Low-Valent Cobalt Catalysis: New Opportunities for C−H Functionalization

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ABSTRACT: Rapid progress in the fields of organometallic chemistry and homogeneous catalysis has made it possible for synthetic chemists to consider using ubiquitous yet unreactive C−H bonds as starting points to construct complex organic molecules. However, a majority of the C−H functionalization reactions currently in use require noble transition metal catalysts and harsh reaction conditions, so researchers have placed a priority on the development of mild and cost-effective catalysts. Given this situation, we wondered whether earth-abundant first-row transition metals could emulate the reactivity of a noble transition metal catalyst and carry out similar C−H functionalization reactions at a lower cost and under milder conditions. We also wondered whether we could use first-row transition metals to achieve hitherto unknown, but useful, C−H functionalization reactions.

This Account summarizes our research on the development of three different types of C−H functionalization reactions using low-valent cobalt catalysts: (1) hydroarylation of alkynes and olefins, (2) ortho C−H functionalization with electrophiles, and (3) addition of arylzinc reagents to alkynes involving 1,4-cobalt migration. Although synthetic chemists have previously paid little attention to cobalt in designing catalytic C−H functionalization reactions, earlier studies, particularly those on stoichiometric cyclometalation, inspired us as we developed the hydroarylation and ortho C−H functionalization reactions.

In these transformations, we combined a cobalt precatalyst, a ligand (such as phosphine or N-heterocyclic carbene (NHC)), and Grignard reagent to generate low-valent cobalt catalysts. These novel catalysts promoted a series of pyridine- and imine-directed hydroarylation reactions of alkynes and olefins at mild temperatures. Notably, we observed branched-selective addition to styrenes, which highlights a distinct regioselectivity of the cobalt catalyst compared with typical rhodium and ruthenium catalysts. The combination of a cobalt−NHC catalyst and a Grignard reagent allows directed aromatic C−H functionalizations with electrophiles such as aldimines, aryl chlorides, and alkyl chlorides or bromides. This second reaction has a particularly broad scope, allowing us to introduce secondary alkyl groups at the ortho position of aryl imines, a difficult reaction to carry out by other means.

Serendipitously, we found that a cobalt−Xantphos complex catalyzed the third type of C−H functionalization: the addition of an arylzinc reagent to an alkyne to afford ortho-alkenylarylzinc species through a 1,4-cobalt migration. This "migratory arylzincation" allowed us to quickly construct a diverse group of functionalized benzothiophenes and benzoselenophenes. Collectively, our studies of cobalt catalysis have provided cost-effective catalysts and milder conditions for existing C−H functionalizations and have led to some unprecedented, attractive chemical transformations.
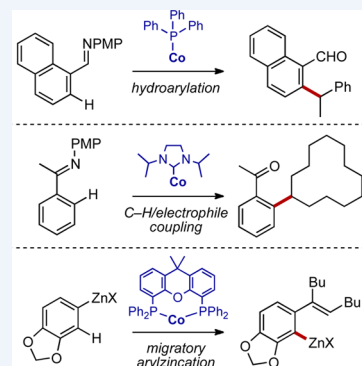
1. INTRODUCTION

The last few decades have witnessed significant progress in the area of transition metal-catalyzed C−H bond functionalization. Numerous C−C and C−heteroatom bond-forming reactions through activation of unreactive C−H bonds have been developed, followed by a growing number of applications to synthetic targets relevant to natural products, pharmaceuticals, and materials.[1,2] While the idea of using C−H bonds as starting points for chemical synthesis has become prevalent, with a survey of the development in this area, one can easily recognize that the majority of currently available C−H functionalization reactions rely on noble transition metal catalysts typically based on palladium, rhodium, or ruthenium and require relatively harsh reaction conditions. Thus, developments of catalysts based on earth-abundant first-row transition metals and

catalysts that allow mild C−H activation are among major challenges.[3,4]

With the above background, we asked ourselves two questions in the hope of making original contributions to this area. First, is it possible to emulate the reactivity of a noble metal catalyst using an appropriately tuned first-row transition metal catalyst? This may not sound unreasonable, because transition metals of the same group in the periodic table often share the same reactivity patterns. But second, more importantly, is it possible to elicit unique reactivity of a first-row transition metal and thereby achieve previously unknown, useful C−H transformations? In addressing these questions, we became interested in the potential catalytic activity of cobalt.

1.1. Background

Though it has not been widely appreciated, cobalt was the first metal used in so-called chelation-assisted C−H bond functionalization. In 1955, before the discovery of the first examples of well-defined cyclometalation,[5,6] Murahashi disclosed an ortho-carbonylation reaction of a Schiff base using $Co_2(CO)_2$ as a catalyst, affording an isoindolinone derivative (Scheme 1a).[7] While the mechanism of this reaction is not very

Scheme 1. Cobalt-Catalyzed C−H Functionalizations Reported before 2009
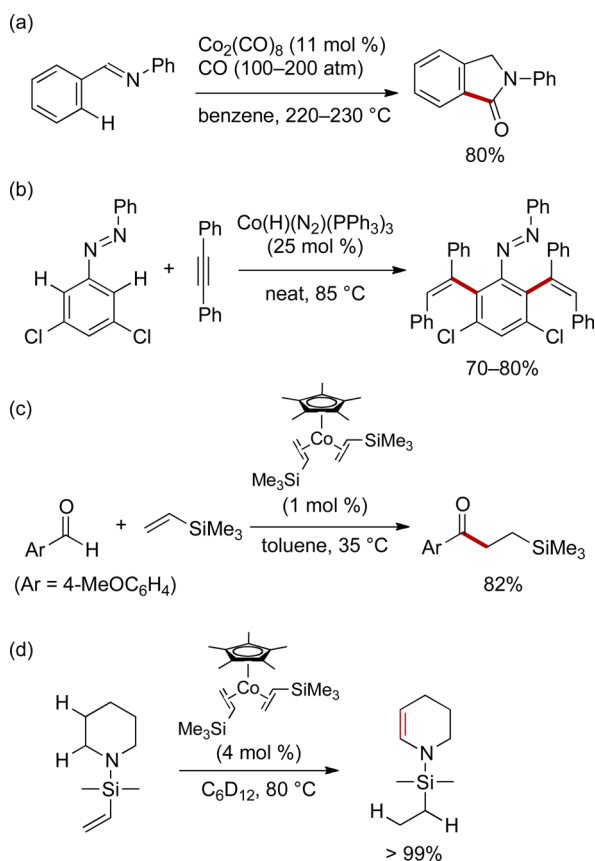
clear even now, it apparently involves cobalt-mediated activation (cyclometalation) of the ortho C−H bond. Despite this seminal report, the use of cobalt in C−H functionalization was sporadic until 2009. In 1994, Kisch reported an ortho-alkenylation reaction of an azobenzene derivative with diphenylacetylene using a cobalt(I) catalyst $Co(H)(N_2)(PPh_3)_3$ or $CoH_3(PPh_3)_3$ to afford an anti-addition product (Scheme 1b).[8] Using $Cp*Co(CH_2=CHSiMe_3)_2$ as a catalyst, Brookhart achieved hydroacylation of olefins[9,10] and isomerization of vinyl(dimethyl)silylamines to ethyl(dimethyl)silylenamines through C(sp³)−H activation (Scheme 1c, d).[11] Brookhart also demonstrated feasibility of C−H activation of simple benzene using the Cp*Co(I) catalyst.[12]

Meanwhile, stoichiometric cyclometalation using a cobalt(I) complex has been extensively studied. In 1993, Klein reported the first example of well-defined cyclometalation reaction using $Co(Me)(PMe_3)_4$ and azobenzene, which occurs at remarkably low temperatures (Scheme 2).[13] The reaction was proposed to involve nitrogen-assisted oxidative addition of the ortho C−H bond to Co(I) followed by reductive elimination of methane. The same complex undergoes cyclometalation of a variety of

Scheme 2. Cyclometalation with $CoMe(PMe_3)_3$
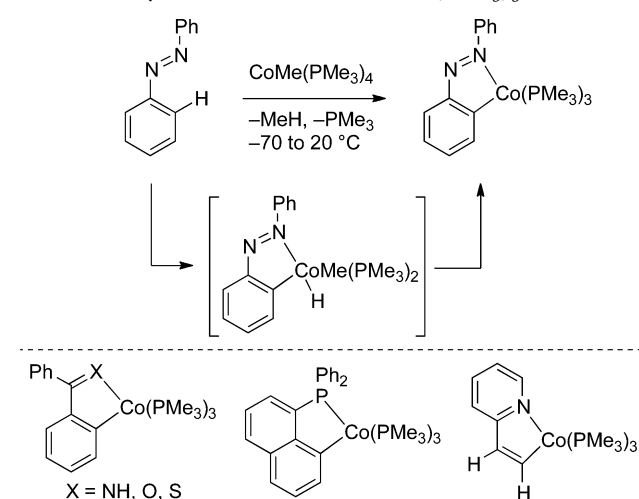
aromatic and olefinic substrates bearing nitrogen,[14] oxygen,[15] sulfur,[16] and phosphorus[17,18] directing groups.
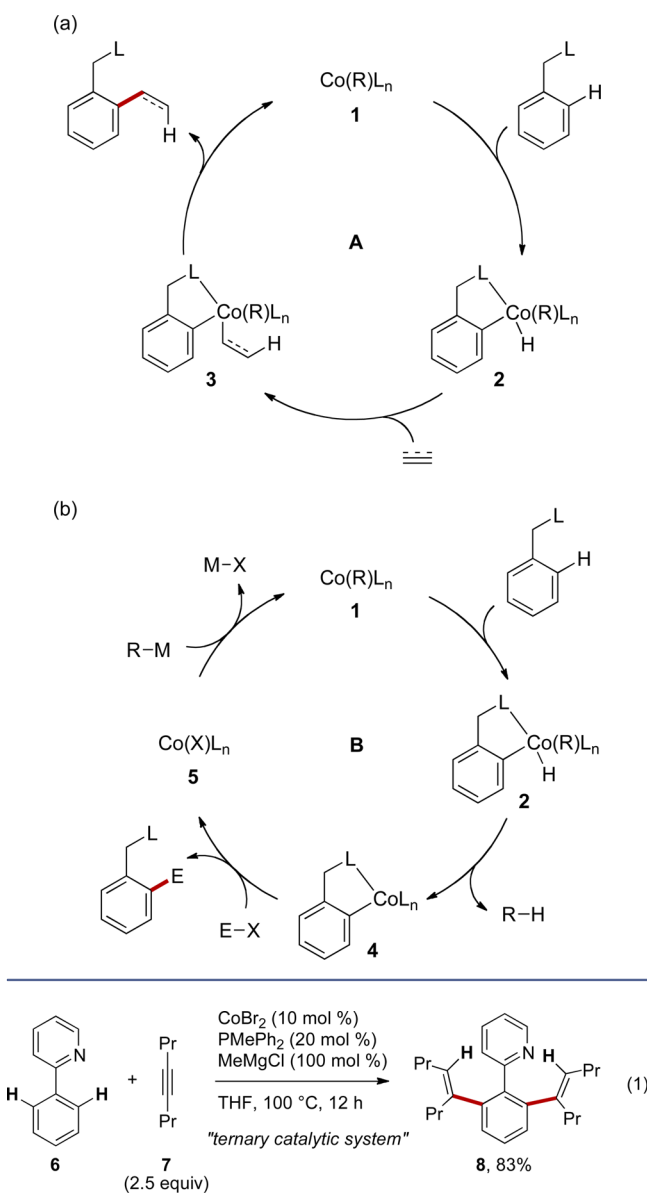
1.2. Hypothetical Catalytic Cycles

In light of the above-discussed earlier studies, we conjectured that cobalt should have significant unexplored potential for catalytic C−H functionalization, particularly for directed ortho C−H functionalization of arenes. Inspired by Klein's cyclometalation, we formulated several hypothetical catalytic cycles for ortho C−H functionalization that involves an organocobalt species $Co(R)L_n$ (**1**), two of which are illustrated in Scheme 3. In catalytic cycle **A**, oxidative addition of the ortho C−H bond to **1** affords an aryl(hydrido)cobalt species **2**, which is followed by insertion of alkene or alkyne into the Co−H bond. Reductive elimination of the resulting intermediate **3** affords a hydroarylation product and regenerates **1**. The organic ligand R behaves as a spectator ligand, which does not participate in any bond-forming processes. In catalytic cycle **B**, oxidative addition of the ortho C−H bond to **1** is followed by reductive elimination of R−H, affording a cyclometalated species **4**. The species **4** is then intercepted by an electrophile (E−X) to afford an ortho-functionalized product and a cobalt species $Co(X)L_n$ (**5**). Transmetalation of **5** with an appropriate organometallic reagent (R−M) regenerates **1**. Studies based on these and other hypotheses as well as serendipitous findings have led us to develop three different types of cobalt-catalyzed C−H functionalization reactions, as discussed below.

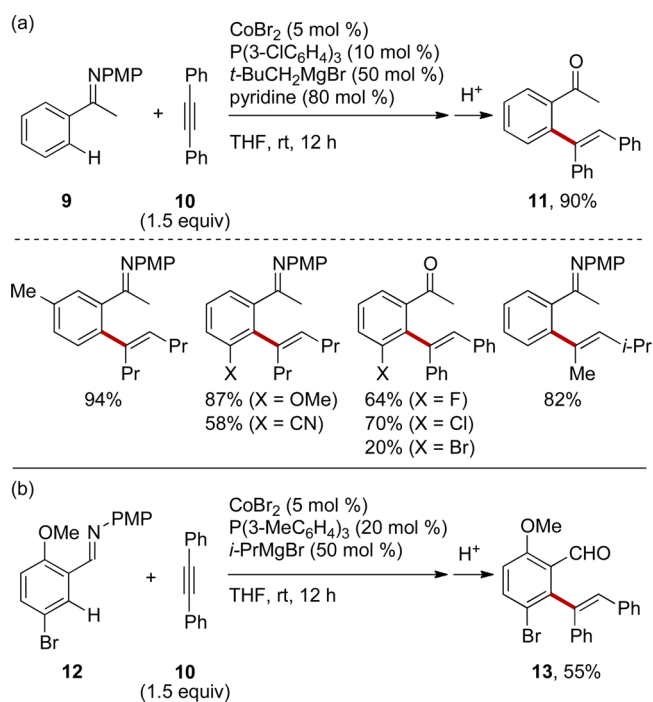## 2. HYDROARYLATION OF ALKYNES AND OLEFINS

2.1. Hydroarylation of Alkynes

Thus far, ruthenium and rhodium catalysts have played dominant roles in chelation-assisted hydroarylation of alkynes and olefins.[19] With the hypothetical catalytic cycle **A** in mind, we first chose 2-phenylpyridine **6** and 4-octyne **7** as model substrates to explore the feasibility of cobalt-catalyzed directed hydroarylation.[20] With extensive screening of reaction conditions, we found that a ternary catalytic system consisting of a cobalt precatalyst ($CoBr_2$), a phosphine ligand ($PMePh_2$), and a reducing agent ($MeMgCl$) promotes the desired hydroarylation in a syn-fashion, affording 2-fold alkenylation product **8** (eq 1).[21] Deuterium-labeling experiments revealed that the ortho-hydrogen atoms of **6** are completely transferred to the vinylic positions of **8**. The importance of this finding does not

Scheme 3. Hypothetical Catalytic Cycles for Cobalt-Catalyzed ortho C−H Functionalization

(a)

A

(b)

B

$$ \text{(1)} $$

"ternary catalytic system"

6   **7**   **8**, 83%
(2.5 equiv)

Scheme 4. Addition of Aryl Ketimine and Aldimine to Alkyne[a]

(a)

CoBr$_2$ (5 mol %)
P(3-ClC$_6$H$_4$)$_3$ (10 mol %)
t-BuCH$_2$MgBr (50 mol %)
pyridine (80 mol %)

THF, rt, 12 h

9   **10**   **11**, 90%
(1.5 equiv)

94%   87% (X = OMe)   64% (X = F)   82%
        58% (X = CN)   70% (X = Cl)
                  20% (X = Br)

(b)

CoBr$_2$ (5 mol %)
P(3-MeC$_6$H$_4$)$_3$ (20 mol %)
i-PrMgBr (50 mol %)

THF, rt, 12 h

12   **10**   **13**, 55%
(1.5 equiv)

[a] PMP = p-methoxyphenyl.

reside in this specific transformation, because the exact same type of reaction was achieved earlier using Wilkinson catalyst.[22] What is more important is that we can emulate the reactivity of the rhodium(I) catalyst with an appropriately tuned cobalt catalyst.

Building on this finding, we managed to expand the scope of aromatic substrates to aryl imines. Addition of an aryl ketimine to an internal alkyne was achieved at room temperature using CoBr$_2$, P(3-ClC$_6$H$_4$)$_3$, and t-BuCH$_2$MgBr as essential catalytic components and pyridine as an additive (Scheme 4a).[23] Thus, the cobalt catalyst allows C−H activation at a much lower temperature than a rhodium(I) catalyst for the same type of reaction.[24] Interestingly, the cobalt catalyst regioselectively activated imines bearing meta-methoxy, cyano, and halogen substituents at the position proximal to these functional groups. Note also that an unsymmetrical alkyne underwent C−C bond formation at the less hindered acetylenic carbon. While the catalytic system for aryl ketimines performed poorly for aryl

aldimines, careful reoptimization allowed the desired reaction using P(3-MeC$_6$H$_4$) and i-PrMgBr (Scheme 4b).[25]

The reaction of deuterium-labeled acetophenone imine again confirmed transfer of the ortho-deuterium atom to the vinylic position of the product. Comparison of initial rates of parent and deuterium-labeled imines gave a large kinetic isotope effect (KIE) of ca. 5, indicating that C−H activation is the turnover-limiting step. Consistent with the KIE, initial rate kinetics revealed first-order dependence on the imine, while a rate saturation behavior was observed against the concentration of the alkyne. Putting these and other observations together, we proposed a catalytic cycle involving (1) precoordination of alkyne to a low-valent cobalt species generated by reduction of the cobalt(II) precatalyst with the Grignard reagent, (2) oxidative addition of the ortho C−H bond to cobalt, (3) migratory insertion of alkyne into the Co−H bond, and (4) reductive elimination to afford the product and regenerate the initial cobalt species (Scheme 5). The regioselectivity for an unsymmetrical alkyne can be rationalized by the preference of a larger substituent to avoid steric repulsion with the cobalt center in the migratory insertion step.

Because a stoichiometric reaction of the cobalt(II) precatalyst and excess t-BuCH$_2$MgBr affords ca. 1 equiv of homocoupling product (t-BuCH$_2$CH$_2t$-Bu), we speculate that the oxidation state of the active cobalt catalyst is zero. In light of the necessity of greater amount of the Grignard reagent than required for the reduction of cobalt(II) to cobalt(0) in this and other reactions, we also suspect that the active catalyst takes the form of an organocobalt(0)ate complex.[26] In any case, further investigation is necessary to support such conjecture.

The imine directing group also allows activation of an olefinic C−H bond. With the aid of a cobalt catalyst generated from CoBr$_2$, P(3-ClC$_6$H$_4$)$_3$, and i-PrMgBr, an α,β-unsaturated imine **14** undergoes annulation with diphenylacetylene **10** to

**Scheme 5. Proposed Catalytic Cycle for the Addition of Aryl Ketimine to Alkyne**
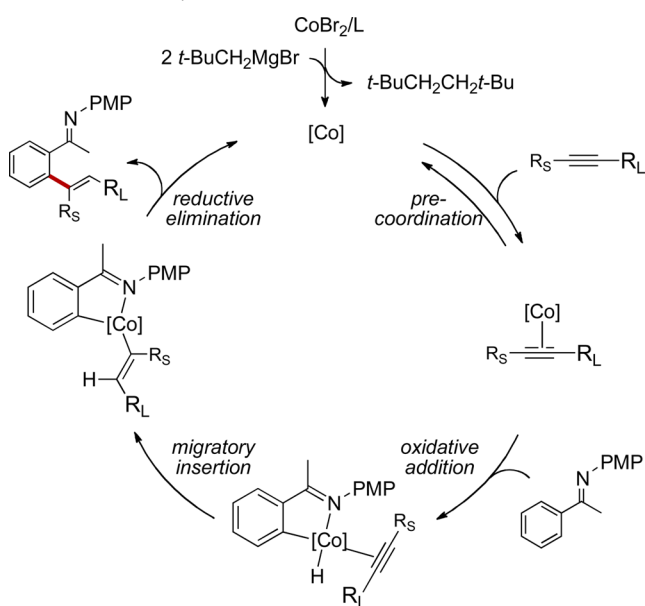
afford a dihydropyridine derivative **15** (Scheme 6).[27] As was proposed for the same type of transformations with rhodium(I)

**Scheme 6. Annulation of α,β-Unsaturated Imine and Alkyne**
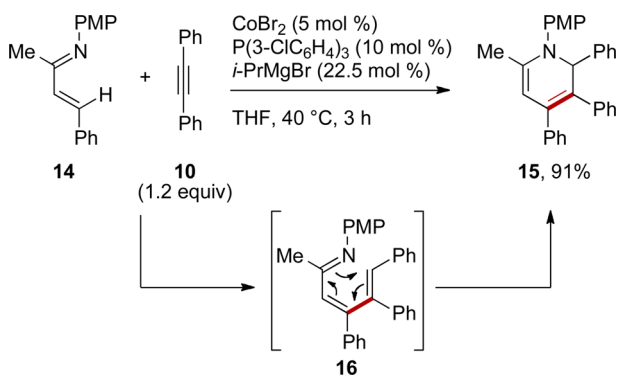
catalysts,[28,29] the reaction presumably involves olefinic C–H activation/alkenylation followed by 6π-electrocyclization of the resulting azatriene intermediate **16**.

The scope of the cobalt catalysis was further expanded with inspiration from Ackermann's work on the use of 2-pyrimidyl group as a removable directing group for C2-functionalization of indole.[30] Thus, a cobalt catalyst generated from CoBr₂, 2-(diphenylphosphinoethyl)pyridine (pyphos), and *t*-BuCH₂MgBr promotes the addition of *N*-pyrimidylindoles to various internal alkynes at room temperature (Scheme 7).[31] The reaction offers a complementary scope of alkynes in comparison with related indole C2-alkenylation reactions such as rhodium(III)-catalyzed hydroarylation.[32]

Besides aromatic and olefinic substrates bearing directing groups, azoles are amenable to cobalt-catalyzed C–H activation. Thus, a cobalt catalyst generated from CoBr₂, bis[(2-diphenylphosphino)phenyl] ether (DPEphos), and Me₃SiCH₂MgCl allows addition of (benz)oxazoles to internal alkynes in a syn-fashion at room temperature, affording C2-alkenylated products (Scheme 8a).[33] The same type of transformation can be achieved for (benzo)thiazoles by

Scheme 7. Addition of *N*-Pyrimidylindoles to Alkynes
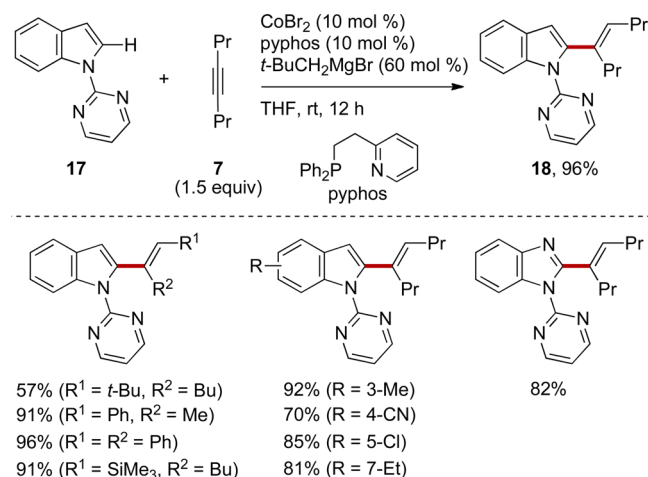
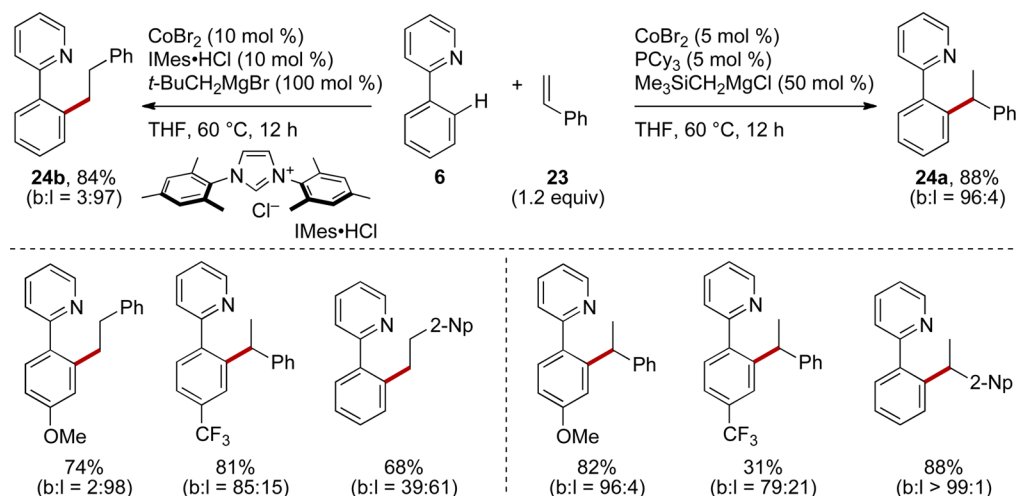**Scheme 8. Addition of Azoles to Alkynes**
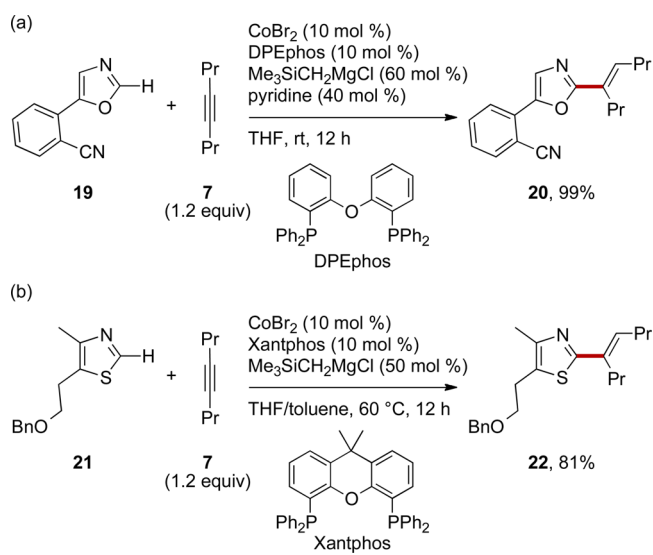
changing the ligand to 4,5-bis(diphenylphosphino)-9,9-dimethylxanthene (Xantphos; Scheme 8b).[34] These cobalt–diphosphine catalysts emulate the ability of a nickel(0)–monophosphine catalyst to promote alkyne hydroheteroarylation,[35] while the latter shows a broader scope of heteroarenes.

2.2. Hydroarylation of Olefins

With the successful development of alkyne hydroarylation reactions, it was natural for us to turn our attention to olefin hydroarylation. We became particularly interested in the reaction of styrenes because of regioselectivity issues. In general, addition reactions of aromatic compounds to styrenes can be classified into two types featuring different substrate scopes and regioselectivity trends, that is, Friedel–Crafts type reaction catalyzed by Lewis acid or Brønsted acid and hydroarylation through transition metal-mediated C–H activation. While the Friedel–Crafts reaction works with electron-rich arenes and affords branched 1,1-diarylethanes,[36] the C–H activation approach often requires arenes bearing directing groups or electron-poor arenes and tends to give linear 1,2-diarylethanes with a few exceptions.[37,38] Importantly, 1,1-diarylethanes appear more frequently in bioactive com-

Scheme 9. Regiodivergent Addition of 2-Arylpyridines to Styrenes[a]

CoBr₂ (10 mol %)
IMes·HCl (10 mol %)
t-BuCH₂MgBr (100 mol %)

THF, 60 °C, 12 h

CoBr₂ (5 mol %)
PCy₃ (5 mol %)
Me₃SiCH₂MgCl (50 mol %)

THF, 60 °C, 12 h

24b, 84%
(b:l = 3:97)

IMes·HCl

6

23
(1.2 equiv)

24a, 88%
(b:l = 96:4)

74%
(b:l = 2:98)

81%
(b:l = 85:15)

68%
(b:l = 39:61)

82%
(b:l = 96:4)

31%
(b:l = 79:21)

88%
(b:l > 99:1)

[a]The ratio b:l refers to the ratio of the branched and linear products.

pounds than 1,2-diarylethanes. Thus, our question is: Is it possible to achieve branched-selective styrene hydroarylation by the C−H activation approach and thereby complement the limitation of the Friedel−Crafts reaction?

Upon examination of the reaction of 2-phenylpyridine and styrene, we encountered unique regioselectivity of cobalt catalysis. Thus, a cobalt catalyst generated from CoBr₂, PCy₃, and Me₃SiCH₂MgCl promoted the reaction to afford a branched adduct **24a** with high regioselectivity (Scheme 9).[39] We were excited with this observation, because ruthenium and rhodium catalysts have been known to exhibit linear selectivity in similar reactions.[19] To our further surprise, the use of an NHC ligand, IMes, instead of PCy₃ caused near complete reversal of the regioselectivity, leading to the formation of a linear adduct **24b**. This regiodivergence was demonstrated for a reasonable range of 2-arylpyridine and styrene derivatives, while in some cases the ligand control was overridden by the electronic nature of the substrate. For example, 2-arylpyridine bearing a trifluoromethyl group afforded the branched adduct as the major product under both the catalytic systems. In another example, the linear selectivity of the Co−IMes catalysis was significantly deteriorated when 2-vinylnaphthalene was used.

Experiments using 2-(pentadeuteriophenyl)pyridine revealed that H/D scrambling among the ortho positions of phenyl-pyridine and the α- and β-positions of styrene takes place prior to C−C bond formation under both the catalytic systems. The simplest mechanistic model that explains these observations involves reversible oxidative addition of the ortho C−H bond to cobalt, reversible insertion of styrene into the Co−H bond leading to a branched or a linear intermediate, and reductive elimination to form the 1,1- or 1,2-diarylethane (Scheme 10). The two insertion pathways compete with each other, while the reductive elimination step governs the regioselectivity. The branched selectivity of the Co−PCy₃ catalysis would originate from stabilization of the branched intermediate and its reductive elimination transition state due to π-benzyl type interaction, while the linear selectivity of the Co−IMes catalysis may be explained by the preference of the IMes ligand to avoid steric congestion.[40]

The branched-selective hydroarylation was extended to aromatic aldimines and ketimines.[41,42] Thus, a variety of aryl
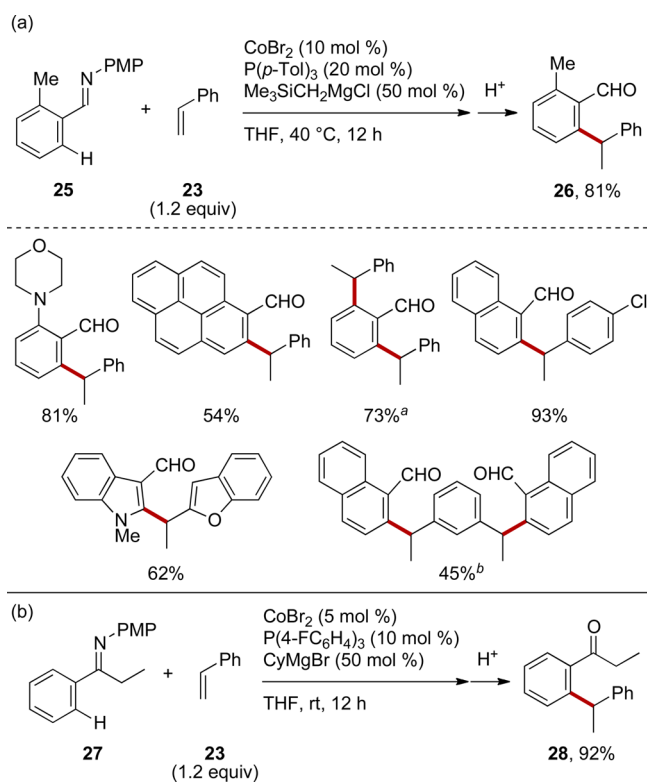
Scheme 10. Proposed Catalytic Cycle for Regiodivergent Addition of 2-Phenylpyridine to Styrene

L = IMes

CoLₙ

L = PCy₃
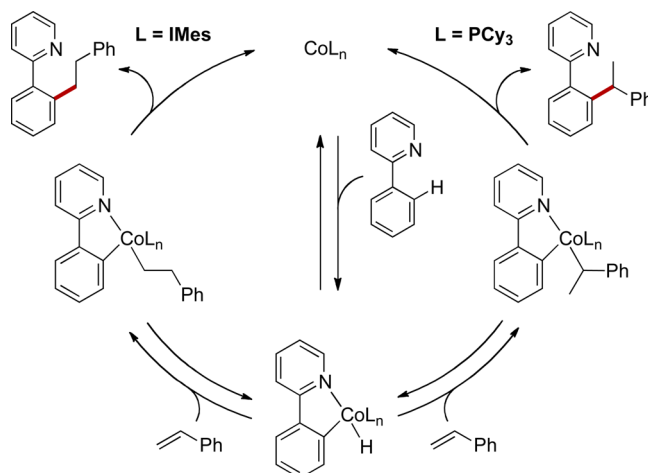
aldimines and styrene derivatives could be coupled using a cobalt catalyst generated from CoBr₂, P(p-Tol)₃, and Me₃SiCH₂MgCl under gentle warming (40 °C), affording the corresponding 1,1-diarylethanes often with exclusive regioselectivity (Scheme 11a). To achieve selective monoaddition, one of the ortho positions needs to be substituted. Otherwise, the reaction tends to give a dialkylation product even with a limited amount of styrene, suggesting that the catalyst does not dissociate from the aldimine moiety after the first alkylation but undergoes second C−H activation. While this and the Co−PCy₃ catalytic systems were only modestly effective for aryl ketimines, another system employing P(4-FC₆H₄)₃ and CyMgBr allowed facile and highly branched selective reaction (Scheme 11b). Note that Matsunaga, Kanai, and co-workers achieved cobalt-catalyzed C4-alkylation of pyridines with styrenes in a branched manner through a hydrometalation−nucleophilic addition mechanism.[43]
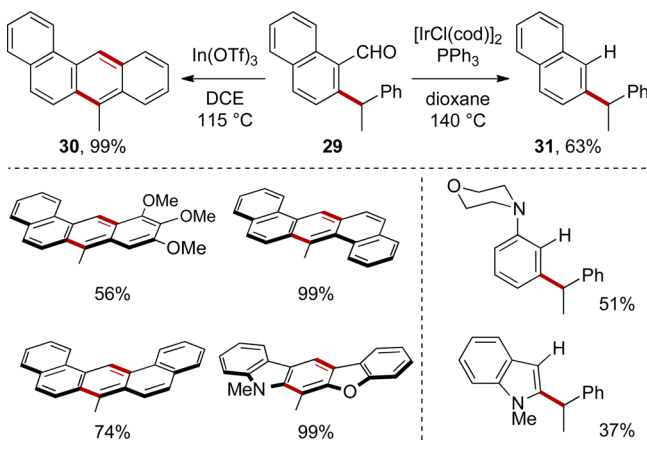
Taking advantage of the ortho-formyl group, the hydro-arylation products can be transformed into anthracene and related derivatives through indium-catalyzed dehydrative cyclization (Scheme 12).[44] Thus, the cobalt catalysis has opened a convenient two-step route to a certain class of

1212

dx.doi.org/10.1021/ar400270x | Acc. Chem. Res. 2014, 47, 1208−1219

Scheme 11. Branched-Selective Addition of Aryl Imines to Styrenes

(a)

Scheme 13. Imine-Directed Hydroarylation of Vinylsilane and Alkyl Olefin

(a)

(b)

(b)

[a]The reaction was performed using 2.4 equiv of styrene. [b]The reaction was performed using 2.5 equiv of aldimine with respect to 1,3-divinylbenzene.
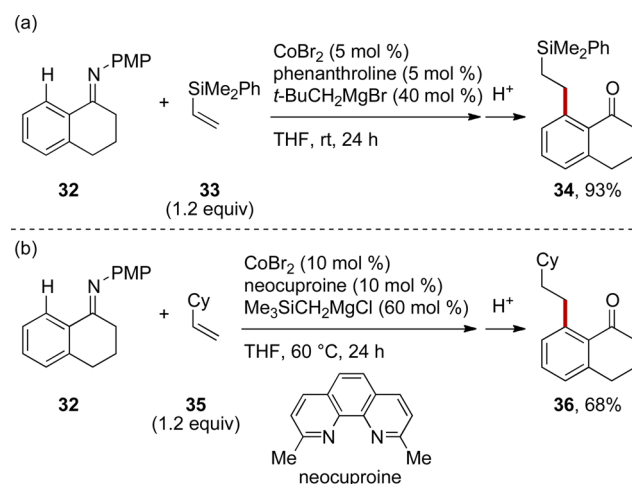
Scheme 12. Transformations of Aldimine−Styrene Adducts

These cobalt catalysts may serve as alternatives to rhodium and ruthenium catalysts for related imine- or ketone-directed olefin hydroarylation.[19,48] Nakamura and co-workers achieved directed olefin hydroarylation of benzamide derivatives using a cobalt catalyst generated from Co(acac)$_3$, DMPU, and CyMgCl.[49]
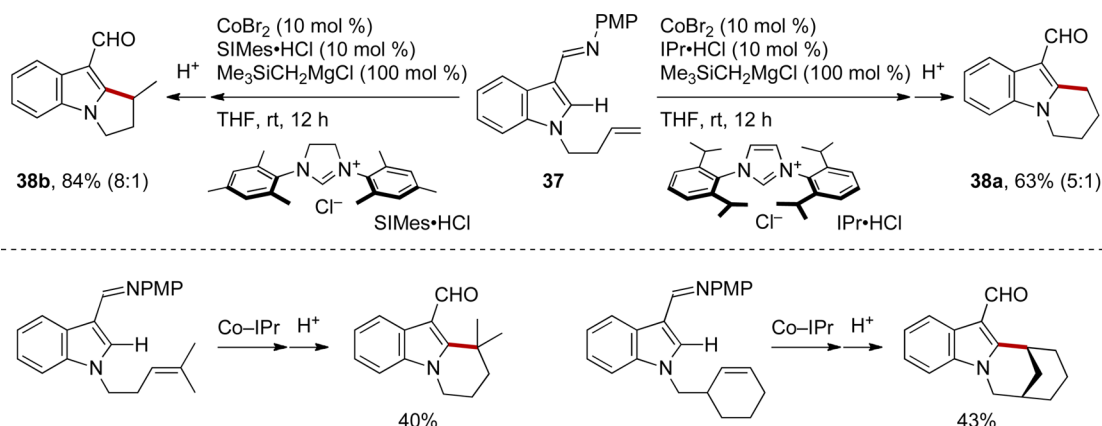
We have further extended the scope of the cobalt catalysis to intramolecular systems. Thus, cobalt−NHC catalytic systems promote intramolecular C2-alkylation of an alkene-tethered indole with an aldimine directing group (Scheme 14).[50] Interestingly, while a cobalt−IPr catalyst promoted regioselective cyclization of an N-homoallylindole **37** to a tetrahydropyridoindole derivative **38a**, a cobalt−SIMes catalyst exhibited selectivity toward a dihydropyrroloindole regioisomer **38b**. Besides the ligand-controlled regiodivergence, the cobalt−NHC catalysis has enabled formation of a quaternary carbon center and a bicyclo[3.3.1] skeleton, which have not been achieved with rhodium(I)-catalyzed intramolecular hydroarylation.[51]

As shown in the above examples, careful choice of the Grignard reagent as well as the ligand is crucial for the catalytic activity. While it is premature to provide a general guideline about the choice of the Grignard reagent, we may note some rules of thumb: Grignard reagents without β-hydrogens, such as t-BuCH$_2$MgBr and Me$_3$SiCH$_2$MgCl, tend to make the reaction clean, possibly because they would not give rise to a cobalt hydride species, a potential cause of side reactions (e.g., reduction of imine, alkyne, or alkene). For substrates sensitive to Grignard reagents (e.g., oxazoles and thiazoles), the use of less nucleophilic Me$_3$SiCH$_2$MgCl is crucial. While secondary alkyl Grignard reagents such as i-PrMgBr and CyMgBr sometimes cause background reactions, for example, reduction of imine, with careful tuning of reaction conditions, they may give rise to highly active catalysts (Schemes 4b, 6, 11b, and catalytic systems of Nakamura and Ackermann). The reason remains unclear at this moment.

3. C−H/ELECTROPHILE COUPLING

As we demonstrated the feasibility of the hypothetical catalytic cycle **A** for hydroarylation of alkynes and alkenes, we turned our attention to the catalytic cycle **B**, that is, C−H functionalization using an electrophile (Scheme 3). Our initial exploration employing an aldimine as the electrophile led to the

polycyclic aromatic hydrocarbons. Alternatively, the aldehyde moiety can be removed by iridium-catalyzed decarbonylation,[45] affording 1,1-diarylethanes with regiochemistry not accessible by the Friedel−Crafts reaction.

Besides styrene derivatives, vinylsilanes and aliphatic olefins can also be used for cobalt-catalyzed directed hydroarylation.[46] Thus, a cobalt−1,10-phenanthroline catalyst smoothly promoted the addition of aryl ketimines to vinylsilanes under room-temperature conditions (Scheme 13a). The reaction of aliphatic olefins was achieved at 60 °C using neocuproine and Me$_3$SiCH$_2$MgCl (Scheme 13b). A similar catalytic system also allowed the addition of N-pyrimidylindole to vinylsilane.[47]

**Scheme 14. Cyclization of Indoles Bearing Olefin Tethers**

development of an addition reaction of 2-arylpyridine to *N*-aryl aldimine using a Co—IPr catalyst and *t*-BuCH₂MgBr, the latter serving as a reducing agent as well as a base (eq 2).[52] The
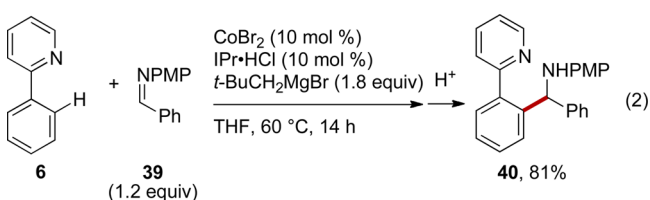
reaction is mechanistically distinct from rhodium(III)- or cobalt(III)-catalyzed addition of 2-arylpyridine to *N*-Boc or *N*-tosyl aldimine, which does not require a stoichiometric base to remove the ortho-hydrogen atom.[53−55]

In the absence of 2-arylpyridine, the same catalytic system promotes self-coupling of two aldimine molecules (Scheme 15). Thus, the reaction of benzaldimine **39** affords a 1-

Scheme 15. Self-Coupling of Aryl Aldimine Followed by Interception with Aldehyde
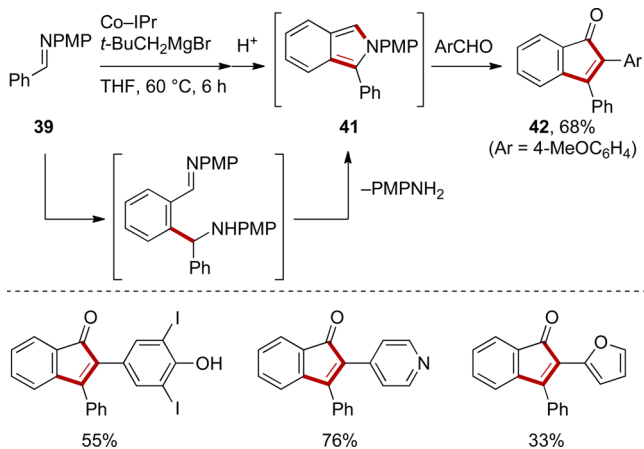

phenylisoindole intermediate **41** through the addition of the ortho position of one aldimine to the C═N bond of another and subsequent deaminative condensation of the aldimine and amine functional groups. The isoindole intermediate is rather unstable in air but can be intercepted by aldehydes to furnish 2,3-diarylindenone derivatives.

The scope of electrophiles was next extended to aryl chlorides.[56] A catalytic system comprising CoBr₂, IMes·HCl,

and *t*-BuCH₂MgBr allows ortho-arylation of acetophenone imine **6** with chlorobenzene **43** at room temperature to afford, upon hydrolysis, a biaryl ketone **44** (Scheme 16).[57] PEt₃ can be
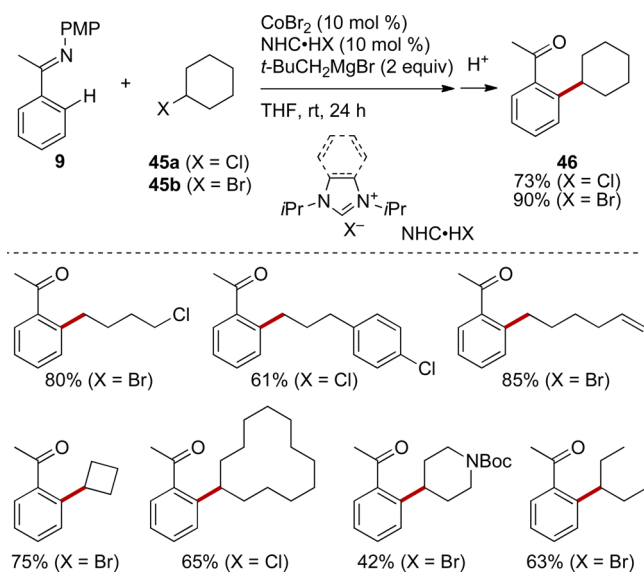
Scheme 16. Ortho-Arylation of Aryl Ketimines with Aryl Chlorides
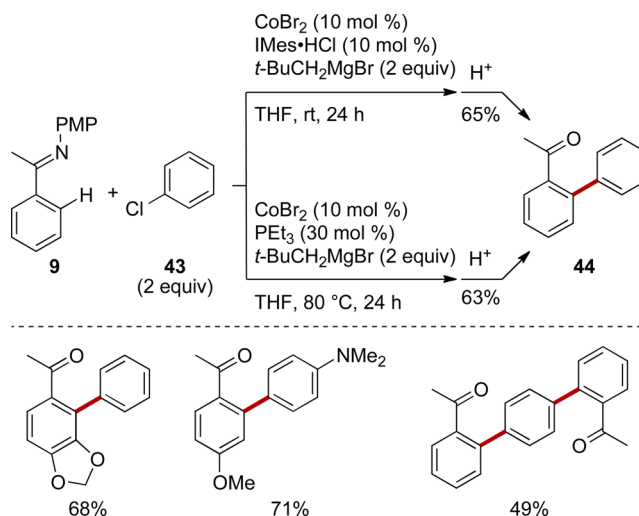
used as an alternative ligand at a higher temperature. A similar cobalt−IMes catalytic system employing CyMgCl and DMPU as base and solvent, respectively, was developed by Ackermann for the ortho-arylation of 2-arylpyridines and N-pyri(mi)-dylindoles with aryl sulfamates, carbamates, and chlorides.[58,59] Oxidative ortho-arylation of 2-arylpyridines with aryl Grignard reagents[60,61] was achieved by Wang, Shi, and co-workers using a Co(acac)₃−TMEDA catalytic system and 2,3-dichlorobutane oxidant.[62]

A cobalt−NHC catalytic system also proved effective for the ortho-alkylation of aryl ketimines.[63] Thus, a cobalt catalyst with a simple NHC preligand *N,N′*-diisopropylimidazolium tetrafluoroborate or its benzo-fused analogue, in combination with *t*-BuCH₂MgBr, promotes room-temperature ortho-alkylation of aryl ketimines with a variety of primary and secondary alkyl chlorides and bromides with notable chemoselectivities (Scheme 17).[64] The reaction may complement the scope of ortho-alkylation via olefin hydroarylation, which is largely limited to the introduction of primary alkyl groups. Nakamura and co-workers achieved ortho-alkylation of benzamides with primary alkyl chlorides using the Co(acac)₂−DMPU catalytic
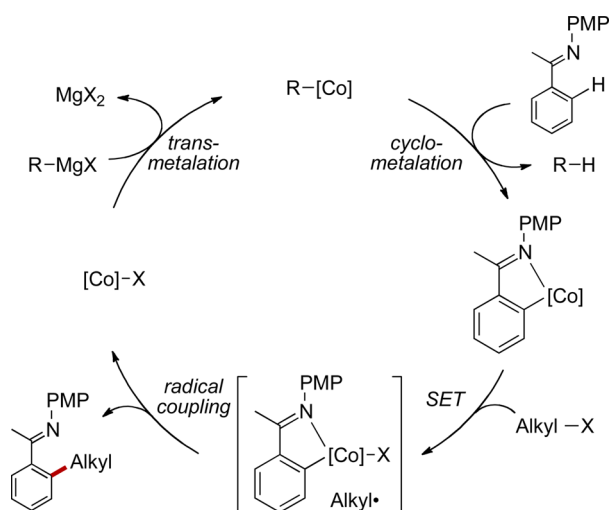
Scheme 17. Ortho-Alkylation of Aryl Ketimines with Alkyl Chlorides and Bromides

4. ARYLZINCATION OF ALKYNES THROUGH 1,4-COBALT MIGRATION

While we succeeded in the development of the above two types of C–H functionalization reactions more or less as we initially envisaged, we found another type of cobalt-catalyzed C–H activation, that is, aromatic C–H activation via 1,4-cobalt migration, rather serendipitously. Some time ago, we found a catalytic effect of a cobalt–diphosphine complex, CoCl$_2$(Xantphos), on Knochel's zinc insertion into aryl halides using Zn·LiCl (eq 3).[67,68] A small amount of the cobalt
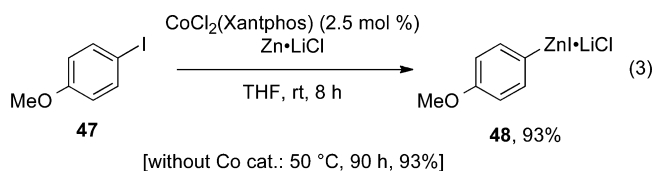
complex significantly accelerates the zinc insertion,[69] thus allowing preparation of a variety of arylzinc reagents in THF from aryl iodides, bromides, and some chlorides.

During exploration of the utility of the thus-prepared arylzinc reagents, we came across an interesting observation. Thus, the Co–Xantphos catalyst was found to catalyze not only zinc insertion into 4-iodoanisole 47 but also addition of the resulting arylzinc reagent to 4-octyne 7 to afford an alkenylation product 49 (Scheme 19a). While Yorimitsu, Oshima, and co-workers

Scheme 19. Cobalt-Catalyzed Addition of Arylzinc Reagent to Alkyne

system,[65] while Ackermann and co-workers demonstrated the utility of their Co–IMes system in ortho-alkylation of 2-arylpyridines and N-pyridylindoles with alkyl chlorides.[59] Nakamura also developed aerobic oxidative ortho-alkylation of benzamides and 2-arylpyridines with primary alkyl Grignard reagents.[66]
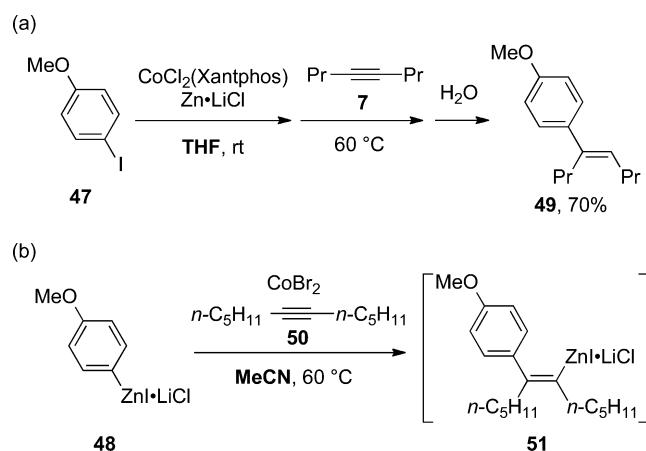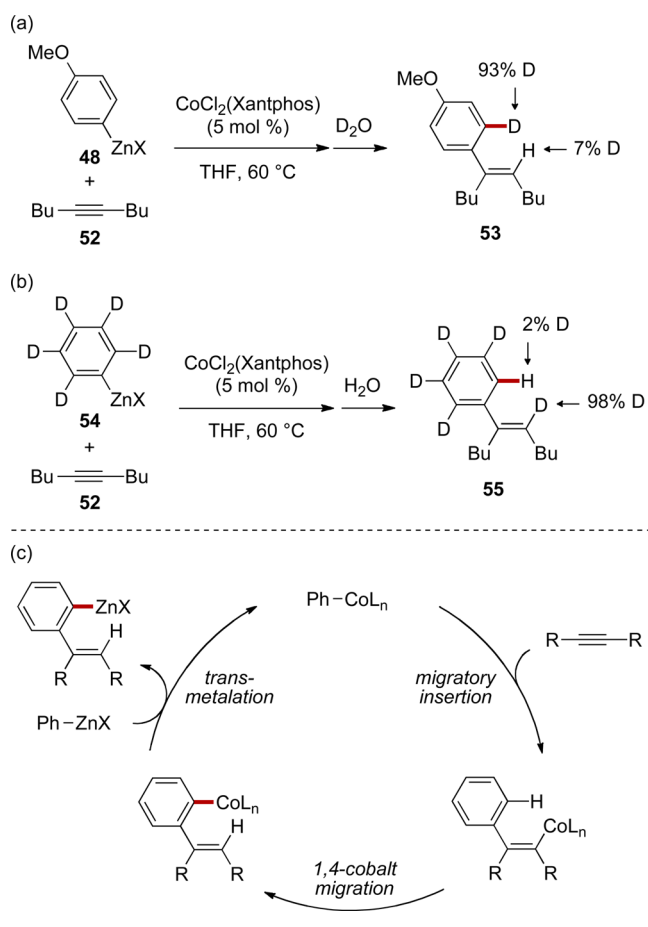
Experiments using a few stereochemical probes suggested that the reaction involves a radical intermediate. Thus, a proposed catalytic cycle involves cyclometalation of aryl imine with an alkylcobalt species generated from the cobalt precatalyst and the Grignard reagent, followed by single-electron transfer (SET) from the cobalt center to alkyl halide (Scheme 18).[26] The following radical C–C coupling affords the product, and transmetalation of the resulting cobalt halide species with the Grignard reagent regenerates the alkylcobalt species.

reported earlier on a CoBr$_2$-catalyzed arylzincation reaction of an unactivated alkyne using Knochel's arylzinc reagent (Scheme 19b),[70] this observation still intrigued us because their reaction worked in MeCN but not at all in THF, the latter being used in our reaction.

The truly unique feature of the Co–Xantphos catalysis was revealed by deuterium-labeling experiments.[71] Quenching of the reaction of 4-methoxyphenylzinc reagent and 5-decyne with D$_2$O led to predominant deuteration of the ortho position rather than the vinylic position (Scheme 20a), while the reaction of pentadeuteriophenylzinc reagent resulted in near complete transfer of one of the ortho-deuterium atoms to the vinylic position (Scheme 20b). These observations indicated the formation of an ortho-alkenylarylzinc species and reminded us of the seminal work of Hayashi on the rhodium(I)-catalyzed hydroarylation of an alkyne with an arylboronic acid through 1,4-rhodium migration.[72,73] In analogy with the rhodium

Scheme 18. Proposed Catalytic Cycle for Ortho-Alkylation with Alkyl Halide

Scheme 20. Deuterium-Labeling Experiments and Proposed Mechanism Involving 1,4-Cobalt Migration

Scheme 21. Migratory Arylzincation Followed by Electrophilic Trapping

catalysis, the Co−Xantphos catalysis appears to involve insertion of alkyne into an arylcobalt species, vinyl-to-aryl 1,4-cobalt migration, and transmetalation between the cobalt−aryl and zinc−aryl bonds to afford an ortho-alkenylarylzinc reagent and regenerate the arylcobalt species (Scheme 20c).

This "migratory arylzincation" reaction is unique in that the product bears a reactive ortho aryl−zinc bond, which can be intercepted by an electrophile. Indeed, the reaction is applicable to various aryl and heteroarylzinc reagents, and the resulting zinc intermediates are amenable to a variety of electrophilic trapping reactions (Scheme 21). Notably, arylzinc reagents bearing fluoro/alkoxy substituents on the meta position or 3-thienyl/3-quinolynylzinc reagents undergo regioselective 1,4-cobalt migration to the proximity of the functional group or the heteroarom, respectively.

The utility of the migratory arylzincation was further demonstrated by its application to the synthesis of benzothiophenes and benzoselenophenes (Scheme 22).[74] Thus, migratory arylzincation is followed by copper-mediated reaction with elemental sulfur, and accompanying C−S cyclization affords a substituted benzothiophene in a one-pot operation. Alternatively, the zinc intermediate is first trapped by iodine, and subsequent copper-catalysis allows C−S/C−Se bond formation/cyclization with elemental sulfur or selenium to afford the corresponding benzochalcogenophene. Thus, these protocols allow expedient preparation of diversely functionalized benzothiophenes and benzoselenophenes that are not readily accessible by common synthetic methods.
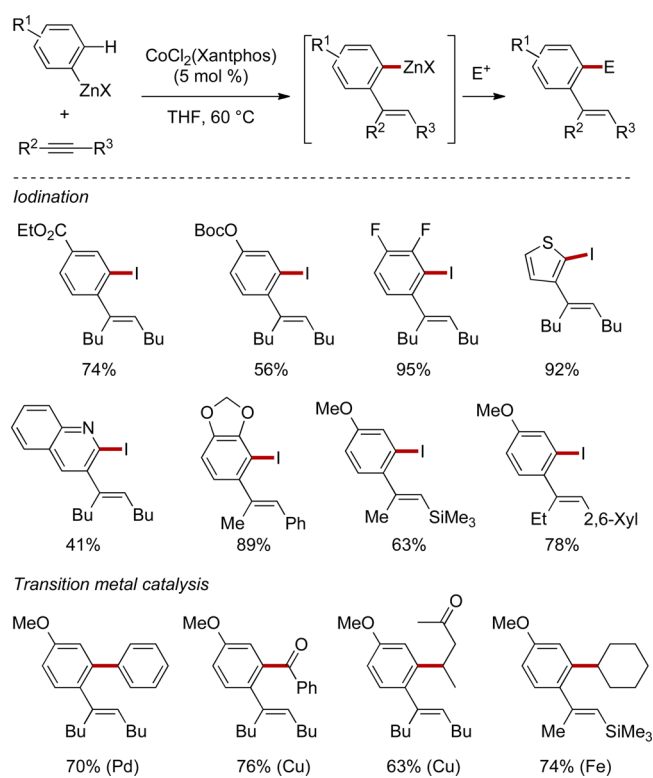
Scheme 22. Modular Synthesis of Benzothiophenes and Benzoselenophenes
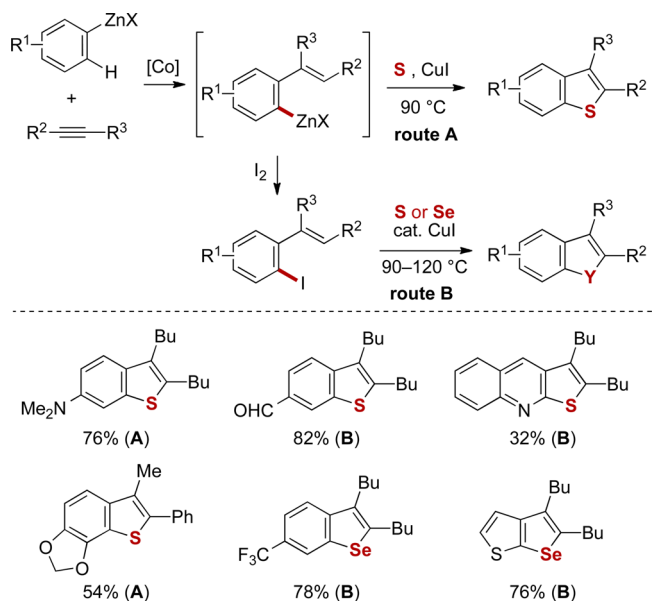
5. CONCLUSIONS

In light of the work described above, now answers to the two questions we raised in the Introduction are clear: First, with appropriate tuning of ligands and reducing agents, low-valent cobalt catalysts can emulate the reactivity of noble transition metal catalysts, rhodium(I) catalysts in particular, toward C−H activation. A series of imine-directed C−H functionalization reactions have been achieved using cobalt catalysts often at very mild temperatures. Second, cobalt catalysts can exhibit unique

reactivity and selectivity in C−H functionalization, thus enabling hitherto unknown or difficult synthetic transformations. Representative examples include branched-selective hydroarylation of styrenes, ortho-alkylation of aryl imines with secondary alkyl halides, and migratory arylzincation of alkynes. New challenges and opportunities emerge along with these studies. For example, enantioselective C−H functionalization and $C(sp^3)$−H functionalization may represent significant challenges for further catalyst/reaction developments. The branched hydroarylation and migratory arylzincation reactions would offer opportunities to synthesize and explore novel π-conjugated systems. Last but not least, further growth of this area requires deeper understanding of the reaction mechanism and the nature of the catalyst, which, given the parallelism between cobalt and iron in stoichiometric C−H activation,[14,16] may also serve as a stepping stone toward the development of iron catalysts for C−H functionalizations.[75]

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Notes

The authors declare no competing financial interest.

Biographies

Ke Gao received his B.Sc. (2006) and M.Sc. (2009) degrees from Fudan University under the supervision of Prof. Jie Wu. He subsequently moved to the group of Prof. Naohiko Yoshikai at Nanyang Technological University, and recently completed his Ph.D. study focused on the development of cobalt-catalyzed C−H bond functionalizations. He is currently pursuing his postdoctoral studies in the group of Profs. Atsuhiro Osuka and Hideki Yorimitsu at Kyoto University.

Naohiko Yoshikai received his B.Sc. (2000), M.Sc. (2002), and Ph.D. (2005) degrees from The University of Tokyo under the guidance of Prof. Eiichi Nakamura, and then served as an Assistant Professor at the same institute (2005−2009). In 2009, he moved to Singapore to join the faculty of Nanyang Technological University as a Nanyang Assistant Professor and a Research Fellow of Singapore National Research Foundation. His research interests are focused on the development and mechanistic study of new transition metal-catalyzed reactions and their synthetic applications.

■ ACKNOWLEDGMENTS

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