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Cobalt Catalysis Involving π Components in Organic Synthesis

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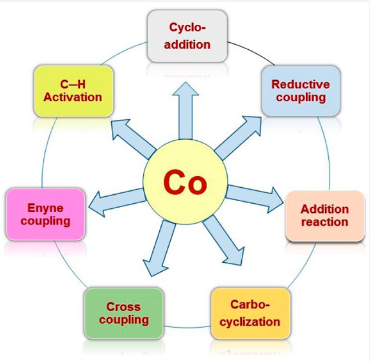
CONSPECTUS: Over the last three decades, transition-metal-catalyzed organic transformations have been shown to be extremely important in organic synthesis. However, most of the successful reactions are associated with noble metals, which are generally toxic, expensive, and less abundant. Therefore, we have focused on catalysis using the abundant first-row transition metals, specifically cobalt. In this Account, we demonstrate the potential of cobalt catalysis in organic synthesis as revealed by our research.

We have developed many useful catalytic systems using cobalt complexes. Overall, they can be classified into several broad types of reactions, specifically [2 + 2 + 2] and [2 + 2] cycloadditions; enyne reductive coupling; reductive [3 + 2] cycloaddition of alkynes/allenes with enones; reductive coupling of alkyl iodides with alkenes; addition of organoboronic acids to alkynes, alkenes, or aldehydes; carbocyclization of *o*-iodoaryl ketones/aldehydes with alkynes/electron-deficient alkenes; coupling of thiols with aryl and alkyl halides; enyne coupling; and C−H bond activation. Reactions relying on π components, specifically cycloaddition, reductive coupling, and enyne coupling, mostly afford products with excellent stereo- and regioselectivity and superior atom economy. We believe that these cobalt-catalyzed π-component coupling reactions proceed through five-membered cobaltacyclic intermediates formed by the oxidative cyclometalation of two coordinated π bonds of the substrates to the low-valent cobalt species. The high regio- and stereoselectivity of these reactions are achieved as a result of the electronic and steric effects of the π components. Mostly, electron-withdrawing groups and bulkier groups attached to the π bonds prefer to be placed near the cobalt center of the cobaltacycle. Most of these transformations proceed through low-valent cobalt complexes, which are conveniently generated in situ from air-stable Co(II) salts by Zn- or Mn-mediated reduction. Overall, we have shown these reactions to be excellent substitutes for less desirable noble-metal systems.

Recent successes in cobalt-catalyzed C−H activation have especially advanced the applicability of cobalt in this field. In addition to the more common low-valent-cobalt-catalyzed C−H activation reactions, an in situ-formed cobalt(III) five-membered complex with a 1,6-enyne effectively couples with aromatic ketones and esters through ortho C−H activation, opening a new window in this research area. Interestingly, this reaction proceeds under milder reaction conditions with broad substrate scope. Furthermore, many of the reactions we have developed are highly enantioselective, including enantioselective reductive coupling of enones and alkynes, addition of organoboronic acids to aldehydes, and the cyclization of 2-iodobenzoates with aldehydes. Overall, this Account demonstrates the versatility and utility of cobalt catalysis in organic synthesis.



1. INTRODUCTION

Transition-metal complexes that catalyze organic transformations play an indispensable role in organic synthesis because of their broad scope, high efficiencies, and ample functional group tolerance.[1] Most of these reactions rely on noble metals such as Pd, Rh, Ru, Ir, and Au.[2] However, these elements are toxic, expensive, and less abundant, severely restricting their applications in sustainable, medicinal, and industrial synthesis. Alternatively, the first-row transition metals are relatively common, far less expensive, and generally tolerated biologically. As such, they have been applied to a series of more sustainable organic transformations over the last few decades.[3]

Cobalt has already been established as a catalyst in the widely known [2 + 2 + 2] cycloaddition,[4a,b] Nicholas reaction,[4c,d] and Pauson−Khand reaction.[5] However, the utility of this metal has been significantly expanded in the last 20 years with the development of additional cycloadditions, reductive couplings, addition reactions, carbocyclizations, cross-couplings, enyne couplings, and C−H activation reactions. We have been interested in this subject for a very long time and have developed many of these new catalytic systems. In this Account, we demonstrate the great potential and utility of cobalt catalysis by outlining our findings.

2. COBALT-CATALYZED CYCLOADDITION REACTIONS

The high affinity of cobalt complexes toward π bonds, including alkene, alkyne, allene, aryne, and C−N systems, is the basis for the wide variety of developed cycloaddition reactions. This

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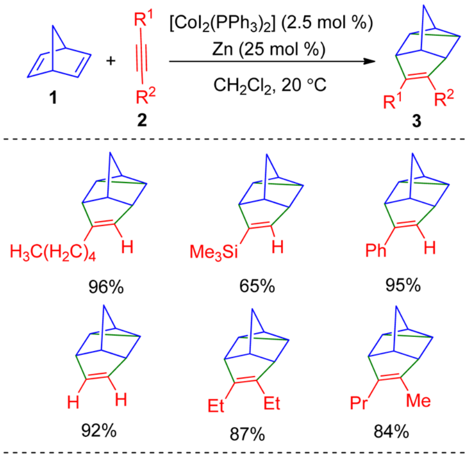
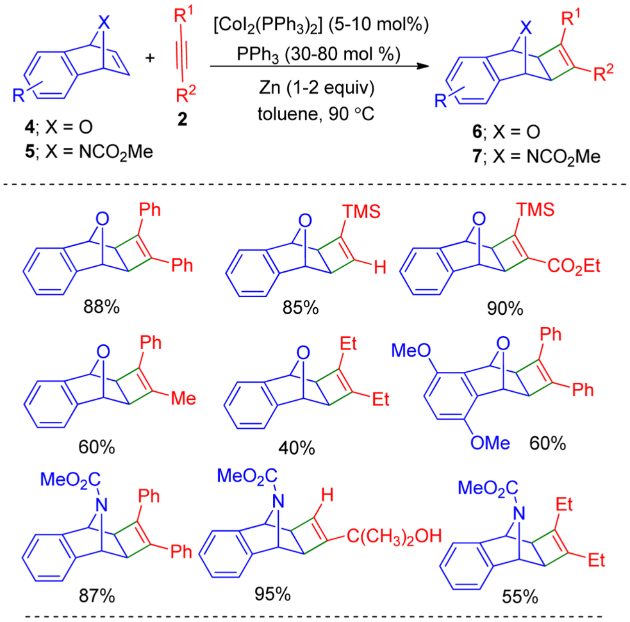
affinity allowed us in 1991 to develop a [2 + 2 + 2] homo-Diels–Alder cycloaddition of norbornadiene (**1**) and both terminal and internal alkynes catalyzed by [$CoI_2(PPh_3)_2$] and Zn powder (Scheme 1);[6a] it should be noted that the reaction also progresses with CoI_2, PPh_3, and Zn, in which case the catalytic complex forms in situ. Excess PPh_3 appears to prevent coordination of norbornadiene to the cobalt center, lowering the product yield. In addition, the reaction does not proceed in the absence of Zn, suggesting that low-valent cobalt complexes are required.

Scheme 1. [2 + 2 + 2] Cycloaddition of Norbornadiene with Alkynes

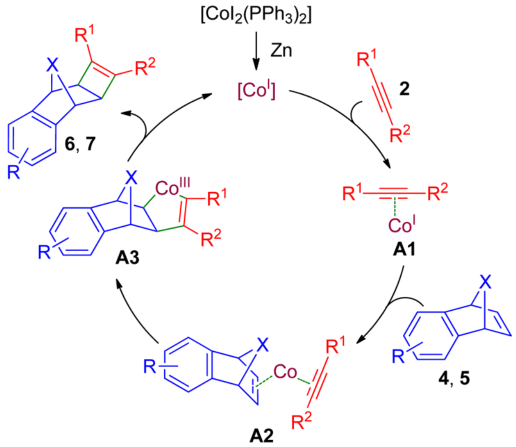


A similar cobalt-catalyzed [2 + 2] cycloaddition of bicyclic alkenes with alkynes allows the synthesis of cyclobutene compounds in high yields with excellent stereoselectivity (Scheme 2); in all cases, the alkyne moiety in the product is at the exo position.[6b] Both 7-oxa- and 7-azabenzonorbornadienes were successfully reacted with alkynes in toluene in the presence of [$CoI_2(PPh_3)_2$], PPh_3, and Zn powder. Note that ≥8 equiv of PPh_3 with respect to cobalt is required to prevent the formation of the [2 + 2 + 2] product. The reaction is likely initiated by the reduction of [$CoI_2(PPh_3)_2$] by Zn powder to yield a Co^I complex; in this case, coordination of the alkyne (**2**) and the bicyclic alkene (**4** or **5**) to Co^I followed by oxidative cyclometalation provides cobaltacyclopentene intermediate **A3**, which in turn produces the final product (**6** or **7**, respectively) and regenerates the catalyst upon reductive elimination (Scheme 3).

Scheme 2. [2 + 2] Cycloaddition of 7-Oxa- and 7-Azabenzonorbornadienes with Alkynes

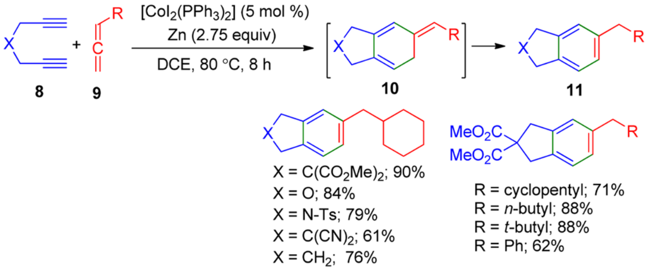


Scheme 3. Mechanism of the [2 + 2] Cycloaddition of 7-Oxa- and 7-Azabenzonorbornadienes with Alkynes



This catalytic system was also applied to the highly regio- and chemoselective [2 + 2 + 2] ene–diyne cycloaddition of 1,6-heptadiynes **8** with allenes **9** (Scheme 4).[7] Interestingly, only the allene terminal double bond participates in this reaction. The reaction proceeds through the cobaltacyclopentadiene intermediate formed from 1,6-heptadiyne and the Co^I complex generated in situ (Scheme 5). Coordination followed by terminal bond insertion into the Co^{III}–carbon bond affords cobaltacycloheptadiene **B3**. Reductive elimination then affords Co^I and the cyclohexadiene, which undergoes rearrangement to give the final product.

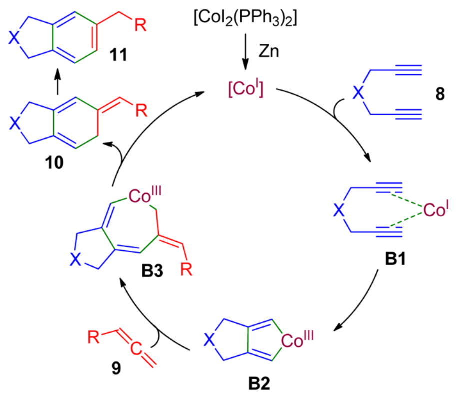
Scheme 4. [2 + 2 + 2] Cycloaddition of 1,6-Heptadiynes with Allenes



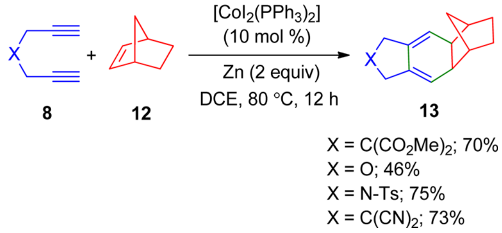
In a similar manner, this catalytic system was applied to the selective [2 + 2 + 2] cycloaddition of 1,6-heptadiynes **8** and norbornene (**12**) (Scheme 6).[8a] This is in contrast to an earlier report by Itoh and co-workers, in which these substrates primarily preferred a [4 + 2] cycloaddition in the presence of a ruthenium catalyst.[8b]

We further demonstrated that a catalytic amount of [$CoI_2(dppe)$] and Zn allow the simple regioselective [2 + 2 + 2] co-cyclotrimerization of alkynyl alcohols **2b** and alkynyl amine **2c** with methyl propiolate (**2a**) to yield benzolactones **15** and

Scheme 5. Mechanism of the [2 + 2 + 2] Cycloaddition of 1,6-Heptadiynes with Allenes

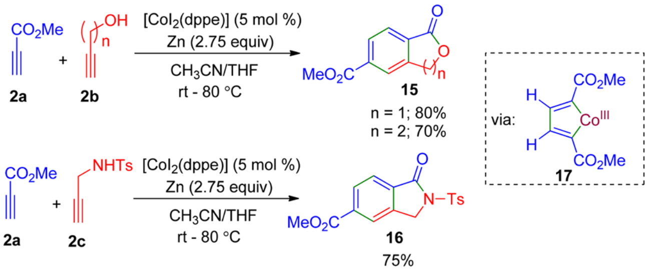


Scheme 6. [2 + 2 + 2] Cycloaddition of 1,6-Heptadiynes with Norbornene



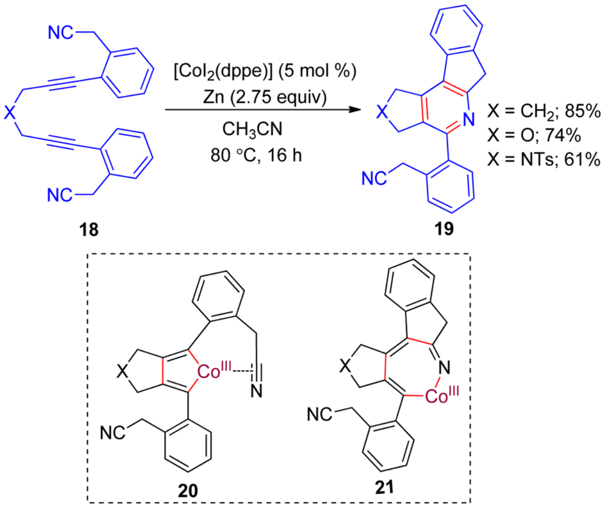
lactam **16**, respectively, in high yields (Scheme 7).[9] This regioselectivity is attributed to the head-to-head oxidative cyclometalation of the propiolate to form cobaltacyclopentadiene intermediate **17**.

Scheme 7. [2 + 2+ 2] Co-cyclotrimerization of Alkynyl Alcohols and Amine with Propiolates



Pyridine formation via the [2 + 2 + 2] cycloaddition of alkynes with nitriles in the presence of transition-metal complexes has been well-studied.[10] In 2007, we demonstrated a new version of this reaction that combines nitrilediynes **18** to form tetra- and pentacyclic pyridines **19** using the $[CoI_2(dppe)]/Zn$ catalyst system (Scheme 8).[11] The reaction proceeds through coordination of Co^I to the diyne group followed by oxidative cyclometalation to form cobaltacyclopentadiene intermediate **20**. Subsequent insertion of the nitrile into the Co−carbon bond affords cobaltacycloheptadiene intermediate **21**, and reductive elimination then provides the pyridine product and recycles the Co^I active species.

Scheme 8. Intramolecular [2 + 2 + 2] Co-cyclotrimerization of Nitrilediynes



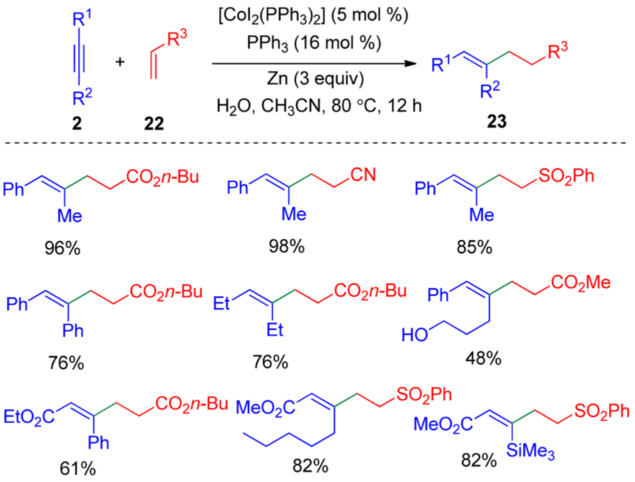
3. COBALT-CATALYZED REDUCTIVE COUPLING REACTIONS

The popular transition-metal-catalyzed regio-, stereo-, and chemoselective reductive couplings of two π components have been applied to alkyne, alkene, allene, and carbonyl compounds as well as their various derivatives.[12] It is believed that all metal-catalyzed reductive coupling reactions proceed though metallacycle intermediates.

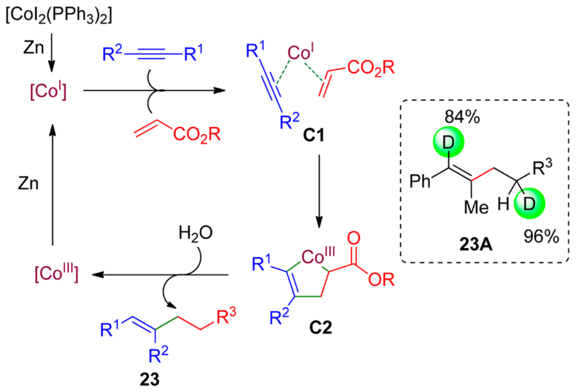
In 2002, we applied this pathway to the coupling of alkynes **2** with activated alkenes **22** in the presence of $[CoI_2(PPh_3)_2]$, PPh_3, H_2O, and Zn in acetonitrile to afford the reductive coupling products **23** in high yields with very high chemo-, regio-, and stereoselectivity (Scheme 9).[13] This reaction is compatible with acrylates, acrylonitrile, and vinyl sulfones. Similarly, both symmetrical and unsymmetrical internal alkynes are susceptible to this reaction.

A plausible mechanism for this reaction is shown in Scheme 10. As in many of the previously discussed reactions, it is likely initiated by the formation of a Co^I active species. Coordination of the alkyne and alkene to this complex followed by oxidative cyclometalation gives Co^{III} metallacycle **C2**, and subsequent

Scheme 9. Reductive Coupling of Internal Alkynes with Activated Alkenes



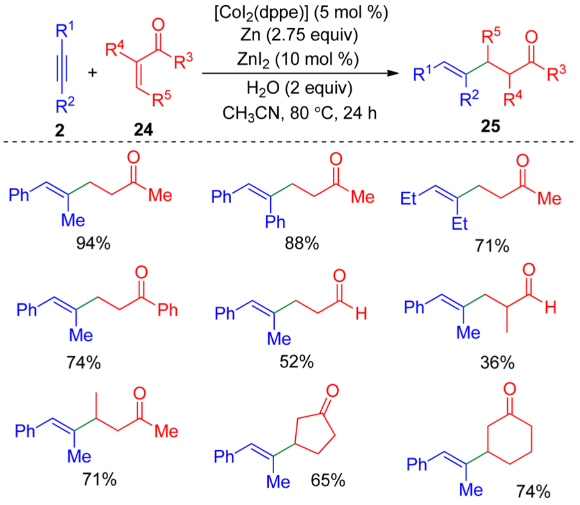
Scheme 10. Mechanism of the Reductive Coupling of Internal Alkynes with Activated Alkenes



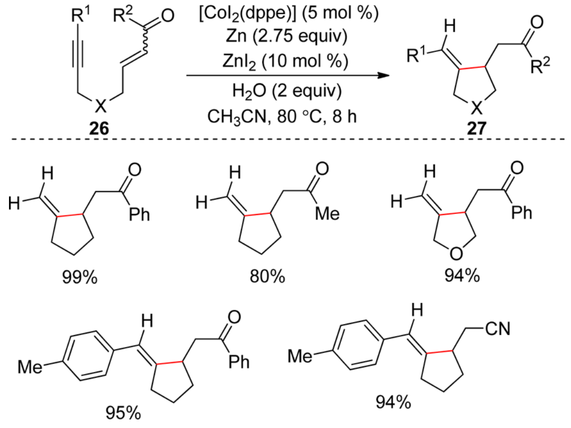
protonation of the intermediate by H_2O affords product **23**; meanwhile, the Co^{III} species is again reduced to Co^{I} by Zn. Reaction of methylphenylacetylene with phenylvinyl sulfone using D_2O as a proton source afforded product **23A**; in this case, deuterium incorporation was measured at 84 and 96% for the olefinic and α-methylene protons, respectively, which strongly supports the proposed reaction mechanism.[13]

Unfortunately, the above reaction conditions do not work for many common alkenes, such as enones and enals. Fortunately, we determined that the presence of a Lewis acid promotes the reactivity of these species and developed a new system in which 10 mol % ZnI_2 was added to the old one; the new system gave reductive coupling products **25** in high yields (Scheme 11).[14]

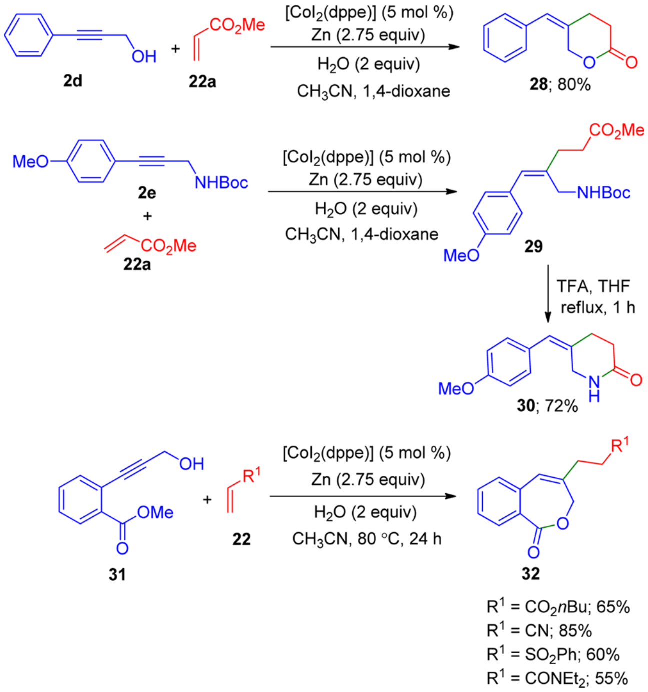
Scheme 11. Reductive Coupling of Internal Alkynes with Enones and Enals



Scheme 12. Intramolecular Reductive Coupling of Alkynes with Activated Alkenes



Scheme 13. Reductive Coupling of Propargyl Alcohols and Amines with Acrylates



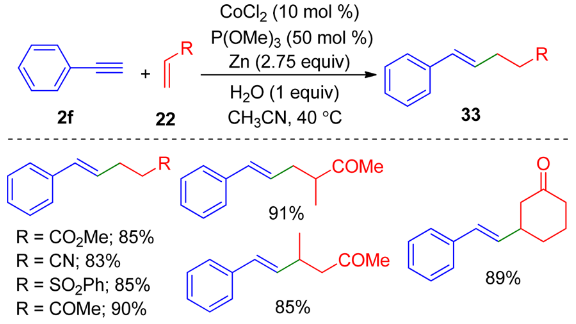
The intramolecular version of this reaction also proceeded smoothly under similar reaction conditions (Scheme 12).[14] Interestingly, terminal alkynes worked well intramolecularly but not intermolecularly.[13,14]

Treatment of propargyl alcohol **2d** and methyl acrylate (**22a**) in the presence of $[CoI_2(dppe)]$, Zn, and H_2O in a mixture of acetonitrile and 1,4-dioxane was shown to offer six-membered lactone **28** in very good yield (Scheme 13).[14] Similarly, protected propargylamine **2e** reacted with **22a** to afford the reductive coupling product **29**, which was transformed to lactam **30** upon heating with trifluoroacetic acid. Meanwhile, seven-membered lactones **32** were synthesized through enyne coupling of activated alkenes with a phenylpropargyl alcohol containing an ester group at the ortho position of the phenyl ring (Scheme 13).[14]

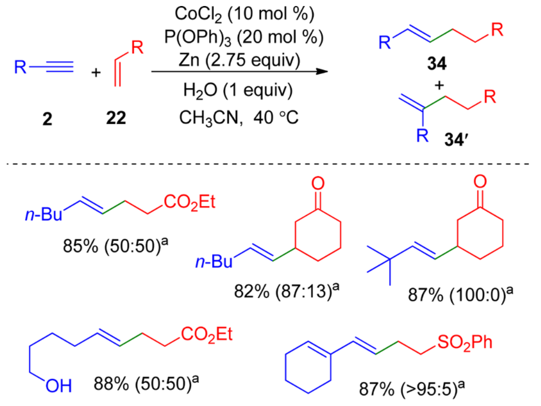
We recently succeeded in the reductive coupling of terminal alkynes with activated alkenes using a $CoCl_2/P(OMe)_3/Zn$ catalyst system.[15] This system greatly suppresses the homo-cyclotrimerization of the terminal alkyne, which in general is the major side reaction of the enyne reductive coupling. A wide variety of regio- and stereoselective 1,2-trans-disubstituted alkenes were obtained from aromatic terminal alkynes (Scheme 14); however, aliphatic terminal alkynes provided a mixture of 1,2-trans- and 1,1-disubstituted terminal alkenes, albeit in high yields (Scheme 15).

These results suggested that enantioselective enyne reductive coupling should be possible as well. We demonstrated this in 2011 using a $CoI_2/(R)$-BINAP, Zn, ZnI_2, and H_2O system, which was very effective in the asymmetric reductive coupling of cyclic

Scheme 14. Reductive Coupling of Aromatic Terminal Alkynes with Activated Alkenes

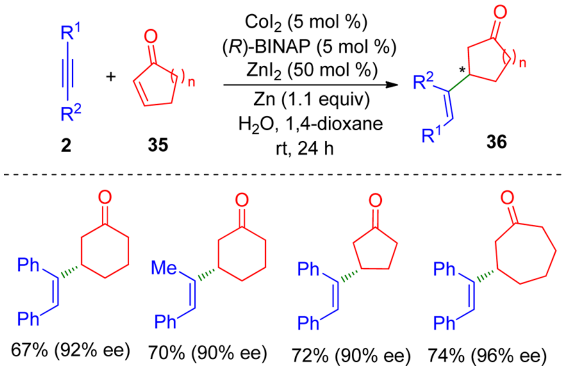


Scheme 15. Reductive Coupling of Aliphatic Terminal Alkynes with Activated Alkenes



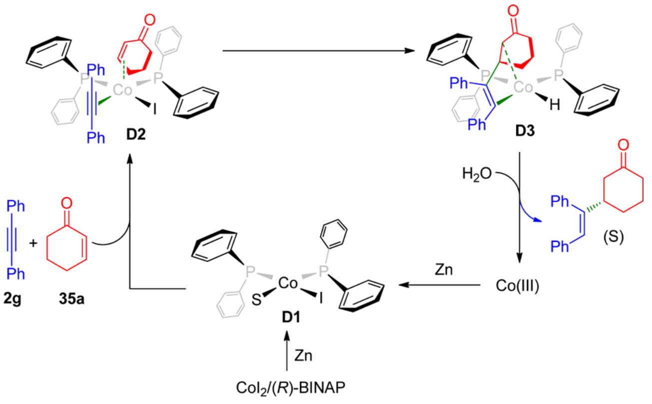
[a]The **34**:**34′** ratio is given in parentheses.

Scheme 16. Cobalt-Catalyzed Enantioselective Reductive Coupling of Alkynes with Cyclic Enones



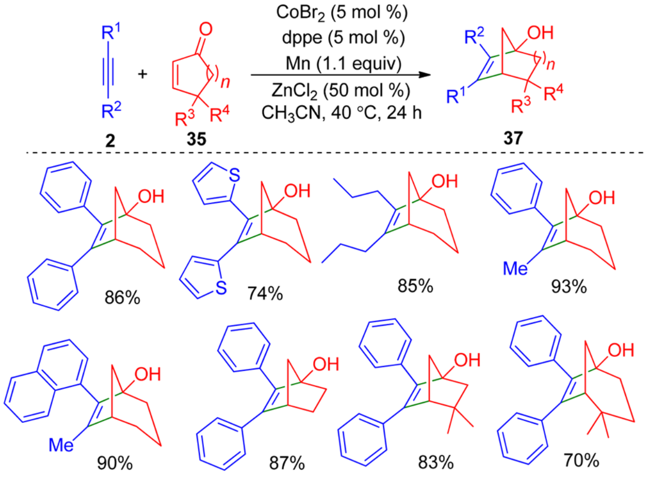
enones and alkynes to give β-substituted ketones **36** enantioselectively (Scheme 16);[16] while many chiral ligands were tested, (*R*)-BINAP showed the highest yields and enantioselectivity. Furthermore, this reaction works well for both symmetrical and unsymmetrical internal alkynes, yielding products with high regio- and enantioselectivity. However, terminal alkynes fail to give the desired products because of their tendency for homo-cyclotrimerization. Products **36** adopt the *S* absolute configuration, as determined by single-crystal structural analysis.

Scheme 17. Mechanism of Cobalt-Catalyzed Enantioselective Reductive Coupling of Alkynes with Cyclic Enones



Scheme 17 presents a possible reaction mechanism. The $[L_nCo^I]$ intermediate **D1** is likely initially formed from CoI_2 and (*R*)-BINAP by Zn reduction. Next, coordination of diphenylacetylene (**2g**) at the equatorial position and the *si* face of cyclohexenone (**35a**) at the axial position of **D1** provides intermediate **D2**. Finally, oxidative cyclometalation followed by protonation gives the final product, while Co^I is regenerated by the reduction of Co^{III}.

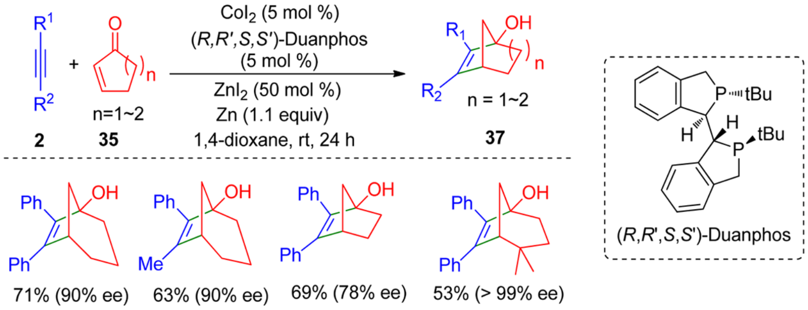
Scheme 18. Reductive [3 + 2] Cycloaddition of Alkynes with Enones



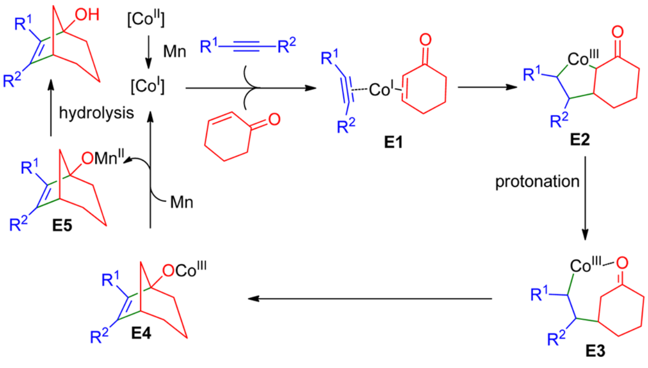
Interestingly, the reaction of alkynes with cyclic enones in the presence of CoI_2, dppe, Mn, and $ZnCl_2$ in acetonitrile or 1,4-dioxane afforded bicyclic tertiary alcohols in high yields (Scheme 18).[17] Zn powder can also be used to replace Mn as the reducing agent. A very dry solution is required for the success of this Co-catalyzed reductive [3 + 2] cycloaddition. The corresponding enyne reductive coupling reaction competes strongly with this cycloaddition during the reaction, and more water appears to favor the reductive coupling reaction. Furthermore, employing enantiomerically pure phosphine ligands yielded an asymmetric reaction, with Duanphos in particular giving high yields and enantioselectivity (Scheme 19).[17]

Scheme 20 provides a possible mechanism for this [3 + 2] reaction. Formation of Co^I initiates the cycle. Next, the alkyne and enone coordinate to the Co^I complex to afford intermediate **E1**. This then undergoes oxidative cyclization to give cobaltacyclopentene intermediate **E2**, which is selectively protonated at the carbon α to the keto group to yield **E3**. Intramolecular insertion of the carbonyl group into the cobalt–

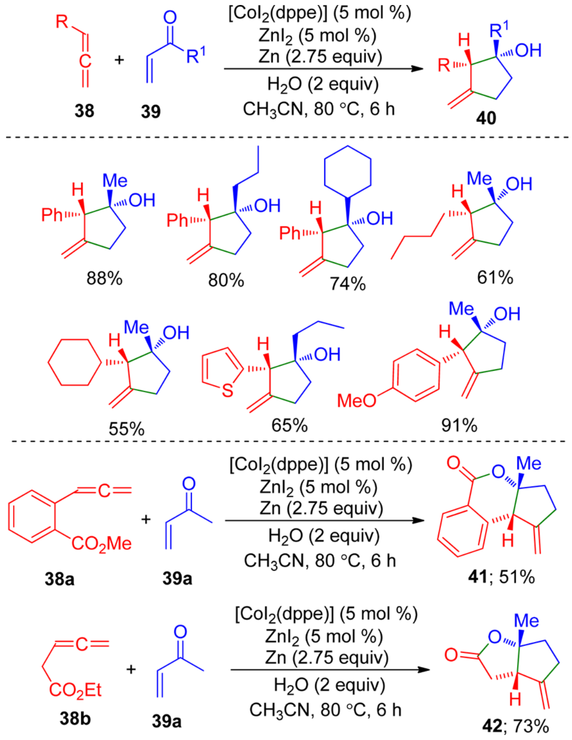
Scheme 19. Enantioselective Reductive [3 + 2] Cycloaddition of Alkynes with Enones



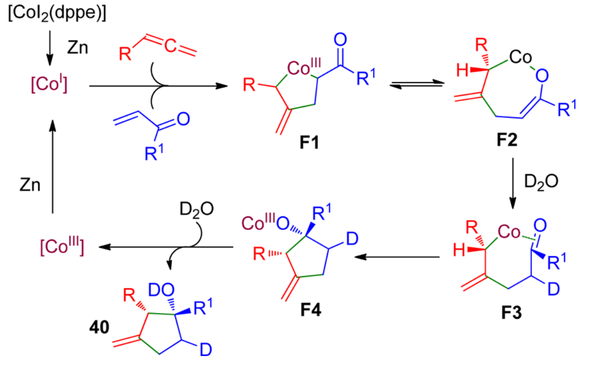
Scheme 20. Mechanism of the Reductive [3 + 2] Cycloaddition of Alkynes with Enones



Scheme 21. Reductive [3 + 2] Cycloaddition of Allenes with Enones



Scheme 22. Mechanism of the Reductive [3 + 2] Cycloaddition of Allenes with Enones



carbon bond forms cobalt alkoxide **E4**, which is reduced by Mn to give **E5** and Co^{I}. Finally, hydrolysis of **E5** affords product **37**.

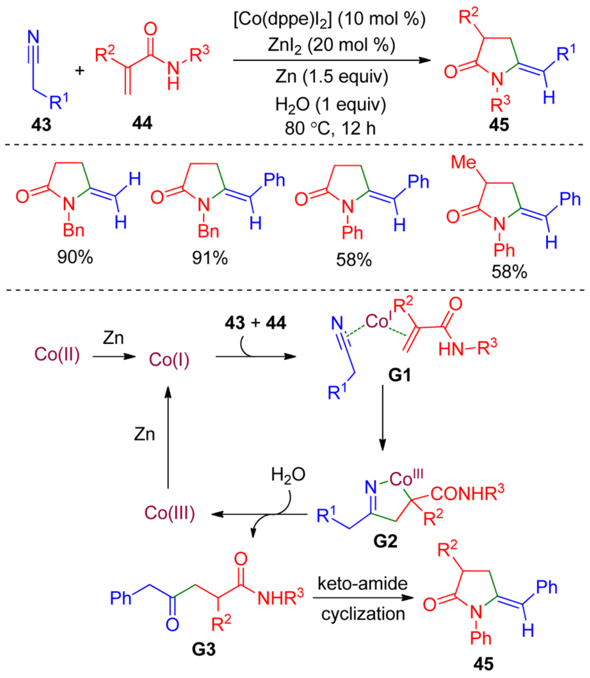
Allenes and enones were also successfully subjected to an intermolecular [3 + 2] reductive cycloaddition by using $[CoI_2(dppe)]$, Zn, ZnI_2, and H_2O in acetonitrile, giving cyclopentanols **40** in high yield with excellent diastereoselectivity (Scheme 21).[18] Interestingly, the reactions of methyl 2-allenylbenzoate (**38a**) and ethyl penta-3,4-dienoate (**38b**) with methyl vinyl ketone (**39a**) gave the double cyclization lactone products **41** and **42**, respectively. A proposed mechanism for this reaction is depicted in Scheme 22. Coordination of the allene and enone to Co^{I} followed by oxidative cyclometalation affords cobaltacyclopentene intermediate **F1**, which is in equilibrium with **F2**. Selective protonation of this species at the carbon α to the carbonyl group leads to **F3**, after which intramolecular insertion of the carbonyl into the carbon−cobalt bond followed by protonation gives the final product **40**.

Nitriles and acrylamides also undergo reductive coupling to give pyrrolidinone products **45** in good to excellent yields with $[CoI_2(dppe)]$, Zn, ZnI_2, and H_2O as the catalyst system (Scheme 23).[19] The reaction likely proceeds through cobaltaazacyclopentene intermediate **G2**. Protonation of **G2** gives reductive coupling product **F3**, which further undergoes keto−amide cyclization to afford pyrrolidinone **45**.

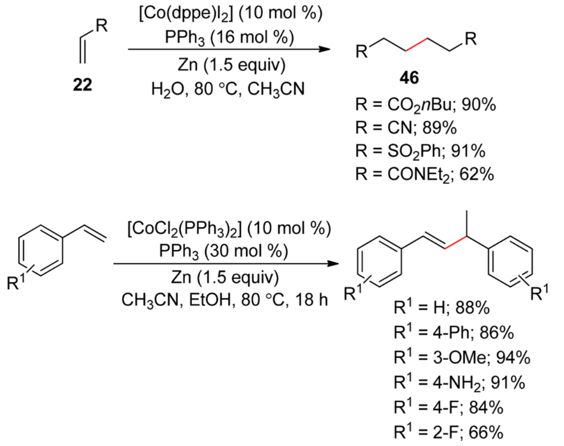
In 2004, we reported an interesting tail-to-tail reductive homodimerization of activated alkenes to give saturated linear products using a $[CoI_2(PPh_3)_2]$, Zn, and H_2O catalytic system (Scheme 24).[20] Alternatively, under similar reaction conditions, vinyl arenes gave head-to-tail dimerization products.

In addition to the reductive coupling of two π components, we also developed a reductive coupling reaction to combine alkyl halides with alkenes (Scheme 25).[21] A range of alkyl iodides and bromides efficiently gave Michael-type addition products. Unlike the Heck coupling, no unsaturated C−C double bond was formed in the reaction. Again, catalysis is initiated by the formation of Co^{I} and continues with the oxidative addition of the alkyl halide to give the Co^{III} intermediate. Coordination of the alkene, subsequent insertion, and finally protonation provide the final product.[21]

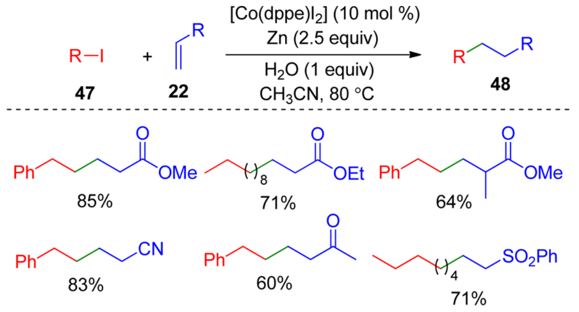
Scheme 23. Reductive Coupling of Nitriles with Acrylamides



Scheme 24. Reductive Homodimerization of Activated Alkenes



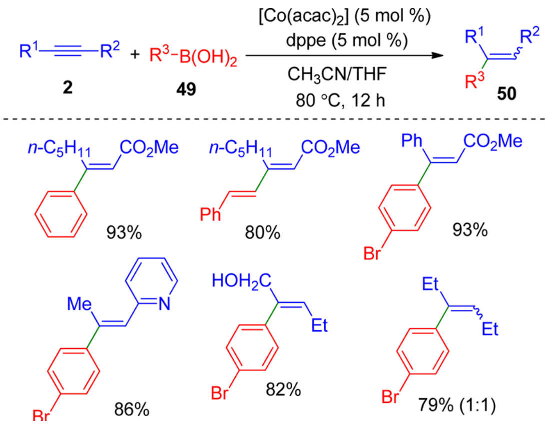
Scheme 25. Reductive Coupling of Alkyl Iodides with Alkenes



4. COBALT-CATALYZED ADDITION REACTIONS

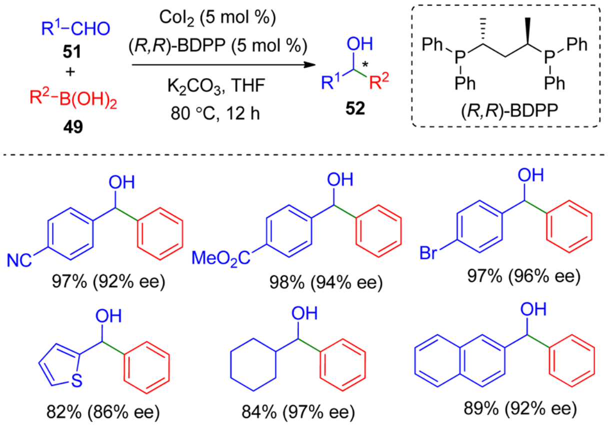
The metal-catalyzed formation of substituted olefins from alkynes is known to work with a variety of metals, including Pd, Rh, and Ni.[22] In 2008, we described the first example of such a reaction using cobalt—in this case, the addition of organoboronic acids to alkynes to give stereo- and regioselective hydroarylation and vinylation products (Scheme 26).[23] The reaction failed to give the expected hydroarylation product when 2-phenyl-1,3,2-dioxaborinane was used instead of phenylboronic acid. This suggested that the organoboronic acid acts as both a transmetalation agent and a proton source. In this case, R^3–$B(OH)_2$ likely undergoes transmetalation with Co^{II} to form R^3–Co^{II}, followed by coordination of the alkyne to R^3–Co^{II}. Next, the carbocobaltation leaves the alkenylcobalt intermediate, giving the final product upon protonolysis.

Scheme 26. Cobalt-Catalyzed Addition of Organoboronic Acids to Alkynes



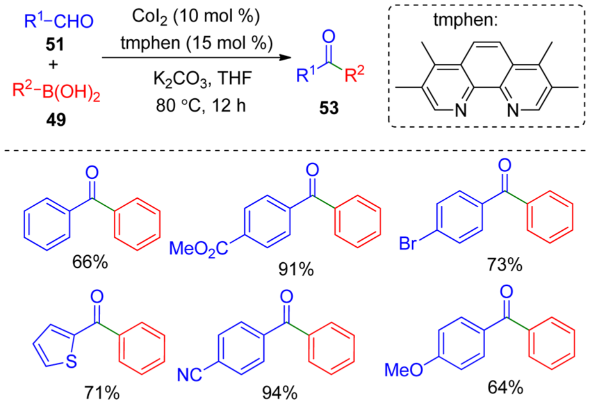
Next, in 2010, we discovered an operationally simple, efficient, and economical method for the enantioselective synthesis of secondary alcohols via the addition of organoboronic acids to aldehydes (Scheme 27).[24] The catalyst system, CoI_2, (*R*,*R*)-BDPP, and K_2CO_3 in tetrahydrofuran (THF), affords secondary alcohols (*S*)-**52** in high yields with excellent ee values, while using (*S*,*S*)-BDPP instead gives the expected products (*R*)-**52**.

Scheme 27. Enantioselective Addition of Organoboronic Acids to Aldehydes



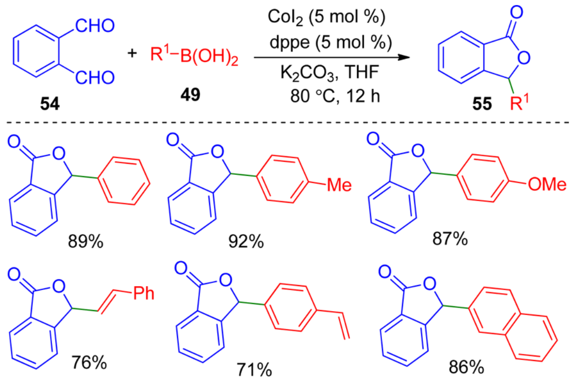
Interestingly, using $CoCl_2$, 3,4,7,8-tetramethyl-1,10-phenanthroline (tmphen), and Cs_2CO_3 as the catalyst system gives ketones instead (Scheme 28).[25] The presence of the bidentate nitrogen tmphen ligand is crucial in this case. The mechanism here likely involves transmetalation of the organoboronic acid to Co^{II} followed by the coordination of the aldehyde to the complex. This in turn allows insertion into the carbon–cobalt bond and subsequent β-hydride elimination, affording the final

Scheme 28. Ketone Formation from Aldehydes and Organoboronic Acids



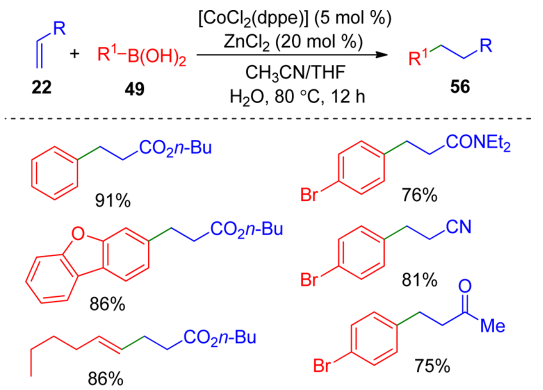
ketone. Likewise, the reaction of phthalaldehyde (**54**) with organoboronic acids in the presence of CoI$_2$/dppe and K$_2$CO$_3$ in THF affords phthalide derivatives **55** in high yields (Scheme 29).[25]

Scheme 29. Phthalide Formation from Phthalaldehyde and Organoboronic Acids



In addition to the previous reactions, we also developed a 1,4-addition of organoboronic acids to activated alkenes (Scheme 30).[26] This reaction is more effective with the bidentate phosphine ligand 1,2-bis(diphenylphosphino)ethane (dppe). It is also worth mentioning that a specific acetonitrile/THF ratio of 3:1 is crucial to obtain a high yield.

Scheme 30. Addition of Organoboronic Acids to Activated Alkenes

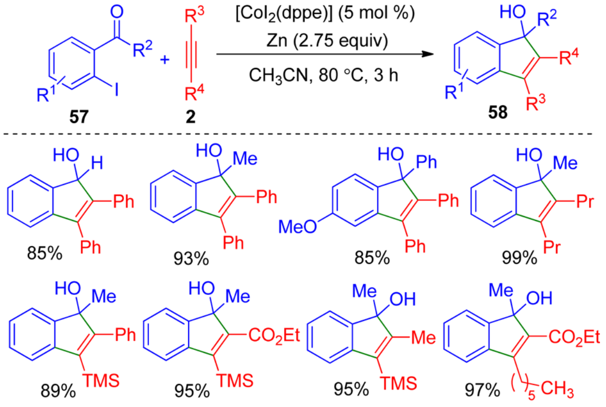


5. COBALT-CATALYZED ANNULATION REACTIONS

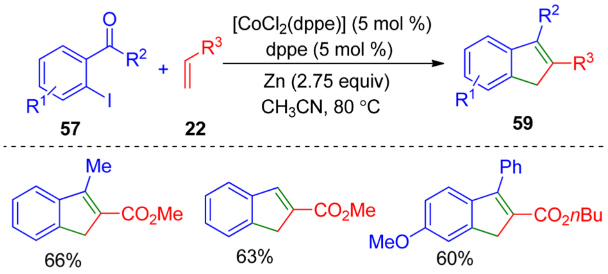
Transition-metal-catalyzed annulation reactions are widely applied in the synthesis of carbocyclic and heterocyclic compounds. Cobalt complexes are particularly useful for these transformations, and we have taken advantage of this fact in our research.[27,28]

In 2003, we disclosed an efficient method for the synthesis of indenols by the carbocyclization of alkynes and either *o*-iodobenzaldehydes or *o*-iodophenyl ketones using the [CoI$_2$(dppe)]/Zn catalyst system (Scheme 31).[29] This technique can also be applied to the synthesis of indene derivatives from *o*-iodoaryl ketones/aldehydes and acrylates (Scheme 32).[30] Preliminary mechanistic studies suggested that the indenol is formed first and undergoes dehydration to give the indene product.

Scheme 31. Formation of Indenols from Alkynes



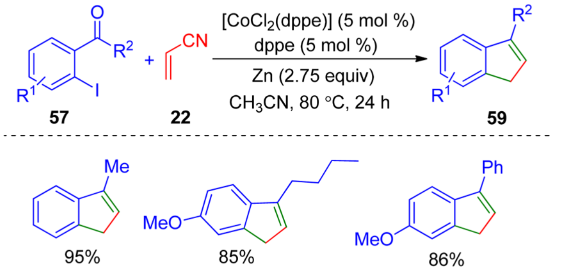
Scheme 32. Indene Formation from Acrylates and 2-Iodophenyl Ketones or Aldehydes



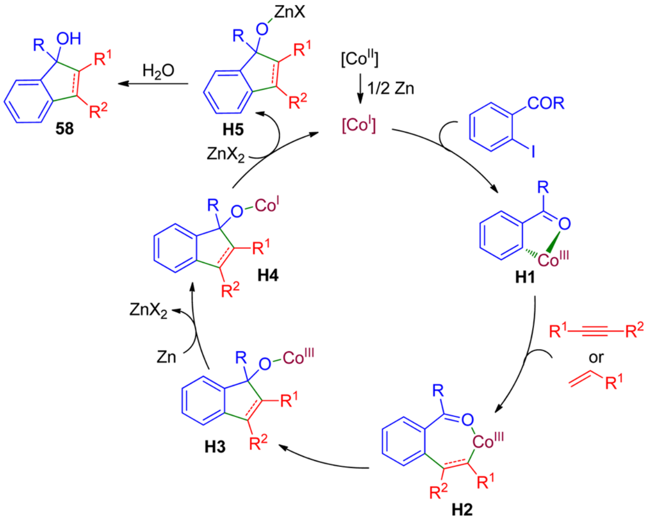
During the course of this research, we observed an interesting reductive decyanation reaction. Treatment of acrylonitrile with 2-iodophenyl ketones in the presence of [CoCl$_2$(dppe)], dppe, and Zn in acetonitrile afforded indenes **59** in excellent yields (Scheme 33).[30] Surprisingly, no cyano group was found in the indene product. In this reaction, acrylonitrile acts as an ethylene source; however, the reason for decyanation is still unclear.[30]

A plausible reaction mechanism for the reaction of *o*-iodoaryl ketones/aldehydes with alkynes/alkenes is presented in Scheme 34. First, Co^{II} is reduced to Co^{I}, after which the *o*-iodoaryl ketone/aldehyde **57** is oxidatively added to the complex. The resulting Co^{III} pentacycle intermediate **H1** coordinates the alkyne/alkene, and subsequent insertion affords the seven-membered cobaltacycle **H2**. Intramolecular nucleophilic addition of the cobalt–carbon bond to the coordinated carbonyl group affords the Co^{III} alkoxide complex **H3**, which is then

Scheme 33. Carbocyclization Reaction of 2-Iodophenyl Ketones with Acrylonitrile



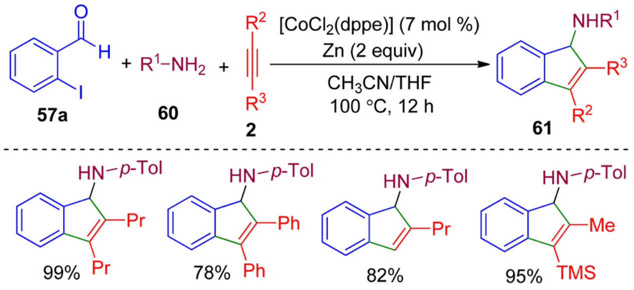
Scheme 34. Mechanism of the Cobalt-Catalyzed Indenol/Indene Synthesis



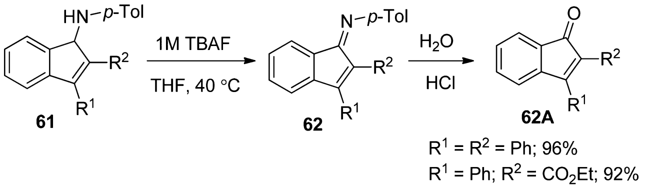
reduced by Zn to give the Co^{I} alkoxide complex **H4**. Transmetalation of **H4** with ZnX_2 followed by hydrolysis gives the desired 1-indenol product **58**, which can further undergo dehydration to give the corresponding indene.[29,30]

The synthesis of isoquinoline derivatives from *o*-halobenzaldimines and alkynes has previously been reported for Pd and Ni complexes by both our group and others.[31] Surprisingly, using cobalt instead affords indenamines in place of isoquinolines.[32] Additionally, the [$CoCl_2$(dppe)]/Zn system is capable of catalyzing the reaction of *o*-iodoarylaldehydes, amines, and alkynes, giving indenamine derivatives in high yields (Scheme 35). Indenamines **61** are then readily converted to indenimines **62** upon treatment with tetrabutylammonium fluoride; finally, these can be hydrolyzed to form indenones (Scheme 36).[32]

Scheme 35. Cobalt-Catalyzed Indenamine Synthesis

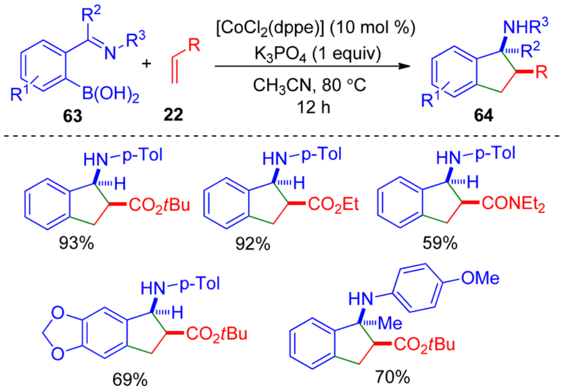


Scheme 36. Synthesis of Indenones from Indenamines

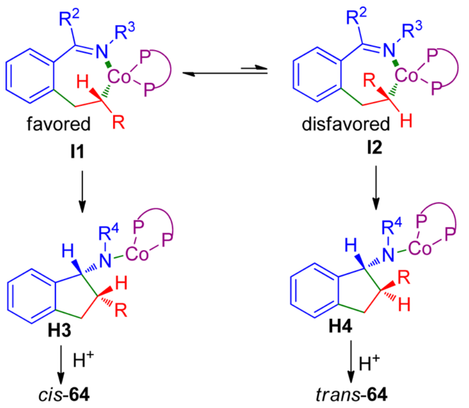


The cobalt-catalyzed [3 + 2] annulation of *o*-iminoarylboronic acids with acrylates provides *cis*-1-aminoindane-2-carboxylic acid derivatives in high yields with excellent regio- and diastereoselectivity (Scheme 37).[26] The reaction is compatible with both aldimine- and ketimineboronic acids. In addition to acrylates, acrylamides also efficiently undergo the reaction, giving indenamine derivatives. However, other activated alkenes, including acrylonitrile, vinyl ketones, and vinyl sulfones, are unreactive. The cis diastereoselectivity of the products may be explained by the models shown in Scheme 38. The expected seven-membered intermediate **I** formed from the *o*-iminoboronic acid and the acrylate has two possible conformers, **I1** and **I2**. Intermediate **I1** places the acrylate ester group at the equatorial position and is therefore more favored, whereas the ester group at the axial position is disfavored because of the strong nonbonding interactions of the ester group with the imine nitrogen and the phosphine ligand.[33]

Scheme 37. Reaction of *o*-Iminoarylboronic Acids with Activated Alkenes



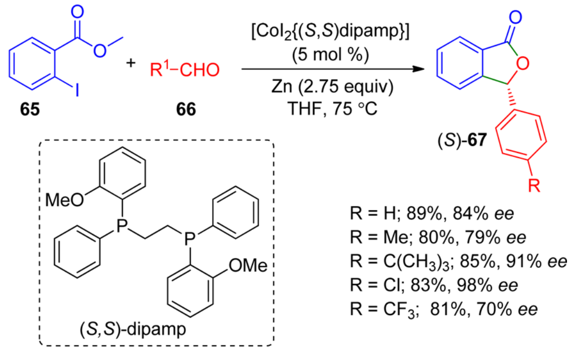
Scheme 38. Stereochemical Model for the Cis Diastereoselectivity of the [3 + 2] Annulation Reaction



In 2007, we reported a phthalide synthesis that proceeded through the cyclization of methyl *o*-iodobenzoate and aromatic aldehydes (Scheme 39).[33] The bidentate chiral phosphine ligand

(*S*,*S*)-dipamp gave high yields and excellent enantioselectivity, as did (*S*,*S*)-BDPP.

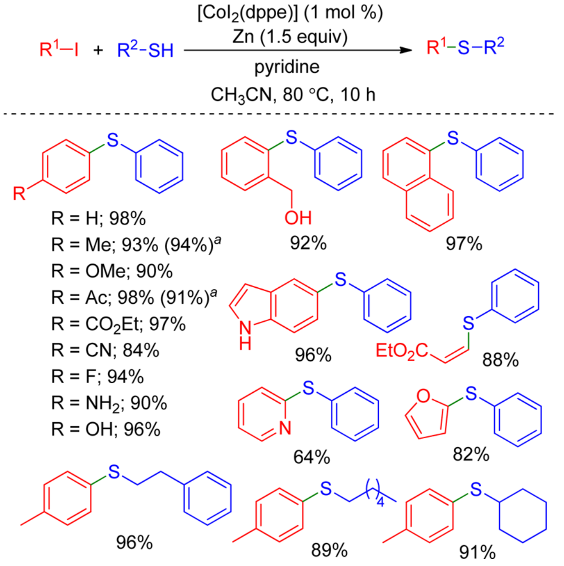
Scheme 39. Enantioselective Synthesis of Phthalides from Methyl 2-Iodobenzoate and Aromatic Aldehydes



6. COBALT-CATALYZED CROSS-COUPLING REACTIONS

Cobalt, like the more toxic and expensive noble metals, has recently been shown to be capable of catalyzing cross-coupling reactions; furthermore, many of the developed reactions show generous functional group tolerance.[3e,f] We successfully developed an efficient method for the formation of carbon–sulfur bonds from thiols and aryl and alkyl halides using [CoI$_2$(dppe)] as a catalyst (Scheme 40).[34] This reaction is compatible with both aryl and alkyl thiols. Aromatic, heteroaromatic, and vinylic iodo compounds have all been effectively coupled with thiols using this protocol.

Scheme 40. Cobalt-Catalyzed Coupling of Thiols with Aryl and Alkyl Halides

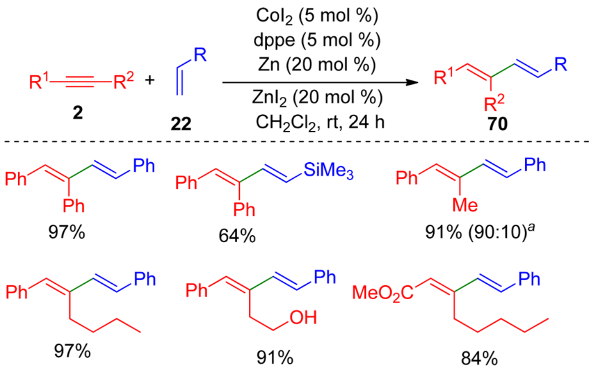


^{a}The product was obtained using R^1–Br.

7. COBALT-CATALYZED ENYNE COUPLING REACTIONS

The transition-metal-catalyzed coupling of alkynes and alkenes is as an efficient and atom-economical method for the synthesis of substituted alkenes and dienes.[35] In 2010, we discovered a cobalt-catalyzed intermolecular enyne coupling reaction that forms 1,3-dienes.[36a] A range of alkynes and styrenes have been successfully coupled in high yields with excellent regio- and stereoselectivity using a CoI$_2$, dppp, Zn, and ZnI$_2$ catalyst system (Scheme 41); control experiments revealed that each catalytic component is needed for the reaction to work. Electron-deficient alkynes require the addition of the bidentate ligand 2,2′-bipyridine and higher reaction temperatures in order to provide high yields. This 1,3-diene formation is complementary to Hilt's cobalt-catalyzed Alder–ene reaction of internal alkynes with terminal alkenes containing allyl hydrogens to give 1,4-dienes.[36b]

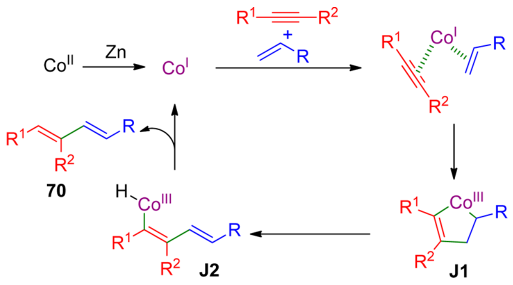
Scheme 41. Cobalt-Catalyzed Intermolecular Coupling of Alkynes and Alkenes



^{a}The regioisomeric ratio is given in parentheses.

A possible mechanism for this reaction is shown in Scheme 42. As usual, the cycle is initiated by reduction of Co^{II} followed by chemoselective coordination of the alkyne and styrene to the Co^{I} complex. Regioselective oxidative cyclometalation then gives the five-membered cobalt complex **J1**, and *β*-hydride elimination gives intermediate **J2**. Finally, this complex undergoes reductive elimination to afford the final product and the active Co^{I} species.

Scheme 42. Mechanism of the Enyne Coupling Reaction

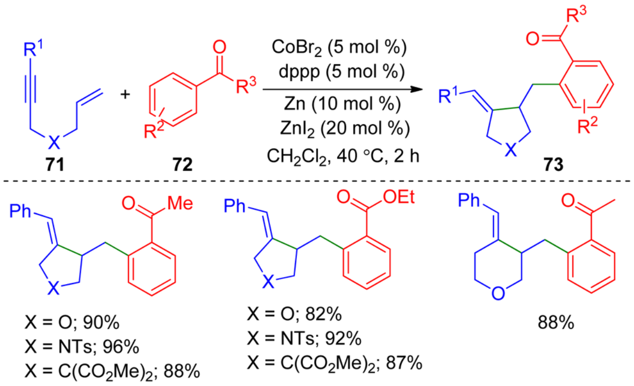


8. COBALT-CATALYZED C–H ACTIVATION REACTIONS

Transition-metal-catalyzed C–H activation reactions have received a great deal of attention in the last two decades and play an indispensable role in organic synthesis. Current research has focused on replacing the expensive noble-metal catalysts typically used in these reactions, such as Pd, Rh, Ru, and Ir, with cheaper, more abundant first-row transition metals, and recent research has made some progress in this regard.[37] In particular, we have reported ortho C–H activation of aromatic ketones and esters triggered by the formation of a cobaltacycle from 1,6-enynes.[38] Our catalyst system consists of CoBr$_2$, dppp, Zn, and

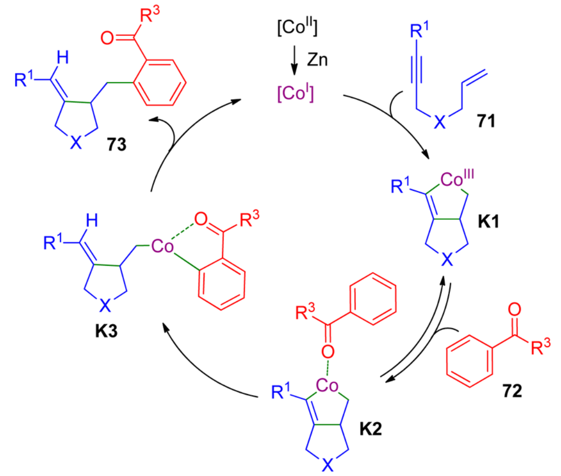
ZnI_2 and efficiently affords functionalized pyrrolidines and dihydrofurans chemo- and stereoselectively (Scheme 43). Notably, this reaction proceeds under milder conditions than those using the Pd and Rh analogues.[39]

Scheme 43. Cobalt-Catalyzed Ortho C−H Activation of Aromatic Ketones/Esters with Enynes



Preliminary mechanistic studies were performed to understand the inherent nature of the reaction. Intra- and intermolecular kinetic isotope effect (KIE) experiments using acetophenone-d_1 and -d_5 gave KIE values of 3.5 and 2.8, respectively. This suggests that C−H bond activation may be the rate-determining step. On this basis, we proposed a possible catalytic cycle that proceeds via five-membered cobaltacycles,[40] as depicted in Scheme 44. As usual, Co^I formation begins the cycle. Next, the enyne coordinates to Co^I, and subsequent oxidative cyclization yields cobaltacyclopentene intermediate **K1**. Complexation of the aryl ketone/ester to **K1** followed by ortho-selective C−H bond activation provides **K3**. Finally, reductive elimination affords the final product **73** and regenerates the active catalyst.

Scheme 44. Mechanism of the Cobalt-Catalyzed Ortho C−H Activation of Aromatic Ketones/Esters with Enynes



9. CONCLUSIONS

In this Account, we have demonstrated through our research that cobalt catalysis plays an important and broad role in modern organic synthesis. Cobalt can be used for many different kinds of reactions, including cycloaddition, reductive coupling, addition, carbocyclization, cross-coupling, enyne coupling, and C−H activation. The greater abundance and decreased toxicity of cobalt promise a more environmentally friendly, economical, and sustainable manner of catalysis compared with the current methods that rely primarily on noble metals.

In many of our cobalt-catalyzed reactions, Zn or Mn metal powder is required. Because of the use of these additional metals, Co^I can be considered a catalytically active species. This makes it especially useful, because it is conveniently generated in situ from air-stable Co^{II} complexes. It should be noted that this reductive approach could be expanded to other first-row transition metals. More detailed mechanistic studies are required in order to understand the true mechanism of these reactions; this will be the focus of our future research, along with the continued development of environmentally friendly, economical, and asymmetric reactions.

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Notes

The authors declare no competing financial interest.

Biographies

Parthasarathy Gandeepan was born in the village of Seeyamangalam in Tamil Nadu, India. He completed his B.Sc. in Chemistry at Arignar Anna Government Arts College (Cheyyar, Tamil Nadu) and his M.Sc. in Organic Chemistry at the Department of Organic Chemistry, University of Madras (Chennai, India). He obtained his Ph.D. in Chemistry in 2012 at National Tsing Hua University (Hsinchu, Taiwan) under the supervision of Professor Chien-Hong Cheng. Currently, he is working as a postdoctoral fellow in the same group. His research interests include transition-metal-catalyzed C−H bond activation, cross-coupling, and multicomponent reactions.

Chien-Hong Cheng, a former Director General of the Department of Natural Sciences, National Science Council, President of Chemical Society, Taiwan, and Vice President for Academic Affairs of National Tsing Hua University (NTHU), currently serves as a Chair Professor at the Department of Chemistry, NTHU, and has also held a National Chair in Chemistry since 2009. His research interests include the development of new synthetic methods using organometallic compounds as catalysts and the synthesis of organic materials and fabrication of devices using these materials for organic light-emitting diodes.

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