Cobalt-catalyzed cross-coupling reactions

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Received (in Cambridge, UK) 28th March 2008, Accepted 25th April 2008
First published as an Advance Article on the web 11th June 2008
DOI: 10.1039/b805142a

In the last few years, we and other groups have demonstrated that economical cobalt salts can advantageously replace expensive and toxic catalysts for cross coupling reactions. These cobalt-catalyzed reactions have considerably extended the range of functionalized compounds. A variety of sensitive functional groups can be tolerated in these coupling reactions and various organic compounds RX could be involved (R = alkyl, alkynyl, aryl, allyl and X = halides: F, Cl, Br, I and even triflates). Here, we describe our contributions in this area for the preparation of a broad range of functionalized compounds from organometallic species or by direct cross-coupling.

1. Introduction

Over the past 30 years, the development of transition metal-catalyzed cross-coupling reactions has revolutionised techniques for the formation of carbon–carbon bonds, especially those involving C(sp^2) centers where typical S_N2 substitutions cannot operate.[1] The cross-coupling reaction class is among the most important in organic synthesis; its methods have profoundly changed the protocols for the construction of natural products, building blocks for supramolecular chemistry and self-assembly, organic materials and lead compounds in medicinal chemistry from simpler entities. The development of efficient new carbon–carbon bond forming reactions by metal-catalyzed cross-coupling is still progressing impressively and significant advances have been achieved. Among the different catalysts, the most commonly employed and reliable metal is palladium, especially when appropriate ligands are present. Although nickel complexes have less general scope, they also have found applications in highly efficient cross-couplings of organometallics with aryl halides. However, both these catalyst systems have disadvantages—the high cost of palladium and the high toxicity of nickel catalysts are two of the more obvious ones—and their use in industrial applications is coming under increasing scrutiny.

Fortunately, inexpensive alternative catalysts are available in the form of simple, effective iron and cobalt salts. These green reactions offer new means for carrying out cross-coupling reactions both economically and ecologically.

All these catalysts have wide scope and excellent tolerance of various functional groups. There has been much elegant work in iron-based catalysis,[2] however cobalt catalysts can sometimes present a higher reactivity for various C–C bond-forming reactions. Moreover, the low cost of cobalt complexes and their interesting mode of action make them an attractive alternative for use in cross-coupling. Such reactions, which have been reported both by us and other groups, are therefore complementary to the recently reported iron-catalyzed processes. In most cross coupling protocols, a major difficulty lies in the preparation of the organometallic reagent, especially when the organic compound bears a reactive group. Reactions using haloarenes as feedstuffs, and therefore eliminate the need to prepare stoichiometric organometallic precursors, have been an area of important recent interest; again, they generally use Pd or Ni catalysts. In recent years, we have been interested in novel carbon–carbon bond formation reactions mediated by catalytic organometallic reagents in the presence of a cobalt halide as the metal source. In this account, we review our recent achievements in cobalt-catalyzed reactions but also include other research closely related in this area.

2. Cobalt cross-coupling reactions *via* functionalized organometallic compounds

2.1 Organomagnesium compounds

Organomagnesium halides are amongst the most classical organometallic reagents and were the first class to become

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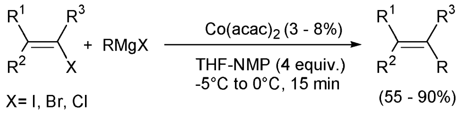
generally useful in synthetic organic chemistry.[3] The reactivity of Grignard reagents alone is quite extensive but their range of applications can be extended significantly if they are used in conjunction with a catalyst. Introducing transition metal salts has greatly expanded the reactivity of Grignard reagents. As with iron,[4] the ability of cobalt salts to catalyze cross-coupling of organic halides with Grignard reagents was recognized quite early; more than half a century ago, Kharasch and Fields[5] investigated the effect of transition metals such as cobalt in reactions between organic halides and Grignard reagents. Because the cross-coupling product was produced though the coupling of two radicals, the reaction was virtually uncontrollable: a mixture of homocoupling, disproportionation and cross-coupling products was obtained. Few advances in cobalt-catalyzed cross-couplings were made until the late 1990s when Cahiez and Avedissian[6] described the stereoselective and chemoselective reaction of vinyl halide with an organomagnesium reagent in the presence of a catalytic amount of $Co(acac)_2$ in a 1 : 1 mixture of NMP–THF (Scheme 1). This provided di- and tri-substituted olefins.

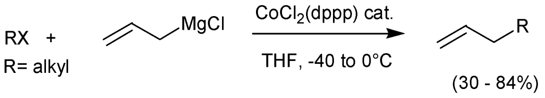


Scheme 1 Cobalt-catalyzed alkenylation of organomagnesium reagents.

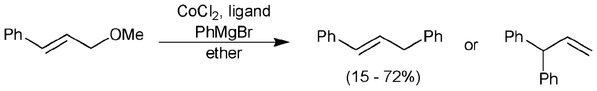
The mechanism of this coupling, which was investigated by Holzer and Hoffman,[7] seems to involve a single-electron transfer mechanism that occurs after oxidative addition of the vinyl halide to the cobalt complex.

More recently, Oshima and co-workers carried out cobalt-catalyzed cross-coupling reactions of alkyl halides with allylic Grignard reagents.[8] Most of these reactions offer unprecedented coupling potential and show reactivity that is generally unattainable with palladium, nickel, copper or even iron catalysts. Such alkyl halide couplings are generally difficult relative to aryl or vinyl halides for two reasons: the reluctance of alkyl halides to undergo the oxidative addition step and the problematic β-hydride elimination from alkylpalladium and –nickel. However, Oshima and co-workers have recently overcome this difficulty using a $CoCl_2(dppp)$ catalyst. This effects the cross-coupling reaction of primary, secondary and tertiary alkyl halides with allylic Grignard reagents (Scheme 2).

The reaction is thought to proceed by transmetalation of the allyl Grignard reagent to cobalt, followed by oxidative addition of the alkyl halide through a pathway involving a single electron transfer from the allylcobalt species to the alkyl halide. This team also described cobalt-catalyzed cross-coupling reactions between allylic ethers or halides and organomagnesium reagents.[9] In the reaction of cinnamyl methyl ether, the formation of the linear product predominates over that of the isomeric branched product (Scheme 3). This regioselectivity can be inverted by the addition of a diphosphine ligand.



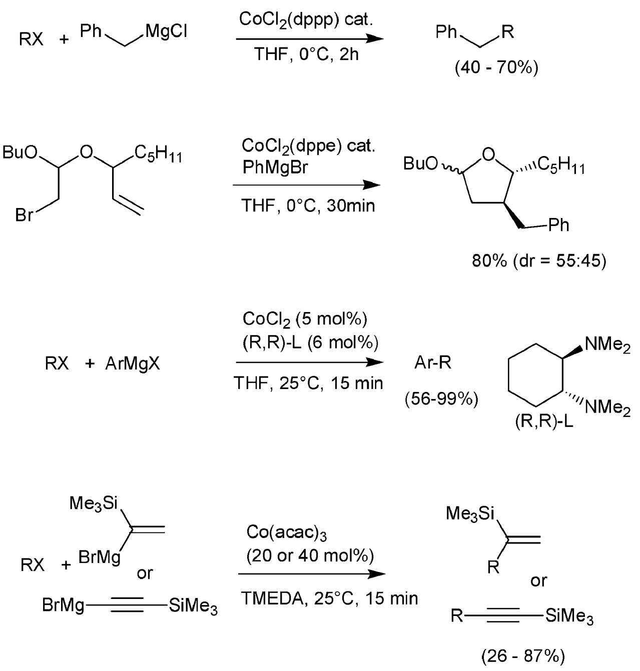
Scheme 2 Cobalt-catalyzed allylation of alkyl halides.



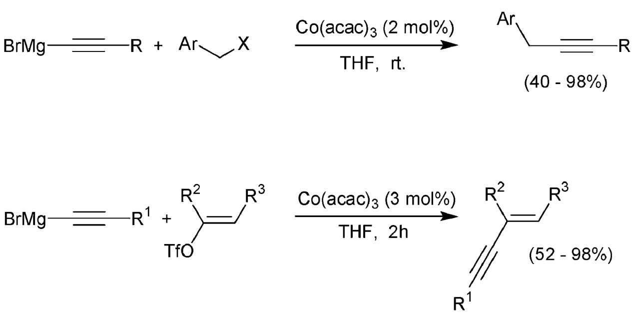
Scheme 3 Cobalt-catalyzed reaction of cinnamyl methyl ether with phenylmagnesium bromide.

It has also been reported that alkyl and benzyl halides, or alkenyl triflates can undergo cross coupling with benzyl[8c,10] aryl,[11] heteroaryl,[12] vinyl[13] or propargyl[13,14] Grignard reagents (Scheme 4 and Scheme 5).

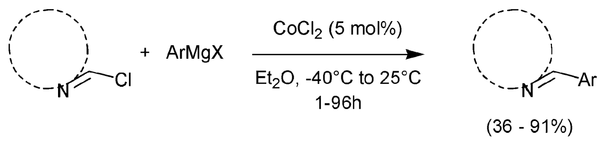
Knochel and co-workers have reported the cross-coupling of aryl Grignard reagents with a variety of heterocyclic chlorides in the presence of catalytic (5 mol%) amounts of $Co(acac)_2$ or $CoCl_2$.[12,15] The best yields were obtained using $CoCl_2$ in diethyl ether (Scheme 6). With 2-chloropyrimidine, the cobalt cross-coupling leads to low yields (28–42%). Catalytic quantities of cobalt powder efficiently replace Co^{II}.



Scheme 4 Cobalt-catalyzed cross-coupling of benzyl, aryl, vinyl or alkynyl Grignard reagents with alkyl halides.

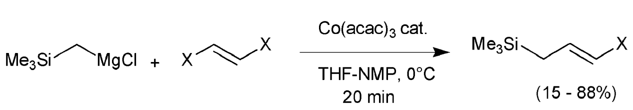


Scheme 5 Cobalt-catalyzed cross-coupling of alkynyl Grignard reagents with benzyl halides or alkenyl triflates.



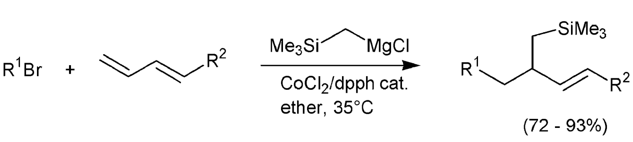
Scheme 6 Co^{II}-catalyzed cross-coupling between heterocyclic chlorides and aryl- or heteroarylmagnesium compounds.

The reaction of trimethylsilylmethylmagnesium chloride with 1,2-dihalogenoethylenes in the presence of 1 mol% of Co^{II} or Co^{III} acetylacetonate[16] in THF or THF-NMP proceeded exclusively in a mono-coupling pathway to provide high yields of 3-trimethylsilyl-1-halogeno-1-propenes with >99% selection for the *E* geometry. This last product allows access to γ-substituted (*E*) allylsilanes (Scheme 7).



Scheme 7 Cobalt-catalyzed mono-coupling of $R_3SiMgCl$ with 1,2-dihaloethylene.

Homoallylsilanes can also be prepared from trimethylsilylmethylmagnesium chloride, 1,3-dienes and alkyl halides under cobalt catalysis. The combination of $CoCl_2$ and 1,6-bis(diphenylphosphino)hexane catalyzes this reaction in good to excellent yields, through a mechanism which involves an alkylhalide derived radical species (Scheme 8).[17]



Scheme 8 Three-component coupling reaction of trimethylsilylmethylmagnesium chloride, 1,3-dienes and alkyl halides.

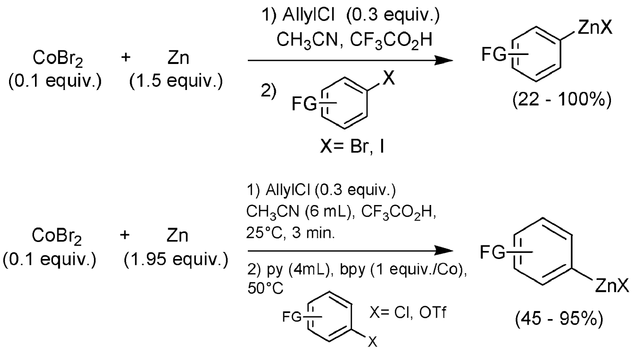
To summarize, cobalt efficiently mediates cross-coupling reactions of various Grignard reagents with different organic halides.

2.2 Organozinc compounds

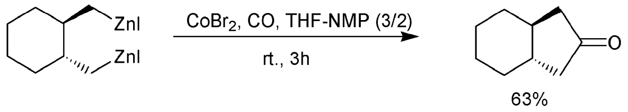
Organozincs[18] have been known, since the preparation of diethylzinc by Frankland in 1849. However, organometallics were rarely used to form new carbon–carbon bonds until Grignard discovered a convenient preparation of the more reactive organomagnesium compounds. The significance of the wide functional group tolerance of organozinc species has been widely recognised recently and the usefulness of these rather unreactive organometallics can be increased by transmetalation; the presence of empty low-lying p-orbitals on the anion, which interact with d-orbitals at the transition metal center generates highly reactive intermediates. This means that organozincs are very valuable reagents. A number of methods are available for their preparation. The direct insertion of zinc metal into organic halides requires both the activation of the metallic zinc by various methods and the use of reactive organic halides such as iodides or activated bromides. The alternative transmetalation of organolithium or organomagnesium compounds with zinc salts is much less attractive, in that the tolerance of reactive functional groups in the precursor is usually lost when Li or Mg based-intermediates are used inasmuch as low temperature is required. Over the past decade, a new method using electrochemical techniques has allowed the preparation of organozinc halides from (especially) aromatic halides in the presence of nickel complexes[19] or simple cobalt salts[20] and it has been shown that these mixtures are useful in homogeneous catalysis. However, electrochemical reactions are generally considered as being quite exotic and more difficult to handle than conventional methods and electrochemical syntheses are rarely applied by organic chemists. The principal reasons for their non-adoption in larger (industrial) scale appear to be: the tendency of electrogenerated Co^I complexes to undergo disproportionation, the unsettled state of α-arylnickel and α-arylcobalt complexes, difficulties arising from electrode poisoning, and the setting up of suitable electrochemical cells. We have therefore developed a related, original, chemical reaction allowing the preparation of aromatic zinc species from the corresponding halides (X = I, Br, Cl) or triflates[21] using a simple cobalt salt and zinc dust activated by traces of acid. These aryl species can be substituted by either electron-donating (X = Br, I) or—withdrawing groups with the nature or position of the substituent having a relatively small influence on the yield (Scheme 9).

In general, direct reaction of organozincs 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. Because of their lower reactivity, organozinc reagents do not tend to produce transition metal ate-complexes (R_nMet^-), and this means that the resulting transition-metal complexes $RMetX_n$ have quite high thermal stability. Thus, the reaction of cobalt(II) bromide with dialkyzincs in THF–NMP furnishes blue solutions of organocobalt intermediates. Rewardingly, these new organocobalt(II) species undergo carbonylations at room temperature under mild conditions to afford symmetrical ketones in satisfactory yield.[22] A catalytic amount of cobalt(II) salt is sufficient to promote the acylation of diorganozincs (Scheme 10).

Dialkylzincs also acylate acid chlorides in the presence of $CoBr_2$ (10 mol%) very rapidly in NMP-THF mixtures at 0 °C

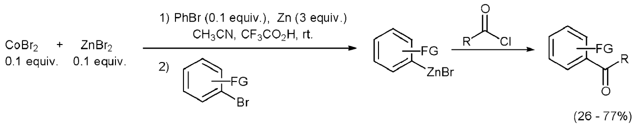


Scheme 9 Synthesis of arylzinc species using cobalt catalysis from aryl compounds.



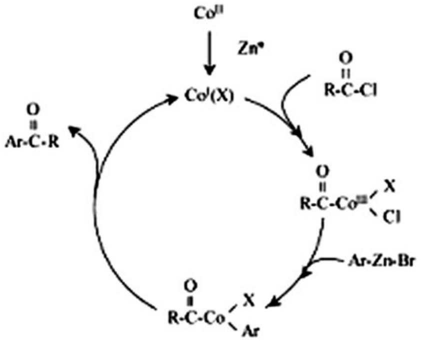
Scheme 10 Carbonylation of diorganozinc species using cobalt catalysis.

to furnish unsymmetrical ketones.[23] We have recently developed a cobalt-catalyzed two-component cross-coupling between arylzinc compounds and acyl chlorides[24] in acetonitrile, which gives aromatic ketones (Scheme 11). The classical protocols for preparing ketones from chemically generated organozincs, which generally involve a transmetalation copper cyanide and subsequent reaction with an acid chloride, fail with electrogenerated organozincs under our conditions. However, they proved to be good sources of the desired ketones under analogous conditions when cobalt salts ($CoBr_2$ 0.1 equiv.) were used. Reaction with the acid chloride then occurs rapidly and gives good yields of aromatic ketones. Although the yields were increased in the presence of 0.1 equiv. $CoBr_2$, additional cobalt is not necessary to obtain the ketone in good yields when aryl zinc species are prepared by the chemical process on the contrary to the acylation of aryl zinc species formed by our electrochemical method using cobalt catalysis. It seems likely that electrogenerated Co^I disproportionates rapidly into solid cobalt, despite the presence of zinc bromide.



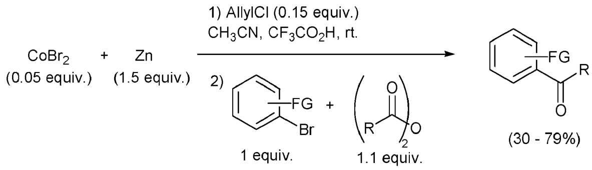
Scheme 11 Synthesis of functionalized arylzinc reagents and their consecutive reaction with acid chlorides.

The proposed mechanism resembles the sequence already postulated for other metals: after the preparation of the oxidative addition of RCOCl to a Co^I complex formed in the previous step (formation of the arylzinc species) provides $RCOCo^{III}Cl$. Transmetalation between this acyl cobalt complex and the arylzinc reagent, followed by reductive elimination, affords the expected ketone and regenerates the Co^I species (Scheme 12).



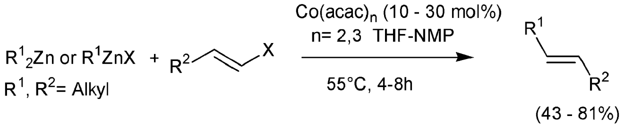
Scheme 12 Proposed mechanism for the acylation of aryl zinc species with acyl chlorides using a cobalt catalysis.

The method could not be used for the coupling of acyl chlorides to aryl bromides in a one-step sequence without using a preformed organozinc species, because of the high reactivity of the acyl chloride with respect to the cobalt species. 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.[25] Here, the ketones are obtained in satisfying yields (30–79%) with respect to the aryl bromide (Scheme 13).



Scheme 13 One-step synthesis of aromatic ketones from functionalized aryl bromides and acid anhydrides.

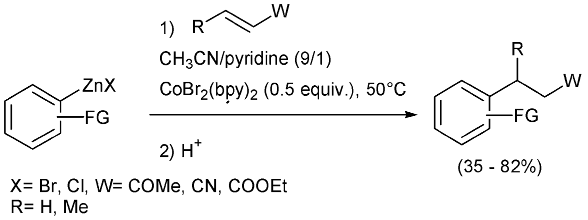
Other cobalt promoted cross-coupling reactions of alkylzinc halides RZnX or dialkylzincs R_2Zn with alkenyl halides have been shown to give alkenes in good yields with retention of double bond configuration (Scheme 14).[26]



Scheme 14 Cobalt-catalyzed alkenylation of zinc organometallics.

Organozinc halides or dialkylzincs compounds can be coupled with alkenyl iodide but the more reactive, and less accessible, dialkylzincs are required for bromoalkenes.

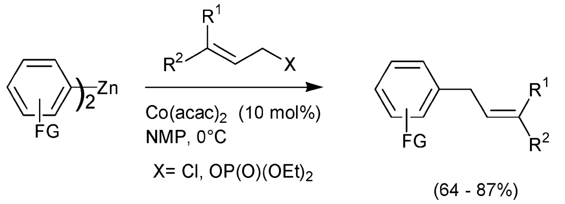
We have also shown that $CoBr_2(bpy)_2$ is a very efficient catalyst for the conjugated addition of electrochemically generated arylzinc compounds (prepared in an acetonitrile–pyridine mixture) to activated olefins (Scheme 15).[27]



Scheme 15 Cobalt-catalyzed cross-coupling between aryl zinc species and activated olefins.

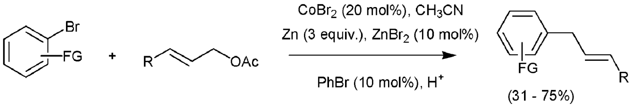
The concentration of cobalt complex in the cross-coupling step influences the reaction rate but not the yield. With 0.3 equivalent of cobalt catalyst *vs.* aryl halide, the aryl zinc compound is consumed after 24 h; this can be compared with 10 h when 1 equivalent was used. However, excess activated olefin is required to maintain acceptable yields of conjugate addition product (40–80%). Satisfactory yields are also obtained under the conditions above when substituents such as a methyl groups are present at the double bond of the electrophile. The role of $CoBr_2(Bpy)_2$, which is essential, has not yet been clarified.

Allyl chlorides or -phosphates react with alkylzinc halides or dialkylzincs in the presence of catalytic amounts of $CoBr_2$.[23] These reactions lead to the simple S_N2-cross-coupling product with full stereochemical retention at the double bonds. Recently, Dunet and Knochel have extended this method using highly functionalized diarylzinc reagents; these were obtained from the corresponding aryl iodides *via* a direct iodine zinc exchange (Scheme 16).[28]



Scheme 16 Cobalt-catalyzed allylation of diarylzinc reagents with allyl chloride.

As noted above, functionalities on aryl nucleus such as esters, ketones, or nitriles are well tolerated, which makes this cross-coupling particularly attractive for the synthesis of polyfunctional target molecules. We have shown that other highly functionalized aryl bromides react, under $CoBr_2$ catalysis, with allylic acetates in the presence of zinc dust in pure acetonitrile.[29] The procedure is the same as described before for the formation of the aryl zinc species except that the allylic acetate, which is present in the medium, reacts directly by cobalt-mediated substitution with the arylzinc compound (Scheme 17).

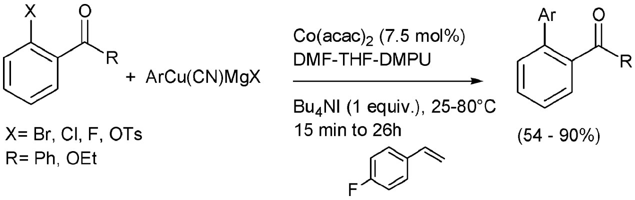


Scheme 17 Cobalt-catalyzed allylation of arylzinc reagents with allyl acetate.

Good yields are obtained with aryl bromides having an electron-withdrawing or -donating group in the *para*, *meta* or *ortho* position. However, the yield decreases with substitution at the allyl acetate on the double bond. With aryl chlorides, no arylzinc species is observed and no cross-coupling occurs. From a mechanistic point of view, we have shown that Co^I undergoes fast complexation with allylic acetate to form an (η^2-allylOAc)-cobalt(I) complex and the arylallyl compound is released upon its S_N2 reaction with the arylzinc species.[30]

2.3 Organocopper compounds

The functional-group compatibility of organocopper reagents with esters, ketones and even aldehydes makes these reagents particularly attractive for multistep synthesis;[31] they should permit complex chemistry to be carried out without the extensive use of protecting groups even when these are required by the corresponding organozincs. Moreover, these organocoppers can be more reactive than the corresponding arylzincs. For instance, no iron-catalyzed cross-coupling reaction of arylzinc reagents with aryl halides has been observed but functionalized aryl copper reagents, prepared by the reaction of the corresponding aryl Grignard with CuCN·2LiCl in DME-THF at 80 °C, smoothly undergo cross-coupling with aryl iodides in the presence of $Fe(acac)_3$ as the catalyst.[32] To extend the scope of organocoppers in cross-coupling reactions, Knochel and co-workers examined different cobalt salts as catalyst. Using $Co(acac)_2$, they showed that a range of functionalized aryl cuprates cross-couple efficiently with a variety of aryl chloride, bromide or tosylates in a DME–THF–DMPU solvent mixture in the presence of 4-fluorostyrene and Bu_4NI as promoters. The reaction leads to polyfunctional biphenyl derivatives and their heterocyclic analogues (Scheme 18).[33] A variety of aryl or heteroaryl cuprates, even those bearing halide substituents, is tolerated.



Scheme 18 Cobalt-catalyzed cross-coupling between aryl halides and arylcopper compounds.

Interestingly, $CoCl_2$, the best catalyst for the cross coupling of organomagnesium compounds, was the worst when arylcopper reagents were used.

In summary, since the pioneering work of Kharasch and co-workers, cobalt-catalyzed carbon–carbon bond formation with organometallic reagents has received increasing attention. Various organometallic compounds such as organomagnesium, organozinc and organocopper reagents can be coupled in simple fashion with various organic compounds using cobalt salts instead of the more common palladium or nickel catalysts; the latter also require (often expensive) ancillary ligands which are not necessary with cobalt. These methods tolerate functional groups on both the organometallic and the organic components in any cases.

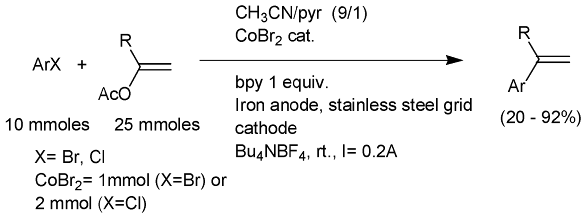
3. Cobalt-catalyzed cross-coupling reaction *via* functionalized organic compounds

A recurring theme in the work described above concerns the synthetic difficulties associated with the preparing the organometallic reagent, especially when its organic precursor bears a reactive group. A particularly interesting area of current research involves the development of chemical or electrochemical processes, which allow the direct activation of organic halides.

3.1 Vinylation of functionalized aryl halides with vinyl acetates

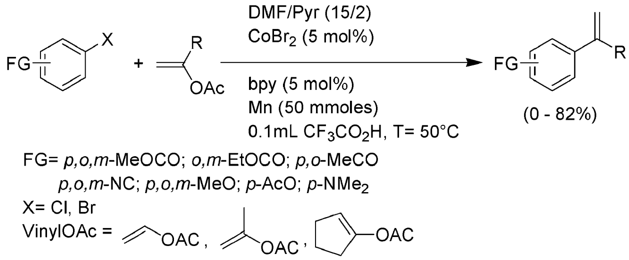
Vinylation of aryl halides is a convenient route for synthesis of styrene derivatives. The Heck reaction, and classical palladium-catalyzed cross couplings of vinylic or aryl organometallic reagents with respectively aryl- or vinylic halides, provide common methods for obtaining these products. Vinylic acetates are not often used due to their relatively low reactivity.

The first direct palladium-catalyzed vinylation from vinyl acetate and iodo aromatics to form *trans*-vinylstyrenes was reported by Arai and Daves[34] in low yields and, more recently, by Rao[35] who has described a related Pd-catalyzed formation of *trans*-stilbenes. A few years ago, we described a cobalt-catalyzed electrochemical vinylation of aryl halides with vinyl acetates.[36] Whilst being advantageous with respect to other methods, this electrochemical process requires a stoichiometric quantity of 2,2′-bipyridine. Various functionalized aromatic and heteroaromatic halides (X = Br, Cl) could be used (Scheme 19).



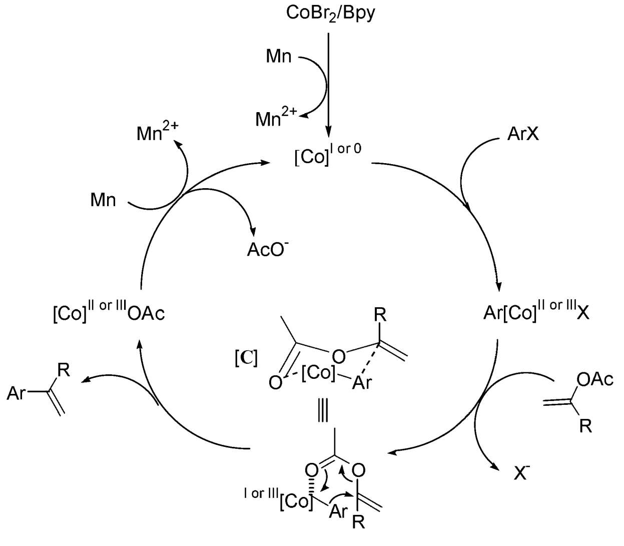
Scheme 19 Cobalt-catalyzed electrochemical vinylation of aryl halides using vinyl acetates.

A purely chemical procedure has been developed from this electrochemical approach, although some important modifications are required.[37] Low-valent cobalt can be generated by manganese reduction of cobalt halides and this system efficiently activates aryl halides. The corresponding "arylcobalt" species undergo cross-coupling with vinyl acetates (Scheme 20).



Scheme 20 General procedure for the cobalt-catalyzed vinylation of functionalized aryl halides with vinyl acetates.

The product vinylarenes were synthesized in the presence of 5 mol% $CoBr_2$(2,2′-bipyridine) in a mixture of DMF–pyridine at 50 °C. The best reducing agent was found to be manganese powder activated by traces of acid. As little as 2 equivalents of Mn relative to ArX is sufficient to afford the coupling product, although reaction times can be shortened by using 10 equivalents; working at 50 °C instead of room temperature also decreases the reaction duration. Pyridine, whilst not an essential co-solvent, also provides a spectacular rate acceleration. 2,2′-Bipyridine is essential for the coupling to proceed but, unlike the case of the corresponding electrochemical process, catalytic amounts suffice. From a mechanistic point of view, it seems likely that Co^{II} associated with 2,2′-bipyridine is reduced to vinyl acetate-stabilised Co^{I} or Co^{0} which is probably further solvated by coordination to vinyl acetate. The low-valent cobalt seems likely to react with the aryl halide by oxidative addition to form an "arylcobalt" species. After ligand exchange, this species is proposed to undergo a substitution reaction with the carbon attached to the acetate group (Scheme 21).



Scheme 21 Proposed mechanism for the vinylation of aryl halides with vinyl acetates.

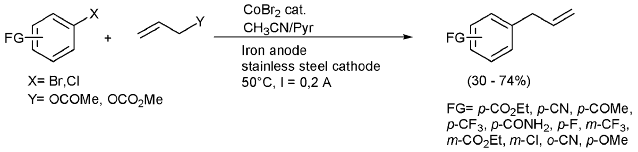
The electronically preferred reaction profile appears to favour aryl group transfer to the carbon attached to the ester group. This suggests the involvement of a six-centered transition state **[C]** wherein the aryl group is well oriented for addition to the more substituted carbon atom of the double bond. After release of the styrene derivative, re-reduction of the cobalt by excess manganese regenerates the $Co^{I\text{ or }0}$ catalyst.

This completes an efficient Co-catalyzed process for the preparation of vinylarenes from a range of aryl or heteroaryl halides and vinyl acetates. To the best of our knowledge, this is the first palladium-free direct preparation of α-styrene derivatives with acceptable yields. Moreover, this very versatile process compares favourably with known procedures involving palladium catalysis since aryl bromides and chlorides can be used advantageously as precursors for the cross-coupling.

3.2 Allylation with allyl acetates

3.2.1 Allylation of functionalized aryl halides. Many natural products include allylbenzene and biaryl groups within their skeletons and substitution reactions of allylic halides with aromatic organometallic reagents, most notably Grignard reagents, have provided an important route to these compounds. Allylarenes can also be synthesized by well-known transition metal catalyzed cross-coupling reactions between allylic acetates and either aromatic organometallic reagents, or directly from aryl halides.

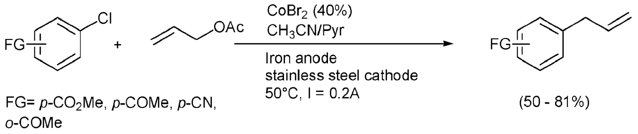
A few years ago, we developed a cobalt-catalyzed electrochemical coupling reaction of various functionalised aryl or heteroaryl halides with allylic acetates and a range of allylic esters.[38] The protocol involves the electroreduction of a mixture of functionalized aromatic or heteroaromatic bromides or chlorides with allylic acetates or carbonates in an electrochemical cell fitted with a sacrificial iron anode. In the presence of cobalt halide and associated pyridine ligand(s) in acetonitrile or DMF, it affords the corresponding coupling product in good yields (Scheme 22).



Scheme 22 Cobalt-catalyzed direct electrochemical cross-coupling between aryl halides and allylic acetates.

We initially studied the coupling reaction between aryl bromides and allyl acetate catalyzed by cobalt bromide in an acetonitrile–pyridine mixture (9 : 1 v/v). These conditions give high yields of coupling product from aryl bromides having either electron-donating or electron-withdrawing groups. It was shown that the yields are independent of the position of the functional group on the aromatic nucleus.

This electroreductive coupling reaction can be extended to aryl chlorides provided that the conditions are modified; this allows full conversion of the ArCl (Scheme 23). Using the conditions with aryl bromides (*i.e.* 1 mmol $CoBr_2$ for 7.5 mmol of ArBr), all the aromatic chloride is not totally consumed. By use of a larger amount of $CoBr_2$ (0.2 equiv. per ArCl), ArCl is consumed but the reaction proceeds slowly. To increase the reaction rate, 0.4 equiv. of $CoBr_2$ per ArCl was used and less allyl acetate is reduced. Aryl chlorides substituted by an electron-withdrawing group give good yields but, when the substituent is an electron–donor, only traces of the coupling product are obtained. In this case, the Co^I allyl acetate complex reacts too slowly with ArCl, with the main reaction product being a hexadiene resulting from the oxidative coupling of allyl acetate.

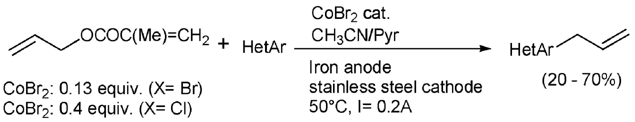


Scheme 23 Coupling reaction between aromatic chloride and allyl acetate.

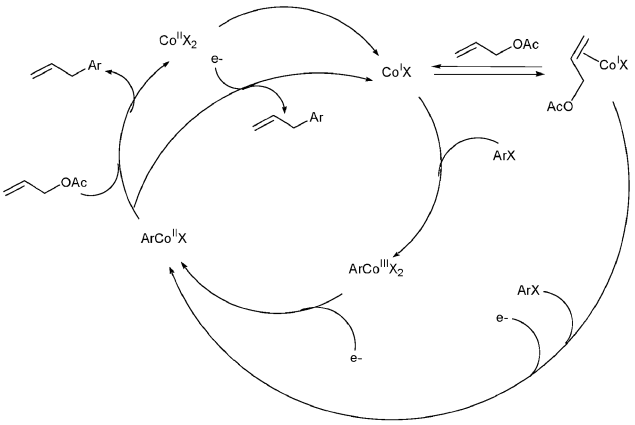
This process can be extended to aryl iodides but their greater reactivity leads to a predominant formation of the homodimer ArAr during the electrolysis. The coupling between several heteroaromatic halides, such as chloro and bromothiophenes and chloroquinaldine, with allyl methacrylate gave optimal results in conditions similar to those used for aromatic halides (Scheme 24). The yields depend on the reactivity of each heteroaromatic halide.

The high efficiency of the cobalt-based catalytic system used in this reaction prompted us to determine its mechanism. This revealed a complex sequence (Scheme 25).[39]

The early steps involve the electrochemical reduction of the Co^{II} precursor into Co^I followed by a fast complexation to allyl acetate. An oxidative addition takes place between the aromatic halides Ar–X and electrogenerated cobalt(I). The resulting σ-arylcobalt(III) species is reduced at the same potential as the original Co^{III}/Co^I couple, to liberate the product.

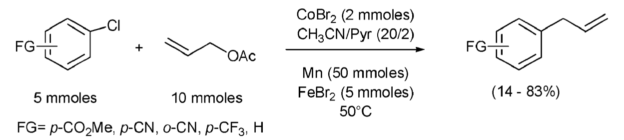


Scheme 24 Cross-coupling reaction between heteroaromatic halides and allyl methacrylates.



Scheme 25 Mechanism of the cobalt-catalyzed electrochemical coupling between aromatic halides and allylic acetates.

These electrochemical methods compare quite favourably with chemical processes. However, because electrochemical syntheses lie outside the normal range of "organic" protocols and are rarely used on greater than laboratory scales, a parallel conventional chemical method is often preferred. We have already demonstrated that purely chemical reactions can frequently be developed from our initial electrochemical process. In this case, the efficient arylation of allylic acetate with aryl chloride can be effected using the same cobalt catalyst and a stoichiometric amount of ferrous bromide based on chloroarene. Manganese powder is used as the reducing agent in a mixture of acetonitrile-pyridine.[29] Because of the low reactivity of Co^I toward arylchlorides, the solution is heated at 50 °C and a large quantity (40 mol%) of $CoBr_2$ is used (Scheme 26).



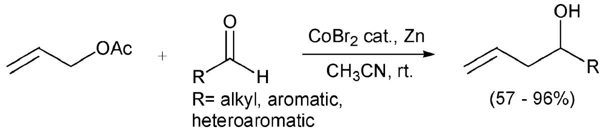
Scheme 26 Aryl chlorides allylation by allyl acetate with Co–Fe–Mn.

Excellent yields of coupling product were obtained, notably with chlorinated derivatives activated by the presence of an electron-withdrawing group. The position of the substituent has no influence. With chlorobenzene, the yield of allylbenzene decreased to 14% according to GC analysis and with chloroanisole, only traces of allylated products are detected. The reaction mechanism is rather complicated due to the presence of iron ions in the acetonitrile/pyridine solution. Manganese dust probably plays the role of a reducing agent, but iron bromide is also susceptible to reduction and to reaction with allyl acetate, even if the presence of the cobalt has been shown to be essential. This system has not yet been studied more deeply.

3.2.2 Allylation of carbonyl compounds and imines.

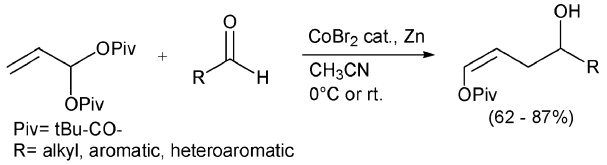
Allylation of carbonyl compounds provides an easy route to homoallylic alcohols. Often, this kind of reaction is palladium catalyzed and a stoichiometric reducing reagent such as Zn,[40] $SnCl_2$,[41] SmI_2[42] or InI[43] is used. These systems work quite nicely for aldehydes. However, for ketones, the situation is more complex: only the SmI_2 reagent allows the allylation to proceed and, because of its powerful reducing properties, a competing dimerisation of the ketone to give pinacol derivatives occurs. Electrochemically-based Pd systems also exist: allylations can be carried out through the electrochemical generation of allylic anions from allylic acetate at Pt electrodes in the presence of a Pd^{II}–Zn^{II} couple.[44]

We have recently shown that cobalt halides in the presence of zinc dust provide an efficient system for the allylation of carbonyl compounds and related derivatives such as imines. With very economical catalyst components, aldehydes show reactivity, which is analogous to the palladium-catalyzed case (Scheme 27).[45]



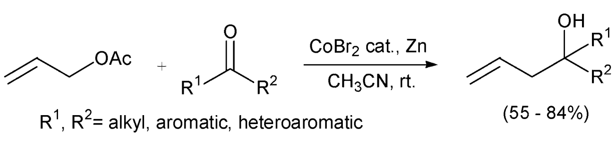
Scheme 27 Allylation of aldehydes by allyl acetate.

The reaction gives the allylation product in yields varying from fair to excellent. Aliphatic, aromatic or heteroaromatic aldehydes have all been shown to be suitable substrates. Furthermore, Trombini and colleagues have recently extended the use of this reagent system to functionalise a vinylketal (Scheme 28) in yields, which were fair to very good.[46]



Scheme 28 Cobalt-catalyzed cross-coupling of allylidene dipivalate to aldehyde.

The major improvement over palladium-catalyzed reactions is the possibility of extending the reaction to ketones (Scheme 29).[45]



Scheme 29 Allylation of ketones by allyl acetate.

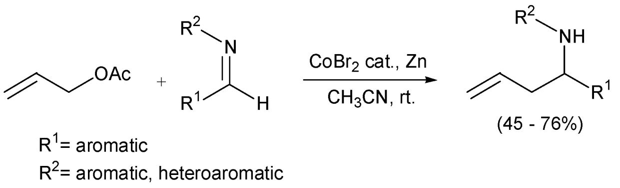
For allyl acetate, yields of cross-coupling products with aliphatic, aromatic and heteroaromatic ketones are good to excellent when the ketone is moderately hindered; reactivity falls off for *e.g.* benzophenone. Very reactive ketones such as ethyl pyruvate are also unsuitable because of formation of pinacol derivatives.

Substituted acetates are also convenient feedstuffs for the Co–Zn catalyzed carbonyl allylation system. With these compounds, the reaction is less rapid under the conditions described above, but leads to only one regioisomer: the electrophile attacks at the more substituted nucleophilic carbon of the allyl functionality. Interestingly, this is the reverse of the selectivity observed in the Pd^0–SmI_2 system.[41]

Moreover, using too bulky allylic acetates or allylic alcohols make the reaction very slow but still possible.

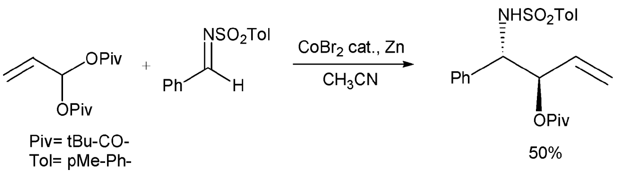
Further extension of our method to the allylation of imines allows the formation of homoallylic amines, which are interesting synthetic intermediates. Imines are generally less reactive than the corresponding carbonyl compounds, and this probably explains the more discrete development of this kind of chemistry. Whilst allylic amines have been synthesised from allyl acetate and aldimine using palladium catalysis,[47] they are usually prepared from allylic halides, which are more reactive than allylic acetates.[48]

Adapting the conditions for the allylation of carbonyl compounds by cobalt catalysis to the aldimine system revealed that the allylic amine can be obtained in fair to good yield if an excess of allylic acetate is used (Scheme 30).[49]



Scheme 30 Cobalt-catalyzed allylation of aldimines by allylic acetates.

Trombini and co-workers have provided an example of a diastereoselective reaction with a substituted allylic derivative (Scheme 31).[46]



Scheme 31 Diastereoselective cobalt-catalyzed cross-coupling of allylidene dipivalate to *N*-benzylidene *p*-toluenesulfonamide.

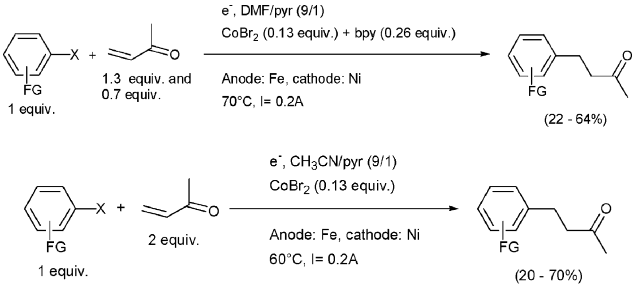
Work concerning the activation of allylic acetate by $CoBr_2$ allows a tentative mechanistic pathway to be proposed. In a preliminary step, cobalt(II) bromide is reduced to Co^I by zinc dust which is preactivated by traces of acid. The Co^I complex undergoes oxidative addition of the allylic acetate to give an η^3-allyl Co^{III} species. Reduction to an η^3-allyl Co^{II} complex follows and this is probably the species which reacts with the carbonyl compound. After the allylation, a Co^{II} species is able to restart the catalytic cycle.

3.3 Cobalt-catalyzed direct conjugate addition to activated olefins

3.3.1 Cobalt-catalyzed direct conjugate addition of aryl halides or triflates onto activated olefins.

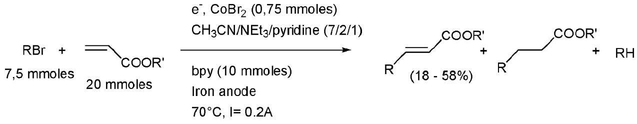
Conjugate addition of organometallic reagents to electron deficient olefins is a powerful method for the formation of new carbon–carbon bonds and yields Michael adducts which are useful synthons to further organic transformations.[50] The importance of this reaction in organic synthesis has resulted in extensive efforts devoted to a variety of synthetic methodologies and new methods are continuously being developed to make this reaction more versatile and more reliable. Classical methods for the regioselective 1,4-addition of aryl halides generally involve a copper–catalyzed reaction using an organometallic compound[51] such as an aryl lithium, Grignard reagent, aryl manganese, or aryl zinc. Other conjugate reactions of organometallic reagents are reported under nickel, palladium or rhodium catalysis.[52] Furthermore, a few years ago, our group developed a process for the addition of an electrochemically prepared aryl zinc species to activated olefins under cobalt catalysis.[27]

Again, the main difficulty of these different methods is the initial preparation of organometallic reagents, especially from functionalized aromatic compounds; as a result, chemical and electrochemical processes have been developed to avoid this step through direct activation of aryl halide. The most commonly used method, homogeneous catalysis involving *in situ* reduction of transition–metal complexes, continues to attract great interest. A complementary, direct electrochemical, arylation of electron deficient olefins performed with a cobalt catalyst in association with a sacrificial anode appears to be an appropriate method for various aromatic halides.[53] However, this electrochemical method presents some limitations, in as much as $CoBr_2$ is only an efficient catalyst for the arylation of methyl vinyl ketone by aryl bromides bearing electron withdrawing groups (Scheme 32).



Scheme 32 Electrochemical cobalt-catalyzed addition of aryl halides to methyl vinyl ketone.

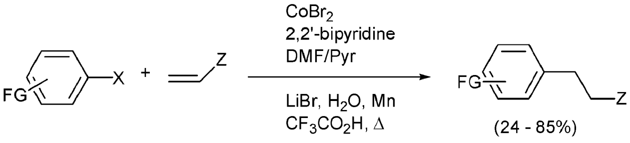
The same process, carried out in a $MeCN–Et_3N$–pyridine solvent mixture, promotes the electrochemical vinylation of aryl bromides (especially those substituted by an electron-donating group) with acrylate esters (Scheme 33).[54]



Scheme 33 Cobalt-catalyzed cross-coupling of aryl or vinyl halides with acrylate esters.

The Heck product often predominates over the conjugated addition. The reaction is stereoselective and gives only *E*-olefins in all cases studied to date. The product ratio is highly dependent upon the nature and concentration of the coligands: 2,2′-bipyridine in a ratio of 1.3 equivalents per equivalent of RX is essential to ensure the Heck product. Indeed, the amount of addition product increases when this proportion is lowered. However, triethylamine and pyridine as bases are not strictly necessary, but enables a higher substitution *vs.* addition product ratio.

We have also developed a chemical procedure for the conjugate addition of aryl bromides, chlorides and triflates bearing electron-donating or withdrawing groups, to various activated olefins (Scheme 34).[55]



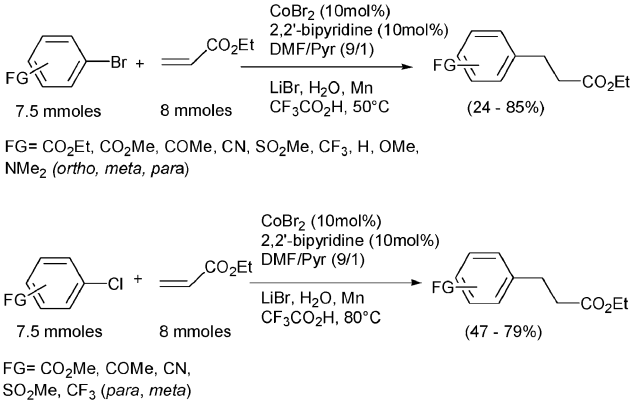
FG= CO_2Et, CO_2Me, COMe, CN, SO_2Me, CF_3, H, OMe, NMe_2 *(ortho, meta, para)*
X= Cl, Br, OTf
Z= CO_2Et, CO_2Me, CN, $CONMe_2$...

Scheme 34 General procedure for the cobalt-catalyzed conjugate addition process.

The one-step method employs $CoBr_2$(2,2′-bipyridine) as the catalyst. Hydrated cobalt bromide is the precursor of choice, with the water apparently serving to diminish the rate of polymerisation of the olefin. The concentration of the cobalt complex affects the reaction rate but not the chemoselectivity of the reaction. The use of a pyridine cosolvent accelerates the reaction and heating the medium allows improved reaction times. 2 equiv. of manganese dust activated by traces of trifluoroacetic acid has been found to deliver the optimum yield, with replacement of the acid by iodine or acetic acid leading to poor results. Addition of LiBr allows the reaction rate and the yields to be increased, with 0.5 equiv. (relative to bromide) proving optimal. It seems likely that a low-valent cobalt species, obtained after reduction by the manganese, activates the aryl halide or triflate. The corresponding "arylcobalt" species undergoes addition to activated olefins to afford conjugate adducts.

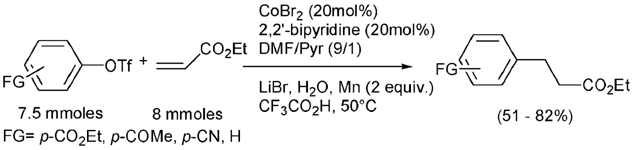
Likewise, various functionalized aryl bromides and chlorides react with alkyl acrylate. However, owing to the lower reactivity of the C–Cl bond, chlorides need intramolecular activation by an electron-withdrawing group and their reactions have to be performed at 80 °C instead of 50 °C, which favours by-product formation. Addition of aryl bromides bearing an electron-withdrawing group leads to excellent yields regardless of the *meta* or *para* position of the substituent. Yields decrease with electron rich nuclei. In these conditions, if the electron donor group is *ortho* to the halide, the reaction becomes difficult (Scheme 35).

The process has also been extended to heteroaromatic bromides such as 3-bromopyridine or 3-bromothiophene.



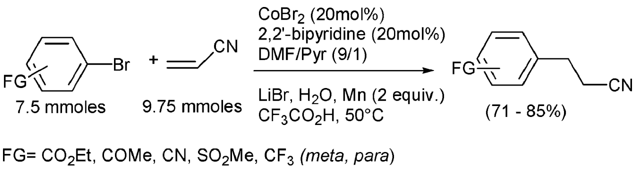
Scheme 35 General procedures for the cobalt-catalyzed conjugate addition of aryl halides (X = Br, Cl) to ethyl acrylate.

The reactivity of aryl triflates has also been investigated. These appear to be less reactive toward oxidative addition at cobalt than aryl bromides and this translates into longer reaction times. Rapid conversion of the triflate group into the corresponding phenol also complicates the reaction. Surprisingly, reactivity in triflate case falls when electro-attracting groups are present. The easiest method for increasing the yield is a simply to increase the quantity of cobalt complex (Scheme 36).



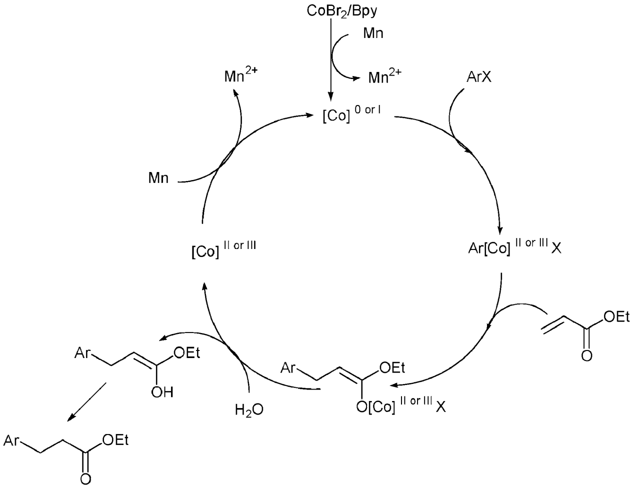
Scheme 36 Cobalt-catalyzed conjugate addition of aryl triflates to ethyl acrylate.

Extending this methodology to allow the conjugate addition of aryl bromides to the less reactive acrylonitrile in good yields (Scheme 37) necessitates using 20 mol% of catalyst and a significant excess of acrylonitrile.



Scheme 37 Cobalt-catalyzed conjugate addition of aryl bromides onto acrylonitrile.

The mechanism given in Scheme 38 has been proposed. The Co^{II} centre, associated with 2,2′-bipyridine and the pyridine solvent, is reduced in a preliminary step by activated manganese to afford Co^{I} or soluble Co^{0} species. These most probably react with ArX by oxidative addition to form an arylcobalt intermediate, which is proposed to effect a nucleophile attack upon the electron-poor olefin through a six-membered transition state. The resulting cobalt enolate can then react with residual water to give the expected 1,4-adduct with release of a Co^{III} or Co^{II} species. Reduction by manganese regenerates the reactive cobalt catalyst.



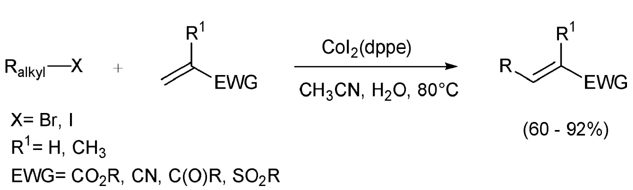
Scheme 38 Proposed mechanism for the cobalt-catalyzed conjugate addition of aryl species.

Globally, the catalyst comprising a simple cobalt halide associated with 2,2′-bipyridine appears to be well suited to couplings of a large variety of halide- and triflate-substituted aromatics substituted by reactive functional groups. It provides an efficient method for the direct 1,4-addition of functionalized aromatics to activated olefins without using stoichiometric organometallic reagents, and affords good to excellent yields under simple and mild conditions.

3.3.2 Cobalt-catalyzed direct conjugate addition of saturated alkyl halides with activated alkenes.

Cheng and co-workers have described a cobalt-catalyzed reductive coupling reaction of alkyl halides to electron withdrawing alkenes in the presence of water and zinc powder in acetonitrile (Scheme 39) which resembles the processes described above.[56]

Under these conditions, unactivated primary, secondary and tertiary alkyl bromides or iodides react with various conjugated alkenes including acrylates, acrylonitrile, methyl vinyl ketone, and vinyl sulfones to give the corresponding Michael-type addition product. Alkyl iodides generally gave better yields than the corresponding bromides; the cobalt complex $CoI_2(dppe)$ proved to be the best catalyst precursor.



Scheme 39 Cobalt-catalyzed reductive coupling of saturated alkyl halides with activated alkenes.

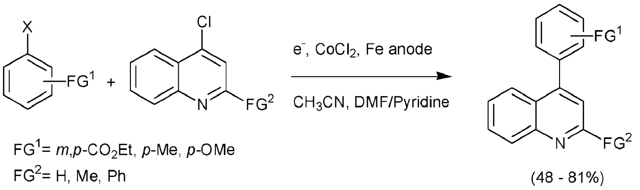
The authors propose a catalytic cycle initiated by the reduction of $CoI_2(dppe)$ to Co^{I} by zinc powder, followed by the oxidative addition of an alkyl halide. This leads to an alkyl cobalt(III) intermediate. Coordination of the conjugated alkene, insertion into the Co–alkyl bond and protonation finally gives the reductive coupling product. The active Co^{I} catalyst is then regenerated through reduction of the Co^{III} species by the excess zinc powder.

Cheng and co-workers could not exclude a mechanism involving an electron transfer from the Co^I complex to an alkyl halide to generate an alkyl radical, followed by the addition of the radical to acrylate and the trapping by the cobalt species to give a Co^{III} intermediate. In our case, with aryl halides, we exclude a mechanism involving an electron transfer. In fact, the reaction conducted in the presence of radical inhibitors (galvinoxyl free radical) affords similar results.

3.4 Cobalt-catalyzed formation of unsymmetrical biaryls

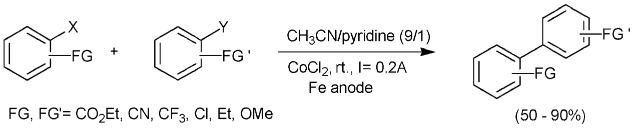
Unsymmetrical biaryls are of great interest in organic chemistry, the biaryl structural motif being encountered in diverse organic processes ranging from supramolecular chemistry to natural product synthesis. Arguably, among the innumerable methods for the construction of aryl–aryl bonds, the most interesting strategies have involved transition-metal-mediated reactions. Generally, these involve the coupling of an organometallic reagent (ArM; M = B, Sn, Si, Zn, Mg, Mn) with either an aryl halide or a pseudo-halide.[57] Each of these requires the preparation of a stoichiometric quantity of organometallic reagent somewhere in the synthetic pathway and generally occurs in the presence of Ni or Pd complexes as catalysts. However, several direct aryl–aryl bond-forming transformations are known; notably, these include the palladium-based reductive coupling of two aryl halides in the presence of a reducing agent.[58]

We have previously developed electrochemical methods involving Co catalysis. Initially, we focussed our attention on the synthesis of 4-phenylquinoline derivatives from phenyl halides and 4-chloroquinolines derivatives.[59] These compounds are obtained in satisfactory to high yields. The choice of an iron rod as the anode is of crucial importance for the efficiency of the electrochemical process (Scheme 40).



Scheme 40 Cobalt-catalyzed electrochemical cross-coupling of functionalized phenyl halides with 4-chloroquinoline derivatives.

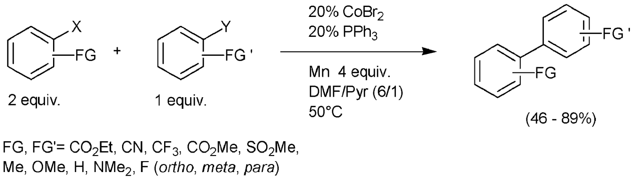
Alternative simple electrochemical methods have also been used to form unsymmetrical biaryls from two different arylhalides using cobalt catalysis.[60] In this process, the cobalt chloride concentration plays a major role: 30 mol% with respect to the less reactive reagent allows good conversion. Pyridine as co-solvent and/or ligand to Co^I is essential. In this case, the iron anode gives better yields but is not essential (Scheme 41).



Scheme 41 Electroreductive cobalt-catalyzed cross-coupling of aryl halides.

Unlike the palladium process, the more reactive aromatic halide is used in excess. The isolated yields are good to excellent. Reactions are less efficient with aryl chlorides than with aryl bromides and no results had previously been reported with aryltriflates. Our early success in applying new cobalt-catalyzed direct procedures as an efficient alternative to the electrochemical methods persuaded us to use this new process with various aryl halides or even triflates. This allowed a cobalt-catalyzed cross-coupling reaction, in which a different cobalt complex is used in combination with manganese dust as the reducing agent, to be developed. Its scope and synthetic utility for the efficient formation of a variety of unsymmetrical biaryl compounds have been established. Our previous studies demonstrated the efficiency of a cobalt halide associated with 2,2′-bipyridine in dimethylformamide in the presence of pyridine for the activation of aryl halides (see sections 3.1 and 3.2).

The low-valent cobalt generated from the chemical reduction with manganese dust of cobalt bromide–triphenylphosphine (1 : 1) mixtures effects the unprecedented coupling of functionalized aryl (heteroaryl) halides or triflates into biaryls (Scheme 42).[61]

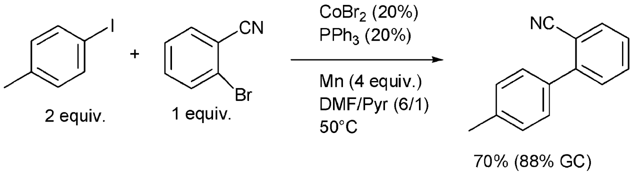


Scheme 42 Cross-coupling of two aryl halides.

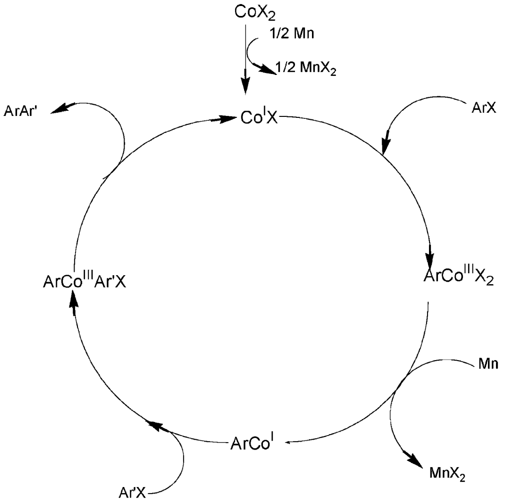
The choice of ligand has a substantial impact on the course of the reaction. The cross-coupling was significantly efficient in a solvent mixture such as DMF-pyridine. Unlike other recently developed cobalt-catalyzed reactions, manganese and zinc reducing agents gave quite different results; zinc was not able to reduce the cobalt associated to phosphine in this solvent mixture and, with this metal, no biaryl compound was formed. In contrast to palladium–catalyzed reactions, the more reactive aryl halide was used in excess (2 equiv.). This novel method gives the expected cross-coupling product generally in good yield with good selectivity after complete conversion of substrates both with an aryl bromide and an aryl iodide and with two aryl bromides with one another. However, a significant difference of reactivity between the two aryl halides decreases the yield. An array of aryl bromides and chlorides have been also shown to couple to one another. Specifically, activated aryl chlorides can undergo cross-coupling with non-activated aryl bromides and activated aryl chlorides. These results prompted us to attempt the synthesis of 2-(4-tolyl)benzonitrile, a key intermediate in the synthesis of Sartan derivatives (Scheme 43).

Functional group interchange at the resulting biaryl compound, which was isolated in 70% yield, provides a wide range of biologically active compounds including Losartan, Irbesartan and Valsartan.[62]

The tolerance of our protocol toward a wide variety of functional groups enables the synthesis of a broad spectrum of



Scheme 43 Synthesis of a key intermediate for the preparation of Sartan derivatives.



Scheme 44 Proposed mechanism for the cobalt-catalyzed formation of biaryls.

valuable compounds, including heterocyclic biaryls, from commercially available chemicals, in satisfactory to high yields under simple and mild conditions. Thus, cobalt catalysis provides an expedient route to functionalized biaryl and heteroaryl–aryl compounds. This catalytic process involves a simple, inexpensive, and environmentally friendly cobalt halide salt and triphenylphosphine, which combine to afford an extremely powerful catalyst for the coupling of a large variety of aromatic reagents. The proposed mechanism in Scheme 44 is comparable to that described for the nickel-catalyzed formation of biaryl compounds, which is favoured in the presence of excess reductant. However, further studies are in progress to elucidate the mechanism of this reaction.

This reaction proceeds with fair to good yields. One again this reaction is more competitive than the reaction catalyzed by palladium or nickel complexes.

4. Conclusion

A wide range of new cobalt-catalyzed cross-coupling reactions has been developed though combining a variety of organometallic reagents with vinyl, alkyl or aryl halides. The mild reaction conditions, high chemoselectivity and low cost of cobalt salts compared to palladium or even nickel, make cobalt-catalyzed cross-coupling reactions a powerful method for carbon–carbon bond formation and a promising area for future development. They seem very likely to find significant applications. Furthermore, in using simple ligands, rather than the very bulky analogues, which are often required for Pd-based systems; they make an excellent complement to Pd and Ni-catalyzed reactions.

Notes and references

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