Cobalt-Catalyzed Cross-Coupling Reactions of Aryl Halides

Corinne Gosmini*[a] and Aurélien Moncomble[a]

Abstract: Cobalt-catalyzed carbon–carbon bond-forming reactions are an indispensable class of reactions in organic synthesis. This economical and ecologically attractive catalyst could replace, in some cases, the well-etablished, expensive palladium and toxic nickel catalytic systems that have dominated the field for many years. Cobalt-catalyzed protocols tolerate various functional groups and present a wide range of reactivity. Moreover, these efficient reactions are very easy to carry out without complex ligands under varied conditions. This review intends to shed light on the fact that cobalt-catalyzed cross-coupling reactions offer an excellent alternative to the usual catalysts. Moreover, these methodologies are sometimes superior, especially for reactions involving alkyl halides.

Keywords: aromatic halide · arylzinc · catalysis · cobalt · cross-coupling

1. Introduction

Transition metal-catalyzed C–C cross-coupling reactions are among the most powerful transformations known to organic chemists, and have received considerable attention over the last decades.[1] For this reason, the development of mild chemo-, regio-, and stereoselective syntheses for the formation of carbon–carbon bonds catalyzed by metal complexes is of great interest. These methods have had a profound impact on the synthesis of natural products, supramolecular complexes, and biologically-active compounds. Classically, most approaches require the use of an organometallic reagent such as organomagnesium, organoboron, organostananes, or organozinc reagents in conjunction with an organic or pseudo halide. The most common implementations of this approach use palladium and nickel complexes, which provide excellent compatibility with many functional groups. However, these common catalysts have some disadvantages, such as the high cost of palladium[2] and the high toxicity of nickel catalysts.[3] The development of broadly applicable, more economical catalysts for cross-coupling is an increasingly important goal in modern synthetic organic chemistry. Fortunately, inexpensive alternative catalysts are available in the form of simple, effective iron and cobalt salts. Although there have been elegant developments in iron-based catalysis,[4] cobalt catalysts can sometimes present a higher reactivity for various carbon–carbon bond-forming reactions. The use of this catalyst for cross-coupling reactions has recently been shown, mainly by Cahiez,[5] Knochel,[6] Oshima,[7] Cheng,[8] and our group;[9] their use for ring formation reactions has also been shown by Vollhardt,[10] Hilt,[11] and Aubert and Malacria.[12]

Cobalt-catalyzed carbon–carbon bond-forming reactions have received particular attention since the pioneering work of Kharasch on the metal-catalyzed homocoupling reaction of aromatic Grignard reagents in the middle of the 20th century.[13]

The generally mild reaction conditions, high functional-group tolerance, and broad availability of cobalt halides contribute to the growing success of this catalyst. The present microreview summarizes our progress over the last few years in cobalt-catalyzed cross-coupling reactions using aryl compounds. In this account, we review our achievements in cobalt-catalyzed reactions involving a functionalized stoichiometric organometallic compound especially an arylzinc species. We also present novel carbon–carbon bond formation reactions mediated by catalytic organocobalt reagents.

2. Cobalt Cross-Coupling Reactions via Arylzinc Species

The first report on cobalt-catalyzed cross-coupling reactions involving an organometallic species described the homocoupling of an aromatic Grignard reagent.[8] Currently, Grignard reagents are still mainly used in cobalt-catalyzed reactions with organic halides.[14] These reactions offer unprecedented coupling potential and show reactivity that is generally unattainable with other catalysts such as palladium, nickel, copper, or even iron. The main

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difficulty with these methods remains the preliminary preparation of the organometallic reagent, especially when reactive functional substituents are present (unless low temperature is required). This drawback can be overcome by synthesizing the corresponding organozinc species directly from organic halides. However, the direct insertion of zinc metal into organic halides requires both the activation of the metallic zinc by various methods and the use of organic halides such as iodides or activated bromides.[15] Over the past decade, electrochemical methods have allowed for the preparation of organozinc halides from functionalized aromatic halides in the presence of simple nickel[16] or cobalt salts.[17] However, electrochemical reactions are generally considered quite exotic and more difficult to handle than conventional methods. The principal reasons for their non-adoption on a larger (industrial) scale are electrode poisoning and the difficulty associated with setting up suitable electrochemical cells. Because these methods are rarely applied by organic chemists on a larger scale, we have recently developed original chemical reactions that allow for the preparation of aromatic zinc species from the corresponding halides or triflates.

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## 2.1. Synthesis of Arylzinc Species Using Cobalt Catalysis

These reactions require commercially available zinc dust and cobalt bromide, along with acetonitrile as solvent in the case of aryl iodides and bromides. The corresponding arylzinc species is converted into an aromatic iodide by addition of iodine and rapidly detected by GC using an internal standard (alkane). This method was applied to various aromatic bromides or iodides bearing electron-donating or -withdrawing groups in the para/meta/ortho positions, leading to good to excellent yields (Equation 1).[18]


$$(1)$$
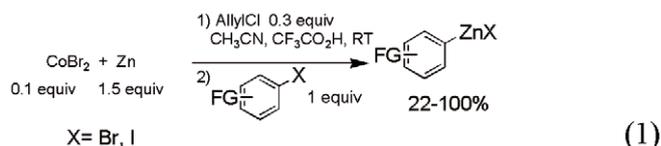
This exact process cannot be employed to activate less reactive compounds such as aromatic chlorides, since the low-valent cobalt (I) generated in situ undergoes fast disproportionation in acetonitrile. In these cases, the cobalt (I) species can be stabilized by the addition of pyridine. Using this approach, it is possible to synthesize organozinc reagents from aryl chlorides bearing an electron-withdrawing group (Equation 2). Under these conditions, the proportion of catalyst needed can be as much as 33 % and reaction times are long.[19]

$$(2)$$
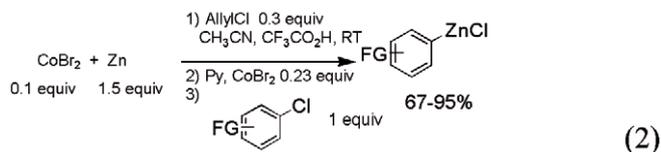
This synthesis process has been improved for aryl chlorides and extended to aryl triflates by replacing $CoBr_2$ with $CoBr_2(Bpy)$ (Equation 3).[20] The bipyridine ligand is essential for the formation of arylzinc reagents from phenol derivatives. This was the first reported synthesis of organozinc triflates.

$$(3)$$
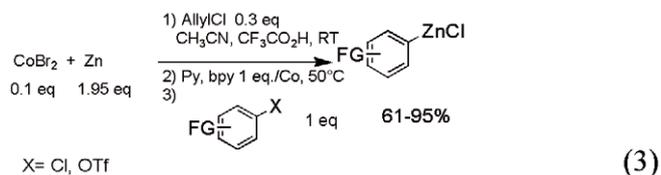
Arylstannanes (Equation 4) and arylboronates (Equation 5) can be obtained from arylbromides via the corresponding arylzinc species by a simple transmetallation

$$ (4) $$
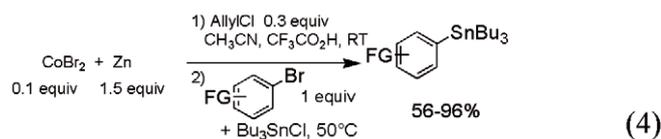
with tributylstannyl chloride[21] and haloboronic ester, respectively.[22]

In general, the direct reaction of organozinc species with carbon electrophiles is low-yielding and inefficient because of the moderate intrinsic reactivity of zinc organometallics. This can be increased by transmetallation with various transition metal salts. The most commonly employed catalysts are Pd, Ni, and Cu. However, in the case of the chemical formation of these arylzinc compounds, which proceeds faster than in the electrochemical preparation, cobalt(I) produced in the medium is found to effectively catalyze some carbon–carbon bond-forming reactions.

2.2. Cobalt-Catalyzed Acylation of Arylzinc Species

Cobalt halides have already been employed as catalysts in the acylation of dialkylzinc reagents to furnish unsymmetrical ketones.[23] From aryl halides, a cobalt-catalyzed two-step cross-coupling reaction was developed between arylzinc species and acyl chlorides.[24] Acylation proceeds in short reaction times and rapidly gives good yields in aromatic ketones (Equation 6).

Unlike the electrochemical approach, the yields are increased in the presence of additional CoBr$_2$, but cobalt is not necessary to obtain the ketone in good yields in the case of chemical preparation of arylzinc species. The proposed mechanism resembles the sequence already postulated for other metals: Co^I formed in the previous step (formation of the arylzinc species) reacts with RCOCl by oxidative addition to provide RCOCo^{III}Cl. Transmetallation between the acyl cobalt complex and the arylzinc reagent, followed by reductive elimination, affords the ex-

pected ketone and regenerates the Co^I species. The high reactivity of acyl chlorides with respect to the cobalt species doesn't allow the one-step sequence and requires a preformed organozinc species. However, the lower reactivity of acid anhydrides allowed the development of a convenient method for the one-step synthesis of unsymmetrical aromatic ketones from aryl bromides (Equation 7).[25] The corresponding ketones are obtained in satisfying yields from the aryl bromide.


$$ (7) $$
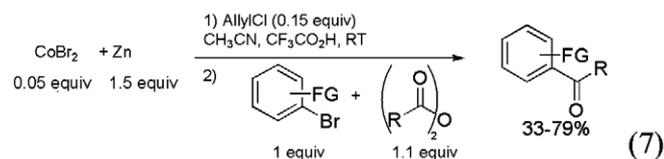
2.3. Cobalt-Catalyzed Formation of Diarylmethanes

Diarylmethanes are ubiquitous structural constituents in pharmacological molecules such as papaverine and beclobrate,[26] and supramolecular structures.[27] Generally, these compounds are obtained via transition metal-catalyzed cross-coupling reactions between aryl halides and benzyl metals.[28] However, the reaction between an arylmetal and a benzyl halide or derivative is reported less frequently.[29] Recently, an efficient cobalt(I)-mediated cross-coupling reaction was reported for the direct synthesis of diarylmethanes using benzyl chlorides and functionalized aromatic halides via an intermediate arylzinc species (Equation 8).[30]

This was the first cobalt-catalyzed reaction that could involve a functionalized arylzinc chloride. Moreover, this versatile process allows for the synthesis of a wide variety of diarylmethanes in a Barbier-fashion for many substrates. Reactions involving more reactive benzylic chlorides substituted in the α-position, or less reactive aryl chlorides, can use a two-step procedure without the need for additional cobalt catalyst. The cobalt salt used for the


$$ (5) $$

$$ (6) $$

$$\text{(8)}$$
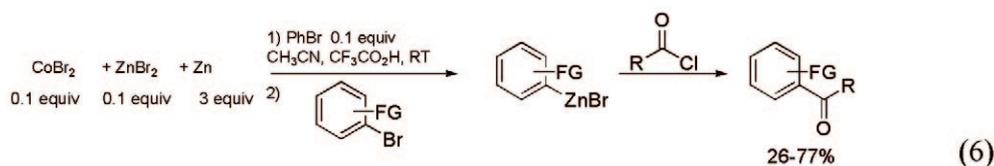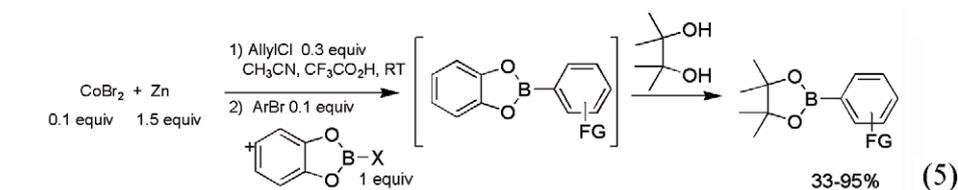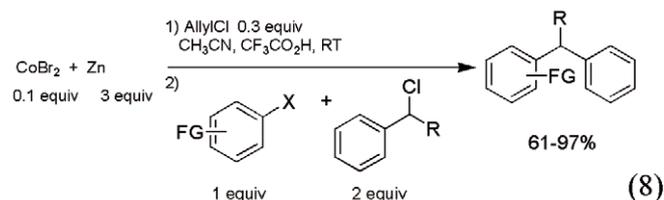
preparation of the arylzinc derivative is also involved in this Negishi-type cross-coupling.

2.4. Cobalt-Catalyzed Formation of Aryldiazines

Aryldiazines, particularly those bearing functional groups, are of interest in the fields of pharmacology, agrochemistry, supramolecular chemistry, and material science.[31] Recently, we have reported an efficient cobalt-mediated cross-coupling reaction for the direct synthesis of 2-aryl-pyrimidines and 2-arylpyridazines from functionalized aromatic halides (Equation 9).[32] Depending on the nature of the aryl halide, this reaction proceeds in one or two steps. With aryl bromides or aryl iodides, the reaction is carried out at 50 °C in the presence of the 2-chloropyrimidines in a Barbier fashion. Because the 2-chloropyrimidine is present from the beginning of the reaction, it can react with the arylzinc derivative as soon as it is formed, which limits the formation of by-products. In the case of compounds less reactive than 2-chloropyrimidines, such as aryl chlorides, the cross-coupling is achieved in a two-step procedure in a mixture of acetonitrile-pyridine at 50 °C. The addition of pyridine allows the stabilization of Co(I) and thus the activation of poorly reactive aryl chlorides.

$$\text{(9)}$$
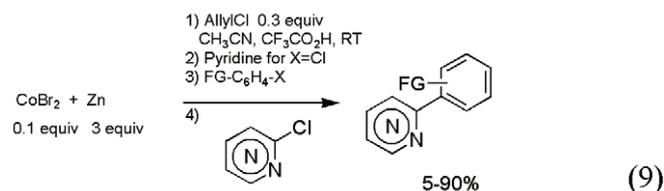
With more reactive 2-chloropyridazines, regarding the oxidative addition of Co(I) into C–Cl bond, the reaction can be carried out in a Barbier fashion with only aryl iodides. Cross-coupling with aryl bromides and chlorides can be conducted in a two-step procedure. In all cases, the corresponding 2-aryldiazines are obtained in satisfactory yields with little dependence on the nature of the halogen. The tolerance of this protocol towards a wide variety of functional groups enables the synthesis of a broad spectrum of compounds. The key step of these procedures is the formation of aromatic organozinc reagents

and their coupling with 2-chlorodiazines using the same cobalt catalyst.

2.5. Cobalt-Catalyzed Arylation or Benzylation of a Halotriazine

1,3,5-triazines constitute the pharmacophore of therapeutic agents used to treat cancer, diabetes, dyslipideamia, microbial infections, or inflammatory diseases.[33] Stemming from the previous results concerning the reactivity of arylzinc species obtained under cobalt catalysis with 2-chlorodiazines, the cross-coupling of various aryl bromides or benzyl chlorides was extended to 2-chloro-4,6-dimethoxy-1,3,5-triazine (Equation 10).[34] Good to excellent yields were obtained with various aryl bromides or benzyl chlorides in a Barbier protocol.

$$\text{(10)}$$
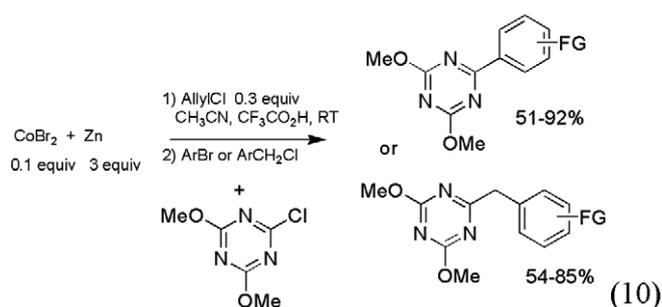
In this cross-coupling, the cobalt catalyst plays an important role in the subsequent cross-coupling reaction with the triazine. This procedure compares favorably and makes an excellent complement to the palladium- or nickel-catalyzed method.

2.6. Cobalt-Catalyzed Allylation of Aryl Bromides

Knochel has previously reported that allyl chlorides or phosphates react with dialkylzincs in the presence of catalytic amounts of CoBr2 by a simple SN2 cross-coupling with full retention at the double bond.[1] The extension of this strategy to diarylzinc reagents was described more recently.[35] These diarylzinc species are obtained from the corresponding aryl iodides via a direct iodine–zinc exchange. Other highly functionalized aryl bromides react with allylic acetate catalyzed by CoBr2 in the presence of zinc dust in acetonitrile (Equation 11).[36]

The procedure is similar to that previously described for the formation of arylzinc species; in this case, the al-

$$\text{(11)}$$
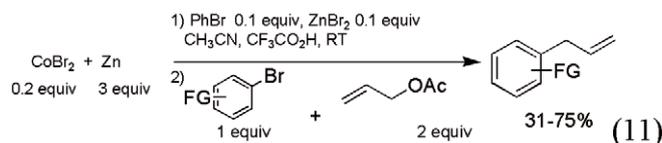
lylic acetate, which is already present in the medium, reacts directly by cobalt-mediated substitution with the arylzinc compound. The corresponding arylallyl is obtained in good yields, with aryl bromides bearing an electron-donating or -withdrawing group at any position. However, yields decrease with substituents on the allyl acetate double bond; furthermore, aryl chlorides do not form the arylzinc species, which prevents cross-coupling from occurring.

In summary, although cobalt-catalyzed carbon–carbon bond formation with organometallic reagents was principally studied with Grignard reagents by several teams, the soft organozinc species generated from aryl bromides or even chlorides are suitable for cross-coupling reactions using cobalt salts instead of the more common palladium or nickel catalysts. The mild conditions and the wide range of functionalized groups such as ester, ketone, or nitrile moieties, both on the organozinc and on the substrate, enable the synthesis of a broad spectrum of valuable compounds. These catalytic reactions involve a simple, inexpensive, and environment-friendly cobalt halide salt without ancillary ligands and compare favorably with procedures involving organozinc species that use other metals catalysts.

3. Cobalt Cross-Coupling Reactions via a Functionalized Catalytic Organocobalt

As described above, the general method for the formation of a carbon–carbon bond involves the coupling of an organometallic reagent. However, the preliminary preparation of organometallic reagents can be challenging, especially when the desired aromatic possesses a reactive moiety. Consequently, chemical and electrochemical processes have been developed that avoid the organometallic formation step by directly activating the organic halide instead. Studies within the realm of cobalt catalysis have provided several direct routes to carbon–carbon bond-formation that maintain the integrity of sensitive functional groups.

3.1. Cobalt-Catalyzed Vinylation of Functionalized Aryl Halides with Vinyl Acetates

Vinylation of aryl halides is a convenient route for synthesis of styrene derivatives. Conventionally, styrenes are synthesized by the Heck reaction or classical palladium-catalyzed cross-coupling of vinylic or aryl organometallic regents with respectively aryl or vinylic halides.[37] Vinylic acetates are unresponsive compared to their counterpart halogenated compounds, and they thus are used infrequently in cross-coupling reactions. A few years ago, we developed a cobalt-catalyzed electrochemical vinylation with vinyl acetates and various functionalized aromatic or heteroaromatic chlorides and bromides (Equation 12).[38]

$$\text{(12)}$$
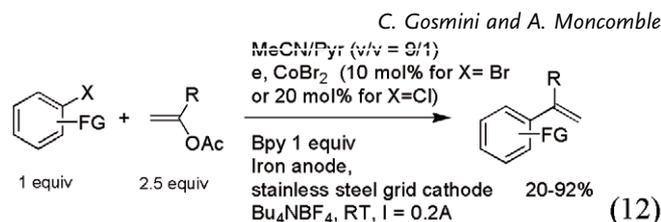
This efficient carbon–carbon bond synthesis successfully leads to α-substituted styrene derivatives in the presence of stoichiometric amount of 2,2′-bipyridine.

This simple procedure appears more efficient than similar reaction involving palladium complexes since aryl bromides and chlorides do not bring difficulties in the cross-coupling. A purely chemical procedure has been derived from this electrochemical approach with some important modifications. In this case, low valent cobalt is generated by manganese reduction of cobalt bromide in the presence of catalytic amount of 2,2′-bipyridine in DMF/pyridine at 50°C instead of CH_3CN/Pyridine at room temperature (Equation 13).[39]

$$\text{(13)}$$
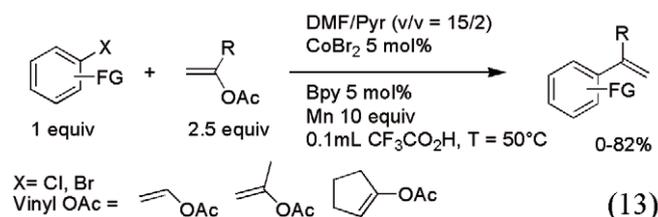
In the electrochemical and chemical procedure, bipyridine is essential for the cross-coupling, and pyridine provides a rate acceleration. From a mechanistic point of view, Co(II) associated to bipyridine is reduced either in vinyl acetate-stabilized Co(I) or Co(0), which is probably further solvated by coordination to vinyl acetate. The resulting low-valent cobalt complex most likely reacts with ArX by oxidative addition to form an ArCo species. This last species could undergo a substitution reaction with the carbon attached to the ester group. This suggests the involvement of a six-centered transition state wherein the aryl group is well oriented for addition to the more substituted carbon atom of the double bond. After release of the styrene derivative, re-reduction of the cobalt by excess manganese regenerates the Co(I) or Co(0) catalyst.

3.2. Cobalt-Catalyzed Formation of Biaryls

The biaryl motif plays a considerable role in various areas ranging from supramolecular chemistry to natural product synthesis.[40] Two classes of reactions that allow access to the biaryl motif are homo- and cross-coupling. In most cases, such reactions involve a stoichiometric quantity of an organometallic reagent and are catalyzed

by palladium or nickel complexes. Symmetrical biaryls can be obtained by oxidative homocouplin, and unsymmetrical biaryls are formed by coupling with an aryl halide or pseudo-halide. Several direct aryl–aryl bond-forming transformations are known, including the palladium-based reductive coupling of two different or identical aryl halides.[41]

We have developed a convenient, cobalt-catalyzed synthesis of various 4-phenyl-quinolines from functionalized phenyl halides and 4-chloroquinoline (Equation 14).[42] The corresponding products are obtained in satisfactory to high yields using a particularly simple electrochemical procedure.

For the efficiency of this electrochemical process, the choice of an iron rod as the anode and the presence of pyridine are of crucial importance. The process has been extended to forming unsymmetrical biaryls from two different aryl halides in the presence of cobalt chloride.[43] The coupling reaction is compatible with various electron-donating or -withdrawing substituents and is also efficient with an ortho substituent on the aromatic halides.


$$(14)$$
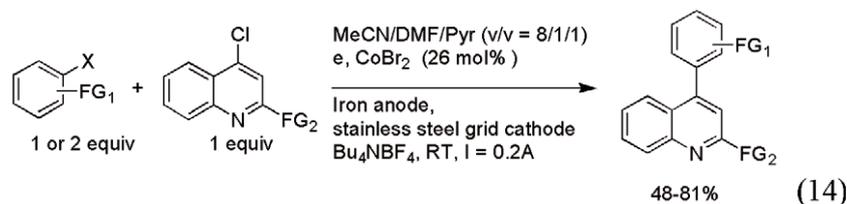
Therefore, the isolated yields are good to excellent. In these electrochemical reactions, the cobalt chloride concentration plays a major role and is relatively elevated (30% with respect to the less reactive reagent). Unlike the palladium process, in this case, the more reactive aromatic halide is in excess.

More recently, we have reported a purely chemical cobalt-catalyzed formation of unsymmetrical biaryl compounds which provides an efficient alternative to electrochemical methods. In line with our previous experiences, we found that the low valent cobalt species generated from the reduction of $CoBr_2$ associated with a ligand can activate aryl or heteroaryl halides or triflates to provide unsymmetrical biaryl compounds (Equation 15).[44] In this case, the cobalt system ($CoBr_2$,PPh_3) is reduced by manganese dust in a mixture of DMF-.

This novel method generally gives the expected cross-coupling product in good yield with good selectivity when the reactivities of the two substrates are similar. An array of aryl halides and aryl triflates bearing electron-donating or -withdrawing group underwent the desired reaction. These results prompted us to attempt the synthesis of 2-(4-tolyl)benzonitrile, a key intermediate in the synthesis of Sartan derivatives. Motivated by this success, we expanded the use of this catalytic system to the direct ho-


$$(15)$$

mocoupling of functionalized aryl halides (Equation 16).[45]

$$(16)$$
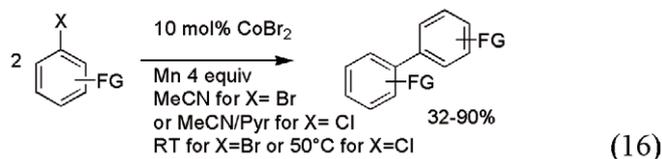
In this homocoupling reaction, cobalt halide is used in combination with manganese dust as reducing agent in acetonitrile. As previously reported, the presence of allyl-chloride at the beginning of the reaction proved to be beneficial since it considerably reduced the amount of reduction compounds of ArX without modifying the kinetics of the reaction. This coupling process was also successfully extended to less reactive aryl chlorides by changing experimental conditions. The reaction was conducted at 50°C and addition of pyridine was required. In this reaction, a ligand was not necessary, but addition of the 1,4-bis-(*m*-xylyl)-1,3-diazadiene proved to be beneficial in terms of reaction rates. Shorter reaction times were obtained when 1,4-bis-(*m*-xylyl)-1,3-diazadiene was used, whatever the nature of the substituent. This procedure enables the synthesis of a broad spectrum of valuable compounds bearing a wide variety of functional groups in satisfactory to high yields under simple and mild conditions.

3.3 Cobalt-Catalyzed Alkylation of Aryl Halides

The incorporation of a new alkyl chain on an aromatic moiety often proceeds by the metal-catalyzed coupling of stoichiometric organometallic derivatives using a large variety of transition metals (Pd, Ni, Fe, Co, Cu, Rh, Mn, V, or Ag).[46] However, it is intriguing to consider a direct approach for cross-coupling which avoids the utilization of preformed organometallic reagents. We have reported a versatile method for the direct, functional-group-tolerant alkylation of aryl halides employing simple catalytic systems of $CoBr_2$/ligand/Mn (Equation 17).[47] $CoBr_2$/iPr_2PhP/Mn has been shown to catalyze efficiently the direct Csp^2–Csp^3 coupling of various aryl bromides and even chlorides with relatively unreactive alkyl bromides bearing a β-hydrogen atom under mild conditions. A wide

$$\text{(17)} \quad 56\text{-}94\%$$
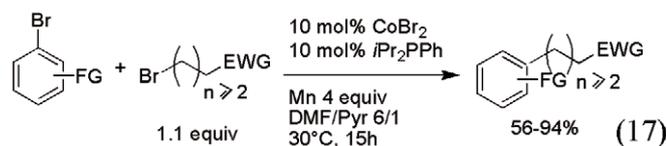
range of functionalized substrates containing ester, nitrile, or ketone moieties, as well as primary or secondary alkyl bromides, were coupled in high yields.

This method is not limited to electron-rich substrates. In the case of more reactive alkyl halides such as benzyl chlorides and ethyl 3-bromopropionate, a different choice of ligand such as 4,4′-dimethyl-2,2′-bipyridine facilitated comparably successful results (Equation 18).

$$\text{(18)} \quad 38\text{-}76\%$$
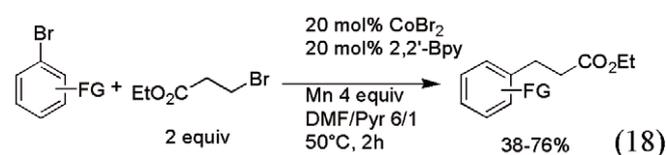
Our current mechanistic hypothesis closely resembles our results describing the synthesis of biaryl compounds using cobalt complexes (Scheme 1).

The key alkyl–aryl cobalt complex formed upon a second, selective oxidative addition into the $C(sp^3)$-Br bond, is believed to display sufficient stability towards unproductive β-hydride elimination. The cross-coupling product obtained by reductive elimination furnishes the regeneration of the catalytic active species.
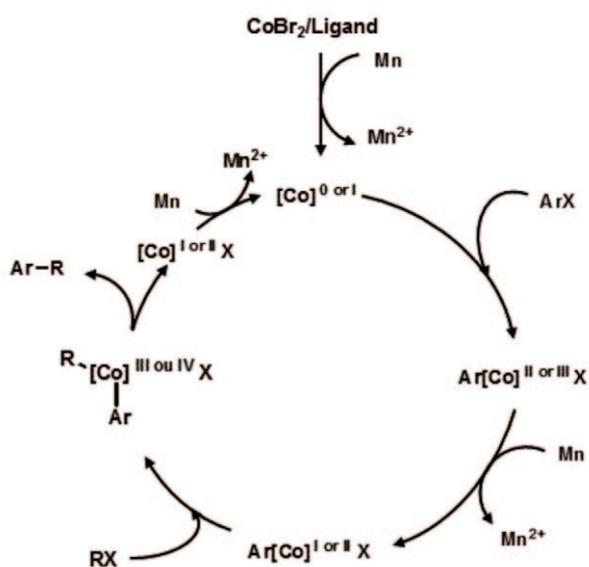
Scheme 1.

3.4. Cobalt-Catalyzed Conjugate Addition of Aryl Compounds to Activated Olefins

The catalytic conjugate addition of carbon nucleophiles to electron-deficient olefins is a an attractive and widely-used tool for C–C bond formation that regularly uses transition-metal catalysts.[48] However, these methods often use air- or moisture-sensitive organometallic species with limited functional group tolerance. To address this shortcoming, we have reported electrochemical and chemical cobalt-catalyzed procedures for the Michael addition onto α,β-unsaturated esters, nitriles, and ketones of various functionalized aryl halides that avoid the formation of such sensitive species. The electrochemical method is only efficient for the arylation of methyl vinyl ketone by aryl bromides bearing electron-withdrawing groups.[49] The chemical procedure catalyzes the addition of aryl bromides, chlorides, and triflates bearing electron-donating or -withdrawing groups onto α,β-unsaturated esters and nitriles.[50] This reaction employs $CoBr_2(2,2'\text{-bi-pyridine})$ as the catalyst and manganese as a stoichiometric reducing agent in a DMF solvent system. The reaction can be accelerated by adding a pyridine cosolvent and heating the medium; yields can be improved by adding LiBr and H_2O. Following this protocol, addition to acrylic ester or nitriles derivatives led to high yields, while additions to α,β-enones afforded the respective 1,4-adducts in much lower yields. Under these conditions, the low-valent cobalt catalyst is not sufficiently reactive since MVK might act as a reasonably strong chelating ligand for cobalt. We have also reported a refined procedure suitable for the direct conjugate addition of aromatic halides or triflates onto methyl vinyl ketone as a representative α,β-enones (Equation 19).[51] More specifically: $CoBr_2$-(Bpy), MVK and H_2O (0.5 equiv) are slowly added to medium containing all reagents at 80 °C, which leads to the corresponding Michael adduct in good yield. The presence of water prevents the formation of an arylzinc intermediate as a productive reaction pathway.

This method represents an interesting alternative to more traditional methods that rely on preformed organometallic coupling reagents.

$$\text{(19)} \quad 45\text{-}83\%$$

4. Summary and Outlook

We have presented various efficient cross-coupling reactions catalyzed by $CoBr_2$. This simple, inexpensive, and

environmentally-friendly cobalt halide salt can be used with or without ligands to synthesize a broad spectrum of valuable compounds. These reactions have the advantage of using commercially available compounds under mild conditions and give the desired products in satisfactory to high yields. These reactions couple a wide range of substrates containing ester, ketone, or nitrile moieties with stoichiometric arylzinc compounds in a Barbier fashion or with catalytic arylcobalt species in the presence of a reductant in high yield. We have demonstrated that the cobalt-based catalytic system compares favorably to, and is complementary to, expensive palladium or toxic nickel-catalyzed methods. Moving forward, we hope to expand the scope of compatible substrates and elucidate the crucial role of zinc or manganese in these reactions.

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