Recent Advances in Enantioselective C–C Bond Formation via Organocobalt Species

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Abstract This Short Review describes recent developments in cobalt-catalyzed enantioselective C–C bond-forming reactions. The article focuses on reactions that most likely involve chiral organocobalt species as crucial catalytic intermediates and their mechanistic aspects.

1 Introduction

Enantioselective catalysis using transition-metal complexes has had a transformative impact on modern synthetic chemistry, and the discovery of novel molecular transformations and the development of diverse chiral ligands and catalysts have gone hand-in-hand to increase the diversity of chiral compounds that are accessible by synthetic chemists. While tremendous success has been achieved by the combination of precious second-row transition metals such as palladium, rhodium, and ruthenium and so-called privileged chiral ligands, enantioselective catalysis using earth-abundant first-row transition metals has received growing attention in the recent years. This is because earth-abundant metal catalysis offers us opportunities to develop cost-effective alternatives to precious-metal catalysts as well as to explore previously unknown unique transformations.

Given this background, this Short Review highlights the recent developments in cobalt-catalyzed enantioselective C–C bond-forming reactions. Here, the author would like to focus on reactions that most likely involve chiral organocobalt species having cobalt–carbon single bonds as crucial catalytic intermediates. As such, reactions employing cobalt-based Lewis acids as well as those involving cobalt carbenoids or cobalt metalloradical species are not discussed.

As the entire field of enantioselective cobalt catalysis was reviewed in 20141 and more recently in early 2018,2 this Short Review aims to focus on some of the most remarkable developments in organocobalt-catalyzed asymmetric C–C bond formations reported in the past five years (2013–2018) and their mechanistic aspects, with brief reference to prior studies in the beginning of each section. Many of the reactions discussed here are achieved using the...
so-called privileged ligands, as shown in Figure 1, which would support the cobalt center with oxidation states ranging from 0 to +3 while providing an effective chiral environment.

![Figure 1 Representative privileged chiral ligands used in enantioselective cobalt-catalyzed C–C bond-forming reactions.](image)

2 Hydrovinylation

Hilt pioneered selective 1,4-hydrovinylation of 1,3-diene with various terminal alkenes using a catalytic system comprised of CoBr₂(dppe), ZnI₂, and reductant such as Zn or Bu₄NBH₄, which afforded 1,4-diene derivatives without generating new stereogenic centers. Vogt reported hydrovinylation of styrene with ethylene using a cobalt(II)-diphosphine catalyst activated by Et₂AlCl, affording the codimerization product with virtually perfect selectivity. Moreover, a promising level of enantioselectivity (ca. 50% ee) was achieved by using Trost type bidentate amido-phosphine ligands. RajanBabu made a major breakthrough in 2010, demonstrating enantioselective hydrovinylation of linear 1,3-diene by using a catalyst derived from CoCl₂–chiral diphosphine (DIOP or BDPP) complex and Me₃Al. The authors further achieved 1,4-selective asymmetric hydrovinylation of 1-vinylcycloalkenes using the (BDPP)CoCl₂ catalyst.

In 2015, RajanBabu reported asymmetric 1,4-hydrovinylation of 2-siloxy-1,3-dienes to afford chiral silyl enol ethers bearing a vinyl group on the β-position (Scheme 2), which are challenging to access by other means.

Scheme 1 Enantioselective 1,4-hydrovinylation of linear 1,3-dienes and its underlying mechanism

Scheme 2 Enantioselective hydrovinylation of 2-siloxy-1,3-dienes
(MAO) at room temperature under 1 atm ethylene. Both acyclic 1,3-dienes and 1-vinylcycloalkenes bearing 2-siloxy group were amenable to the reaction, affording the corresponding products with high enantioselectivity.

In 2016, Schmalz reported enantioselective hydrovinylation of vinylarenes under low-pressure ethylene (Scheme 3). A CoCl₂ complex supported by a chiral phosphine-phosphite bidentate ligand L₁, upon activation with Et₂AlCl, promoted hydrovinylation of various functionalized styrenes and vinylheteroarenes under 1.2 atm ethylene, affording the branched products in good yields with enantioselectivities of >90% ee for many cases. This represents a significant advance on Vogt’s earlier catalytic system, which required high-pressure ethylene (30 atm) and reached moderate enantioselectivity up to 50% ee. The catalytic system also efficiently promoted hydrovinylation of β-substituted styrenes, albeit with varying degrees of enantioselectivity.

In 2017, RajanBabu reported asymmetric codimerization of 1,3-dienes 1 and acrylates 12 through a 1,4-hydrovinylation process to afford 1,4-diene derivatives 13 (Scheme 4a). Distinct from the previously developed Me₃Al- or MAO-activated catalytic systems, the reaction was achieved by using a new catalytic system featuring the combination of [(S,S)-BDPP]CoBr₂, Zn, and Lewis acid such as sodium tetrakis[3,5-bis(trifluoromethyl)phenyl] borate (NaBARF). Zn is assumed to reduce Co(II) to Co(I), while NaBARF is proposed to abstract the remaining bromide on cobalt, thus generating a cationic (diphosphine)CoI species 14 (Scheme 4b). The species 14 would accept coordination of the diene and the acrylate to give an intermediate 15 and then undergo enantioselectivity-determining oxidative cyclization to give a seven-membered cobaltacycle 16. Subsequent β-hydride elimination and reductive elimination of the resulting allyl(hydrido)cobalt species 17 would afford the hydrovinylation product.

Most recently, RajanBabu reported a novel cobalt-catalyzed tandem process involving [2+2] cycloaddition between 1,3-enyne 18 and ethylene followed by enantioselective hydrovinylation of the resulting vinylcyclobutene 19, leading to cyclobutanes 20 bearing a chiral all-carbon quaternary center (Scheme 5a). A catalyst generated by the activation of chiral phosphinooxazoline (Ph-PHOX)-supported CoCl₂ with Et₂AlCl or Me₃Al promoted the tandem process at mild temperature under balloon pressure of ethylene, affording the cyclobutane products with enantioselectivities up to 96% ee. As was proposed for the above codimerization (Scheme 4b), a cationic Co(I) species is proposed as the catalytically active species (Scheme 5b). The [2+2] cycloaddition proceeds via oxidative cyclization of...
1,3-enyne and ethylene to give a cobaltacyclopentene 21 followed by its reductive elimination. The resulting vinylcyclobutene coordinates to Co(I) as a 1,3-diene (22), and then undergoes oxidative cyclization with another molecule of ethylene to form a cobaltacycloheptene 23. This is followed by β-hydride elimination, α-π-π isomerization of the resulting allylcobalt(III) species (24a to 24b to 24c), and reductive elimination to give the product 20 and liberate the cationic Co(I) species.

3 C–H Functionalization

Cobalt-catalyzed C–H bond functionalization represents an emerging area of homogeneous catalysis. In less than ten years, hundreds of C–C and C–heteroatom bond-forming reactions have been developed using low-valent or high-valent cobalt catalysts. While most of these reactions were achieved using achiral catalysts or do not generate chirality, a few examples of cobalt-catalyzed enantioselective C–H functionalization have appeared.

In 2014, Yang and Yoshikai reported enantioselective intramolecular hydroacylations of ortho-acylbenzaldehyde 25 and ortho-alkenybenzaldehyde 27, affording phthalide 26 and indanone 28, respectively (Scheme 6a,b). The reactions were achieved by appropriate combinations of cobalt(II) salt, chiral diphosphine, and metallic reductant such as In or Zn, with efficiency and selectivity comparable to those of rhodium catalysts developed earlier. The reactions were proposed to proceed through oxidative addition of the aldehyde C–H bond to Co(I), insertion of the C=α bond into the Co–H bond of the resulting acyl(hydrido)cobalt species, and reductive elimination. While the scope of ortho-alkenybenzaldehydes was somewhat limited under the originally reported conditions, Yoshikai later developed a modified catalytic system to achieve enantioselective hydroacylation of ortho-alkenybenzaldehydes 27′, bearing trisubstituted alkene moieties (Scheme 6c). Remarkably, various substrates with varying alkene E/Z ratios underwent cyclization to afford trans-2,3-disubstituted indanones 28′ with high diastereo- and enantioselectivities. Deuterium-labeling experiments suggested that (E)-27′ is straightforwardly transformed into trans-28′ through C–H oxidative addition, alkene insertion to form a six-membered cobaltacycle 30, and reductive elimination. On the other hand, a part of (Z)-27′ was suggested to undergo E/Z isomerization via a five-membered cobaltacycle 31 and then afford trans-28′ via 29 and 30, while the majority would initially produce cis-28′ via 29′ and 30′, followed by epimerization to trans-28′.

In 2017, Dong disclosed cobalt-catalyzed enantioselective intramolecular hydroacylation of α,α-bis(allyl)aldehydes 32, leading to cyclobutane derivatives 33. A catalyst generated upon reduction of [(S,S)-BDPP]CoCl2 with Zn promoted the desymmetrization process to afford cyclobutane 33, bearing an all-carbon quaternary center, with high enantio- and diastereoselectivities, in preference to the regioisomeric cyclopentanone product 34. A comparable performance was attained using Et2Zn as the reductant instead of Zn. The cyclobutane formation is distinct from the reaction pathways of the same substrate under rhodium catalysis. A Co(0) species was proposed as the catalytically active species on the basis of control experiments. Bidentate coordination of the substrate to the Co(0) species (35) would be followed by C–H oxidative addition to give an acyl(hydrido)cobalt species 36. This species then undergoes desymmetrizing olefin insertion, and reductive elimination of the cobaltacycle 37 furnishes the cyclobutane product.

![Scheme 6 Enantioselective intramolecular hydroacylation leading to chiral phthalides or indanones](image-url)
Yoshikai demonstrated that low-valent cobalt–phosphine catalysts promote branched-selective hydroarylation of styrenes assisted by N(sp²) directing groups such as pyridine and imine. This type of reaction was rendered enantioselective by using 3-iminoindole derivative as the substrate (Scheme 8). Thus, a catalyst generated from Co(acac)₃, a chiral phosphoramidite, and Me₃SiCH₂MgCl promoted the addition of N-Boc-protected 3-iminoindoles to vinylarenes to afford the branched hydroarylation products with enantioselectivities up to 86% ee.

In 2017, Ackermann reported hydroarylation reactions of 1-alkenes with N-(2-pyridyl)indoles catalyzed by a Cp*Co(III) complex [Cp*Co(CO)]₂, achieving control over the linear/branched selectivity. Thus, a catalyst generated from Co(acac)₃, a chiral phosphoramidite L₂, and Me₃SiCH₂MgCl was synthesized from the corresponding known 1,5-cyclooctadiene complex and Amberlyst 15 as crucial additives (Scheme 9). The branched products were obtained with good to high regioselectivities and enantioselectivities up to 86% ee. The reaction is proposed to involve base-assisted internal electrophilic substitution (BIES)-C–H metation, insertion of the alkene into the Co–aryl bond, and protodemetalation of the Co–alkyl bond. Experimental and theoretical mechanistic investigations indicated that Amberlyst 15 facilitates the reaction by breaking a hydrogen-bonded dimer of L₃, which, as a monomer, participates in the enantioselectivity-determining protodemetalation step.

4 Cycloaddition and Cyclization

[2+2+2] Cycloaddition of alkynes and [2+2+1] cycloaddition of alkene, alkene, and carbon monoxide (Pauson–Khand reaction) are among the most prototypical reactions catalyzed by low-valent cobalt complexes. This and other cobalt-catalyzed cycloaddition reactions of unsaturated hydrocarbons have been extensively explored over many years. Some of these cycloaddition reactions were made enantioselective prior to 2013. Catalysts generated from cobalt salts, chiral phosphines, and reductants proved effective for homo-Diels–Alder reaction between norbornadiene and alkyné, [4+2+2] cycloaddition between 1,3-diene and norbornene, [6+2] cycloaddition between cycloheptatriene and alkyné, and domino enantioselective [4+2] cycloaddition between 1-boryl-1,3-diene and alkyné/metalloene diastereoselective allylboration of aldehyde. Catalysts generated from Co₂(CO)₈ and chiral diphosphine ligands were developed for asymmetric Pauson–Khand reactions of 1,6-enynes. Dicobalt complexes derived from alkyné–Co₂(CO)₈ complexes and chiral P,S-ligands proved effective for stoichiometric or catalytic intermolecular Pauson–Khand reaction of norbornadiene. Chiral indenyl-cobalt(1) catalysts were developed for [2+2+2] cycloaddition between 1-aryl-1,7-diyne and nitrile and [2+2+2] cycloaddition between 1-phosphoryl-2-naphthylalkyne and carbon monoxide (Pauson–Khand reaction) between 1-aryl-1,7-diyne and nitrile. In 2016, Hapke reported the synthesis of two chiral indenyl-Co(1) complexes and their applications to enantioselective [2+2+2] cycloaddition (Scheme 10). The complex C₂ was synthesized from the corresponding known 1,5-cyclooctadiene complex C₁ by photoinduced ligand exchange.
with P(OEt)$_3$, while the complex C3 was newly synthesized from chiral binaphthol. C1 was known to promote the cycloaddition between 1,6-diyne 43 and nitrile such as PhCN to afford the axially chiral biaryl 44 in excellent yield and enantioselectivity under photoactivation. The authors found that C2 could be activated thermally without photoirradiation, while the yield and enantioselectivity of 44 were moderate. C3 did not induce enantioselectivity, presumably because the chiral backbone of the indenyl ligand was too far from the cobalt center.

In the same year, Hapke disclosed enantioselective [2+2+2] cycloadditions catalyzed by chiral low-valent cobalt catalysts generated in situ (Scheme 11). Thus, a combination of CoBr$_2$, (R,R)-N-PINAP, Zn and ZnI$_2$ gives rise to an active catalyst, which promotes cyclotrimerization of triyne substrates 45 to afford axially chiral biaryl products 46 with enantioselectivities up to 85% ee. Besides PINAP-type ligands, chiral P,N-ligands such as QUINAP and iPr-PHOX displayed moderate enantioselectivities, suggesting that the formation of either five- or six-membered P,N-chelated cobalt species was essential. On the other hand, chiral diphosphines such as BINAP and Et-DUPHOS failed to induce any enantioselectivity.

In 2015, Riera and Verdaguer reported the synthesis of new N-bridged chiral bisphosphanes and their use for challenging catalytic intermolecular Pauson–Khand reaction (Scheme 12a). Thus, the bisphosphane-bridged dicobalt–acetylene complex C4 promoted the reaction between norbornadiene and trimethylsilylacetylene to afford the cyclopentenone derivative 47a with up to 97% ee, although the applicability of this and related catalysts to other alkynes was limited. More recently, Riera and Verdaguer reported the synthesis of another dicobalt complex C5 supported by the QuinoxP* ligand and its performance in the same intermolecular Pauson–Khand reaction (Scheme 12b). The catalyst showed high catalytic efficiency toward terminal alkynes, while the enantioselectivity remained modest. The highest enantioselectivity of 43% ee was achieved for the reaction using cyclopropylacetylene to give 47b.

In 2018, Wu and Yoshikai reported cobalt-catalyzed chemodivergent intramolecular reactions between a vinylcyclopropane and an alkyne involving C–C bond cleavage (Scheme 13a). A low-valent cobalt–diphosphine catalyst generated in polar non-coordinating solvents such as 1,2-dichloroethane (DCE) promoted [5+2] cycloaddition of 48 to give a cycloheptene derivative 49, while analogous catalyst in coordinating solvents such as MeCN, DMA, and N-methyl-2-pyrrolidone (NMP) promoted cycloisomerization (homo-ene reaction) to afford a triene product 50. The latter reaction was made enantioselective using QuinoxP*
in DMA, with high enantioselectivities (90–99% ee). These reactions were proposed to involve alkyne/alkene oxidative cyclization on cationic Co(I) and β-carbon elimination of the resulting cobaltacyclopentene 51 to afford an eight-membered cobaltacycle 52 (Scheme 13b). The common intermediate 52 would undergo either C–C reductive elimination to give the [5+2] cycloadduct 49 or β-hydride elimination and C–H reductive elimination to give the homo-ene product 50. DFT calculations suggested that, in the absence of a coordinating solvent (S), 52 prefers to undergo C–C reductive elimination assisted by intramolecular coordination of the distal C=C bond. On the other hand, solvent coordination was found to selectively stabilize the β-hydride elimination/C–H reductive elimination pathway.

The above cycloaddition and cyclization reactions likely involve oxidative cyclization of π-reactants on low-valent cobalt as the initial and often enantioselectivity-determining step. Ge and co-workers disclosed enantioselective cyclizations initiated by a different elementary step; that is, hydrometalation. Thus, hydroborylative cyclization of O-, N-, or C-tethered 1,6-enynes 55 and 55′ with pinacolborane (HBpin) was achieved by using a catalytic system comprised of Co(acac)₂ and QuinoxP* to afford chiral five-membered ring products with alkanyl boronate 56 or alkyl boronate (57) moieties, respectively, with high enantioselectivity (Scheme 14a,b). The chemoselectivity of the reaction is primarily controlled by the steric nature of the alkyne moiety. Unhindered alkyne substrates prefer the formation of alkanyl boronate products 56, while hindered substrates bearing bulky R group or non-hydrogen R' substituent selectively afford alkyl boronate products 57. Ge further extended the scope of the hydroborylative cyclization to amide-tethered 1,6-enynes 58 bearing 1,1-disubstituted olefin moieties, affording γ-lactam and related compounds bearing quaternary stereogenic centers (Scheme 13c). The reaction was achieved with a modified catalytic system using Duanphos in MeCN. The reaction was proposed to proceed through chelation of a chiral cobalt hydride with the enyne substrate (60), insertion of the alkyn moiety to Co–H (61), and enantioselective insertion of the alkene moiety (62), followed by the reaction of the alkylcobalt species 62 with HBpin to give the product 59 and regenerate the cobalt hydride.

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5 Addition of Carbon Nucleophiles

Prior to 2013, several notable examples of cobalt-catalyzed enantioselective C–C bond formation via the addition of organocobalt species to polar C=X bond, Michael acceptor, or strained C=C bond were reported by the groups of Cheng and Hayashi, where the organocobalt species were generated by oxidative addition, transmetalation, or depro-
tonation. Thus, these examples include cyclization of o-iodo- 
benzoates with aldehydes, addition of arylboronic acids to 
aldehydes, and addition of TIPS-acetylene to α,β-unsatu-
rated ketones, α,β,γ,δ-unsaturated esters, and oxa- or 
azabicyclic alkenes.

Zhao reported cobalt-catalyzed chemodivergent re-
actions between oxabicyclic alkenes 63 and potassium allyl-
trifluoroborate to afford either hydroallylation products 64 
or ring-opening allylation products 65 (Scheme 15). The for-
mer reaction proceeded using ligand-free CoBr₂ as a cata-
ylist and tetrabutylammonium iodide and EtOH as addi-
tives. The addition a diphosphine ligand such as dppp was 
found to switch the chemoselectivity toward ring-opening, 
which allowed the development of an enantioselective vari-
ant using BDPP. The reaction was proposed to involve syn-
allylicolation of the alkene to form a common allylcobalt 
intermediate 66, the fate of which (i.e., protonolysis or β-
oxygen elimination) would depend on the ligand on cobalt.

Zhao demonstrated the competence of chiral cobalt–di-
phosphine catalysts for enantioselective alkylation of ac-
tivated ketones and imines with alkynylboronic acids (Scheme 16). Using the combination of CoI₂ and BDPP or 
Duanphos, α-ketoesters 67 were alkylnated with β-aryl- 
or alkyl-substituted vinylboronic acids or β,β-dimethylvinyl-
boronic acid 68 to afford tertiary allylic alcohols 69 with 
moderate to high enantioselectivities (Scheme 16a). Similar 
catalytic systems using Duanphos also proved effective for 
the alkylation of isatin derivatives 70 and cyclic sulfonyl 
aldimines 72 (Scheme 16b, c). The latter substrates dis-
played particularly high enantioselectivities (98 to ~99% ee).

Zhang reported cobalt-catalyzed enantioselective alkylation of cyclic ketimines with potassium allyltrifluoroborate (Scheme 17). A catalyst derived from Co(CO₃)₂·6H₂O and chiral bisoxazoline (Ph-BOX) promoted the alkylation of cy-
clic N-sulfonyl ketiminoesters (R² = ester) or ketimines (R² = 
alkyl) 74 to afford homoallylamine products 75 with good 
to excellent enantioselectivities up to 99% ee. The reaction 
using substituted allyltrifluoroborate (R³ = Me or Bu) 
showed moderate diastereoselectivity (3:1), with excellent 
enantioselectivities for both the diastereomer products (see 
the product 75c). On the basis of strong positive nonlinear 
effect, a bimetallic transition state 76, in which one cobalt 
center acts as a Lewis acid to activate the imine and the sec-
ond transfers the allyl group, was proposed.

Cheng reported enantioselective [3+2] annulation re-
action between ortho-iminoaryl boronic acids 77 or bromides 
80 and alkenes 78 to form chiral 1-aminoindenes 79 
(Scheme 18). The reaction of arylboronic acids 77 was 
achieved using a CoCl₂-chiral phosphinooxazoline (Ph-PHOX) 
catalyst in the presence of catalytic ZnCl₂ and NaHCO₃,

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**Scheme 15** Enantioselective alkylation of oxabicyclic alkenes with potassium allyltrifluoroborate

**Scheme 16** Enantioselective alkylation of activated ketones and imines

**Scheme 17** Enantioselective alkylation of cyclic N-sulfonyl ketimines
while the reaction of aryl bromides 80 proceeded using analogous CoCl$_2$–phosphinooxazoline (iPr-PHOX) catalyst in combination with Zn as the reductant. The former reaction was proposed to proceed through transmetalation between the boronic acid and the Co(II) catalyst, intramolecular addition of the resulting arylcobalt(II) to the imine, and protodemetalation, without redox of the cobalt center. On the other hand, the latter reaction was considered to involve a catalytically active cobalt(1) species, which would undergo oxidative addition of the C–Br bond, intramolecular arylation of the resulting arylcobalt(III) species, protodemetalation, and reduction of Co(III) to Co(I).

![Scheme 18 Enantioselective [3+2] annulation between ortho-iminoaryl boronic acids/bromides and alkynes](image)

Scheme 18 Enantioselective [3+2] annulation between ortho-iminoaryl boronic acids/bromides and alkynes

6 Cross-Coupling

The transition-metal-catalyzed cross-coupling using alkyl electrophiles has undergone remarkable progress over the last two decades. Particularly notable is the emergence of catalysts based on first-row transition metals such as nickel, cobalt, and iron. In comparison with conventional palladium catalysts, these catalysts are unique in that they can be readily engaged in single-electron processes such as electron transfer to a variety of alkyl halides to generate the corresponding alkyl radicals. This mechanistic feature has offered opportunities to develop enantioselective cross-coupling of racemic alkyl halides via radical intermediates. Indeed, a diverse set of enantioselective alkyl-aryl and alkyl-alkyl couplings using nickel catalysts have been pioneered by the Fu group, while cobalt-catalyzed cross-coupling has also undergone significant, if not as spectacular, progress.

In 2014, Bian and co-workers reported cobalt-catalyzed enantioselective Kumada coupling between α-bromoesters 81 and aryl Grignard reagents (Scheme 19a). The reaction was achieved by the combination of Co$_2$ precatalyst and a chiral bisoxazoline ligand Bn-BOX in tetrahydrofuran (THF) at –80 °C, affording a variety of chiral α-arylesters 82 in moderate to excellent yields with enantioselectivities up to 97% ee. The same group later achieved analogous Negishi coupling using a modified bisoxazoline ligand L4 under milder conditions at –25 °C (Scheme 19b). Again, a variety of chiral α-arylesters 82 were obtained in good yields with high enantioselectivities. Radical clock experiments on the latter reaction system indicated the involvement of an alkyl radical, which would be generated by single-electron transfer to the α-bromoester.

![Scheme 19 Enantioselective cross-coupling between α-bromoesters and arylmetal reagents](image)

Scheme 19 Enantioselective cross-coupling between α-bromoesters and arylmetal reagents

7 Conclusion

This review has described the significant progress in cobalt-catalyzed enantioselective C–C bond-forming reactions involving organocobalt species in the last several years, which has actually coincided with the progress in other types of cobalt-catalyzed enantioselective transformations such as hydrogenation, hydrosilylation and hydrosilation. These new developments were made possible owing to the ability of cobalt species, often in the low-valent state, to engage in various elementary processes such as oxidative cyclization of π-substrates, migratory insertion of C=C, C≡C, and C=X bonds, C–H activation, and single-electron transfer. Notably, many of the reactions discussed here do not represent simple emulation of known precious-transition-metal-catalyzed reactions, and are unique even as racemic transformations. From the results discussed here as well as his own experience, the author expects significant further developments in not only the reaction types discussed here, but also others such as reductive coupling of unsaturated substrates.
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