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ADVANCED SYNTHESIS & CATALYSIS

Recent Advances in Ene Reactions with Carbon Enophiles

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Dedicated to Prof. Dr. Günter Helmchen on the occasion of his 85th birthday.

Abstract: Ene reactions are inter- or intramolecular addition reactions between a four-electron "ene" component and a two-electron enophile functionality, in which two π-bonds and a C–H (or metal–C) σ-bond are rearranged into one π-bond and two σ-bonds. One of the newly formed σ-bonds is a carbon–carbon bond, while the other is the rearranged a C–H (or metal–C) bond. This transformation enables the formation of structurally and functionally complex ene products in a single step. Originally, ene reactions were discovered as concerted and stepwise pericyclic elementary processes. However, increasing mechanistic insight—gained through both experimental and computational studies—along with extensive empirical methodological work, has paved the way to a plethora of ene-type reactions involving carbon enophiles. Since 2012, the already well-established transition metal-catalyzed variants of ene reactions have significantly expanded. Moreover, highly reactive aryne intermediates—generated in situ either by fluoride induced elimination from *ortho*-silyl aryltriflates at room temperature, or by hexadehydro-Diels–Alder reaction of a 1,3-diyne with an alkyne (both inter- and intramolecularly)—find increasing application in novel ene-type sequences. Propargyl ene reactions also gain traction, particularly because the resulting ene-allenes serve as highly valuable intermediates in the design of domino sequences that lead to complex polycyclic fused structures. Finally, the implementation of ene reactions in polymer chemistry for the synthesis of functionalized polymers and renewable unsaturated raw materials has emerged as a promising alternative to the use of purely petrochemistry based substrates.

Keywords: addition, alder ene reaction, alkenes, alkynes, allenes, arynes, catalysis, cycloisomerization

1. Introduction

Ene reactions were first reviewed in 1969,[1] and over the more than five decades since, they have continued to attract steady interest. Numerous variants have been devised and developed, and significant progress has been made in concise synthetic methodologies based on the application of ene reactions. In the previous review from 2013, ene reactions with carbon enophiles were comprehensively discussed, covering most relevant reviews and original research in the literature until 2012.[2] A particularly famous transformation is the Alder ene reaction, which involves an ene component bearing a hydrogen atom in the allylic (or heteroallylic) position reacting with alkenes or alkynes as enophiles. A special subclass is the Conia ene reaction,[3] in which the ene partner is typically an enol tautomer (or a phenol), and this transformation often proceeds in an intramolecular fashion.

Alder ene reactions can proceed either in an intermolecular fashion—as addition of an ene and an enophile—or intramolecularly as a cycloisomerization, where both ene and enophile functionalities are present in the same molecule (**Scheme 1**). In pericyclic ene-reactions, which proceed via a concerted fashion (synchronously or asynchronously), six electrons (four π- and two σ-electrons) are reorganized through a cyclic transition state. Like other

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pericyclic processes, the Alder ene reaction is stereogenic, as the transformation of at least one sp^2-hybridized center into a tetrahedral configuration leads to the creation of stereocenters. The migration of the ene hydrogen also occurs in a stereospecific manner in the pericyclic Alder ene reaction. Oppolzer's formal replacement of the migrating hydrogen atom with a metal gave rise to the class of "metallo-ene" reactions,[4] which in many cases, still follow the principles of pericyclic reactivity. However, in metal mediated or even metal catalyzed ene reactions, a stepwise reaction mechanism involving organic and/or organometallic elementary steps must also be considered. In these cases, the stereochemical outcome is typically selective rather than stereospecific.

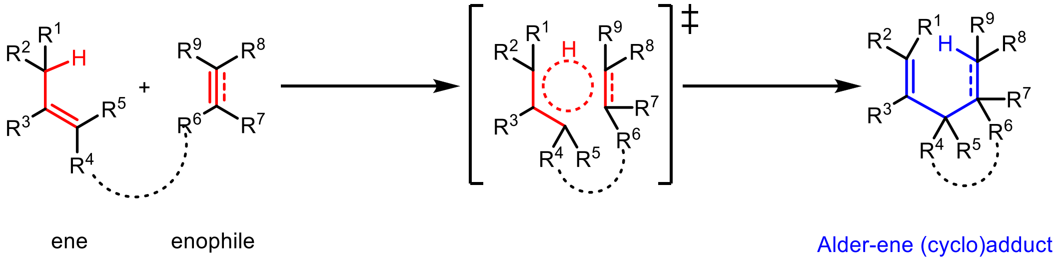
Over the past decade, numerous advances in the development of Alder ene reaction variants have been made, alongside a deeper theoretical understanding enabled by markedly improved quantum chemical calculations. For instance, in a density functional theory (DFT)-computational study on the Alder ene reaction with propene and seven enophiles, Fernández and Bickelhaupt revealed that albeit the reactions possess significant aromaticity in the transition state the activation strain governs the overall activation barrier.[5] Computationally, the reaction barrier decreases for the enophiles in the following order: ethene, ethyne, formaldimine, methyl acrylate, formaldehyde, methylenephosphane, methanethial.

Computational investigations on the Alder ene cycloisomerization of different 1,6-dienes at M06-2X(PCM)/TZ2P level of theory were conducted to understand the impact of geminal substitution patterns in the enophile of the *cis*/*trans*-selectivity of the cyclization process.[6] The activation strain model of chemical reactivity (ASM–distortion interaction model) reveals that the origin of the *cis*-selectivity as a consequence of an early transition state. Activating substituents in turn favor asynchronous transition states as a consequence of a lower activation barrier caused by stabilizing orbital and electrostatic interactions. This leads preferentially to the *trans*-products.

Li and coauthors just very recently reported that liquid 1-hexene crystallizes at 4.3 GPa and polymerizes at 18 GPa at room temperature, forming olefins.[7] Gas chromatography, mass spectrometry, vibrational spectroscopy, as well as in situ neutron diffraction and theoretical calculations clearly support that an Alder ene reaction takes place between two hexene molecules under high pressure conditions forming regioisomeric dimers, i.e., branched and linear products.

Furthermore, a long-sought answer to a question, whether biosynthetic pericyclases,[8] i.e., the enzymatic Alder ene reaction, might exist, was recently unraveled by a synergistic interplay between computation and experiment. Two homologous groups of pericyclases were shown to catalyze distinct reactions and their selectivity were rationalized by computational studies.[9] Indeed, one group indeed catalyzes an Alder ene reaction, which has been previously unknown in biology, while other group catalyzes hetero-Diels–Alder reactions.

This review considers major advancements in ene reactions with carbon enophiles from 2013 to 2025. As in the previous overview,[2] only the formation of



Scheme 1. General mechanistic rationale of concerted Alder ene reactions.

carbon–carbon bonds between ene components and alkenes, alkynes, arynes, and allenes will be treated. The differentiation between intermolecular (Alder ene additions) and intramolecular reactions (Alder ene cycloisomerization) will not be completely separated as in the previous overview, but rather the focus will be guided by enophiles and enes. However, within the corresponding subchapters inter- and intramolecular ene reactions will be (wherever possible) separately treated. As a new contribution also ene reactions for functionalizing double bonds in polymers or renewable raw materials will be covered, due to the steadily increasing interest in sustainable materials science. All other ene reactions, e.g. Schenk ene reaction or carbonyl ene reaction, are not covered in this review.

2. Carbon Enophiles in Ene Reactions

Ene reactions typically employ alkenes as the ene component; consequently, the focus often lies on the choice of the enophile, which may engage in inter- or intramolecular reactions to yield either ene adducts or ene cycloisomerization products.

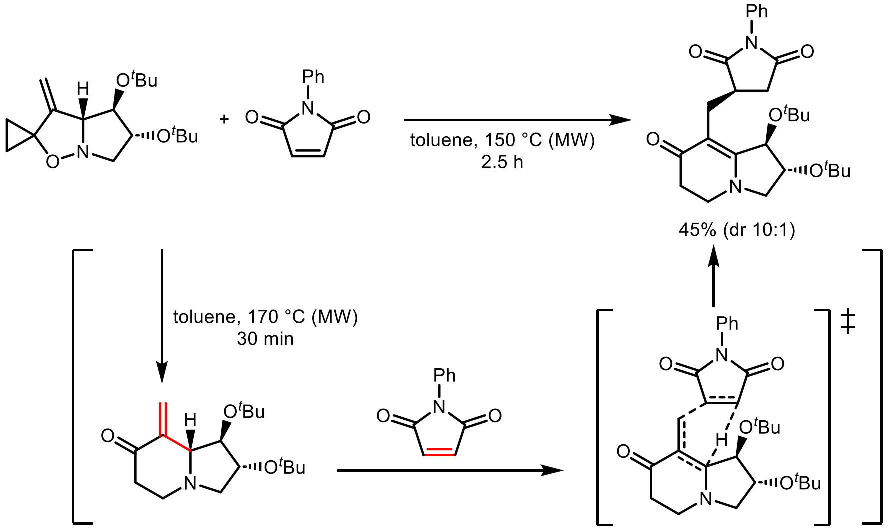
2.1. Alkenes as Enophiles

2.1.1. Intermolecular Ene Reactions with Electron-Deficient Alkenes as Enophiles

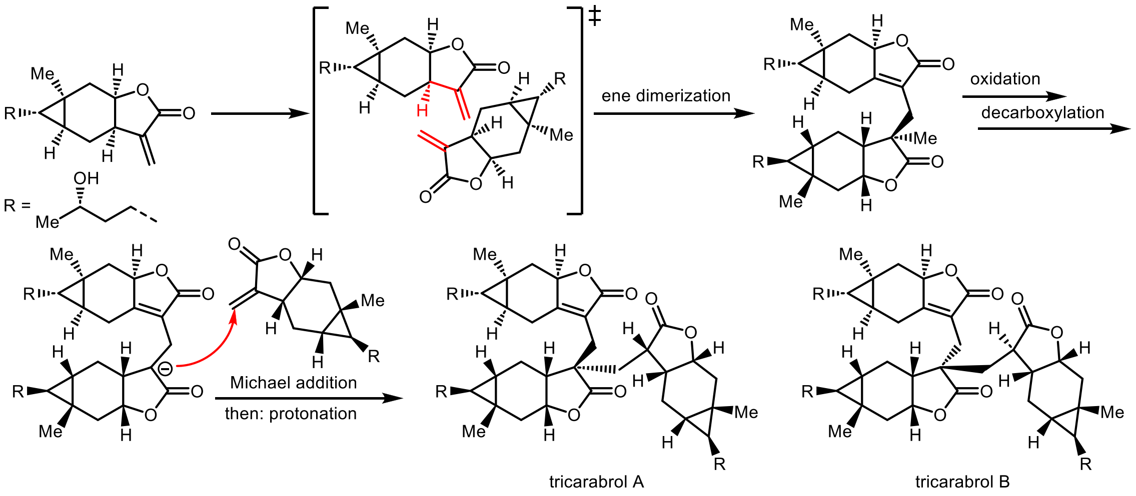
Pericyclic reactions, as well as the ene reaction, with normal electron demand proceed best between an electron-rich 4-electron partner (ene) and an electron-poor 2-electron partner (enophile). In particular, exo-methylene reactants reveal a high reactivity due to minimal steric interactions.

It was known that 1,3-dipolar cycloaddition of nitrones with *exo*-substituted methylenecyclopropanes give 4-methylene-5-spirocyclopropane isoxazolidines, which can undergo the thermal Brandi–Guarna rearrangement to tetrahydropyridones.[10] In one case, the latter was shown to be directly trapped by *N*-phenyl maleimide in sense of a domino Brandi–Guarna rearrangement-ene sequence (**Scheme 2**).[11]

Tricarabrols are sesquiterpene lactone trimers with considerable biological activity, for instance with anti-inflammatory effect of tricarabrol A. Goodpaster, Ye, and coauthors reasoned that the biosynthetic formation of tricarabrols A and B might commence by an Alder ene dimerization of a common tricyclic sesquiterpene lactone (**Scheme 3**).[12] The dimer is



Scheme 2. Domino isoxazolidine–indolizidinone rearrangement-ene reaction.



Scheme 3. Biosynthetic rationale for the formation of the sesquiterpene lactone trimers tricarabrols A and B starting with an Alder ene dimerization.

then oxidized and decarboxylated to undergo the concluding Michael addition of a third equivalent of the sesquiterpene lactone to furnish both tricarabrols as diastereomers.

Ouyang, Tian, and coworkers reported interesting reaction sequences of 1,2-dihydroquinolines with 3-olefinic oxindoles.[13] While a chiral phosphoramide Brønsted acid catalyst gave rise to $[2+2]$ cycloaddition products in good to excellent yields (up to 95%) and with high stereoselectivities (up to $>99\%$ ee, $>20{:}1$ dr). However, trifluoromethanesulfonic acid as a stronger Brønsted acid catalyst furnished ene reaction products in high yields (up to 77%), which were isolated as Boc-protected enols (**Scheme 4**).

1,4-Dihydropyridines, such as NADH(P) play a pivotal role in the redox metabolism. Although, the direct hydride transfer represents the commonly accepted mechanism, an Alder ene-like pathway was proposed by Saez, Vogt-Geisse, and Vohringer-Martinez as a plausible alternative according to computations on the ab initio and density functional levels of theory.[14] Accordingly, the transition state is found to be asynchronous fashion with significant aromatic features (**Scheme 5**).

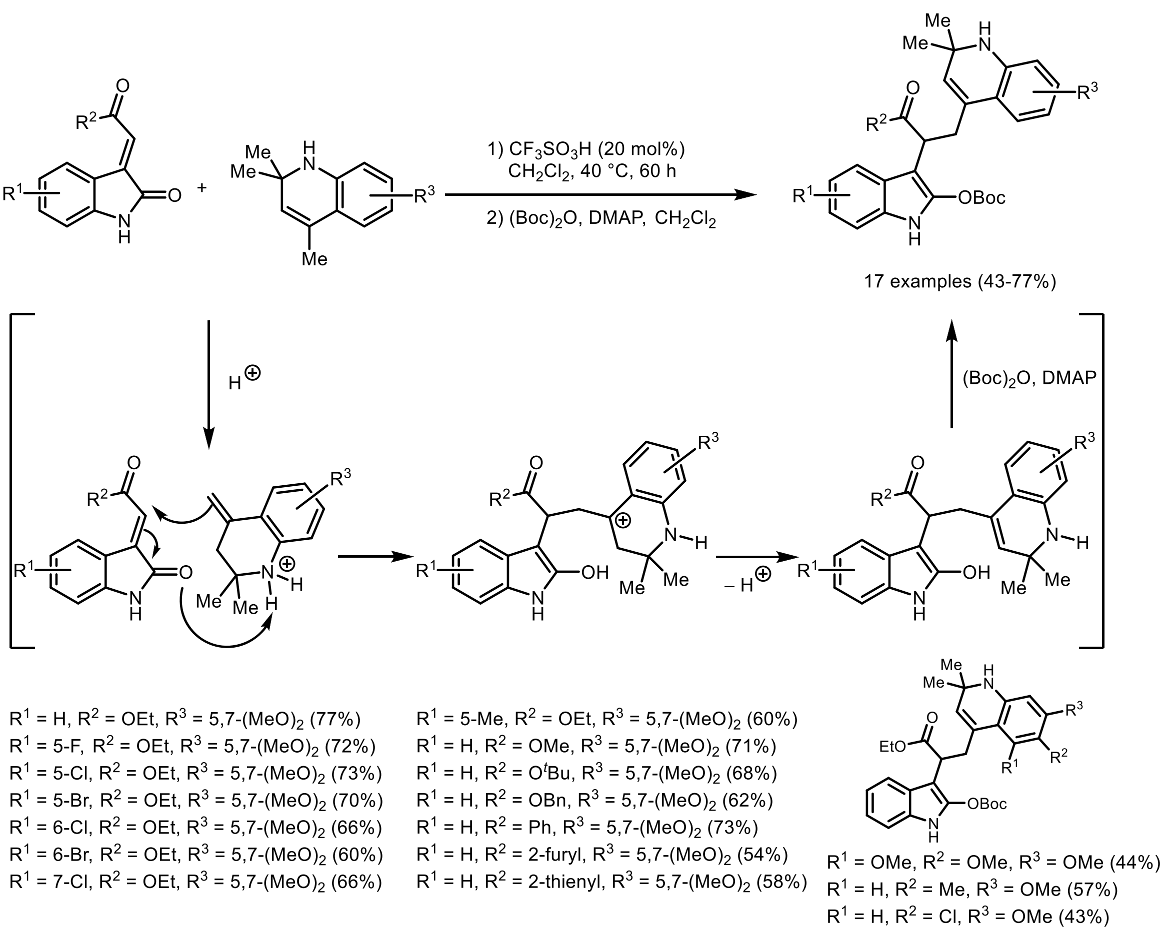
Enaminones play a key role in heterocycle synthesis and the reaction with α,β-unsaturated acid chlorides to give α-pyridones is known as aza-anellation reaction.[15,16] Based on a previously reported consecutive four-component coupling-addition-aza-anellation-Pictet-Spengler synthesis of tetrahydro-β-carbolines,[17,18] Ries, Aouane, and Müller optimized the Michael addition step in the sequence by catalysis with ytterbium triflate, thereby lowering the reactants to almost equistoichiometric ratios and reported a substance library of 21 compounds (**Scheme 6**).[19] The aza-anellation, i.e., the formal ene reaction, is triggered by addition of acroyl chloride as and enophile. In addition, the mechanism of concluding aza-anellation, which sets the stage for the acyliminium ion to terminate via Pictet–Spengler reaction was studied by DFT calculations. The corresponding activation energies underline that the aza-anellation proceeds via an ene reaction.

Nucleophilic enamines were shown by Chataigner and coauthors to react with nitroindole in an unprecedented dearomatizing formal ene reaction to give with regio- and diastereoselectivity the corresponding indoline derivatives (**Scheme 7**).[20]

Enes also can be formed en route and transformed in situ. Particularly impressive cases are intramolecular Diels-Alder reactions of vinyl (hetero)arene, since intramolecular $[4+2]$ cycloadditions proceed faster than their intermolecular versions. Here, the intramolecular Diels–Alder reaction of a vinyl (hetero)arene, providing the diene with a tethered dienophile, forms a dearomatized 5-methylenecyclohexa-1,3-diene intermediate.

Zubkov showed that *N*-aryl-3-phenylallylamines and maleic anhydride react in boiling 1,4-dioxane in the sense of a intramolecular Diels-Alder-intermolecular Alder ene domino synthesis in a pseudo four-component fashion to give polysubstituted *N*-arylbenzo[*f*]isoindole-4-carboxylic acids in moderate yields with excellent diastereoselectivity (**Scheme 8**).[21] Some of the title compounds revealed moderate activity against the influenza virus A/Puerto Rico/8/34 (H1N1), in one case with a significant selectivity index.

The dearomatized cycloadduct either aromatizes back to the tricyclic product, or, in presence of an enophile might conclude via an Alder ene reaction. Therefore, Zubkov and coauthors have proposed a three-component synthesis of polysubstituted benzo[f]isoindole-4-carboxylic acid derivatives from 3-arylallylamines, maleimides, and maleic anhydride, furnishing the title compouds in domino *N*-acylation-$[4+2]$ cycloaddition-Alder ene process with excellent diastereoselectivity and moderate to good yields (**Scheme 9**).[22] The sequence proceeds

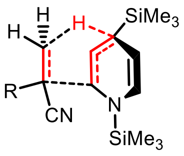


$R^1 = H$, $R^2 = OEt$, $R^3 = 5,7\text{-}(MeO)_2$ (77%)
$R^1 = 5\text{-}F$, $R^2 = OEt$, $R^3 = 5,7\text{-}(MeO)_2$ (72%)
$R^1 = 5\text{-}Cl$, $R^2 = OEt$, $R^3 = 5,7\text{-}(MeO)_2$ (73%)
$R^1 = 5\text{-}Br$, $R^2 = OEt$, $R^3 = 5,7\text{-}(MeO)_2$ (70%)
$R^1 = 6\text{-}Cl$, $R^2 = OEt$, $R^3 = 5,7\text{-}(MeO)_2$ (66%)
$R^1 = 6\text{-}Br$, $R^2 = OEt$, $R^3 = 5,7\text{-}(MeO)_2$ (60%)
$R^1 = 7\text{-}Cl$, $R^2 = OEt$, $R^3 = 5,7\text{-}(MeO)_2$ (66%)

$R^1 = 5\text{-}Me$, $R^2 = OEt$, $R^3 = 5,7\text{-}(MeO)_2$ (60%)
$R^1 = H$, $R^2 = OMe$, $R^3 = 5,7\text{-}(MeO)_2$ (71%)
$R^1 = H$, $R^2 = O^tBu$, $R^3 = 5,7\text{-}(MeO)_2$ (68%)
$R^1 = H$, $R^2 = OBn$, $R^3 = 5,7\text{-}(MeO)_2$ (62%)
$R^1 = H$, $R^2 = Ph$, $R^3 = 5,7\text{-}(MeO)_2$ (73%)
$R^1 = H$, $R^2 = 2\text{-furyl}$, $R^3 = 5,7\text{-}(MeO)_2$ (54%)
$R^1 = H$, $R^2 = 2\text{-thienyl}$, $R^3 = 5,7\text{-}(MeO)_2$ (58%)

$R^1 = OMe$, $R^2 = OMe$, $R^3 = OMe$ (44%)
$R^1 = H$, $R^2 = Me$, $R^3 = OMe$ (57%)
$R^1 = H$, $R^2 = Cl$, $R^3 = OMe$ (43%)

Scheme 4. Trifluoromethanesulfonic acid catalyzed Alder ene-type addition of 1,2-dihydroquinolines with 3-olefinic oxindoles.



Scheme 5. Aromatic asynchronous Alder ene-like transition state in a hydride transfer from a 1,4-djhydropyridine to an acrylonitrile according to calculations.

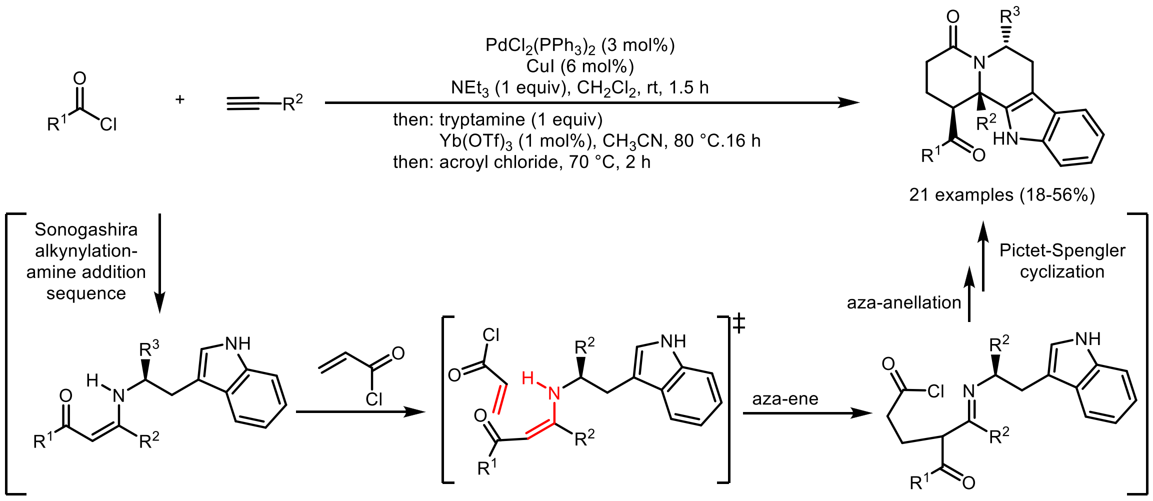
under thermal conditions and can also be catalyzed by ytterbium triflate as a Lewis acid catalyst. Mechanistic evidence was obtained from dynamic ^{19}F NMR studies and DFT calculations. The latter suggest that the intramolecular Diels–Alder reaction of vinylarenes (IMDAV) is the rate-determining step followed by an energetically favored *exo*-transition state of the concluding Alder ene reaction.

Similarly, 2-vinylthiophenes react with *N*-phenylmaleimide in a domino pseudothree-component Diels-Alder–Alder ene reaction to give the corresponding 1:2 products rather than the expected Diels–Alder adducts.[23] However, switching to 2-(1′-cycloalkenyl) thiophenes and 2-(1′-cycloalkenyl)benzo[b]thiophenes as substrates not only allows for identifying the corresponding Diels-Alder adducts in many cases and in good yield as unisomerized products. Interestingly, only Diels–Alder adducts of 5–7-membered cycloalkenyl thiophenes isomerize to the aromatized thiophene products. However, with an excess of *N*-phenylmaleimide the initially formed Diels–Alder adducts directly furnish the twofold adducts as a consequence of an *endo*-Diels–Alder and an *endo*-Alder ene reaction, as seen from structure analyses (**Scheme 10**).[24]

2.1.2. Intramolecular Ene Reactions with Electron-Deficient Alkenes as Enophiles

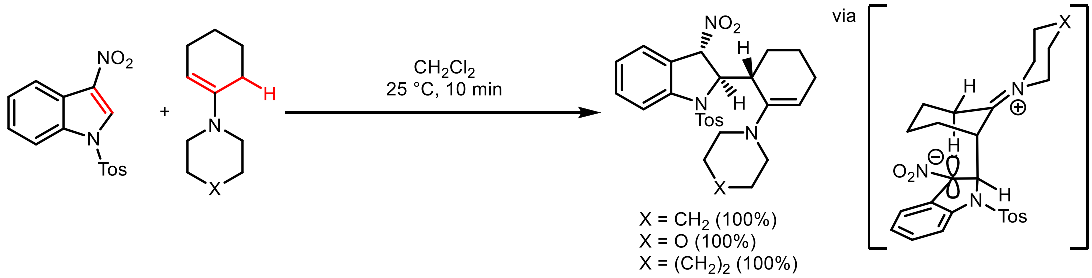
The intramolecular ene reaction is a key approach to polycyclic fused (anellated) structures and has therefore attracted significant interest in the total synthesis of complex natural products.

A retro-Diels–Alder reaction of an acetal precursor liberates the ene-motif for intramolecular Alder ene (IMAE) cyclization that provided the key intermediate in three-total syntheses of norrisolide-type spongian diterpenes cheloviolene C, seconorrisolide B, and seconorrisolide C (**Scheme 11**).[25]



R^1 = 2-thienyl, R^2 = ^{n}Bu, R^3 = H (31%)
R^1 = Ph, R^2 = ^{n}Bu, R^3 = H (27%)
R^1 = p-MeC$_6$H$_4$, R^2 = ^{n}Bu, R^3 = H (18%)
R^1 = p-MeOC$_6$H$_4$, R^2 = ^{n}Bu, R^3 = H (19%)
R^1 = p-BrC$_6$H$_4$, R^2 = ^{n}Bu, R^3 = H (40%)
R^1 = o-FC$_6$H$_4$, R^2 = ^{n}Bu, R^3 = H (56%)
R^1 = p-O$_2$NC$_6$H$_4$, R^2 = ^{n}Bu, R^3 = H (37%)
R^1 = 2-thienyl, R^2 = Ph , R^3 = H (25%)
R^1 = p-MeOC$_6$H$_4$, R^2 = H, R^3 = H (48%)
R^1 = p-BrC$_6$H$_4$, R^2 = ^{n}Bu, R^3 = CO$_2$Me (18%)
R^1 = 6-Cl-pyrid-3-yl, R^2 = ^{n}Bu, R^3 = H (30%)
R^1 = 6-Cl-pyrid-3-yl, R^2 = Ph, R^3 = H (34%)
R^1 = 6-Cl-pyrid-3-yl, R^2 = cyclopropyl, R^3 = H (19%)
R^1 = 6-Cl-pyrid-3-yl, R^2 = ^{n}Bu, R^3 = CO$_2$Me (20%)
R^1 = 2-thienyl, R$_2$ = (N-Tos)indol-3-yl (32%)
R^1 = p-MeC$_6$H$_4$, R$_2$ = (N-Tos)indol-3-yl (36%)
R^1 = p-MeOC$_6$H$_4$, R$_2$ = (N-Tos)indol-3-yl (33%)
R^1 = o-FC$_6$H$_4$, R$_2$ = (N-Tos)indol-3-yl (26%)
R^1 = p-BrC$_6$H$_4$, R$_2$ = (N-Tos)indol-3-yl (50%)
R^1 = Ph, R$_2$ = (N-Tos)indol-3-yl (34%)
R^1 = 6-Cl-pyrid-3-yl, R$_2$ = (N-Tos)indol-3-yl (48%)

Scheme 6. Consecutive four-component coupling-addition aza-anellation Pictet–Spengler synthesis of tetrahydro-β-carbolines.



Scheme 7. Dearomatizing Alder ene-type addition of 3-nitroindole and enamines to give indoline derivatives.

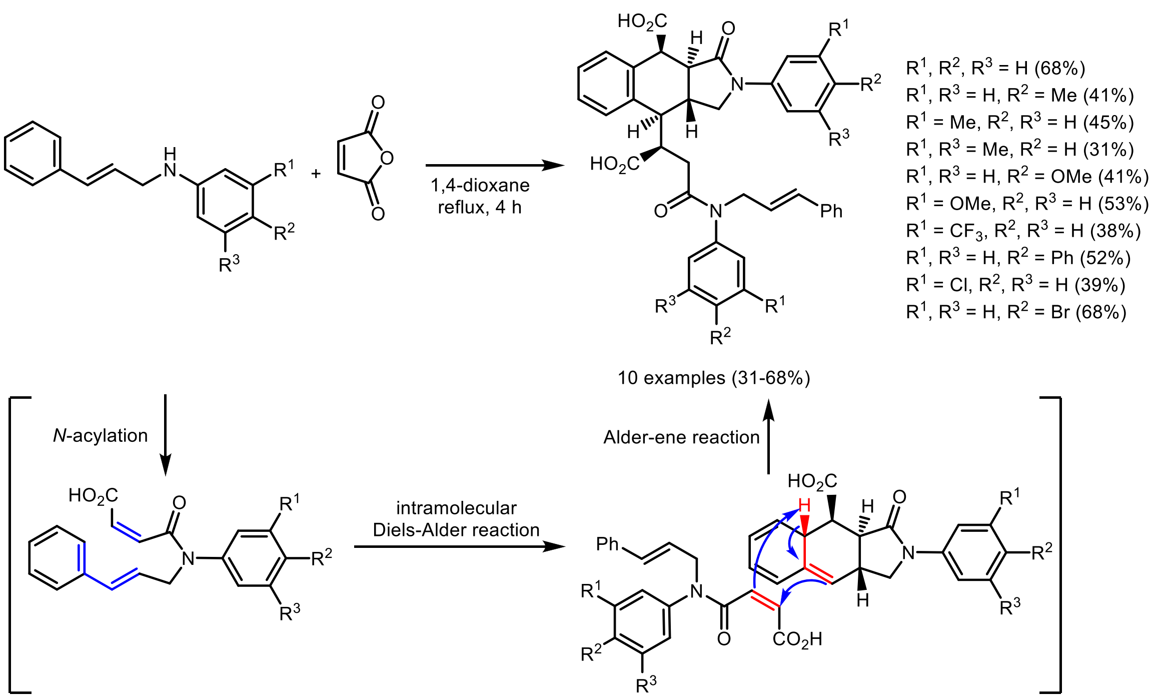
Under flash vacuum pyrolysis of maleic anhydride adducts bearing alkenyl or alkynyl ene moieties a general synthetic strategy to *cis*-fused bicyclic γ-butyrolactones in high yields and excellent levels of stereoselectivity was disclosed, which proceeds via the retro-Diels-Alder reaction followed by ene cycloisomerization (**Scheme 12**).[26] Difluoromethyl or trifluoromethyl substitution at the γ-position accelerate the rate of the intramolecular conjugate ene reaction.

In their study on the stereospecificity of the cyclization of (E)- and (Z)-2-alkenyl esters and amides of ethenetricarboxylate Yamazaki and coauthors found that the attempted preparation of (E)/(Z)-2-butenyl and pentenyl amides undergo gradually an intramolecular ene reaction at room temperature (**Scheme 13**).[27] At 80 °C, the (Z)-alkenyl amides were selectively cycloisomerized to *cis*-substituted ene adducts, whereas the (E)-amides gave rise to *cis*- and *trans*-substituted ene adduct mixtures (**Scheme 14**).

Remarkably, also cationic enophiles arising from a Nazarov cyclization follow the pericyclic paradigm of Alder ene reactions. Kalesse and coworkers recognized in the asymmetric total synthesis of (−)-illisimonin A that the tricyclic carbon framework could be traced back to a spirocyclic intermediate, which, in turn can be formed by a domino Nazarov-ene bicyclization (**Scheme 15**).[28] The same group had previously established this hitherto unprecedented cationic [π^4s + π^2s] pathway of the ene reaction embedded in a spirocyclization.[29]

2.1.3. Intramolecular Ene Reactions with Electroneutral Alkenes as Enophiles

In 1992, Heathcock reported as biomimetic access to daphniphyllium alkaloids an impressive polycyclization



Scheme 8. Pseudofour-component intramolecular Diels–Alder-intermolecular Alder ene domino synthesis of polysubstituted *N*-arylbenzo[*f*]isoindole-4-carboxylic acids.

cascade, which can be considered as a cationic domino sequence.[30] Tantillo studied this sequence by means of DFT calculations, which indeed support the concatenation of a [4 + 2] cycloaddition and a Alder-type ene reaction with an iminium ion as the ene component (**Scheme 16**).[31]

Likewise,[3,3] sigmatropic rearrangements also provide an initiation to give a dearomatized ene intermediate, which can be trapped with a tethered enophile. In the course of their study on aromatic Claisen rearrangements of benzyl ketene acetals to (*ortho*-toyl) acetates McGreary and coauthors discovered that an ω-pentenyl substituent at the benzylic position took part in trapping the isotoluene intermediate formed in the Claisen rearrangement by intramolecular trapping in an IMAE reaction (**Scheme 17**).[32]

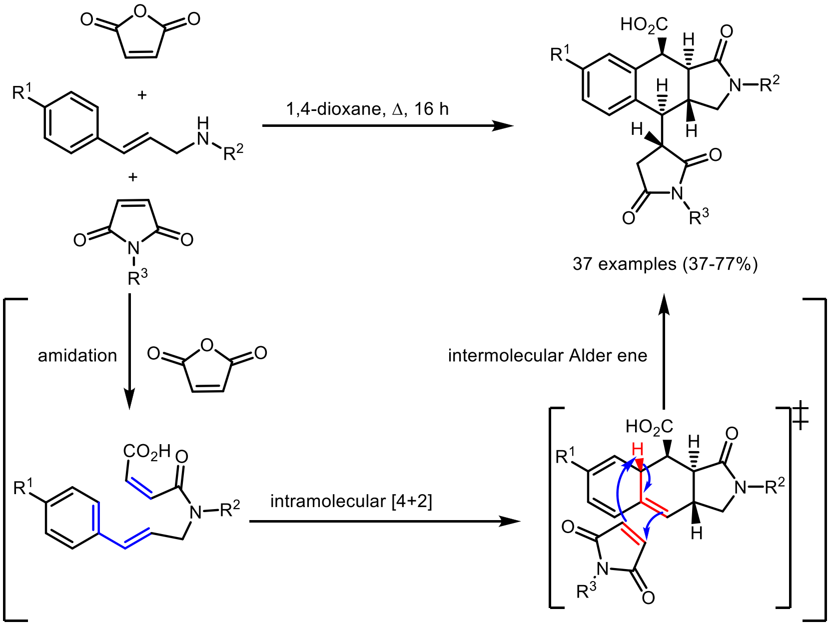
2.2. Alkynes as Enophiles

Alkynes as enophiles react with alkenes as enes to give nonconjugated dienes, either as addition or cycloisomerization products, when the reaction proceeds under pericyclic conditions. Lewis acid catalysts lower the LUMO of the enophile, either by coordination to an additional conjugated electron-withdrawing group or via π-coordination. Of particular interest are ene reactions between unactivated alkyne enophiles and alkene enes, which are predominantly facilitated by transition metal catalysis cycles via coordination, oxidative cyclization, β-hydride elimination, and reductive elimination pathways. Natural product syntheses based on metallacycle-mediated cross-coupling and Alder ene-type cycloisomerization have been reviewed in 2016 by Micalizio and coauthors.[33] Furthermore, silver catalysis, due to the "alkynophilicity" has received considerable attention and has significantly advanced the transformation portfolio of alkynes, for instance alkynylation, hydrofunctionalization, cycloaddition, cycloisomerization, and cascade reactions.[34] Therefore, transition metal catalyzed alkyne ene reactions, both inter- and intramolecularly, have gained increasing interest in the past decades.

2.2.1. Intermolecular Ene Reactions with Electron-Deficient Alkynes as Enophiles

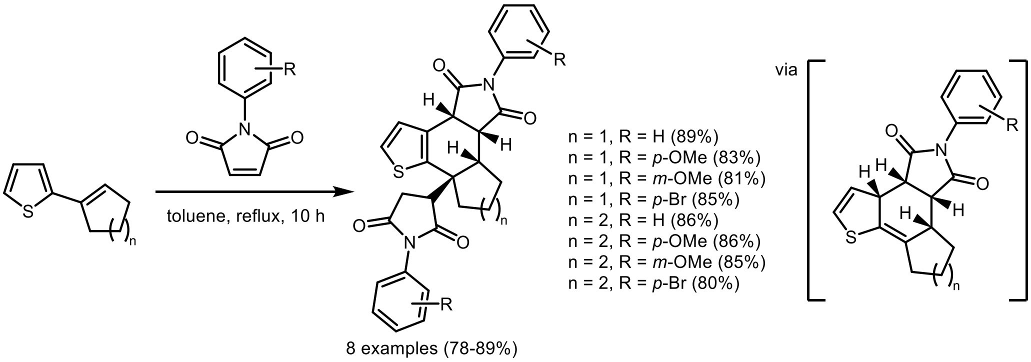
Styrene were shown to react in a Diels–Alder ene domino pseudo-three-component reaction in the presence of a zinc(II) Lewis acid catalyst to give a series of dihydronaphthalene derivatives in moderate to good yields (**Scheme 18**).[35] DFT calculations and experiments with isotope labeling underline that two consecutive pericyclic reactions occur and that the Diels–Alder reaction is the rate-determining step.

A mono-gold(I) complex together with triflic acid was shown to catalyze the [4 + 2]-Diels–Alder reaction on an ynone with a styrene to give an 3,8a-dihydronaphthalene intermediate that reacts with a second equivalent of ynone, activated by the gold complex to give the pseudothree-component product of a



R^1 = H, R^2 = ^{i}Pr, R^3 = Me (58%)
R^1 = H, R^2 = ^{c}Pr, R^3 = Me (63%)
R^1 = H, R^2 = Bn, R^3 = Me (67%)
R^1 = H, R^2 = Ph, R^3 = Me (48%)
R^1 = MeO, R^2 = Ph, R^3 = Me (51%)
R^1 = H, R^2 = p-FC_6H_4, R^3 = Me (85%)
R^1 = H, R^2 = ^{i}Pr, R^3 = Et (54%)
R^1 = H, R^2 = ^{c}Pr, R^3 = Et (67%)
R^1 = H, R^2 = Bn, R^3 = Et (53%)
R^1 = H, R^2 = Ph, R^3 = Et (81%)
R^1 = MeO, R^2 = Ph, R^3 = Et (37%)
R^1 = H, R^2 = p-FC_6H_4, R^3 = Et (77%)
R^1 = H, R^2 = ^{i}Pr, R^3 = p-$O_2NC_6H_4$ (40%)
R^1 = H, R^2 = ^{c}Pr, R^3 = p-$O_2NC_6H_4$ (74%)
R^1 = H, R^2 = Bn, R^3 = p-$O_2NC_6H_4$ (63%)
R^1 = H, R^2 = Ph, R^3 = p-$O_2NC_6H_4$ (50%)
R^1 = MeO, R^2 = Ph, R^3 = p-$O_2NC_6H_4$ (60%)
R^1 = H, R^2 = p-FC_6H_4, R^3 = p-$O_2NC_6H_4$ (66%)
R^1 = H, R^2 = ^{i}Pr, R^3 = Ph (50%)
R^1 = H, R^2 = ^{c}Pr, R^3 = Ph (44%)
R^1 = H, R^2 = Bn, R^3 = Ph (75%)
R^1 = H, R^2 = Ph, R^3 = Ph (67%)
R^1 = MeO, R^2 = Ph, R^3 = Ph (66%)
R^1 = H, R^2 = p-FC_6H_4, R^3 = Ph (44%)
R^1 = H, R^2 = p-BrC_6H_4, R^3 = Ph (62%)
R^1 = H, R^2 = p-$EtO_2CC_6H_4$, R^3 = Ph (47%)
R^1 = H, R^2 = p-MeC_6H_4, R^3 = Ph (45%)
R^1 = H, R^2 = p-$MeOC_6H_4$, R^3 = Ph (40%)
R^1 = H, R^2 = p-EtC_6H_4, R^3 = Ph (52%)
R^1 = H, R^2 = 3,5-$Me_2C_6H_3$, R^3 = Ph (66%)
R^1 = H, R^2 = m-MeC_6H_4, R^3 = Ph (49%)
R^1 = H, R^2 = m-$F_3CC_6H_4$, R^3 = Ph (47%)
R^1 = H, R^2 = m-ClC_6H_4, R^3 = Ph (66%)
R^1 = H, R^2 = o-$MeOC_6H_4$, R^3 = Ph (71%)
R^1 = H, R^2 = Ph, R^3 = Ph (40%)
R^1 = H, R^2 = Ph, R^3 = p-$O_2NC_6H_4$ (47%)
R^1 = H, R^2 = o-$MeOC_6H_4$, R^3 = Ph (41%)

Scheme 9. Three-component acylation-intramolecular [4 + 2]-Alder ene synthesis of benzo[*f*]isoindoles derivatives.

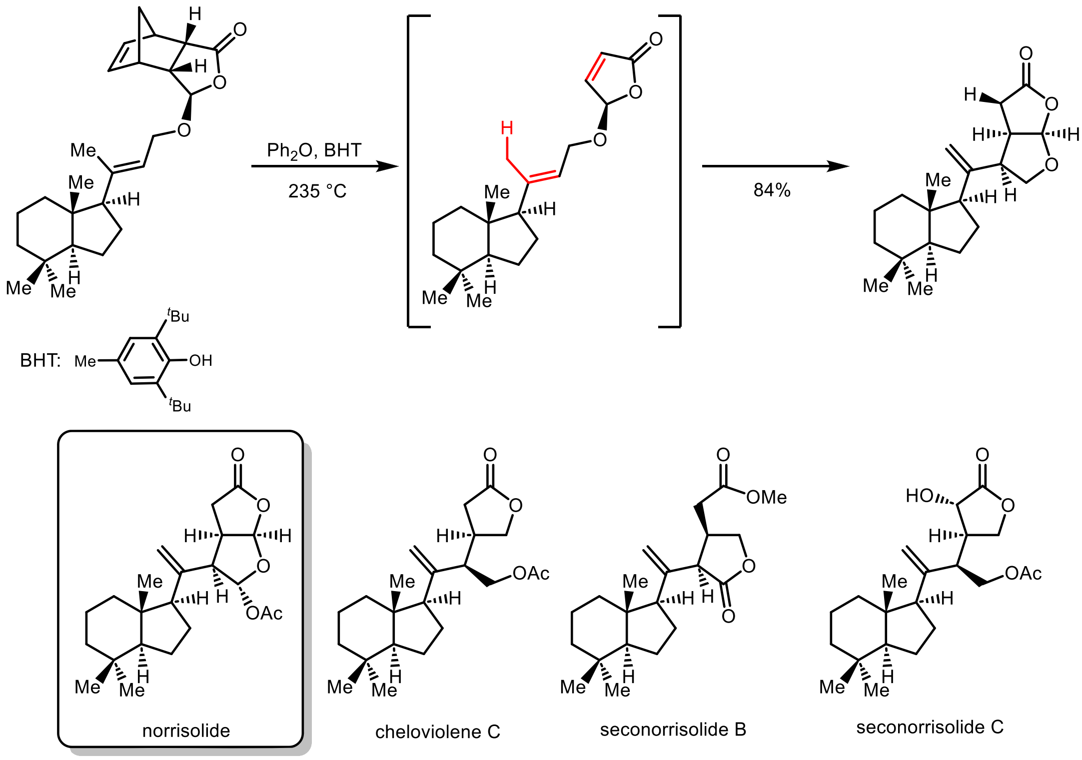


Scheme 10. Domino pseudothree-component Diels–Alder–Alder ene sequence.

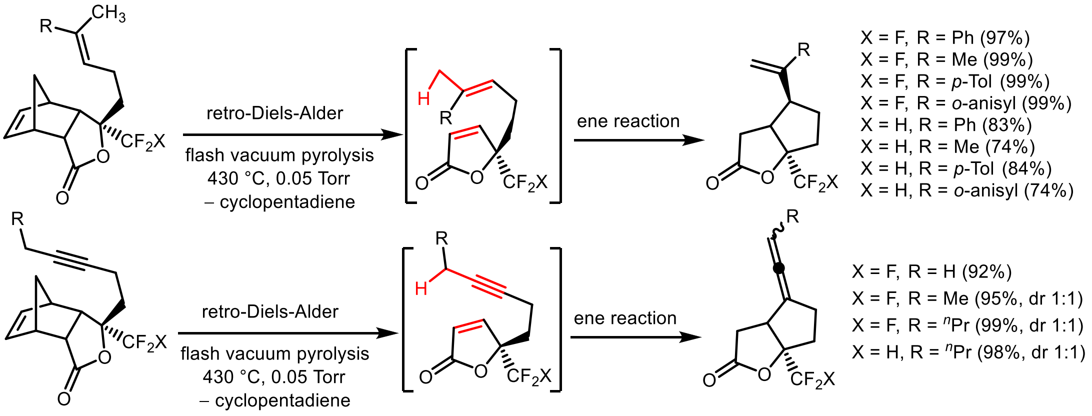
domino-Diels–Alder–Alder ene sequence (**Scheme 19**).[36] The mechanistic rationale suggests a dual Bronsted-acid-gold catalysis and in presence of an enantiomerically enriched or enantiomerically pure BINOL-phosphoamidate ligand the process was also conducted enantioselectively (**Scheme 20**).

Among many milestones in Trost's academic research[37] Ru-catalyzed alkyne–alkene coupling adopt a pivotal point, which has found application in several complex molecules' synthesis and is still ongoing.

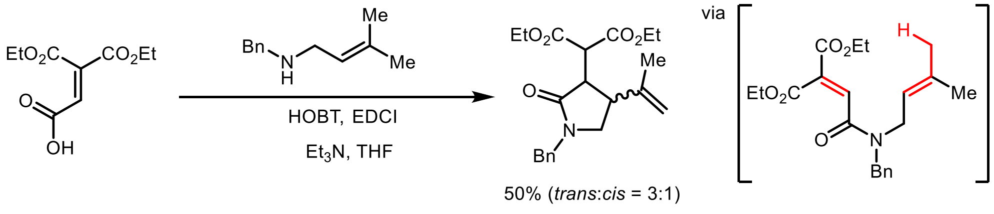
Trost and Quintard reported a short asymmetric synthesis for the proposed structure of of a butanolide



Scheme 11. The in situ generated Alder ene motif in the total syntheses of norrisolide-type spongian diterpenes cheloviolene C, seconorrisolide B, and seconorrisolide C.

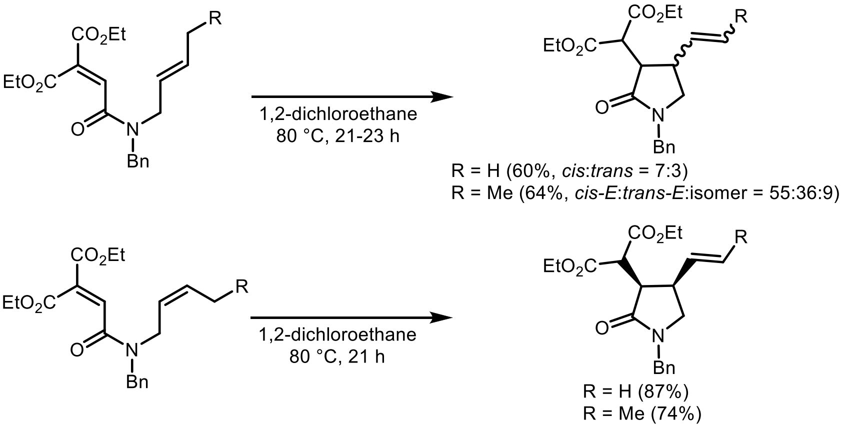


Scheme 12. Retro-Diels–Alder-ene cycloisomerization sequence to *cis*-fused bicyclic γ-butyrolactones.

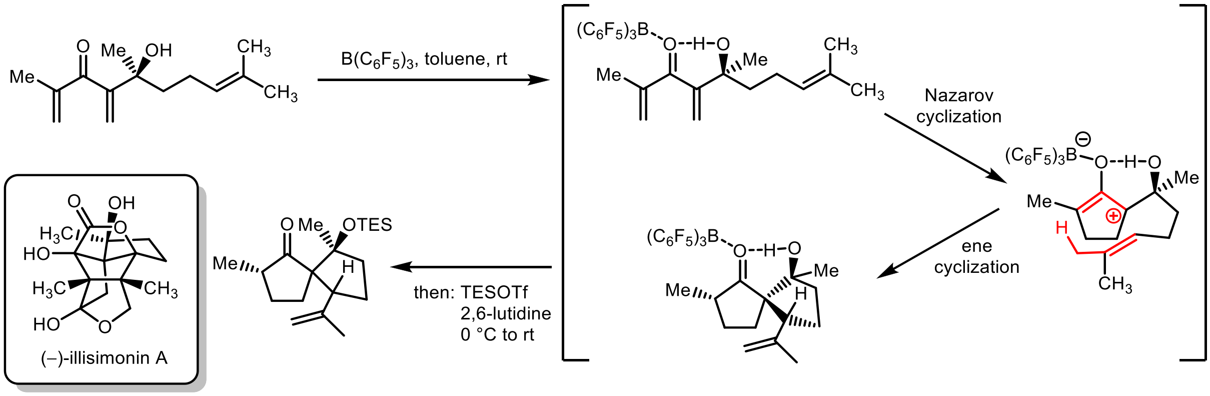


HOBT: 1-hydroxybenzotriazole
EDCI: 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide

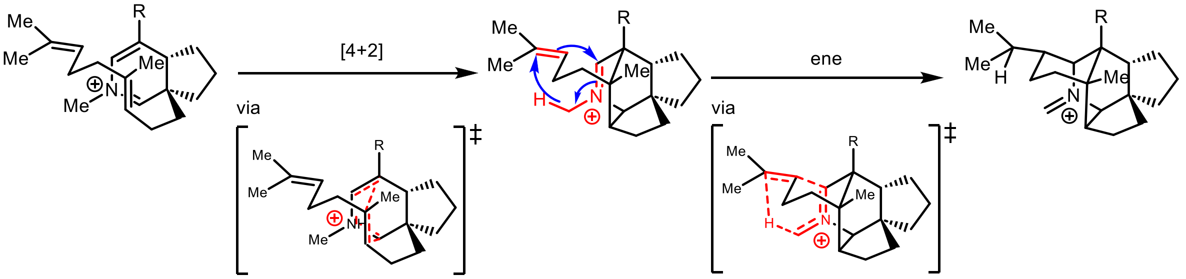
Scheme 13. Attempted preparation of a tethered diene amide substrate (see bracket) leading to an Alder ene cycloisomerization product.



Scheme 14. Stereoselectivity of the Alder ene cycloisomerization of (*E*)/(*Z*)-2-butenyl and pentenyl amides.



Scheme 15. Nazarov-ene spirocyclization in the asymmetric total synthesis of (−)-illisimonin A.

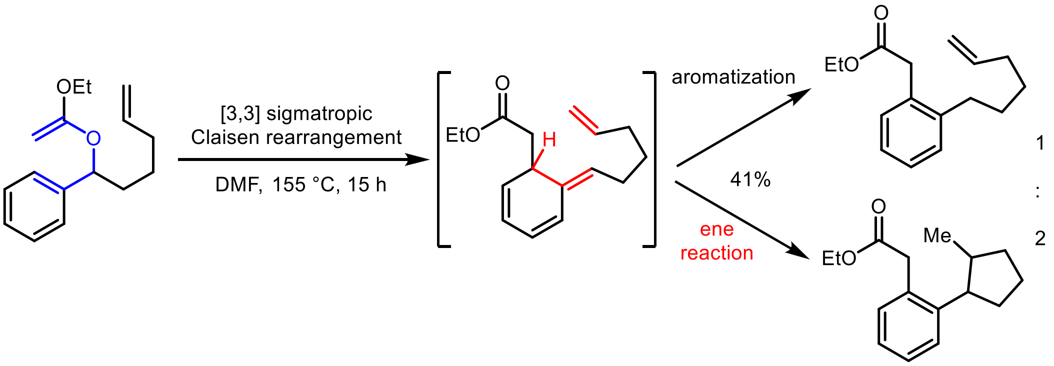


Scheme 16. DFT-calculated Diels–Alder–Alder ene scenario of the cationic polycyclization cascadein the synthesis of daphniphyllium alkaloids.

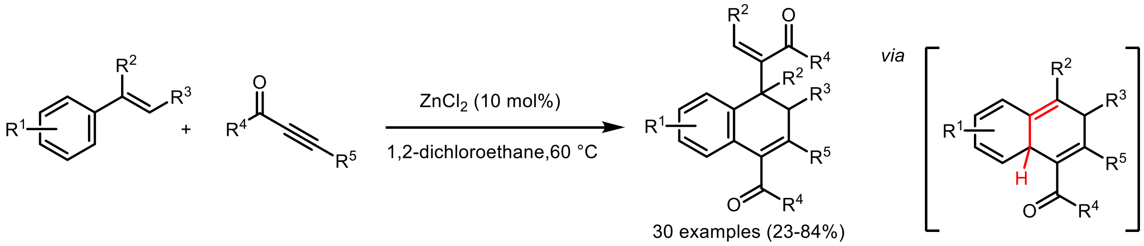
isolated from corals using multiple highly selective catalytic steps, including the Ru-catalyzed alkyne-allyl coupling (**Scheme 21**). Interestingly, the comparison of spectroscopic data of the synthetic sample of the asymmetric synthesis and reported data for trocheliophorolide B underline that the reported structural assignment was obviously wrong.[38]

2.2.2. Intramolecular Ene Reactions with Electron-Deficient Alkynes as Enophiles

1,6-Enynes tethered via an imide bridge were reported to give a facile access to functionalized succinimides via a thermal IMAE reaction with broad scope and good to excellent yields (**Scheme 22**).[39] Kinetic isotope effect



Scheme 17. Claisen–Alder ene domino sequence.



R^1, R^2, R^3, R^5 = H, R^4 = Ph (76%)
R^1, R^2, R^3, R^5 = H, R^4 = *o*-MeC_6H_4 (71%)
R^1, R^2, R^3, R^5 = H, R^4 = *o*-$MeOC_6H_4$ (65%)
R^1, R^2, R^3, R^5 = H, R^4 = *o*-HOC_6H_4 (74%)
R^1, R^2, R^3, R^5 = H, R^4 = *o*-FC_6H_4 (62%)
R^1, R^2, R^3, R^5 = H, R^4 = *o*-BrC_6H_4 (76%)
R^1, R^2, R^3, R^5 = H, R^4 = *p*-MeC_6H_4 (57%)
R^1, R^2, R^3, R^5 = H, R^4 = *p*-$MeOC_6H_4$ (58%)
R^1, R^2, R^3, R^5 = H, R^4 = *p*-FC_6H_4 (84%)
R^1, R^2, R^3, R^5 = H, R^4 = *p*-$F_3CC_6H_4$ (77%)
R^1, R^2, R^3, R^5 = H, R^4 = *p*-$O_2NC_6H_4$ (46%)
R^1, R^2, R^3, R^5 = H, R^4 = *m*-FC_6H_4 (78%)
R^1, R^2, R^3, R^5 = H, R^4 = 1-naphthyl (66%)
R^1, R^2, R^3, R^5 = H, R^4 = β-styryl (72%)
R^1, R^2, R^3, R^5 = H, R^4 = *n*-pentyl (41%)
R^1, R^2, R^3 = H, R^4 = OMe, R^5 = CO_2Me (47%)
R^1 = *p*-Me, R^2, R^3 , R^5 = H, R^4 = Ph (60%)
R^1 = *p*-^{t}Bu, R^2, R^3 , R^5 = H, R^4 = Ph (55%)
R^1 = *p*-F, R^2, R^3 , R^5 = H, R^4 = Ph (69%)
R^1 = *p*-Cl, R^2, R^3 , R^5 = H, R^4 = Ph (65%)
R^1 = *p*-Br, R^2, R^3 , R^5 = H, R^4 = Ph (75%)
R^1 = *p*-F_3C, R^2, R^3 , R^5 = H, R^4 = Ph (43%)
R^1 = *o*-Cl, R^2, R^3 , R^5 = H, R^4 = Ph (61%)
R^1 = *o*-Br, R^2, R^3 , R^5 = H, R^4 = Ph (52%)
R^1 = *m*-Br, R^2, R^3 , R^5 = H, R^4 = Ph (64%)
R^1 = 2,5-Me_2, R^2, R^3 , R^5 = H, R^4 = Ph (55%)
R^1, R^3, R^5 = H, R^2 = Me, R^4 = Ph (43%)
R^1, R^3, R^5 = H, R^2 = Ph, R^4 = Ph (27%)
R^1, R^2, R^5 = H, R^3 = Me, R^4 = Ph (63%, *trans*)
R^1, R^2, R^5 = H, R^3 = Ph, R^4 = Ph (23%, *trans*)

Scheme 18. Zinc halide-catalyzed Diels–Alder–Alder ene domino sequence in a pseudothree-component fashion.

was found to be 1.19 for the position of the transferred ene-hydrogen. In agreement with literature precedence and since the reactions were performed under air a step wise mechanism via a diradical intermediate appears to be plausible.

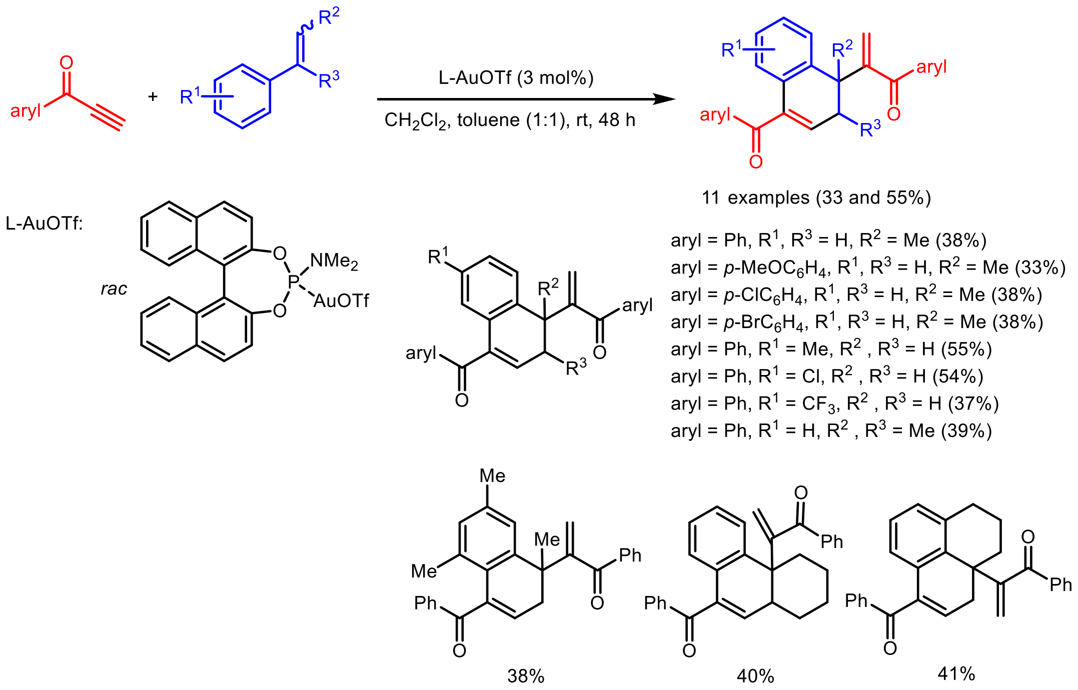
Enynes are well suited substrates for metal catalyzed cycloisomerizations and among them, in particular, formal Alder ene cycloisomerization have been successfully employed in the synthesis of complex sesquiterpenoids as reviewed by Zografos and coauthors.[40]

Enantioselective transition metal catalyzed Alder ene-type cycloisomerizations have considerably received attention and the progress in Pd-, Rh-, and even Pt-catalyzed processes have been extensively reviewed and chiral C_2-symmetric chelating diphosphane ligands, as well as PHOX-type ligands and bisoxazolines have been playing a key role in the methodological development.[41]

Porous BINAP-based metal–organic frameworks (MOFs) metalated with Rh complexes were shown to provide highly active and enantioselective single-site solid catalysts for the asymmetric cyclizations of 1,6-enynes, among those also Alder ene-type cycloisomerizations.[42]

Based upon the enantioselective Rh-catalyzed Alder ene cycloisomerization of ester- and ether-tethered alkyne allyl alcohols Muschelknautz, Rominger, and Müller have concatenated a Rh-catalyzed hydrogenations in the sense of a consecutive sequentially Rh-catalyzed processes in a one-pot fashion to access chiral alkylidene butyrolactone β-hydroxyethanes (**Scheme 23**) and alkylidene tetrahydrofuran β-aminoethanes (**Scheme 24**).[43] The excellent levels of enantioselectivity of the Alder ene step is maintained in the subsequent hydrogenation reaction, which proceed without further catalyst addition, i.e., in a catalyst economic fashion.

Zhang and coworkers reported a highly enantioselective rhodium(I)-catalyzed Alder ene-type cycloisomerization of 1,7-enynes as an excellent access to fused

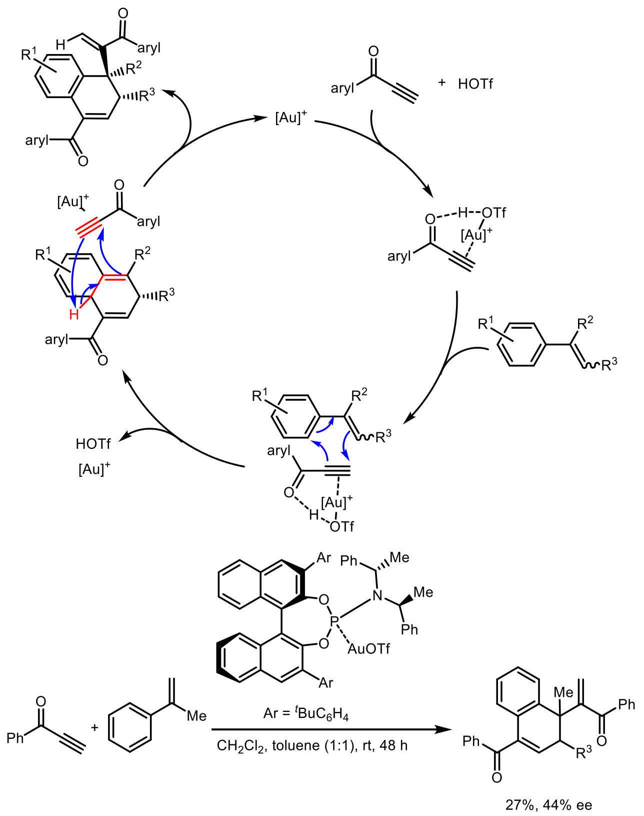


Scheme 19. Gold-catalyzed domino Diels–Alder–Alder ene sequence in a pseudothree-component fashion.

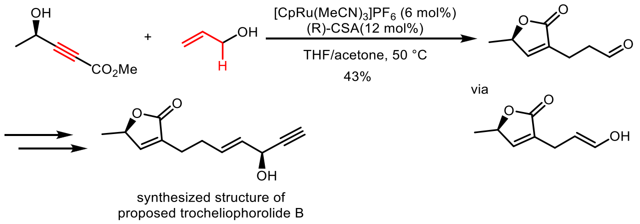
six-membered heterocycles with high levels of enantioselectivity (**Scheme 25**).[44]

The prostacyclin (PGI2) analog Treprostinil is a drug that has been marketed for the treatment of pulmonary arterial hypertension. Zhang and coauthors successfully employed the enantioselective Rh-catalyzed enyne cycloisomerization with (*Sc*,*Rp*)-Duanphos) as a chiral chelating ligand for constructing the multisubstituted cyclopentanone core, a new type of interphenylene prostaglandin scaffold, with high yield and excellent chemoselectivity (**Scheme 26**) on the way to (+)-Treprostinil.[45]

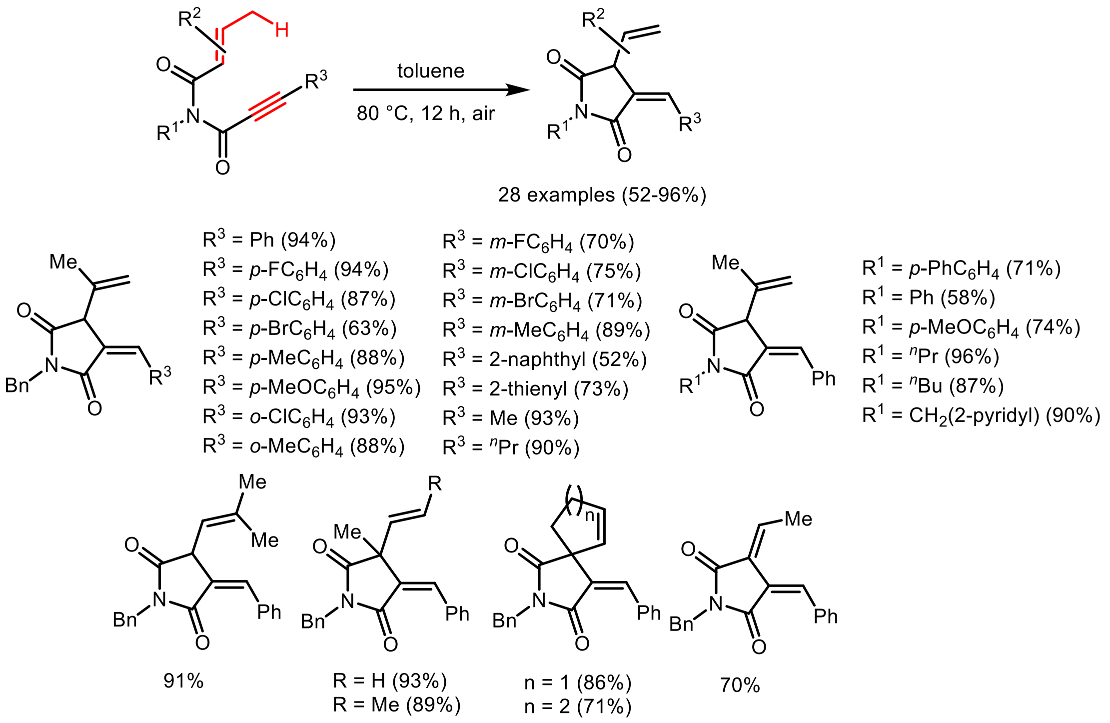
Shin and coworkers discovered that silver-catalyzed cycloisomerizations of propiolamide derived 1,6-enynes selectively furnished Alder ene-type 1,4-dienes (**Scheme 27**), where $AgNTf_2$ surpasses typical Au and Pt catalysts in both selectivity and reactivity.[46] Mechanistic test reactions strongly advocate for



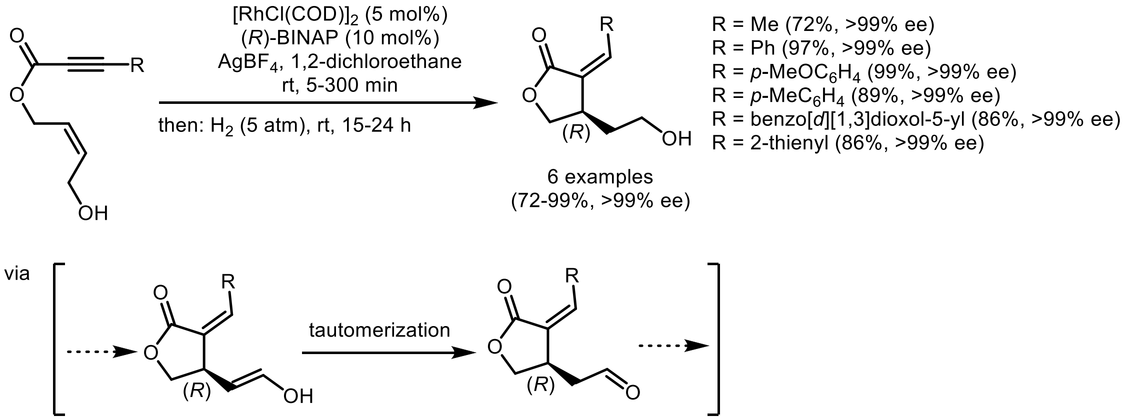
Scheme 20. Mechanistic rationale and enantioselective variation of the domino gold-catalyzed Diels–Alder–Alder ene sequence.



Scheme 21. Ru-catalyzed alkyne–allyl alcohol coupling in the key step of the total synthesis of acetogenin trocheliophorolide B.



Scheme 22. Alder ene cycloisomerization of imide tethered 1,6-enynes tethered to functionalized succinimides.



Scheme 23. Sequentially Rh-BINAP-catalyzed enantioselective cycloisomerization-hydrogenation synthesis of alkylidene butyrolactone β-hydroxyethanes.

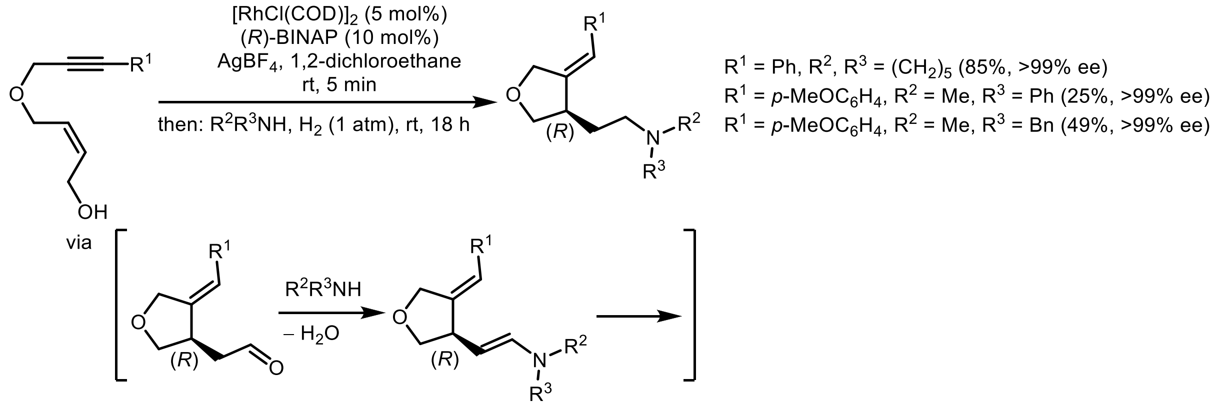
the involvement of silver carbenoids as relevant intermediates (**Scheme 28**).

2.2.3. Intermolecular Ene Reactions with Electroneutral Alkynes as Enophiles

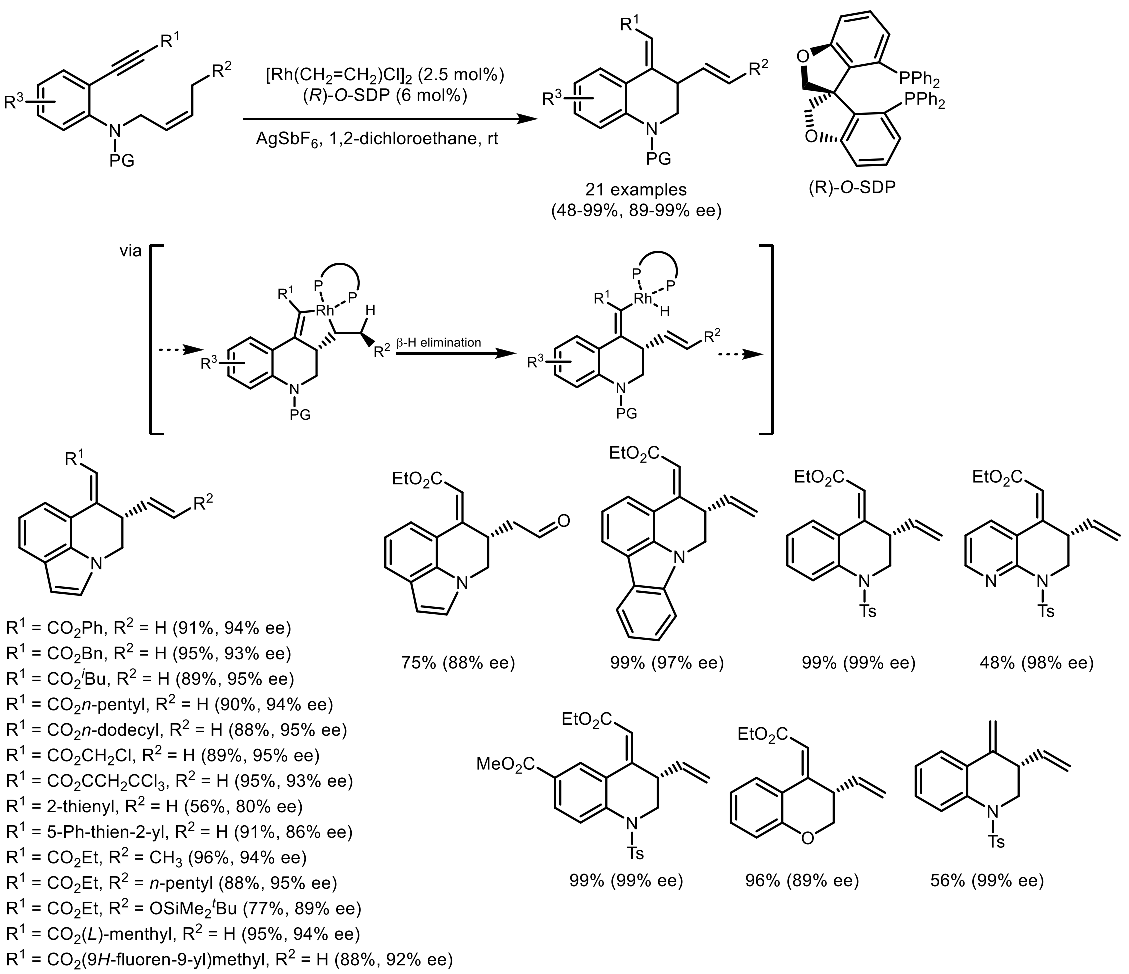
For nonactivated alkynes, transition metal catalyzed ene reactions have become an important tool, also by expanding the reactivity and selectivity portfolio by employing various different metal catalysts.

Hilt has mainly paved the road to establishing cobalt-catalyzed Alder ene reactions and in a recent report he also discussed the regiodiverse aspects of neutral Diels–Alder reaction and the Co- versus Ru-catalyzed Alder ene reaction.[47]

Erver and Hilt successfully employed the metal-catalyzed Alder ene reaction as a key step in the synthesis of the biologically active cyanobacterials credneramide A and B, as well as credneric acid (**Scheme 29**).[48] While the ruthenium-catalyzed ene-yne-addition furnished the linear Z-chloro diene, the cobalt-catalyzed process furnished the branched diene in good yield and excellent stereoselectivity. This chloro diene could be directly transformed to credneramide A

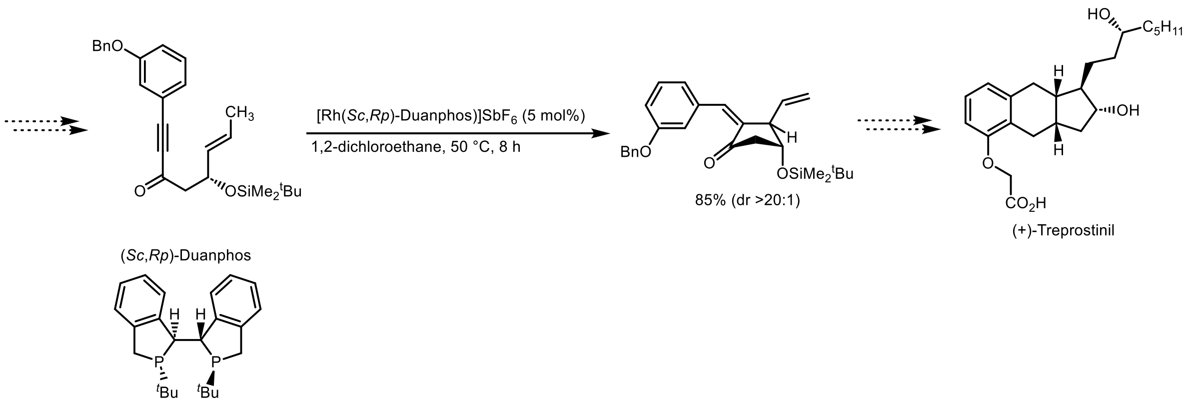


Scheme 24. Sequentially Rh–BINAP-catalyzed enantioselective cycloisomerization-hydrogenation synthesis of alkylidene tetrahydrofuran β-aminoethanes.

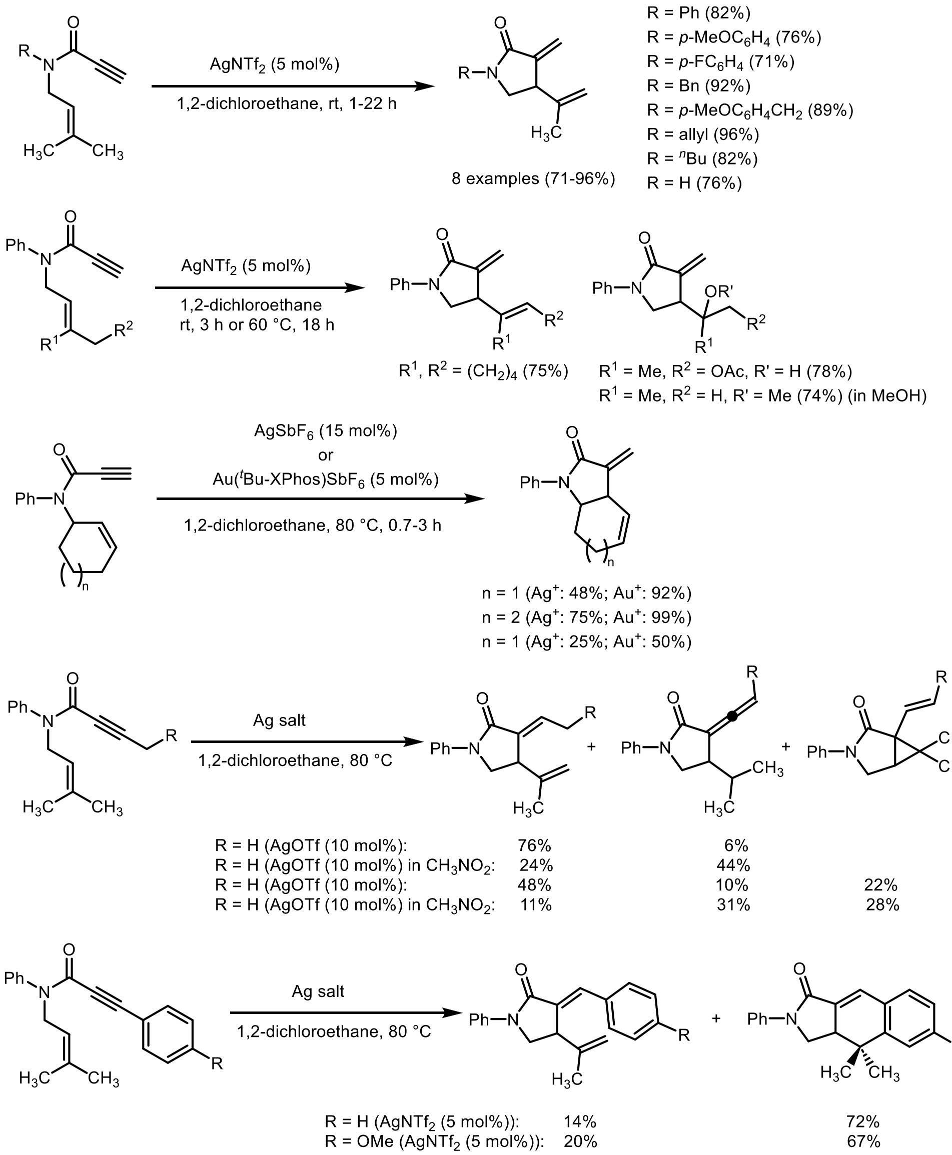


Scheme 25. Enantioselective rhodium(I)-catalyzed Alder ene-type cycloisomerization of 1,7-enynes furnishing fused six-membered heterocycles.

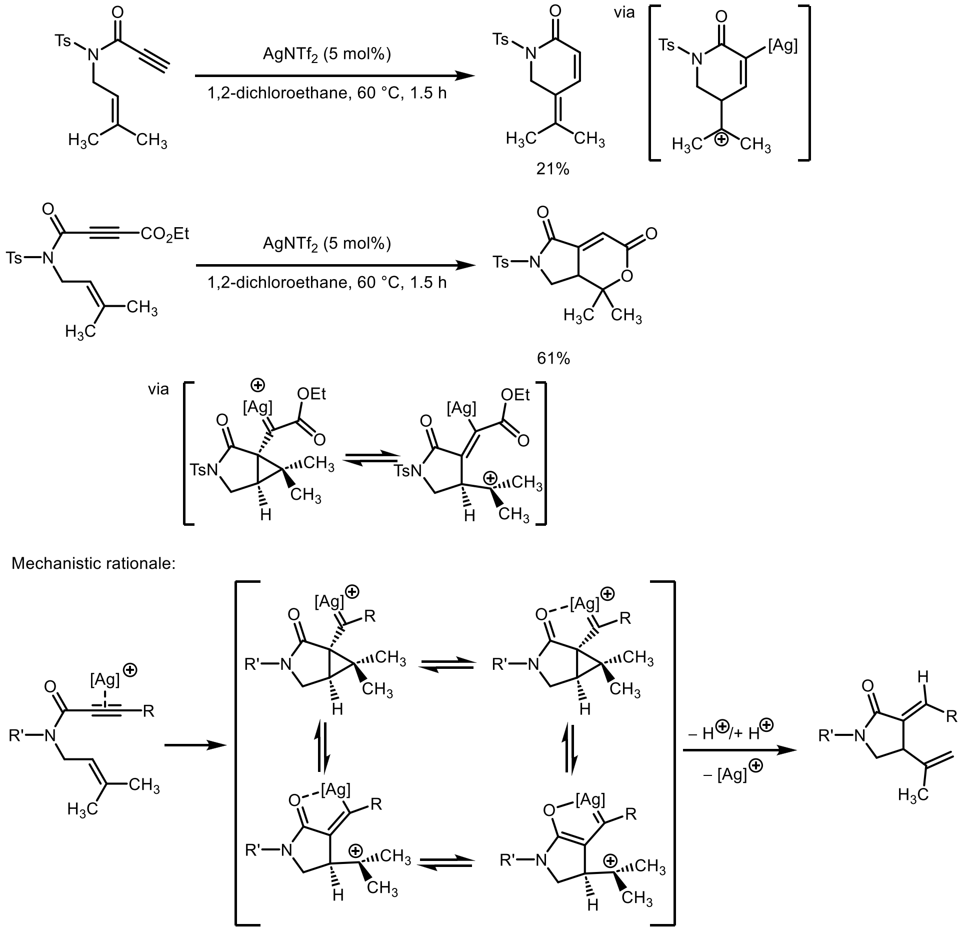
and B by amidation. It is noteworthy to mention that also the Ru-catalyzed process starting from a trimethylsilyl-substituted alkyne underwent the selective formation of the branched product with amide-functionalized alkenes and subsequent stereospecific *ipso*-chlorination gave rise to the natural products.



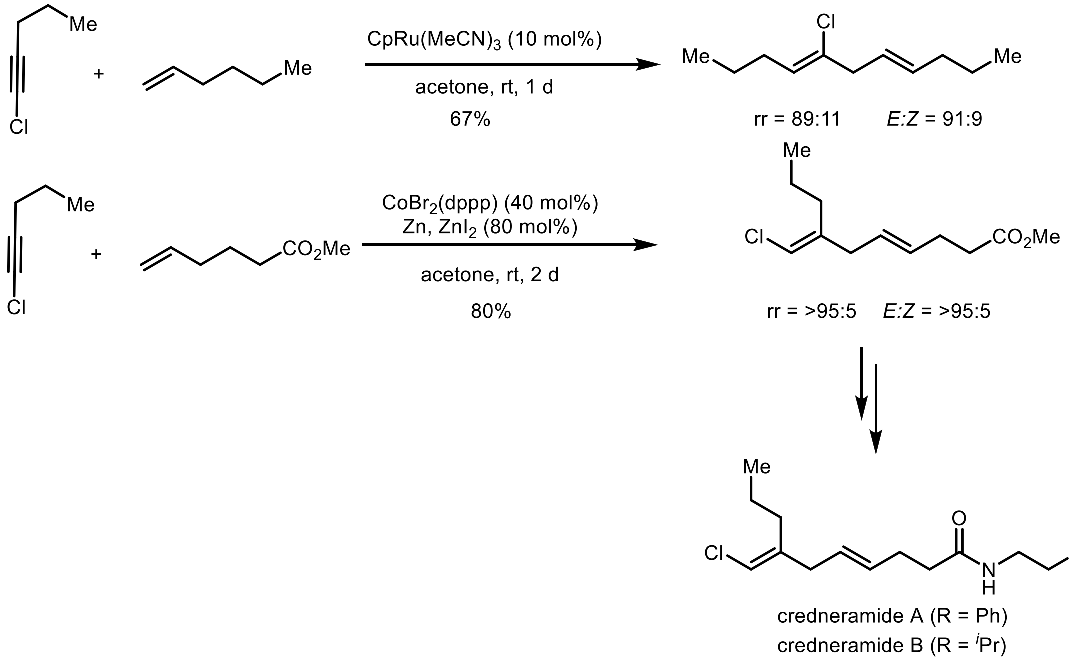
Scheme 26. Enantioselective Rh-catalyzed Alder ene cycloisomerization with (*Sc*,*Rp*)-Duanphos) as a chiral ligand as a key step in the total synthesis of (+)-Treprostinil.



Scheme 27. Cycloisomerization of propiolamide derived 1,6-enynes.



Scheme 28. Selectivity issues of propiolamide derived 1,6-enynes and mechanistic rationale of the cycloisomerization.

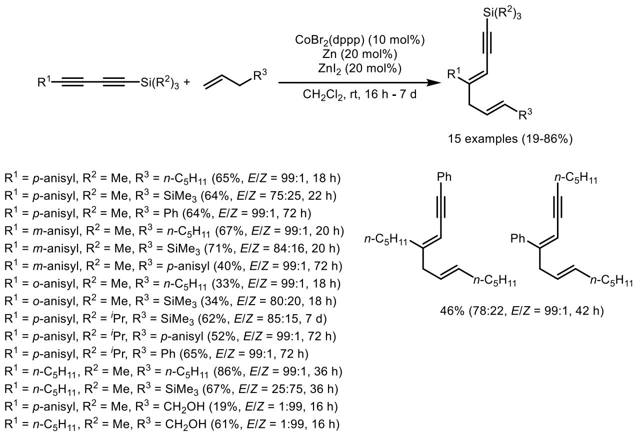


Scheme 29. Co- and Ru-catalyzed Alder ene reaction for the synthesis of credneramide A and B.

The same group could show that homoallylpinacol boronic ester is an excellent substrate for cobalt-catalyzed Alder ene reactions with 1-phenyl-1-propyne in a consecutive three-component cobalt-catalyzed Alder ene-allylboration reaction (**Scheme 30**).[49] The Alder ene step generates *E*-configured intermediates that are transformed to the *syn*-configured homoallyl alcohols in excellent levels of diastereoselectivity.

The Co-catalyzed [2 + 2] cycloaddition/Alder ene manifold was investigated by ^{13}C kinetic isotope effects at natural abundance by Xiang and Meyer.[50]

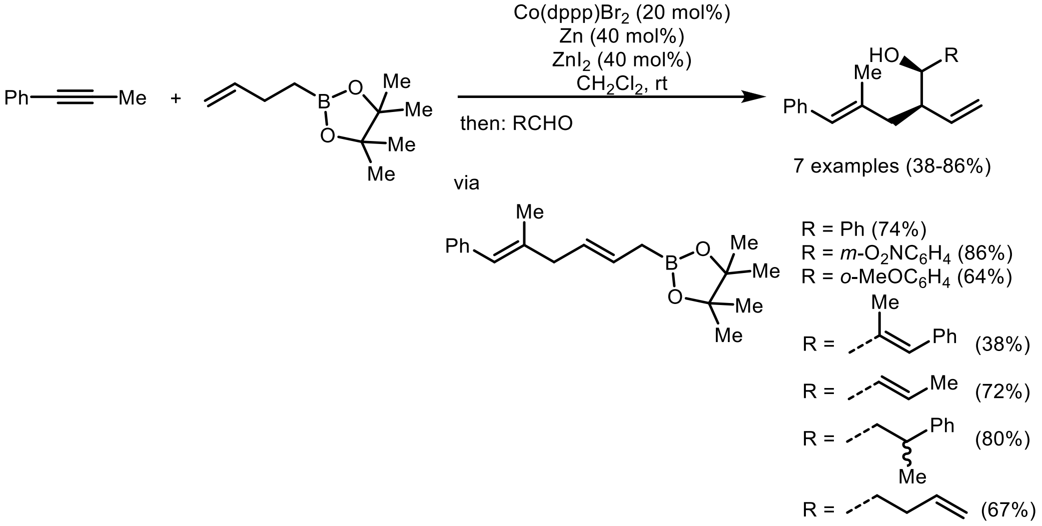
With unsymmetrically substituted butadiynes as enophile substrates, the regioselectivity of the Alder ene reaction with terminal alkenes as enes can be controlled by the employed catalyst system.[51] While ruthenium catalysts give rise to formally branched alkynyl substituted skipped dienes (Lee), cobalt catalysis furnishes the corresponding formally linear isomers (**Scheme 31**). Weber and Hilt reported the observed complementary regioselectivity with many examples (**Scheme 32**). Interestingly, simple alkene ene substrates furnish exclusively the *E*-configuration, while 3-buten-1-ol resulted in the corresponding *Z*-double bond, caused by the coordination of hydroxy group to the cobalt center.



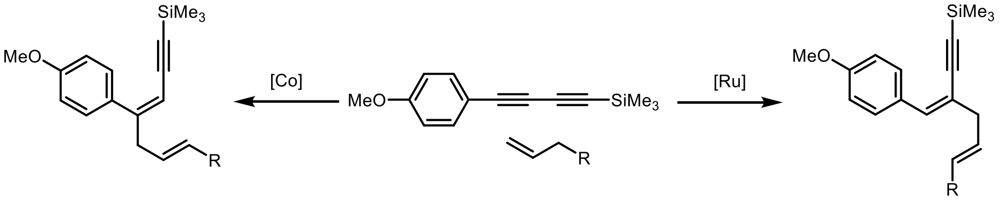
R^1 = *p*-anisyl, R^2 = Me, R^3 = *n*-C_5H_{11} (65%, *E*/*Z* = 99:1, 18 h)
R^1 = *p*-anisyl, R^2 = Me, R^3 = $SiMe_3$ (64%, *E*/*Z* = 75:25, 22 h)
R^1 = *p*-anisyl, R^2 = Me, R^3 = Ph (64%, *E*/*Z* = 99:1, 72 h)
R^1 = *m*-anisyl, R^2 = Me, R^3 = *n*-C_5H_{11} (67%, *E*/*Z* = 99:1, 20 h)
R^1 = *m*-anisyl, R^2 = Me, R^3 = $SiMe_3$ (71%, *E*/*Z* = 84:16, 20 h)
R^1 = *m*-anisyl, R^2 = Me, R^3 = *p*-anisyl (40%, *E*/*Z* = 99:1, 72 h)
R^1 = *o*-anisyl, R^2 = Me, R^3 = *n*-C_5H_{11} (33%, *E*/*Z* = 99:1, 18 h)
R^1 = *o*-anisyl, R^2 = Me, R^3 = $SiMe_3$ (34%, *E*/*Z* = 80:20, 18 h)
R^1 = *p*-anisyl, R^2 = ^{i}Pr, R^3 = $SiMe_3$ (62%, *E*/*Z* = 85:15, 7 d)
R^1 = *p*-anisyl, R^2 = ^{i}Pr, R^3 = *p*-anisyl (52%, *E*/*Z* = 99:1, 72 h)
R^1 = *p*-anisyl, R^2 = ^{i}Pr, R^3 = Ph (65%, *E*/*Z* = 99:1, 72 h)
R^1 = *n*-C_5H_{11}, R^2 = Me, R^3 = *n*-C_5H_{11} (86%, *E*/*Z* = 99:1, 36 h)
R^1 = *n*-C_5H_{11}, R^2 = Me, R^3 = $SiMe_3$ (67%, *E*/*Z* = 25:75, 36 h)
R^1 = *p*-anisyl, R^2 = Me, R^3 = CH_2OH (19%, *E*/*Z* = 1:99, 16 h)
R^1 = *n*-C_5H_{11}, R^2 = Me, R^3 = CH_2OH (61%, *E*/*Z* = 1:99, 16 h)

Scheme 32. Cobalt-catalyzed Alder ene reaction.

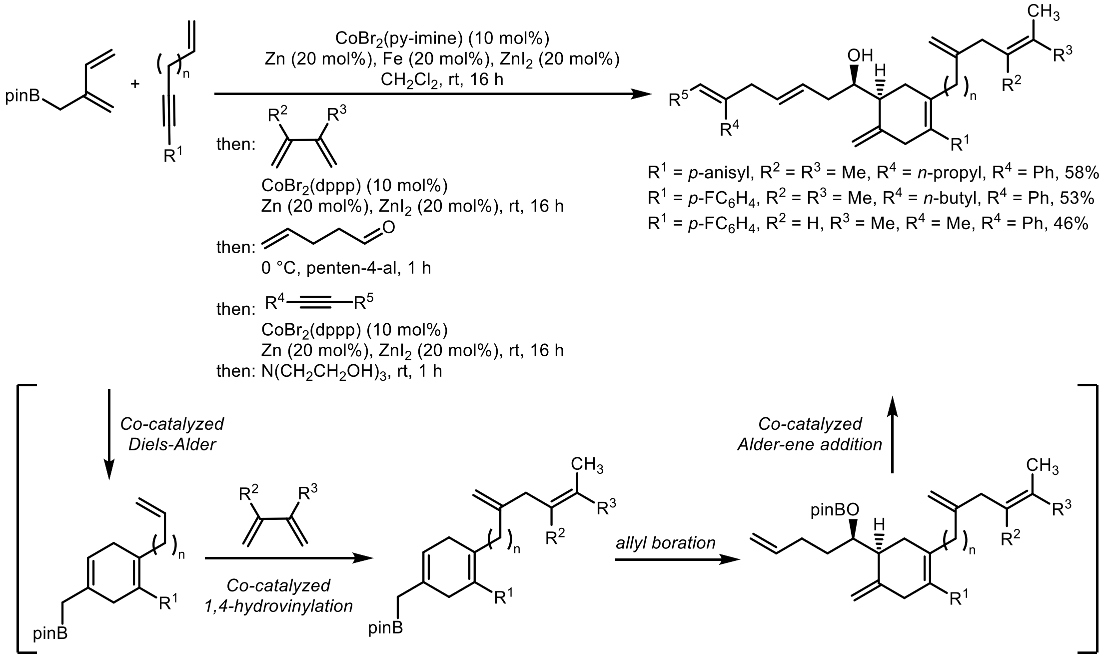
Erver and Hilt reported an impressive consecutive five-component synthesis of complex products in good yields starting from boroprene (a pinacolatoboron-functionalized isoprene), embedding Co-catalyzed Diels–Alder reaction, Co-catalyzed 1,4-hydrovinylation, allyl boration, and Co-catalyzed Alder ene addition in a



Scheme 30. Consecutive three-component cobalt-catalyzed Alder ene–allylboration reaction.

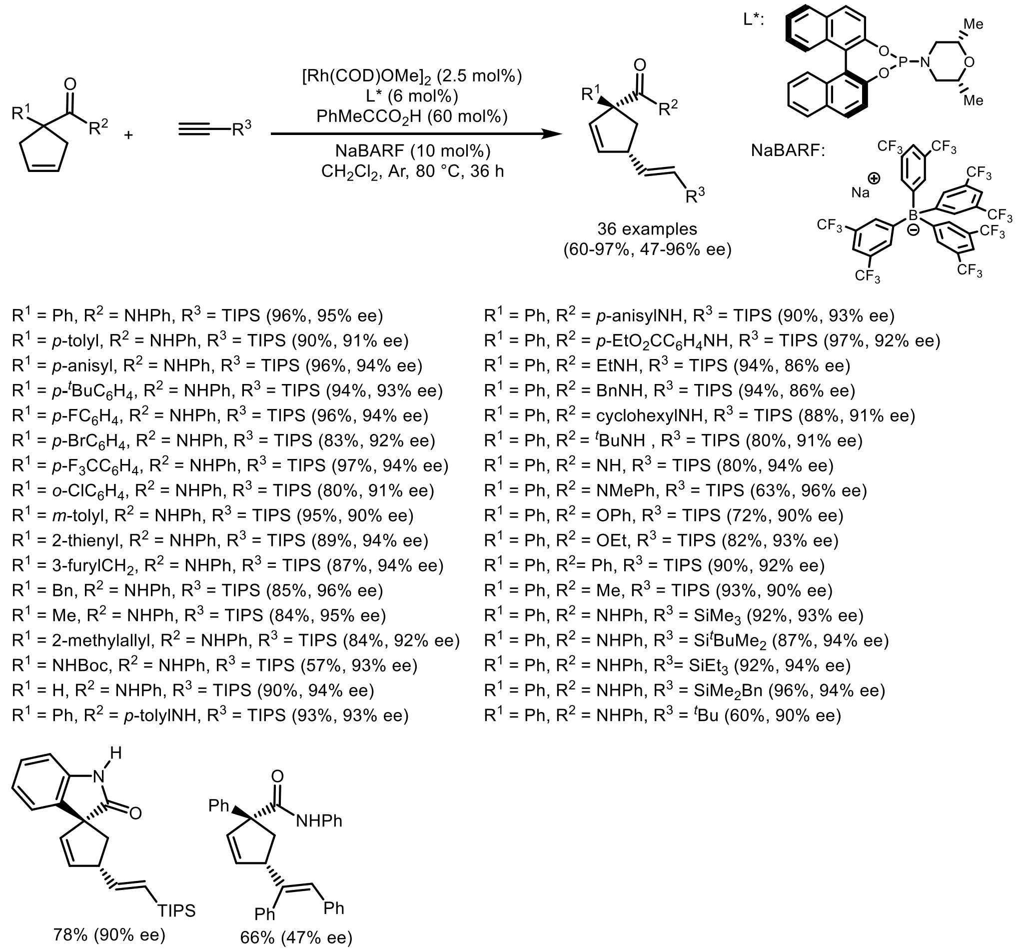


Scheme 31. Complementary regioselectivity of cobalt- and ruthenium catalyzed Alder ene reactions with an unsymmetrical diyne substrate.



R^1 = *p*-anisyl, R^2 = R^3 = Me, R^4 = *n*-propyl, R^4 = Ph, 58%
R^1 = *p*-FC_6H_4, R^2 = R^3 = Me, R^4 = *n*-butyl, R^4 = Ph, 53%
R^1 = *p*-FC_6H_4, R^2 = H, R^3 = Me, R^4 = Me, R^4 = Ph, 46%

Scheme 33. Consecutive triply cobalt-catalyzed five-component Diels–Alder-1,4-hydrovinylation-Allylboration-Alder ene addition sequence.



R^1 = Ph, R^2 = NHPh, R^3 = TIPS (96%, 95% ee)
R^1 = *p*-tolyl, R^2 = NHPh, R^3 = TIPS (90%, 91% ee)
R^1 = *p*-anisyl, R^2 = NHPh, R^3 = TIPS (96%, 94% ee)
R^1 = *p*-$^tBuC_6H_4$, R^2 = NHPh, R^3 = TIPS (94%, 93% ee)
R^1 = *p*-FC_6H_4, R^2 = NHPh, R^3 = TIPS (96%, 94% ee)
R^1 = *p*-BrC_6H_4, R^2 = NHPh, R^3 = TIPS (83%, 92% ee)
R^1 = *p*-$F_3CC_6H_4$, R^2 = NHPh, R^3 = TIPS (97%, 94% ee)
R^1 = *o*-ClC_6H_4, R^2 = NHPh, R^3 = TIPS (80%, 91% ee)
R^1 = *m*-tolyl, R^2 = NHPh, R^3 = TIPS (95%, 90% ee)
R^1 = 2-thienyl, R^2 = NHPh, R^3 = TIPS (89%, 94% ee)
R^1 = 3-furylCH_2, R^2 = NHPh, R^3 = TIPS (87%, 94% ee)
R^1 = Bn, R^2 = NHPh, R^3 = TIPS (85%, 96% ee)
R^1 = Me, R^2 = NHPh, R^3 = TIPS (84%, 95% ee)
R^1 = 2-methylallyl, R^2 = NHPh, R^3 = TIPS (84%, 92% ee)
R^1 = NHBoc, R^2 = NHPh, R^3 = TIPS (57%, 93% ee)
R^1 = H, R^2 = NHPh, R^3 = TIPS (90%, 94% ee)
R^1 = Ph, R^2 = *p*-tolylNH, R^3 = TIPS (93%, 93% ee)
R^1 = Ph, R^2 = *p*-anisylNH, R^3 = TIPS (90%, 93% ee)
R^1 = Ph, R^2 = *p*-$EtO_2CC_6H_4NH$, R^3 = TIPS (97%, 92% ee)
R^1 = Ph, R^2 = EtNH, R^3 = TIPS (94%, 86% ee)
R^1 = Ph, R^2 = BnNH, R^3 = TIPS (94%, 86% ee)
R^1 = Ph, R^2 = cyclohexylNH, R^3 = TIPS (88%, 91% ee)
R^1 = Ph, R^2 = ^tBuNH , R^3 = TIPS (80%, 91% ee)
R^1 = Ph, R^2 = NH, R^3 = TIPS (80%, 94% ee)
R^1 = Ph, R^2 = NMePh, R^3 = TIPS (63%, 96% ee)
R^1 = Ph, R^2 = OPh, R^3 = TIPS (72%, 90% ee)
R^1 = Ph, R^2 = OEt, R^3 = TIPS (82%, 93% ee)
R^1 = Ph, R^2= Ph, R^3 = TIPS (90%, 92% ee)
R^1 = Ph, R^2 = Me, R^3 = TIPS (93%, 90% ee)
R^1 = Ph, R^2 = NHPh, R^3 = $SiMe_3$ (92%, 93% ee)
R^1 = Ph, R^2 = NHPh, R^3 = Si^tBuMe_2 (87%, 94% ee)
R^1 = Ph, R^2 = NHPh, R^3= $SiEt_3$ (92%, 94% ee)
R^1 = Ph, R^2 = NHPh, R^3 = $SiMe_2Bn$ (96%, 94% ee)
R^1 = Ph, R^2 = NHPh, R^3 = ^tBu (60%, 90% ee)

78% (90% ee)
66% (47% ee)

Scheme 34. Enantioselective intermolecular rhodium-catalyzed Alder ene type reaction of cyclopentenes with silylacetylenes.

one-pot fashion with excellent regio- and diastereoselectivity (**Scheme 33**).[52]

The enantioselective intermolecular Alder ene reaction of enes and alkyne enophiles still remains scarcely investigated to date. Yao and coauthors reported an interesting version of an enantioselective intermolecular Alder ene reaction by desymmetrizing a *meso*-cyclopentene bearing a metal directing carbonyl group that enables a simple diastereofacial selection of the double bond (**Scheme 34**).[53] A chiral BINOL-phosphoamidate ligand allows the cationic rhodium complex to exert excellent diastereotopic discrimination for the alkene insertion of the vinyl silane moiety and good to excellent yields and high levels of enantioselectivities were obtained. Mechanistic investigations with deuterated alkynyl silanes and isotope scrambling suggest that a rhodium-vinylidene intermediate plays a crucial role in the formation of the vinyl-Rh-complex that coordinates to the cyclopentene substrate (**Scheme 35**).

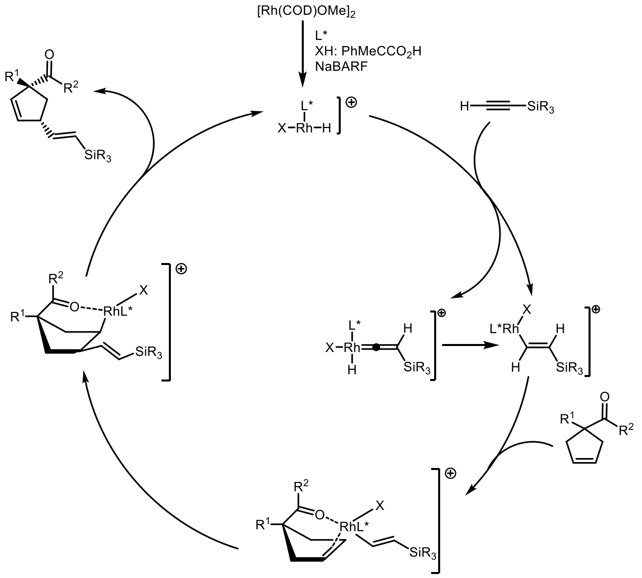
Bai, Lan, and coauthors tackled by DFT calculations the mechanism of Ru-catalyzed Alder ene type alkene–alkyne coupling reactions and discovered a novel 1,5-H-shift mechanism (**Scheme 36**).[54] Accordingly, after coordination of alkyne and alkene at the cationic CpRu complex, the oxidative cyclometallation forms a ruthenacyclopentene intermediate. The 1,5-H shift occurs via agnostic interaction and generates coordinate diene complex in the sense of a reductive elimination—coordination intermediate. Sequential ligand exchange constructs the final product and regenerates the active catalyst. This computationally derived model validates the observed stereoselectivity and the regioselectivity is governed by the electronic effect and the six-membered ring tension.

Fürstner, Thiel, and coauthors investigated the recognition of the dual binding mode of propargyl and allyl alcohol substrates to [Cp*Ru] fragments in highly regioselective intermolecular Alder ene-type additions (**Scheme 37**).[55] The inherent chirality at the putative complex intermediates set the stage for an efficient relay of stereochemical information (**Scheme 38**). Additional information on the principles governing regio- and stereocontrol was obtained by an X-ray structure of a Cp*Ru complex with an intact enyne ligand, and by computational data.

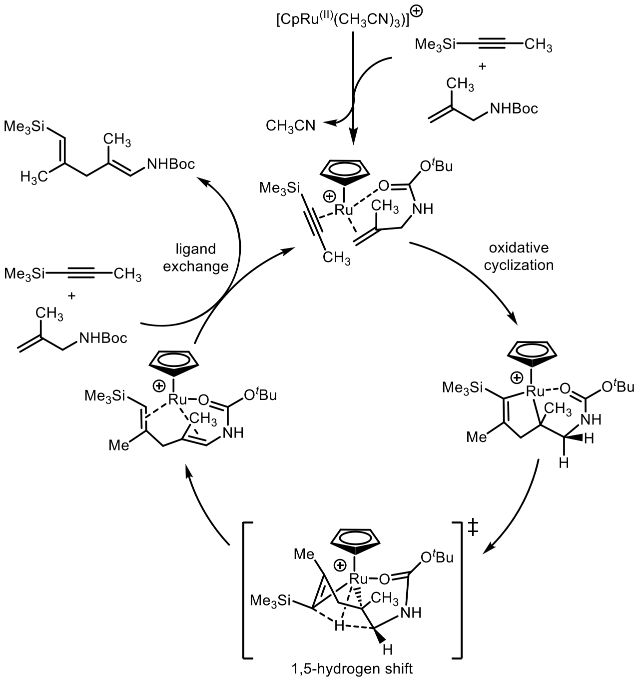
2.2.4. Intramolecular Ene Reactions with Electroneutral Alkynes as Enophiles

Selander and coauthors compiled a review article summarizing advances on carbo- and heterocyclization of alkynes by indium(Iii) compounds as Lewis acid catalysts.[56] These complexes are also able to catalyze Conia ene reactions, where the alkyne substrate serves as enophile, mostly in intramolecular transformations but also in a few intermolecular cases.

Yne-allylic esters were shown to react with 1,3-dicarbonyl compounds by remote regioselective Cu-catalyzed nucleophilic substitution in ε-position via a copper–allenylidene complex to give [4 + 1] anellation products with excellent levels of enantioselectivity (**Scheme 39**).[57]



Scheme 35. Mechanistic rationale of the enantioselective intermolecular rhodium-catalyzed Alder ene type reaction of cyclopentenes with silylacetylenes.

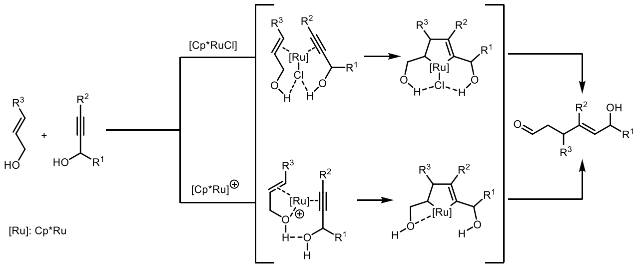


Scheme 36. Mechanism of a Ru-catalyzed Alder ene type alkene–alkyne coupling reactions embedding a novel 1,5-H-shift.

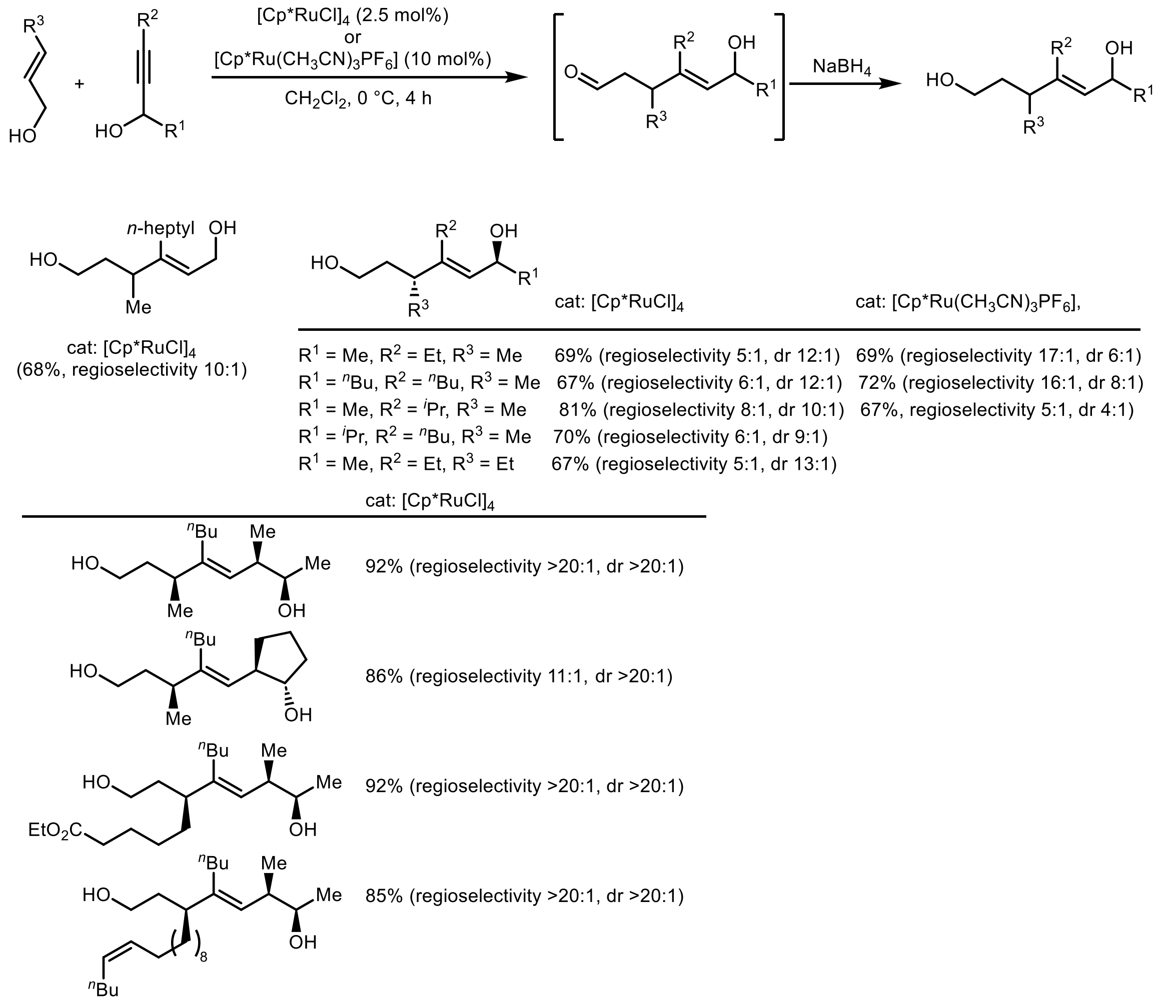
The substitution product either undergoes cyclization via an anionic path way or, as supported by quantum chemical calculations, in the sense of a Conia ene reaction, where the enolizable dicarbonyl moiety represents the ene part and the copper-alkynyl part the enophile.

Alkynyl-β-ketoesters or β-amidoesters were shown to undergo catalytic asymmetric Conia ene cycloisomerization, employing a heterometallic rare earth element—silver complex—bearing N-salicylacyl amino acid ortho–hydroxy anilides as chiral ligands to receive the cycloisomerized *exo*-methylencyclopentane products with moderate to good yields and good to excellent levels of enantioselectivity.[58]

Since the advent of palladium(II)-catalyzed Alder ene-type cycloisomerizations almost four decades ago,[59] heteroatom-linked 1,6-enynes have increasingly received attention, predominantly due to the ease of formation of hexahydro–indoles and –benzofurans—bicyclic constituents of alkaloids and other natural products—in a highly diastereoselective fashion. In 2015, Banwell and coauthors have compiled an instructive review on Pd-catalyzed IMAE reactions and their application.[60] In a more recent overview, Yadav and Ramasastry have updated the tremendous achievements of IMAE in the synthesis of complex molecules that underline the powerful methodological and strategical approach.[61]



Scheme 38. Mechanistic rationale on putative intermediates and peripheral interactions in organizing the substrates as ligands.



cat: [Cp*RuCl]4
(68%, regioselectivity 10:1)

	cat: $[Cp^*RuCl]_4$	cat: $[Cp^*Ru(CH_3CN)_3PF_6]$,
R^1 = Me, R^2 = Et, R^3 = Me	69% (regioselectivity 5:1, dr 12:1)	69% (regioselectivity 17:1, dr 6:1)
R^1 = ⁿBu, R^2 = ⁿBu, R^3 = Me	67% (regioselectivity 6:1, dr 12:1)	72% (regioselectivity 16:1, dr 8:1)
R^1 = Me, R^2 = ⁱPr, R^3 = Me	81% (regioselectivity 8:1, dr 10:1)	67%, regioselectivity 5:1, dr 4:1)
R^1 = ⁱPr, R^2 = ⁿBu, R^3 = Me	70% (regioselectivity 6:1, dr 9:1)	
R^1 = Me, R^2 = Et, R^3 = Et	67% (regioselectivity 5:1, dr 13:1)	

cat: $[Cp^*RuCl]_4$

92% (regioselectivity >20:1, dr >20:1)

86% (regioselectivity 11:1, dr >20:1)

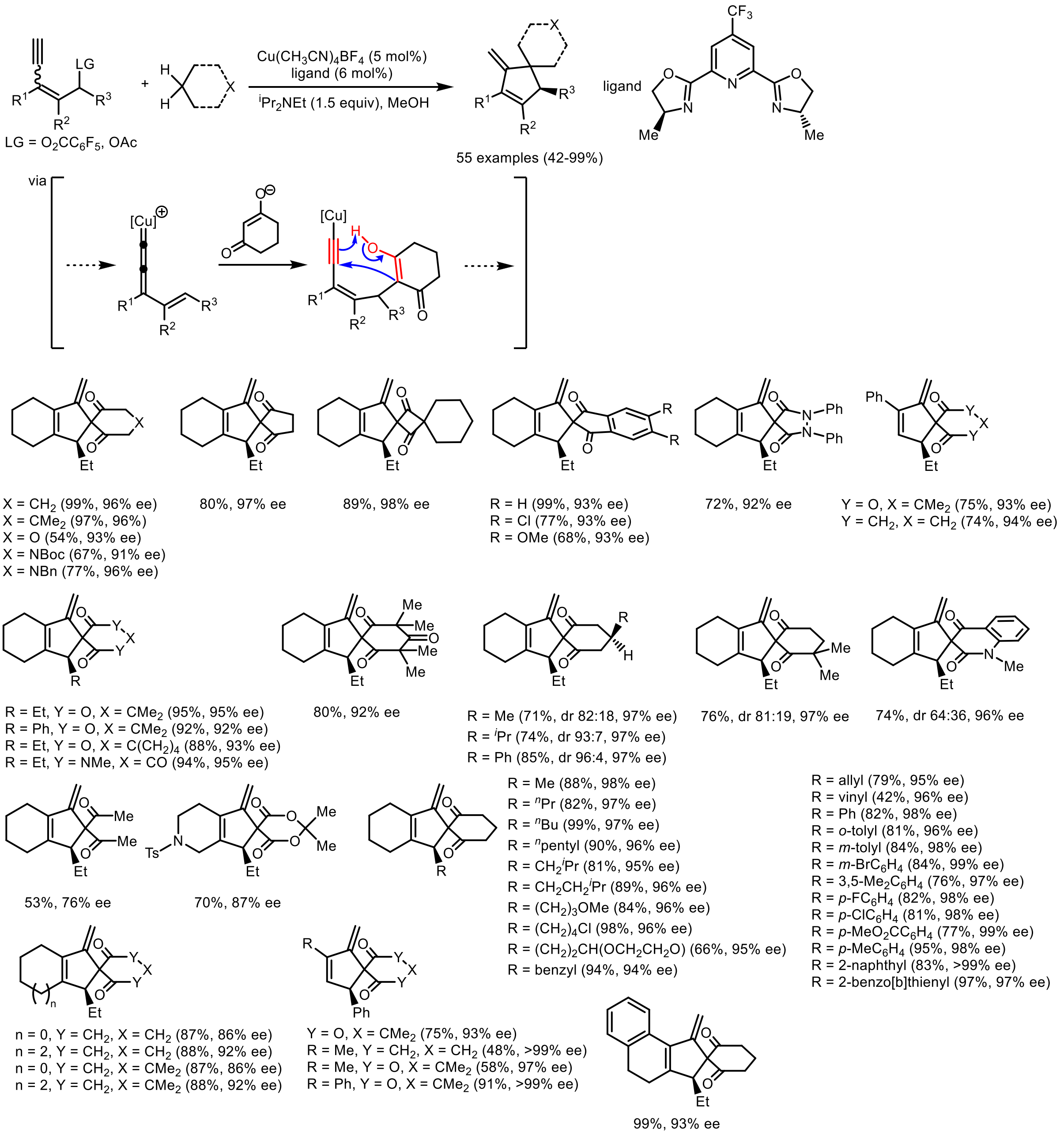
92% (regioselectivity >20:1, dr >20:1)

85% (regioselectivity >20:1, dr >20:1)

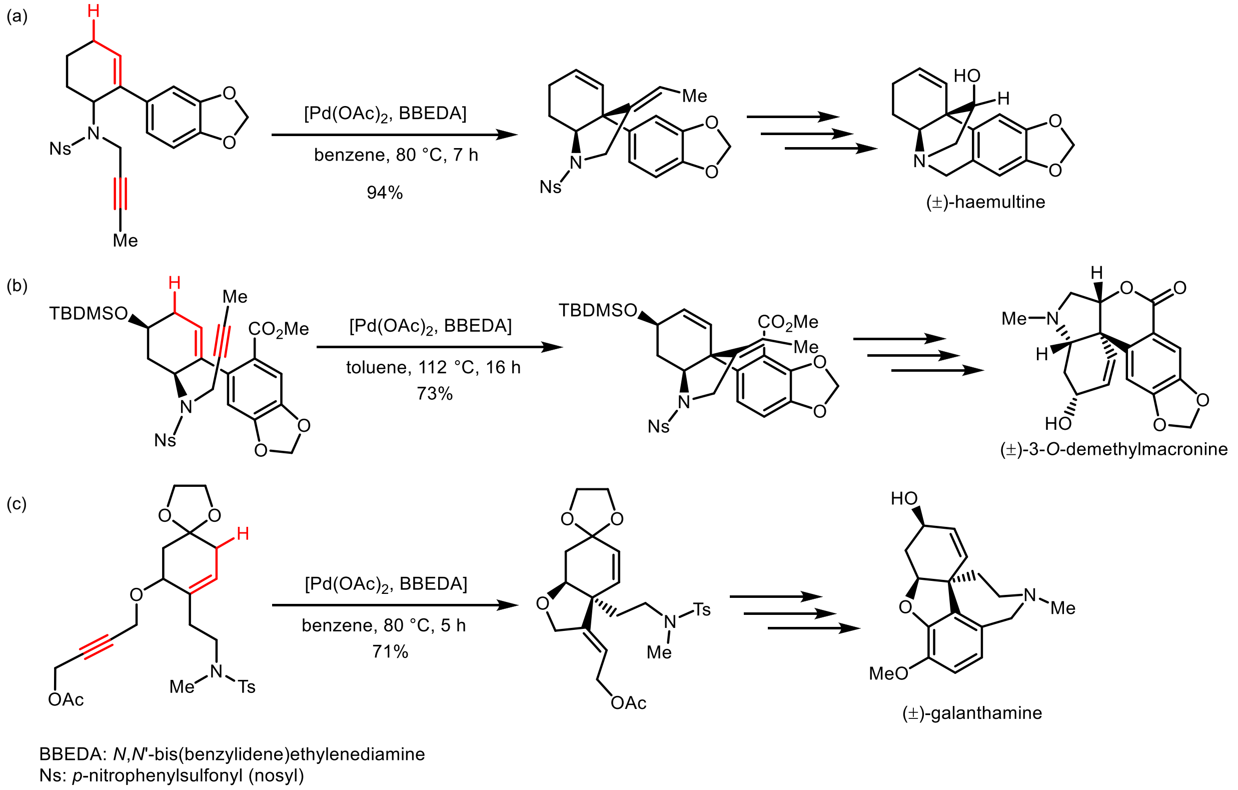
Scheme 37. Intermolecular hydroxy-directed alkyne–alkene coupling by ruthenium-catalyzed Alder ene-type reaction.

For instance, the Pd-catalyzed IMAE cycloisomerization via the Pd(II)/Pd(IV) pathway could be successfully applied for diastereoselectively establishing the arylhexahydroindole scaffold in the total synthesis of racemic crinine alkaloid haemultine by Banwell and coauthors (**Scheme 40a**).[62] Likewise, the same group achieved the racemic synthesis of the tazettine-type alkaloid 3-*O*-demethylmacronine, where the IMAE and a lactam-to-lactone rearrangement are strategically employed to establish the haemanthidine alkaloid framework (Scheme 40b).[63] Similarly, the IMAE cycloisomerization proved beneficial on the way to amaryllidaceae alkaloid (±)-galanthamine (Scheme 40c).[64]

Banwell and coauthors reported Pd-catalyzed IMAE sequences of *O*- and *N*-linked 1,6-enynes that are most effectively transformed with a triethylsilyl group (**Scheme 41** and **42**).[65] The scope of ring size as well as functionalization is fairly broad, which makes the silylated cycloisomerized products interesting substrates for



Scheme 39. Enantioselective copper-catalyzed yne–allylic substitution-Conia ene sequence via copper-allenylidene/alkynyl-copper intermediates.

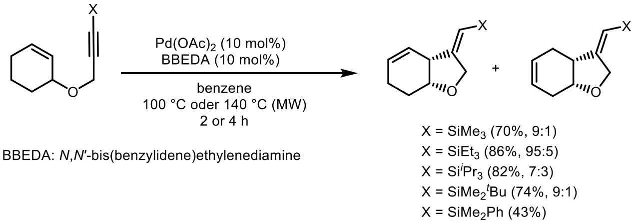


Scheme 40. Pd-catalyzed IMAE cycloisomerization as the diastereoselective key step in the synthesis of a) crinine alkaloid (±)-haemultine, b) tazettine-type alkaloid (±)-3-*O*-demethylmacronine, and c) tetracyclic Amaryllidaceae alkaloid (±)-galanthamine.

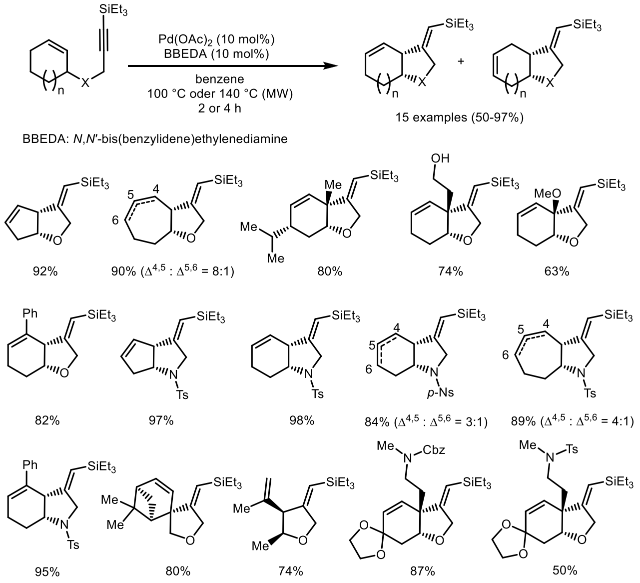
further functionalization by *ipso*-substitution of the triethylsilyl moiety.

A monoallenylidene bisphosphane Pd(II) catalyst was identified to efficiently catalyze the cycloisomerization of 1,6-enynes, also in the sense of a new type of IMAE reaction, where six-membered rings were formed by a cationic Pd-catalyst induced formally by 6-vinyl*endo-exo-dig* pathway, followed by deprotonation/protodepalladation (**Scheme 43**).[66]

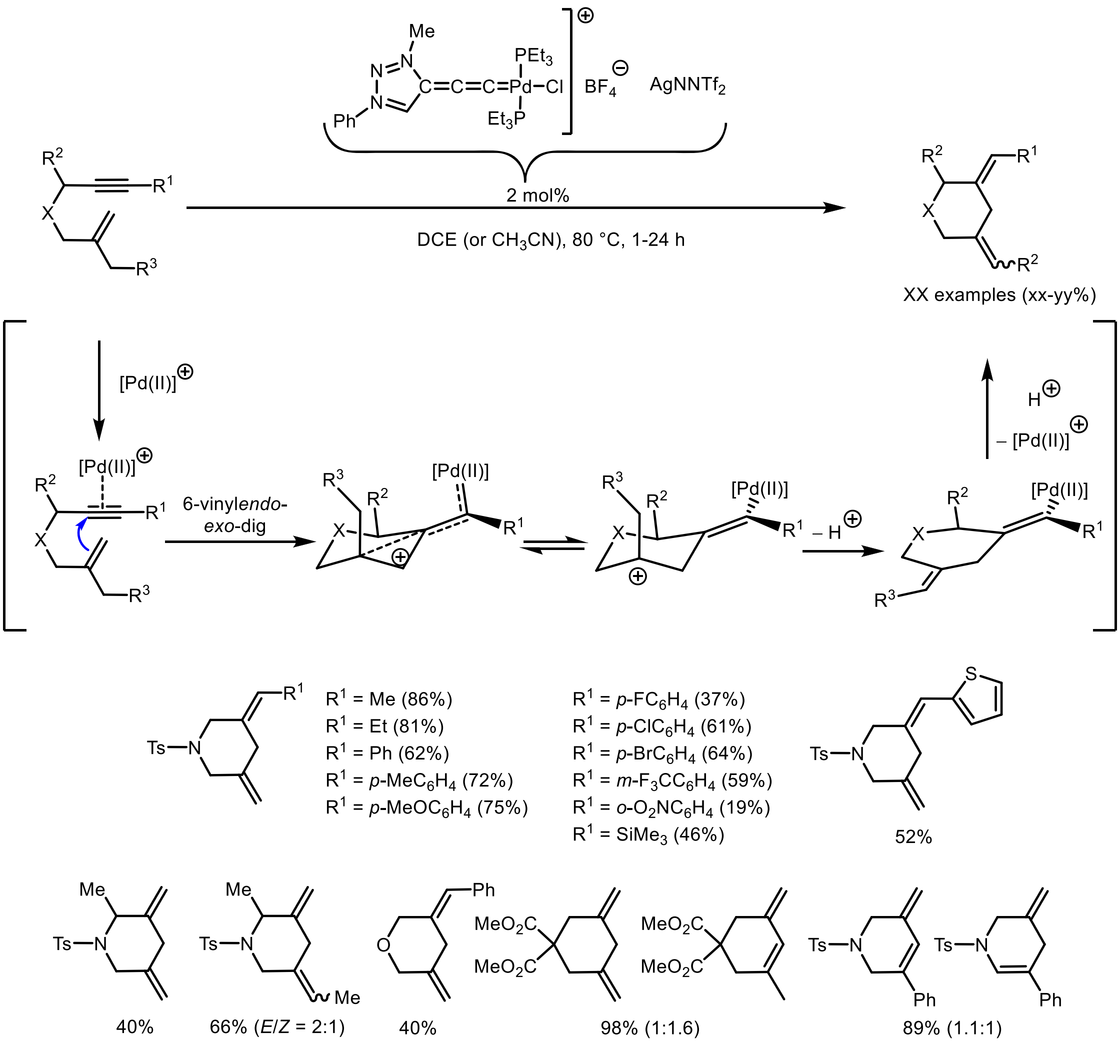
Chai and coauthors demonstrated the IMAE reaction of *ortho*-(P- phosphole sulfide)-substituted tolane derivatives bearing the required 1,6-enyne functionality to give benzo-fused bicyclo[3.3.0] scaffolds high yields and excellent regioselectivity (**Scheme 44**).[67] 1-(*P*-phosphole sulfide) functionalized naphthalenes with 8-arylethynyl substituents likewise furnish naphtho-fused bicyclo[4.3.0] skeletons, as well as [2 + 2] cycloaddition products (**Scheme 45**).



Scheme 41. Intramolecular Pd-catalyzed Alder ene cycloisomerization of various silyl-capped substrates.



Scheme 42. Intramolecular Pd-catalyzed Alder ene cycloisomerization of various *O*- and *N*-linked 1,6-enyne substrates.

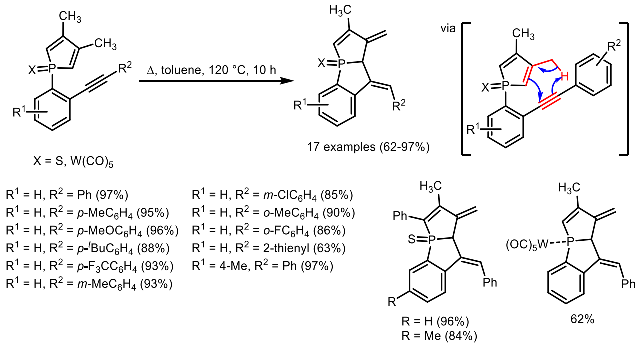


Scheme 43. Formal 6-vinyl*endo*-*exo*-*dig* cycloisomerization of 1,6-enynes catalyzed by a cationic monoallenylidene bisphosphane Pd(II) catalyst.

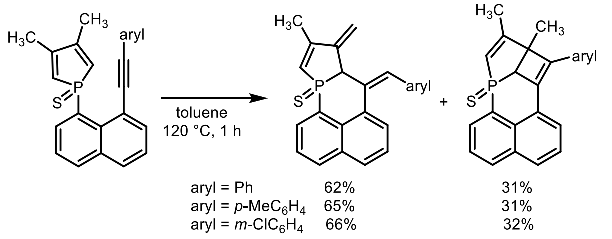
2.2.5. Intramolecular Ene Reactions with Electron-Rich Alkynes as Enophiles

While 1,6-enynes often undergo the Alder ene cycloisomerization in the 5-*exo*-*trig* mode (type I Alder ene reaction),[68] Shen, Xu, and coauthors reported the unsual type II Alder ene reaction of *N*-tosyl ynamides tethered to cycloalkenes as ene moieties (**Scheme 46**).[69] The observed 6-*endo*-*trig* cycloisomerization is most efficiently promoted by a silver catalyst in boiling 1,2-dichloroethane.

Zhu and coauthors just very recently reported an Alder ene cycloisomerization of 1,6-enynimines, in situ

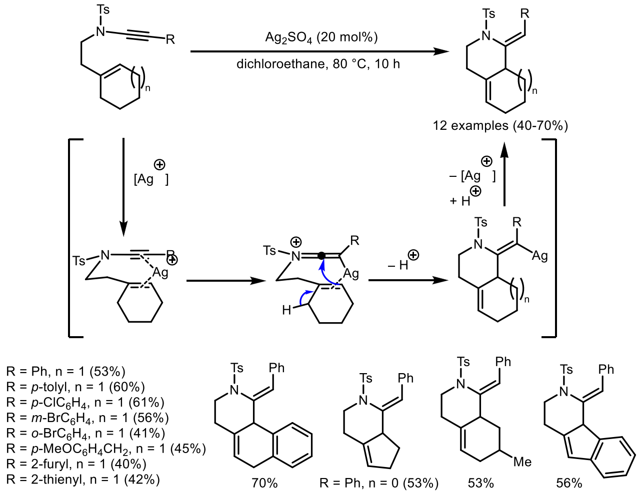


Scheme 44. Anellation of phosphole sulfides via Alder ene cycloisomerization corresponding 1,6-enyne substrates.



Scheme 45. Anellation of phosphole sulfides via competing Alder ene cycloisomerization and [2 + 2] cycloaddition with naphthalene substrates.

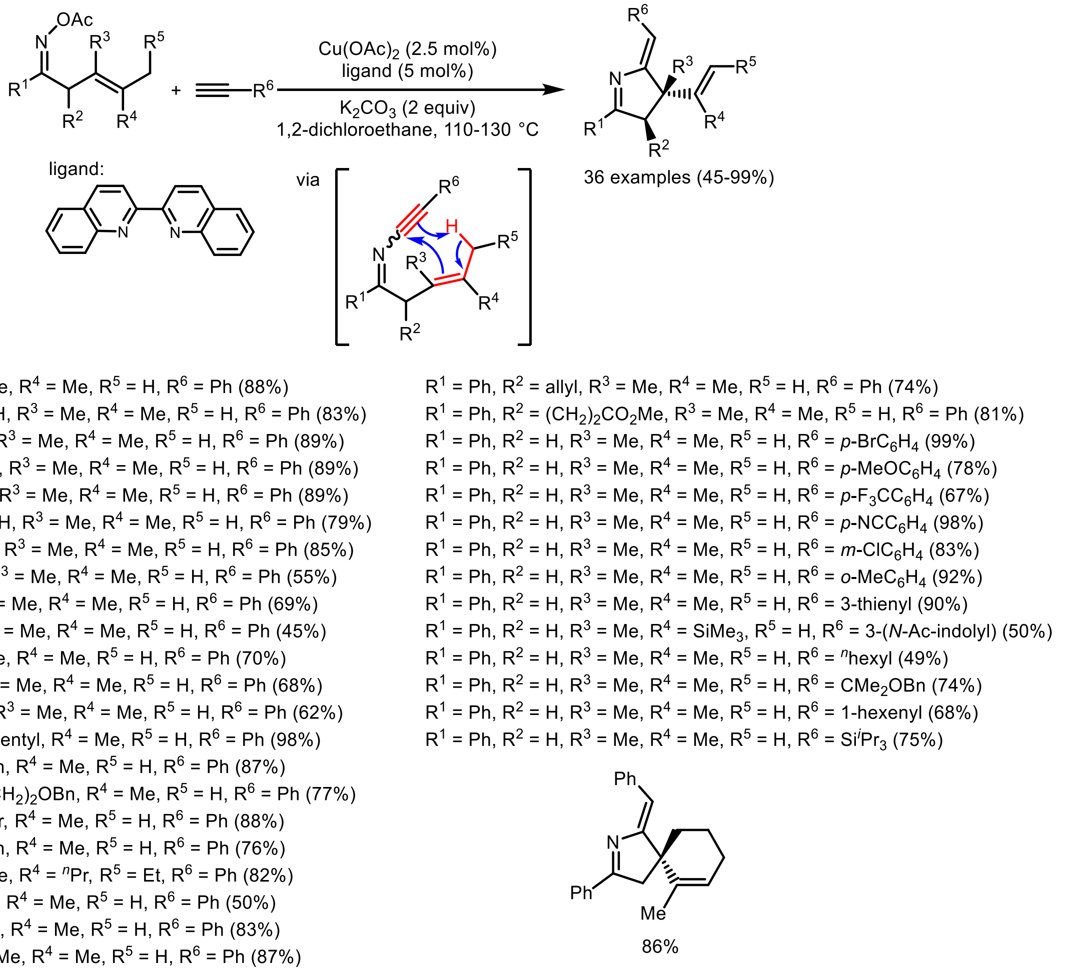
generated by Cu-catalyzed cross-coupling of β,γ-unsaturated oxime esters with terminal alkynes, to give polysubstituted 1-pyrrolines in good to excellent yield (**Scheme 47**).[70] This methodology was in addition successfully employed as the first step in the first and concise synthesis of the monoterpene indole alkaloid borrecapine (**Scheme 48**).



Scheme 46. Enantioselective variation of the domino gold-catalyzed Diels–Alder–Alder ene sequence.

2.3. Arynes as Enophiles

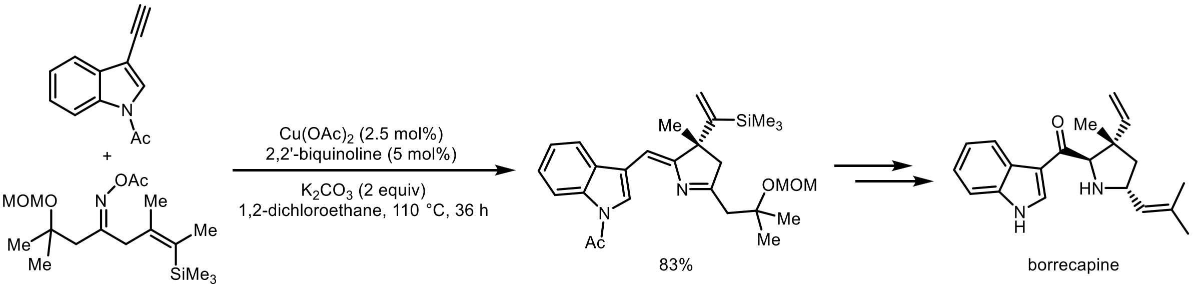
The chemistry of arynes as highly reactive intermediates has become a golden thread within the past one and a half decades and methods of their generation and implementation in reactions and sequences has been extensively reviewed.[71] Arynes are versatile highly reactive intermediates that can be employed as modules for the construction of *ortho*-disubstituted arenes, often in the sense of dienophiles or dipolarophiles in $[\pi^4 s + \pi^2 s]$-cycloadditions, giving rise to a plethora of carbo- and heterocyclic compounds in a single step. Besides Diels–Alder reactions also transition metal-free multicomponent couplings and arylations arose from this concept.[72] In addition, benzynes and their entry to 1,2-benzdiyne equivalents in the presence of a suitable leaving group enables numerous options for vicinal di- and multifunctionalization of arenes in a highly step-



R^1 = Ph, R^2 = H, R^3 = Me, R^4 = Me, R^5 = H, R^6 = Ph (88%)
R^1 = p-$MeOC_6H_4$, R^2 = H, R^3 = Me, R^4 = Me, R^5 = H, R^6 = Ph (83%)
R^1 = p-BrC_6H_4, R^2 = H, R^3 = Me, R^4 = Me, R^5 = H, R^6 = Ph (89%)
R^1 = p-$F_3CC_6H_4$, R^2 = H, R^3 = Me, R^4 = Me, R^5 = H, R^6 = Ph (89%)
R^1 = m-ClC_6H_4, R^2 = H, R^3 = Me, R^4 = Me, R^5 = H, R^6 = Ph (89%)
R^1 = m-$MeOC_6H_4$, R^2 = H, R^3 = Me, R^4 = Me, R^5 = H, R^6 = Ph (79%)
R^1 = 2-naphthyl, R^2 = H, R^3 = Me, R^4 = Me, R^5 = H, R^6 = Ph (85%)
R^1 = 2-thienyl, R^2 = H, R^3 = Me, R^4 = Me, R^5 = H, R^6 = Ph (55%)
R^1 = 2-furyl, R^2 = H, R^3 = Me, R^4 = Me, R^5 = H, R^6 = Ph (69%)
R^1 = β-styryl, R^2 = H, R^3 = Me, R^4 = Me, R^5 = H, R^6 = Ph (45%)
R^1 = ^{i}Pr, R^2 = H, R^3 = Me, R^4 = Me, R^5 = H, R^6 = Ph (70%)
R^1 = ^{n}pentyl, R^2 = H, R^3 = Me, R^4 = Me, R^5 = H, R^6 = Ph (68%)
R^1 = $(CH_2)_2Ph$, R^2 = H, R^3 = Me, R^4 = Me, R^5 = H, R^6 = Ph (62%)
R^1 = Ph, R^2 = H, R^3 = ^{n}pentyl, R^4 = Me, R^5 = H, R^6 = Ph (98%)
R^1 = Ph, R^2 = H, R^3 = Bn, R^4 = Me, R^5 = H, R^6 = Ph (87%)
R^1 = Ph, R^2 = H, R^3 = $(CH_2)_2OBn$, R^4 = Me, R^5 = H, R^6 = Ph (77%)
R^1 = Ph, R^2 = H, R^3 = ^{i}Pr, R^4 = Me, R^5 = H, R^6 = Ph (88%)
R^1 = Ph, R^2 = H, R^3 = Ph, R^4 = Me, R^5 = H, R^6 = Ph (76%)
R^1 = Ph, R^2 = H, R^3 = Me, R^4 = ^{n}Pr, R^5 = Et, R^6 = Ph (82%)
R^1 = Ph, R^2 = H, R^3 = H, R^4 = Me, R^5 = H, R^6 = Ph (50%)
R^1 = Ph, R^2 = H, R^3 = Et, R^4 = Me, R^5 = H, R^6 = Ph (83%)
R^1 = Ph, R^2 = Me, R^3 = Me, R^4 = Me, R^5 = H, R^6 = Ph (87%)

R^1 = Ph, R^2 = allyl, R^3 = Me, R^4 = Me, R^5 = H, R^6 = Ph (74%)
R^1 = Ph, R^2 = $(CH_2)_2CO_2Me$, R^3 = Me, R^4 = Me, R^5 = H, R^6 = Ph (81%)
R^1 = Ph, R^2 = H, R^3 = Me, R^4 = Me, R^5 = H, R^6 = p-BrC_6H_4 (99%)
R^1 = Ph, R^2 = H, R^3 = Me, R^4 = Me, R^5 = H, R^6 = p-$MeOC_6H_4$ (78%)
R^1 = Ph, R^2 = H, R^3 = Me, R^4 = Me, R^5 = H, R^6 = p-$F_3CC_6H_4$ (67%)
R^1 = Ph, R^2 = H, R^3 = Me, R^4 = Me, R^5 = H, R^6 = p-NCC_6H_4 (98%)
R^1 = Ph, R^2 = H, R^3 = Me, R^4 = Me, R^5 = H, R^6 = m-ClC_6H_4 (83%)
R^1 = Ph, R^2 = H, R^3 = Me, R^4 = Me, R^5 = H, R^6 = o-MeC_6H_4 (92%)
R^1 = Ph, R^2 = H, R^3 = Me, R^4 = Me, R^5 = H, R^6 = 3-thienyl (90%)
R^1 = Ph, R^2 = H, R^3 = Me, R^4 = $SiMe_3$, R^5 = H, R^6 = 3-(*N*-Ac-indolyl) (50%)
R^1 = Ph, R^2 = H, R^3 = Me, R^4 = Me, R^5 = H, R^6 = ^{n}hexyl (49%)
R^1 = Ph, R^2 = H, R^3 = Me, R^4 = Me, R^5 = H, R^6 = CMe_2OBn (74%)
R^1 = Ph, R^2 = H, R^3 = Me, R^4 = Me, R^5 = H, R^6 = 1-hexenyl (68%)
R^1 = Ph, R^2 = H, R^3 = Me, R^4 = Me, R^5 = H, R^6 = Si^iPr_3 (75%)

Scheme 47. IMAE reaction of 1,6-enynimines in situ generated by copper catalyzed alkynylation of O-acetyl oximes to give 1-pyrrolines.



Scheme 48. Application of the IMAE reaction of 1,6-enynimines in situ generated by copper catalyzed alkynylation in the total synthesis of borrecapine.

economical fashion.[73] Most relevant for their application in complex molecules' synthesis, the generation of arynes and their intra- or intermolecular ene-type transformation have become a major focus in the past decade.

Multicomponent reactions have extensively evolved over the years, based upon the programmed reactivity of arynes in the sense of a relay in electrophile–nucleophile trapping reactions, as summarized by Ghorai and Lee.[74] A general and mild access to arynes is the reaction of *ortho*-silyl aryltriflates with cesium fluoride at room temperature.[75,76] Particularly interesting is the employment of in situ generated arynes as enophiles in aryne ene reactions, which has recently summarized in a comprehensive review by Yang and Jones.[77]

2.3.1. Intermolecular Ene Reactions with Arynes as Enophiles

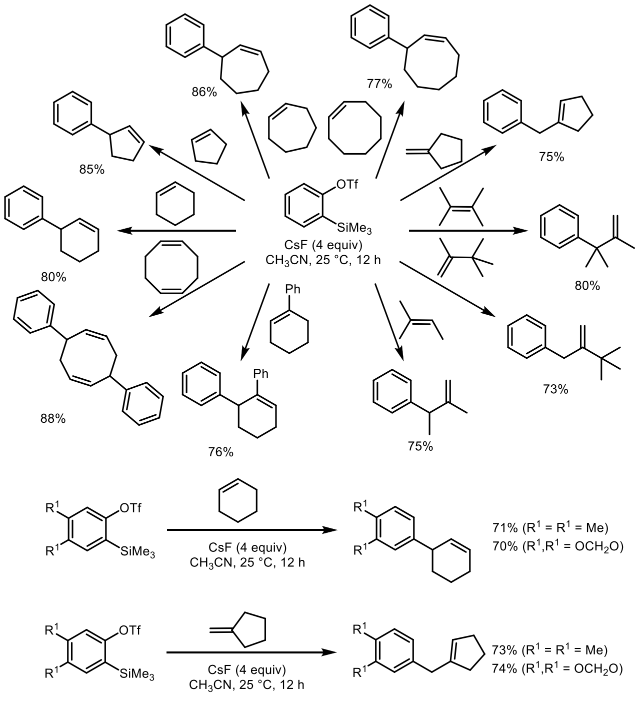
Arynes from Ortho-Silyl Aryltriflates by Elimination: In the presence of acyclic and cyclic alkenes benzyne reacts in situ with acyclic and cyclic alkenes to give the corresponding intermolecular Alder ene products (**Scheme 49**).[78]

Hantzsch esters (with methyl groups in 2- (or 6-) positions) can be considered as ene substrates as well. Jones and coworkers have illustrated that Hantzsch esters unsubstituted in 4-position readily react with in situ generated arynes via 2-arylation (**Scheme 50**), while 4-monosubstituted Hantzsch esters with 2-methyl substituents react via 3-arylation (**Scheme 51**).[79] The experimental findings were backed up with DFT calculations supporting the intermolecular concerted pericyclic aryne–ene process.

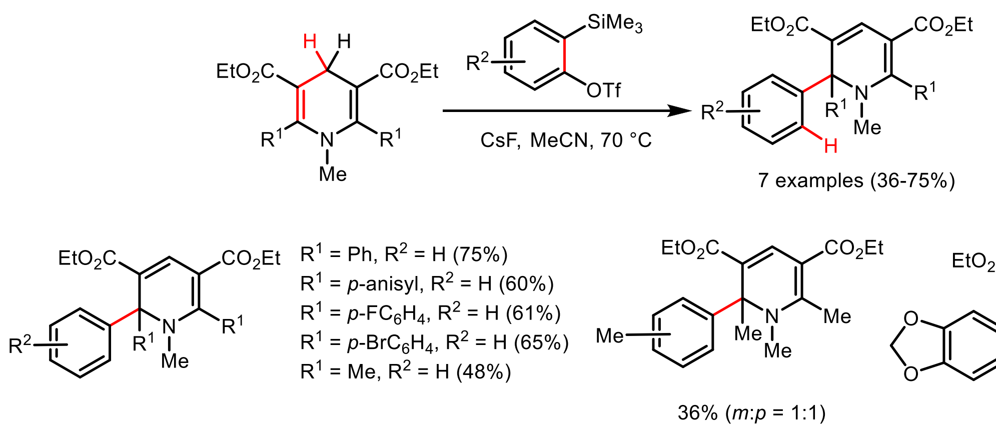
Ganesh and coauthors showed that conformationally locked styrenes, such as methylene indane and methylene tetralin derivatives readily undergo aryne Alder ene reactions to give aryl-substituted indenes (**Scheme 52**) and dihydronaphthalenes (**Scheme 53**) in moderate to good yield.[80] Competition of multiple aryne Diels–Alder versus aryne Alder ene reaction was studied with indene products, as expected from literature precedence with indenes,[81] and with a dihydronaphthalene (**Scheme 54**). While the indenes furnished two subsequent Diels–Alder cycloadditions, the latter underwent the aryne Alder ene reaction.

Arynes easily react with vinyl arenes via cycloadditions to give ene intermediates. Therefore, sequences of Diels–Alder–Alder ene reactions with in situ generated arynes were reported.

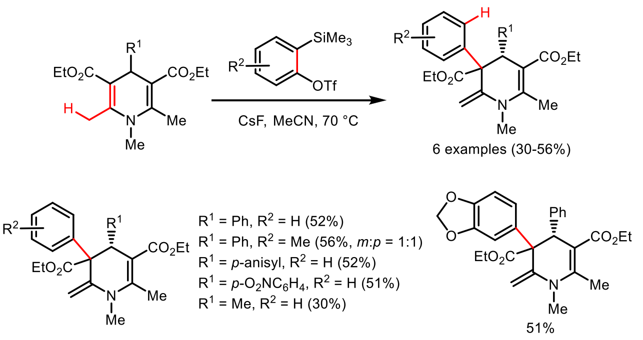
Triggered by an aryne Diels–Alder reaction *N*-tosyl vinylaziridines were readily transformed under mild and metal-free conditions by aromatizing ring-opening of the aziridine and a subsequent aryne–ene reaction to give 2-(phenanthren-9-yl)ethan-1-sulfamides in 1,4-dioxane (**Scheme 55**).[82] Switching the fluoride source from KF to CsF and the solvent from 1,4-dioxane led to a concatenation of an *N*-arylation with aryne and thereby to the corresponding *N*-aryl-2-(phenanthren-9-yl)ethan-1-



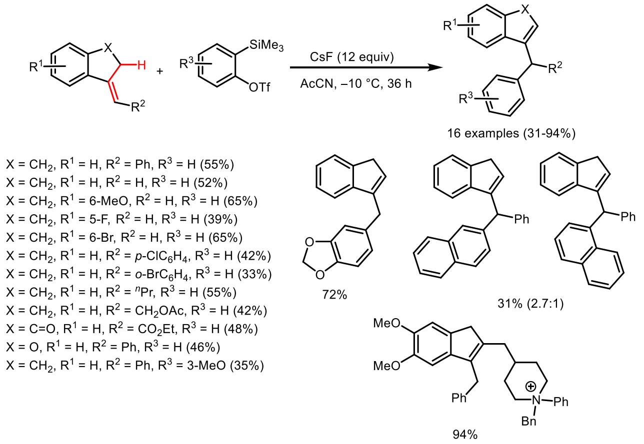
Scheme 49. Intermolecular Alder ene reaction of in situ generated arynes with olefins.



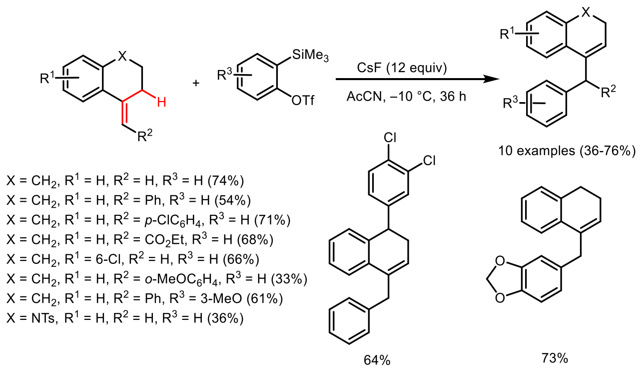
Scheme 50. C2-arylation of Hantzsch esters by aryne-ene reaction.



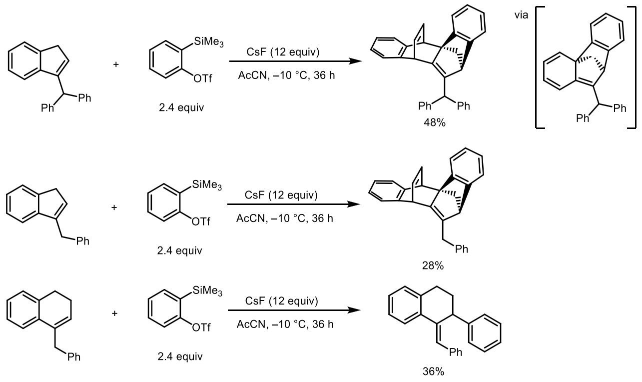
Scheme 51. C3-arylation of Hantzsch esters by aryne-ene reaction.



Scheme 52. Aryne Alder ene reaction with conformationally locked styrenes to give aryl-decorated indenes.



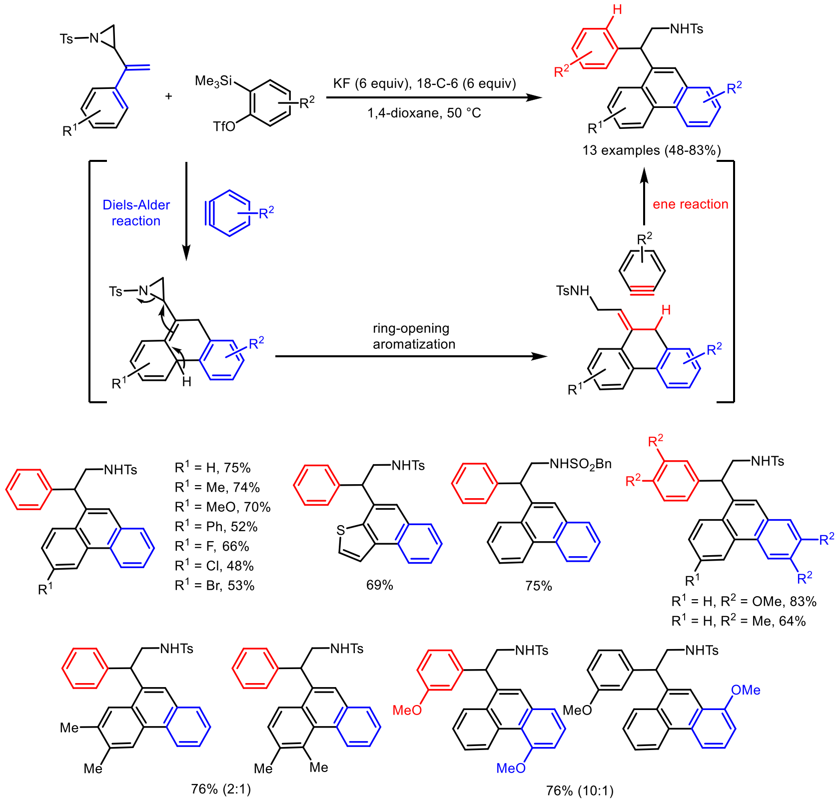
Scheme 53. Aryne Alder ene reaction with conformationally locked styrenes to give aryl-decorated dihydronaphthalenes.



Scheme 54. Aryne Alder ene versus multiple Diels-Alder reaction with benzyl or benzhydryl substituted indene and dihydronaphthalene.

sulfamides (**Scheme 56**). A similar reactivity and, therefore, access to functionalized phenanthrenes was reported by the same authors for vinyl epoxide and vinyl cyclopropane substrates.[83]

Chenoweth and coauthors provided an experimental and computational (DFT) investigation of the reaction of a 1,2,4,5-tetrazine and an excess of aryne, two highly energetic molecules, in the sense of a pseudo-multicomponent process.[84] The study was accompanied by a detailed analysis of the products and the computational assignment of their formation as a consequence of pericyclic and polar elementary steps, including rearrangements (**Scheme 57**).



Scheme 55. Aryne–Diels–Alder-ring-opening-ene sequence in 1,4-dioxane for the synthesis of NH-2-(phenanthren-9-yl)ethan-1-sulfamides.

He, Dai, and coworkers showed that aza-Morita–Baylis–Hillman adducts readily react with in situ generated benzyne to give a separable mixture of *N*-arylation products by aryne insertion and of 4-quinolones upon insertion-cyclization-ene arylation (**Scheme 58**).[85]

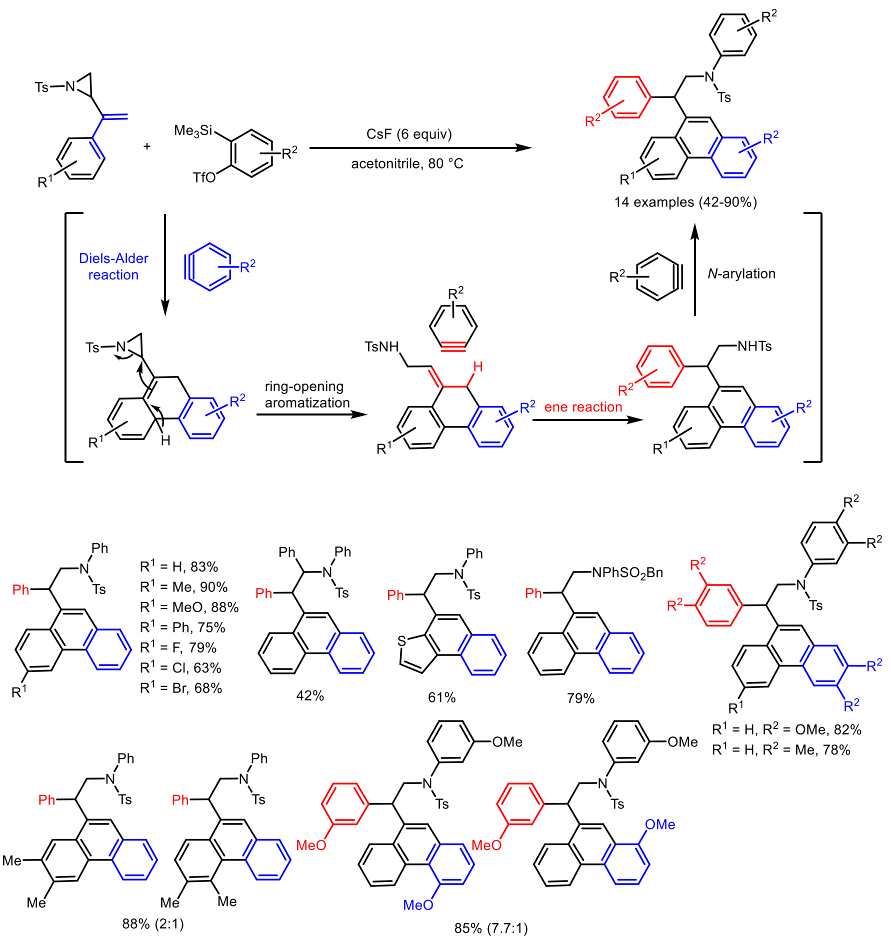
Azaheptafulvenes were shown to readily take part in a domino sequence of [8 + 2] cycloaddition with in situ generated arynes followed by an ene-arylation with a second equivalent of aryne (**Scheme 59**).[86] Further excess of aryne even led to an additional cycloaddition with the cycloheptatriene moiety in the sense of a [8 + 2] cycloaddition-aryl-ene-[6 + 2] domino reaction (**Scheme 60**). In addition, heteroazulenes were (**Scheme 61**) also successfully employed in the [8 + 2] cycloaddition-ene-arylation to give polycyclic anellated indole scaffolds (**Scheme 62**).

Lan and Li showed that stannum-ene reactions of benzyne and cyclohexyne, enophiles with significant ring strain, proceed smoothly with particularly a broad scope and excellent chemoselectivity for the in situ generated cyclohexyne (Scheme 62 and **63**).[87] DFT calculations revealed furthermore that cyclohexyne in both stannum- and hydrogen-ene reactions proceed through late transition states caused by higher distortion energies in comparison to based benzyne reactions. The enlarged energy gap of the former favors the excellent chemoselectivity in the cyclohexyne-ene reaction.

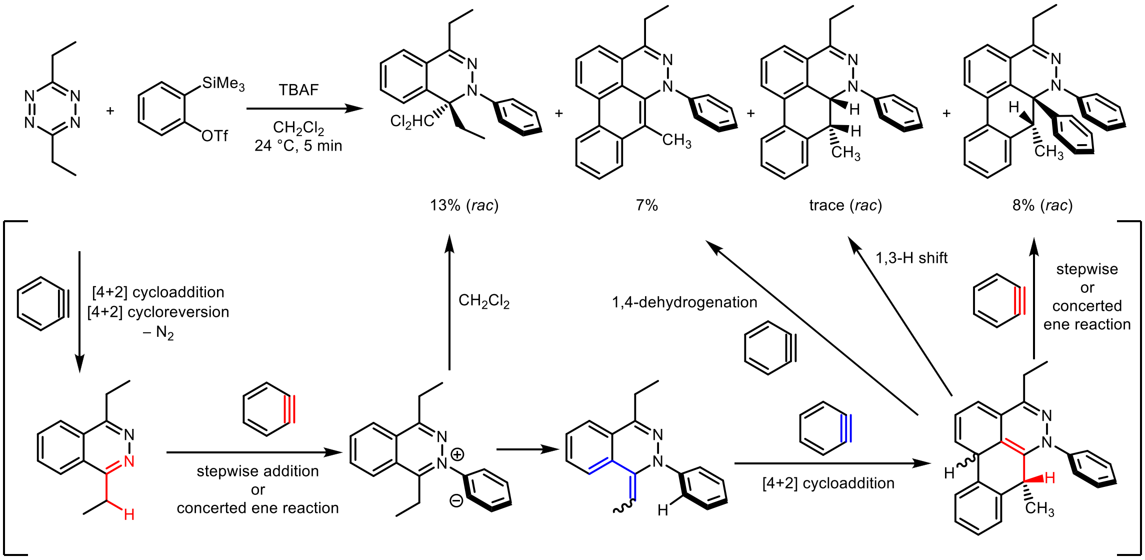
Arynes via Hexadehydro-Diels-Alder (HDDA) Reaction: Hoye and coauthors have explored a strategy to benzynes through a hexadehydro-Diels–Alder reaction (HDDA) of a 1,3-diyne with an alkyne as suitable a diynophile to generate the highly reactive benzyne intermediate, which can be efficiently trapped by aryne-typical cycloaddition.[88] This motif was then further developed to ene reactions (for intramolecular versions, see 2.3.2).

Arynes in situ generated from bis-1,3-diynes by HDDA can be reacted with a variety of functionalized trisubstituted and 1,1-disubstituted alkenes with varying selectivity (**Scheme 64–66**).[89] The alkene geometry of di- and trisubstituted alkenes is crucial for the reactivity and alkenes with *cis*-positioned allylic hydrogen atoms are reactive, in contrast to the reactivity in the intramolecular version.

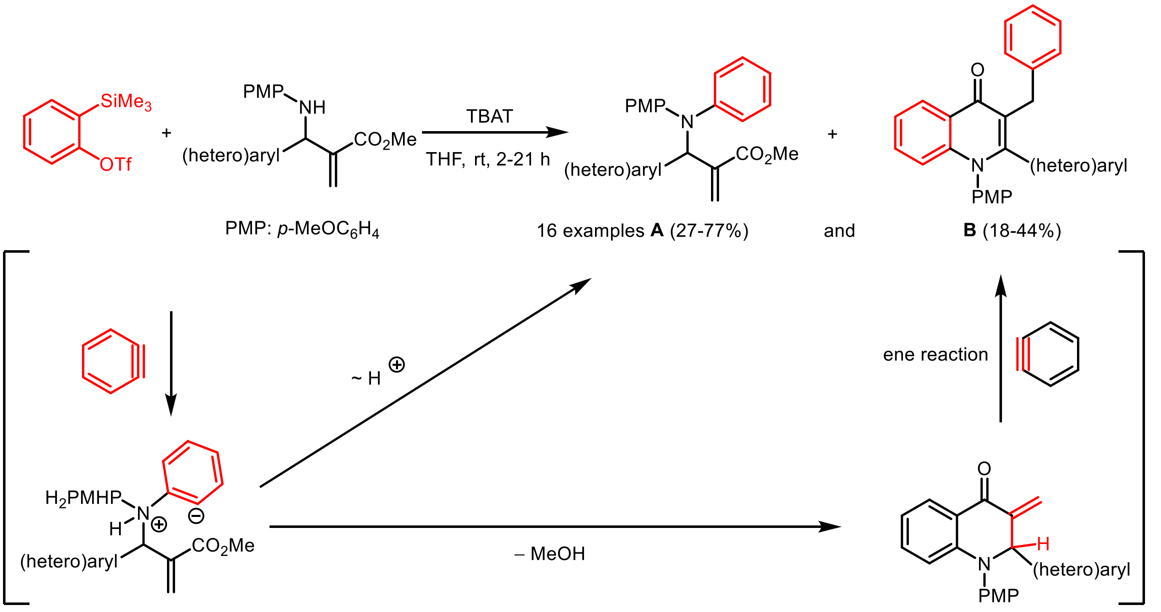
Lee and coauthors unraveled that aryne intermediates formed by HDDA dichotomize in intermolecular reactions depending on the functionalization of the ene substrate either toward Alder ene or (cyclo)addition reactions.[90] While various trisubstituted and 1,1-disubstituted alkenes, such as methallyl amine, prenyl azide, and methacrylic acid, preferentially give addition products of the polar heteroatom functionalities, the formation of Alder ene products formed from the alkene segment (**Scheme 67**). The selectivity, however, depends on the substituent pattern of the alkene. In particular, α,β-unsaturated aldehydes lead to the formation of 2-chromene derivatives



Scheme 56. Aryne–Diels–Alder-ring-opening-ene-*N*-arylation sequence in acetonitrile for the synthesis of *N*-aryl-2-(phenanthren-9-yl) ethan-1-sulfamides.



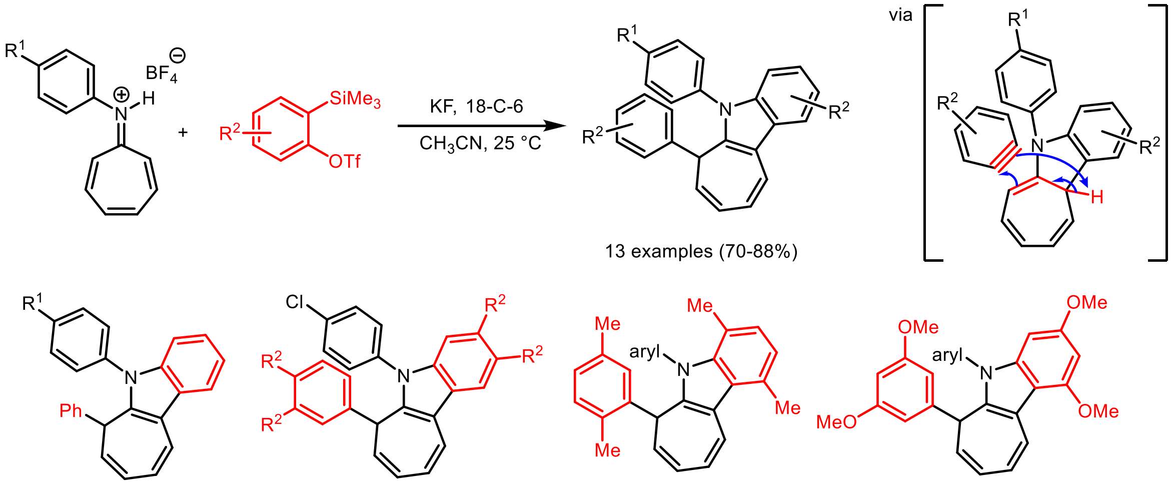
Scheme 57. Ene reaction-initiated sequence of [4 + 2] cycloaddition-ene and rearrangement processes.



TBAT: tetrabutylammonium difluorotriphenylsilicate

(hetero)aryl = *o*-MeOC$_6$H$_4$ (**A** 55%; **B** 44%)
(hetero)aryl = *m*-MeOC$_6$H$_4$ (**A** 54%; **B** 23%)
(hetero)aryl = *o*-MeC$_6$H$_4$ (**A** 77%; **B** 18%)
(hetero)aryl = *m*-ClC$_6$H$_4$ (**A** 57%; **B** 39%)
(hetero)aryl = *m*-BrC$_6$H$_4$ (**A** 58%; **B** 28%)
(hetero)aryl = 2-naphthyl (**A** 56%; **B** 32%)
(hetero)aryl = 1-naphthyl (**A** 27%; **B** 26%)
(hetero)aryl = 2-thienyl (**A** 48%; **B** 22%)
(hetero)aryl = Ph (**A** 60%; **B** 36%)
(hetero)aryl = *p*-ClC$_6$H$_4$ (**A** 56%; **B** 36%)
(hetero)aryl = *p*-FC$_6$H$_4$ (**A** 50%; **B** 35%)
(hetero)aryl = *p*-BrC$_6$H$_4$ (**A** 51%; **B** 42%)
(hetero)aryl = *p*-MeO$_2$CC$_6$H$_4$ (**A** 58%; **B** 32%)
(hetero)aryl = *p*-MeC$_6$H$_4$ (**A** 30%; **B** 43%)
(hetero)aryl = *p*-^{i}PrC$_6$H$_4$ (**A** 66%; **B** 21%)
(hetero)aryl = *p*-MeOC$_6$H$_4$ (**A** 67%; **B** 30%)

Scheme 58. 4-Quinolones by insertion-cyclization-ene arylation of aza-Morita–Baylis–Hillman adducts with benzyne.



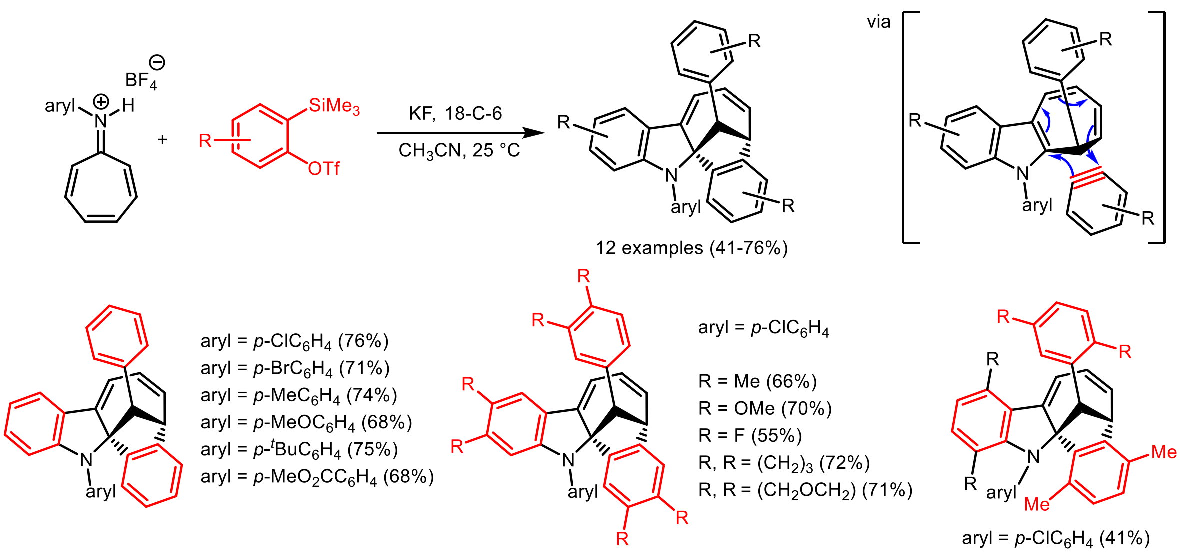
R^1 = Cl (88%)
R^1 = Br (88%)
R^1 = Me (84%)
R^1 = OMe (81%)
R^1 = *t*Bu (83%)
R^1 = CO$_2$Me (72%)

R^2 = Me (80%)
R^2 = OMe (78%)
R^2 = F (70%)
R^2, R^2 = (CH$_2$)$_3$ (82%)
R^2, R^2 = (CH$_2$OCH$_2$) (74%)

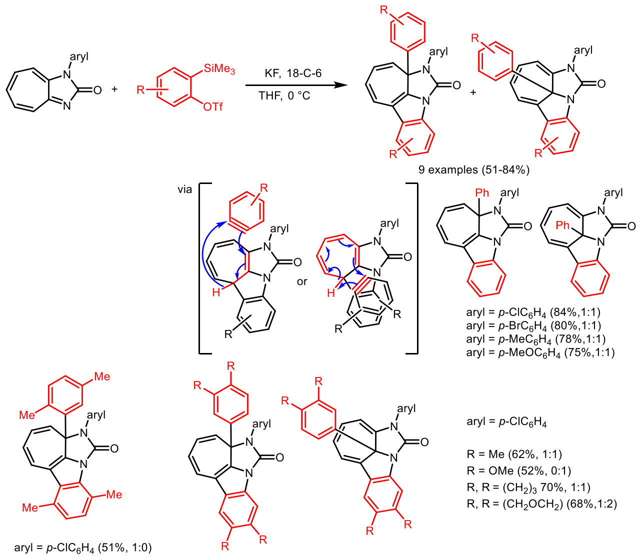
Scheme 59. [8 + 2] cycloaddition-aryl ene sequence with azaheptafulvenes and arynes as enophile components.

via an HDDA-intermolecular [2 + 2]-cycloaddition-[4π]-electrocyclic ring-opening-[6π]-electrocyclization sequence (**Scheme 68**).

1-Ferrocenyl substituted cyclohexene/pentene as ene substrates were shown to successfully undergo the HDDA-ene sequence with symmetrical bisdiynes to



Scheme 60. [8 + 2] cycloaddition-aryl ene-[6 + 2] cycloaddition sequences with azaheptafulvenes and arynes as enophile components.



Scheme 61. [8 + 2] cycloaddition-aryl ene sequences with heteroazulenes and arynes as enophile components.

furnish the ene-coupled products with highly regioselectivity and excellent yield (**Scheme 69**).[91] DFT calculations revealed that the positioning of the ferrocenyl substituent causes a lowering of the transition state activation enthalpy in comparison to cyclohexene.

Benzynes can be trapped with phenols as ene components and thereby allow for formation of aryl phenol. Hoye and coauthors showed that tethered bisdiynes can be efficiently transformed to aryne intermediates via HDDA reaction, which are trapped by phenols in a subsequent ene reaction to give unsymmetrical phenolic biaryls bearing the hydroxy group in *ortho*-position via the intermediacy of a cyclohexadienone that tautomerizes to the product (**Scheme 70**).[92] The concept was expanded to other tetherings of yne–diyne structures furnishing similar products from HDDA-phenol ene reaction (**Scheme 71**).

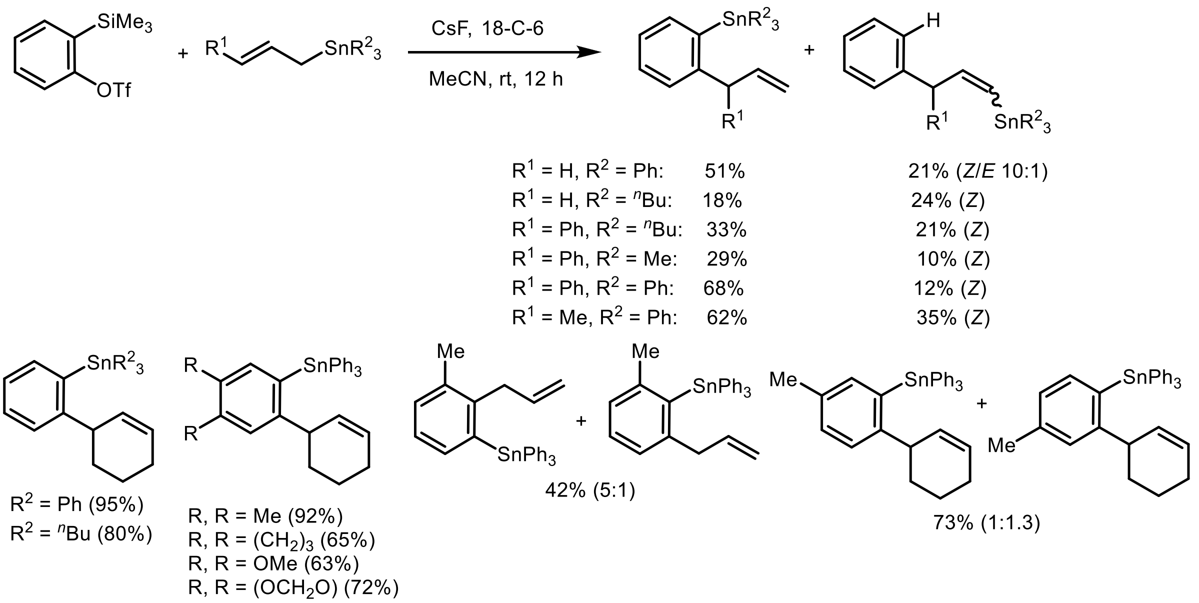
Statins have been shown in numerous studies to be quite cytotoxic, which represents a potential for developing new drugs with their conjugates. Hu and coauthors have very recently employed the HDDA for generating highly reactive bicyclic arynes that react with statins or ethyl abietate in a concluding intermolecular Alder ene reaction (**Scheme 72**).[93] Noteworthy, starting from lovastatin, mevastatin, or simvastatin the lactone moiety, which is the biological active group of statins, was cleaved during the course of the sequence, which proceeds with good yields (**Scheme 73**). Biological assays showed that these novel statin-derived scaffolds are moderately active against the proliferation of cancer cells with IC_{50} values in the micromolar range.

2.3.2. Intramolecular Ene Reactions with Arynes as Enophiles

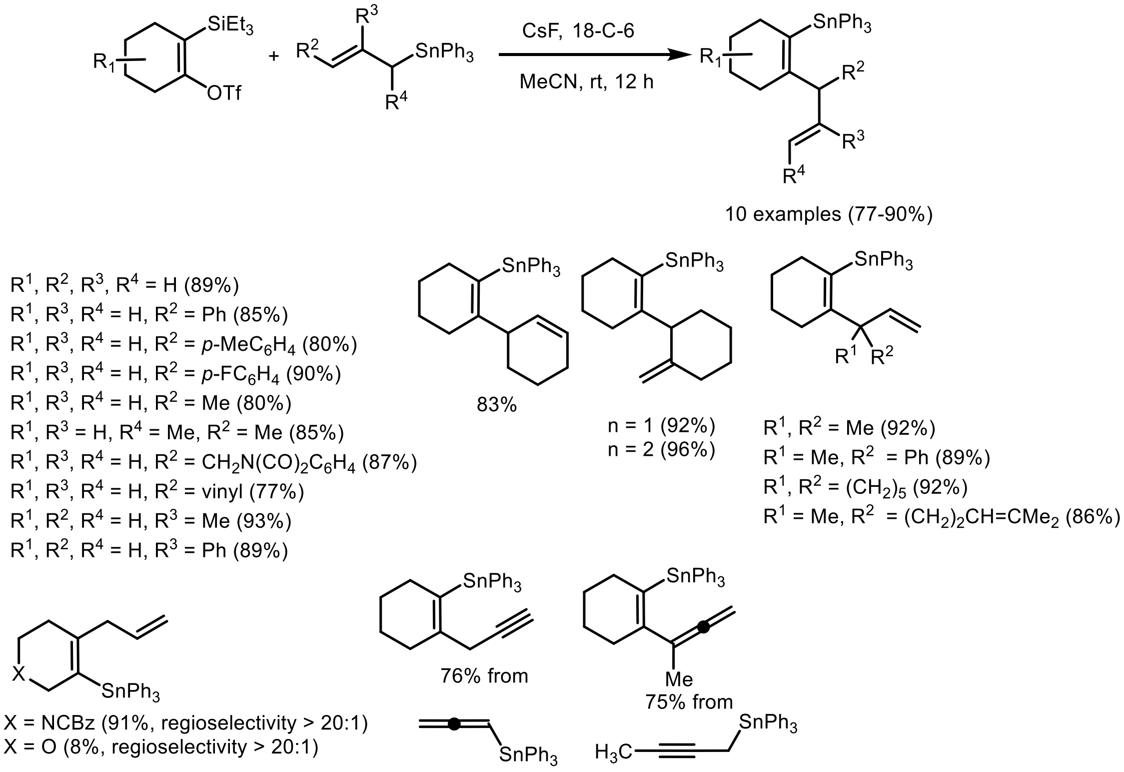
The arynes prove particularly advantageous in the synthesis of complex polycyclic arene fused natural products as reviewed by Tadross and Stoltz.[94] Therefore, arynes with a tethered ene functionality proved best for establishing aryne ene reactions.

The intramolecular aryne-ene reaction is a general and high yielding anellation and experimental and computational studies by Lautens and coauthors showed that electronic nature of the aryne intermediate and olefin geometry are decisive to the success of the transformation (**Scheme 74**).[95]

The methodology is quite broad in scope and precedes largely in high yield and with high levels of



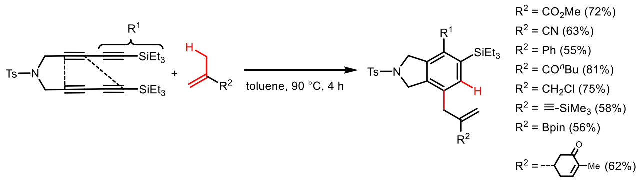
Scheme 62. Benzyne stannum-ene reaction.



Scheme 63. Cyclohexyne stannum-ene reaction.

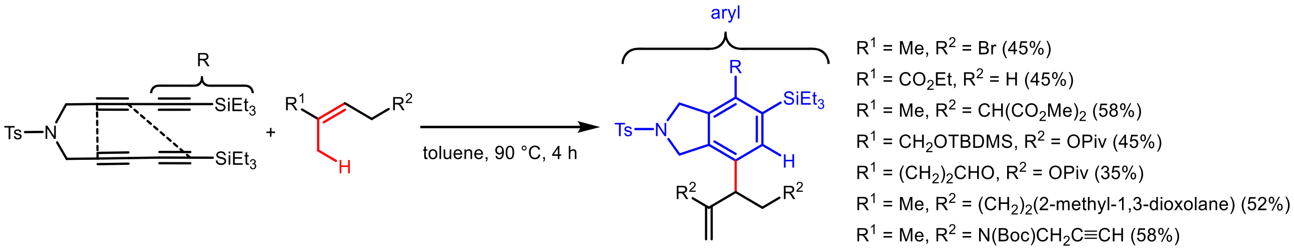
diastereoselectivity for adjacent centers of the anellation position (**Scheme 75** and **76**). For illustrative application, the intramolecular aryne–ene reaction was successfully used in the formal synthesis of the ethanophenanthridine alkaloid (±)-crinine (**Scheme 77**).

Li and coauthors reported a domino aryne anellation reaction taking advantage of a nucleophile addition-ene sequence, where a 1,2-benzdiyne equivalent is generated en route starting from *ortho*-triflato,*ortho′*-tosylato trimethylsilylbenzenes as an entry to benzo-fused

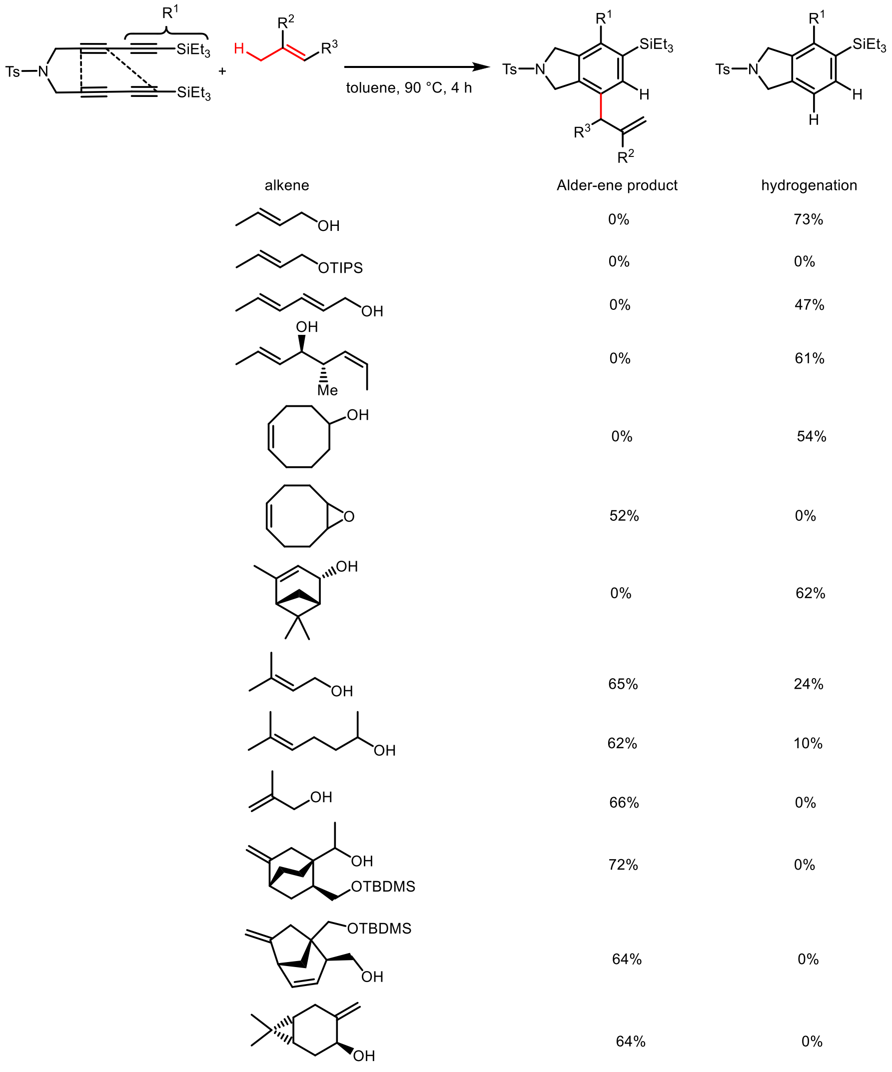


Scheme 64. HDDA-ene sequence of symmetrical bisdiynes with 2-substituted propenes as ene substrates (in red).

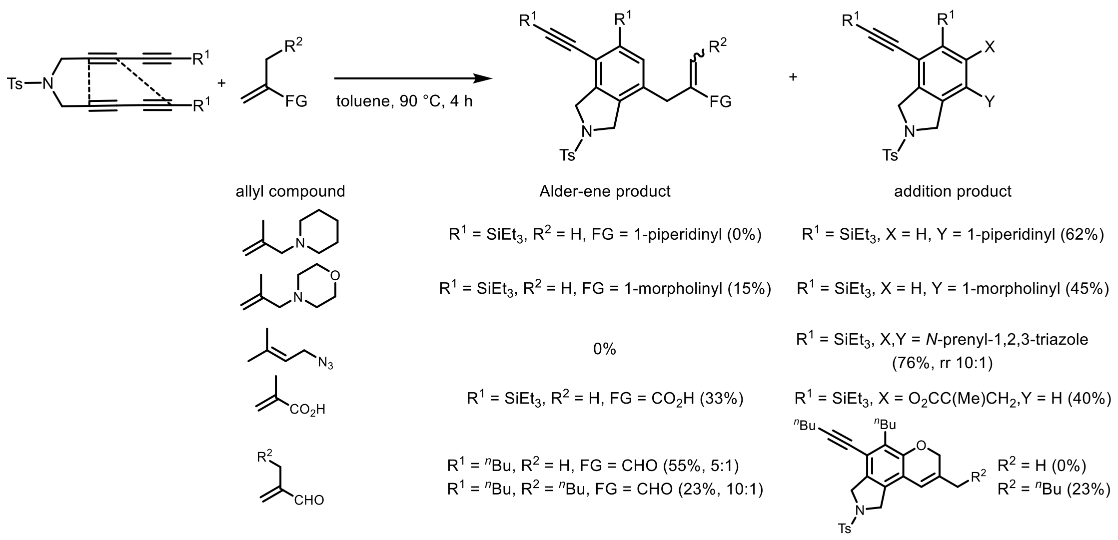
N-heterocyclic scaffolds (**Scheme 78**).[96] The scope of this domino process is fairly broad allowing for anellation of different ring-sizes and even polycyclic scaffolds (**Scheme 79**) as well as variation on the benzo core (**Scheme 80**). In addition, this methodology has been successfully employed in the concise synthesis of an orphan drug for growth hormone deficiency, i.e., ibutamoren mesylate (**Scheme 81**).



Scheme 65. HDDA-ene sequence of symmetrical bisdiynes with 2-substituted propenes as ene substrates (in red).

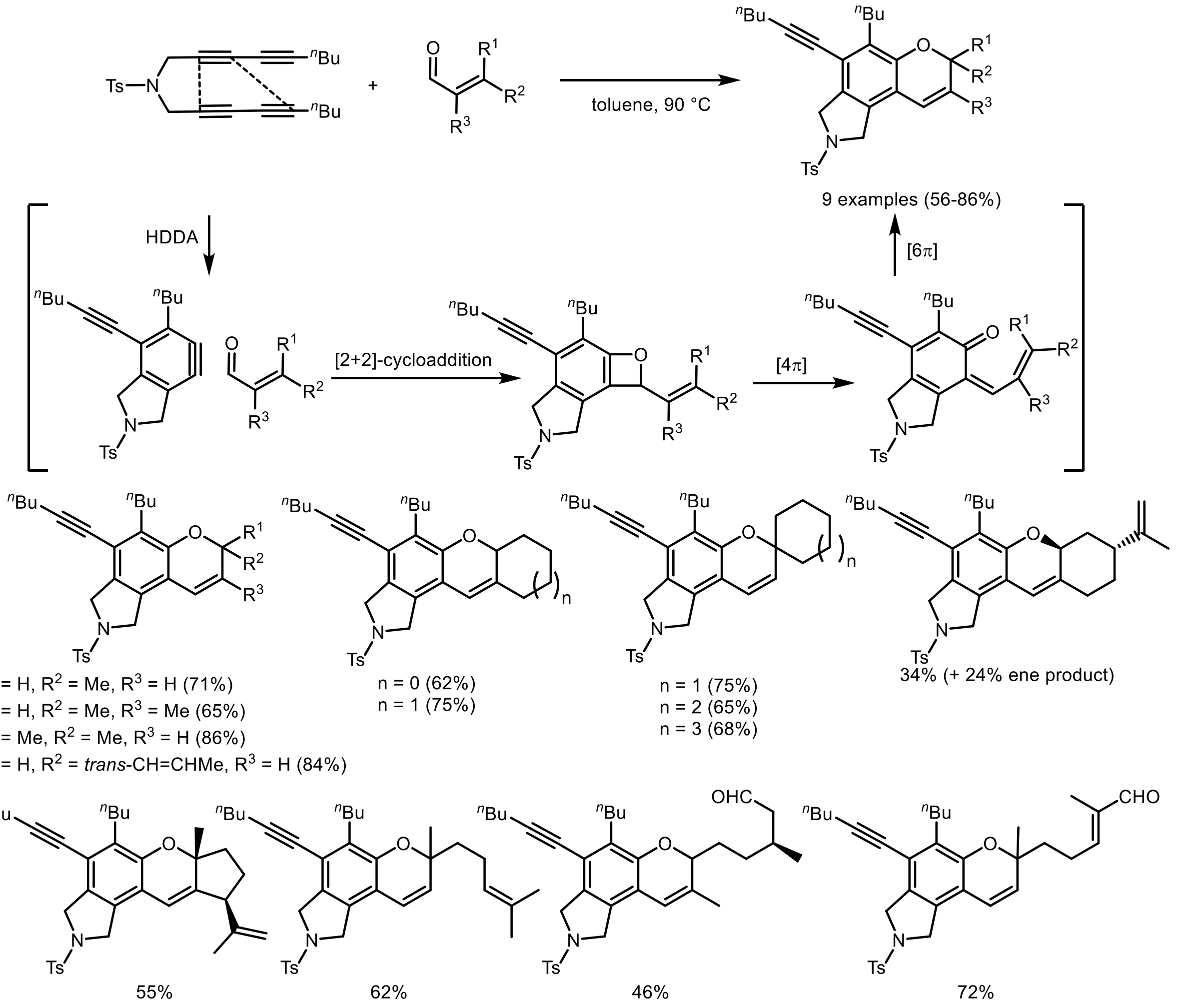


Scheme 66. HDDA-ene versus HDDA-hydrogenation of symmetrical bisdiynes with ene substrates bearing alcohol and/or ether functionality.

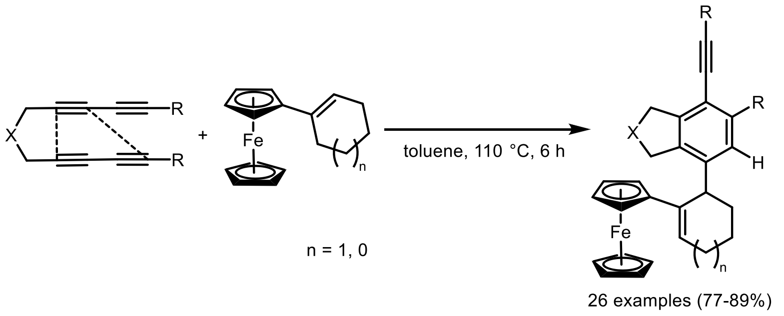


allyl compound	Alder-ene product	addition product
	R^1 = $SiEt_3$, R^2 = H, FG = 1-piperidinyl (0%)	R^1 = $SiEt_3$, X = H, Y = 1-piperidinyl (62%)
	R^1 = $SiEt_3$, R^2 = H, FG = 1-morpholinyl (15%)	R^1 = $SiEt_3$, X = H, Y = 1-morpholinyl (45%)
	0%	R^1 = $SiEt_3$, X,Y = *N*-prenyl-1,2,3-triazole (76%, rr 10:1)
	R^1 = $SiEt_3$, R^2 = H, FG = CO_2H (33%)	R^1 = $SiEt_3$, X = $O_2CC(Me)CH_2$,Y = H (40%)
	R^1 = ^{n}Bu, R^2 = H, FG = CHO (55%, 5:1) R^1 = ^{n}Bu, R^2 = ^{n}Bu, FG = CHO (23%, 10:1)	R^2 = H (0%) R^2 = ^{n}Bu (23%)

Scheme 67. Dichotomy of the reactivity of ene substrates after the initial generation of the aryne intermediate by HDDA of symmetrical bisdiynes furnishing ene and (cyclo)addition products.

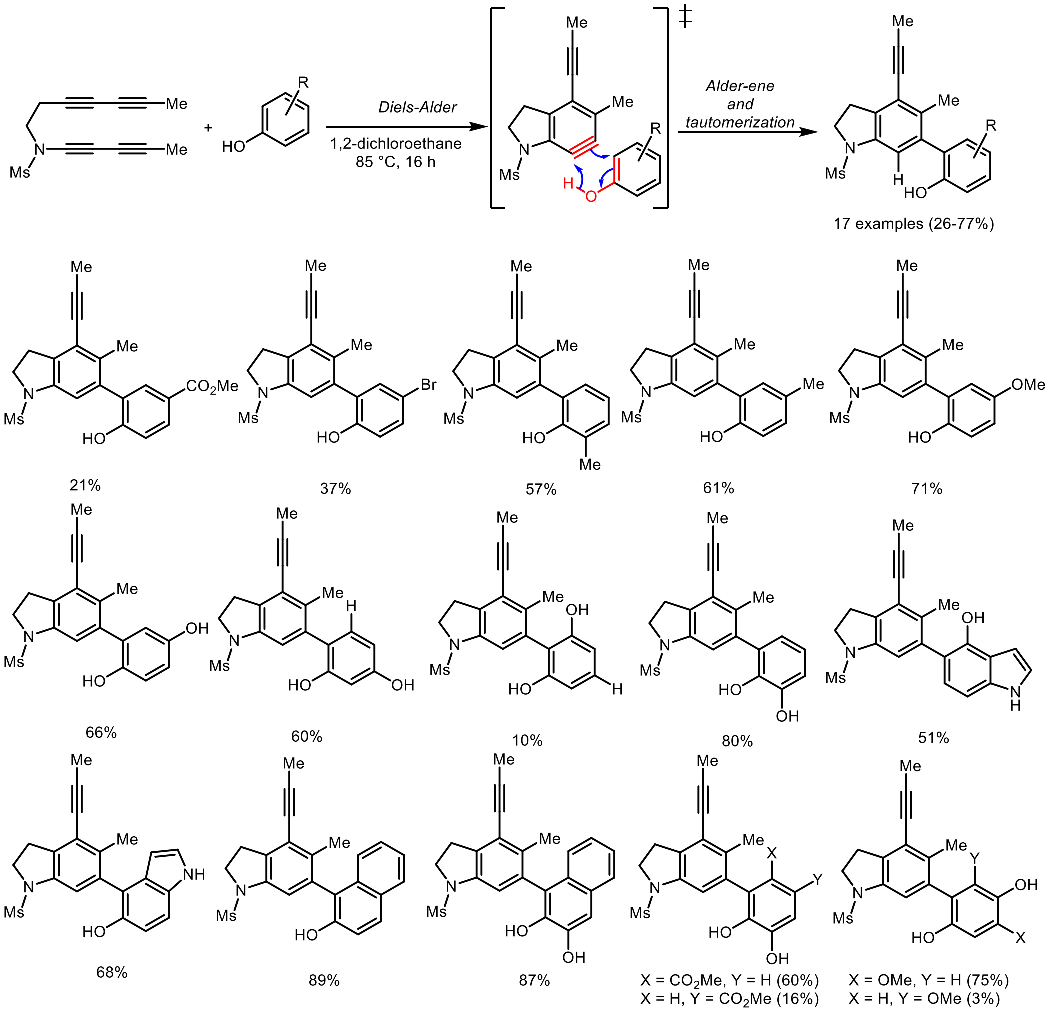


Scheme 68. Mechanistic rationale of the formation of 2-chromene derivatives from α,β-unsaturated aldehydes by HDDA-intermolecular [2 + 2]-cycloaddition-[4π]-electrocyclic ring-opening-[6π]-electrocyclization sequence.

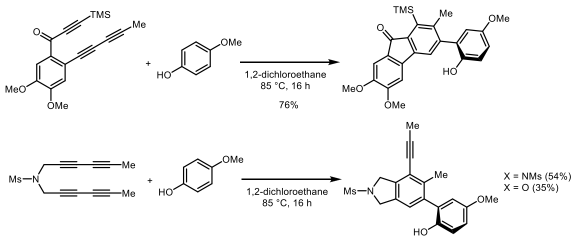


R = Ph, X = $C(CO_2Me)_2$, n = 1 (83%)
R = Ph, X = $C(CO_2Et)_2$, n = 1 (85%)
R = Ph, X = $C(CO_2{}^iPr)_2$, n = 1 (81%)
R = *m*-tolyl, X = $C(CO_2Me)_2$, n = 1 (80%)
R = *p*-ClC_6H_4, X = $C(CO_2Me)_2$, n = 1 (85%)
R = *m*-ClC_6H_4, X = $C(CO_2Me)_2$, n = 1 (89%)
R = *p*-FC_6H_4, X = $C(CO_2Me)_2$, n = 1 (83%)
R = *p*-EtC_6H_4, X = $C(CO_2Me)_2$, n = 1 (80%)
R = *p*-anisyl, X = $C(CO_2Me)_2$, n = 1 (82%)
R = *m*-FC_6H_4, X = $C(CO_2Et)_2$, n = 1 (87%)
R = *p*-tolyl, X = $C(CO_2Et)_2$, n = 1 (81%)
R = *p*-EtC_6H_4, X = $C(CO_2Et)_2$, n = 1 (79%)
R = *p*-FC_6H_4, X = $C(CO_2Et)_2$, n = 1 (84%)
R = *p*-ClC_6H_4, X = $C(CO_2Et)_2$, n = 1 (83%)
R = *m*-ClC_6H_4, X = $C(CO_2Et)_2$, n = 1 (85%)
R = *p*-EtC_6H_4, X = $C(CO_2{}^iPr)_2$, n = 1 (80%)
R = *p*-ClC_6H_4, X = $C(CO_2{}^iPr)_2$, n = 1 (83%)
R = *m*-ClC_6H_4, X = $C(CO_2{}^iPr)_2$, n = 1 (86%)
R = *m*-tolyl, X = $C(CO_2{}^iPr)_2$, n = 1 (82%)
R = ^{n}Bu, X = NTos, n = 1 (79%)
R = ^{n}pentyl, X = NTos, n = 1 (77%)
R = Ph, X = $C(CO_2Me)_2$, n = 0 (82%)
R = Ph, X = $C(CO_2Et)_2$, n = 0 (83%)
R = Ph, X = $C(CO_2{}^iPr)_2$, n = 0 (82%)
R = *p*-EtC_6H_4, X = $C(CO_2Me)_2$, n = 0 (80%)
R = *p*-ClC_6H_4, X = $C(CO_2{}^iPr)_2$, n = 0 (85%)

Scheme 69. HDDA-ene sequence of symmetrical bisdiynes with 1-ferrocenyl substituted cyclohexene/pentene as ene substrates.

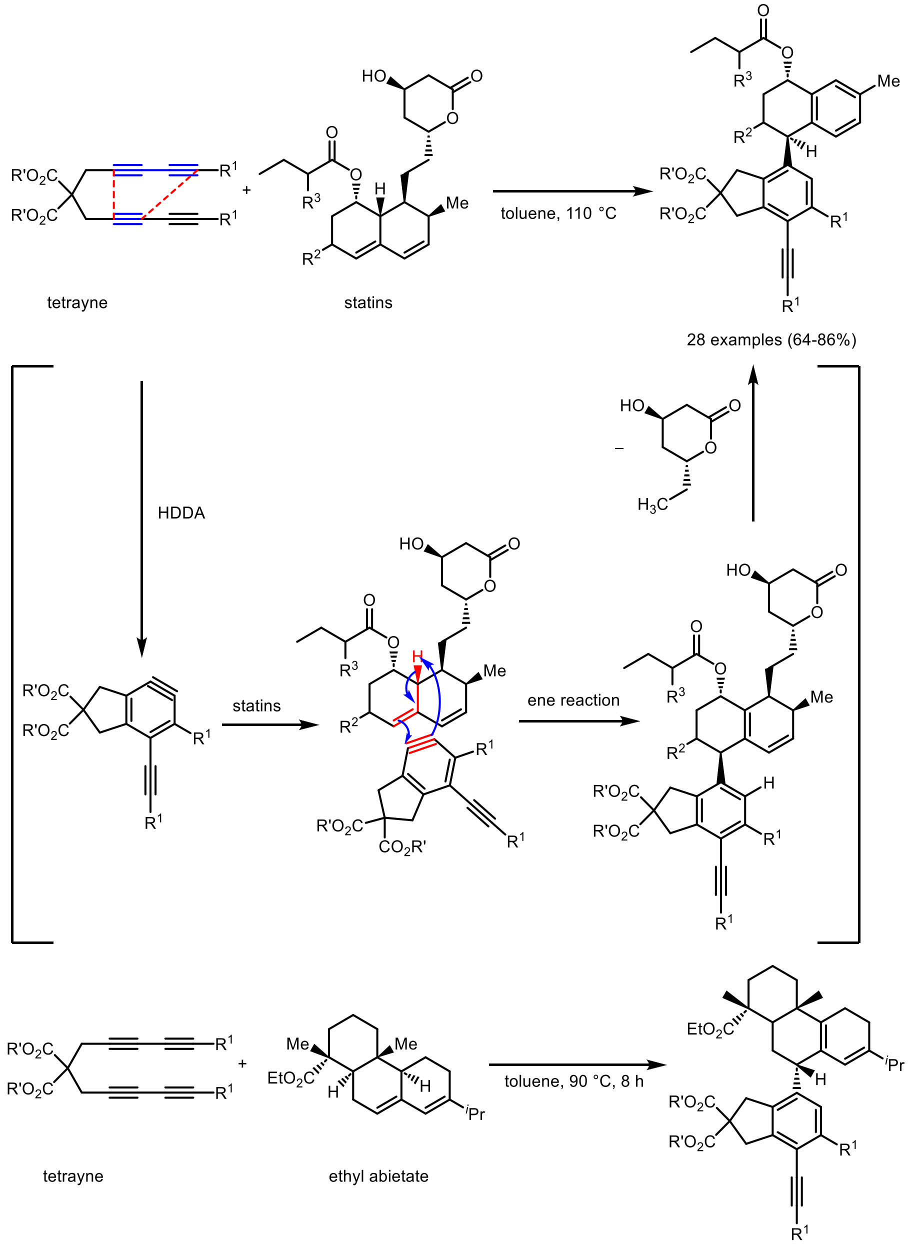


Scheme 70. *ortho*-Hydroxy biaryls via hexadehydro-Diels–Alder (HDDA) benzyne formation and in situ trapping with monosubstituted phenols, catechol, resorcinol, and hydroquinone, hydroxyindoles, naphthols, and catechol derivatives.



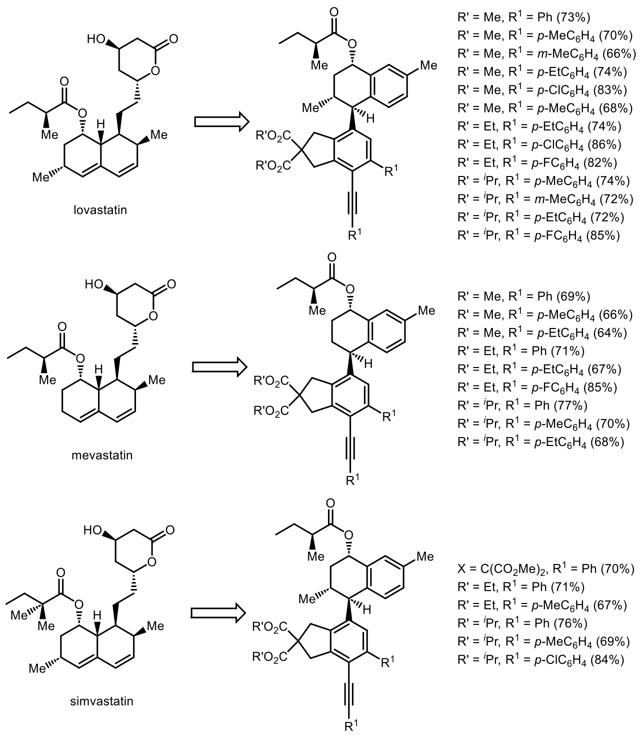
Scheme 71. Further types of diyne-yne tethering and their transformation by HDDA-phenol ene reaction.

Tethered yne–diynes thermally form bicyclic benzynes by HDDA, which react in situ as enophiles with the tethered *meta*-tolyl moiety as the ene component in the sense of an aromatic ene reaction (**Scheme 82**).[97] The concept was further elaborated by addressing the reactive methylene cyclohexadiene intermediate with reactive carbon and heteroatom enophiles to create cascades of HDDA-intramolecular–intermolecular ene sequences (**Scheme 83**).

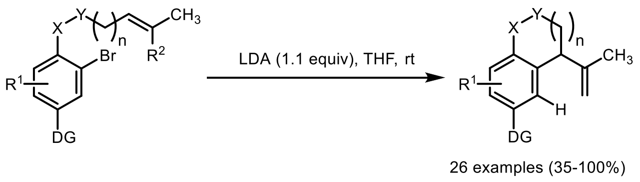


R' = Me, R^1 = *m*-MeC_6H_4 (79%)
R' = Et, R^1 = *p*-EtC_6H_4 (79%)
R' = ^{i}Pr, R^1 = *p*-EtC_6H_4 (77%)

Scheme 72. HDDA-ene synthesis of lignan skeletons.



Scheme 73. Antiproliferative modified lignan skeletons derived from aryne intermediates and statins.



Scheme 75. Model reaction for elucidating the electronic nature of the aryne in aryne-tethered allyl Alder ene cycloisomerization.

Benzocyclobutenes formed by HDDA–Alder ene sequences from tethered triynes with ligated prenyl moiety as ene fragment experience a particularly high thermodynamic barrier that can be overcome by strain relief of the of aryne intermediate caused by a gearing effect of an *ortho*-substituent on the ene moiety. This induced steric pressure can even be enhanced by hydrogen bonding to the carbonyl group in the tether (**Scheme 84**).[98] Lee and coworkers have exemplified HDDA–Alder ene sequences to give benzocyclobutenes by probing the gearing effect of various *ortho*-substituents (**Scheme 85**), variation of the ene moiety (**Scheme 86**) and the triyne tether (**Scheme 87**). Competition between intra- and intermolecular Alder ene reaction was probed by addition of β-pinene, which only led to its incorporation if the reaction was conducted neat (**Scheme 88**). Internal competition of two ene fragments led exclusively to the formation of the ene product arising from diminished strain, i.e., the anellation of a six-membered ring rather than a four-membered ring.

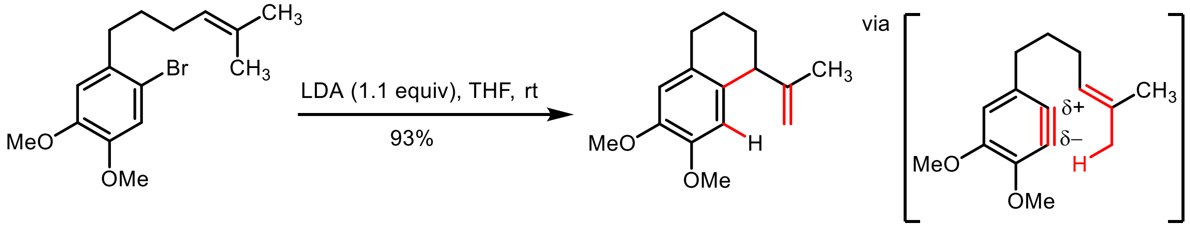
The substitution pattern of allenes as tethered enes in HDDA-sequences determines whether Alder ene products, [2 + 2] cycloadditions or decomposition occurs (**Scheme 89** and **90**).[99] Le and Lee also revealed that benzene-tethered triynes ligated to allenes as ene moieties undergo HDDA-ene sequences (**Scheme 91**).

Lee and coworkers reported silver-catalyzed and thermal sequences of bis-1,3-diynes with tethered enes in the side-chain to proceed via putative formation of aryne intermediates that act as enophiles to concomitantly react in Alder ene cyclization to give polycycles very efficiently (**Scheme 92** and **93**).[100] In case of unsymmetrically substituted bis-1,3-diynes, only the diyne forming the aryne with proximity of the tethered ene functionality productively leads to the concluding Alder ene cyclization, while the unproductive aryne formation might lead to polymerization (**Scheme 94**).

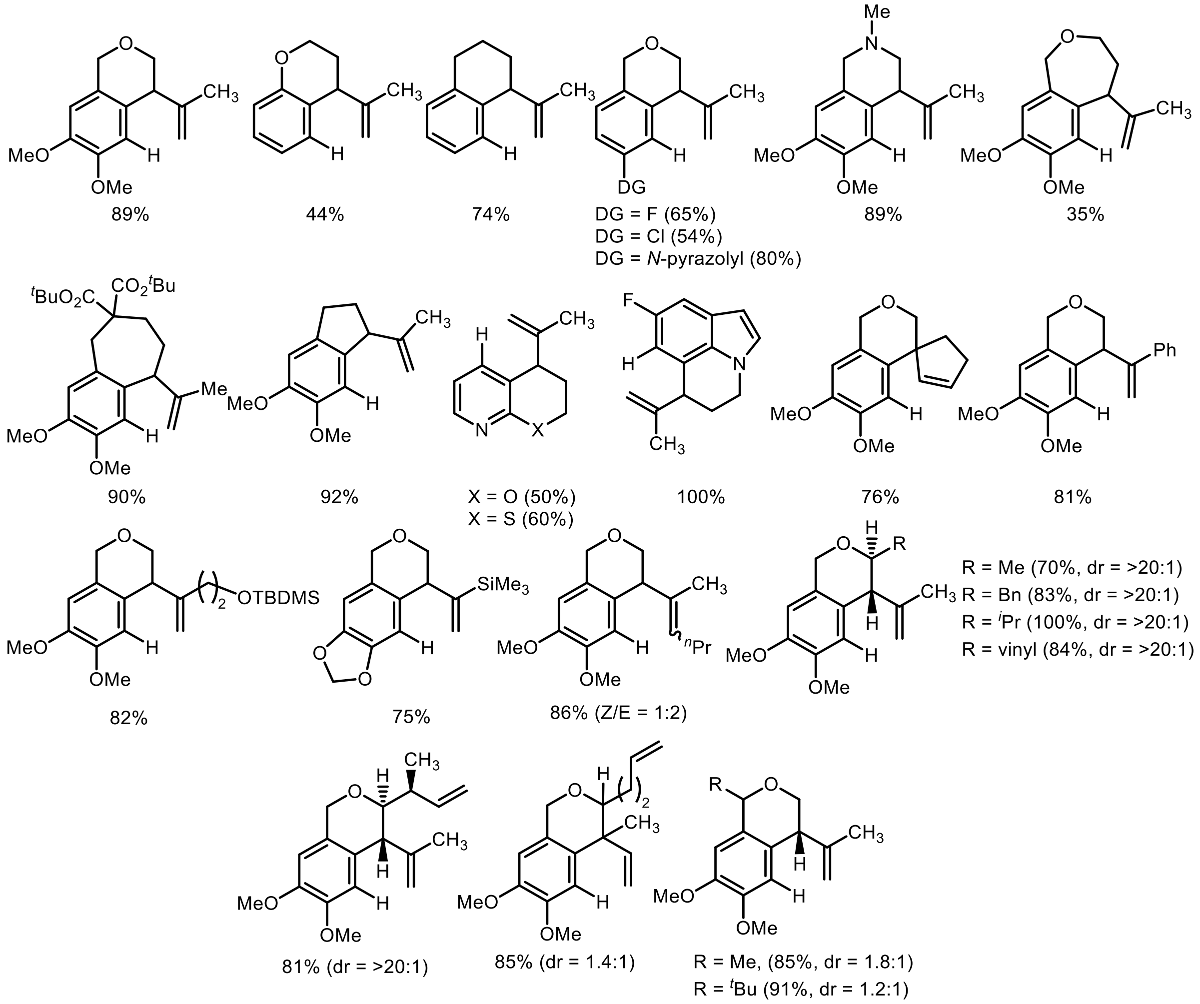
Upon attaching long chain tethers between a tosylamide ligated tetraynes and the terminal ene hetero-macrocycles fused with an indoline or isoindoline moiety became readily available.[101] The employed ene reactions are either type-I and type-II Alder ene cyclization for medium-sized rings (**Scheme 95**) or type-II ene reactions for macrocycles up to 46-membered rings (**Scheme 96**). The tethers themselves might also contain ether, ester, alkene, as well as cyclic tethers placed between the aryne and the ene moieties.

2.4. Allenes as Enophiles

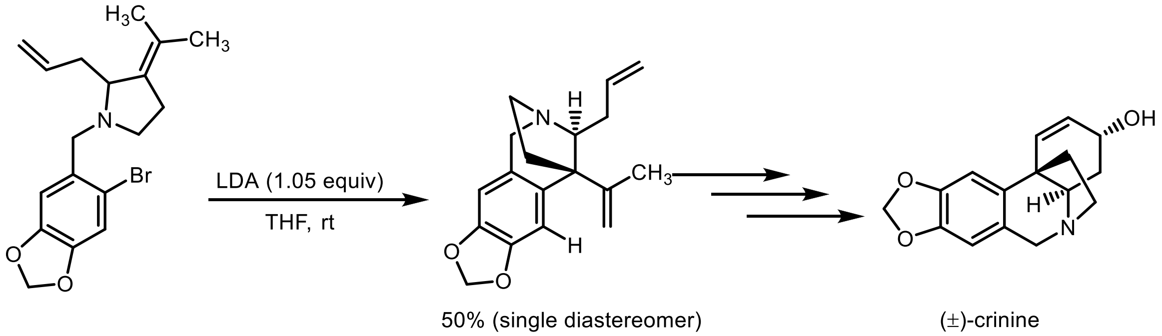
Allenes as enophiles in ene-type cycloisomerization lead to allyl derivatives, where the double bond is embedded in the newly formed ring system (**Scheme 97**). Depending on the nature of the tether



Scheme 74. Model reaction for elucidating the electronic nature of the aryne in aryne-tethered allyl Alder ene cycloisomerization.



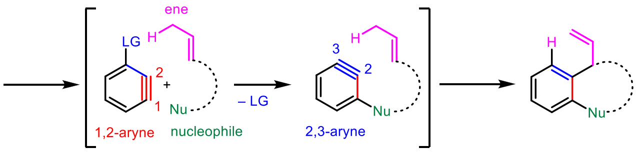
Scheme 76. Scope of the intramolecular aryne–ene reaction.



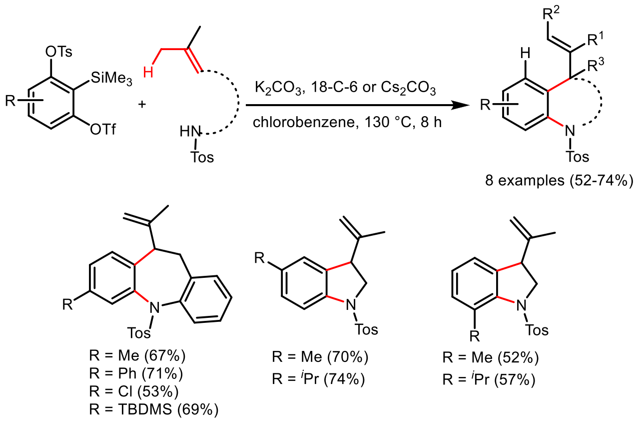
Scheme 77. Aryne–ene cyclization as the key step in the formal synthesis of (±)-crinine.

the barrier for the cyclizing ene reaction becomes quite low. Therefore, allene forming reactions, such as nucleophilic displacement with propargyl-allene rearrangement or cross-coupling reactions with propargyl substrates can become suitable entries to allene enophiles.

Propargylic carbonates bearing a methallyl group in *ortho*-position are substrates for cuprate mediated S_N2'-reaction to give allenes as intermediates. In most cases, Siri, Nechab, and coworkes could show that the allene serves as enophile in the subsequent Alder ene reaction in a domino fashion (**Scheme 98**).[102]



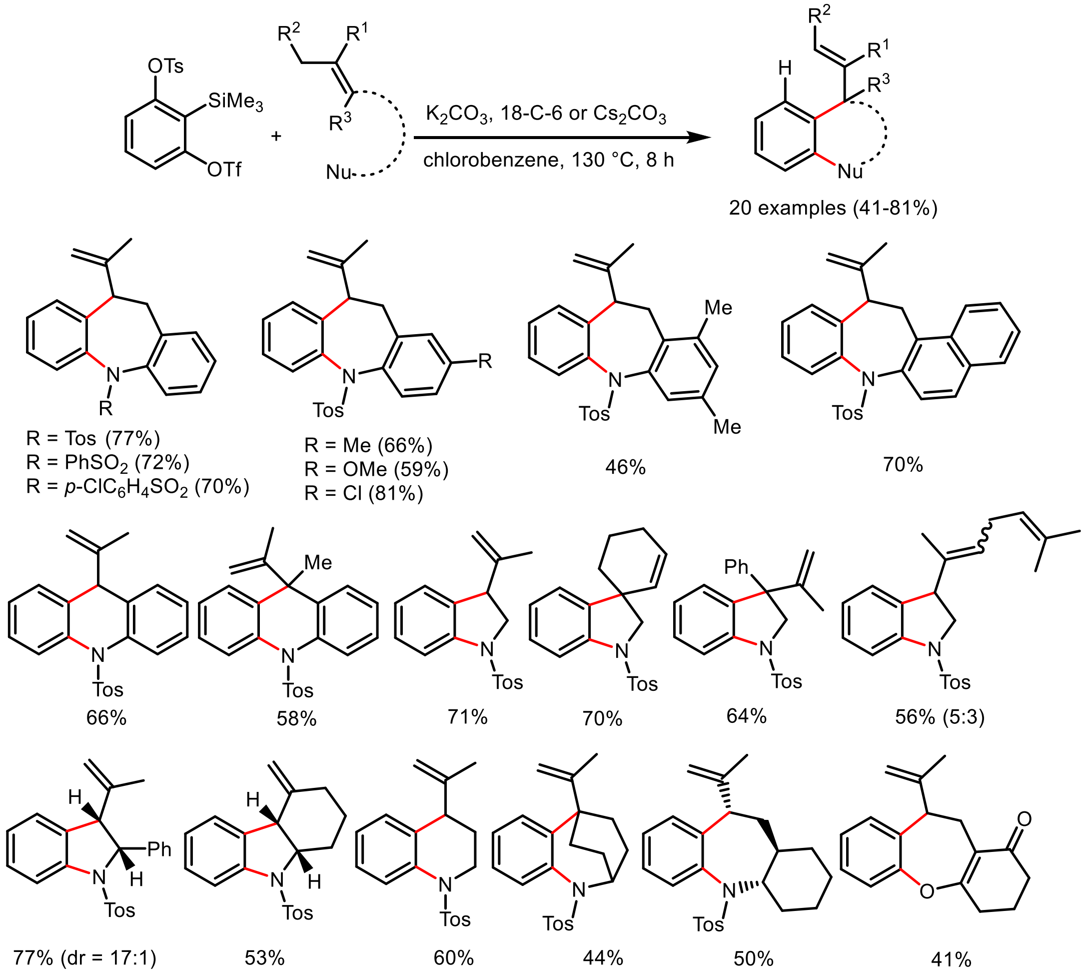
Scheme 78. 1,2-Aryne equivalents and concept of sequential arynophile trapping in domino synthesis of benzo-fused *N*-heterocyclic scaffolds.



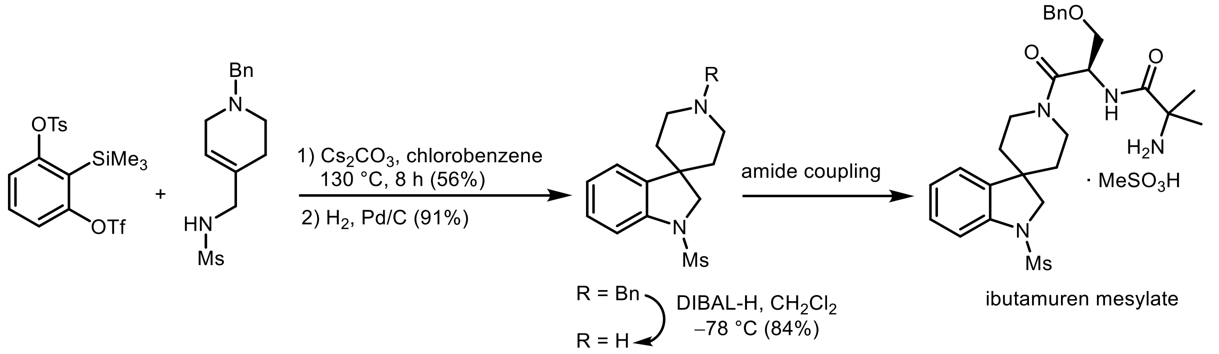
Scheme 80. Variation of 1,2-aryne equivalents in nucleophile addition-ene anellation sequences.

The same group also showed that propargylic carbonates participate in a Suzuki-type arylation with arylboronic acids to generate allenes that in situ undergo Alder ene cycloisomerization (**Scheme 99**).[103] The sequence forms indenes possessing two stereogenic elements, a stereocenter and a chiral axis. The atropisomers are highly configurationally stable and levels of diastereomeric ratios of up to >98:2 were obtained.

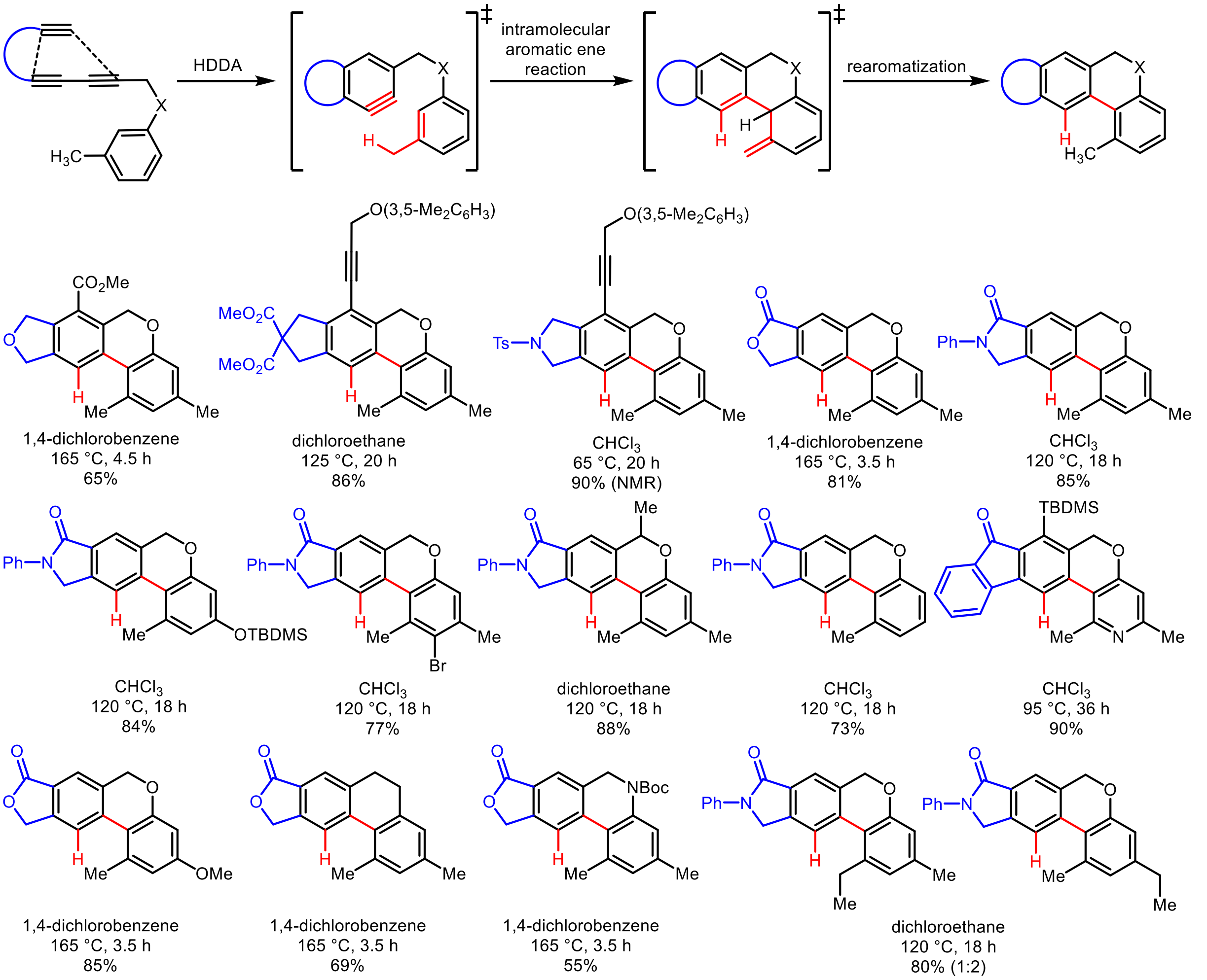
Nechab and coauthors have disclosed an elegant axial-to-center chirality conversion of original axially chiral benzylidene cyclanes into enantioenriched indenes with good to excellent control of diastereo- and enantioselectivity by a domino sequence of copper-catalyzed homologation of terminal alkynes, followed by in situ isomerization to the allenoate and concluding Alder ene cycloisomerization (**Scheme 100**).[104]



Scheme 79. Aromatic and aliphatic *N*-nucleophiles in nucleophile addition-ene anellation sequences of 1,2-aryne equivalents.



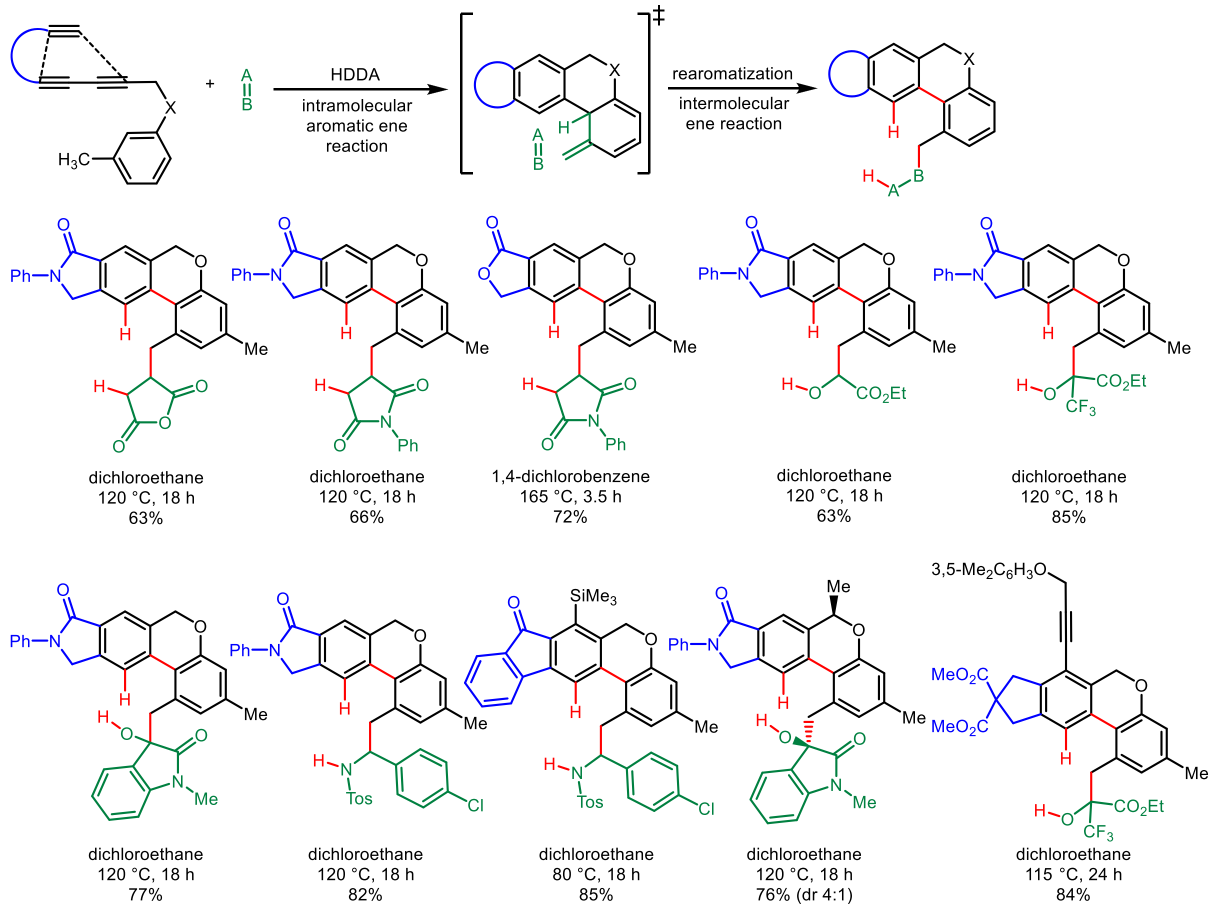
Scheme 81. Application of the nucleophile addition-ene anellation sequence in the synthesis of the orphan drug ibutamoren mesylate for growth hormone deficiency.



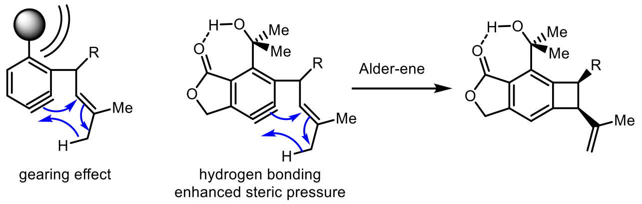
Scheme 82. The concept and examples of hexadehydro-Diels–Alder-intramolecular aromatic ene cascades.

Zhou, Hao, and coauthors chose, in the synthesis of the diterpenoid aberrarone, a cross-coupling-isomerization-IMAE cyclization cascade for efficiently assembling the 6-5-5 tricyclic skeleton of the natural product (**Scheme 101**).[105]

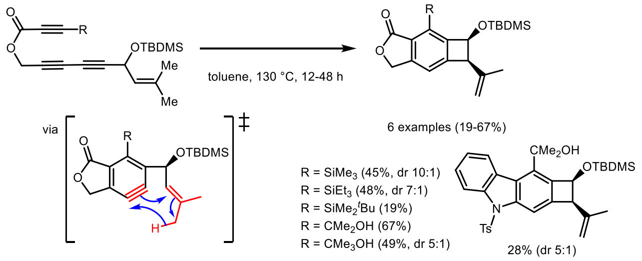
An efficient synthesis of 4-diphenylphosphoryl) methy1-2,3-dihydro-1*H*-pyrroles and furans based upon a amine catalyzed propargyl–allenyl isomerization-Alder ene domino reaction was reported by Lu and coworkers (**Scheme 102**).[106] The obtained



Scheme 83. The concept and examples of hexadehydro-Diels–Alder-intramolecular aromatic ene-intermolecular Alder ene cascades.



Scheme 84. Gearing effect of the *ortho*-substituent and hydrogen bonding induced steric pressure.



Scheme 85. HDDA-Alder ene sequence forming benzocyclobutenes.

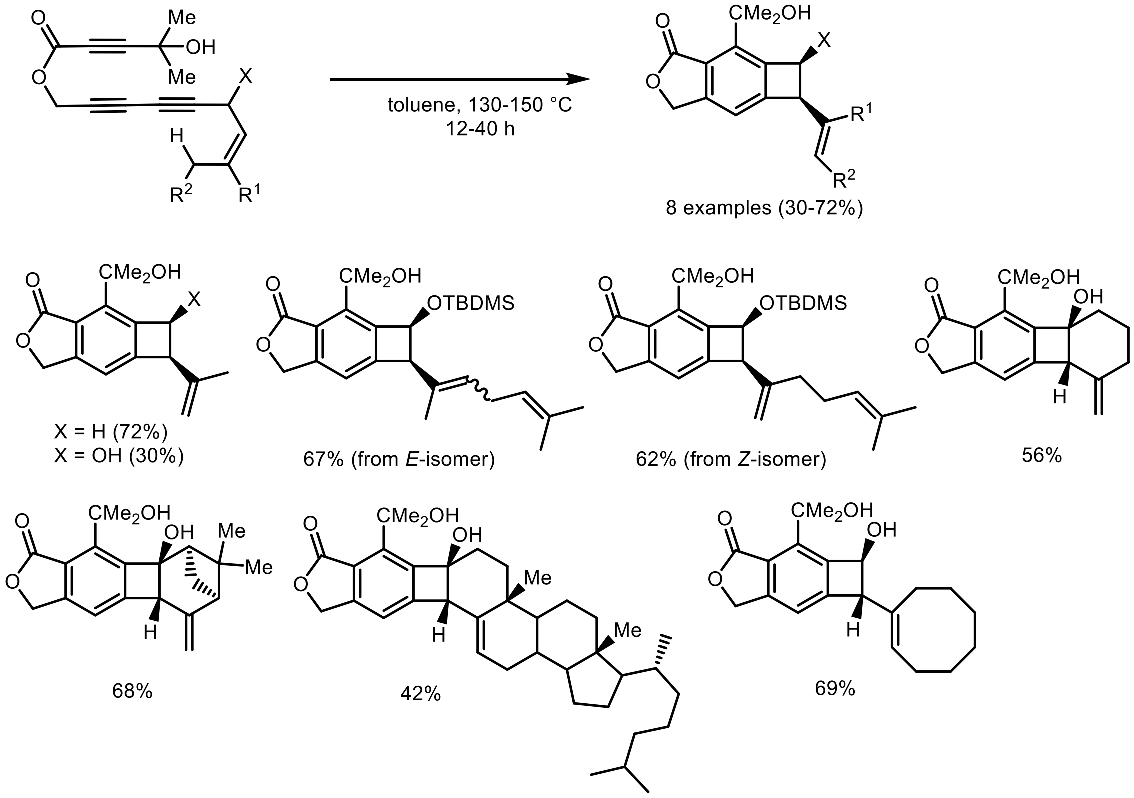
phosphanoxide was readily transformed by Wittig-Horner reaction for elaborating the side chain functionalization of the heterocycle.

3. Carbon Enes in Ene Reactions

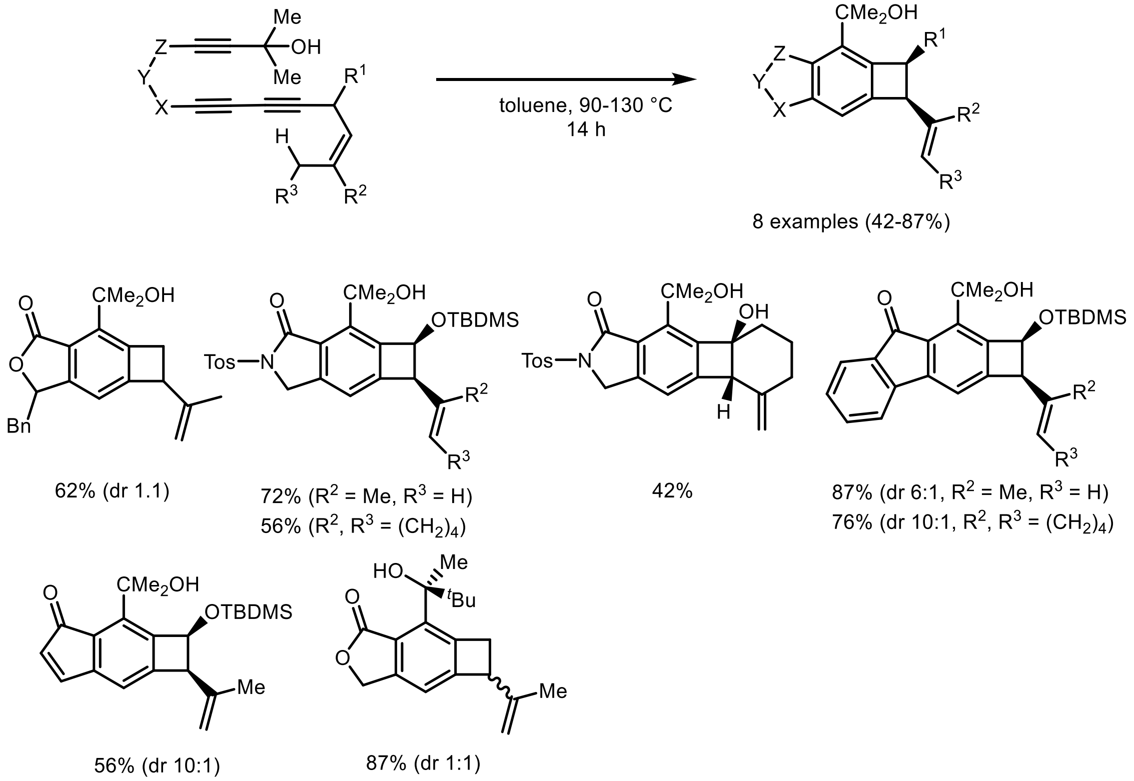
3.1. Alkynes as Enes in Ene Reactions (propargyl Ene Reaction)

While alkenes and their heteroanalogs, such as enamines, imines, enols, and phenols, are quite common ene functionalities, carbon enes like alkynes and allenes have still been quite rare. However, in the past decade, the former have become increasingly important topics, especially since alkynes, bearing propargyl hydrogen atoms can also be introduced by Pd-catalyzed alkynylation, i.e., under mild conditions.

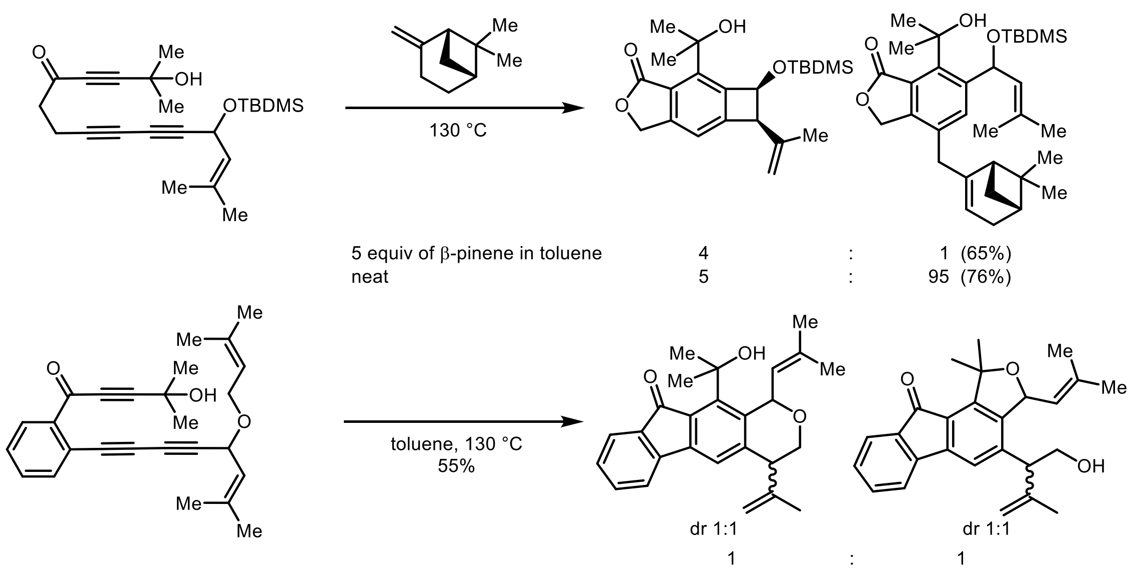
Alkynes bearing propargyl protons as ene components in ene-type cycloisomerizations, i.e., propargyl ene reactions, result in the generation of allenes (**Scheme 103**). The resulting enallenes are conjugated and therefore well-suited for participating in pericyclic follow-up reactions. In combination with alkyne enophiles elegant accesses to vinyl-allenes and a plethora



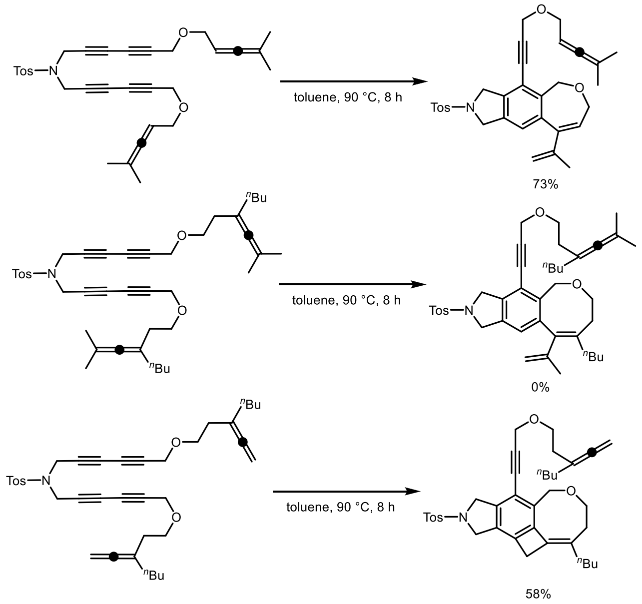
Scheme 86. HDDA–Alder ene sequence to benzocyclobutenes with variation of the ene donor moiety.



Scheme 87. HDDA–Alder ene sequence to benzocyclobutenes with variation of triyne tether.



Scheme 88. HDDA-Alder ene sequence inter- versus intramolecular competition and preference of strainfree anellation products.



Scheme 89. HDDA-ene sequences of bisdiynes symmetrically substituted with allenes as ene moieties.

of subsequent follow-up reaction can be envisioned for creating complex polycyclic scaffolds mostly in a domino fashion.

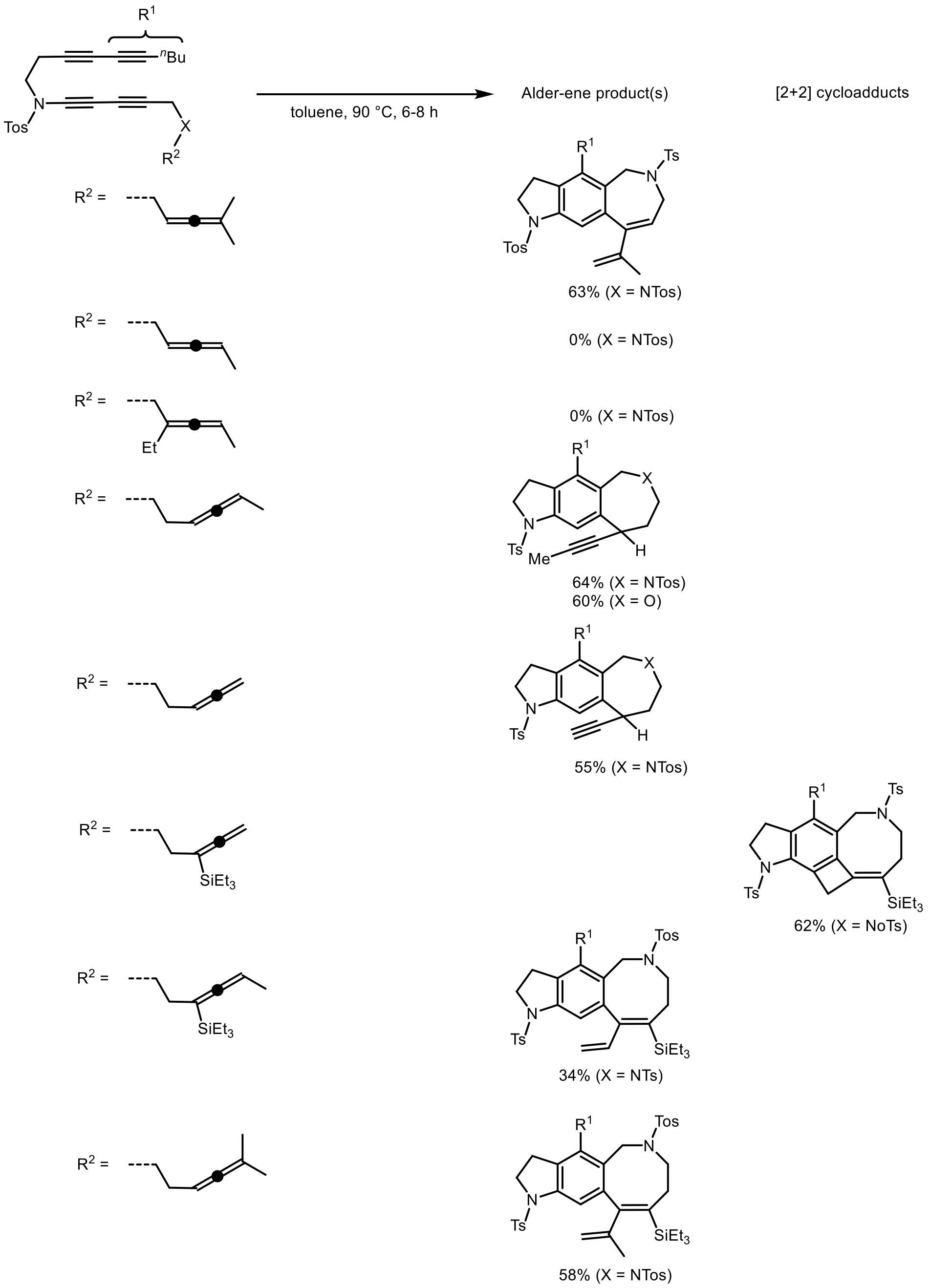
Lan, Danheiser, and Houk posed and answered the question why nature avoids the concerted thermal [2 + 2 + 2] cycloaddition of undeca-5,10-diynenitrile to the tricyclic hexahydrodicyclopenta[b, d]pyridine by DFT calculation with the M06-2X functional and 6-311+G(d) basis set.[107] Indeed, the propargyl ene-reaction of the two alkyne moieties is the rate determining step which concludes with an intramolecular Diels–Alder reaction of the ene–allene with the tethered nitrile to give after hydrogen transfer the trimerization product (**Scheme 104**).

Danheiser and coauthors reported a propargyl ene cycloisomerization-aza-Diels–Alder-elimination reaction of tethered yne-diynes with ethyl *N*-(tosyl)iminoacetate to give anellated multisubstituted pyridines in moderate yields (**Scheme 105**).[108] The anellation key step is the [4 + 2] cycloaddition of the highly reactive vinylallene intermediate and the subsequent elimination proceeds with concomitant aromatization. Employing a 2-sulfonylpyridine for the aza-Diels–Alder directly leads to the concluding aromatization to give the corresponding anellated pyridines in moderate to good yields (**Scheme 106**).

Lee and coauthors reported a new type of benzanellation triggered by nucleophilic addition of trifluormethylthiolate (**Scheme 107**).[109] The IMAE reaction of triynes with the carbonyl substituted yne as an ene moiety and the inner yne of the diyne as the enophile precedes the conjugate addition of $AgSCF_3$ in the presence of trifluoroethanol, followed by hydrogen shift and 6π-electrocyclization, and concluding a [1,3]-H shift (**Scheme 108**).

Furthermore, Lee and coauthors showed that amide tether triynes undergo an Alder ene to generate an allene amide that reacts with amine to give, after electrocyclization and formal 1,3-H shift amine-substituted arenes in moderate yield (**Scheme 109**).[110]

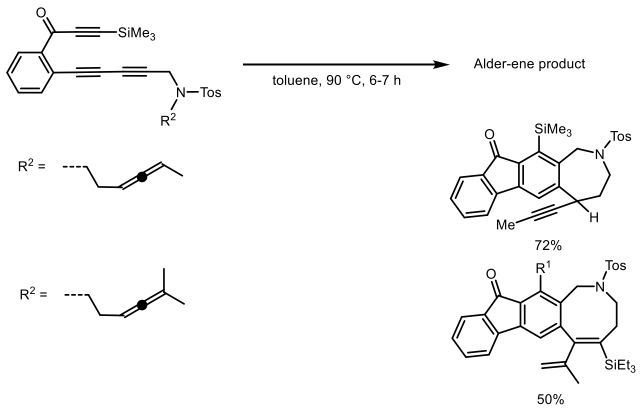
Lee and coauthors also reported a novel mode of benzanellation of the thermal or Grubbs II-catalyzed reaction of ester-tethered 1,3,8-triynes with concomitant incorporation of a nucleophile (**Scheme 110– 112**).[111] A mechanistic rationale was founded on DFT calculations. The sequence commences with the IMAE cycloisomeriziation



Scheme 90. HDDA-ene/[2 + 2] cycloaddition sequences of ynamide-tethered tetraynes tethered to different allenes as ene moieties.

furnishing the allene–enyne intermediate. The alkynyl substituent on this intermediate determines the formation of distinct aromatized products. While silyl substituents lead to the incorporation of the nucleophile in the benzo core (Scheme 110 and 111), for aryl substituents, the nucleophiles are ligated at the benzhydrylic carbon atom (Scheme 112). The formation of regioisomers in the latter case originate from the formation of two allene–enyne regioisomers. Grubbs II catalyst was found beneficial in sequences with acetic acid, whereas with other nucleophiles the process is purely thermal. Therefore, it is assumed that the Ru-catalyst is equilibrating the allenyl–enyne intermediate after the thermal Alder ene cycloisomerization. In addition, internally tethered nucleophiles finally lead to double anellation products.

Zhu, Lan, Shen, and coauthors found domino sequences after an initiating Sonogashira alkynylation of 1-(2-iodophenyl)-3-arylprop-2-yn-1-ones with propargyl ethers to selectively give 11H-benzo[*b*]fluoren-11-ones as a consequence of an alkynyl–propargyl ene-type cycloisomerization-electrocyclization-elimination sequence (**Scheme 113**).[112] The debenzylation



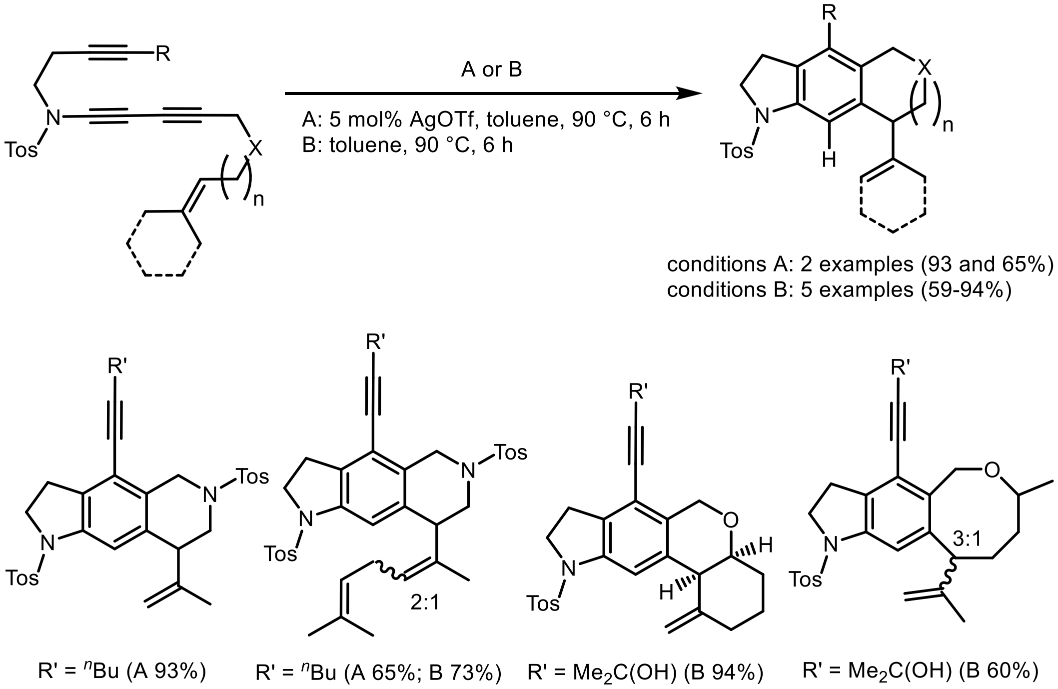
Scheme 91. HDDA-ene sequence of benzene-tethered triynes ligated to allenes as ene moieties.

under the reaction conditions very likely occurs in the sense of an antarafacial [3,5]-sigmatropic fragmentation. The key intermediate is an allene–enone, which also can be trapped by internal Diels–Alder reaction with tethered dienophiles (**Scheme 114**). Upon employing propargyl sulfonamides as substrates, instead of an ene-cyclization a propargyl–allenyl isomerization furnishing yne–allenes led to the formation cyclobuta[b] naphthalen-3(1H)-ones as a consequence of a concluding intramolecular [2 + 2] cycloaddition.

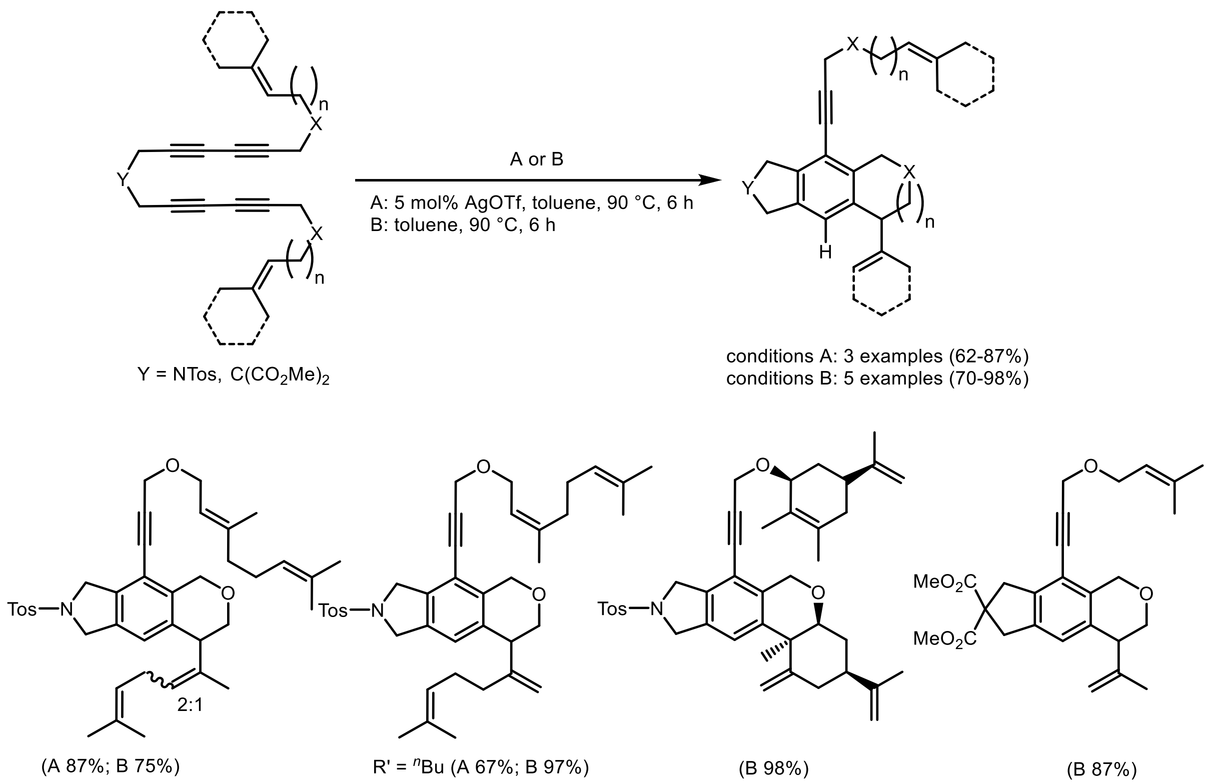
Alkynylation of *ortho*-iodo arylalkynones with propargylic ethers of indoles bearing unactivated alkenes were shown under mild reaction conditions to initiate a domino sequence of propargyl-ene reaction and intramolecular [4 + 2] cycloaddition giving rise to the formation of hexacyclic dihydropyrido[1,2-*a*]indoles with broad substrate scope and high diastereoselectivity (**Scheme 115**).[113] In turn, *N*-propargylic allylic ethers reacted to furnish polycyclic intermediates that were transformed by treatment with trifluoroacetic acid to give fused pyrido[1,2-*a*]indole products (**Scheme 116**).

The same concept was employed for synthesizing 7,12-dihydroindeno[1,2-*a*]fluorenes starting from 1-(2-iodophenyl)-3-arylprop-2-yn-1-ones and *o*-alkynyl phenyl *O*-alkyl propargyl ethers via domino alkynylation-Alder ene cycloisomerization-Diels–Alder-isomerization sequence (**Scheme 117**).[114] Interestingly, upon using *o*-alkynyl phenyl *O*-alkyl propargyl ether as a substrate a bifurcation takes place on the stage of the indenone–allenyne intermediate to give either directly the [4 + 2] cycloadduct and the arene product or after a Claisen-type rearrangement and [4 + 2] cycloaddition the corresponding allyl-substituted cyclohexadiene (**Scheme 118**).

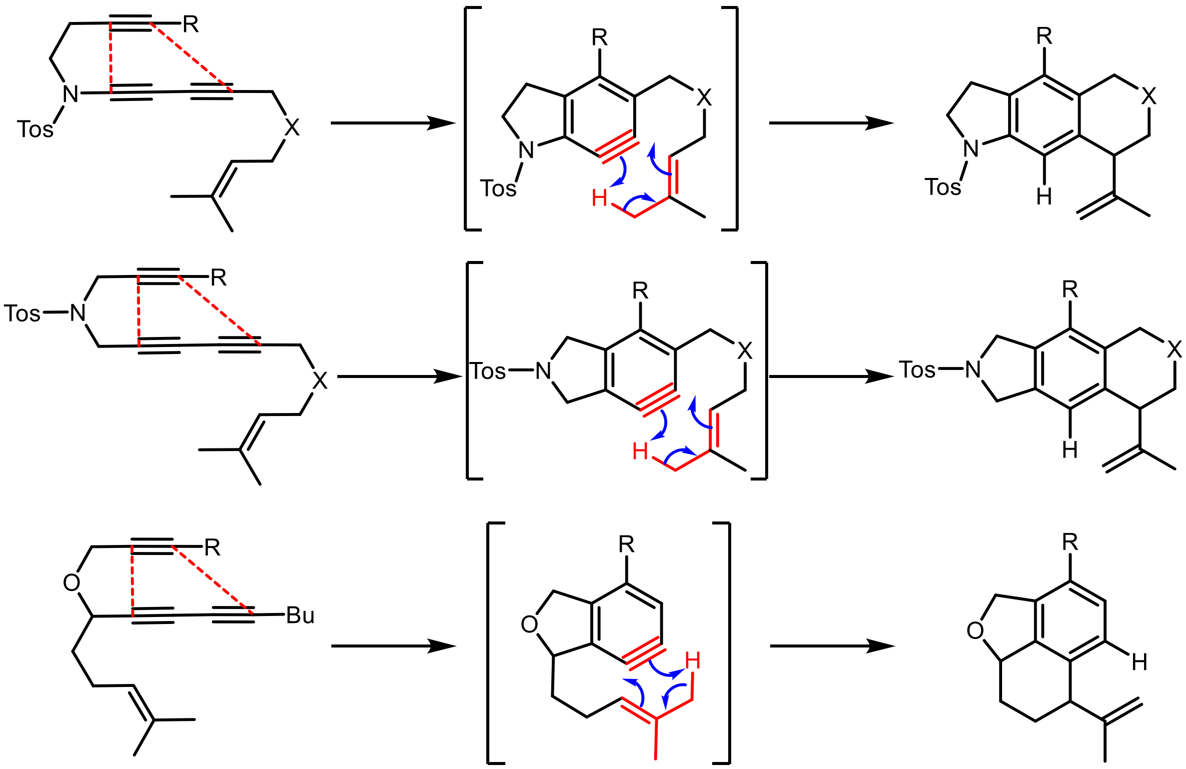
Zhu, Liu, and coauthors further followed the alkynylation–Alder ene-cyclization-Diels–Alder concept by using benzene-tethered furan-ynes as coupling partners, which in the sequence form fused hexacyclic indenone-furan scaffolds (**Scheme 119**), whereas propargyl furfuryl ethers as alkyne substrates give an entry to pentacyclic indenone-spirodifurans (**Scheme 120**).[115]



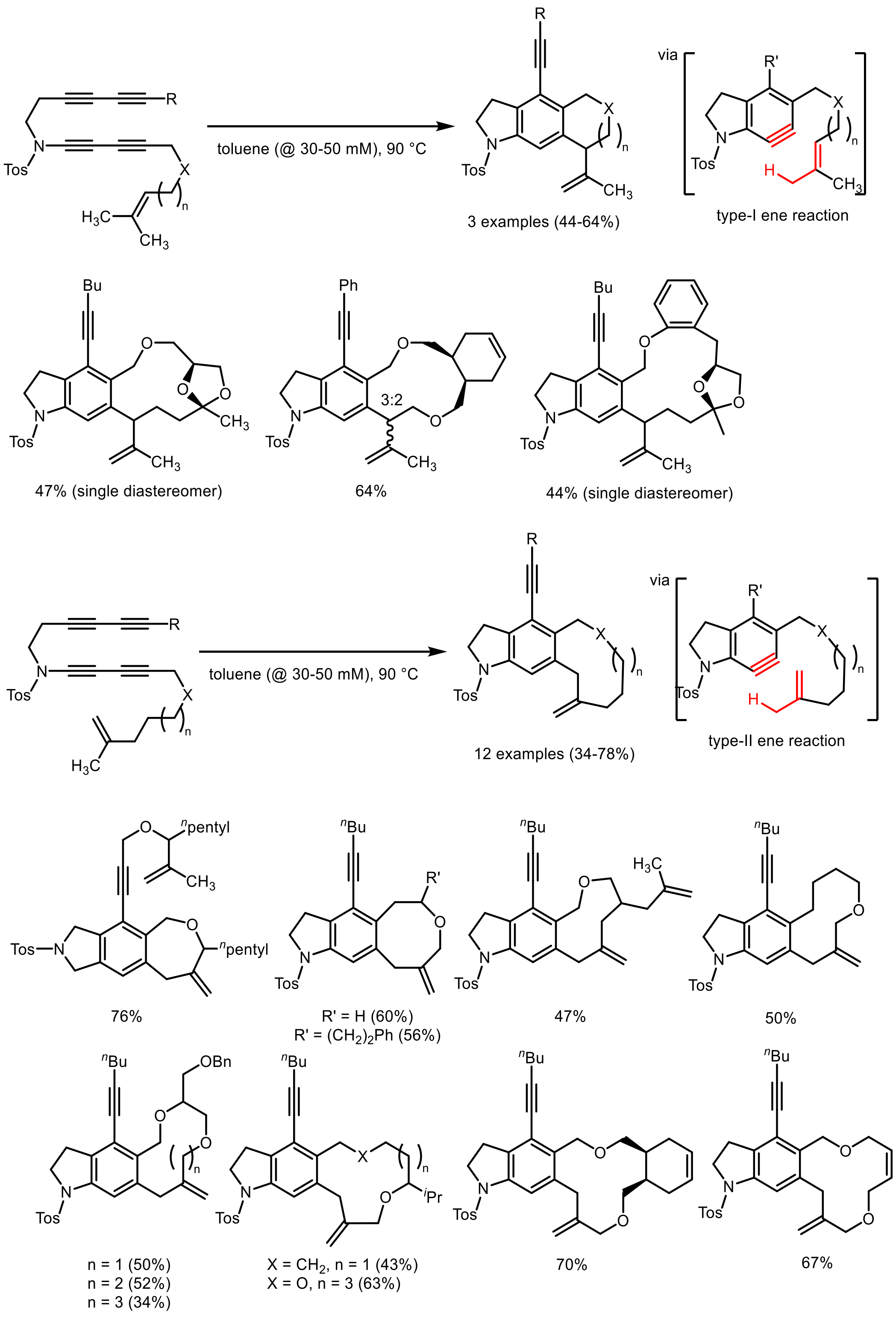
Scheme 92. Silver-catalyzed and thermal Alder ene reaction via putative aryne intermediates and selected examples of the cycloisomerization products.



Scheme 93. Silver-catalyzed and thermal Alder ene reaction of arynes from symmetrical diyne substrates and selected examples of the cycloisomerization products.

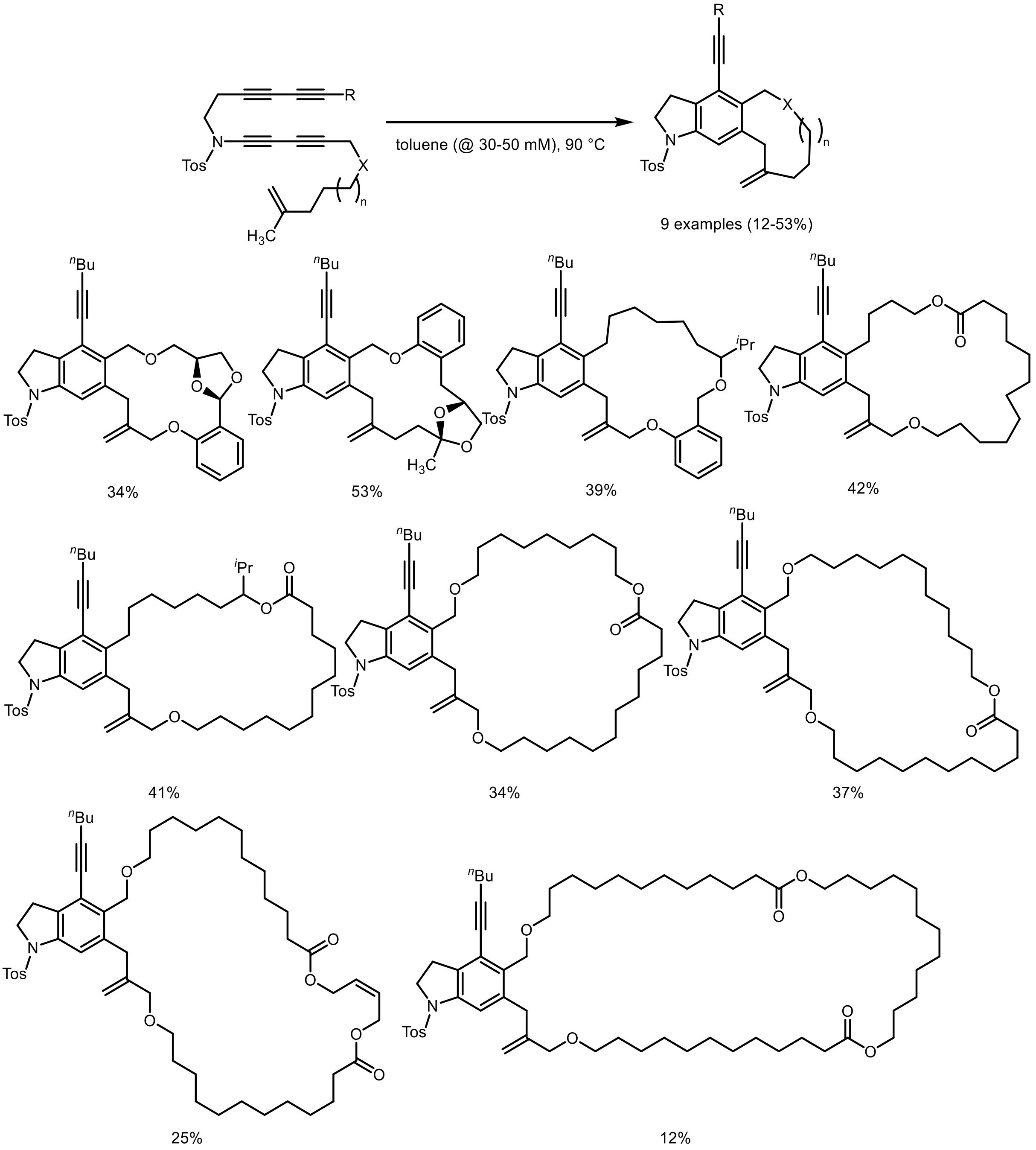


Scheme 94. Productive diyne-yne cyclization with concomitant of Alder ene reaction of the benzyne intermediate.

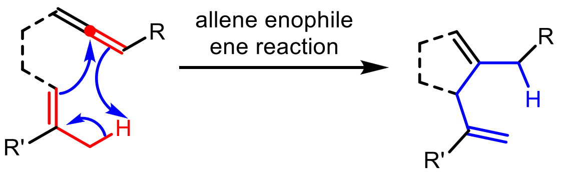


Scheme 95. Synthesis of medium-sized rings by type-I and type-II Alder ene cyclization.

Lee and coauthors showed that 1,3-diynyl propiolates after intramolecular progargyl ene reaction furnishing enyne-allenes can as well react again with unrearranged substrate in an intermolecular Diels–Alder reaction to give persubstituted bicyclic benzene derivatives in the sense of a formal [2 + 2 + 2] cycloaromatization of three alkyne moieties (**Scheme 121**).[116] In the presence of an external alkyne, enyne–allenes can be as well trapped



Scheme 96. Macrocyclization by type-II Alder ene reaction.

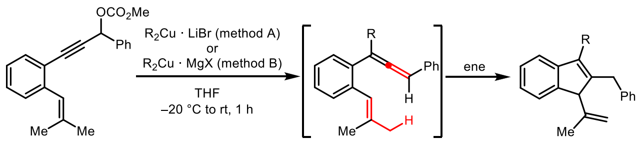


Scheme 97. Cyclizing ene reaction with allenes as enophile component.

enyne-allene to generate more diverse arene products (**Scheme 122**).

3.2. Allenes as Enes in Ene Reactions (allenyl and Allene Ene Reaction)

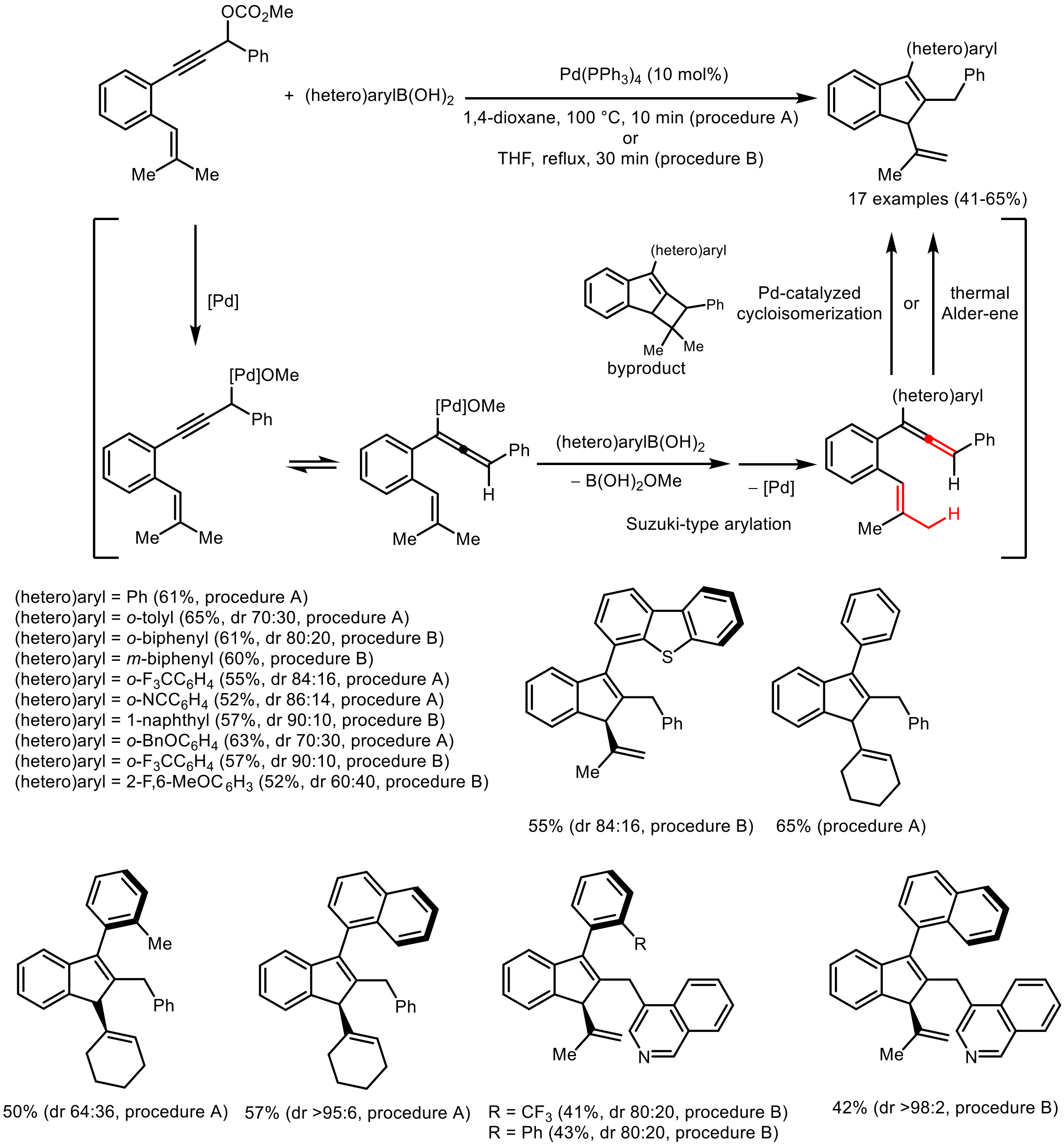
An allene as the ene component an ene-type cycloisomerizations can act in a twofold fashion. In the case, where the allenyl hydrogen is transferred, the



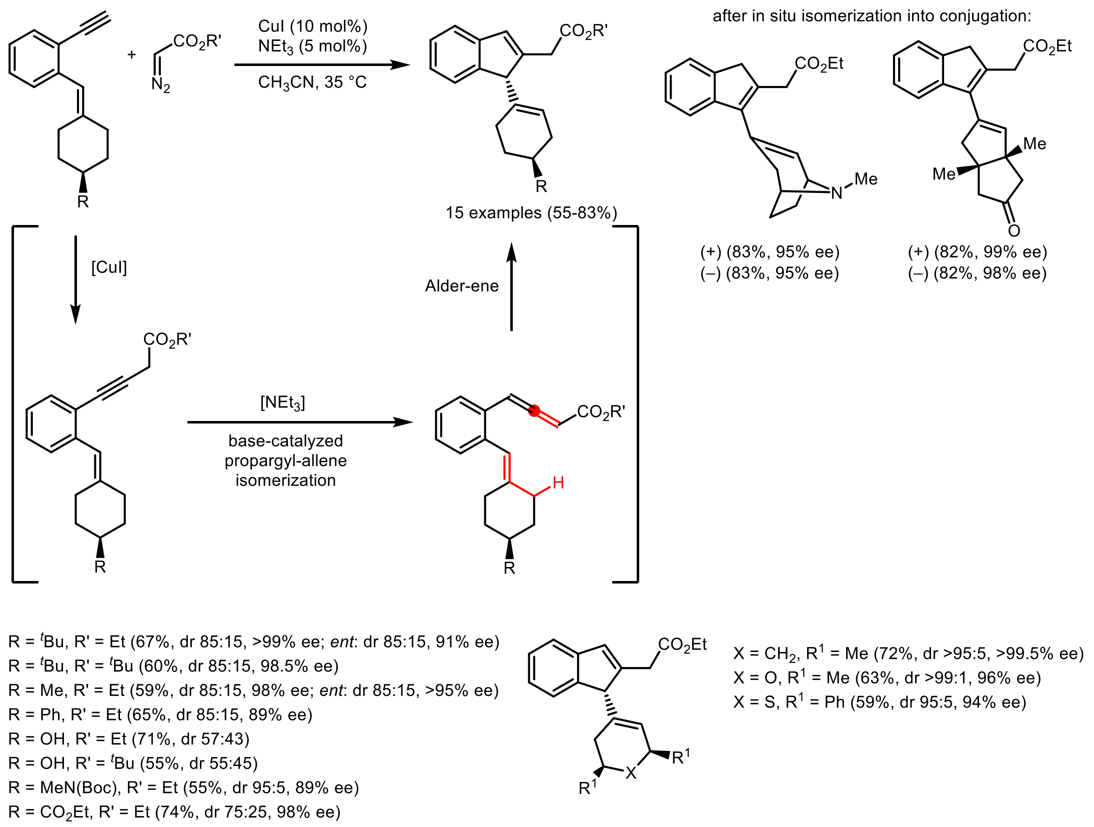
R = Me (35%) A	0	:	100
R = ^{n}Bu (57%) A	0	:	100
R = ^{i}Bu (60%) A	0	:	100
R = TMSCH$_2$ (58%) A	0	:	100
R = ^{t}Bu (60%) A	97	:	3
R = Ph (56%) B	25	:	75
R = ^{i}Pr (67%) B	0	:	100
R = Et (67%) B	0	:	100
R = Me (64%) B	95	:	5

Scheme 98. Cuprate substitution-triggered generation of allenes for domino-ene reaction with the tethered methallyl ene moiety.

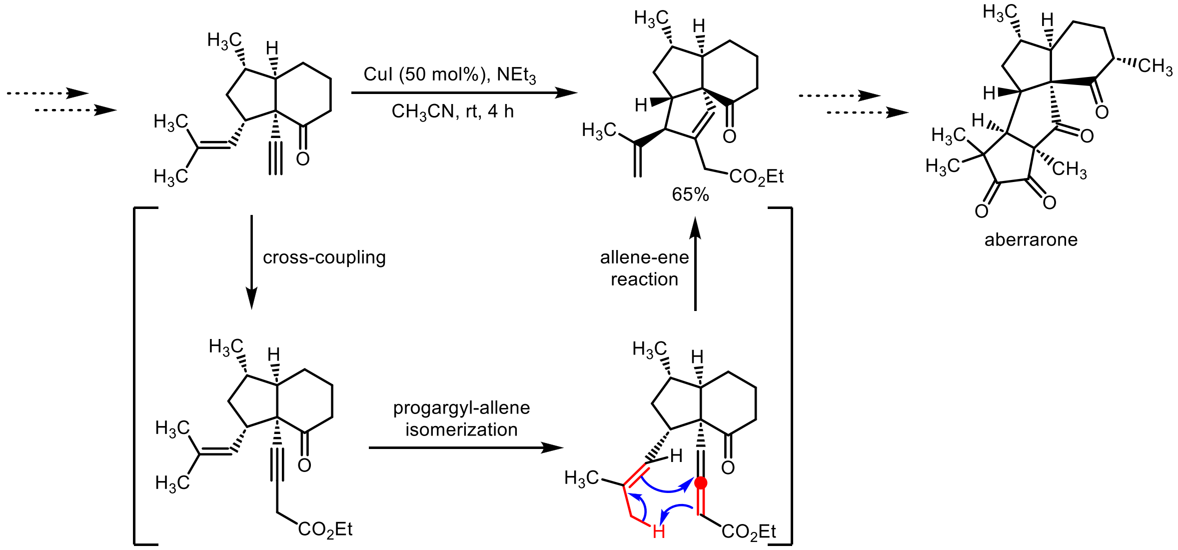
cyclizing bond formation occurs at the other end of the allene functionality and as a consequence an alkyne functionality arises from the pericyclic process (**Scheme 123**A). While, if the allyl–hydrogen is transferred the cyclizing bond formation occurs at the central carbon atom of the allene, which finally leads to the formation of a diene moiety, where one double bond is a part of the newly formed ring system (Scheme 123B). 1,6 -Allenynes were shown to undergo a thermal thermal IMAE reaction to give a-methylene-g-lactams (**Scheme 124**).[117] Computational and deuterium labeling studies invoke that the mechanism proceeds via a nonradical pathway.



Scheme 99. Domino diastereoselective Suzuki-type arylation-Alder ene sequence for the synthesis of diastereoatropisomeric indenes.

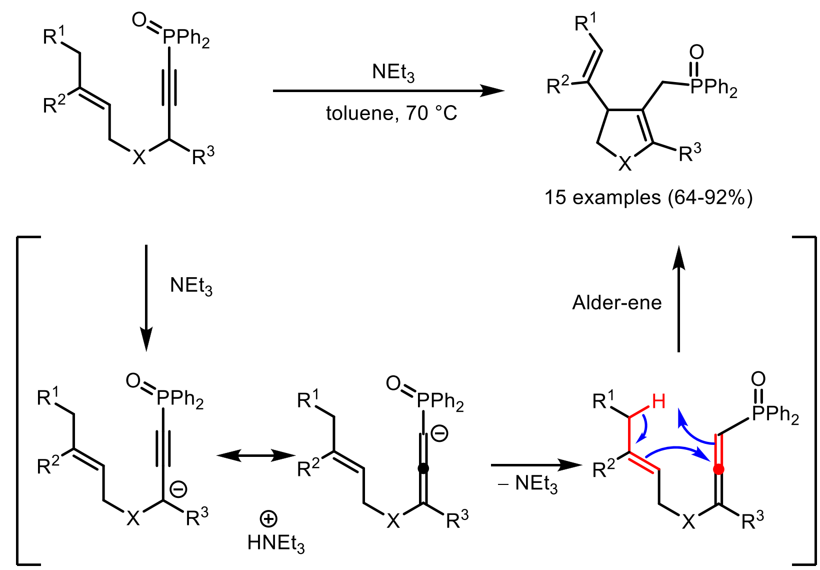


Scheme 100. Diasterero- and enantioselective axial-to-center chirality conversion of axially chiral benzylidene cyclanes to indenes initiated by alkyne-homologization-isomerization-Alder ene cyclization.



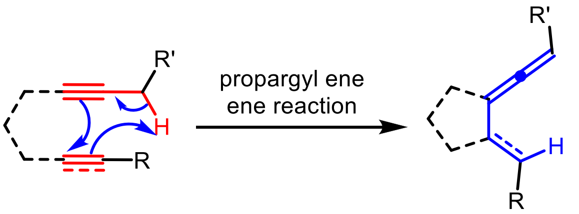
Scheme 101. Cross-coupling-isomerization-IMAE cyclization cascade in the total synthesis of diterpene aberrarone.

Osipov and coauthors took advantage of the copper-catalyzed reaction between allenynes with tosylazide to give after ketenimine rearrangement isolable amidino-ligated allene-enes that react at higher temperature to give highly functionalized proline derivatives bearing terminal alkynes by intramolecular allene-ene cycloisomerization (**Scheme 125**).[118] Most advantageously, the obtained 3-ethynyl substituted prolines can be

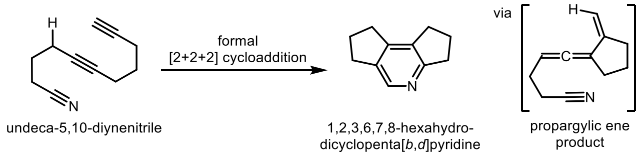


X = NTs, R^1, R^2, R^3 = H (85%)
X = NTs, R^1, R^3 = H, R^2 = Me (92%)
X = NTs, R^1, R^2, R^3 = Me (88%)
X = NTs, R^1 = ^{n}Bu, R^2, R^3 = H (80%)
X = NMs, R^1, R^2, R^3 = H (65%)
X = NMs, R^1, R^3 = H, R^2 = Me (87%)
X = O, R^1 = H, R^2 = Me, R^3 = Ph (75%)
X = O, R^1 = H, R^2 = Me, R^3 = *p*-ClC$_6$H$_4$ (64%)
X = O, R^1 = H, R^2 = Me, R^3 = *p*-MeC$_6$H$_4$ (65%)
X = O, R^1 = H, R^2 = Me, R^3 = 2-furyl (71%)
X = O, R^1 = H, R^2 = Me, R^3 = 2-thienyl (89%)
X = O, R^1, R^2 = (CH$_2$)$_4$, R^3 = 2-furyl (57%)
X = O, R^1, R^2 = H, R^3 = 2-furyl (85%)
X = O, R^1 = ^{n}Bu, R^2 = H, R^3 = 2-furyl (67%)
X = O, R^1, R^2 = H, R^3 = 2-thienyl (85%)

Scheme 102. Isomerization-Alder ene domino sequence.



Scheme 103. Cyclizing ene reaction with allenes as enophile component.



Scheme 104. DFT-calculated lowest energy pathway of the intramolecular [2 + 2 + 2] cycloaddition with a propargyl ene reaction as the rate determining step.

transformed into 3-triazolyl proline derivatives by CuAAC with a series of azides.

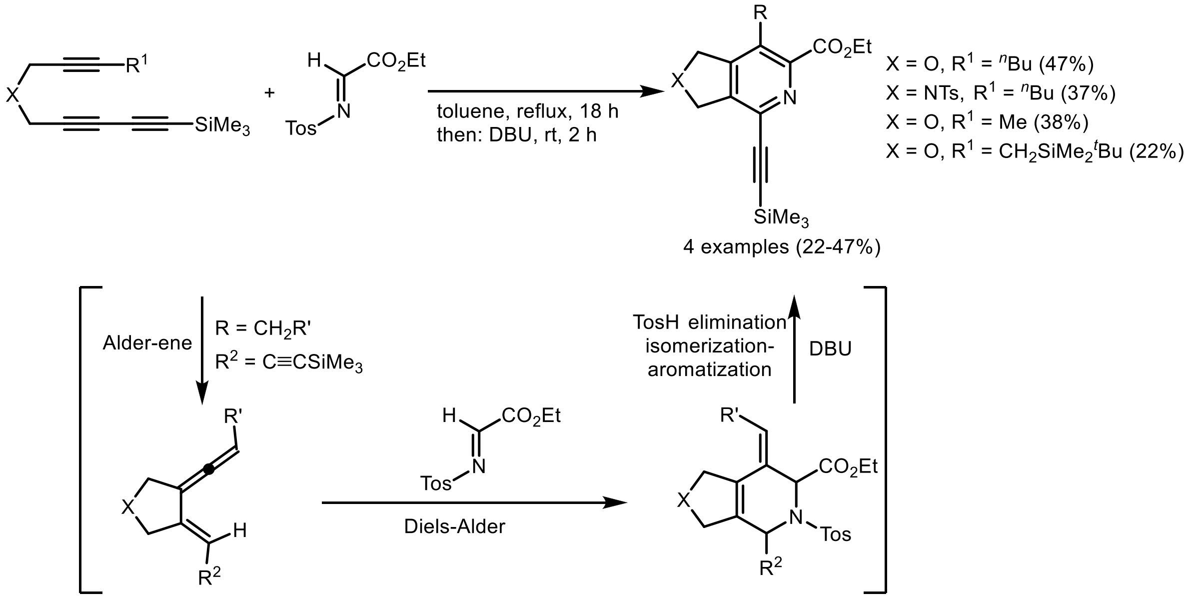
Copper nanoparticles immobilized on functionalized microcrystalline cellulose were shown to efficiently catalyze Alder ene reaction of allenynamides giving selectively rise to the formation of pyrrolines (2,5-dihydropyrroles) in toluene as a solvent, whereas pyrroles are generated in chloroform as a consequence of the isomerization of pyrrolines (**Scheme 126**).[119]

4. Metalla Ene Cyclizations

While in the previous overview[2] metalla ene reactions still represented a topic of intensive investigation, the last decade rather showed that very specific applications were reported, tackling complex synthetic challenges in natural product synthesis or difficile mechanistic problems.

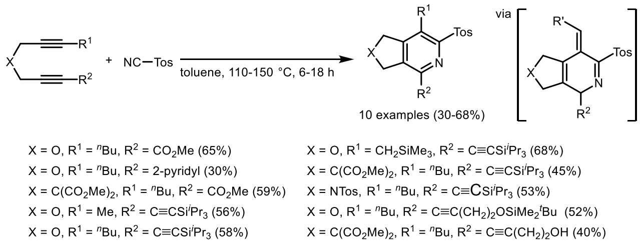
Mulzer and coauthors disclosed concise stereoselective syntheses of the diterpene skeleton of elisabethin A employing the Pd-catalyzed ene anellation of the cyclopentane ring (**Scheme 127**). This efficient key step opened out into the formal syntheses of the related diterpenes elisapterosin B and colombiasin A.[120]

Huang and coauthors found a novel Pd-catalyzed Oppolzer-type cyclization of *ortho*-styryl substituted enynes mediated by an aminomethyl cyclopalladated complex, in situ generated from *O*,*N*-formaldehydacetals, to give functionalized benzofulvenes with good yields and excellent stereoselectivity (**Scheme 128**).[121]

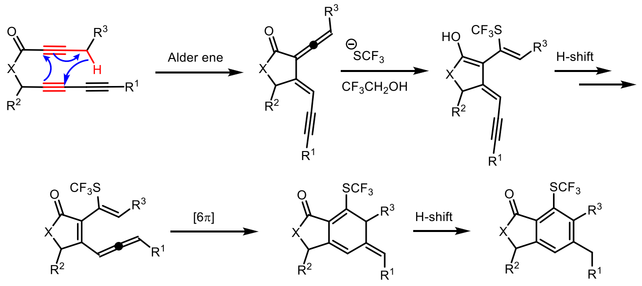


Scheme 105. Propargyl ene cycloisomerization-aza-Diels–Alder-elimination synthesis of anellated multisubstituted pyridines.

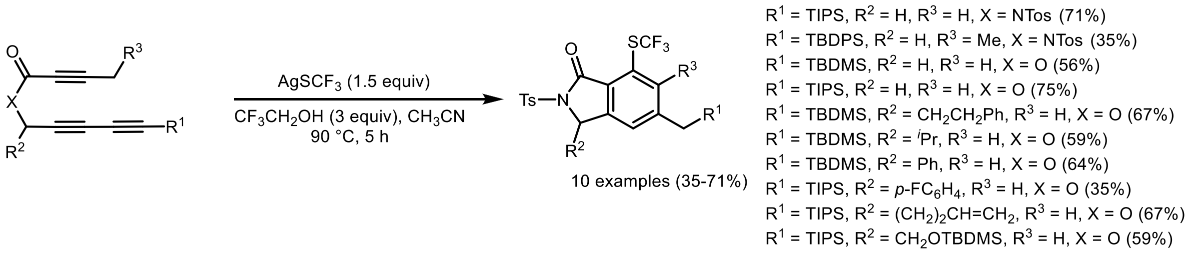
Dicobaltoctacarbonyl, known as a dinuclear complex to mediate the Pauson–Khand cyclization of enynes to give cyclopentenones in the sense of an alkene–alkyne–carbon monoxide cycloaddition, was found to be efficient for the cycloisomerization of arylene 1,7-enynes to give 2,3-dihydroindene derivatives (**Scheme 129**).[122] The mechanistic rationale, similar to the Pauson–Khand reaction, invokes an isomerization of the alkene, which might occur on the stage of the dicobalt(hexacarbonyl) alkyne complex via allylic CH insertion and cobalt hydride insertion. The catalytic version of this process was shown to proceed smoothly with a set of different Lewis base ligands (**Scheme 130**).



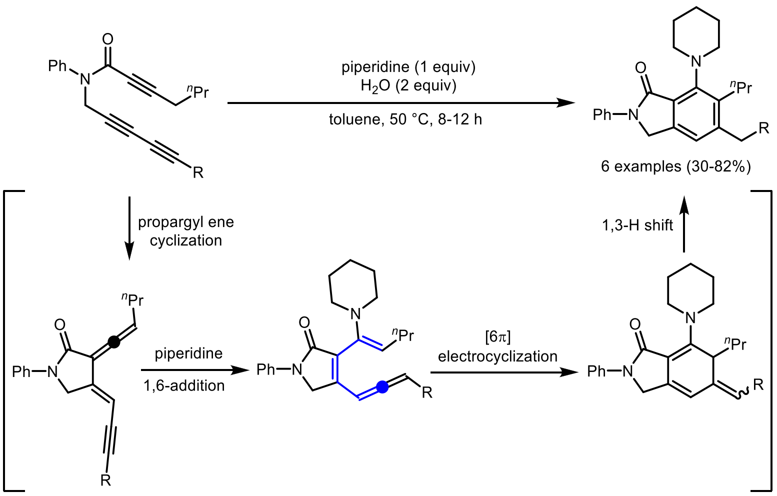
Scheme 106. Propargyl ene cycloisomerization-aza-Diels–Alder-isomerization domino synthesis of anellated multisubstituted pyridines.



Scheme 108. Mechanistic rationale of the Alder ene cyclization-nucleophilic addition-aromatization sequence.

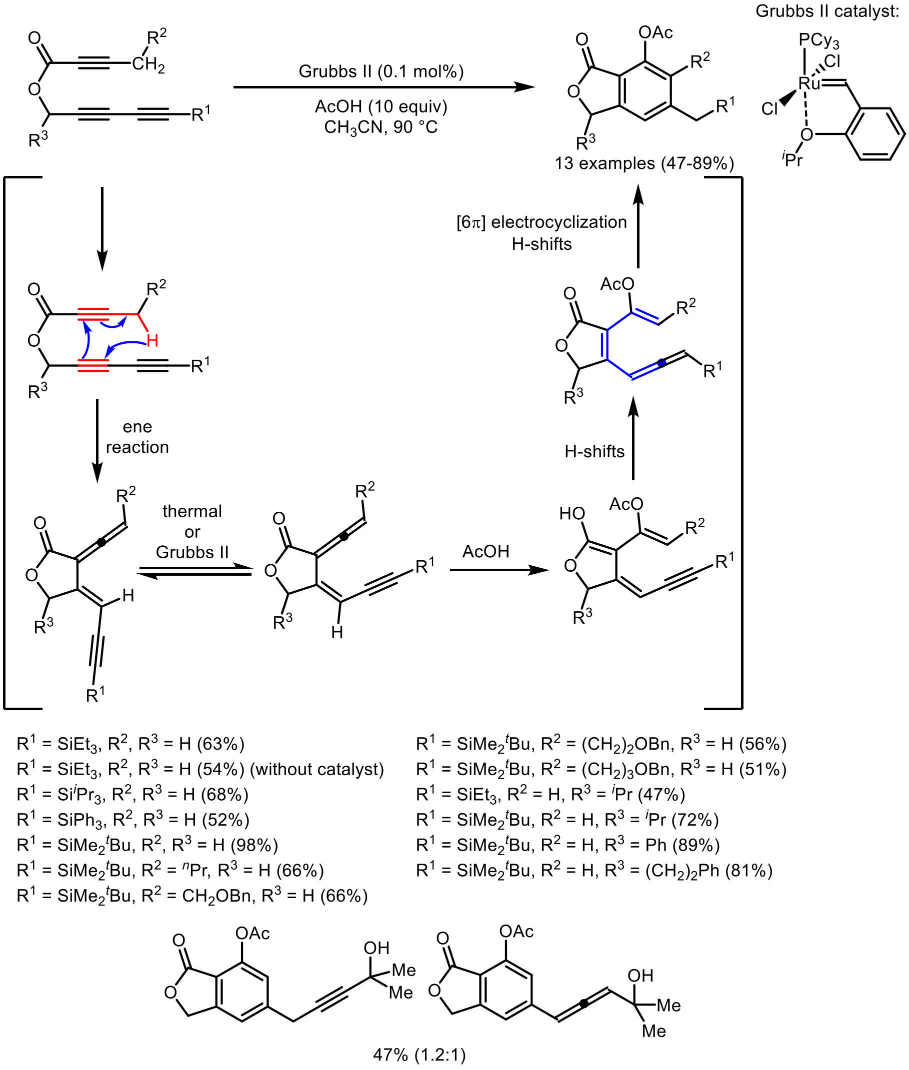


Scheme 107. Alder ene cyclization-nucleophilic addition-aromatization sequence.



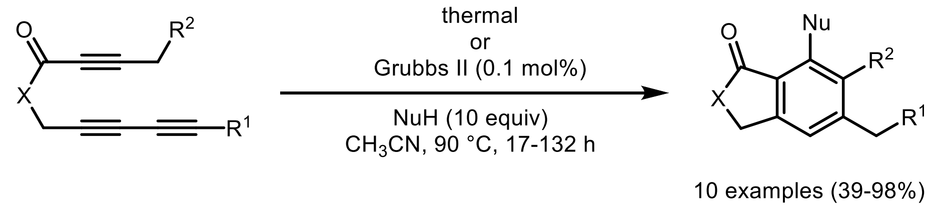
R = Ph (42%)
R = 1-cyclohexenyl (42%)
R = $CH_2OSiMe_2{}^tBu$ (45%)
R = ${}^nBu$ (30%)
R = H (33%)
R = $SiMe_3$ (82%)

Scheme 109. Triyne-ene-electrocyclization-1,3-H shift domino synthesis of piperidine-substituted isoindones.



R^1 = $SiEt_3$, R^2, R^3 = H (63%)
R^1 = $SiEt_3$, R^2, R^3 = H (54%) (without catalyst)
R^1 = Si^iPr_3, R^2, R^3 = H (68%)
R^1 = $SiPh_3$, R^2, R^3 = H (52%)
R^1 = $SiMe_2{}^tBu$, R^2, R^3 = H (98%)
R^1 = $SiMe_2{}^tBu$, R^2 = ${}^nPr$, R^3 = H (66%)
R^1 = $SiMe_2{}^tBu$, R^2 = CH_2OBn, R^3 = H (66%)
R^1 = $SiMe_2{}^tBu$, R^2 = $(CH_2)_2OBn$, R^3 = H (56%)
R^1 = $SiMe_2{}^tBu$, R^2 = $(CH_2)_3OBn$, R^3 = H (51%)
R^1 = $SiEt_3$, R^2 = H, R^3 = ${}^iPr$ (47%)
R^1 = $SiMe_2{}^tBu$, R^2 = H, R^3 = ${}^iPr$ (72%)
R^1 = $SiMe_2{}^tBu$, R^2 = H, R^3 = Ph (89%)
R^1 = $SiMe_2{}^tBu$, R^2 = H, R^3 = $(CH_2)_2Ph$ (81%)

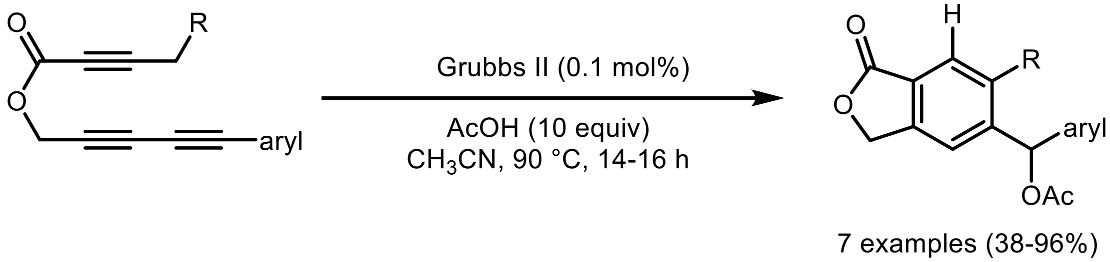
Scheme 110. Benzanellation of ester-tethered 1,3,8-triynes initiated by a propargyl-alkyne Alder ene step in the presence of acetic acid as a nucleophile and DFT-based tentative mechanistic rationale.



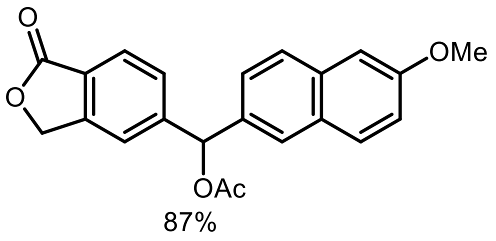
X = O, Nu = OMe, R^1 = $SiMe_2{}^tBu$, R^2 = H (98%)
X = O, Nu = OMe, R^1 = $SiMe_2{}^tBu$, R^2 = ^iPr (63%)
X = NPh, Nu = OMe, R^1 = $SiMe_2{}^tBu$, R^2 = H (85%)
X = NTos, Nu = OMe, R^1 = $SiMe_2{}^tBu$, R^2 = ^nPr (92%)
X = NTos, Nu = OAc, R^1 = $SiMe_2{}^tBu$, R^2 = ^nPr (39%)[a]
X = NTos, Nu = OMe, R^1 = $SiMe_2{}^tBu$, R^2 = H (69%)
X = NTos, Nu = Br, R^1 = $SiMe_2{}^tBu$, R^2 = H (49%)
X = NTos, Nu = OAc, R^1 = $SiMe_2{}^tBu$, R^2 = H (53%)[a]
X = CMe_2, Nu = OMe, R^1 = $SiMe_2{}^tBu$, R^2 = ^nPr (84%)
X = CMe_2, Nu = OAc, R^1 = $SiMe_2{}^tBu$, R^2 = ^nPr (56%)[a]

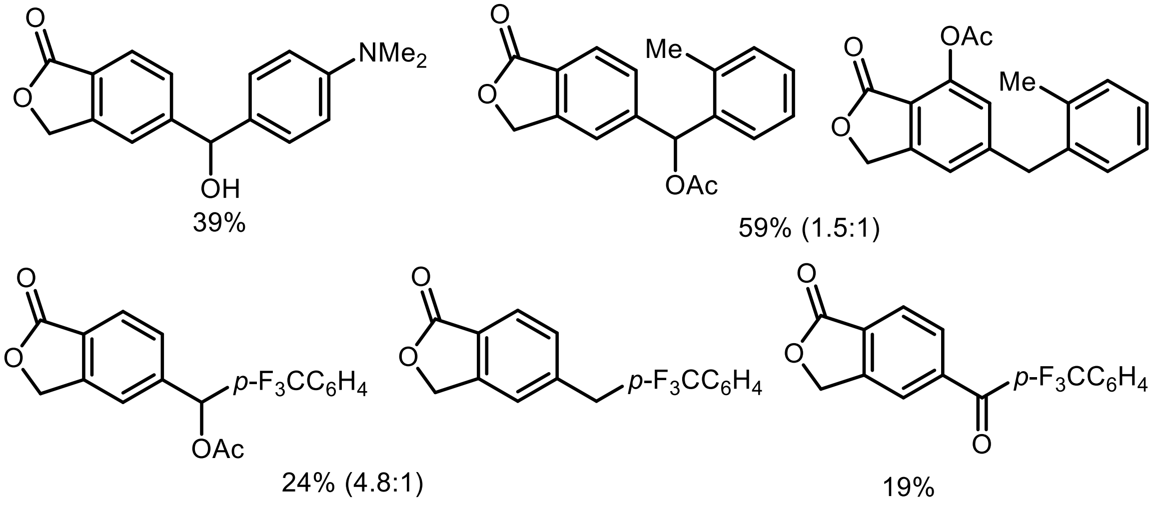
[a] In the presence of Grubbs II (0.1 mol%)

Scheme 111. Benzanellation of 1,3,8-triynes with various tethers and nucleophiles.

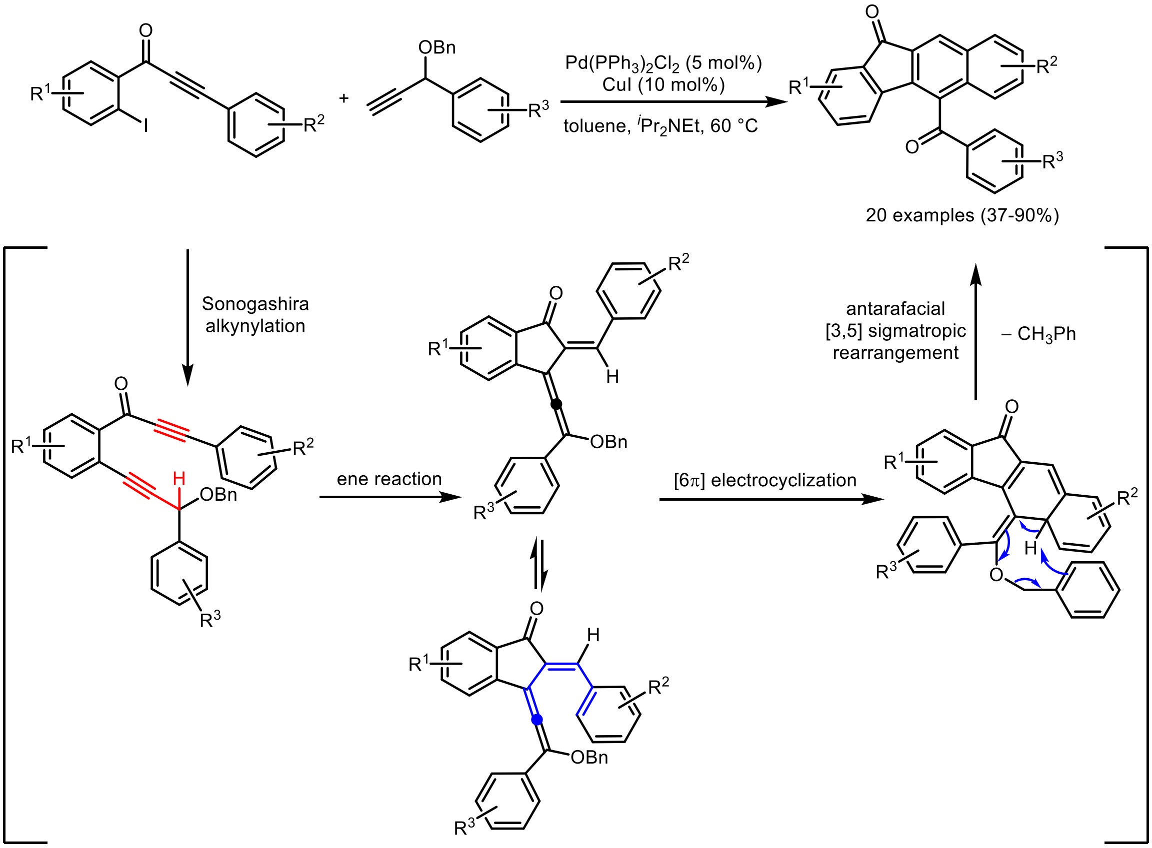


R = H, aryl = p-ClC_6H_4 (61%)
R = H, aryl = p-$MeOC_6H_4$ (96%)
R = ^nPr, aryl = Ph (38%)
R = ^nPr, aryl = p-$MeOC_6H_4$ (79%)



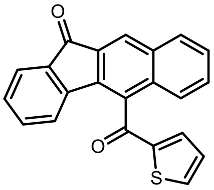


Scheme 112. Benzanellation of 1,3,8-triynes with aryl substituent on the diyne moiety.

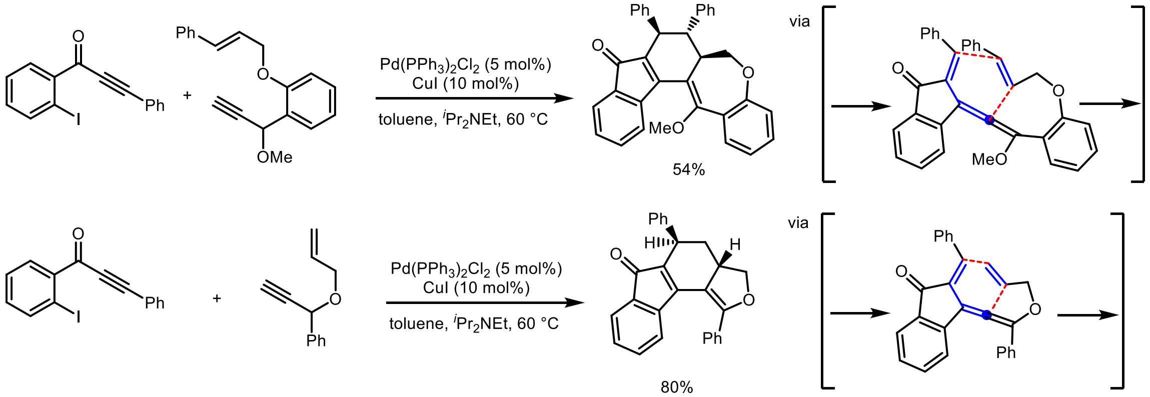


R^1, R^2, R^3 = H (73%)
R^1 = 5-MeO, R^2, R^3 = H (73%)
R^1 = 4-Cl, R^2, R^3 = H (63%)
R^1 = 5-Br, R^2, R^3 = H (68%)
R^1 = 6-Me, R^2, R^3 = H (38%)
R^1, R^3 = H, R^2 = 4-Et (63%)
R^1, R^3 = H, R^2 = 4-Cl (65%)
R^1, R^3 = H, R^2 = 4-MeO (78%)
R^1, R^3 = H, R^2 = 4-CN (64%)
R^1, R^3 = H, R^2 = 2-MeO (65%)

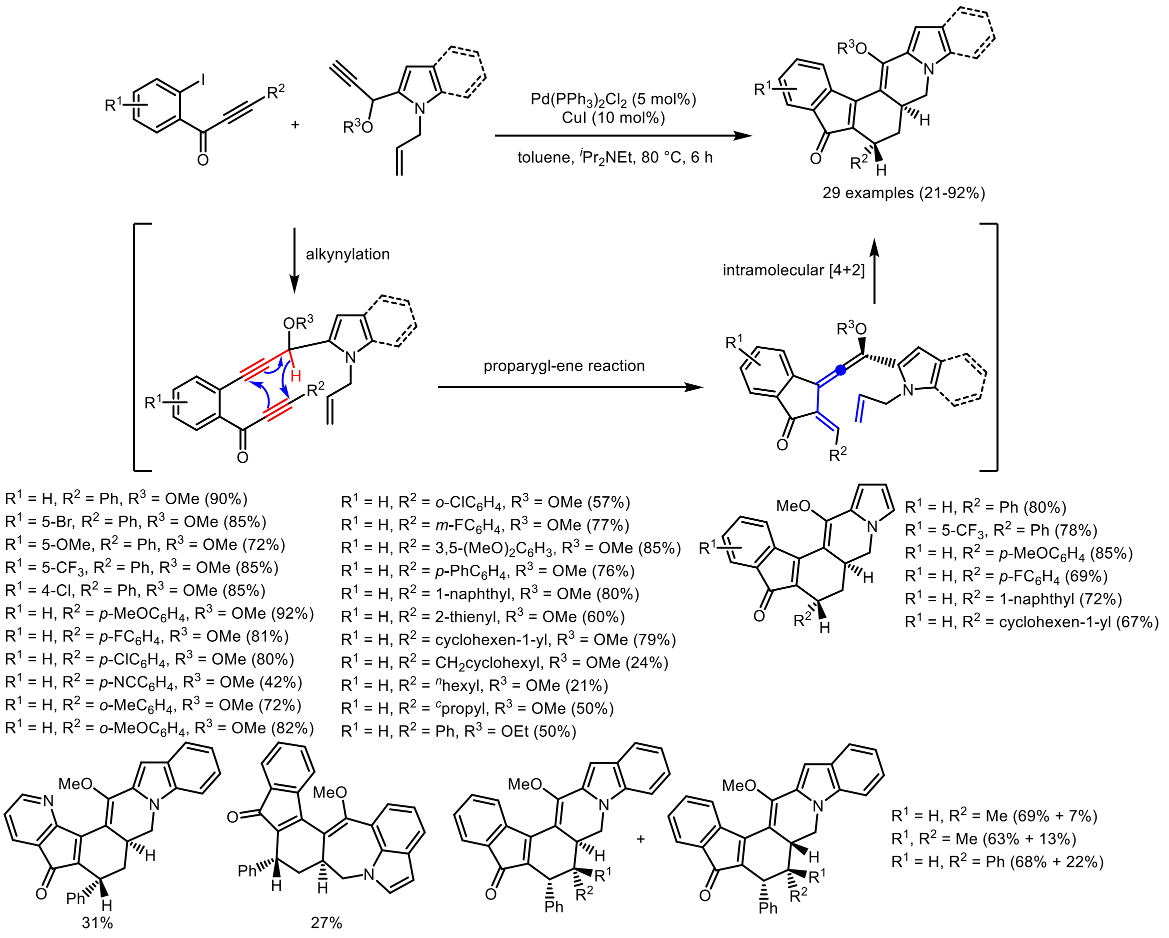
R^1, R^2 = H, R^3 = 4-Cl (78%)
R^1, R^2 = H, R^3 = 4-MeO (80%)
R^1, R^2 = H, R^3 = 2-MeO (78%)
R^1 = 5-MeO, R^2 = H, R^3 = 4-Cl (63%)
R^1 = 4-Cl, R^2 = H, R^3 = 2-MeO (61%)
R^1 = 4-Cl, R^2 = H, R^3 = 4-Cl (80%)
R^1 = H, R^2 = 4-F$_3$C, R^3 = 4-Cl (57%)
R^1 = H, R^2 = 4-MeO, R^3 = 4-Cl (71%)
R^1 = H, R^2 = 4-MeO, R^3 = 4-MeO (90%)



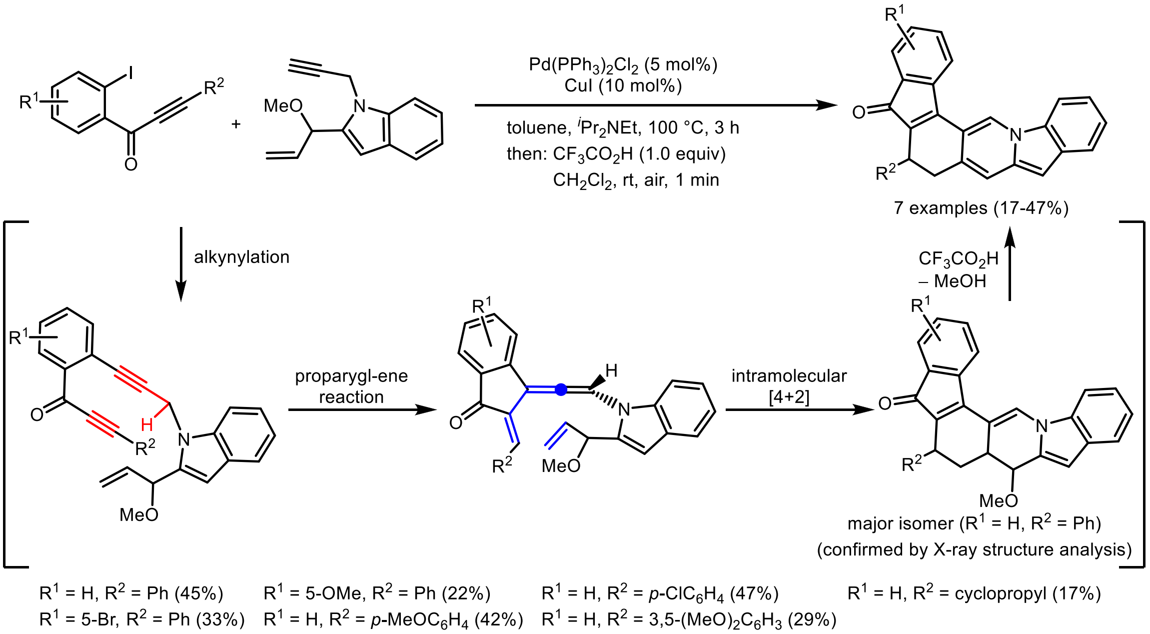
Scheme 113. Coupling-ene-type cycloisomerization-electrocyclization elimination domino synthesis of 11H-benzo[*b*]fluoren-11-ones.



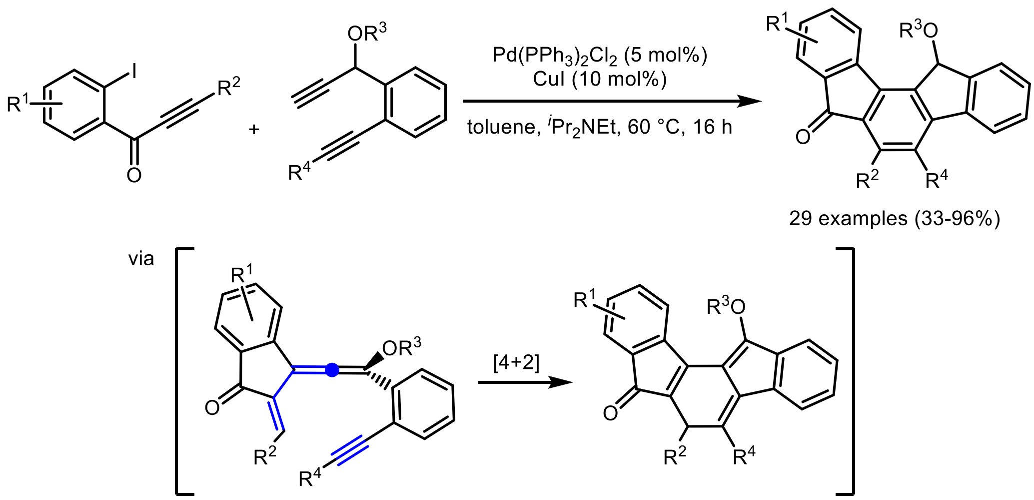
Scheme 114. Intramolecular trapping of the allene–enone intermediate with a tethered dienophile.



Scheme 115. Alkynylation-Alder ene-Diels–Alder domino synthesis of dihydropyrido[1,2-*a*]indoles and a dihydroazepino[3,2,1-*hi*]indole.

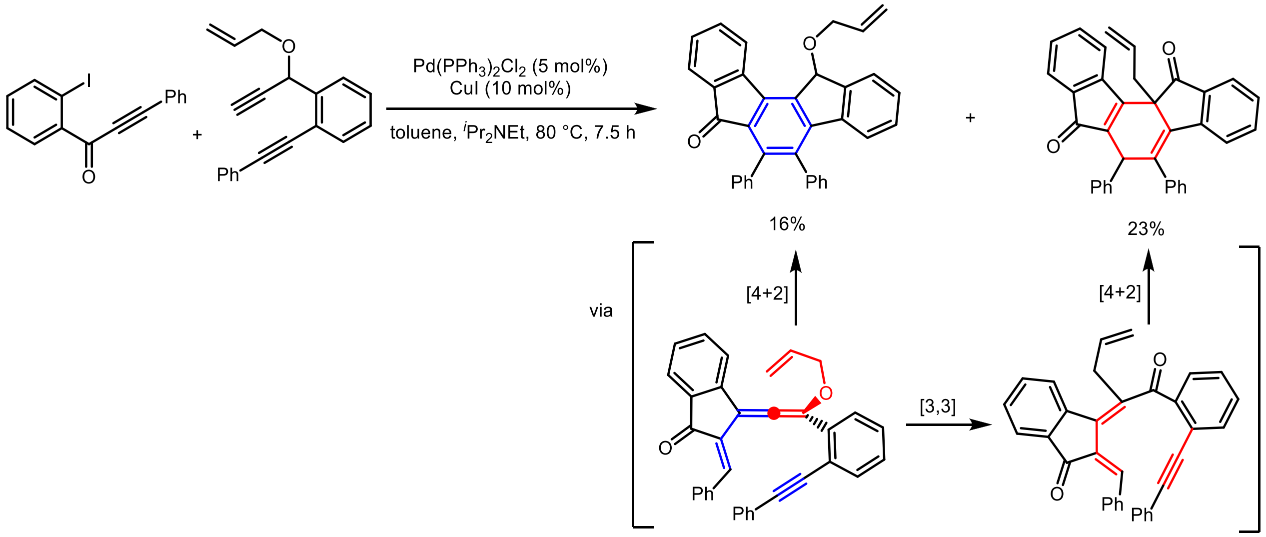


Scheme 116. Alkynylation-Alder ene-Diels–Alder domino synthesis of pyrido[1,2-*a*]indoles.

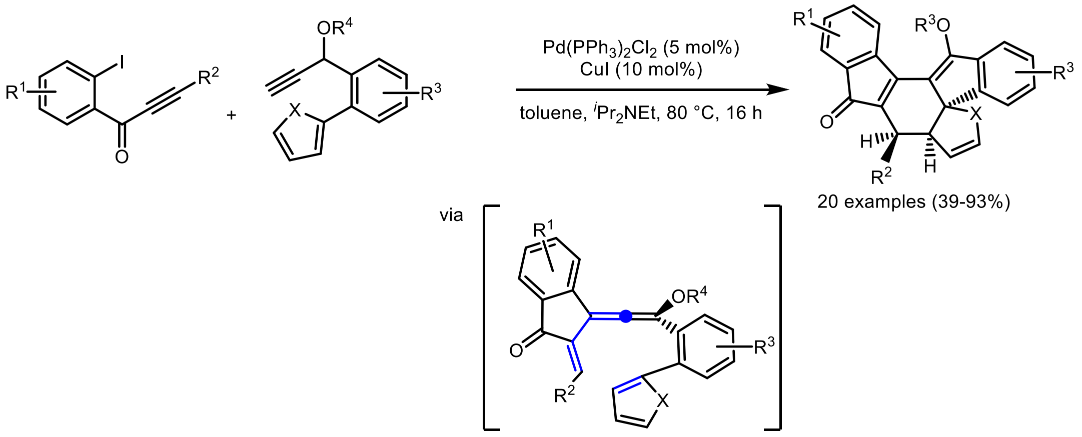


$R^1 = H$, $R^2 = Ph$, $R^3 = MeO$, $R^4 = Ph$ (92%)
R^1 = 5-MeO, $R^2 = Ph$, $R^3 = MeO$, $R^4 = Ph$ (71%)
R^1 = 4-F_3C, $R^2 = Ph$, $R^3 = MeO$, $R^4 = Ph$ (74%)
R^1 = 4-Cl, $R^2 = Ph$, $R^3 = MeO$, $R^4 = Ph$ (83%)
R^1 = 5-Br, $R^2 = Ph$, $R^3 = MeO$, $R^4 = Ph$ (86%)
$R^1 = H$, R^2 = 1-naphthyl, $R^3 = MeO$, $R^4 = Ph$ (81%)
$R^1 = H$, R^2 = *p*-NCC_6H_4, $R^3 = MeO$, $R^4 = Ph$ (68%)
$R^1 = H$, R^2 = *p*-FC_6H_4, $R^3 = MeO$, $R^4 = Ph$ (77%)
$R^1 = H$, R^2 = *m*-FC_6H_4, $R^3 = MeO$, $R^4 = Ph$ (71%)
$R^1 = H$, R^2 = *o*-ClC_6H_4, $R^3 = MeO$, $R^4 = Ph$ (96%)
$R^1 = H$, R^2 = 3,5-$(MeO)_2C_6H_3$, $R^3 = MeO$, $R^4 = Ph$ (62%)
$R^1 = H$, R^2 = *p*-EtC_6H_4, $R^3 = MeO$, $R^4 = Ph$ (77%)
$R^1 = H$, R^2 = *o*-MeC_6H_4, $R^3 = MeO$, $R^4 = Ph$ (78%)
$R^1 = H$, R^2 = *p*-$Ph_2NC_6H_4$, $R^3 = MeO$, $R^4 = Ph$ (89%)
$R^1 = H$, R^2 = *p*-$Me_2NC_6H_4$, $R^3 = MeO$, $R^4 = Ph$ (40%)
$R^1 = H$, R^2 = *p*-PhC_6H_4, $R^3 = MeO$, $R^4 = Ph$ (80%)
$R^1 = H$, R^2 = *p*-$F_3CC_6H_4$, $R^3 = MeO$, $R^4 = Ph$ (74%)
$R^1 = H$, R^2 = 2-thienyl, $R^3 = MeO$, $R^4 = Ph$ (75%)
$R^1 = H$, R^2 = 1-cyclohexenyl, $R^3 = MeO$, $R^4 = Ph$ (94%)
$R^1 = H$, R^2 = cyclopropyl, $R^3 = MeO$, $R^4 = Ph$ (57%)
$R^1 = H$, R^2 = ^{n}hexyl, $R^3 = MeO$, $R^4 = Ph$ (33%)
$R^1 = H$, $R^2 = Ph$, $R^3 = MeO$, R^4 = *p*-$MeOC_6H_4$ (92%)
$R^1 = H$, $R^2 = Ph$, $R^3 = MeO$, R^4 = *m*-MeC_6H_4 (87%)
$R^1 = H$, $R^2 = Ph$, $R^3 = MeO$, R^4 = *p*-ClC_6H_4 (92%)
$R^1 = H$, $R^2 = Ph$, $R^3 = MeO$, R^4 = 2-thienyl (84%)
$R^1 = H$, $R^2 = Ph$, $R^3 = MeO$, R^4 = ^{n}Bu (52%)
$R^1 = H$, R^2 = *p*-$Ph_2NC_6H_4$, $R^3 = MeO$, R^4 = *p*-$MeOC_6H_4$ (77%)
$R^1 = H$, $R^2 = Ph$, $R^3 = BnO$, $R^4 = Ph$ (86%)
$R^1 = H$, $R^2 = Ph$, $R^3 = Et_3SiO$, $R^4 = Ph$ (65%)

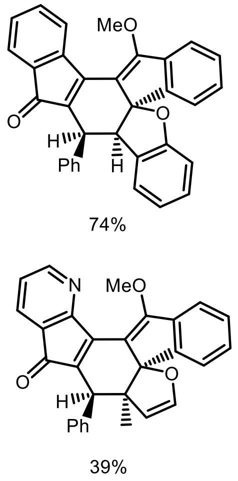
Scheme 117. Alkynylation-Alder ene-Diels–Alder domino synthesis of 7,12-dihydroindeno[1,2-*a*]fluorenes.



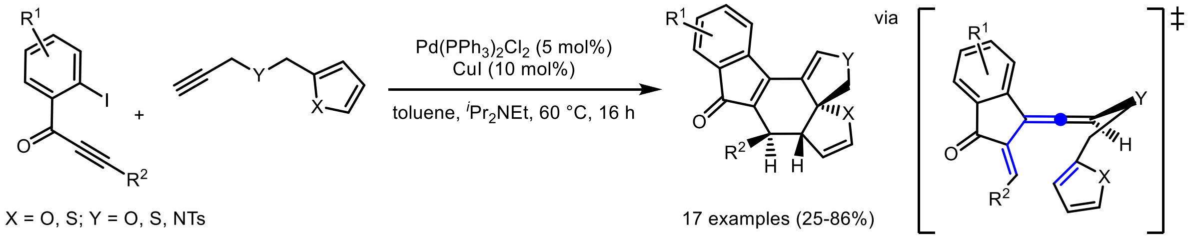
Scheme 118. Bifurcation of the alkynylation-Alder ene-Diels–Alder domino synthesis of a 7,12-dihydroindeno[1,2-*a*]fluorene for an *o*-alkynyl phenyl *O*-alkyl propargyl ether substrate.



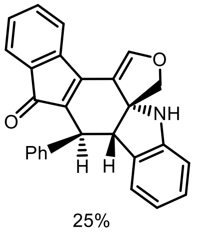
R^1 = H, R^2 = Ph, R^3 = H, R^4 = Me, X = O (91%)
R^1 = H, R^2 = *o*-ClC_6H_4, R^3 = H, R^4 = Me, X = O (90%)
R^1 = H, R^2 = *p*-$MeOC_6H_4$, R^3 = H, R^4 = Me, X = O (87%)
R^1 = H, R^2 = *m*-FC_6H_4, R^3 = H, R^4 = Me, X = O (64%)
R^1 = H, R^2 = *o*-$MeOC_6H_4$, R^3 = H, R^4 = Me, X = O (93%)
R^1 = H, R^2 = *p*-NCC_6H_4, R^3 = H, R^4 = Me, X = O (82%)
R^1 = H, R^2 = *p*-PhC_6H_4, R^3 = H, R^4 = Me, X = O (90%)
R^1 = H, R^2 = 1-naphthyl, R^3 = H, R^4 = Me, X = O (50%)
R^1 = H, R^2 = 2-thienyl, R^3 = H, R^4 = Me, X = O (91%)
R^1 = H, R^2 = cyclopropyl, R^3 = H, R^4 = Me, X = O (51%)
R^1 = H, R^2 = 3,5-$(MeO)_2C_6H_3$, R^3 = H, R^4 = Me, X = O (91%)
R^1 = 5-F_3C, R^2 = Ph, R^3 = H, R^4 = Me, X = O (59%)
R^1 = 5-MeO, R^2 = Ph, R^3 = H, R^4 = Me, X = O (90%)
R^1 = 5-Br, R^2 = Ph, R^3 = H, R^4 = Me, X = O (90%)
R^1 = 4-Cl, R^2 = Ph, R^3 = H, R^4 = Me, X = O (84%)
R^1 = H, R^2 = Ph, R^3 = 4-MeO, R^4 = Me, X = O (90%)
R^1 = H, R^2 = Ph, R^3 = H, R^4 = Bn, X = O (55%)
R^1 = H, R^2 = Ph, R^3 = 4-MeO, R^4 = Me, X = S (73%)



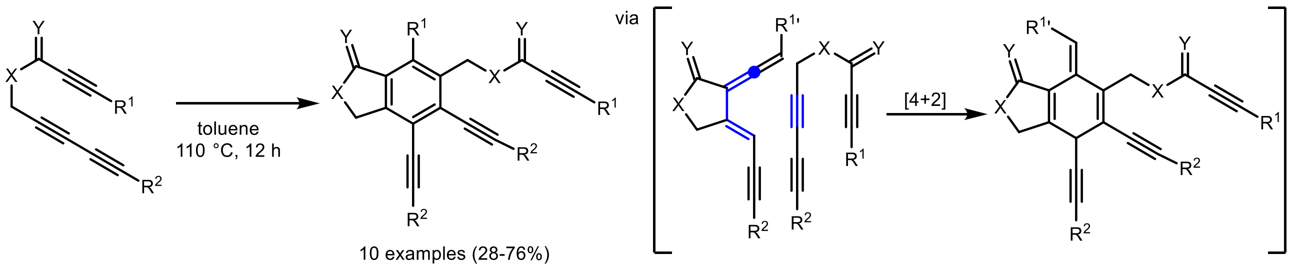
Scheme 119. Alkynylation-Alder ene-Diels–Alder domino synthesis of hexacyclic indenone-furan scaffolds.



R^1 = H, R^2 = Ph, X = O, Y = O (67%)
R^1 = 5-Br, R^2 = Ph, X = O, Y = O (66%)
R^1 = 5-OMe, R^2 = Ph, X = O, Y = O (57%)
R^1 = H, R^2 = *o*-ClC_6H_4, X = O, Y = O (48%)
R^1 = H, R^2 = *p*-FC_6H_4, X = O, Y = O (52%)
R^1 = H, R^2 = 2-thienyl, X = O, Y = O (32%)
R^1 = H, R^2 = *p*-PhC_6H_4, X = O, Y = O (30%)
R^1 = H, R^2 = Ph, X = S, Y = O (72%)
R^1 = 5-Br, R^2 = Ph, X = S, Y = O (42%)
R^1 = 5-F, R^2 = Ph, X = S, Y = O (46%)
R^1 = 5-OMe, R^2 = Ph, X = S, Y = O (60%)
R^1 = H, R^2 = *o*-$MeOC_6H_4$, X = S, Y = O (57%)
R^1 = H, R^2 = 2-thienyl, X = S, Y = O (35%)
R^1 = H, R^2 = *p*-PhC_6H_4, X = S, Y = O (36%)
R^1 = H, R^2 = Ph, X = O, Y = S (58%)
R^1 = H, R^2 = Ph, X = O, Y = NTos (86%)



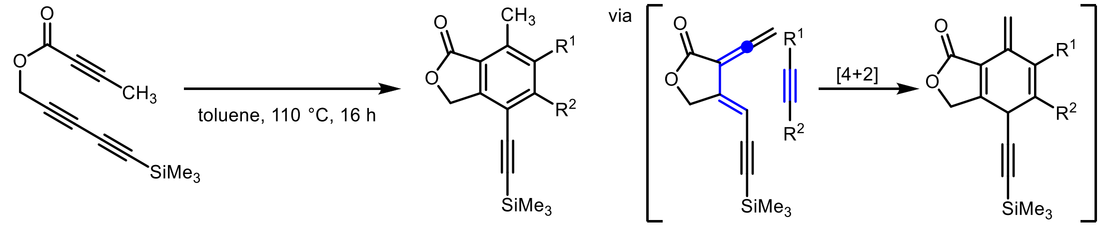
Scheme 120. Alkynylation-Alder ene-Diels–Alder domino synthesis of pentacyclic indenonespirodifurans.



10 examples (28-76%)

X = O, Y = O, R^1 = CH$_3$, R^2 = SiMe$_3$ (76%)
X = O, Y = O, R^1 = ^{n}Pr, R^2 = SiMe$_3$ (52%)
X = O, Y = O, R^1 = ^{n}Bu, R^2 = SiMe$_3$ (54%)
X = O, Y = O, R^1 = cyclohexyl, R^2 = SiMe$_3$ (28%)
X = O, Y = O, R^1 = (CH$_2$)$_2$OBn, R^2 = SiMe$_3$ (58%)
X = O, Y = O, R^1 = (CH$_2$)$_2$OBn, R^2 = ^{n}Bu (58%)
X = O, Y = O, R^1 = Me, R^2 = ^{n}Bu (70%)
X = O, Y = O, R^1 = ^{n}Bu, R^2 = ^{n}Bu (53%)
X = O, Y = H,H, R^1 = CH$_3$, R^2 = SiMe$_3$ (72%)
X = O, Y = H,H, R^1 = CH$_3$, R^2 = *p*-MeOC$_6$H$_4$ (74%)

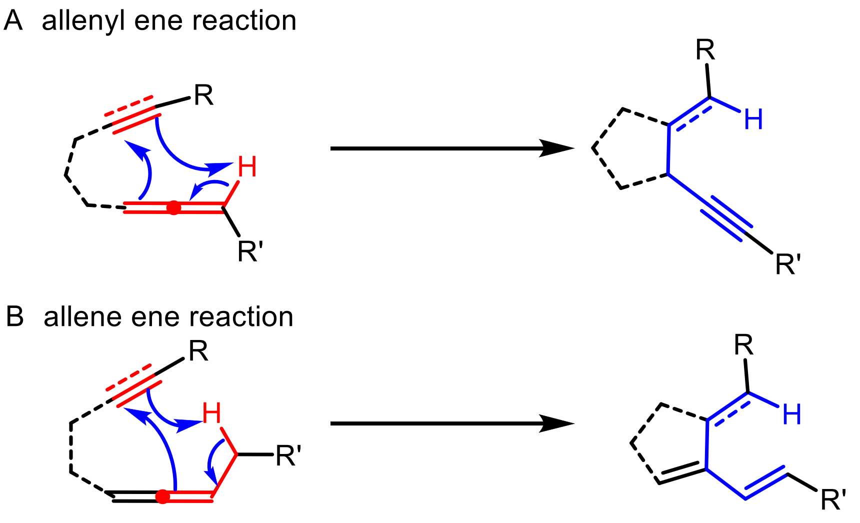
Scheme 121. Formal [2 + 2 + 2] dimerization of triynes via Alder ene-Diel–Alder sequence.



9 examples (72-80%)

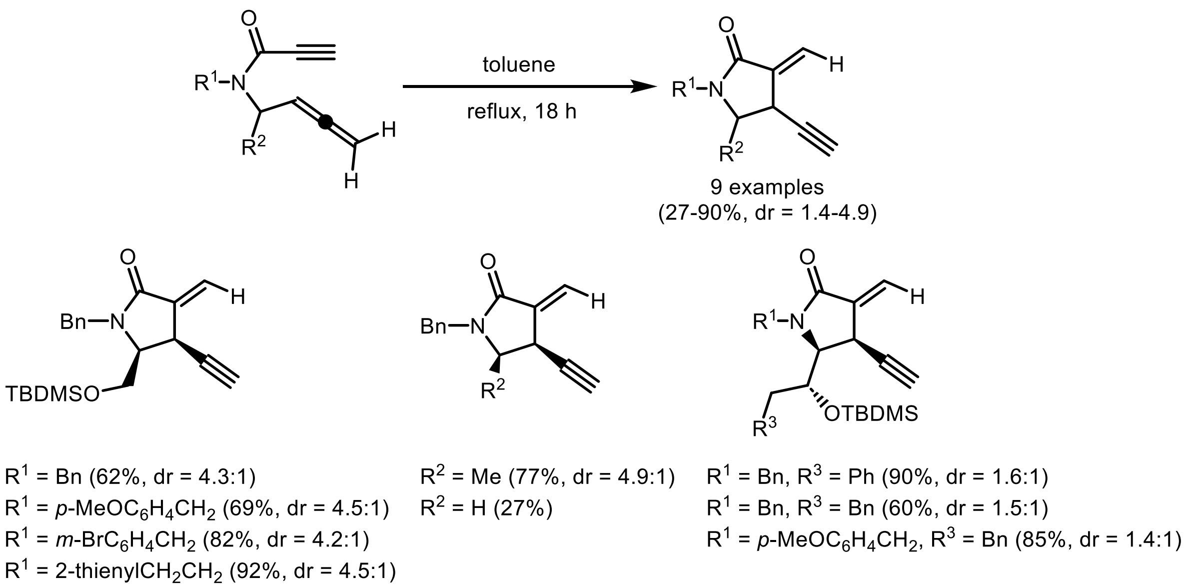
R^1 = CH$_2$OH, R^2 = C≡CSiMe$_3$ (76%)
R^1 = CH$_2$OH, R^2 = C≡C^{n}Bu (73%)
R^1 = CH$_2$OCH$_2$C≡CCH$_3$, R^2 = C≡CSiMe$_3$, + dimer (72%, 2:1)
R^1 = CH$_2$OH, R^2 = C≡CH, + dimer (90%, 4:1)
R^1 = H, R^2 = CH$_2$C≡C^{n}Bu, + dimer (75%, 1:4)
R^1 = H, R^2 = Ph (82%)
R^1 = H, R^2 = (CH$_2$)$_2$OH (44%)
R^1 = H, R^2 = SiMe$_3$, + dimer (70%, 1:1)
R^1 = H, R^2 = CMe$_2$OH, + dimer (82%, 1:1)

Scheme 122. Formal [2 + 2 + 2] dimerization of triynes via Alder ene–Diel–Alder sequence.

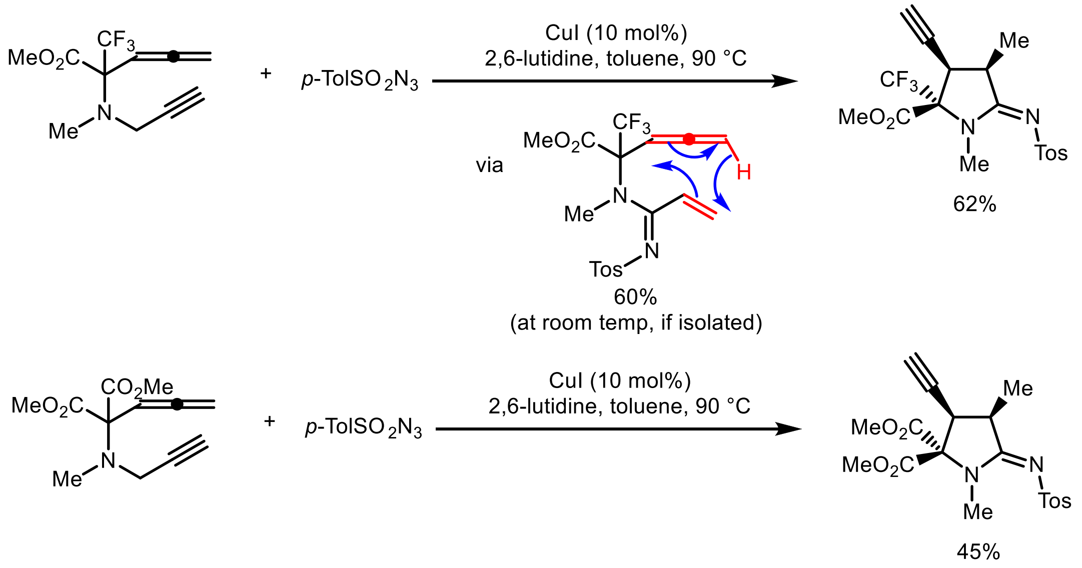

A allenyl ene reaction

B allene ene reaction

Scheme 123. Cyclizing ene reaction with A) allenes as enes via reaction of the allenyl part furnishing alkynes and B) with allenes via reaction of allyl part furnishing embedded dienes.



Scheme 124. α-Methylene-γ-lactams by thermal IMAE reaction of 1,6-allenynes.



Scheme 125. Diastereoselective synthesis of proline derivatives by allene–ene reaction initiated from allene–ynes via ketenimine rearrangement.

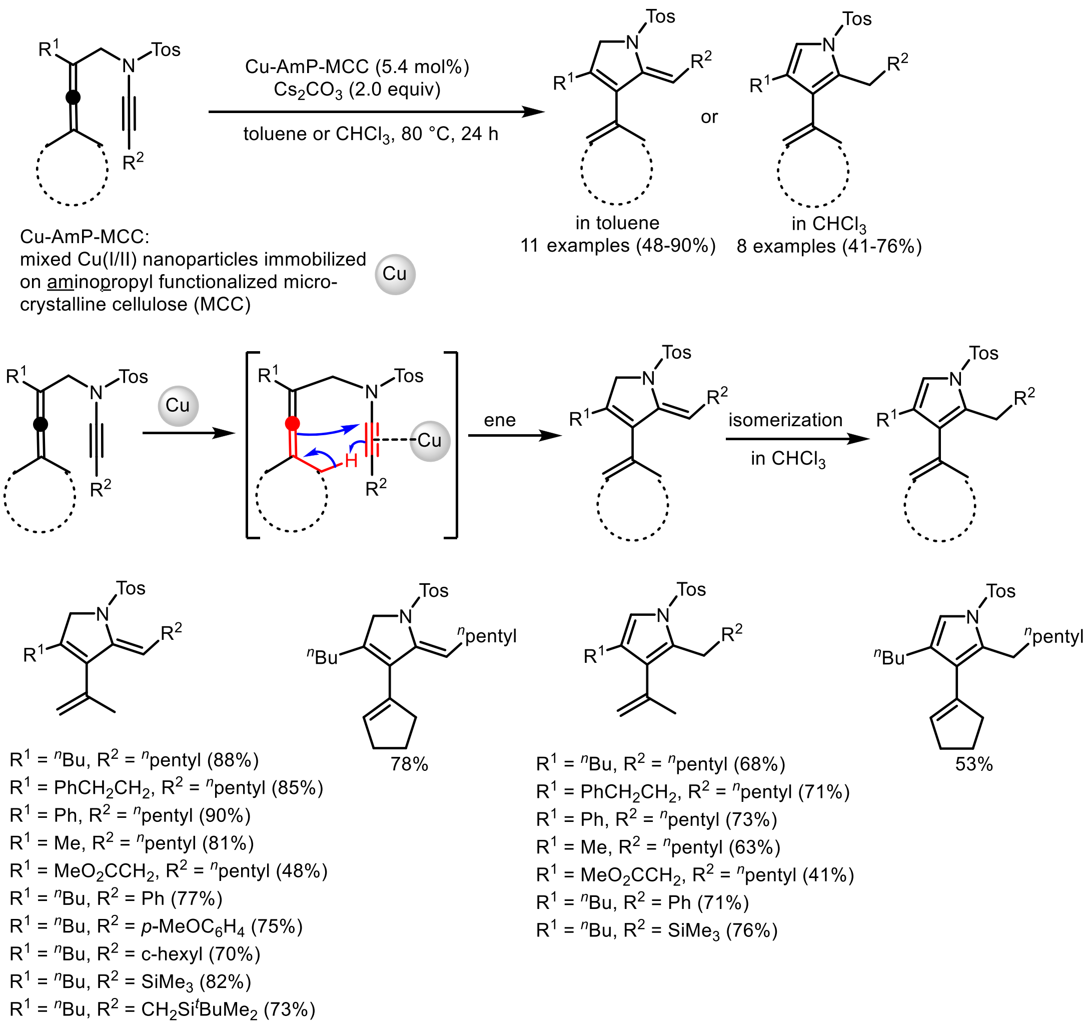
5. Miscellaneous

Under miscellaneous, several ene reactions with quite unusual enophiles are presented. Some of them have been intensively investigated in the past, yet, still new features and structure were disclosed within the past decade. Types of enophiles are cyclopropenes and bicyclobutanes.

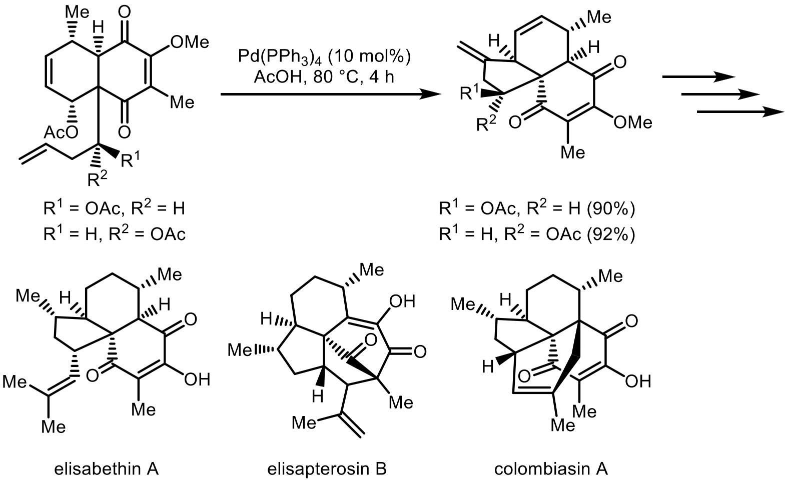
Thermal Alder ene cycloisomerizations of cyclopropenes bearing alkene moiety were shown to proceed highly diastereoselectively furnishing a series of functionalized (hetero)spiro[2.4]heptanes with excellent *trans*-diasterero-selectivity (**Scheme 131**).[123]

Pérez-Castells and coauthors disclosed an elegant one-pot alkenylation-Alder ene cycloisomerization of cyclopropenes give (aza)spiro[2.4]-heptanes and spiro[2.5]octanes in high yields in a stereoselective fashion (**Scheme 132**).[124]

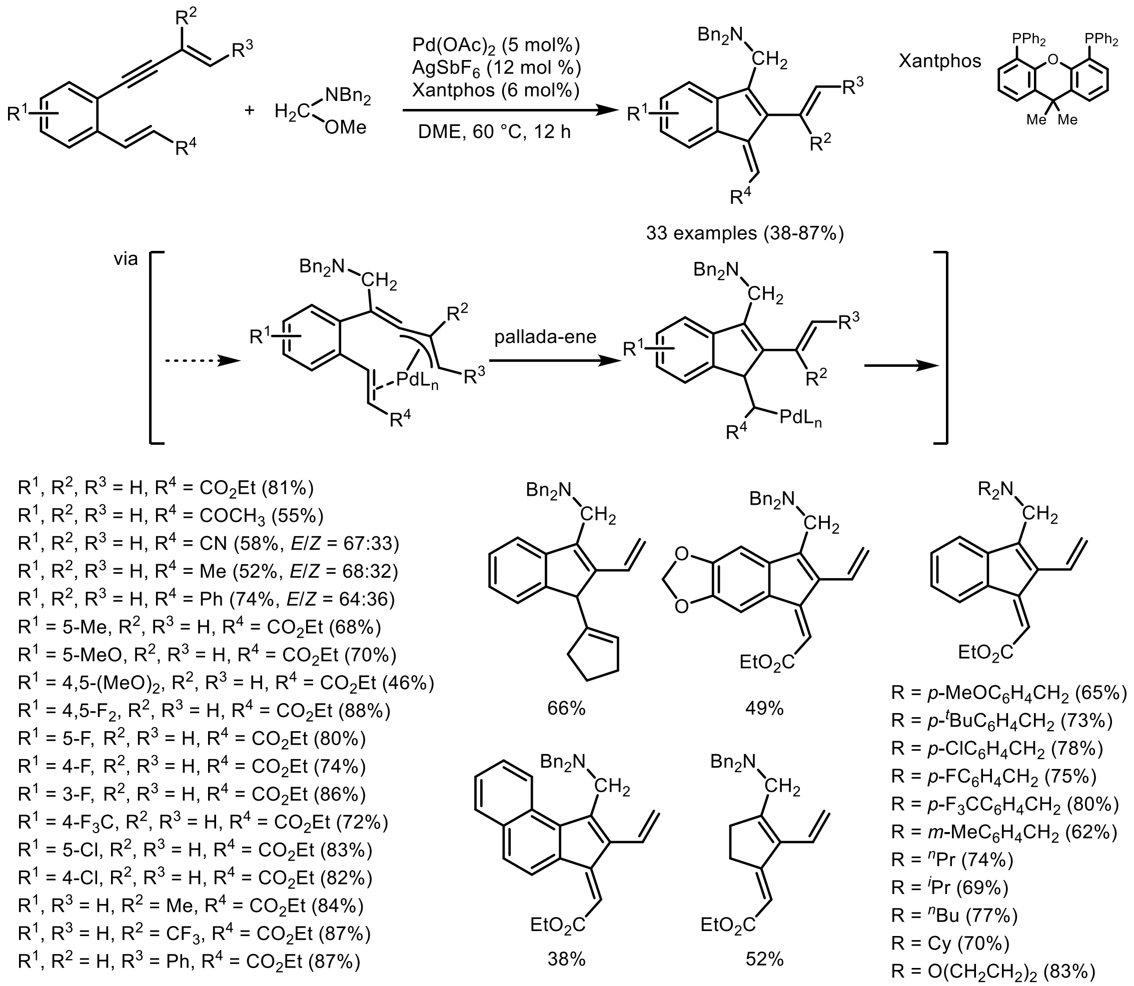
Methyl 1,3-cyclohexadiene 2-carboxylate was shown to undergo thermal pericyclic dimerization reactions, i.e., Diels–Alder reaction and the unusual [6 + 4]-ene reaction (**Scheme 133**).[125]



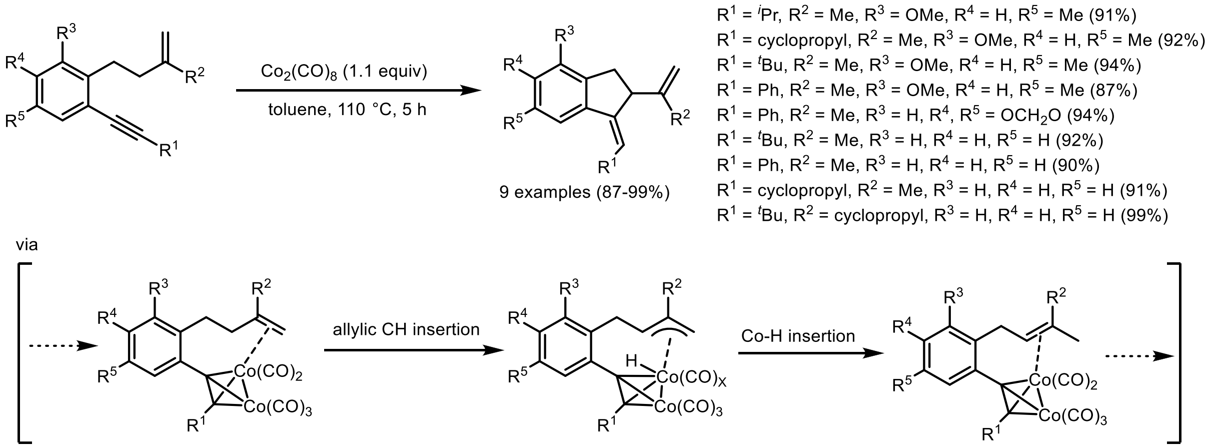
Scheme 126. Immobilized Cu-nanoparticle catalyzed Alder ene cyclization of allenynamides to pyrrolines (in toluene) or pyrroles (in chloroform).



Scheme 127. Pd-catalyzed pallada-ene cyclization as a key step in the stereoselective formal otsynthesis of diterpenes elisapterosin B and colombiasin A as well as of derivatives of elisabethin A.

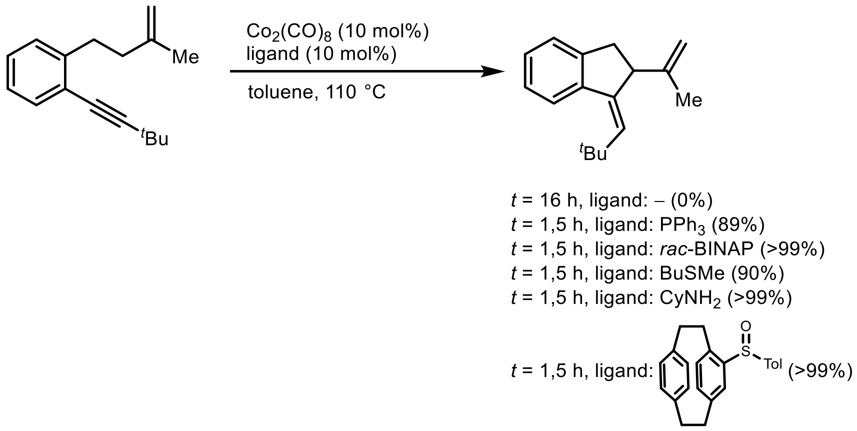


Scheme 128. Synthesis of aminomethylated benzofulvenes via Pd-catalyzed aminomethylative Oppolzer-type cyclization of *ortho*-styryl substituted enynes.

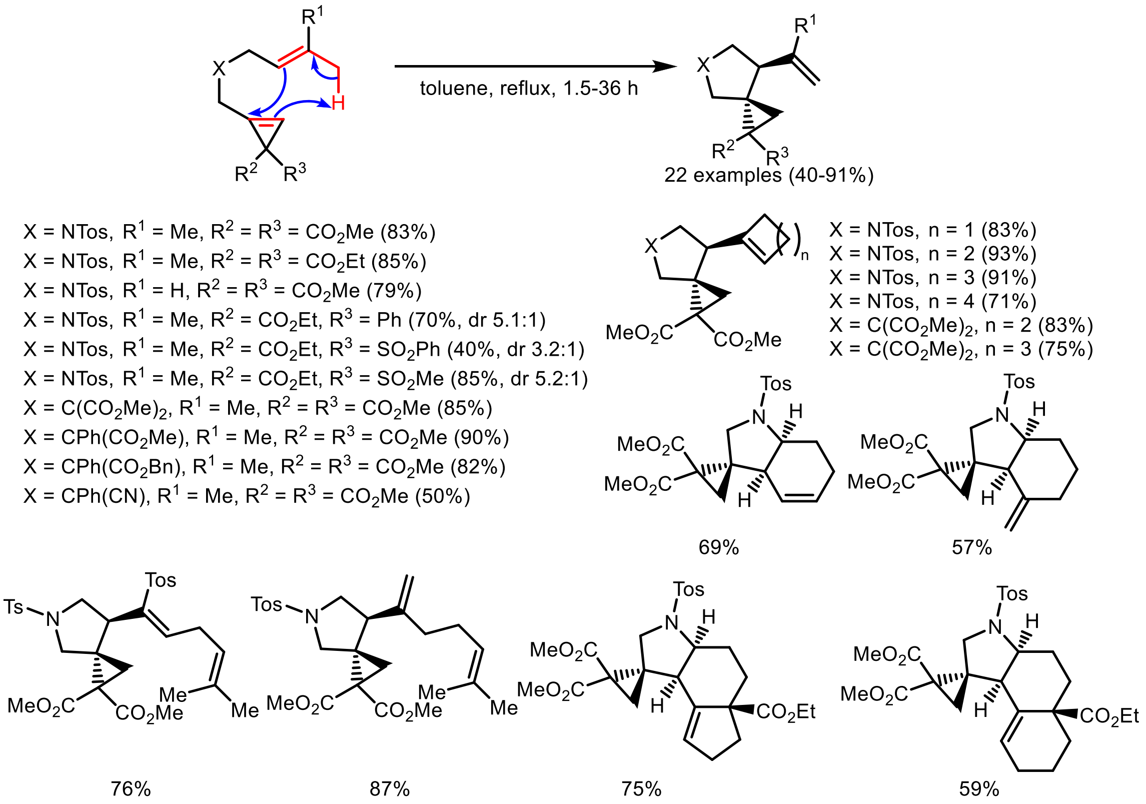


Scheme 129. Cobalt-mediated cycloisomerization of 1,7-enynes.

Chen, Houk, and Cammi reported detailed quantum chemical calculations on thermal dimerizations of 1,3-cyclohexadiene at ambient and very high pressures using the extreme pressure-polarizable continuum model (XP-PCM).[126] The computed high-pressure reaction profiles showed that the reaction barrier is more



Scheme 130. Cobalt-catalyzed cycloisomerization of a 1,7-enyne.

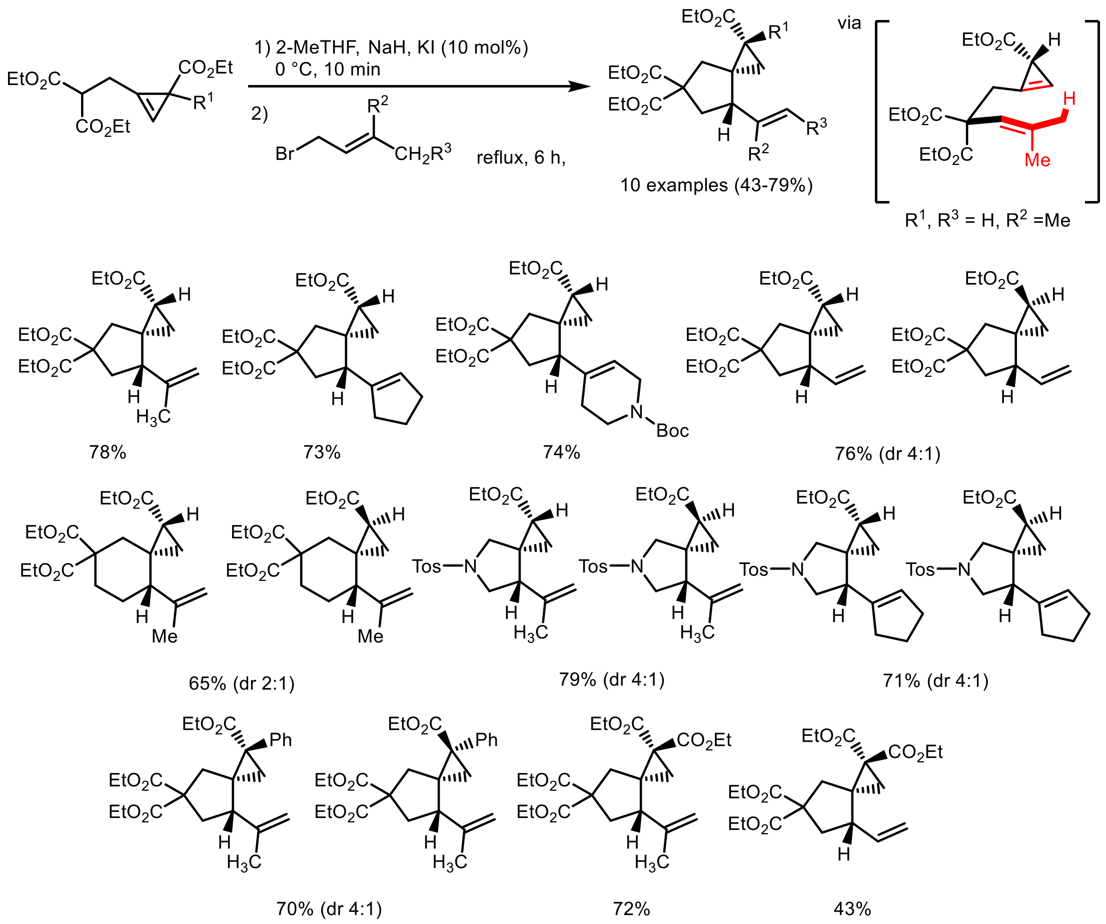


Scheme 131. Alder ene cycloisomerization of alkene-tethered cyclopropenes to functionalized (hetero)spiro[2.4]heptanes with excellent *trans*-diastereroselectivity.

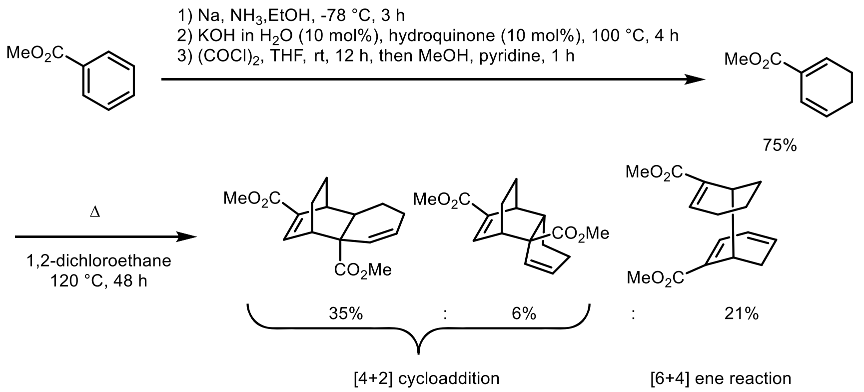
considerably lowered in concerted reactions than in stepwise processes, such as for the [6 + 4] ene reaction. The computed activation volumes by XP-PCM were found to excellently match with experimental data, thereby verifying competing mechanisms in the thermal dimerization of 1,3-cyclohexadiene.

Besides organic components in ene reactions, also carboryne (1,2-dehydro-o-carborane), known for similar reactivity in cycloadditions as benzyne, was shown to react with toluene besides [4 + 2] cycloaddition as well in domino [4 + 2]-homo-Diels-Alder reaction, benzylic CH-insertion and ene-[2 + 2] cycloaddition sequences, however, only as minor byproducts (**Scheme 134**).[127]

Alkenes and oximes can react either by [3 + 2] dipolar cycloaddition to form isoxazolidines or by ene-like reaction, where the oxime is the ene component, to give nitrones. The corresponding products from intramolecular reactions of alkenyl oximes are bicyclic

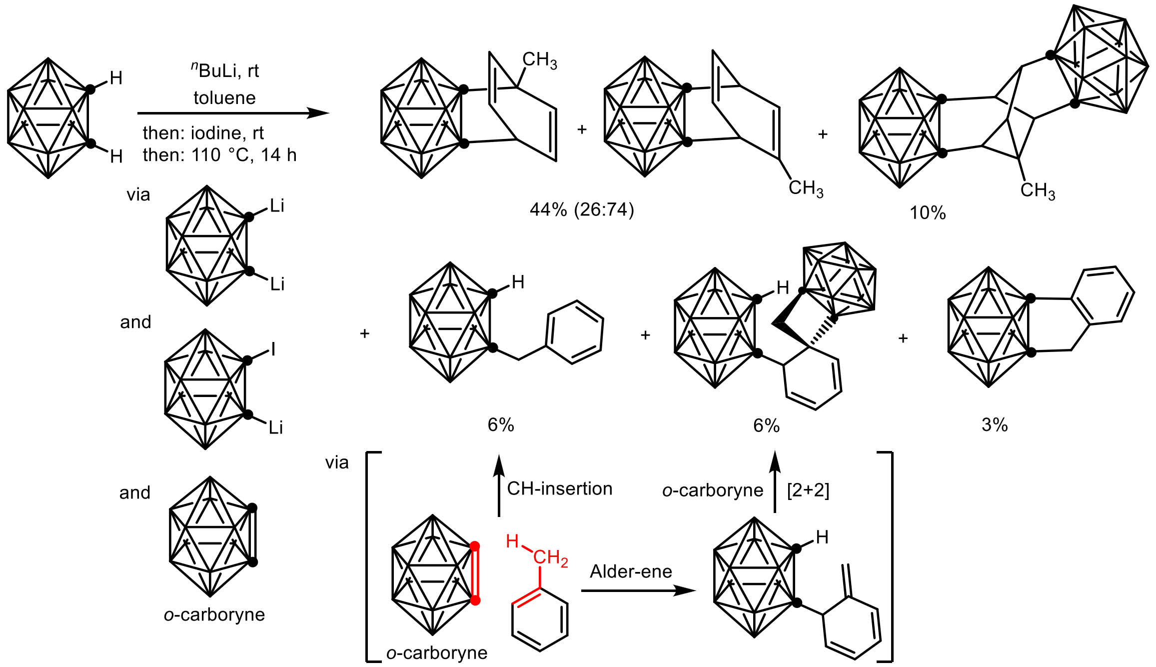


Scheme 132. Stereoselective one-pot alkenylation-Alder ene cycloisomerization of cyclopropenes to give (aza)spiro[2.4]-heptanes and spiro[2.5]octanes.

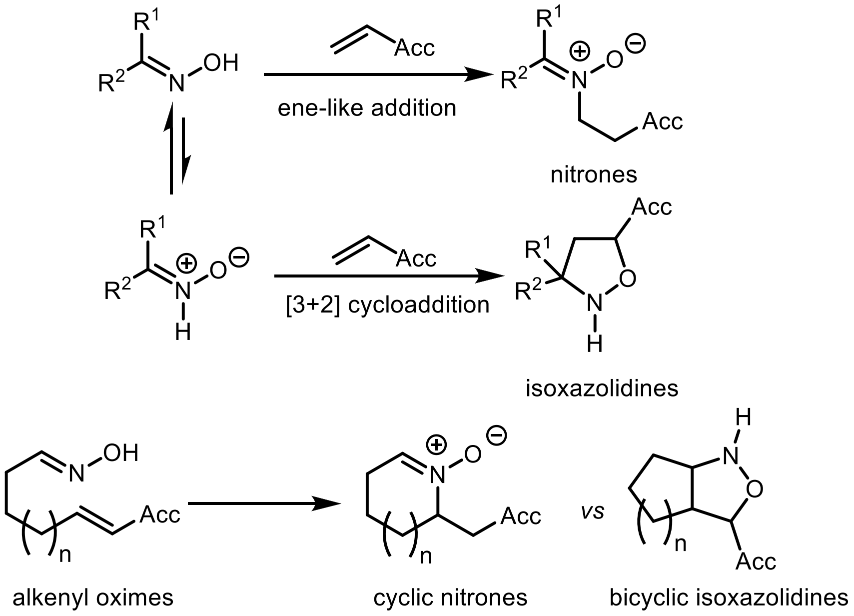


Scheme 133. Synthesis of methyl 1,3-cyclohexadiene 2-carboxylate and dimerization via [4 + 2] cycloaddition and [6 + 4] ene reaction.

isoxazolidines or cyclic nitrones (**Scheme 135**).[128] In a computational study, Merino and coauthors investigated the synchronicity for both inter- and intramolecular versions. The activation barriers for the dipolar cycloaddition in intermolecular reactions are often too high, therefore, only the favored ene-like reactions with electron-poor alkenes can be predicted as experimentally feasible. However, for intramolecular reaction, ene-like processes and oxime olefin cycloadditions are competing and the activation barriers are considerably lower for



Scheme 134. Reaction of *o*-carboryne with toluene via cycloaddition, insertion, and ene-[2 + 2] cycloaddition sequences.

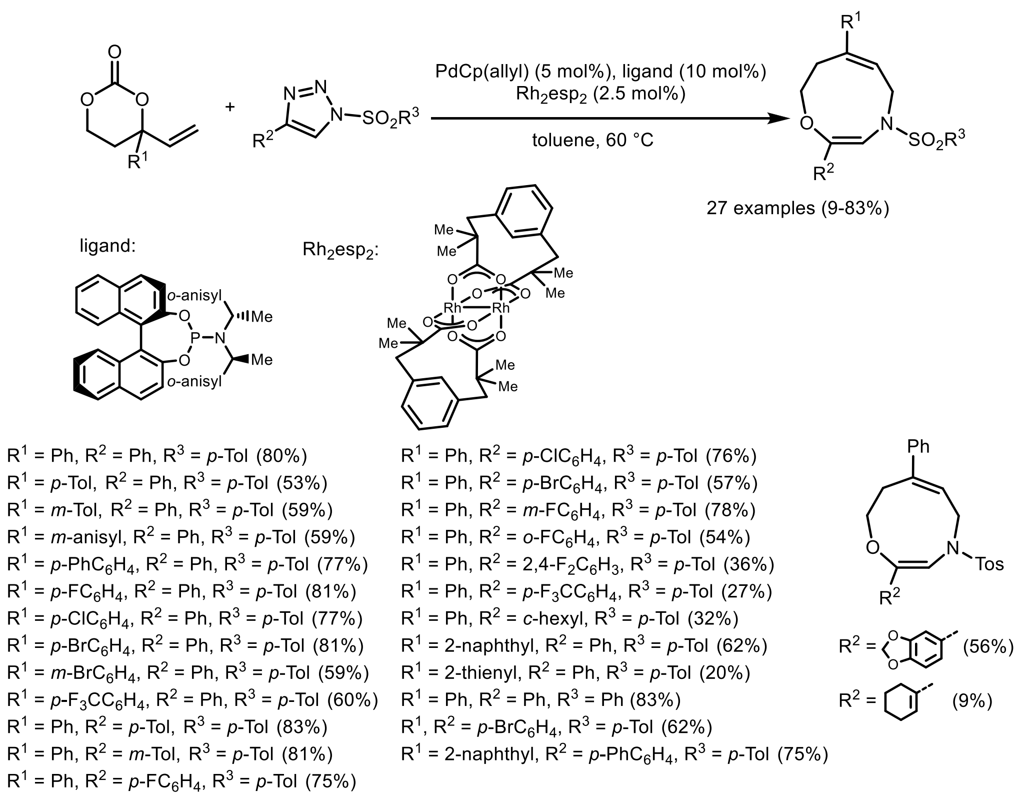


Scheme 135. Intermolecular (oxime and alkene) and intramolecular (alkenyl oxime) reactions according to the ene-like and [3 + 2] cycloaddition pericyclic manifold.

both reactions. Thereby, the behavior of up to 26 hitherto unknown substrates can be predicted.

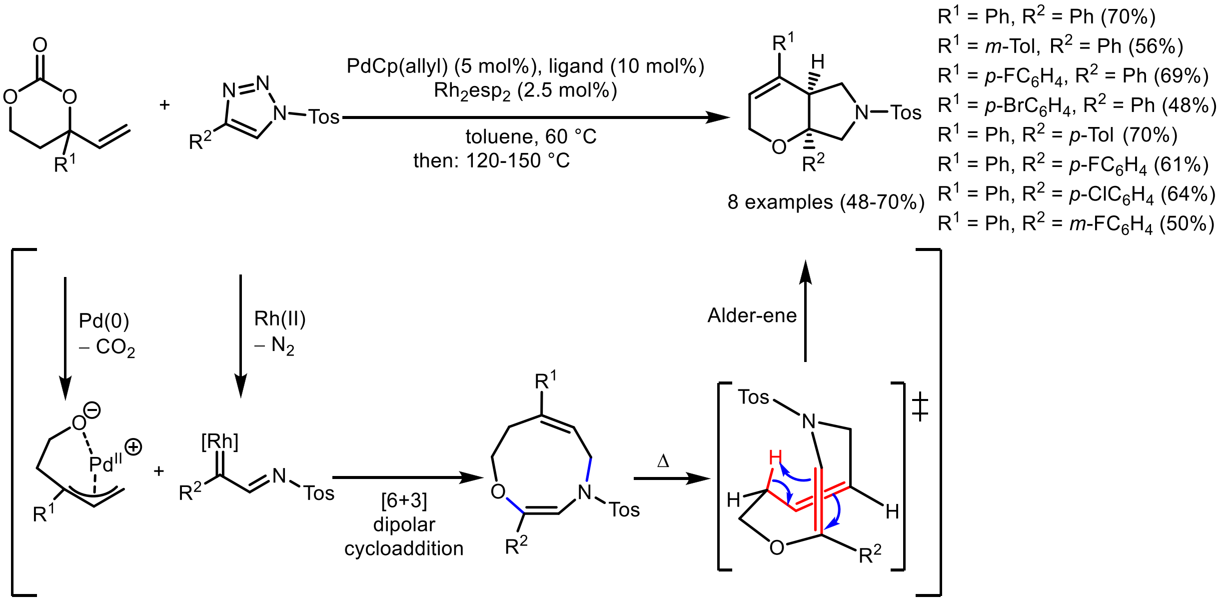
Lee, Ahn, and Lee reported a Pd(0)/Rh(II) dual catalytic [6 + 3] dipolar cycloaddition to give oxazonines in moderate to good yields (**Scheme 136**).[129] In a consecutive one-pot fashion a subsequent intramolecular transannular Alder ene rearrangement was achieved to *cis*-fused [4.3.0] bicyclic compounds, such as hexahydropyranopyrroles in good yields (**Scheme 137**).

Pronin and coauthors reported a formal indiumbromide catalyzed ene reaction of ketone-derived silyl enolethers and terminal alkynes to give 2-siloxy-1,4-dienes and β,γ-unsaturated ketones containing quaternary α-carbon centers (**Scheme 138**).[130] Test reactions



R^1 = Ph, R^2 = Ph, R^3 = p-Tol (80%)
R^1 = p-Tol, R^2 = Ph, R^3 = p-Tol (53%)
R^1 = m-Tol, R^2 = Ph, R^3 = p-Tol (59%)
R^1 = m-anisyl, R^2 = Ph, R^3 = p-Tol (59%)
R^1 = p-PhC_6H_4, R^2 = Ph, R^3 = p-Tol (77%)
R^1 = p-FC_6H_4, R^2 = Ph, R^3 = p-Tol (81%)
R^1 = p-ClC_6H_4, R^2 = Ph, R^3 = p-Tol (77%)
R^1 = p-BrC_6H_4, R^2 = Ph, R^3 = p-Tol (81%)
R^1 = m-BrC_6H_4, R^2 = Ph, R^3 = p-Tol (59%)
R^1 = p-$F_3CC_6H_4$, R^2 = Ph, R^3 = p-Tol (60%)
R^1 = Ph, R^2 = p-Tol, R^3 = p-Tol (83%)
R^1 = Ph, R^2 = m-Tol, R^3 = p-Tol (81%)
R^1 = Ph, R^2 = p-FC_6H_4, R^3 = p-Tol (75%)
R^1 = Ph, R^2 = p-ClC_6H_4, R^3 = p-Tol (76%)
R^1 = Ph, R^2 = p-BrC_6H_4, R^3 = p-Tol (57%)
R^1 = Ph, R^2 = m-FC_6H_4, R^3 = p-Tol (78%)
R^1 = Ph, R^2 = o-FC_6H_4, R^3 = p-Tol (54%)
R^1 = Ph, R^2 = 2,4-$F_2C_6H_3$, R^3 = p-Tol (36%)
R^1 = Ph, R^2 = p-$F_3CC_6H_4$, R^3 = p-Tol (27%)
R^1 = Ph, R^2 = c-hexyl, R^3 = p-Tol (32%)
R^1 = 2-naphthyl, R^2 = Ph, R^3 = p-Tol (62%)
R^1 = 2-thienyl, R^2 = Ph, R^3 = p-Tol (20%)
R^1 = Ph, R^2 = Ph, R^3 = Ph (83%)
R^1, R^2 = p-BrC_6H_4, R^3 = p-Tol (62%)
R^1 = 2-naphthyl, R^2 = p-PhC_6H_4, R^3 = p-Tol (75%)

Scheme 136. Pd(0)/Rh(II) dually catalyzed [6 + 3] dipolar cycloaddition synthesis of oxazonines.

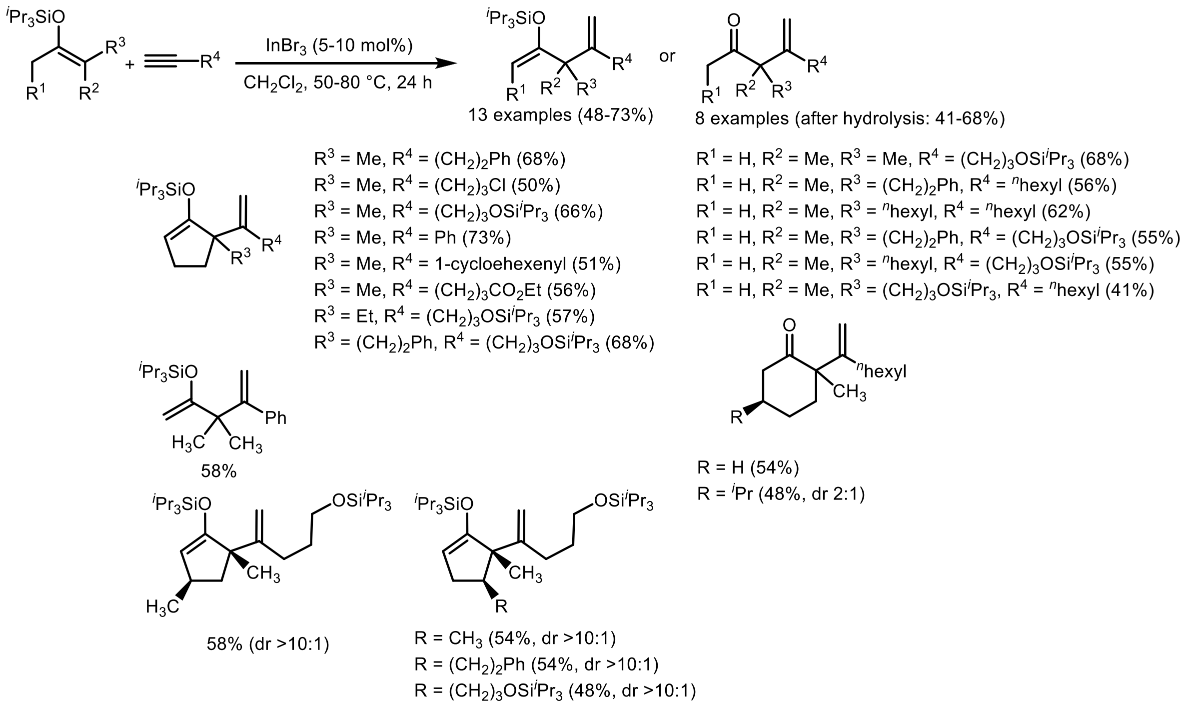


R^1 = Ph, R^2 = Ph (70%)
R^1 = m-Tol, R^2 = Ph (56%)
R^1 = p-FC_6H_4, R^2 = Ph (69%)
R^1 = p-BrC_6H_4, R^2 = Ph (48%)
R^1 = Ph, R^2 = p-Tol (70%)
R^1 = Ph, R^2 = p-FC_6H_4 (61%)
R^1 = Ph, R^2 = p-ClC_6H_4 (64%)
R^1 = Ph, R^2 = m-FC_6H_4 (50%)

Scheme 137. Pd(0)/Rh(II) dually catalyzed [6 + 3] dipolar cycloaddition-Alder ene synthesis of hexahydropyranopyrroles.

indicate that the reaction sequence begins with an indium-mediated alkyne activation and ene-type reaction, which occurs under desilylation. The tris(isopropyl)silyl group is reintroduced again at a later stage.

The central C–C bond in bicyclo[1.1.0]butanes was shown by Bai and coauthors to readily participate in an intermolecular Alder ene reaction with β-fluoroalkyl-α,β-unsaturated ketones giving rise at 80 °C to the



13 examples (48-73%)

R^3 = Me, R^4 = $(CH_2)_2Ph$ (68%)
R^3 = Me, R^4 = $(CH_2)_3Cl$ (50%)
R^3 = Me, R^4 = $(CH_2)_3OSi^{i}Pr_3$ (66%)
R^3 = Me, R^4 = Ph (73%)
R^3 = Me, R^4 = 1-cycloehexenyl (51%)
R^3 = Me, R^4 = $(CH_2)_3CO_2Et$ (56%)
R^3 = Et, R^4 = $(CH_2)_3OSi^{i}Pr_3$ (57%)
R^3 = $(CH_2)_2Ph$, R^4 = $(CH_2)_3OSi^{i}Pr_3$ (68%)

8 examples (after hydrolysis: 41-68%)

R^1 = H, R^2 = Me, R^3 = Me, R^4 = $(CH_2)_3OSi^{i}Pr_3$ (68%)
R^1 = H, R^2 = Me, R^3 = $(CH_2)_2Ph$, R^4 = ^{n}hexyl (56%)
R^1 = H, R^2 = Me, R^3 = ^{n}hexyl, R^4 = ^{n}hexyl (62%)
R^1 = H, R^2 = Me, R^3 = $(CH_2)_2Ph$, R^4 = $(CH_2)_3OSi^{i}Pr_3$ (55%)
R^1 = H, R^2 = Me, R^3 = ^{n}hexyl, R^4 = $(CH_2)_3OSi^{i}Pr_3$ (55%)
R^1 = H, R^2 = Me, R^3 = $(CH_2)_3OSi^{i}Pr_3$, R^4 = ^{n}hexyl (41%)

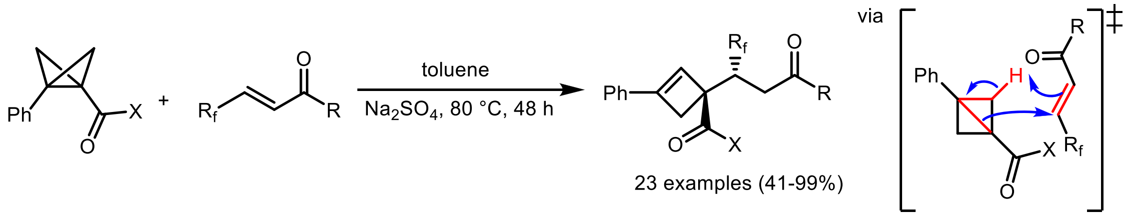
58%

R = H (54%)
R = ^{i}Pr (48%, dr 2:1)

58% (dr >10:1)

R = CH_3 (54%, dr >10:1)
R = $(CH_2)_2Ph$ (54%, dr >10:1)
R = $(CH_2)_3OSi^{i}Pr_3$ (48%, dr >10:1)

Scheme 138. Intermolecular $InBr_3$-catalyzed formal ene synthesis of 2-siloxy-1,4-dienes and β,γ-unsaturated ketones from ketone-derived silyl enol ethers and terminal alkynes.



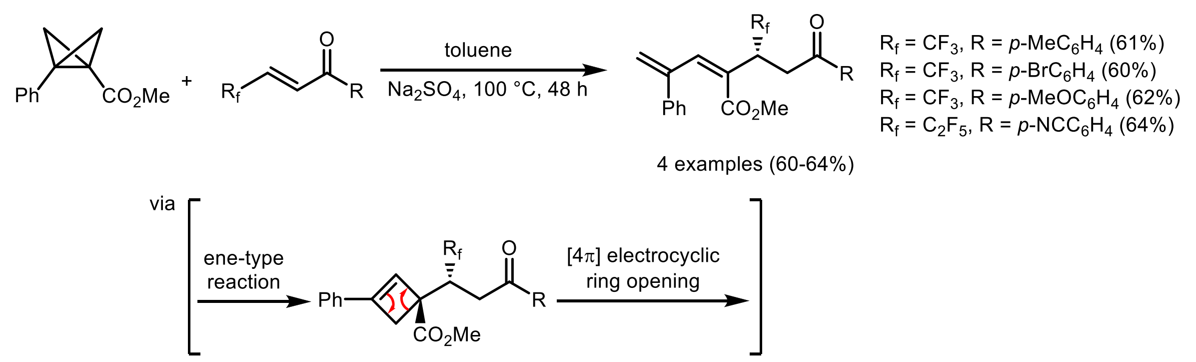
23 examples (41-99%)

X = OMe, R_f = CF_3, R = *p*-MeC_6H_4 (91%, dr 17:1)
X = OMe, R_f = CF_3, R = Ph (93%, dr 18:1)
X = OMe, R_f = CF_3, R = *p*-FC_6H_4 (84%, dr >20:1)
X = OMe, R_f = CF_3, R = *p*-ClC_6H_4 (95%, dr >20:1)
X = OMe, R_f = CF_3, R = *p*-BrC_6H_4 (72%, dr 14:1)
X = OMe, R_f = CF_3, R = *p*-$O_2NC_6H_4$ (90%, dr >20:1)
X = OMe, R_f = CF_3, R = *p*-$F_3CC_6H_4$ (70%, dr 20:1)
X = OMe, R_f = CF_3, R = *p*-$MeOC_6H_4$ (90%, dr 14:1)
X = OMe, R_f = CF_3, R = *m*-FC_6H_4 (99%, dr 20:1)
X = OMe, R_f = CF_3, R = *m*-ClC_6H_4 (95%, 17:1)
X = OMe, R_f = CF_3, R = *m*-BrC_6H_4 (94%, dr 15:1)
X = OMe, R_f = CF_3, R = *m*-$F_3CC_6H_4$ (70%, dr 20:1)
X = OMe, R_f = CF_3, R = *o*-FC_6H_4 (80%, dr 18:1)
X = OMe, R_f = CF_3, R = *o*-BrC_6H_4 (63%, dr 20:1)
X = OMe, R_f = CF_3, R = 2-furyl (95%, dr 20:1)
X = OMe, R_f = CF_3, R = 2-naphthyl (96%, dr 18:1)
X = OMe, R_f = C_2F_5, R = *p*-NCC_6H_4 (98%, dr >20:1)
X = OMe, R_f = C_2F_5, R = *p*-MeC_6H_4 (73%, dr >20:1)
X = OMe, R_f = C_2F_5, R = *p*-BrC_6H_4 (99%, dr >20:1)
X = OMe, R_f = C_2F_5, R = *p*-$MeOC_6H_4$ (41%, dr >20:1)
X = OBn, R_f = CF_3, R = *p*-MeC_6H_4 (76%, dr 17:1)
X = *N*-(2,4-Me_2pyrazolyl), R_f = CF_3, R = *p*-MeC_6H_4 (75%, dr 17:1)
X = NMeOMe, R_f = CF_3, R = *p*-MeC_6H_4 (85%, dr >20:1)

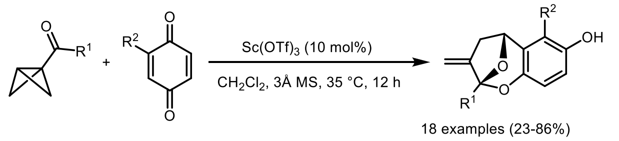
Scheme 139. Alder ene-type addition of bicyclo[1.1.0]butanes as ene-type partners with β-fluoroalkyl-α,β-unsaturated ketones as enophiles.

diastereoselective formation of cyclobutene-substituted β-fluoroalkyl ketones in good to excellent yields (**Scheme 139**).[131] The unusual function of the bicyclo[1.1.0]butane as an ene-type partner is driven by the strain release. At 100 °C the ene-type product transform by electrocyclic cyclobutene ring opening to give the corresponding conjugated 1,3-butadienes (**Scheme 140**).

In a similar fashion, upon a study of Lewis acid catalyzed reactions of bicyclo[1.1.0]butanes with quinones, Chen, Zhou, and coworkers discovered that monosubstituted bicyclo[1.1.0]butane ketones with quinones react



Scheme 140. Alder ene-electrocyclic ring opening sequence of bicyclo[1.1.0]butanes and β-fluoroalkyl-α,β-unsaturated ketones to give conjugated 1,3-butadienes.

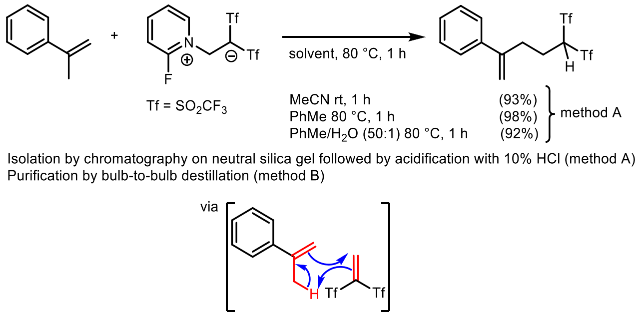


R^1 = 2-naphthyl, R^2 = CO$_2$Me (86%)
R^1 = 2-naphthyl, R^2 = CO$_2$Et (65%)
R^1 = 2-naphthyl, R^2 = CO$_2$^{i}Pr (74%)
R^1 = 2-naphthyl, R^2 = CO$_2$^{t}Bu (87%)
R^1 = 2-naphthyl, R^2 = CO$_2$Bn (78%)
R^1 = 2-naphthyl, R^2 = CO$_2$CH$_2$(3-BrC$_6$H$_4$) (53%)
R^1 = 2-naphthyl, R^2 = CO$_2$CH$_2$(4-BrC$_6$H$_4$) (62%)
R^1 = 2-naphthyl, R^2 = CO$_2$CH$_2$allyl (82%)
R^1 = 2-(5-MeOnaphthyl), R^2 = CO$_2$Me (47%)
R^1 = 2-(6-MeOnaphthyl), R^2 = CO$_2$Me (51%)
R^1 = Ph, R^2 = CO$_2$Me (41%)
R^1 = 2-thienyl, R^2 = CO$_2$Me (23%)
R^1 = cyclohexyl, R^2 = CO$_2$Me (51%)
R^1 = cyclobutyl, R^2 = CO$_2$Me (51%)
R^1 = ^{i}Pr, R^2 = CO$_2$Me (62%)
R^1 = ^{t}Bu, R^2 = CO$_2$Me (76%)
R^1 = ^{n}Bu, R^2 = CO$_2$Me (74%)
R^1 = Bn, R^2 = CO$_2$Me (62%)

Scheme 141. Unexpected Alder ene-electrocyclic ring opening sequence of substituted bicyclo[1.1.0]butanes and a quinone derivatives to give fused benzoxepines and scope of the reaction.

to undergo a Alder ene-4π electrocyclic ring-opening-[4 + 2] cycloaddition sequence, to give fused benzoxepines in good yields (**Scheme 141**).[132]

Gem-Bis(triflyl)ethylene ($Tf_2C{=}CH_2$) is a quite electron deficient alkene and a suitable reaction partner in cycloadditions. Matsumoto and coworkers could show that $Tf_2C{=}CH_2$ also participates in Alder ene reactions with alkenes bearing allylic hydrogen atoms, i.e., enes, as the enophile partner in solvent systems of variable polarity (**Scheme 142**).[133] Therefore, this unusual enophile can be readily employed for the introduction of the superacidic bis(triflyl)methyl group in corresponding *E*-alkenes, also in Alder ene–Alder ene or Alder ene–Diels–Alder sequences in a pseudo-multicomponent fashion (**Scheme 143**).



Isolation by chromatography on neutral silica gel followed by acidification with 10% HCl (method A)
Purification by bulb-to-bulb destillation (method B)

Scheme 142. Alder ene reactions of α-methyl styrene with in situ generated $Tf_2C{=}CH_2$ from the zwitterion 2-(2-fluoropyridin-1-ium-1-yl)−1,1-bis((trifluoromethyl)sulfonyl)ethan-1-ide.

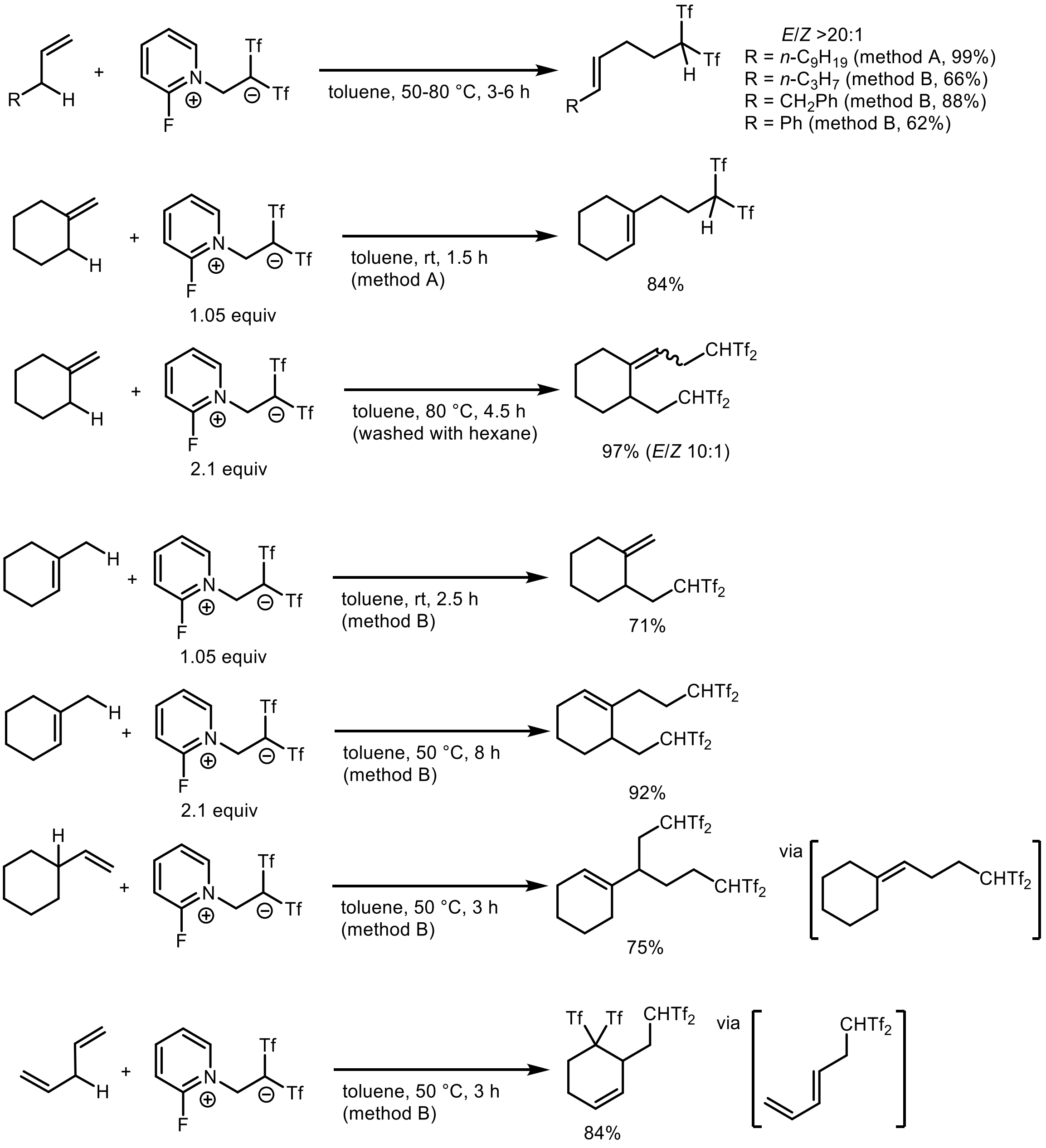
6. Ene Reactions for Functionalization of Polymers and Renewable Raw Materials

The last chapter in this overview on ene reactions with carbon enophiles is dedicated rather to an applied aspect. As so often, once organic reactions become mature they tend to be increasingly applied to molecular materials in the ongoing quest to find new applications, eventually new products with special performance. A major advantage of ene reactions is that they often proceed without additives in a thermal fashion, simultaneously introducing a new functionality by either the ene or enophile. A second relevant aspect of applied research utilizing ene reactions is the functionalization of renewable raw materials for creating products with specific properties. Renewable raw materials offer the immense advantage that they are quite abundant and as bioproducts quite easily accessible.

Functionalization of alkene monomers, in particular unsaturated fatty acids as renewable resources, as well as of polymers containing alkenyl end groups or double bonds in the repeating units can be very well derivatized by thermal or catalyzed ene reactions with conjugated olefinic or acetylenic enophiles. These postsynthetic polymer products are often studied for improving materials' performances in various applications.

Polyisobutenes find many applications ranging from additives of lubricants and gasolines to adhesives. Maleination of polyisobutene is readily achieved by thermal Alder ene reaction with maleic anhydride (**Scheme 144**).[134,135]

In the discussion of alternating radical copolymerization of maleic anhydride or related acceptor comonomers with α-olefins, Nifant'ev and coauthors also considered the possibility of Alder ene side reactions between olefin

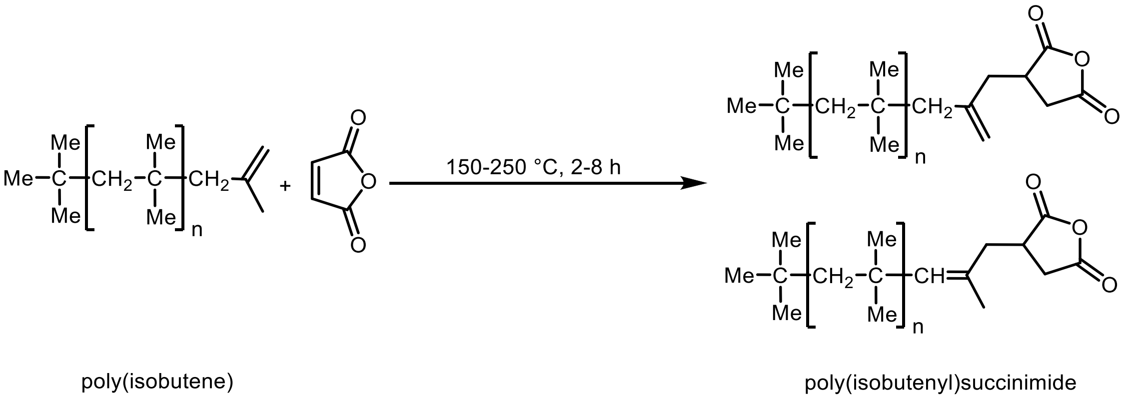


Scheme 143. Alder ene reactions of alkenes with in situ generated $Tf_2C{=}CH_2$and sequences.

enes and maleic anhydride enophile.[136] Accompanying DFT calculations revealed that free enthalpies of activation $\Delta G = 33.9$ kcal mol^{-1} suggest this mode of side reactions only to occur at elevated reaction temperatures.

Low melt viscosity polymeric *O*-Allyl aralkyl phenolic resins (OAX) can be cross-linked with bismaleimides at elevated temperature either by direct Alder ene addition of allyl ether moieties and maleimide enophile part, or after Claisen rearrangement to allyl phenol moieties, which then serve as ene component for Alder ene reaction with the maleimide enophiles.[137–139] With increasing maleimide loading the glass transition temperature T_g, the thermal stability, and the crosslink density the cocured polymer network can be increased. With OAX transformed by thermally Claisen rearrangement the generated phenols were reacted with *N*-(*p*-carbonylchlorophenyl)maleinimide by polymer analogs esterification to give single strand multiply ene and enophile decorated sites (one component resin) for inter- and IMAE cross-linking to cured thermally stable resins.[140]

Polymers resulting from Alder ene and/or Diels–Alder cross-linking of natural rubber furnishing by subsequent cross-linking upon vulcanization with sulfur (high temperature curing) rubber-type thermally stable materials.[141] Similar curing effects were also reported for natural rubber/chloroprene rubber blends formed



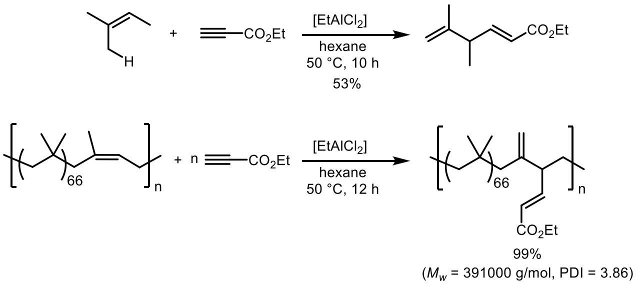
Scheme 144. Maleination of polyisobutene by thermal Alder ene reaction with maleic anhydride.

by Alder ene/Diels–Alder-sulfurization cross-linking with bismaleimides.[142] The Alder ene cross-linked *cis*-isoprene rubber can be vulcanized at high temperature reversion free.[143]

[CHECKED] Maleic anhydride-grafted polybutadiene was reacted by anhydride opening acylation of with aramid fibers resin to give an excellent fiber dispersion, both in the visual image of the molded sheet and the scanning electron microscope image of the fractured surface.[144] This resin can be further cross-linked with bismaleimide via Alder ene and Diels–Alder reactions furnishing materials with enhanced fiber-matrix adhesion.

Starting from renewable eugenol, i.e., 4-allyl-2-methoxyphenol, a trifunctional phosphate monomer serves as a starting point for Alder ene/Diels–Alder cross-linking polymerization to generate a series of thermosets by variation of the core units of the bismaleimides. With *N*, *N*'−1,3-phenylene bismaleimide and polydimethylsiloxane bismaleimide excellent thermal properties with elevated degradation temperatures could be obtained.[145]

Jia and coauthors reported grafting of thermoplastic elastomer isobutylene-isoprene rubber with ethyl propiolate via polymer analogous Alder ene reaction to give a polymer derivative with geminal vinylidene-acrylate motifs that are well-suited for curing cross-linking by radical reaction peroxide or bismaleinimide by Alder ene reaction (**Scheme 145**).[146]



Scheme 145. Lewis acid catalyzed Alder ene model reaction of 2-methyl-2-butene and ethylpropiolate and polymer analogous Alder ene functionalization of isobutylene-isoprene rubber.

Functionalization of double bonds of unsaturated fatty acids, as they occur as triglycerides in vegetable oils, by reaction with maleic anhydride provides a facile entry to materials that can enhance water dispersion of oils as used in industrial applications. In a model study with *trans*-3-octene, methyl oleate, and ethyl linoleate as reference systems for the reaction with maleic anhydride comprehensive ^{1}H NMR spectra of the alkenyl succinic anhydride moieties bound to the organic chains were clearly assigned.[147] The ene reaction of unsaturated fatty acids of triglyceride oils with vinyltrialkoxysilanes was studied with ^{1}H NMR and thermogravimetric analysis for characterizing the obtained grafting products.[148] This grafting of vinyltrimethoxysilane onto natural oils from soybean, canola and Abyssinian oils represents a one-component, moisture activated cure system the employed natural oils.

Soybean oil is particularly rich in multiple unsaturated fatty acid residues in the triglyceride. Zhou, Huang, and Wang showed that maleinization of soybean oil with maleic anhydride and subsequent ammonolysis furnished highly water-soluble maleamic acid decorated soybean oil, which was employed as a green, renewable material for sizing paper.[149] At elevated temperature, Rh catalysts have been shown to mediate and/or catalyze the maleination of monounsaturated fatty acids.[150] In a mass spectrometric mechanistic study, grafting maleic anhydride onto the double bonds of unsaturated acids was investigated.[151] The occurrence of multiple addition products with and without shift of the double bonds indicated that both ene and radical mechanisms might be operative.

7. Conclusion

After more than 80 years since their discovery by Alder, Pascher, and Schmitz in 1943,[152] the reaction later named the (Alder) ene reaction has become an evergreen among addition and cyclization reactions involving unsaturated functionalities. Characteristic features of this unique, highly atomeconomical bond-forming process are the coupling of densely functionalized or substituted enes (alkenes, alkynes, or allenes bearing a transferable hydrogen atom in allylic, propargylic, or allenyl position) with enophiles (alkenes, alkynes, allenes, and arynes). The reaction typically displays excellent regio- and stereoselectivity and increases the molecular, structural, and functional complexity of the resulting products—closely resembling the well-known Diels–Alder reaction.

While pericyclic processes have remained dominant, metal-mediated (metalla-ene reactions) and catalyzed cycloisomerizations and additions have increasingly enriched the synthetic chemist's toolbox for accessing ene-type products. Particularly over the past decade, transformations involving arynes as highly reactive enophile components have gained importance. For the construction of complex polycarbo- and heterocyclic structures, the pericyclic nexus has once again proven to be exceptionally powerful.

Moreover, Alder ene reactions are now increasingly applied in the synthesis of complex molecules, making the methodology highly relevant for the preparation of functional compounds in both the life sciences and materials science. Considering the decades-long prevalence of ene reactions in organic synthesis, it is very likely that this golden thread is spun further to expand, particularly through the inclusion of heteroatom-containing enes and enophiles, in both uncatalyzed and catalyzed variants. Clearly, the sky is the limit for ene reactions.

Acknowledgments

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Conflict of Interest

The author declare no conflict of interest.

Data Availability Statement

Data sharing not applicable to this article as no datasets were generated or analyzed during the current study.

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