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Advances in Tandem Reactions with Organozinc Reagents

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The design and implementation of tandem reactions provides organic chemists with numerous challenges, in particular that of undesired cross-reactivity between substrates. Among organometallics, the use of organozinc reagents in tandem reactions provides several advantages as a result of their broad functional group tolerance, and compatibility with transition metals. This review highlights prominent examples of recent advances in tandem reactions with organozinc reagents that illustrate their potential in organic synthesis.

1. Introduction

Tandem reactions refer to synthetic strategies that combine multiple reaction steps into a single synthetic operation.[1] By doing so, molecular complexity may be achieved rapidly, and in a single pot. Compared to the corresponding stepwise sequences of reactions, tandem approaches can save time, energy, labor, and minimize the generation of waste. Moreover, the synthetic intermediates involved need not be stable enough for isolation, because they are quickly transformed by subsequent reactions into lower energy species. In certain cases, the reaction profiles of tandem reactions are different than those of the corresponding stepwise reaction sequences, creating new reaction pathways, and often leading to different products. For these reasons, the design and implementation of tandem reactions, while challenging, remains an important and valuable endeavor, as witnessed by the number of reviews covering various aspects of these reactions.[2-10]

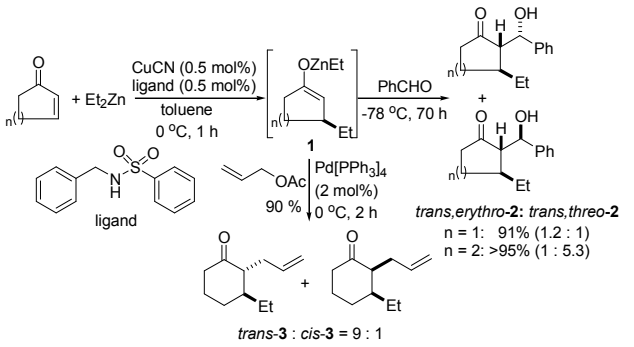
Organozinc reagents have been widely used in organic synthesis for more than 150 years. Their use in tandem reactions is particularly advantageous because they tolerate a variety of functional groups, and can be easily coupled with transition metal-catalyzed reactions to expand their utility.[11-13] Numerous new tandem reactions have recently been developed using various organozinc reagents; examples include diorganozincs, bis(iodozincio)methane,[14] Reformatsky reagents,[15] allylzinc, and allenylzinc reagents. As a general strategy, the development of tandem reactions with organozinc reagents combines a first nucleophilic addition to a π-system (α,β-unsaturated carbonyl compounds, ketones, nitriles, and carbon-carbon multiple bonds) that generates a new organozinc intermediate, and a subsequent trapping, inter- or intramolecularly, with a variety of electrophilic functional groups with or without the aid of transition metal catalysts. The aim of this review is to highlight prominent tandem reactions with organozinc reagents, underscoring their potential in organic synthesis.

2. Tandem 1,4-addition of diorganozinc and bis(iodozincio)methane/electrophilic trapping

The 1,4-addition of organozinc reagents to α,β-unsaturated carbonyl compounds, followed by the inter- or intramolecular electrophilic trapping of the resulting zinc enolate intermediates has been the subject of the most intensive investigations. Enantioselective variants of this tandem transformation now encompass diverse α,β-unsaturated substrates. Various kinds of functional groups have been explored as terminal electrophiles, including aldehydes, ketones, tosylates, oxocarbenium ions (by way of acetal ionization), esters, and nitriles. In 2009, Feringa and Knochel independently published excellent reviews focused on Cu-catalyzed enantioselective tandem 1,4-addition/electrophilic trapping reactions.[16,17] Therefore, only a few prominent and additional examples of asymmetric 1,4-addition/electrophilic trapping reactions will be presented in this review.

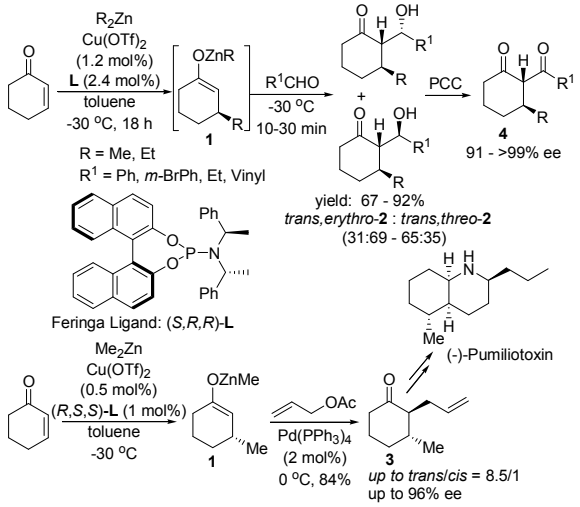
Tandem 1,4-addition of dialkylzinc/aldol reaction with aldehydes. Noyori and co-workers reported the first example of the Cu-catalyzed conjugate addition-electrophilic trapping of organozinc reagents (Scheme 1).[18] A dialkylzinc was added to cyclic enones regioselectively in the presence of a *N*-benzylbenzenesulfonamide ligand to form the zinc enolate **1**, which was then trapped with benzaldehyde to afford the conjugate addition-aldol adduct as a mixture of *trans,erythro*-**2** and *trans*,*threo*-**2** in high yields with moderate selectivity. The *erythro/threo* selectivity is dependent on ring size. The zinc enolate intermediate **1** (n = 2) could also be reacted with allyl acetate using a Pd catalyst to give a mixture of *trans*-**3** and *cis*-**3** in 90% yield with *trans/cis* = 9:1 selectivity.

Scheme 1.



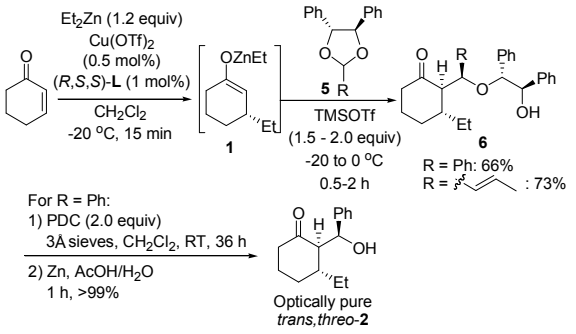
The asymmetric version of the conjugate addition/aldol/Pd-catalyzed allylation reaction was first reported by Feringa and co-workers (Scheme 2).[19] The conjugate addition of dialkyl- and diarylzinc was carried out in the presence of $Cu(OTf)_2$ and a chiral phosphoamidate ligand **L** to generate the chiral zinc enolate intermediate **1**, which was then reacted with an aldehyde to afford a mixture of *trans, erythro*-**2** and *trans, threo*-**2** in high yields (67-92%) with moderate *erythro/threo* selectivities. The PCC oxidation of the mixture of **2** provided a single isomer of the diketone **4** with up to >99% ee. The chiral zinc enolate intermediate **1** could react with allyl acetate in the presence of $Pd(PPh_3)_4$ to afford *trans*-**3** as the major isomer (*trans/cis* = 8-8.5/1) with 96% ee in 84% yield, enabling the asymmetric synthesis of (-)-pumiliotoxin C (Scheme 2).[20,21] The synthetic utility of this asymmetric tandem conjugate addition-aldol reaction has been further demonstrated in the enantioselective synthesis of prostagrandin E1 methyl ester.[22,23]

Scheme 2.



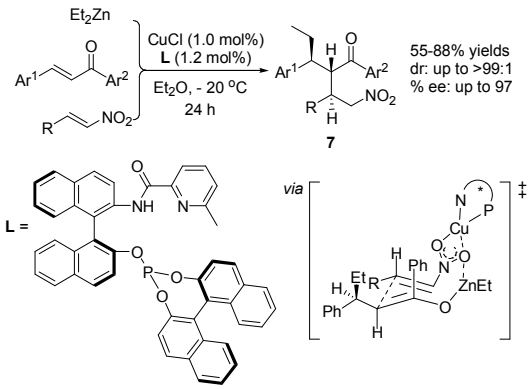
Tandem 1,4-addition of dialkylzinc/aldol reaction with acetals. Alexakis and co-workers extended the asymmetric tandem conjugate addition/aldol reaction of dialkylzinc reagents to acetals as a terminal electrophile, in which a stoichiometric amount of a Lewis acid such as TMSOTf or $BF_3{\cdot}Et_2O$ is required to activate the acetal (Scheme 3).[24] For an example, the chiral zinc enolate **1**, generated *in situ* from the $Cu(OTf)_2$-catalyzed enantioselective conjugate addition of diethylzinc to cyclohexenone using Feringa's chiral phosphoamidate ***ent*-L**, reacted with chiral acetals **5** in the presence of 1.6 equiv of TMSOTf to give the *trans*-disubstituted ketones **6** as a single diastereomer. Those were then converted to the optically pure *trans, threo*-**2** in nearly quantitative yield.

Scheme 3.



Tandem copper-catalyzed dual 1,4-addition with diethylzinc. Huang and co-workers developed a tandem copper-catalyzed highly diastereoselective and enantioselective dual 1,4-addition of diethylzinc to acyclic enones, followed by trapping with nitroalkenes as terminal electrophiles (Scheme 4).[25] The tandem dual 1,4-addition reactions performed in the presence of 1.0 mol % CuCl with 1.2 mol % of a chiral phosphite-pyridine ligand afforded various γ-nitro ketones **7** in 55-88% yields with up to >99:1 dr and 97% ee. The authors proposed an eight-membered cyclic Zimmermann-Traxler-like transition state to account for the observed stereoselectivity. According to this rationale, the chiral (*E*)-zinc enolate was involved, and the R-substituent of the nitroalkene adopts a pseudoequatorial position to give the *anti*-product. However, enones bearing alkyl substitutents were not investigated.

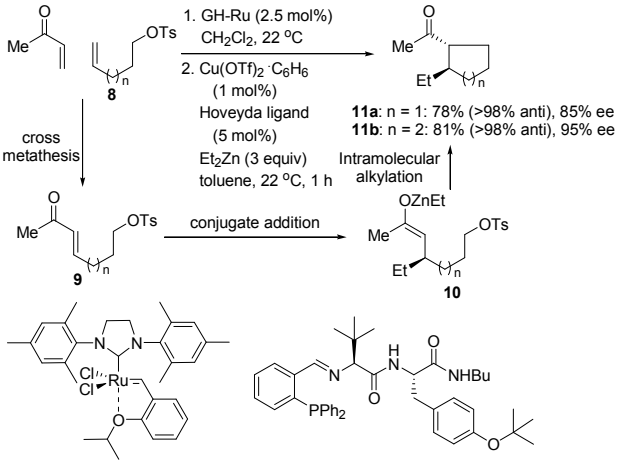
Scheme 4.



Tandem Ru-catalyzed cross metathesis/1,4-addition of dialkylzinc/intramolecular alkylation. Hoveyda and co-workers have combined in a sequence a tandem asymmetric conjugate addition of dialkylzinc reagents and subsequent intramolecular alkylation with a prior olefin cross-metathesis using the Grubbs-

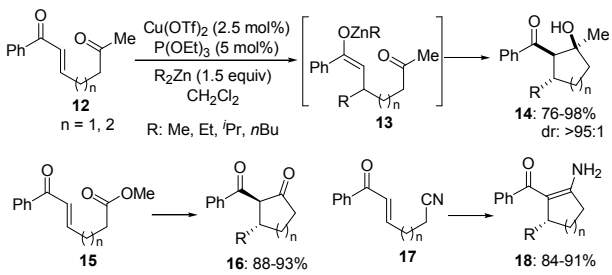
Hoveyda Ru-catalyst (GH Ru) that assembles the acyclic enone substrate (Scheme 5).[26] The presence of the Ru-catalyst did not affect either the Cu-catalyzed conjugate addition reaction that proceeds with a chiral dipeptide phosphine ligand or the final intramolecular alkylation. The *trans*-disubstituted five- (n = 1) and six-membered (n = 2) carbocycles **11** were thus synthesized with up to 95% enantioselectivity. However, when the tether length was elongated to n = 3, the intramolecular alkylation of the corresponding zinc enoate **10c** (n = 3) did not occur, and the sequence gave the conjugate addition product 91% yield with 95% ee. This tandem conjugate addition/alkylation concept could also be extended to intermolecular alkylation.[27]

Scheme 5.



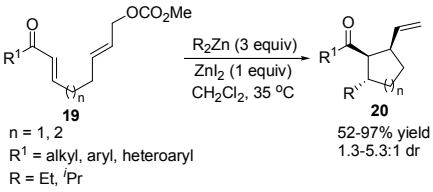
Tandem 1,4-addition of dialkylzinc/intramolecular aldol, Dieckmann, and Blaise reactions. The Cu-catalyzed tandem conjugate addition of dialkylzinc/intramolecular alkylation reaction with acyclic aliphatic enones was further extended by Krische and co-workers by changing the terminal electrophiles to ketones, esters, and nitriles (Scheme 6).[28] The Cu-catalyzed conjugate addition proceeded effectively in the presence of triethyl phosphite, and the zinc enolate intermediate **13** reacted with the ketone intramolecularly to give the aldol addition product **14** in high yields with up to >95:1 diastereoselectivity. The zinc enolate intermediates, generated from the keto-esters **15** and cyanoketones **17**, reacted efficiently with tethered ester and nitrile groups to accomplish the Cu-catalyzed tandem conjugate addition/Dieckmann and Blaise cyclization reactions to provide the diketones **16** and enaminoketones **18** in high yields, respectively.

Scheme 6.



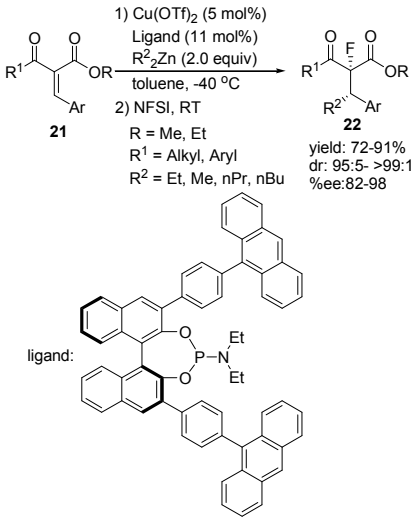
Tandem 1,4-addition of dialkylzinc/allylic substitution. It has also been demonstrated that an allylic carbonate could act as the terminal electrophile for the conjugate addition-electrophilic trapping strategy (Scheme 6).[29] One interesting finding is that the tandem conjugate addition of diorganozinc reagents/allylic substitution reaction proceeded efficiently with enones **19**, tethered to terminal allylic carbonates, in the presence of a stoichiometric amount of ZnI_2 and without the use of a copper catalyst. The carbocyclic compounds **20** are formed in moderate to good yields with 1.3-5.3:1 diastereoselectivities. Such allylic S_N2' reaction of zinc enolates without the aid of a transition metal-catalyst is not common.

Scheme 7.



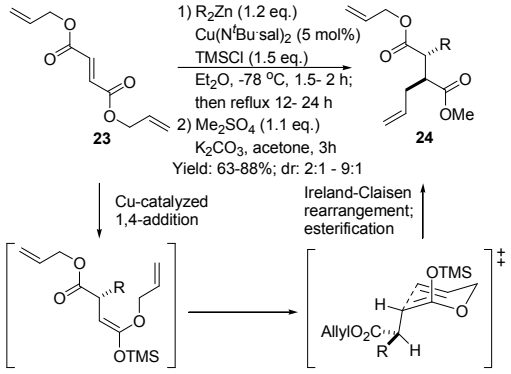
Tandem 1,4-addition of dialkylzinc/fluorination. As recently as 2011, Ma and co-workers reported a tandem 1,4-addition/fluorination of acyclic arylidene β-ketoesters **21** with dialkylzinc reagents, in the presence of $Cu(OTf)_2$ and chiral phosphoramidate ligands that bear bulky aromatic groups at the 3,3'-positions (Scheme 8).[30] *N*-fluorobenzenesulfonimide (NFSI) was used as the terminal electrophile to afford the chiral fluorinated products **22** with adjacent tertiary and quaternary stereocenters in high yield (up to 91%) with excellent diastereo- and enantioselectivities (up to dr = 99:1 and 98% ee).

Scheme 8.



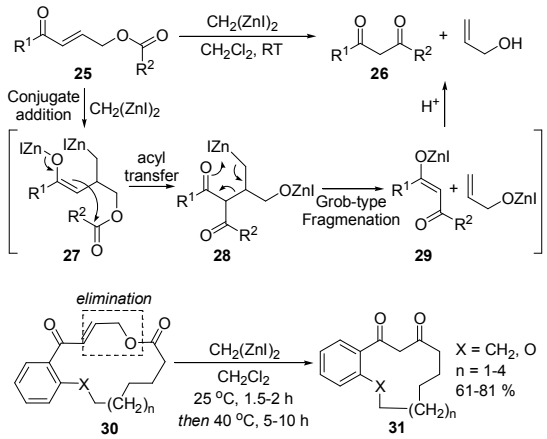
Tandem 1,4-addition of dialkylzinc/Ireland-Claisen rearrangement. Johnson and Bausch reported that the tandem 1,4-addition of dialkylzinc reagents/Ireland-Claisen rearrangement could proceed with allyl fumarates **23** in the presence of a Cu catalyst such as CuBr·SMe_2 or Cu(N^tBu·sal)$_2$, bis(*N-tert*-butylsalicylideneaminato)copper(II), to afford the substituted unsymmetrical succinic acid derivatives **24** in good yields with low to moderate diastereoselectivities (Scheme 9).[31]

Scheme 9.

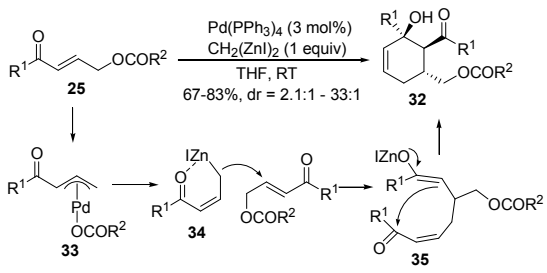


***Tandem 1,4-addition of bis(iodozincio)methane/acyl-transfer/Grob-type fragmentation*.** In 2010, Sanda and Matsubara developed a tandem 1,4-addition of bis(iodozincio)methane/intramolecular acylation/Grob-type fragmentation cascade to form 1,3-diketones (Scheme 10).[32] The 1,4-addition of bis(iodozincio)methane to the enone **25** generated the zinc enolate **27**, which reacted with the ester group in a Dieckmann fashion to form **28**. The Grob-type fragmentation of **28** eliminated the allylic alcohol moiety to afford the zinc enolate of 1,3-diketone **29**. This protocol was successfully applied to the macrocyclic enones **30** to afford the corresponding diketones **31**. In the presence of a palladium catalyst, the reaction of bis(iodozincio)methane with the γ-acyloxy-α,β-unsaturated ketones **25** provided the 3,4,5-trisubstituted cyclohexene derivatives **32** with variable diastereoselectivities.[33] The π-allyl complex **33** was alkylated with bis(iodozincio)methane to form the γ-zincated enone **34**, which added to a second equivalent of enone **25** to generate the zinc enolate **35**. The intramolecular aldol reaction of **35** afforded the polysubstituted cyclohexenols **32** (Scheme 11).

Scheme 10.

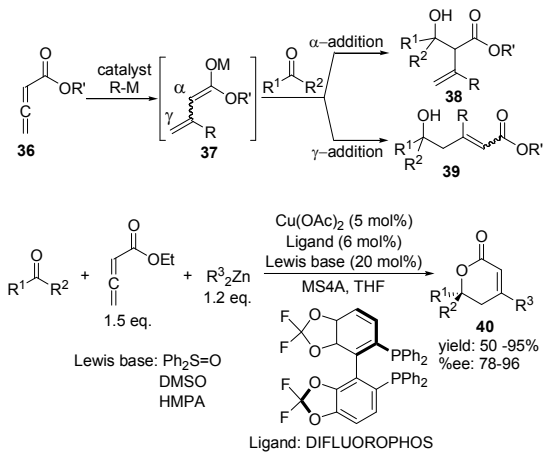


Scheme 11.



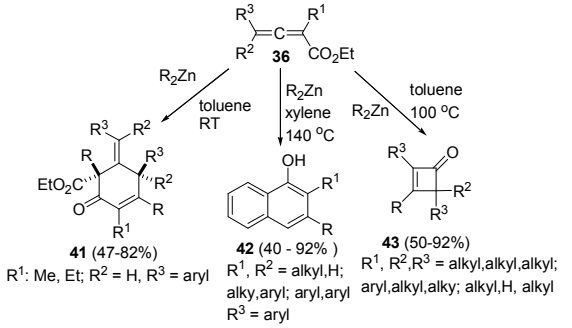
Tandem alkylative aldol reaction of diorganozinc with allenoates. The 2,3-allenoate **36** is also a well-known Michael acceptor for organometallic nucleophiles such as Grignard reagents,[34] with which the addition occurs at the center carbon atom regioselectively to form the metal dienolates **37,** affording β,γ-unsaturated alkanoates upon protonation. The metal dienolate intermediate **37** could also react with a carbonyl electrophile in two different α- and γ-addition pathways, providing the β-hydroxy ester **38** and δ-hydroxy ester **39**, respectively. Controlling these reaction pathways is highly challenging. Shibasaki and co-workers reported the catalytic regio- and enantioselective alkylative aldol reaction of allenic esters and ketones with dialkylzinc reagents using a Cu(OAc)$_2$-DIFLUORPHOS complex towards the synthesis of the functionalized δ-lactones **40** with high enantioselectivity (Scheme 12).[35,36] The addition of molecular sieves and a Lewis base such as Ph_2S=O, DMSO, or HMPA is important for obtaining a high yield, and to suppress the undesired α-addition pathway.

Scheme 12.

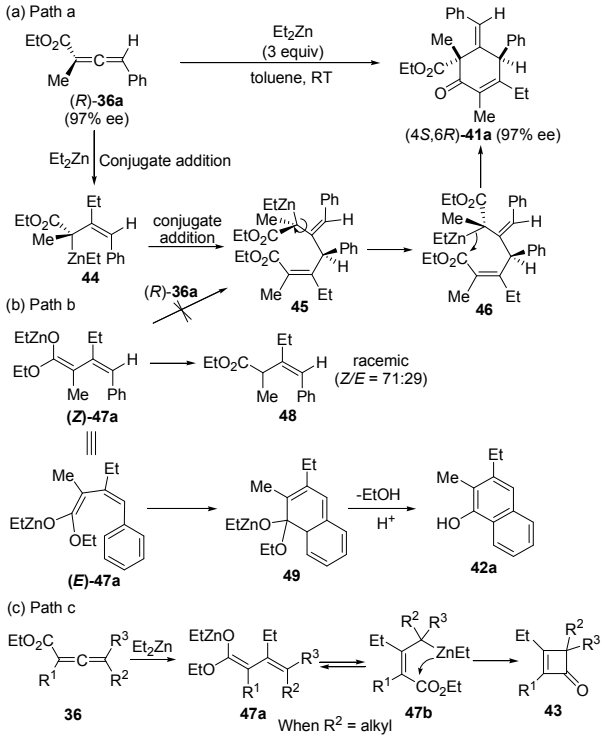


Tandem conjugate addition of dialkylzinc reagents/cyclization with allenoates. Ma and co-workers found some interesting divergent 1,4-addition/cyclization reactions of 2,3-allenoates **36** with diorganozinc reagents, in which the dominant reaction products were determined by the reaction conditions and the substituents of the allenoates (Scheme 13).[37] The reaction of the 2-alkyl-4-aryl substituted allenoates **36** (R^1 = alkyl, R^3 = aryl) with dialkylzinc reagents at room temperature in toluene afforded the highly substituted 5-benzylidenecyclohex-2-enones **41** through a regio- and stereoselective double conjugate addition/cyclization cascade. In contrast, when the same allenoate was added to a solution of diaryl or dialkylzinc solution at high temperature (140 °C), the corresponding naphthol **42** was formed.[38] For allenoates devoid of aryl substituents at C4 (R^2 and R^3 are alkyl), the cyclobutenones **43** were formed as the major product.[39] Mechanistic pathways for these reactions have been proposed as shown in Scheme 14. The addition of a dialkylzinc nucleophile to an enantiomerically enriched allenoate, for example the optically active (*R*)-**36a** with 97% ee occurred in a stereospecific manner at the center carbon atom to generate the C-bound optically active α-zincate alkenoate intermediate **44**. A second Michael addition of the γ-carbon atom of intermediate **44** to the center carbon atom of the allene moiety in (*R*)-**36a** afforded **45** with high stereoselectivity. Its conformer **46** then undergoes a Dieckmann condensation to form the six-membered ring (4*S*,6*R*)-5-benzylidenecyclohex-2-enones **41a** with 97% ee, indicating that the reaction is highly stereospecific (path a in Scheme 14). Owing to the steric interaction between the Ph group of the 2,3-allenoate and the approaching allylic group in **46**, the *Z* stereoselectivity for the *exo* C=C bond is high. By contrast, the O-bound zinc dienolate intermediate (*Z*)-**47a**, generated by the transmetallation of magnesium dienolate with $ZnBr_2$, indicated the low reactivity of this tautomer toward the allenoate, and thus provided the β,γ-unsaturated alkanoates **48** as the major product along with less than 10% of racemic **41a**. Based on these results, the possibility that the racemic zinc dienolate (*Z*)-**47a** reacts with (*R*)-**36a** to afford the optically active cyclic product **41a** was ruled out. However, at higher reaction temperatures, the (*E*)-zinc dienolate (*E*)-**47a** formed predominantly, and was claimed to undergo a Friedel-Crafts-type reaction - although this may alternatively be construed of as a 6π-electrocyclization followed by an elimination and aromatization - to form the naphthol **42a** *via* **49** (path b in Scheme 14). For allenoates **36** devoid of aryl substituents at C4 (R^2 and R^3 are alkyl), the O-bound zinc dienolate (*Z*)-**47a** isomerizes to a C-bound zinc **47b** that is sufficiently nucleophilic to cyclize upon itself and form the cyclobutenones **43** (path c in Scheme 14)

Scheme 13.



Scheme 14.



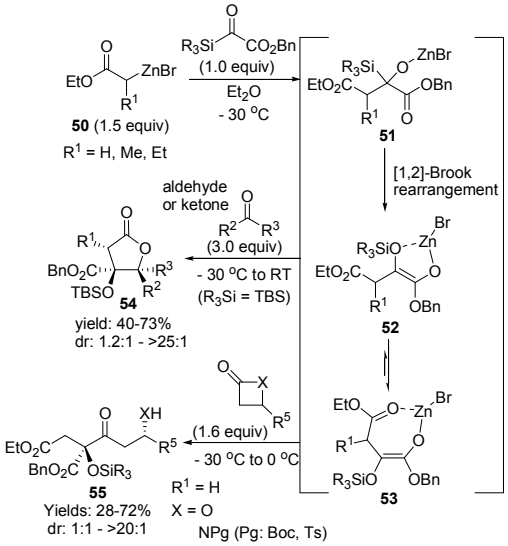
3. Tandem reactions with Reformatsky reagents

Activated zinc metal inserts into the carbon-halogen bond of an α-halo ester to form a zinc enolate (Reformatsky reagent), which reacts with carbonyl electrophiles to afford β-hydroxy esters (Reformatsky reaction), as it was discovered in 1887.[15,40] Spectroscopic and crystallographic studies of Reformatsky reagents derived from α-halo esters showed that the enolate is present as the C-bound zinc bromide, which exists as a dimer in THF solvent.[41-45] The Reformatsky reaction goes through a six-membered chair-like transition state to form the zinc bromide complex of the β-hydroxy ester. The reaction of a Reformatsky

reagent with a nitrile, known as the Blaise reaction,[46,47] has long been utilized for the synthesis of β-ketoesters and β-enaminoesters.[48,49] However, the tandem use of Reformatsky reagents has not been systematically investigated until recently.

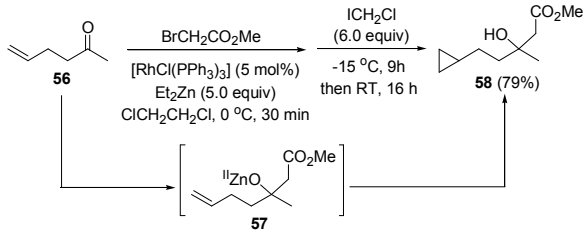
Tandem Reformatsky/[1,2]-Brook/Reformatsky reaction. In 2009, Johnson and Greszler disclosed an elegant and highly diastereoselective synthesis of γ-butyrolactones through a double Reformatsky reaction (Scheme 15).[50] The reaction of Reformatsky reagents **50** (R^1 = H, Me), generated from α-bromo esters and zinc, with silyl glyoxylates produced the corresponding O-bound zinc bromide complex of the hydroxy ester **51**. This intermediate underwent a [1,2]-Brook rearrangement[51] to form a new zinc enolate **52** capable of a second addition to an aldehyde or ketone. This second addition is followed by a lactonization providing the corresponding γ-butyrolactones **54** with high diastereoselectively (up to dr = >25:1) and yields in the range of 40 – 73%. The alkyl group (R^1) in the substituted Reformatsky reagents **50** is a likely determinant of the facial selectivity in the second Reformatsky reaction. Equilibration of the kinetically formed (*Z*)-enolate **52** to the more stable (*E*)-isomer **53**, driven by the formation of a stronger chelate with the pendent ethyl ester, allowed the β-stereocenter to influence the approach of the electrophile to the unhindered diastereotopic face of **53**. The zinc enolate **53** also reacted with β-lactones or N-protected β-lactams, undergoing tandem Reformatsky/[1,2]-Brook rearrangement/Claisen condensations to afford the polysubstituted ketones **55** with high diastereoselectivity.[52,53] This tandem reaction has been applied to the formal synthesis of leustroducsin B.

Scheme 15.



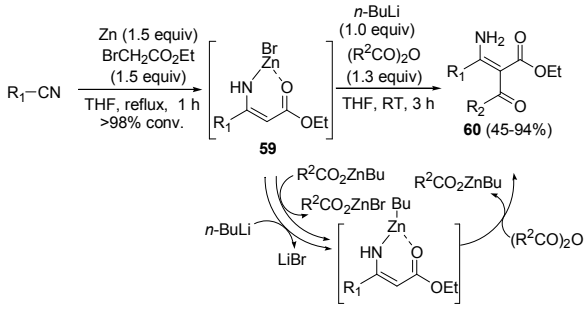
Tandem one-pot Reformatsky/cyclopropanation. Cossy and co-workers reported the tandem one-pot Reformatsky/cyclopropanation of ω-unsaturated ketones **56** to produce ω-cyclopropyl alcohols **58**, which proceeds with diethylzinc in the presence of Wilkinson's catalyst, [$RhCl(PPh_3)_3$] (Scheme 16).[54] The Rh-catalyzed diethylzinc-induced Reformatsky reaction[55] of methyl bromoacetate produced the olefinic carbinol **57**. The cyclopropanation of the olefin was accomplished with (chloromethyl)ethylzinc, formed by the reaction of diethyl zinc with chloroiodomethane, which is the carbenoid precursor in this cyclopropanation.[56,57]

Scheme 16.



Tandem Blaise/electrophilic trapping reactions. The Blaise reaction proceeds *via* the zinc bromide complex of the β-enaminoester **59**. The hydrolytic workup of this reaction intermediate under either acidic or basic conditions provides the corresponding β-ketoester or β-enaminoester, respectively. The Blaise reaction intermediate **59** possesses unique features in that it combines an enamine moiety, nucleophilic at C and/or N, with an electrophilic α,β-unsaturated ester, enabling reactions with electrophiles, nucleophiles, or both. In 2008, Lee and co-workers recognized the potential of the Blaise reaction intermediate **59** as a functionalized organozinc reagent for tandem reactions.[59] The Blaise reaction intermediate **59**, formed by the addition of a Reformatsky reagent, generated *in situ* from ethyl bromoacetate and zinc, to the nitrile **58**, reacted chemoselectively with anhydrides in the presence of an equivalent of *n*-BuLi as an additive to afford the α-acylated β-enaminoester **60** in good yields (Scheme 17).

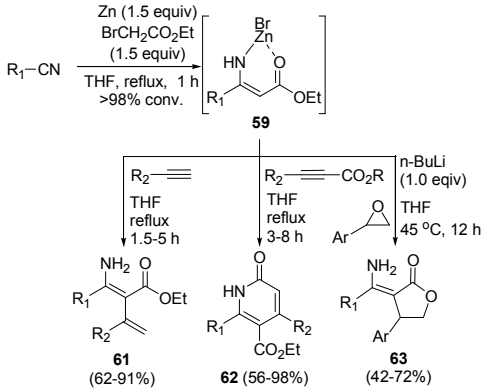
Scheme 17.



n-BuLi substitutes the bromide at zinc for an electron-donating butyl group, increasing the nucleophilicity of the Blaise reaction intermediate **59**. Even in the presence of only 10 mol % of *n*-BuLi, the same levels of reactivity and chemoselectivity were obtained. The catalytic cycle may involve the generation of R^2CO_2ZnBu, which in turn would react with the Blaise reaction intermediate **59** resulting in the more reactive *n*-butylzinc complex and inert R^2CO_2ZnBr. The tandem Blaise-acylation product, α-acylated β-enaminoester **60**, can be used in the regioselective synthesis of pyrazoles.[59,60] Since then, various tandem reactions using the Blaise reaction intermediate **59** have been developed by the same group (Scheme 18). The tandem reaction of **59** with terminal alkynes proceeded regio- and

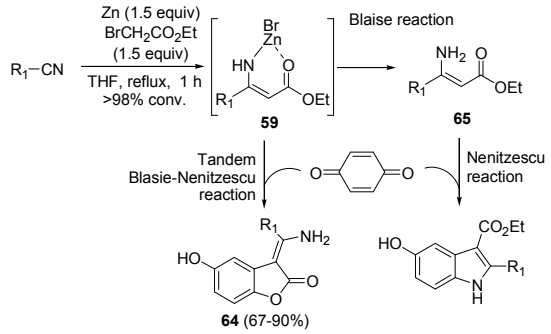
chemoselectively to afford the corresponding α-vinylated β-enaminoester **61** in good to excellent yields (62-91%).[61,62] Taking advantage of the C- and N-nucleophilicity of the Blaise reaction intermediate, the tandem reaction of **59** was carried out with propiolates, which have two electrophilic carbon centers, to afford the 2-pyridones **62** in up to 98% yield.[63] It has been also found that the Blaise reaction intermediate **59** can be reacted with epoxides by using one equivalent of *n*-BuLi as an additive to give the α-(aminomethylene)-γ-butyrolactones **63** in moderate yields, demonstrating the ambiphilic nature of the Blaise reaction intermediate.[64]

Scheme 18.



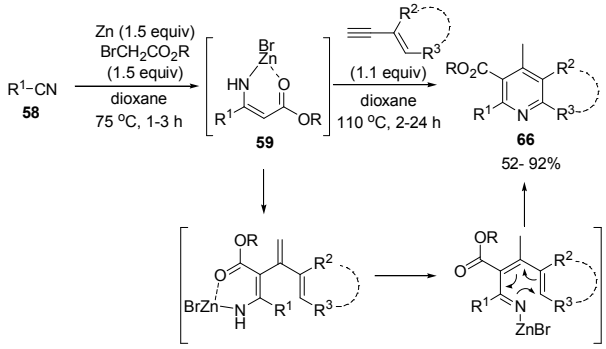
More recently, Lee and co-workers developed the tandem Blaise-Nenitzescu reaction for the one-pot synthesis of 5-hydroxy-α-(aminomethylene)benzofuran-2(*3H*)-ones **64** from nitriles (Scheme 19).[65] In contrast to the reaction of benzoquinones with the isolated β-enaminoesters **65**, providing indoles (Nenitzescu reaction), the tandem reaction of the Blaise reaction intermediate **59** with benzoquinone afforded the benzofuranones **64** in good to excellent yields (67-90%). The different selectivity for the tandem Blaise-Nenitzescu reaction was ascribed to the increased electrophilicity of the ester carbonyl group, which was activated by coordination with zinc bromide.

Scheme 19.



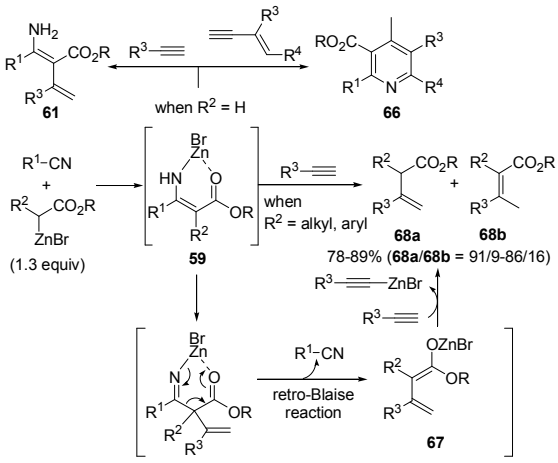
Tandem Blaise/vinylation/electrocyclization with 1,3-enynes. An efficient tandem one-pot process was developed for the synthesis of the polysubstituted pyridines **66** with complete regioselectivity (Scheme 20).[66] The reaction proceeds *via* the regio- and chemoselective addition of the Blaise reaction intermediate **59** to the cyclic- and acyclic 1,3-enynes followed by an isomerization/cyclization/aromatization cascade. This convenient and straightforward process is characterized by high yields and good functional group tolerance. The tandem method is versatile as it allows for access to polysubstituted pyridines that are not otherwise easily accessible.

Scheme 20.



Interestingly, it has been observed that the reaction pathways of the α-substituted Blaise reaction intermediate with 1-alkynes are changed to undergo *retro*-Blaise reaction generating α-vinylated zinc enolates **67** (Scheme 21).[67] Upon protonation by abstraction of the acidic hydrogen from terminal alkynes prior to workup, these tandem sequences afford a mixture of α-vinylated alkanoates **68a** and **68b** in which the unconjugated product dominates (**68a**/**68b** = 91/9 to 86/16). In this reaction sequence, the nitrile acts as a reversible mediator that allows the formal addition of an unstabilized ester enolate to a terminal alkyne. The corresponding direct addition is inherently impossible due to the acid-base reaction between enolates and the acidic C_{sp}-H of 1-alkynes. The same α-substituent effect on the reaction pathway has been observed in the reaction with 1,3-enynes, which lead to α-dienylated esters.

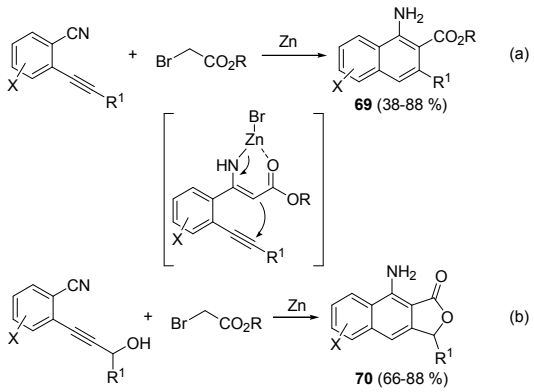
Scheme 21.



In 2014, Fan and Srinivasan independently reported that the Blaise reaction of *o*-alkynylarenenitriles could be a convenient method to prepare naphthalene aminoesters **69**, from a Blaise reaction intermediate that undergoes a *6-endo-dig* carboannulation (Scheme 22a).[68,69] By using this reaction as a key step, a concise and versatile synthetic route for the synthesis of

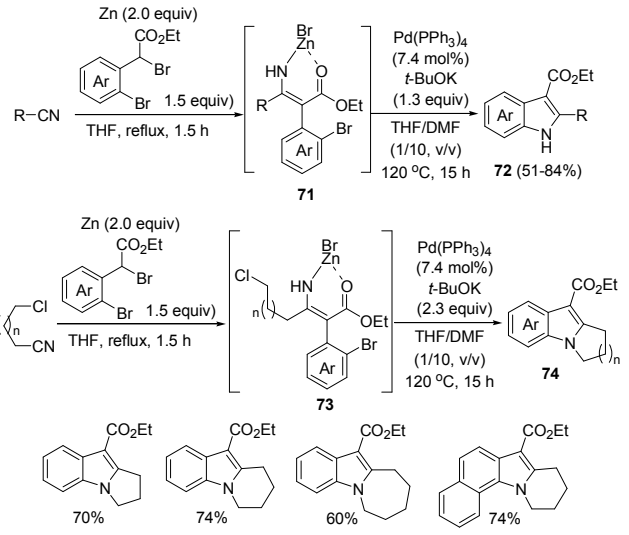
aryl naphthalene lactone lignans **70** was also developed (Scheme 22b).

Scheme 22.

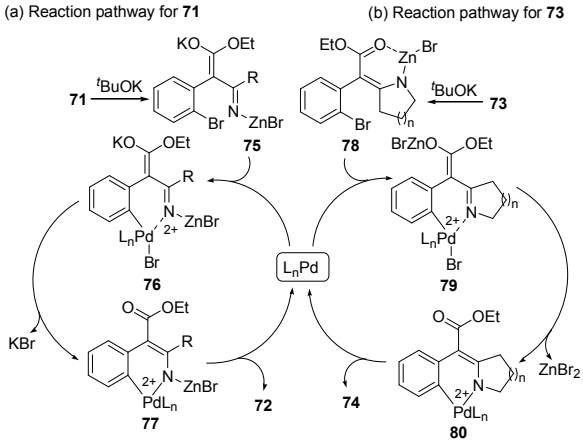


Tandem Blaise/Pd-catalysis. In 2011, Lee and co-workers combined the classical Blaise reaction with a modern palladium-catalyzed C-N coupling reaction to achieve a new indole synthesis (Scheme 23).[70] The Blaise reaction intermediate **71**, formed by the reaction of a nitrile and a Reformatsky reagent, generated in situ from ethyl (*o*-bromophenyl)-α-bromoacetate and zinc, was treated with 7.4 mol% of $Pd(PPh_3)_4$ and 1.3 equiv of *t*-BuOK in DMF at 120 ˚C for 15 h to afford the indoles **72** in 51-84% yields. Both aliphatic and aromatic nitriles are suitable for the reaction and, in the case of the latter, both electron donating and withdrawing substituents such as CH_3, CH_3O, CF_3, F, CO_2Et, and CN, are tolerated. This reaction can be extended to the synthesis of 1,2-*a*-fused indoles **74** by using ω-chloroalkylnitriles, through the chemoselective intramolecular N-alkylation/palladium-catalyzed C-N coupling reaction of the Blaise reaction intermediate **73**. The chemoselective intramolecular alkylation reaction proceeds prior to the palladium-catalyzed C-N coupling reaction.[71] The necessity for added *t*-BuOK suggested that the nucleophilicity of **71** is not sufficiently high for the nucleophilic substitution on the arylpalladium(II) bromide intermediate. The proposed mechanisms for the formation of indole **72** and 1,2-*a*-fused indole **74** are depicted in Scheme 24. The N-H proton of **71** was deprotonated to form the zincated iminoenolate **75**. The oxidative addition of Pd(0) affording **76**, followed by nucleophilic substitution formed the Pd(II) species **77**. Reductive elimination resulted in **72**-ZnBr, which was converted to the product indole **72** upon hydrolytic workup. For the formation of the 1,2-*a*-fused indole **74**, the chemoselective intermolecular alkylation occurred first to form the zinc bromide complex **78**, which then isomerized to zinc enolate to form the Pd(II) species **79**. Nucleophilic substitution forming **80**, followed by reductive elimination afforded the fused indole **74**. Interestingly, these reactions differ from the intermolecular coupling reaction of the α-unsubstituted Blaise intermediate **59** with 1,2-diiodobenzene, which did not proceed in the presence of a palladium catalyst, but did so in the presence of copper(I) iodide to provide indoles in moderate yields.[72]

Scheme 23.



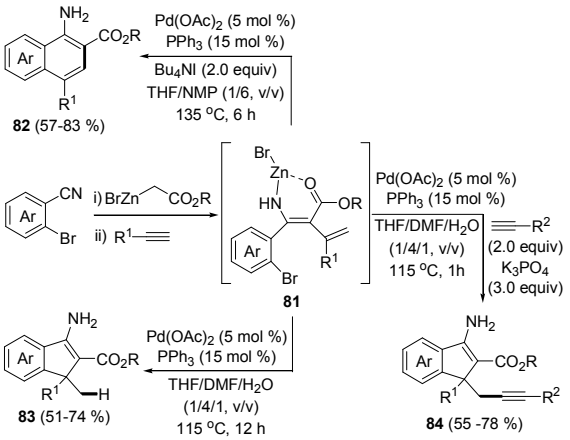
Scheme 24.



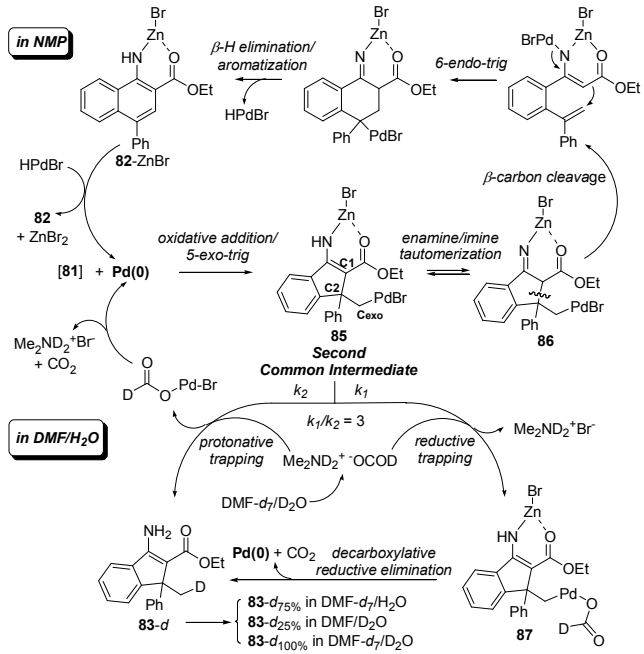
In 2014, the tandem use of the Blaise reaction in palladium catalysis was further extended with the report of a solvent-controlled divergent synthesis of naphthalene aminoesters **82** and amino indenes **83** and **84** from the common *o*-bromoaryl nitriles (Scheme 25).[73] Treatment of the Blaise reaction intermediate **81** in *N*-methyl-2-pyrrolidinone (NMP) with a Pd catalyst formed *in situ* from $Pd(OAc)_2$ and PPh_3 afforded the naphthalene aminoester **82**. By contrast, when the solvent was changed to DMF/H_2O, the tandem catalytic reaction pathways of **81** were redirected to give the hydrodehalogenated aminoindene **83** in good yields. Formation of **83** suggested the formation of σ-bonded complex **85** as a second common intermediate via oxidative addition of Pd(0) into the Ar-Br bond, followed by a Heck-type 5-*exo*-*trig* carbopalladation. The postulated σ-carbopalladate **85** could indeed be intercepted with an acetylide nucleophile to afford the alkynylated aminoindenes **84** in good yields. It has been proposed that σ-carbopalladate **85** may be in equilibrium with its imine tautomer **86**. In the absence of β-hydrogen, a β-carbon cleavage from **86** (C1–C2 bond cleavage) could occur to afford a stabilized Pd-enolate. The latter would undergo a subsequent 6-*endo* cyclization, followed by β-H elimination/aromatization to give **82**-ZnBr and HPdBr. Reductive

elimination of HBr regenerates Pd(0), completing the catalytic and freeing the amino naphthalene **82**. The formation of aminoindene **83** in DMF/H_2O is ascribed to the protolysis and to the reductive trapping of σ-carbopalladate **85** via the Pd-formate **87** undergoing decarboxylative reductive elimination. On the basis of deuterium-labelling experiments, it has been suggested that dimethylammonium formate, generated from DMF and H_2O, can effect wither the protolysis of **85** or its reduction with a relative rates of $k_1/k_2 = 3$ (Scheme 26).

Scheme 25.

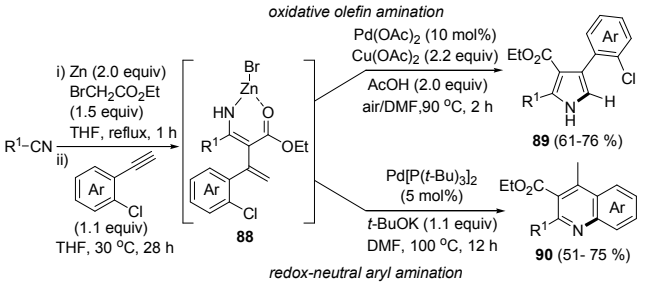


Scheme 26.



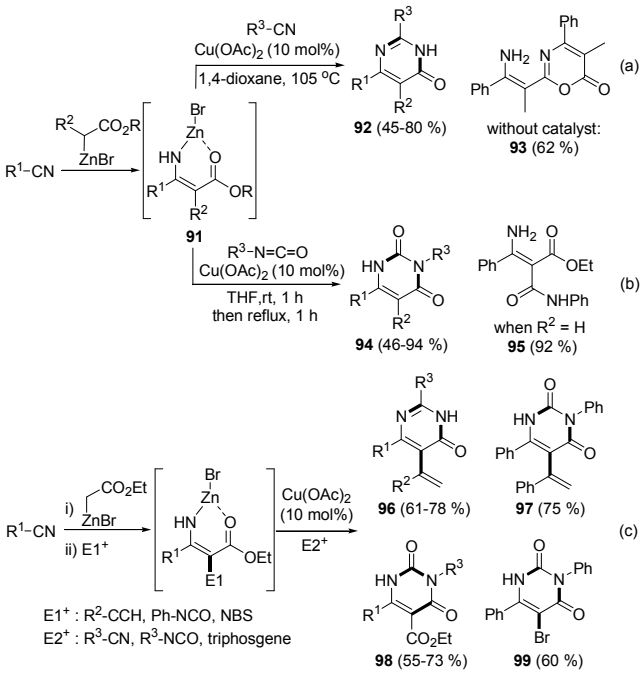
Palladium catalyst-controlled tandem divergent reactions have also been developed taking the intermediate **88**, formed with *o*-chloro phenylacetylenes, as a starting point to afford pyrroles **89** and quinolines **90**. When **88** was subjected to the oxidative olefin amination conditions composed of $Pd(OAc)_2$ (10 mol%), $Cu(OAc)_2$ and AcOH in DMF solvent, the pyrrole **89** was formed in good yields. Under these reaction conditions, a variety of pyrroles can be synthesized starting from nitriles, Reformatsky reagents, and alkynes in one-pot manner.[74] By contrast, the same intermediate **88** undergoes a redox-neutral aryl amination in the presence of 5 mol% $Pd[P(^t\text{-Bu})_3]_2$ to afford quinoline **90** (Scheme 27).[73]

Scheme 27.



Tandem Blaise/Cu-catalysis. Lee and co-workers also combined the Blaise reaction intermediate with copper-catalyzed reactions for the one-pot syntheses of pyrimidine-4-ones **92** and pyrimidin-2,4-diones **94** (Scheme 28).[75, 76] The intermediate **91** bearing an α-substituent ($R^2 \neq H$) reacted with nitriles in the presence of 10 mol% $Cu(OAc)_2$ catalyst to afford pyrimidine-4-ones **92** in up to 80% yield. With an α-unsubstituted intermediate **59** (R^1 = Ph, R^2 = H), the 5-benzoylated pyrimidin-4-one ($R^1 = R^3$ = Ph) was isolated. In addition, in the absence of copper catalyst, the intermediate **91** was dimerized to give oxazinone **93** in 62 % yield (Scheme 28a). The copper-catalyzed tandem reaction of **91** with aryl- and alkyl isocyanates could afford pyrimidine-2,4-diones **94** in moderate to excellent yields. However, under the same reaction conditions, the α-unsubstituted intermediate **59** (R^1 = Ph, R^2 = H) acts as a C-nucleophile toward phenyl isocyanate to afford α-carbamoylated β-enaminoester **95** in excellent yield of 92% (Scheme 28b). Combining the nucleophilicity at C α-unsubstituted intermediate **59** toward 1-alkynes, isocyanates, and *N*-bromosuccimide with these copper-catalyzed reactions allowed the installation of various functional groups at the 5-position of pyrimidin-4-ones and pyrimidine-2,4-diones. For example, tandem reaction of **59** with a terminal alkyne, followed by copper-catalyzed reactions with either a nitrile or an isocyanate afforded the 5-vinylated **96** and **97**, respectively. Conversely, 5-ester functionalized pyrimidine-2,4-diones **98** were obtained by the sequential reactions of the α-unsubstituted Blaise reaction intermediate **59** with isocyanates and triphosgene. 5-Bromopyrimidine-2,4-diones **99** could also be synthesized with the use of NBS as the first electrophile (Scheme 28c).

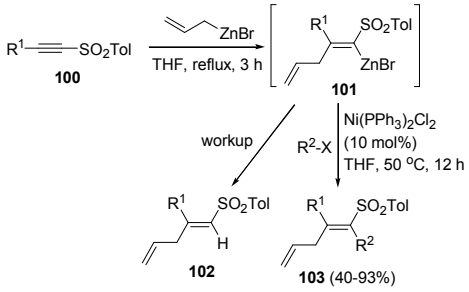
Scheme 28.



4. Tandem reactions with allylzinc and alkynylzinc reagents

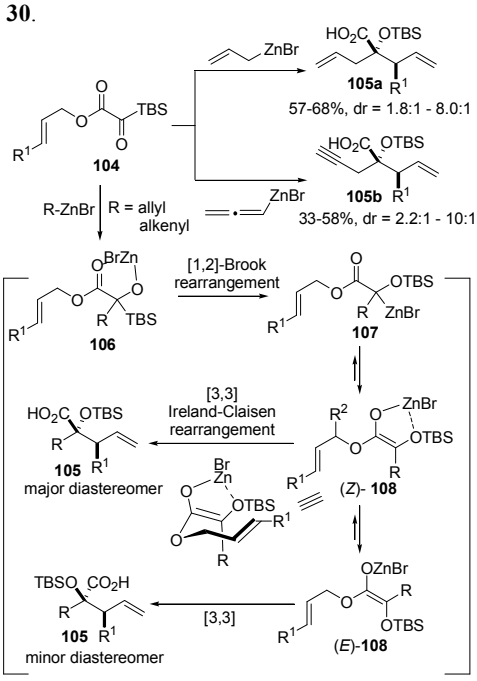
Conjugate addition of allylzinc bromide/nickel-catalyzed Negishi cross-coupling. Xie and co-workers reported a tandem one-pot synthesis of tetrasubstituted olefins containing a 1,4-diene structural unit that proceeds through the allylzincation of acetylenic sulfones, followed by a Ni-catalyzed Negishi cross-coupling (Scheme 29).[77] The addition of the allylzinc bromide, generated in situ from allyl bromide and zinc, to the acetylenic sulfone **100** proceeded efficiently with high regio- and chemoselectivity to produce the (*Z*)-vinylzinc bromide intermediate **101**, whose stereochemistry was confirmed after isolation of the 1,4-pentadiene **102**. The Negishi cross-coupling of the vinylzinc bromide **101** with aryl halides, allyl halides and benzyl halides in the presence of 10 mol% of $Ni(PPh_2)_2Cl_2$ catalyst afforded the tetrasubstituted olefins **103** in 40-93% yields without erosion of the stereochemistry. Cu-catalyzed conjugate addition of organozinc reagents to alkynyl sulfoxides[78] and sulfoximines have also been investigated.[79]

Scheme 29.



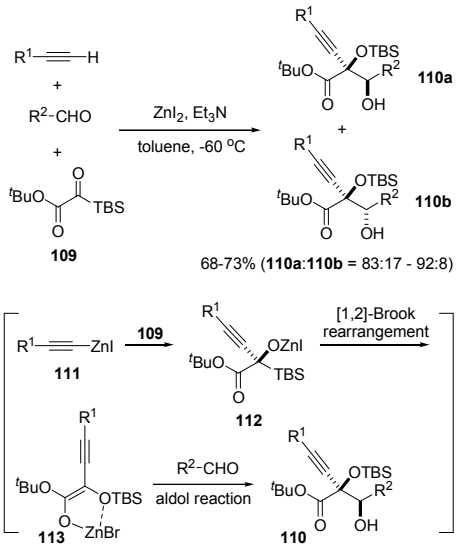
Tandem Brook/Ireland-Claisen rearrangements of allylzinc and allenylzinc bromide with silyl glyoxalates. Johnson and Schmitt reported in 2010 the tandem Brook/Ireland-Claisen rearrangement of allylzinc and allenylzinc bromides with silyl glyoxalates **104** to afford the doubly unsaturated α-silyloxy acids **105** in moderate yields with variable diastereoselectivity (Scheme 30).[80] The nucleophilic addition of allylzinc or allenylzinc bromides to acylsilanes is understood to give the tetrahedral intermediate **106**, which undergoes a [1,2]-Brook rearrangement forming **107**, which is in equilibrium with both the (*Z*)- and (*E*)-glycolate enolates **108**. At this point, the allylic ester enolate **108** presumably undergoes an Ireland-Claisen rearrangement *via* the well-understood transition state wherein the enolate geometry dictates the stereochemistry of the product to afford the doubly unsaturated acid **105**. The stereochemical outcome of the reaction is consistent with a (*Z*)-enolate intermediate proceeding through a chair-like transition state. This reaction can also be carried out with other organometallic nucleophiles, such as with MeMgBr/TMSOTf, the lithium enolate of *tert*-butyl acetate, or diethylzinc.

Scheme 30.



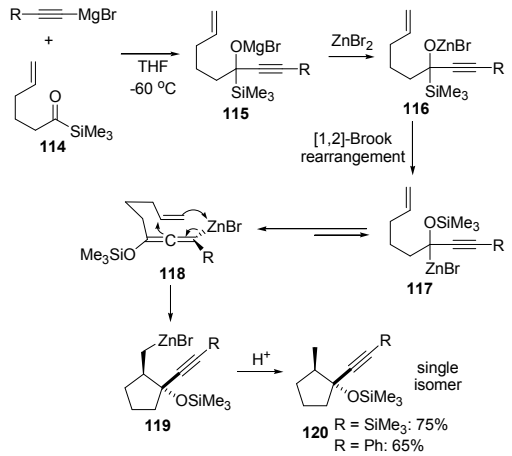
Tandem alkynylation/Brook rearrangement/aldol reaction of silyl glyoxaylates. Johnson et al. also developed a three-component coupling reaction of silyl glyoxalates **109**, terminal alkynes, and aldehydes to furnish the β-hydroxyesters **110** that bear two contiguous stereocenters (Scheme 31).[81] The addition of zinc acetylide **111**, presumably formed *in situ* from the terminal alkyne, ZnI_2, and Et_3N, with the silyl glyoxalate occurred chemoselectively, and afforded the tetrahedral intermediate **112**, which undergoes a [1,2]-Brook rearrangement to afford the glycolate zinc enolate **113**. An aldol reaction of **113** with the aldehyde afforded the β-hydroxyester **110** in good yield with high diastereoselectivity. It has also been shown that an enantioselective variant of this reaction is possible using chiral amino alcohols such as (+)-*N*-methylephedrine as ligands.

Scheme 31.



Tandem alkynylation/Brook rearrangement/ene-allene carbocyclization of acyl silanes. Marek and co-workers developed a new tandem reaction for the carbocyclization of propargylic zinc reagents (Scheme 32).[82] In this work, an alkynyl Grignard was reacted with the acylsilane **114** to form the alkynylated intermediate **115**. Transmetalation with $ZnBr_2$, forming the zinc alkoxide **116**, promoted the Brook rearrangement to afford the propargylic zinc species **117**, which is in equilibrium with the allenylzinc species **118**. The Zn-en-allene carbocyclization reaction may proceed stereospecifically through a 5-*exo*-*dig*-mode to lead the corresponding cyclopentylmethylzinc derivatives **119**, which upon protonation with HCl afford **120** in good yields.

Scheme 32.

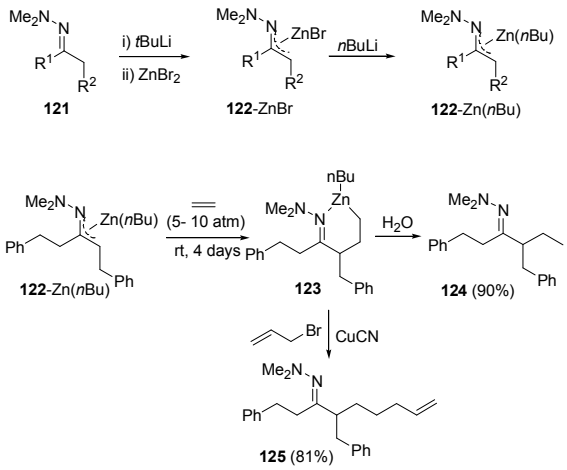


5. Tandem carbozincation/electrophilic trapping.

In 1997, Nakamura and co-workers reported the first example of addition of a zinc azaenolate to an unactivated carbon-carbon double bond.[83] Since this seminal report, a steady stream of contributions has enriched this field. Those follow two main directions. On one hand, zinc azaenolates derived mainly from hydrozones and imines provide, after carbometalation and hydrolysis, α-alkylated ketones in an overall process that can be regarded as an "olefinic aldol reaction". On the other hand, the inter- and intramolecular carbometallation of unactivated carbon-carbon double bonds with zinc enolates and amides has also been developed, especially in the case of α- and β-aminoesters, in an overall process that can be regarded as a "carbo-Reformatsky reaction".

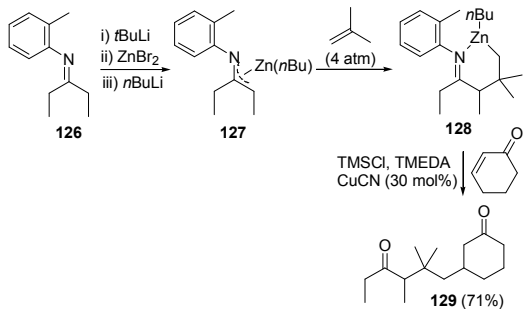
Tandem carbozincation with zincated hydrazones/electrophilic trapping. Zinc azaenolates derived from cyclic and acyclic *N*,*N*-dimethylhydrazones **121** were reported to give the corresponding carbometallation adducts in moderate to high yields (30-90%) (Scheme 33).[83] For example, the zinc azaenolate **122**-Zn(*n*Bu), which was prepared by the metallation of hydrazone **121** (R^1 = $Ph(CH_2)_2$, R^2 = $PhCH_2$) with *t*BuLi followed by transmetallation with $ZnBr_2$ and ligand exchange with *n*BuLi, reacted with ethylene to provide the carbometallated zinc species **123**, and after hydrolytic workup, the α-ethylated hydrazone **124** was formed in 90% yield. The use of the butylated species **122**-Zn(*n*Bu) was found to be essential for an efficient addition since other species such as **122**-ZnBr, **122**-ZnMe, or **122**-Zn(*t*Bu) were far less reactive. The carbometallated zinc species **123** could react with carbon electrophiles, such as allyl bromides after transmetallation with a copper(I) salt, thus providing a one-pot, three-component coupling reaction to afford **125** in 81% yield.

Scheme 33.



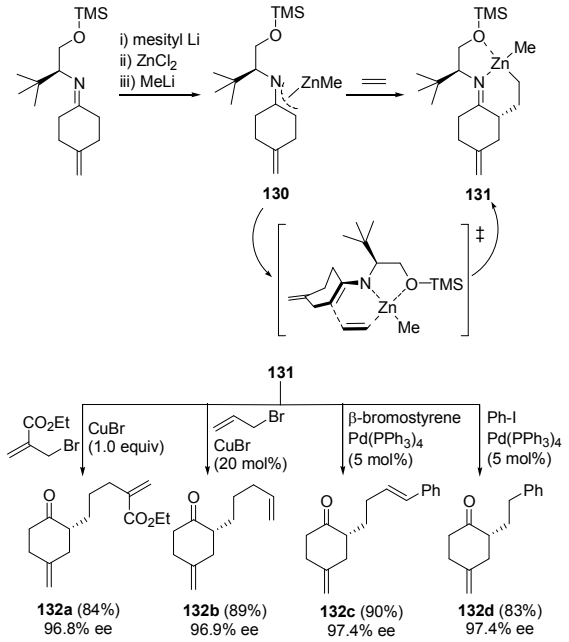
Tandem carbozincation with zinc enamides/electrophilic trapping. While the addition of zincated hydrazones proceeded conveniently with ethylene, yields for additions to substituted alkenes were found to be generally too low to be synthetically useful. Nakamura and co-workers investigated the use of zinc enamides **127** obtained by deprotonation of the imines **126** with ^{t}BuLi or LDA (for kinetic enamides) followed by transmetallation with a suitable zinc salt (Scheme 34).[84] As exemplified with the organozinc compound **127**, the carbometallation adduct proved stable under these conditions and could thus undergo subsequent reactions with electrophiles either directly or with catalysts such as Pd or Cu to afford products such as **129**.

Scheme 34.



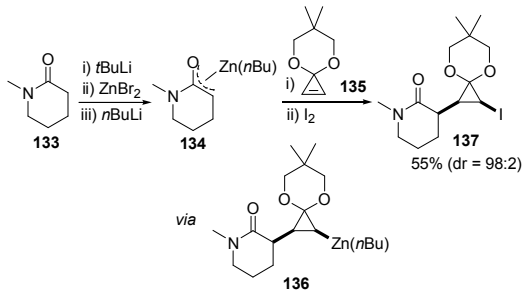
Zinc enamides prepared from imines derived from (*S*)-valinol or (*S*)-*tert*-leucinol were reported to add to ethylene in a diastereoselective manner.[85] For example, the zinc enamide **130** reacted with ethylene to produce the γ-zincioimine intermediate **131**, which can be trapped with an electrophile in the presence of Pd- or Cu-catalysts to afford ketones **132a-132d** in high yields with high levels of enantioselectivity (Scheme 35). The sense of stereoinduction was rationalized by a six-membered transition state that involves a Zn-O interaction, resulting in the shielding of one of the faces of the enamide by the bulky *tert*-butyl group. However, the generalization of this method to alkenes other than ethylene resulted in lower yields and/or diastereoselectivities. Moreover, acyclic imine precursors led to the formation of the corresponding ketones in only low to moderate enantiomeric excess.

Scheme 35.

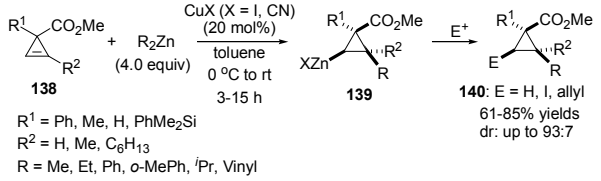


Tandem carbozincation with zinc enolates of esters and amides/electrophilic trapping. The low reactivity of the zinc enolates of esters and amides toward unactivated alkenes limits their application in tandem reactions. Only the strained cyclopropenone acetal **135** was found to be a suitable substrate for the intermolecular addition of the zinc enolates of amides and lactams.[86] The zincated δ-lactam **134** derived from amide **133** reacted with the strained cyclopropenone acetal **135** to form the cyclopropyl zinc species **136**, which was subsequently functionalized by electrophilic trapping with iodine to give **137** in 55% yield with excellent 1,2-diastereoselectivity (dr = 98:2) (Scheme 36). Fox and co-workers also reported the tandem carbozincation of cyclopropene ester derivatives **138** with diorganozinc reagents, in which the ester group can be used as a *syn*-directing group to give the intermediate zinc complex **139**. This inermediate was successfully trapped with various electrophiles such as a proton, iodine, and allyl bromide to afford **140** with *syn*-diastereoselectivity (Scheme 37).[87] Tandem carbozincations and electrophilic trapping of spiro[2.5]oct-1-enes with Et_2Zn have also been reported by the group of Richey.[88]

Scheme 36.

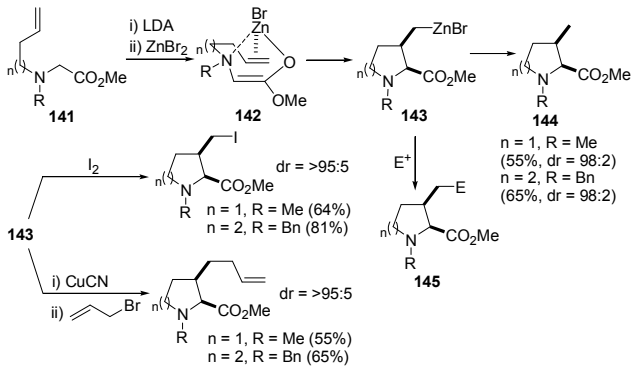


Scheme 37.



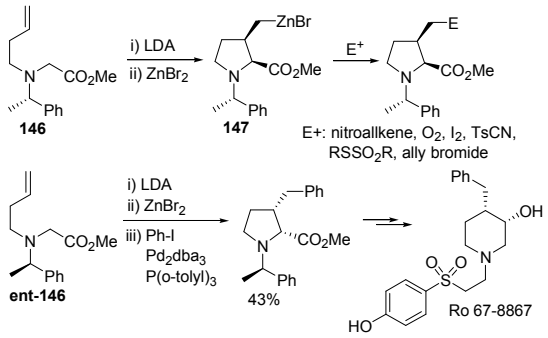
Normant and co-workers reported, simultaneously with others, the carbometallation reaction of the α-(*N*-alkenylamino)esters **141** (Scheme 38).[89-92] The Reformatsky-type reagent **142**, obtained by the deprotonation of α-aminoester **141** followed by transmetallation with $ZnBr_2$, underwent intramolecular addition leading to alkyl zinc species **143**, which provided the pyrrolidines and piperidines **144** in moderate yields upon hydrolysis. The carbocyclization was completely diastereoselective, affording exclusively the *cis* diastereomer. The Zn-enolate intermediates **142**, where the O-bound enolate eclipses the terminal reacting double bond, were proposed to explain the *cis*-selectivity. The alkylzinc species **143** were further reacted with different electrophiles to afford the diversely substituted pyrrolidines and piperidines **145**.

Scheme 38.



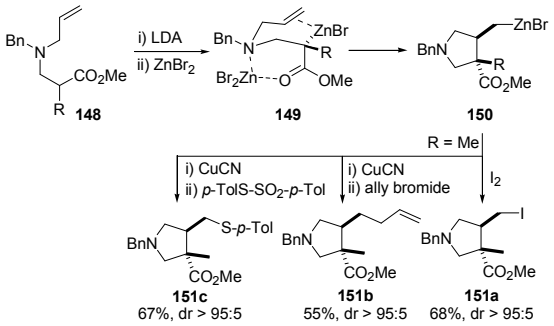
Karoyan and co-workers reported an asymmetric version of the carbozincation of zinc enolate of α-aminoester **146** using the (*S*)-1-phenylethyl amino group as a stereoinducer (Scheme 39).[93] The carbocyclization reaction of the zinc enolate of this chiral α-aminoester has been used to prepare proline chimeras of proteogenic amino acids through the electrophilic trapping of the enantiopure *cis*-3-(zinciomethyl)prolines **147** with nitroalkenes, molecular oxygen, iodine, tosyl cyanide, $RSSO_2R$, and allyl bromides. The resulting diverse aminoacid derivatives were then included in biologically active peptides to establish structure-activity relationships.[94-97] The trapping of the enantiopure *cis*-3-(zinciomethyl)prolines **147** with aryl iodides under the catalytic effect of palladium has also been developed,[98] and was applied to the asymmetric synthesis of Ro 67-8867, a NMDA 2B receptor antagonist.[99]

Scheme 39.

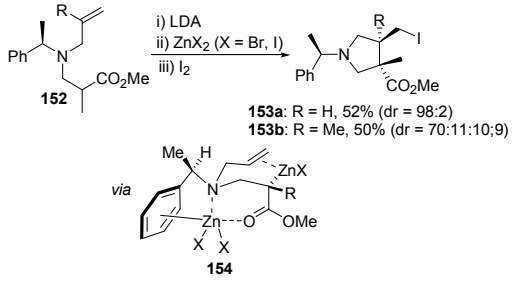


The carbocyclization of zinc-enolates derived from β-aminoesters has also been developed by Normant and co-workers (Scheme 40).[100] The intramolecular carbozincation of zinc enolates **149**, prepared from the β-(*N*-allylamino)esters **148** by deprotonation with LDA followed by transmetallation with a $ZnBr_2$, led to the alkylzinc intermediate **150** affording β-proline analogues upon hydrolysis in good yields (52-82%) with excellent diastereoselectivities (dr = 87:13-95:5). The use of ZnI_2 and/or reverse addition (addition of the Li–enolate to a zinc bromide solution) was necessary in some cases to prevent competitive β-eliminations, especially for R = H. Unlike what is encountered in the case of the α-aminoester, the *trans* isomer was formed as a major stereoisomer. The bridging C-bound zinc-enolate intermediate **149** accounts for the observed *trans* selectivity. Electrophilic trapping of the alkyl zinc intermediate **150** allowed further functionalization to afford the polysubstituted β□prolines **151a-151c**. An enantioselective version using the chiral 1-phenylethylaminoester **152** was also developed (Scheme 41).[101] The *trans*-pyrrolidines **153** were obtained in a diastereo- and enantiomerically enriched form. Cyclization via the C-zincated intermediate **154** involving zinc chelation between the ester carbonyl and the nitrogen was here again proposed to account for the observed selectivities. The chirality transfer would result from an interaction between the chelated zinc salt and the aryl moiety.

Scheme 40.

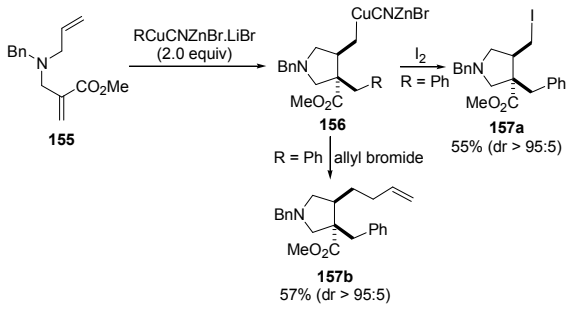


Scheme 41.



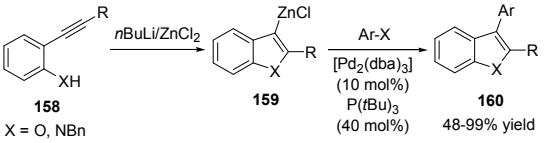
Tandem conjugate addition of a copper-zinc reagent/carbocyclization/electrophilic trapping. Chemla and co-workers reported that the reaction of alkyl- vinyl-, and arylcopper-zinc reagents, RCu(CN)-ZnBr, with the (*N*-allylamino)enoate **155** underwent a conjugate addition/carbocyclization domino process to afford pyrrolidines **157** *via* the metallo β□prolines **156** as intermediates (Scheme 42).[102-104] The electrophilic trapping of **156** (R = Ph) with iodine and allyl bromide afforded the polysubstituted pyrrolidines **157a** and **157b**, respectively, in moderate yields with excellent diastereoselectivities.[102] The enoate **155** also reacted with dialkylzincs to give the corresponding pyrrolidines with moderate to high levels of diastereoselectivity (49-98% yields, dr = 75:25 up to 96:4).[103] The conjugate addition/carbocyclization process could also be carried out with β-allyloxy enoates providing polysubstituted terahydrofurans.[104]

Scheme 42.



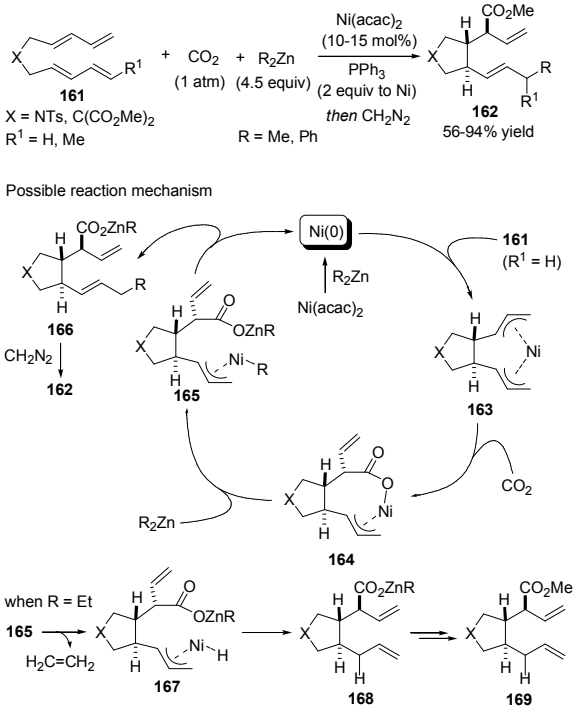
Tandem intramolecular cyclization/Pd or Cu-catalyzed trapping. Nakamura and co-workers reported that the zincated 2-allkynylphenol or anilines **158** could intramolecularly cyclize in a 5-*endo-dig* mode to result in the corresponding 3-zinciobenzoheteroles **159**, which can be trapped with aryl halides in the presence of 10 mol% of $[Pd_2(dba)_3]$ and 40 mol% of P(*t*-Bu)$_3$ to afford 3-arylated benzofurans and indoles in up to 99% yield (Scheme 43).[105] In the presence of a stoichiometric amount of CuCN·2LiCl, the 3-zincated intermediate **159** could also be trapped with different electrophiles such as allyl bromides, aldehydes, and Michael acceptors.[106]

Scheme 43.



Tandem Ni-catalyzed carboxylative carbocyclization of bis-1,3-dienes with diorganozinc reagents. Mori and co-workers have reported a nickel-catalyzed regio- and stereoselective tandem carboxylative carbocyclization-methylation or phenylation of bis-1,3-dienes **161**. Using dimethylzinc and diphenylzinc as reactants affords cyclic compounds **162** in good to excellent yields after esterification (Scheme 44).[107] It has been proposed that the bis-π-allylnickel complex **163** is formed by the oxidative cycloaddition of bis-diene **161** to a Ni(0) complex. Subsequent insertion of CO_2 into the nickel-carbon bond affords carboxylate **164**. The role of R_2Zn in this reaction is probably the regeneration of a Ni(0) complex via a transmetalation/reductive elimination process. Thus, complex **164** reacts with R_2Zn to provide nickel complex **165**, which may undergo reductive elimination reproduces a Ni(0) complex and provide carboxylate **166**, which was methylated with diazomethane to give ester **162**. The intermediate **165**, generated from Et_2Zn (R = Et), can easily undergo β-hydride elimination to afford complex **167**. Reductive elimination from **167** provides carboxylate **168** on the route to ester **169**. The same group reported an enantioselective version of this reaction that employ a chiral monodentate ligand, (*S*)-MeO-MOP, to give optically active **162** in up to 96% ee.[108]

Scheme 44.

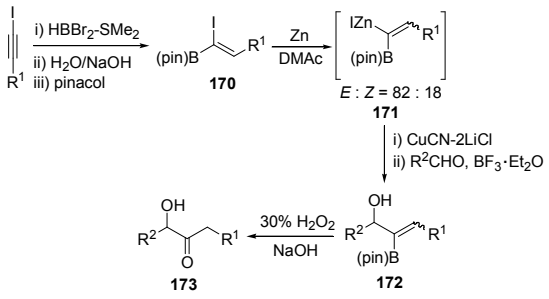


6. Tandem reactions with bimetallic zinc reagents

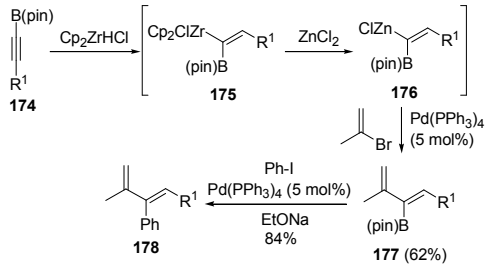
Bimetallic reagents possess two nucleophilic sites in a same molecule, which enables them to react with two different electrophiles sequentially. In the pioneering work of Knochel and co-workers, 1-alkenyl-1,1-boron zinc bimetallic reagents **171** were generated by reaction of the 1-iodoalkenyl boronate esters **170** with zinc in DMAc (Scheme 45).[109] Unfortunately, the insertion of zinc into the C–I bond did not proceed with stereochemical fidelity but provided a mixture of double bond isomers (*E*:*Z* = 82:12), limiting the utility of these 1,1-bimetallic reagents. The reaction of the resulting 1-alkenyl-1,1-boron zinc reagents with CuCN resulted in the formation of 1,1-copper boron derivatives, which were subjected to a variety of electrophiles. For example, the reaction of the 1,1-copper boron bimetallic with aldehydes in the presence of $BF_3{\cdot}OEt_2$ provided the vinyl boronate ester addition products **172**. After standard workup, the resulting *E*:*Z* mixture of **172** was treated with 30% H_2O_2 to provide the α-hydroxy ketones **173** in 74-87% yield (50-58% yield from the 1-iodoalkynes). In related work, Srebnik and co-workers examined the hydrozirconation of alkynyldioxaborolanes **174** with the Schwartz reagent, Cp_2ZrHCl, to generate the 1-alkenyl-1-boron zirconium intermediates **175** (Scheme 46).[110-112] Transmetallation of the Zr-C bond allowed for selective coupling reactions to be performed with retention of the stereochemistry of the alkenyl group. The reaction of **175** with $ZnCl_2$ generated the 1,1-boron zinc reagent **176**. In the presence of 5 mol% $Pd(PPh_3)_4$ and an alkenyl bromide, a Negishi coupling ensued with formation of the dienyl boronate **177** in 62% isolated yield. In the next step, treatment of **177** with PhI, EtONa, and 5 mol% $Pd(PPh_3)_4$ provided the Suzuki-Miyaura coupling product **178** in 84% yield. Walsh and co-workers extended Srebnik's work to 1-alkenyl-1,1-diboro intermediates **179** through the

hydroboration of the B(pin)-substituted alkynes **174** with dicyclohexylborane (Scheme 47).[113] The B-vinyl bond of the dicyclohexyl alkenyl borane undergoes rapid and chemoselective transmetallation with dialkylzinc reagents to generate the 1,1-boron zinc complex **180**. The more reactive Zn-C bonds react with aldehydes to generate the B(pin)-substituted zinc alkoxide intermediate **181**, which can be directly employed in Suzuki-Miyaura cross-couplings with vinyl, phenyl, and alkynyl halides to provide the functionalized allylic alcohols **182** in good yields.

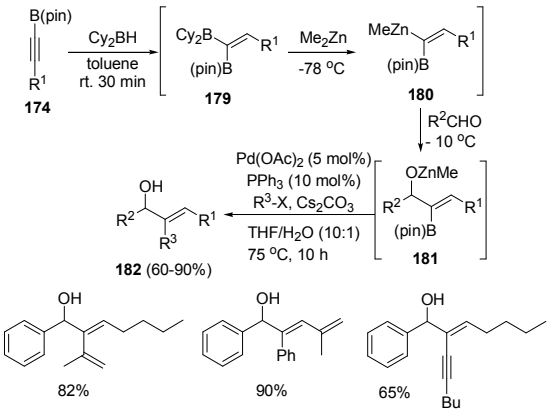
Scheme 45.



Scheme 46.

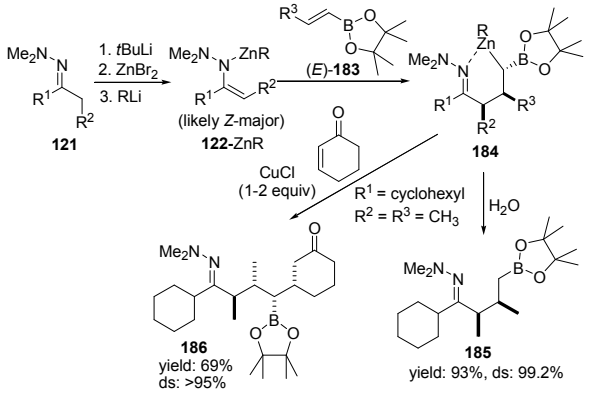


Scheme 47.



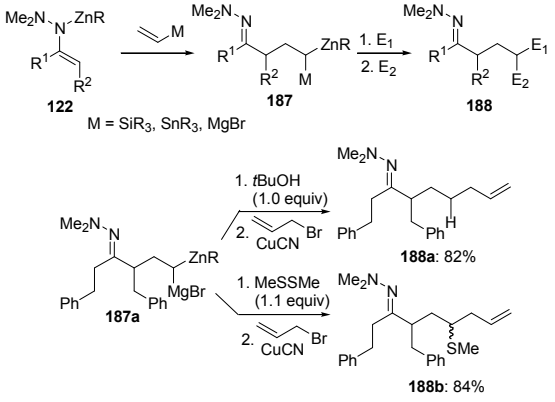
Nakamura and co-workers extended the carbozincation of zincated hydrazones to prepare the 1,1-boron zinc bimetallic reagent **184** through the regioselective addition of the zinc azaenolate **122**, derived from hydrazones **121**, to the vinyl boronate **183** (Scheme 48).[114] The addition of the zinc azaenolate **122** to the vinyl boronate **183** proceeded regioselectively and stereospecifically. For example, the reaction of (*Z*)-**122** with (*E*)-**183** afforded the *syn/anti*-**184**. Density functional theory calculations suggested a metallo-ene mechanism consisting in the formation of a π-complex between a zincated hydrazone and a vinylboronate followed by the six-centered bond reorganization of a highly ordered boat conformation transition state.[115] Quenching of the boron zinc bimetallic species **184** (R^1 = cyclohexyl, R^2 = R^3 = CH_3) with water afforded the boron-functionalized hydrazones **185** in high yield and high distereoselectivity. The bimetallic intermediate can also be used in copper-catalyzed coupling reactions. For example, the alkylzinc species **184** reacted with cyclohexenone in the presence of CuCl to afford the boron-functionalized hydrazone **186** in 69% yield with >95% diastereoselectivity. The boron functionality could potentially be utilized for further reactions such as Suzuki-Miyaura couplings.

Scheme 48.



The extensive work of Nakamura and co-workers proved that other vinyl metals, including vinylsilanes,[116] vinylstannanes,[117] and vinylmagnesium bromides,[118] could also act as π-electrophiles toward the zinc azaenolates **122**, leading to the bimetallic intermediates **187** (M = SiR_3, SnR_3, MgBr), which could then react with two-different electrophiles (Scheme 49). For example, the magnesium zinc bimetallic reagent **187a** was reacted sequentially with one equivalent of *t*BuOH to protonate the C–Mg bond, and then with allyl bromide in the presence of stoichiometric amount of CuCN for the allylation of C–Zn bond to afford **188a** in 82% yield. Similarly, treatment of **187a** with $(MeS)_2$, followed by allyl bromide and CuCN afforded the homoallylic thioether **188b** in 84% yield.[116]

Scheme 49.



7. Conclusions

The great benefits associated with tandem reactions have ensured their sustained popularity in organic synthesis. In particularly, the use of organozinc reagents in tandem reactions offers several advantages over other organometallic reagents, such as a broad functional group tolerance and compatibility with transition metals, thus allowing for the design of new tandem reactions. The examples highlighted in this review demonstrate the power of organozinc reagents in tandem reactions. Despite their high potential and benefits, tandem reactions based on organozinc reagents and in particular their catalytic variants have yet to reach maturity. Given the increasing demands for economical and environmentally benign synthetic methods, tandem reactions are destined to play an integral role in many synthetic endeavors. Moreover, there are currently relatively few examples of catalytic asymmetric tandem reactions with organozinc reagents, and it is likely that these will become increasingly prominent in years to come, with transition metal and organocatalytic processes at the vanguard of this movement. In order to push forward the state of the art in these sequences, a precise understanding of the reaction mechanism and kinetics of each transformation will be required to design and implement new tandem reactions with organozinc reagents. These advances in fundamental knowledge, combined with a large dose of intellectual flexibility and creativity, will undoubtedly lead to even more spectacular applications of organozinc reagents in tandem reactions.

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Notes and references

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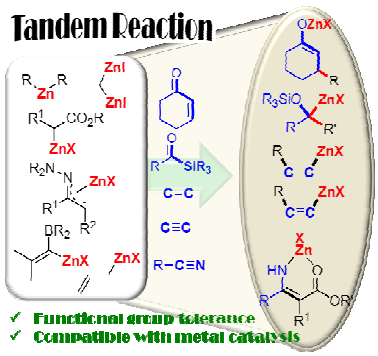

A review of recent advances in tandem reactions with organozinc reagents that highlight their utility in organic synthesis (118 Refs).