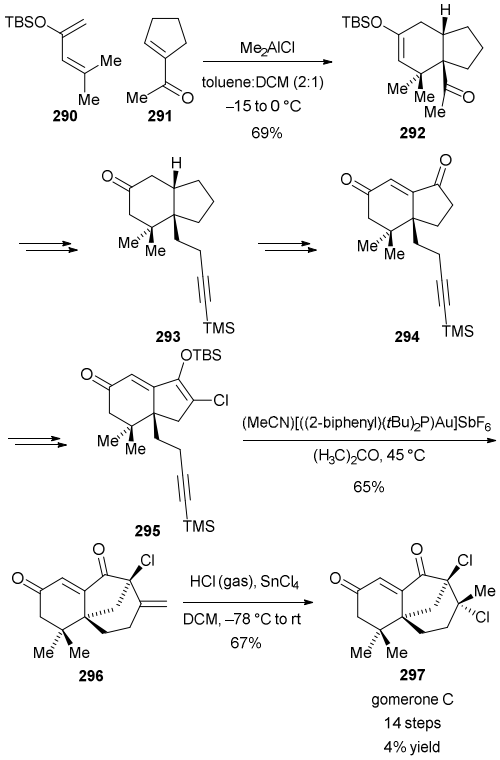


Scheme 84 Three-step synthesis of (±)-muscone.

5.2.2. (±)-Gomerone C

Gomerone C together with two other chlorinated sesquiterpenes were firstly isolated from *Laurencia majuscula* by Cueto and co-workers in 2008, who elucidated the structure of all the tricyclic compounds.[87] Carreira's synthesis of gomerone C remains the sole total synthesis to date of these structurally complex natural products.[88] They argued that due to Bredt's rule the chlorine substituent at the bridgehead atom could not be installed *via* enolate chemistry. Thus, they decided to pursue a strategy in which the chlorine atom is introduced prior to the ring closure.

Starting from the commercially available enone **291** and the diene **290**, a selective Diels-Alder cycloaddition provided the bicyclic diastereomer **292** in 69% yield (Scheme 85).



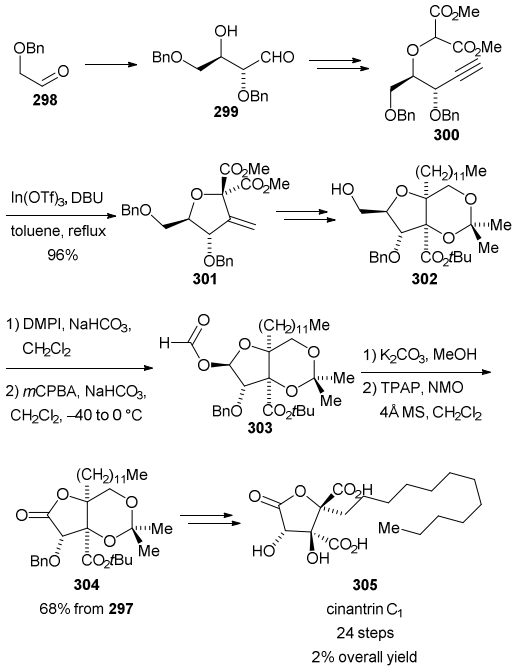
Scheme 85 Total synthesis of gomerone C by Carreira and co-workers.

Then the acetyl group was converted into a terminal alkyne and subsequently transformed into the homologue TMS-protected alkyne **293** by means of a formyl group installation/hydrogenation/Ohira-Bestmann reagent-induced rearrangement/silylation sequence. With the alkyne **293** available, the correct oxidation pattern of **294** was established *via* dehydrogenation using *N*-*tert*-butyl phenylsulfinimidoyl chloride (Mukaiyama's reagent) and oxidation with the CrO_3·dimethylpyrazole complex. The newly generated enedione **294** was then converted into the corresponding TBS-enol ether and treated with several chlorination agents. Only Bu_4NCl_3 (Mioskowski's reagent) gave the desired chlorinated cyclization precursor **295**, which then underwent a 6-*exo*-selective Conia-ene reaction with an Echavarren-type gold(I) catalyst. Finally, the total synthesis was finished with the hydrochlorination of the exocyclic double bond. Interestingly, NOE experiments revealed a different relative configuration of gomerone C; thus, the previous structures of gomerone B and C had to be revised.

5.2.3. (−)-Cinatrin C_1

The class of cinatrins was isolated from fermented *Circinotrichum falcatisporum* RF-641 by Itazaki and co-workers in 1992.[89] As rat platelet phospholipase A_2 (PLA_2) inhibitors they could possibly be used as anti-inflammatory compounds.[90] Their highly substituted structure, containing a five-membered lactone moiety with three adjacent stereogenic centres, in combination with their potential application in pharmacy renders them desirable targets for organic synthesis. In 2013 Hatakeyama and co-workers reported on a new strategy for the synthesis of cinatrin C_1, relying on a Conia-ene reaction, followed by a subsequent dihydroxylation and lactonization.[91]

After fruitless efforts to generate the furanon ring *via* an oxidation in *α*-position to the ring oxygen, they decided to establish the lactone motif by Baeyer-Villiger rearrangement. Therefore, they started their total synthesis from benzylated glycolaldehyde **298** with a prolin-catalyzed self-aldolization. Using the Ohira-Bestmann homologization and a rhodium-catalyzed O-H insertion, the resulting aldehyde **299** was converted into the cyclization precursor **300** (Scheme 86). The following $In(OTf)_3$/DBU-catalyzed Conia-ene reaction selectively yielded the 5-*exo* product **301** in 96%, which was then converted into the cyclic acetal by various redox and protection operations as well as a Wittig reaction to attach the alkyl chain to the bicyclic system. In the following steps, the carbonyl group of the lactone was formed by hydrogenation of the primary benzyl protected alcohol, oxidation to the corresponding aldehyde, Baeyer-Villiger oxidation, saponification of the formate **303**, and subsequent oxidation to the lactone **304**. After the acetal cleavage, oxidation to the acid, esterification, deprotection, and HPLC purification cinatrin C_1 was obtained in 2% overall yield after 24 steps.



Scheme 86 Synthesis of the PLA2-inhibitor (−)-cinatrin C_1.

5.2.4. (−)-Teucvidin

Terpenes have gained a tremendous prominence in nature. Diterpenoids represent a subgroup of these terpenes and may consist of various open-chain or cyclic primary scaffolds. Terpene natural products exhibit a wide range of biological activities, especially clerodane diterpenes. Unfortunately, no enantioselective synthesis for the preparation of the structurally sophisticated 9-*nor*-clerodane teucvidin was known till 2012.

Based on their work on the efficient formation of the tricyclic furanochromanon skeleton of phomactin A Lee and co-workers envisioned a total synthesis of (−)-teucvidin.[92] With the highly evolved cyclization precursor **306** they performed a substrate-controlled Michael/Conia-ene cascade that led to the 6-*exo*-derived *cis*-decalin **308** in good yield as a single diastereomer (Scheme 87). Subsequently, the aldehyde was reduced to avoid side reactions during the *m*CPBA epoxidation and was then reinstalled by standard oxidation. An interesting TBAF-induced dealkoxylation/ decarbonylation/cyclization sequence furnished the tricylic furanodecalin ring system of **305**. An *O*-allylation of the aldehyde group of **309**, followed by a thermal Claisen rearrangement led to the formation of the quaternary stereogenic centre. Then the furan **310** underwent oxidative methoxylation and cleavage of the generated acetal under acidic conditions to yield **311**. Finally, the lactone moiety was installed *via* oxidation, ozonolysis, and nucleophilic attack of furanyl lithium. Thus, teucvidin was obtained in 22% yield in 12 steps.

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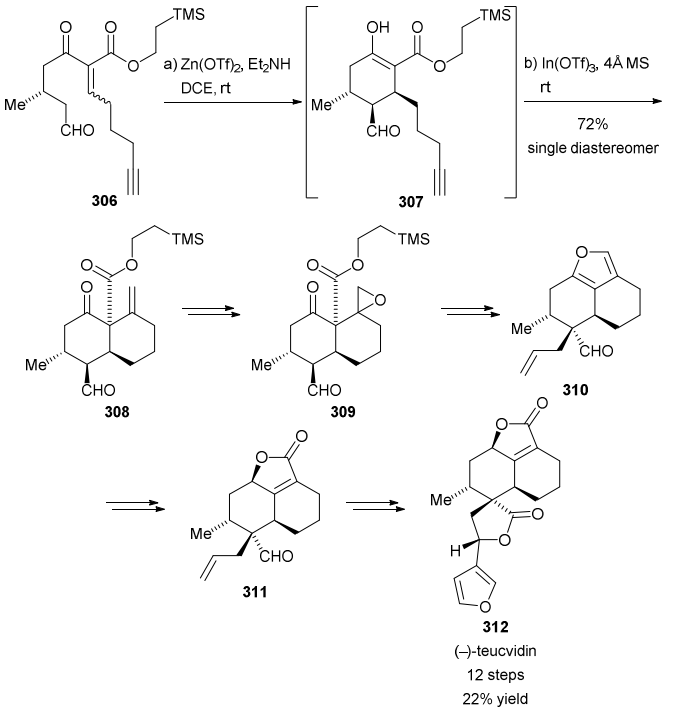
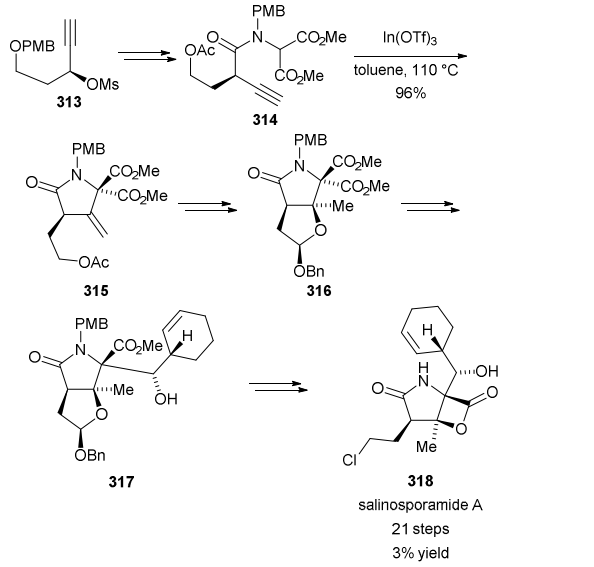


Scheme 87 Synthesis of the 9-*nor*-clerodane (−)-teucvidin.

5.2.5. (−)-Salinosporamide A

The secondary metabolite from the marine actimycete *Salinospora tropica*, Salinosporamide A, has been found to exhibit attractive biological activity.[93] For example, proteasome activity is effectively inhibited by a nanomolar concentration of this alkaloid. Furthermore, due to its high cytotoxicity for various cell lines, it may be used as an anticancer drug.[94] For the synthesis of salinosporamide A Hatakeyama and co-workers envisaged a route including a Conia-ene reaction, a diastereoselective ester reduction, and an intramolecular oxygen transfer as key steps.[41]

First Hatakeyama and co-workers had to prepare the cyclization precursor **314** from **313** (Scheme 88). Treatment of the mesylate **313** with the corresponding aldehyde in the presence of a palladium(0) catalyst and diethyl zinc, followed by oxidative deprotection, acetylation, and desilylation led to the formation of a primary alcohol. Oxidation and amidation installed the C-H-acidic 1,3-dicarbonyl moiety. Interestingly, **314** underwent partial cyclization during column chromatography. However, the cyclized product **315** was obtained with an In-catalyzed 5-*exo* selective Conia-ene reaction in excellent yield without any isomerization observed. After the hydrolysis of the acetate and the oxidation to the corresponding aldehyde, the benzylated lactol was formed *via* a two-step cyclization using the Danishefsky's protocol. Then a diastereoselective $NaBH_4$-reduction of the former dicarbonyl moiety and treatment with cyclohexenyl zinc chloride formed the carbinol motif. After the oxidation to the lactone, *N*-deprotection, acetal cleavage, and lactonization the resulting



Scheme 88 Synthesis of the salinosporamide A alkaloid.

primary alcohol was converted into the chloride to yield salinosporamide in 3% yield over 21 steps.

5.2.6. (+)-Neooxazolomycin

Uemura and co-workers were the first to isolate neooxazolamycin in 1985 (Figure 11).[95] The skeleton of this alkaloid is remarkably manifold and includes a polyene attached oxazole ring, a bicyclic lacton-lactam moiety in combination with several stereogenic centres. Although oxazolomycins have a broad range of biological activity, only the total synthesis of neooxazolomycin, as one of the few members of this class of natural products, is known so far.[96] Whereas the left-hand fragment is easier available, the enantioselective formation of the bicyclic structure in the right hand segment still remains especially crucial. Therefore, only the synthesis of the right hand segment and the final steps of the total synthesis will be discussed here (Scheme 89).

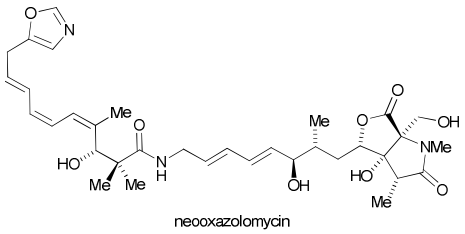
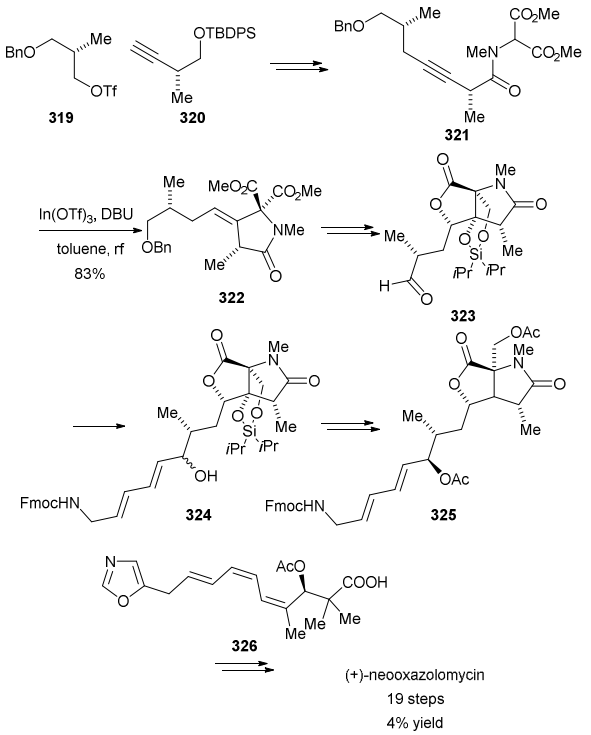


Figure 11 Oxazole alkaloid neooxazolomycin.

First the starting materials **319** and **320** were coupled to give an internal alkyne, which then was oxidized to the corresponding carboxylic acid and upon amidation yielded the cyclization precursor **321**.[41] Under substrate control, the key step Conia-ene reaction generated the lactam ring with an exocyclic double bond *via* a 5-*exo* cyclization. It is noteworthy to record that Hatakeyama and co-workers have never observed epimerization during the cyclization reaction. By means of a

diastereoselective OsO_4-catalyzed dihydroxylation, subsequent lactonization, and Fujisawa reduction/silylation sequence a dioxasilinane was obtained, which upon debenzylation and oxidation gave the aldehyde **323**.



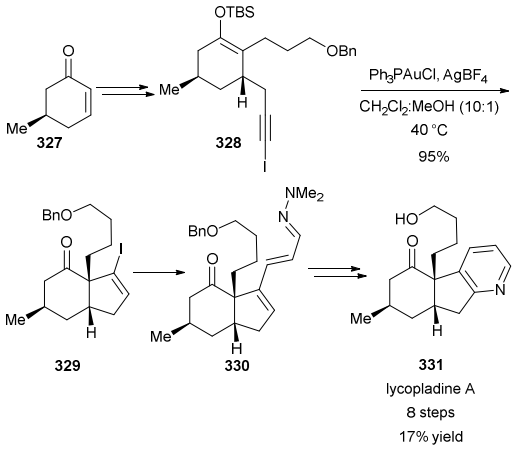
Scheme 89 Hatakeyama's total synthesis of (+)-neooxazolomyin.

The Nozaki-Hiyama-Kishi reaction turned out to exhibit the best properties to convert **323** into the alcohol **324**, however, with no diastereocontrol on the diastereomeric ratio. Nonetheless, a single diastereomer was obtained by oxidation and selective reduction. The final steps in the synthesis of the right-hand segment were the cleavage of the cyclic silyl ether and acetylation of the alcohol moieties. After the amidation of **325** with the carboxylic acid **326** and subsequent deacetylation, (+)-neooxazolomycin was obtained in 18 steps starting from **319** in 4% overall yield. In 2011 Hatakeyama and co-workers presented the total synthesis of oxazolomycin A, which is a derivative of neooxazolomycin and contains a four-membered instead of a five-membered lactone.[97]

5.2.7. Lycopladine A

Toste and co-workers applied their work on the gold-catalyzed Conia-ene reaction to the synthesis of lycopladine A, which is a natural occurring cytotoxic compound isolated from *lycopodium complantum*.[98,99] The hydrindanone backbone with the fused pyridyl ring makes lycopladine A a good target for their new methodology.

The total synthesis started with an oxidative iodination of the enone followed by a Suzuki-Miyaura coupling. The 1,4-addition of tributylallenyl stannane and the exchange of the terminal alkyne proton with an iodine atom furnished **328**, which underwent a diastereoselective 5-*endo* Conia-ene reaction. A second Suzuki-Miyaura coupling installed the hydrazine moiety, which upon heating isomerized to the corresponding *cisoide* conformer that allowed for an electrocyclic ring closure. A subsequent rearomatization-driven elimination of dimethyl amine completed the tricyclic core structure. Finally, the debenzylation was performed under transfer hydrogenation conditions to obtain lycopladine A in merely eight steps in 17% yield (Scheme 90).



Scheme 90 Asymmetric total synthesis of lycopladine A.

6. Conclusions

Since the first reports of the thermal intramolecular addition of enols to alkynes, this field of research has blossomed under its leading experts. A myriad of metals have been shown to promote Conia-ene and related reactions in catalytical amounts, acting *via* different modes of substrate activation. For most systems, the major emphasis is given to the cyclization of ketoesters and malonates affording five or six-membered carbocycles, but examples reporting on the formation of hetereocycles or large-rings are continuously increasing. With the high level of efficiency provided, the develpmont of asymmetric versions and applications in natural product synthesis have gained considerable attention. Nonetheless, many problems associated with Conia-ene reactions still need to be addressed and in the future the following developments are desirable: (1) Better mechanistic understanding for metal catalysts, especially in the field of dual activation; (2) Quantum mechanical calculations to gain further insights into regioselectivity and diastereoselectivity; (3) a stronger focus on internal alkynes and the development of protocols, which circumvent common problems like regioselectivity; (4) more catalytic systems which enable the cyclization of alkyne-tethered unactivated ketones under mild conditions avoiding the use of silylenolethers; (5) asymmetric protocols with a broader applicability, including the formation of heterocycles or six-membered rings; (6) more investigations towards the use of alkenes.

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Notes and references

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