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

Naohiko Yoshikai* 0000-0002-8997-3268
Division of Chemistry and Biological Chemistry, School of Physical and Mathematical Sciences, Nanyang Technological University, Singapore 637371, Singapore
nyoshikai@ntu.edu.sg
Published as part of the 50 Years SYNTHESIS – Golden Anniversary Issue

Received: 27.10.2018
Accepted: 05.11.2018
Published online: 03.12.2018

License terms: Creative Commons Attribution 4.0 International License

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

## 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 Bu₃NBH₄ which afforded 1,4-diene derivatives without achiral and chiral ligands, and the scope of both the racemic dienes, including the effect of promoters, the screening of ment.

In 2010, RajanBabu reported full details of the development of (asymmetric) 1,4-hydrovinylation of linear 1,3-dienes and its underlying mechanism.

In 2015, RajanBabu reported full details of the development of 1,4-hydrovinylation of linear 1,3-dienes 8 to afford chiral silyl enol ethers 9 bearing a vinyl group on the β-position (Scheme 2), which are challenging to access by other means. The reaction was achieved by using a catalyst generated from (DIOP)-CoCl₂ or (BDPP)CoCl₂ complex and methylaluminoxane.
(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 hydrovinylnation of vinylarenes under low-pressure ethylene (Scheme 3). A CoCl$_2$ complex supported by a chiral phosphine-phosphite bidentate ligand L$_1$, upon activation with Et$_2$AlCl, promoted hydrovinylation of various functionalized styrenes and vinylheteroarenes 10 under 1.2 atm ethylene, affording the branched products 11 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 and acrylates 12 through a 1,4-hydrovinylation process to afford 1,4-diene derivatives 13 (Scheme 4a). Distinct from the previously developed Me$_3$Al- or MAO-activated catalytic systems, the reaction was achieved by using a new catalytic system featuring the combination of [(S,S)-BDPP]CoBr$_2$, 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)Co$^+$ 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 CoCl$_2$ with Et$_2$AlCl or Me$_3$Al 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 followed by its reductive elimination. The resulting vinyliclobutene coordinates to Co(I) as a 1,3-diene, and then undergoes oxidative cyclization with another molecule of ethylene to form a cobaltacycloheptene. This is followed by β-hydride elimination, α-π-α isomerization of the resulting allylcobalt(III) species (Co(I) species. Elimination to give the product by epimerization to give the product). 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 hydroacylation of ortho-acylbenzaldehyde and ortho-alkenybenzaldehyde affording phthalide and indanone, respectively (Scheme 6a,b). The reactions were achieved by appropriate combinations of cobalt(I) 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=XY bond into the Co–H bond of the resulting acyl(hydrido)co-

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 hydroacylation of ortho-acylbenzaldehyde and ortho-alkenybenzaldehyde affording phthalide and indanone, respectively (Scheme 6a,b). The reactions were achieved by appropriate combinations of cobalt(I) 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=XY bond into the Co–H bond of the resulting acyl(hydrido)co-

In 2017, Dong disclosed cobalt-catalyzed enantioselective intramolecular hydroacylation of α,α-bis(allyl)aldehydes, leading to cyclobutane derivatives (Scheme

<table>
<thead>
<tr>
<th>R1</th>
<th>R2</th>
<th>R3</th>
</tr>
</thead>
<tbody>
<tr>
<td>H</td>
<td>R2</td>
<td>R3</td>
</tr>
<tr>
<td>R1</td>
<td>H</td>
<td>R3</td>
</tr>
<tr>
<td>R1</td>
<td>R2</td>
<td>H</td>
</tr>
</tbody>
</table>
Yoshikai demonstrated that low-valent cobalt–phosphine catalysts promote branched-selective hydroarylation of styrenes assisted by N(spin) 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 L2, and Me$_3$SiCH$_2$MgCl 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)$_2$I], achieving control over the linear/branched selectivity. Thus, linear selectivity is observed using a catalytic system comprised of the Co(III) complex and AgSbF$_6$ while the selectivity switches to branched by the addition of catalytic carboxylic acid (1-Ad-CO$_2$H). Building on this result, very recently, Ackermann disclosed an enantioselective hydroarylation of allylbenzenes with N-pyridyldiindole derivative using Cp*Co(III) catalyst and chiral carboxylic acid (Scheme 9). Enantioselective hydroarylation of allylbenzene with N-pyriddyldiindole derivative using Cp*Co(III) catalyst and chiral carboxylic acid.

4 Cycloaddition and Cyclization

[2+2+2] Cycloaddition of alkynes and [2+2+1] cycloaddition of alkyne, 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 alkylene. [4+2+2] cycloaddition between 1,3-diene and norbornene, [6+2] cycloaddition between cycloheptatriene and alkylene, and domino enantioselective [4+2] cycloaddition between 1-boryl-1,3-diene and alkynediastereoselective allylboration of aldehyde. Catalysts generated from Co$_2$(CO)$_8$ 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-phenyl-2-naphthylalkyne and acetylene, both generating axially chiral products. 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 CoBr₂, (R,R)-N-PINAP, Zn and ZnI₂ 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 bispophosphate-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 48 (Scheme 13a) was achieved with a catalytic system comprised of Co(acac)2 and QuinoxP* to afford chiral five-membered ring products with alkenyl boronate 56 or alkyl boronate (57) moieties, respectively, with high enantioselectivity (Scheme 14a,b).18 The chemoselectivity of the reaction is primarily controlled by the steric nature of the alkyne moiety. Unhindered alkyne substrates prefer the formation of alkynyl 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).19 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 alkyne 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.

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 α-iodobenzoates with aldehydes,\(^40\) addition of arylboronic acids to aldehydes,\(^41\) and addition of TIPS-acetylene to α,β-unsaturated ketones,\(^42\) α,β,γ,δ-unsaturated esters,\(^43\) and oxo- or azabicyclic alkenes.\(^44\)

Zhao reported cobalt-catalyzed chemodivergent reactions between oxabicyclic alkenes 63 and potassium allyl trifluoroborate to afford either hydroallylation products 64 or ring-opening allylation products 65 (Scheme 15).\(^45\) The former reaction proceeded using ligand-free CoBr\(_2\) as a catalyst and tetrabutylammonium iodide and EtOH as additives. The addition a diphosphine ligand such as dppp was found to switch the chemoselectivity toward ring-opening, which allowed the development of an enantioselective variant using BDPP. The reaction was proposed to involve syn-allylicolation of the alkene to form a common allylcovalent 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-phosphate catalysts for enantioselective alkenylation of activated ketones and imines with alkénylboronic acids (Scheme 16).\(^46\) Using the combination of Co\(_2\) and BDPP or Duanphos, α-ketoesters 67 were alkenylated with β-aryl- or alkyl-substituted vinylboronic acids or β,β-dimethylvinylboronic 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 alkenylation of isatin derivatives 70 and cyclic sulfonyl aldimes 72 (Scheme 16b, c). The latter substrates displayed particularly high enantioselectivities (98 to >99% ee).

Zhang reported cobalt-catalyzed enantioselective alkenylation of cyclic ketimes with potassium allyl trifluoroborate (Scheme 17).\(^47\) A catalyst derived from Co(ClO\(_4\))\(_2\)-6H\(_2\)O and chiral bisoxazoline (Ph-BOX) promoted the alkenylation of cyclic N-sulfonyl ketiminoesters (R\(^2\) = ester) or ketimines (R\(^2\) = alkyl) 74 to afford homoallylamine products 75 with good to excellent enantioselectivities up to 99% ee. The reaction using substituted allyl trifluoroborate (R\(^3\) = 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 second transfers the allyl group, was proposed.

Cheng reported enantioselective [3 + 2] annulation reaction between ortho-iminoaryl boronic acids 77 or bromides 80 and alkynes 78 to form chiral 1-aminoindenes 79 (Scheme 18).\(^48\) The reaction of aryloboronic acids 77 was achieved using a CoCl\(_2\)-chiral phosphinoxazoline (Ph-PHOX) catalyst in the presence of catalytic ZnCl\(_2\) and NaHCO\(_3\),
while the reaction of aryl bromides 80 proceeded using analogous CoCl$_2$–phosphinoxazoline (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(I) 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).

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 CoI$_2$ 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.”

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 hydrosilylation. 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.

Funding Information

Ministry of Education Singapore (MOE2016-T2-2-043)
Acknowledgment

We thank the Ministry of Education (Singapore) and Nanyang Technological University (MOE2016-T2-2-043) for financial support.

References

(9) Pagar, V. V.; RajanBabu, T. V. Science 2018, 361, 68.