Cobalt–Catalyzed C–C Bond–Forming Reactions via Chelation–Assisted C–H Activation

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Abstract: The development of chelation–assisted C–H functionalization reactions has long been driven by noble transition metal catalysts, despite the obvious economic benefits of using earth–abundant transition metals. In this context, seminal reports in the literature suggest the potential of cobalt complexes as catalysts for C–H functionalization. This account summarizes our studies on the development of a series of cobalt–based catalysts for chelation–assisted C–H functionalization reactions such as addition of C–H bonds across carbon–carbon multiple bonds (hydroarylation), and coupling between C–H bonds and organic electrophiles. These studies have demonstrated that cobalt catalysts not only serve as mild and cost–effective alternatives to noble metal catalysts for existing C–H functionalizations, but also enable hitherto unknown or difficult transformations, including branched–selective hydroarylation of styrenes and ortho–alkylation using unactivated secondary alkyl halides.

1. Introduction

Transition metal–mediated, chelation–assisted C–H activation has been arguably the most extensively practiced strategy for the regioselective cleavage of unreactive C–H bonds and their conversion to C–C and C–heteroatom bonds. Since the groundbreaking work of Murahashi and coworkers on the ruthenium–catalyzed ortho–alkylation of aromatic ketones with olefins, catalysts based on second–row transition metals such as ruthenium, rhodium, and palladium have been extensively developed for so–called directed C–H functionalization. On the other hand, the use of their first–row homologues, i.e., iron, cobalt, and nickel, for such transformations has been sporadic until recently, despite the potential economic and environmental benefits. This situation may appear somewhat strange considering that almost all transition metals, including those in the first–row, are known to participate in a stoichiometric cyclometalation reaction, which is a critical elementary step for directed C–H functionalization.

Among the first–row transition metals, cobalt has shown, though not very frequently, its ability to undergo chelation–assisted C–H activation in either a catalytic or a stoichiometric manner since the early days of this field. In 1955, Murahashi reported on a cobalt carbonyl–catalyzed ortho–carbonylation reaction of benzaldehyde under CO pressure to afford an isoindolinone derivative, which most likely involves cobalt–mediated activation (cyclometalation) of the ortho C–H bond (Scheme 1a). In 1994, Kisch and coworkers reported an ortho–alkenylation reaction of an azobenzene derivative with diphenylacetylene catalyzed by Co(H)(N2)(PPh3)3 or CoH3(PPh3)3 (Scheme 1b). Studies on stoichiometric cyclometalation reactions of various aromatic and olefinic substrates with a cobalt(I) complex CoMe(PMe3)2 have continued ever since an initial report of Klein and coworkers in 1993 (Scheme 1c).

Given this background, we envisioned that cobalt should have significant, if not yet fully explored potential for chela-

Scheme 1. Catalytic and stoichiometric C–H activation with cobalt complexes.

tion of styrenes, (3) hydroarylation of vinylsilanes and simple olefins, and (4) ortho–arylation and alkylation using organic halides (Scheme 2).\(^5\)

2. Cobalt–Catalyzed Directed Hydroarylation of Alkynes

At the outset of our exploration of cobalt-catalyzed C–H functionalization, our primary question was whether a cobalt catalyst could promote the Murai-type hydroarylation reaction of olefins or alkynes. Inspired by Klein’s cyclometalation reaction (Scheme 1c), which was proposed to go through C–H oxidative addition and reductive elimination of methane, we formulated a hypothetical catalytic cycle for such transformations (Scheme 3). This catalytic cycle features a low–valent organocobalt species \(\text{Co(R)}\text{L}_n\), as an active catalyst and involves three elementary steps, that is, C–H oxidative addition, insertion of alkene or alkyne into the Co–H bond, and reductive elimination. With Kisch’s reaction of azobenzene and diphenylacetylene (Scheme 1b) in mind, we chose 2-phenylnylpyridine and 4-octyne as model substrates to explore the feasibility of this catalytic cycle. To generate the putative organocobalt species, various combinations of cobalt salts (CoX\(_n\)), ligands (L), and organometallic reagents (R–M) were examined.

Scheme 3. Hypothetical catalytic cycle for cobalt–catalyzed directed hydroarylation.

A ternary catalytic system consisting of CoBr\(_2\), PMePh\(_2\), and MeMgCl was found to promote the desired reaction in a syn-fashion to give a trisubstituted alkene product in good yield (Scheme 4).\(^6\) In agreement with the hypothetical catalytic cycle (Scheme 3), deuterium-labeling and crossover experiments demonstrated that the ortho–hydrogen atoms of 2-phenylnylpyridine are completely transferred to the vinlyc positions of the product. This transformation has been achieved previously using the Wilkinson catalyst,\(^7\) and may not be considered synthetically attractive because of the limited utility of the pyridyl group. Nevertheless important is that its discovery has opened the way to emulating the reactivity of a rhodium(I) catalyst using a cobalt–based catalyst.

Building on this initial finding, we succeeded in using aryl ketimines as substrates for cobalt–catalyzed alkyne hydroarylation. Thus, an imine derived from an acetophenone derivative and \(p\)-anisidine can be efficiently alkylated with the aid of a cobalt catalyst generated from CoBr\(_2\), P(3-ClC\(_6\)H\(_4\))\(_3\), iBuCH\(_2\)MgBr, and pyridine (Scheme 5).\(^8\) The reaction takes place at a distinctly lower temperature (i.e., room temperature) than is required for a related reaction using a rhodium(I) catalyst.\(^9\) Exploration of the scope of this reaction clarified some mechanistically and synthetically notable features. First, the reaction of an unsymmetrically substituted alkyne results in C–C bond formation at the less-hindered acetylenic carbon atom. Second, imines bearing meta–methoxy, cyano, and halogen substituents underwent C–H functionalization at the position proximal to those substituents. While similar secondary directing effects of alkoxy and fluorine substituents have been observed in other transition metal–catalyzed C–H functionalizations,\(^10\) such had not been the case for cyano, chloro, and bromo substituents.

Scheme 4. Addition of 2-phenylnylpyridine to 4-octyne

On the basis of a series of kinetic and isotope-labeling experiments, we proposed the catalytic cycle outlined in Scheme 6. Upon generation of a low–valent cobalt species from the cobalt precatalyst and the Grignard reagent, an alkyne can undergo reversible coordination to the cobalt center, which is followed by directed C–H oxidative addition of an aryl imine. Subsequent migratory insertion of the alkyne into the Co–H bond and reductive elimination of the resulting dioxogencobalt species afford the ortho–alkenylation product and regenerate the active catalyst. A large H/D kinetic isotope effect and a first–order dependence of the reaction rate on the concentration of the imine indicated that the C–H oxidative addition step is rate-limiting. The pre–coordination of alkyne
was suggested from saturation kinetics observed at high alkyne concentrations. The regioselectivity for an unsymmetrical alkyne can be explained by the preference for minimizing steric repulsion around the cobalt center in the alkyne insertion step.

Scheme 6. Proposed catalytic cycle for the imine–directed alkyne hydroarylation.

The scope of this cobalt-catalyzed directed alkyne hydroarylation has been further extended to aryl aldimines, α,β-unsaturated imines, and indoles bearing an N-pyrimidyl group (Scheme 7). Note that the reaction of an α,β-unsaturated imine is followed by 6π-electrocyclization to afford a dipyridylamine derivative. It appears that there is no universally applicable cobalt catalyst for C–H functionalization, because each of these reactions required careful tuning of the ligand and the Grignard reagent. Such a narrow scope of for each particular catalytic system may be considered a downside of cobalt catalysis, because for rhodium catalysis, a single catalyst (e.g., Wilkinson catalyst) allows a reasonably broad range of C–H functionalizations. However, with the optimized cobalt catalysts most of the desired C–H alkenylation reactions can be achieved at or around room temperature, which is lower than is required for the same type of reactions using rhodium(I). Note that a rhodium(I)-catalyzed variant has not been reported for the reaction of an N-pyrimidylindole (Scheme 7c). This reaction also shows a scope of alkenes complementary to that of a related indole C2-alkenylation using a rhodium(III) catalyst.

3. Cobalt–Catalyzed Directed Hydroarylation of Styrenes

Encouraged by the successful development of directed hydroarylation reactions of alkenes, we moved on to investigate hydroarylation of styrenes. Our attention was initially drawn to the reactivity of styrene. Hydroarylation reactions of styrene via transition metal–mediated C–H activation typically exhibit linear selectivity and give 1,2-diarylethanes, while a few exceptional cases have been reported to show branched selectivity leading to 1,1-diarylethanes. In contrast to related reactions using ruthenium- and rhodium–phosphine catalysts, a cobalt–phosphine catalyst generated from CoBr2, PCy3, and Me3SiCH2MgCl was found to promote the addition of 2-phenylpyridine to styrene in a branched manner with high regioselectivity (Scheme 8). We were further surprised to find that the use of an N–heterocyclic carbene ligand (IMes) and tBuCH2MgBr instead of PCy3, and Me3SiCH2MgCl, respectively, led to a near complete reversal of the regioselectivity. While this regiodivergent hydroarylation was achieved for a reasonable variety of 2-arylpymidines and cobalt catalysts most of the desired C–H alkenylation reactions can be achieved at or around room temperature, which is lower than is required for the same type of reactions using rhodium(I). Note that a rhodium(I)-catalyzed variant has not been reported for the reaction of an N-pyrimidylindole (Scheme 7c). This reaction also shows a scope of alkenes complementary to that of a related indole C2-alkenylation using a rhodium(III) catalyst.

Scheme 7. Directed alkyne hydroarylation reactions using cobalt catalysts.

(a) CoBr2 (5 mol %) P(3-MeC6H4Bu)2 (20 mol %) Ph-MgBr (50 mol %) r.t., THF (15 equiv) H+ 88%

(b) CoBr2 (5 mol %) P(3-C6H4Bu)2 (10 mol %) Ph-MgBr (22.5 mol %) Ph, THF, 40 °C (1.5 equiv) Ph 91%

(c) CoBr2 (5 mol %) pybox (5 mol %) tBuCH2MgBr (60 mol %) Ph, THF, rt (1.2 equiv) pybox 93%

styrenes, in some cases the electronic nature of the substrates overrode the ligand control.

When deuterated 2-phenylpyridine was used as the substrate, extensive H/D scrambling between the ortho positions of 2-phenylpyridine and the α- and β-positions of styrene was observed under both the Co–PCy₃ and the Co–IMes catalytic systems. With the assumption that these catalytic systems share the same catalytic cycle (Scheme 3), we consider that the H/D scrambling results from the reversibility of the C–H oxidative addition and the styrene insertion steps (Scheme 9). The insertion of styrene can take place in either a branched or a linear manner, and these two pathways should be competing with each other. The regioselectivity then is likely determined in the reductive elimination step. The branched selectivity of Co–PCy₃ catalysis may be attributed to stabilization of the branched alkylcobalt species due to η₃-benzyl type coordination, while the sterically less hindered linear alkylcobalt species may be preferred in the presence of the sterically-shielding IMes ligand.

This unique branched-selective styrene hydroarylation was also achieved using aryl aldimines and ketimines as substrates. A catalyst generated from CoBr₂, PPh₃, or P(p-Tol)₃, and Me3SiCH2MgCl promotes the addition of an aryl aldimine to styrene at 40 °C, affording the corresponding 1,1-diarylethane product with high regioselectivity (Scheme 10). The reaction of an ortho-unsubstituted aldimine afforded an ortho-dialkylated product as the major product even when the amount of styrene was limited. This observation may be ascribed to strong coordination of the aldimine moiety to the catalyst. Thus, the catalyst would not dissociate from the substrate after the first alkylation, but rather performs a second C–H activation. By intramolecular dehydrative cyclization using In(OTf)₃ or HCl, the 1,1-diarylethane products could be readily converted to anthracene and related polycyclic aromatic hydrocarbons (Scheme 11).

As was the case for alkyne hydroarylation, a change of the directing group from aldimine to ketimine required reoptimization of the catalytic system. Fortunately, the combination of CoBr₂, P(4-FC₆H₄)₃, and cyclohexylmagnesium bromide allowed efficient addition of an aryl ketimine to styrene with high branched selectivity at room temperature (Scheme 12). The use of other triarylphosphines such as PPh₃, P(p-Tol)₃, and P(4-MeOC₆H₄) instead of P(4-FC₆H₄)₃ did not deteriorate the regioselectivity but did lead to lower yields. This was also the case when other Grignard reagents such as Me₃SiCH₂MgCl and t-BuCH₂MgBr were used instead of CyMgBr.

Attempts to use β-substituted styrenes as substrates for cobalt-catalyzed hydroarylation have met with limited success. Thus, in the presence of a cobalt–NHC catalyst, an imine derived from indole–3-carboxaldehyde underwent addition to β-alkyl, –aryl, and –silyl styrenes to afford the corresponding products.
1,1-diarylated derivatives in moderate to good yields (Scheme 13), while this catalytic system proved ineffective for other aryl aldimines and ketimines. Note that the reaction of a Z-isomer took place more smoothly than that of an E-isomer.

Scheme 13. Addition of 3'-iminoundole derivative to β-substituted styrenes.

Cobalt–catalyzed alkene hydroarylation has also been achieved in an intramolecular manner using an indole substrate bearing an alkene tether and an aldimine directing group on the 1- and 3-positions, respectively (Scheme 15). Interestingly, an N-homoallylindole substrate underwent regiodivergent cyclization using IPr and SIMes ligands, selectively affording tetrahydropyridoindole and dihydropyrrololindole isomers respectively. In addition to this particular example, 5-endo, 6-exo, and 6-exo-type cyclizations were achieved using either of these catalytic systems.

Scheme 15. Intramolecular directed hydroarylation on an indole platform.

As described above, among the aryl imines examined for cobalt–catalyzed hydroarylation, the one prepared from indole 3-carboxaldehyde is reactive enough to undergo addition to β-substituted styrenes (Scheme 13). We found that this imine also reacts with non-conjugated aryl alkenes through a tandem alkene isomerization–hydroarylation process (Scheme 16). Thus, allyl-, homoallyl-, and bishomoallylbenzene participated in the reaction to afford the corresponding 1,1-diarylated products in moderate to good yields, without formation of other possible regioisomers. Deuterium-labeling experiments suggested involvement of the secondary Grignard reagent in the C–H activation—a mechanistic complexity that requires further investigation.

Scheme 16. Tandem alkene isomerization–hydroarylation leading to 1,1-diarylated alkenes.

Concurrently with our studies, other research groups have also reported notable examples of cobalt–catalyzed hydroarylation of alkenes and alkynes. Nakamura and coworkers developed an ortho–alkylation reaction of secondary benzamides with alkenes using a cobalt catalyst generated from Co(acac)$_3$, DMPU, and CyMgCl. We speculate that, like our reactions,
this reaction involves a catalytic cycle consisting of C–H oxidative addition, alkene insertion, and reductive elimination. Matsunaga, Kanai, and coworkers achieved a C4-alkylation reaction of pyridines and quinolines using a cobalt hydride catalyst based on a distinct mechanistic hypothesis. Thus, a mechanism involving hydrometallation of alkene, nucleophilic addition of the resulting alkylcobalt species to pyridine, and catalyst–regenerating recombination has been proposed. The same research group has achieved a redox-neutral C–H alkenylation/annelation reaction of N-carbamoylindoles with alkynes catalyzed by a Co(II) complex.

5. Cobalt–Catalyzed Ortho–Arylation and Alkylation of Arenes with Organic Halides

On the basis of the stoichiometric cycloaddition reaction of the organocobalt complex (Scheme 1c), we could formulate another hypothetical catalytic cycle for directed C–H functionalization (Scheme 17). Chelation-assisted C–H oxidative addition to a low-valent organocobalt species RCoL₃ is followed by reductive elimination of R–H, affording a low-valent cobaltacycle intermediate. This intermediate is then intercepted by an electrophile R’–X to afford an ortho-functionalization product and a cobalt species Co(X)L₃. Subsequent transmetallation with an organometallic reagent R–M regenerates the initial catalytic species.

In line with the above hypothesis, we developed an ortho-arylation reaction of aryl ketimines with aryl chlorides. A catalytic system consisting of CoBr₂, IMes·HCl, and tBuCH₂MgBr promoted the arylation reaction at room temperature and afforded, upon acidic hydrolysis, a biaryl ketone in moderate to good yield (Scheme 18). In some cases, the use of PE₅ instead of the NHC ligand was necessary to achieve the desired reaction. Here, the Grignard reagent serves not only as a reductant to generate an active cobalt catalyst but also formally as a stoichiometric base to remove the ortho-hydrogen atom of the imine substrate. Independently, Song and Ackermann achieved ortho-arylation of 2-arylpiperidines and N-pyridylindoles with aryl sulfonates and carbamates using a catalytic system consisting of Co(acac)₃, IMes·HCl, CyMgBr, and DMPU solvent. Later, they found that the same catalytic system is also effective for ortho-arylation using aryl chlorides.

Generally speaking, the mechanism of transition metal-mediated C(sp³)-halogen bond activation and that of C(sp²)-halogen bond activation can be very different. Nevertheless, the successful development of the ortho-arylation reaction prompted us to investigate ortho-alkylation using alkyl halides. Such a reaction, if achieved with a broad range of primary and secondary alkyl halides, would be attractive because it would complement the scope of directed alkene hydroarylation reactions, which have difficulty in achieving efficient and selective introduction of secondary alkyl groups. At the time we started our investigations, several examples of transition metal-catalyzed ortho-alkylation with alkyl halides had already been developed. However, only a limited number of examples of moderate-yielding secondary alkylations of this type were known. Among these examples was an ortho-alkylation reaction of benzamide derivatives using a catalytic system consisting of Co(acac)₂, DMPU, and CuMgCl. The reaction, developed by Nakamura and coworkers, worked efficiently with primary alkyl chlorides but sluggishly with a secondary one.

Using a catalytic system consisting of CoBr₂, an N,N-diisopropylimidazolium salt, and neopentylimagnesium bromide, ortho-alkylation of aromatic imines with alkyl halides could be achieved efficiently at room temperature (Scheme 19). The reaction is applicable to a broad range of primary and secondary alkyl chlorides and bromides, and it is also notable for its unique chemoselectivity. For example, selective cleavages of alkyl bromide and chloride were achieved in the presence of alkyl chloride and aryl chloride moieties, respectively.

The same cobalt–NHC catalytic system proved effective for the ortho-alkylation of 2-arylpipridines (Scheme 20). In contrast to the case of aryl imines, when the ortho-positions are not hindered, the reaction produced a mixture of monoo- and dialkylation products. The latter product could be obtained in a good yield by using large excess of the Grignard reagent and alkyl halide. This is also in notable contrast with the cobalt–IMes-catalyzed ortho-alkylation reaction of 2-arylpipridines developed by Ackermann and coworkers, which exclusively afforded monooalkylation products.

Mechanistic experiments using radical clocks and stereo-
chemical probes provided insight into the nature of the carbon–halogen bond cleavage step in the alkylation reaction. The reaction of 6-bromo-1-hexene afforded the expected alkylation product (with a small degree of olefin isomerization) along with an ortho-cyclopentylmethylated product, which would have formed through cyclization of a 5-hexenyl radical (Scheme 21a). The ratio of these products turned out to be sensitive to the reaction temperature. The reaction of enantio-enriched 2-bromooctane resulted in a racemic mixture of the alkylation product (Scheme 21b). On the basis of these and other observations, we proposed a catalytic cycle involving a radical species (Scheme 22). Cyclometalation of the imine with an organocobalt species is followed by single-electron transfer from the cobalt center to alkyl halide, which gives rise to the corresponding alkyl radical. Subsequent coupling of the alkyl radical and the cobaltacyclic results in ortho-alkylation. The resulting cobalt halide species is converted to the alkylcobalt species through transmetallation with the Grignard reagent.

Besides the ortho-arylation and alkylation reactions, we have developed ortho C–H functionalization reactions using other electrophiles, that is, addition of 2-arylp yridine to arylamines, self-coupling of aryl aldimines, and ring-opening alkylation of 2-arylp yridines with azidine derivatives. Interestingly, all of these reactions are uniquely promoted by the combination of a cobalt–bulky NHC catalyst and neopentylmagnesium bromide.

Cobalt-catalyzed C–H/electrophile coupling reactions have also been actively developed by other groups. As already mentioned, the Nakamura group achieved ortho-alkylation of benzamides with alkyl chlorides using under mild conditions, and the Ackermann group developed the Co–IMes system that is broadly applicable to arylation and alkylation of 2-arylp yridines and N-arylpyridinolines. An appropriate combination of an organometallic reagent and an oxidant serves as a "formal organic electrophile" for cobalt-catalyzed C–H functionalization. As successful examples of such reactions, Wang, Shi, and coworkers developed ortho-arylation of 2-arylp yridines using the combination of an aryl Grignard reagent and 2,3-dichlorobutane, while Nakamura and coworkers achieved ortho-alkylation of benzamides and 2-arylp yridines using alkyl Grignard reagents under air.
Matsunaga, Kanai, and coworkers demonstrated the utility of high-valent \(\text{Cp}^*\text{Co}(\text{III})\) catalysts for the ortho \(\text{C}-\text{C}\) functionalization using electrophiles such as \(\text{N}-\text{tosylamines,}\ \alpha,\beta-\) unsaturated carboxyl compounds, and tosyl azide.\(^{65}\)

6. Conclusion

As summarized in this account, cobalt catalysts, with appropriate tuning by ligands and reducing agents, allow for a variety of aromatic and vinylc \(\text{C}-\text{C}\) functionalization reactions directed by coordination to an sp\(^2\) nitrogen atom, such as addition reactions of \(\text{C}-\text{H}\) bonds across carbon–carbon multiple bonds of alkenes and coupling reactions between \(\text{C}-\text{H}\) bonds and organic electrophiles. The cobalt catalysts not only serve as cost-effective alternatives to rhodium(I) catalysts in some of these reactions, but also exhibit unique reactivity and selectivity that have not been achieved with noble metal catalysts. For example, cobalt–phosphine catalysts uniquely promote branched–selective addition of aryl imines and 2-arylpiperidines to styrenes to afford 1,1-diarylethanes, which has opened an expedient route to polycyclic aromatic hydrocarbons. The cobalt–NHC–catalyzed ortho-alkylation of aryl imines and 2-arylpiperidines has enabled the hitherto difficult introduction of secondary alkyl groups, presumably through a unique combination of cyclometalation and single–electron transfer processes. Our future work will focus on further expansion of the scope of \(\text{C}-\text{H}\) functionalization through the elaboration of cobalt catalysts. To achieve this goal, it will also be crucial to gain deeper insight into the mechanisms of \(\text{C}-\text{H}\) activation and other key elementary reactions of cobalt complexes.

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PROFILE

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