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Cobalt-Catalyzed C(sp²)-CN Bond Activation: Cross-Electrophile Coupling for Biaryl Formation and Mechanistic Insight

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ABSTRACT: Herein, we report a cross-electrophile coupling of benzonitrile derivatives and aryl halides with a simple cobalt-based catalytic system under mild conditions to form biaryl compounds. Even though the cobalt catalyst is able to activate the C(sp²)-CN bond alone, the use of the AlMe₃ Lewis acid enhances the reactivity of benzonitriles and improves the cross-selectivity with barely any influence on the functional group compatibility. X-Ray structure determination of an original low-valent cobalt species combined with catalytic and stoichiometric reactions reveal a catalytically active cobalt(I) species towards the aryl halide partner. On the other hand, experimental insights, including cyclic voltammetry experiments, suggest the involvement of a cobalt complex of a lower oxidation state to activate the benzonitrile derivative. Finally, DFT calculations support the proposed mechanistic cycle involving two low-valent cobalt species of different oxidation states to perform the reaction.

KEYWORDS: cobalt, catalysis, benzonitriles, reductive cross-coupling, biaryl, cross-electrophile coupling

Introduction

Benefiting from more than 50 years of research, noble metals have a longstanding record in the field of homogeneous catalysis.¹ However, the depletion of their resources,² implying high costs and sustainability issues,³ has stimulated the search for non-noble metals surrogates. These studies have revealed unsuspected reactivities,⁴ and notably led to the development of first-row transition metal-catalyzed cross-electrophile coupling reactions that have emerged as a powerful tool to create carbon-carbon (C-C) bonds in particular for biaryl formation.⁵ In contrast with the traditional redox-neutral couplings, cross-electrophile couplings require no preliminary preparation of a stoichiometric nucleophilic organometallic species, which makes them more straightforward and often allows better functional group tolerance. First mainly based on the activation of two halide derivatives,⁵ the limited availability and difficult synthesis of such substrates have led chemists to consider other types of electrophiles to perform such reactions.⁶

In this area, one of the biggest challenges remains the activation of thermodynamically stable C-C bonds. In particular, even though great improvements have been made recently, metal-catalyzed activation of unstrained C-C bonds^{7,8} is still largely underdeveloped.^{7,9} Among them, the activation of C(sp²)-CN bond is believed to have a great potential to develop original synthetic methodologies.¹⁰ Indeed, benzonitriles are relatively abundant¹¹ and more and more readily accessible from ubiquitous functional

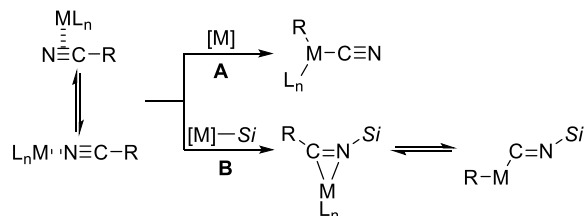
groups.¹² They are also quite stable under various reaction conditions, which makes them appealing for late-stage cross-coupling reactions. Therefore, despite its high bond dissociation energy (PhCN~132 kcal.mol⁻¹),¹³ chemists have been attracted to activate this unstrained C(sp²)-CN bond with transition metals.

Stoichiometric activation studies¹⁴ with different metals have revealed two major activation pathways (Scheme 1a). The first pathway involves mainly electron-rich metal(0) complexes which insert via oxidative addition into the C(sp²)-CN bond (pathway **A**).^{14,15} The second activation mode relies on the assistance of silicon, in which the prior formation of a silylated complex is followed by the migratory insertion of the nitrile into the M-Si bond (pathway **B**).^{14,16} Among metals reported to activate C(sp²)-CN bonds, Ni, Rh and Pd have been mainly applied in catalysis.^{7,9b,17} Notably, in cross-coupling reactions,¹⁸ apart from a particular cross-coupling between benzonitrile and azole derivatives,¹⁹ thus, necessitating to employ a nickel(0)/alkyl phosphine catalyst to be able to activate the C(sp²)-CN bond via pathway **A**, biaryl formation from benzonitriles has been reported using nickel catalyst with organometallic coupling partners²⁰ such as aryl Grignard reagents,^{21,22} arylboronic esters²³ as well as arylmanganese compounds (Scheme 1b).²⁴ The use of such organometallic species makes easy the reduction of nickel(II)/alkyl phosphines pre-catalysts into nickel(0) active species, which can then insert into the C(sp²)-CN bond according to pathway **A**. However, the use of nucleophilic species might sometimes be incompatible with late-stage derivatization

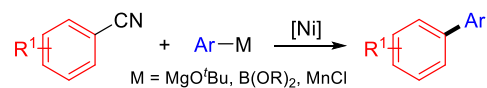
and sensitive functional groups. Chatani *et al.*²⁵ disclosed a rhodium-catalyzed assisted with silicon (pathway **B**) cross-electrophile coupling from benzonitrile derivatives (Scheme 1c) which could overcome these drawbacks. Nevertheless, high temperature and restriction to intramolecular arylation reduces its applicability.

Scheme 1. (a) Different metal-catalyzed activation pathways. (b) Redox-neutral coupling with benzonitrile derivatives and nucleophilic organometallic reagents. (c) Intramolecular cross-electrophile coupling from benzonitrile derivatives. (d) Intermolecular cross-electrophile coupling from benzonitrile derivatives (this work).

(a) Activation pathways

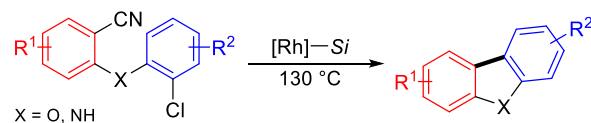


(b) Redox-neutral coupling (Miller, Shi, Wang)



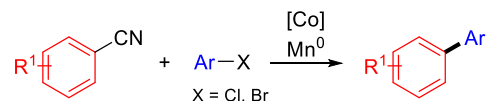
- prefunctionalization step
- nucleophilic species handling
- limited functional group tolerance

(c) Intramolecular cross-electrophile coupling (Chatani)



- limited to intramolecular arylation
- elevated temperatures

(d) Intermolecular cross-electrophile coupling (this work)



- intermolecular cross-electrophile coupling
- mild conditions
- first-row transition metal catalysis
- functional group tolerance

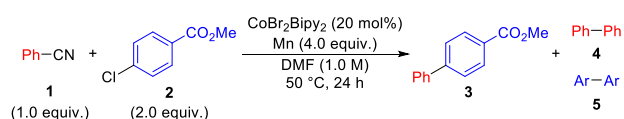
Cobalt complexes have already shown to be efficient catalysts to perform cross-electrophile coupling reactions.^{5b,26,27} Moreover, we and others have revealed the great ability of cobalt complexes to perform cross-coupling reactions of partners other than halide derivatives.²⁸ Therefore, as part of our continuous effort to develop efficient couplings from more stable and available halide surrogates, we disclose herein an attractive cobalt-catalyzed intermolecular cross-electrophile coupling to form biaryls from benzonitrile derivatives under mild conditions (Scheme 1d). The major challenge of such intermolecular coupling is to favor cross-selectivity from two electrophilic starting materials displaying the same reactivity towards transition metals.⁵ In the present methodology, the difficult activation of benzonitriles makes this challenge even bigger. To the best of our knowledge, this is the first example

of catalytic cross-coupling reactions involving C-CN activation with cobalt.²⁹

Results and Discussion

Optimization study. The optimized conditions of the reaction are shown in Table 1. Reaction of benzonitrile (**1**) and methyl 4-chlorobenzoate (**2**) in the presence of pre-formed $\text{CoBr}_2\text{Bipy}_2$ (20 mol%) (see S4.) and Mn powder (4.0 equiv.) in DMF at 50 °C for 24 h afforded the heterocoupling product (**3**) in 62% yield (entry 1) along with homocoupling products of both partners (**4** and **5**) in 7% and 30% respectively and about 20% of **1** unreacted. In the same conditions, $\text{NiBr}_2(\text{dme})$ associated with 2,2'-bipyridine ligand afforded a much lower yield (12%), highlighting the advantage of developing new cobalt-catalytic systems for cross-electrophile couplings (see Table S1 entry 20).

Table 1. Optimization of the reaction conditions^a

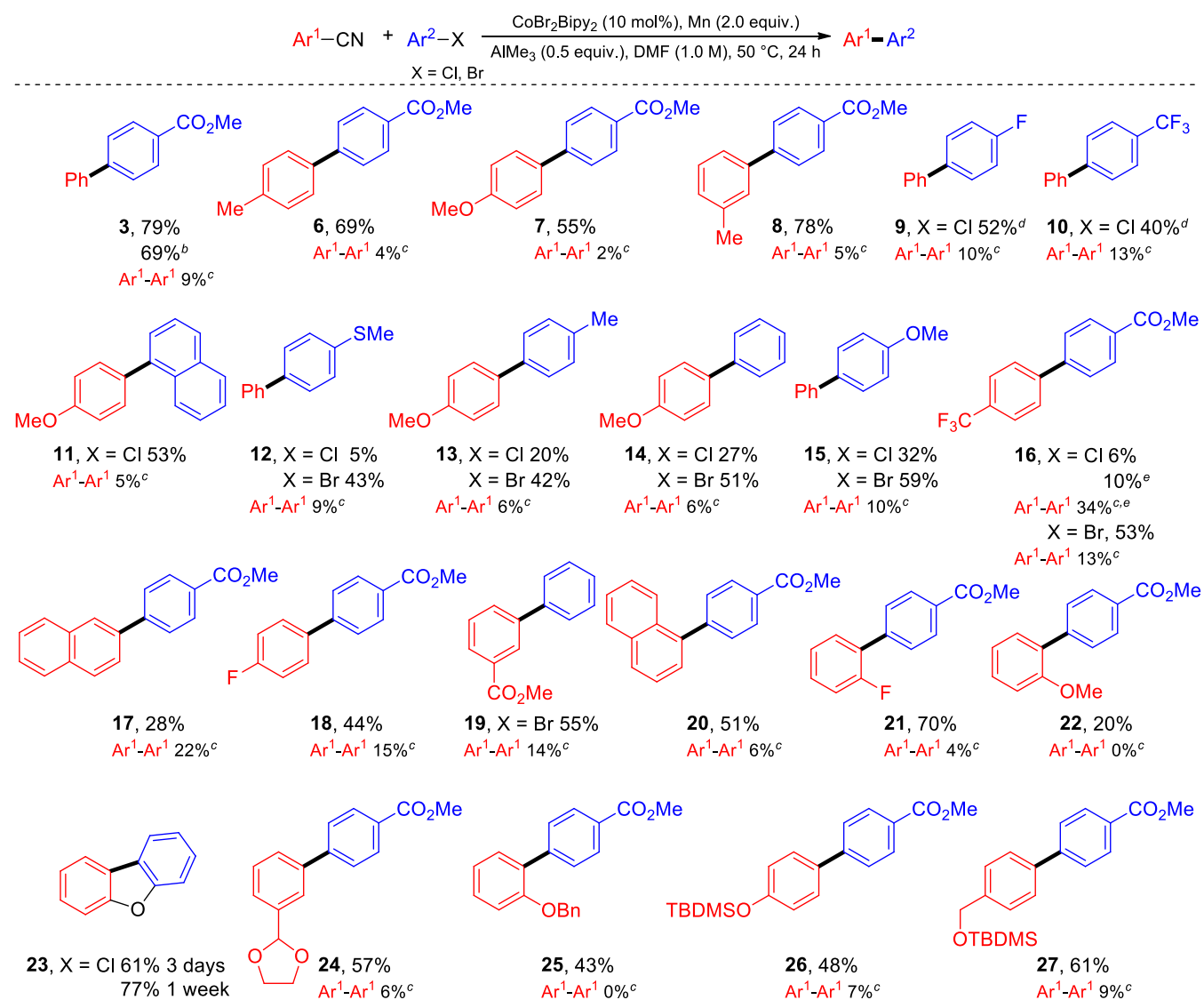


entry	deviation from standard conditions	yield 3 (%) ^b	yield 4 (%) ^b	yield 5 (%) ^{b,c}
1	none	62	7	30
2	CoBr_2 (20 mol%), PPh_3 (40 mol%)	5	2	44
3	CoBr_2 (20 mol%), dtbbipy (40 mol%)	37	5	34
4	DMF/Pyridine (10/1) instead of DMF	55	10	34
5	80 °C instead of 50 °C	35	6	37
6	$\text{Me}_3\text{SiSiMe}_3$ (1.0 equiv.) as additive	69	10	24
7	BPh_3 (1.0 equiv.) as additive	44	6	28
8	AlMe_3^d (1.0 equiv.) as additive	81	9	18
9	$\text{CoBr}_2\text{Bipy}_2$ (10 mol%) and AlMe_3^d (0.5 equiv.) as additive	79	9	18

Deviation from entry 9 as new standard conditions

10	1.5 equiv. of Mn	81	9	17
11	1.5 equiv. ArCl	62	13	16
12	Without $\text{CoBr}_2\text{Bipy}_2$	0	0	0
13	Without Mn	9	3	1

^aReaction conditions: benzonitrile **1** (1 mmol, 1.0 equiv.), methyl 4-chlorobenzoate **2** (2 mmol, 2.0 equiv.), $\text{CoBr}_2\text{Bipy}_2$ (20 mol%), Mn powder (4.0 equiv.), *N,N*-dimethylformamide (DMF) (1 M), 50 °C, 24 h. See the SI for full optimization details. ^bYield determined by GC using pentadecane as internal standard. ^cYield calculated towards **2**. ^dSolution of AlMe_3 (2 M) in toluene. Bipy: 2,2'-bipyridine; dtbbipy: 4,4'-di-tert-butyl-2,2'-bipyridine.

Table 2. Scope of the reaction^a

^aReactions performed on 1 mmol scale - Isolated yields. ^b10 mmol scale. ^cGC yield using n-pentadecane as internal standard. ^dNMR yield. ^eWithout AlMe₃.

A first screening of different kinds of ligands (see Table S1) showed the great superiority of *N,N*-heterocyclic ones to perform the reaction (entry 2). Changing the simple 2,2'-bipyridine ligand for bulkier and electron-rich ones resulted in lower conversion of **1** (entry 3). Interestingly, contrary to many cobalt-catalyzed cross-electrophile couplings reported in DMF,^{28b,30} pyridine as co-solvent is of no use to improve the transformation of **5**. Whereas elevated temperature is crucial for some methodologies reported to activate C-CN bond,^{19,20,23,25} in our case, rising the temperature above 50 °C showed a detrimental effect (entry 5), with higher amounts of remaining **1**, and **5**. To diminish the quite significant amount of **1** unreacted, we therefore tried to add some additives (see Table S4).

Indeed, previous reports have shown that the use of additives dramatically facilitated the insertion of transition-metal catalysts into the C(sp²)-CN bond of benzonitrile derivatives, either by assistance¹⁶ or by acting as Lewis acid to weaken the C(sp²)-CN.³¹ The use of hexamethyldisilane showed only a slight improvement of the yield (entry 6), suggesting its prominent role as Lewis acid than as an assistant to the insertion, like in the method developed by Chatani.^{20a,25} Whereas BPh₃^{19,31b,c} (entry 7) was prejudicial to the reactivity, AlMe₃^{31c,d} displayed the best efficiency to overcome the lack of reactivity of **1** (entry 8). The use of AlMe₃ not only increased the selectivity (see Figure S1 and S2) towards the formation of **3**, significantly reducing the amount of **5** to 18%, but also enabled us to maintain high yield with lower catalyst loading (entry 9) and reductant quantity (entry 10), actually close to the

stoichiometry (see Table S6 entry 6). However, a reduced amount of **2** resulted in a lower yield (entry 11), yet still satisfactory in case a high-value halide derivative is used. Finally, no product was detected when cobalt catalyst was removed (entry 12), whereas a small amount of product could be observed without Mn (entry 13). Indeed, AlMe₃ might play the role of the reductant but is not adequate to perform the reaction as sole reducing agent (see Table S5 entry 5).

Scope of the reaction. With the optimized conditions in hand, we then investigated the scope of the title transformation (Table 2). The reaction works in accordance with most cross-electrophile couplings catalyzed by cobalt previously reported^{5b,26,27,30} and is highly sensitive to the electronic properties of the substrates, sometimes necessitating tuning of the coupling partners to induce cross-selectivity. It should be pointed out that the superior reactivity of aryl iodides compared to aryl cyanides mainly led to the homo-coupling products of the aryl iodide substrates instead of cross-coupling products. For benzonitrile (**3**) or derivatives bearing moderately electron-donating groups (EDG) (**6**, **7**, **8**), the cross-coupling performed smoothly with activated chloroaryl derivatives bearing electron-withdrawing groups (EWG) (**9**, **10**, **11**). Unsurprisingly, when reacted with electron-rich aryl chlorides for which the oxidative addition is less favorable, the benzonitrile derivatives preferably dimerized to give lower yields (**12**, **13**, **14**, **15**). Nevertheless, better selectivities were obtained when using more reactive bromoaryl analogues. In the same way, highly electron-rich benzonitriles showed poor or no reactivity, presumably due to a difficult oxidative addition, even with an increased amount of activating Lewis acid (see S9.2.).

On the contrary, benzonitriles bearing strongly EWG (**16**) or moderately EWG at an activated position (**17**, **18**) showed great reactivity but preferentially dimerized, leading to lower yield when reacted with chloroaryl derivatives under standard reaction conditions. While removing AlMe₃ proved not sufficient enough (**16**), choosing the more reactive bromoaryl counterpart as coupling partner usually afforded the cross-coupled product in good yields (**16**, **19**). As for benzonitriles bearing moderately EWG (**20**, **21**), the cross-coupling performed easily with an activated arylchloride partner in good to very good yields.

Steric hindrance, such as methyl group in *ortho*-position of any of the coupling partners, was not well tolerated due to favored dimerization of the other unhindered partner (see S9.2). Unlike its homolog in *para*-position, 2-methoxybenzonitrile afforded 2-hydroxybenzonitrile as major product, coming from the deprotection of the starting material mediated by AlMe₃ (**22**).³² This deprotection is thus promoted by the proximity of AlMe₃ to the methoxy group, clearly indicating its chelation to the nitrile moiety in order to activate it. However, when no side reactions are competing, high yields can be reached even though longer reaction times are needed, like in an intramolecular reaction (**23**). Interestingly, despite the presence of AlMe₃, sensitive functional groups like acetals (**24**), benzyl- (**25**) and even silyl-protected phenols (**26**) or alcohols (**27**)

usually gave good yields with only small amounts of deprotected starting material even in *ortho*-position.

Mechanistic insight. Intrigued by the unusual reactivity of this simple cobalt-based catalytic system towards stable benzonitrile derivatives, we then focused on obtaining some insight into the mechanism of the reaction.³³ In particular, a plot of the time dependence for the reaction progress for products **3** and **5** at the beginning of the reaction (see Figure S3) showed two different induction periods for each substrates to be activated, with **2** being reacted faster than **1**. This peculiar observation encouraged us to investigate mainly which species could be able to activate both partners.

Above all, we started to study the nature of the catalysis. We envisioned that two types of catalyst could be able to perform such cross-coupling after reduction of the cobalt pre-catalyst by Mn powder. On one hand, homogeneous low-valent cobalt species could be the active catalyst. On the other hand, heterogeneous catalysis might be effective with either cobalt nanoparticles³⁴ or a blend of activated cobalt/manganese metals involved. To verify the nature of the catalysis, we submitted a solution of pre-catalyst CoBr₂Bipy₂ in DMF to reduction with Mn powder overnight. The resulting dark blue supernatant of reduced species was submitted to the mercury drop test³⁵ with coupling partners **1** and **2** separately (see S3.2) If heterogeneous cobalt metal catalyst was involved, no reactivity would be observed with Hg⁰ due to metal poisoning, by amalgamating or adsorbing on the metal surface. Yet, significant amounts of methyl benzoate (**9**) and **5** (**13**) were observed from the reaction of **2** with the supernatant, regardless of the presence of Hg⁰. The reactivity of the remaining activated cobalt/manganese blend was also evaluated with **2** and this time, no reactivity was observed. While these results seem to be consistent with homogeneous catalysis, surprisingly, similar experiments with **1** led to no reactivity in all cases (see S3.2), preventing us from drawing any conclusion.

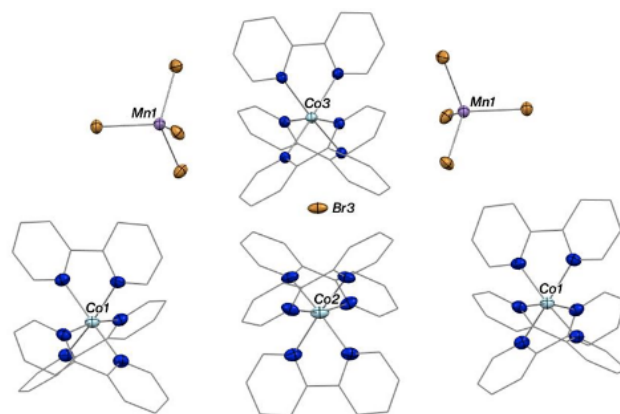
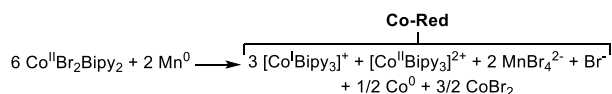


Figure 1. ORTEP of reduced cobalt complex **Co-Red** [3 [Co^I-Bipy₃]⁺; [Co^{II}Bipy₃]²⁺; 2 [MnBr₄]²⁻; Br⁻] at 50% probability ellipsoids with H atoms and solvent omitted and 2,2'-bipyridine ligands in wireframe for clarity.

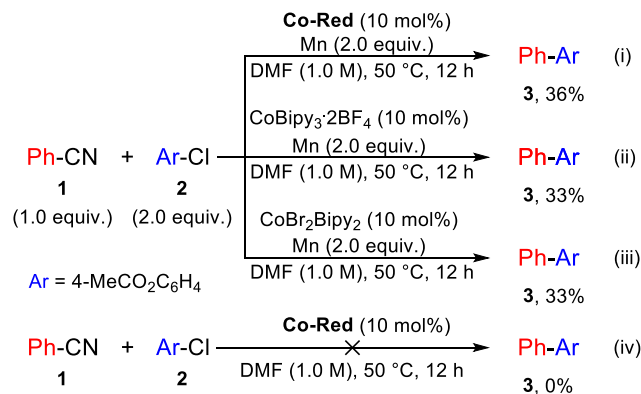
Whereas it seems well-established that Co^{II} pre-catalysts afford Co^I species after reduction by Zn powder,^{5b,36} we could not find any report indicating clearly the resulting oxidation state after reduction by Mn powder. From the previous dark blue solution, crystals of a cobalt reduced species were grown and isolated in 65% yield (see S4.). The resulting **Co-Red** species crystallize in P6₃22 space group. A grown structure with integer chemical formula is shown in Figure 1. Electroneutrality principle allowed the attribution of oxidation states for each Co atoms with a resulting 3/1 ratio of Co^IBipy₃/Co^{II}Bipy₃. A close look at characteristic bond distances (see Table S9) and comparison with literature values³⁷ validated the 3/1 ratio found and indicated a charge repartition mainly centered on the metallic atoms in the solid state of Co^I(Bipy⁰)₃ (see S6. for full details on X-Ray structure solving).³⁷ Moreover, the X-Ray structure of **Co-Red** is consistent with the observation by Anson *et al.*³⁸ that Co^I complexes of less than three 2,2'-bipyridines per cobalt have a high propensity to redistribute their ligands to fill their coordination sites in order to gain stability. Since the ligand redistribution is believed to generate cobalt(0),^{38,39} this led us to propose the following equation for the formation of **Co-Red** (Equation 1). Besides, this result points out the importance of having investigated the nature of the catalysis. Finally, this process of reduction/ligand redistribution would be in accordance with the induction period previously observed (Figure S3).



Equation 1. Equation of reduction/ligand redistribution of CoBr₂Bipy₂ by Mn powder.

We thus performed catalytic experiments in DMF at 50 °C for 12 h in the presence of Mn (2.0 equiv.), and employing either **Co-Red** (Scheme 2(i)) or CoBipy₃·2BF₄³⁷ (Scheme 2(ii)) as pre-catalyst. Both complexes afforded the same yield of cross-coupled product than CoBr₂Bipy₂

Scheme 2. Catalytic reactions in DMF (1.0 M), 50 °C, 12 h with Mn (2.0 equiv.) and (i) Co-Red; (ii) CoBipy₃·2BF₄; (iii) CoBr₂Bipy₂ as pre-catalyst. (iv) Catalytic reactions in DMF (1.0 M), 50 °C, 12 h using Co-Red as pre-catalyst without Mn.^a



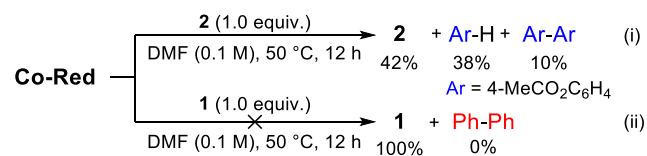
^aYields determined by GC using n-pentadecane as internal standard.

(Scheme 2(iii)) in the same conditions, highlighting that complexes of cobalt surrounded by three 2,2'-bipyridine ligands are suitable pre-catalysts for the transformation and the possible involvement of such species as catalytic active species. Interestingly, removal of Mn with **Co-Red** as pre-catalyst in similar conditions did not lead to any cross-coupling product, indicating the essential role of Mn within the catalytic cycle (Scheme 2(iv)).

We then focused on stoichiometric reactions of **Co-Red** with **1** and **2** separately (Scheme 3). To our delight, 58% of **2** was converted into methyl benzoate (ArH 38%) and dimethyl biphenyl-4,4'-dicarboxylate **5** (Ar-Ar 10%) confirming **Co-Red** to be an active species with halogenoaryl derivatives (Scheme 3(i)).⁴⁰ Control stoichiometric experiment with CoBipy₃·2BF₄ indeed confirmed that only Co^I species of **Co-Red** is active towards **2** (see Scheme S11).

In accordance with what has previously been suggested during the mercury drop test (see S3.2), **Co-Red** did not seem to exhibit any reactivity towards **1** since stoichiometric reaction did not lead to any conversion (Scheme 3(ii)). However, interestingly, precipitation of cobalt complexes of the mixture with toluene and analysis of the toluene supernatant in GC showed appreciable amount of free 2,2'-bipyridine ligand (see Scheme S12). In contrast, the same experiment carried out with CoBipy₃·2BF₄ instead (see Scheme S13) produced only traces amount of free 2,2'-bipyridine, suggesting that the displacement of the ligand by **1** preferably occurs with the Co^IBipy₃ rather than the Co^{II}Bipy₃ complex composing **Co-Red** (Figure 1). Besides, computational data confirmed that the substitution of one 2,2'-bipyridine ligand by one benzonitrile **1** is indeed energetically more favorable with Co^IBipy₃ than Co^{II}Bipy₃ (see S.8.1).

Scheme 3. Stoichiometric reactions with Co-Red in DMF (0.1 M), 50 °C, 12 h and (i) 2. (ii) 1.^a



^aYields determined by GC using n-pentadecane as internal standard.

Concurrently, we performed cyclic voltammetry experiments. To avoid any complexity of the cyclic voltammograms due to the mixture of Co^IBipy₃/Co^{II}Bipy₃ of **Co-Red**, all the experiments were made with the complex Co^IBipy₃ generated in situ by reduction of CoBipy₃·2BF₄ in DMF by Mn. Figure 2 shows the cyclic voltammograms obtained of Co^IBipy₃ either alone (**A**) or mixed beforehand with **1** in DMF for 12 h at 50 °C (**B**). Cyclic voltammogram of **A** revealed a 2-electron reduction wave at E° = -1.55 V vs. SCE, which corresponds to the Co^I/Co⁰ couple. The partially reversible 1-electron wave at E_p^{ox} = -0.86 V vs. SCE can be assigned to the oxidation of Co^I into Co^{II} species.³⁸ By comparison, cyclic voltammogram of **B** disclosed a slower

electron transfer, presenting also a 2-electron reduction wave, but at $E^\circ = -1.58$ V vs. SCE.

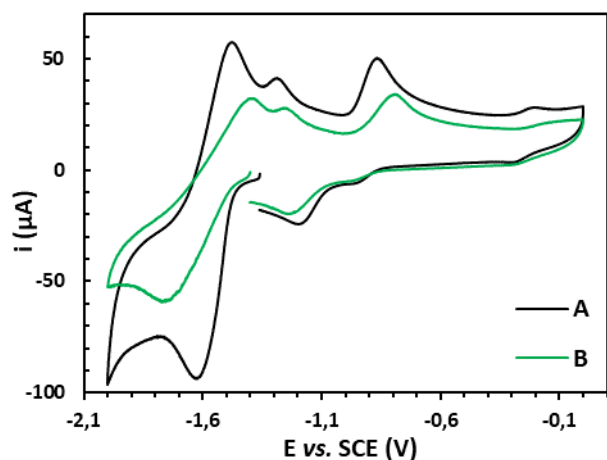
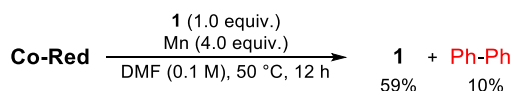


Figure 2. Cyclic voltammograms of **A** and **B** in DMF. **A**: 1 mM $[\text{Co}^{\text{I}}\text{Bipy}_3]^+$; **B**: 1 mM $[\text{Co}^{\text{I}}\text{Bipy}_3]^+$ mixed beforehand with **1** in DMF; glassy carbon working electrode; scan rate 1 V.s⁻¹. Supporting electrolyte: 100 mM tetrabutylammonium tetrafluoroborate. See SI S.7 for full experiment details.

The combination of this result together with the observation of free 2,2'-bipyridine ligand and DFT calculations, confirmed the formation of a new cobalt species, which could be consistent with $[\text{Co}^{\text{I}}\text{Bipy}_2(\text{PhCN})]$ (**Co1**), and could then be possibly reduced by Mn (see Figure S9). Indeed, even though we observed no clear sign of reactivity following the reduction step in the timescale of cyclic voltammetry (5 V/s down to 50 mV/s), adding Mn powder to a stoichiometric mixture of **Co-Red** and **1** did lead to the conversion of 41% of **1** and the formation of biphenyl **4** (Ph-Ph) in 10% yield after stirring in DMF at 50 °C for 12 h (Scheme 4).

Scheme 4. Stoichiometric reactions with **Co-Red**, **1** and Mn in DMF (0.1 M), 50 °C, 12 h.^a

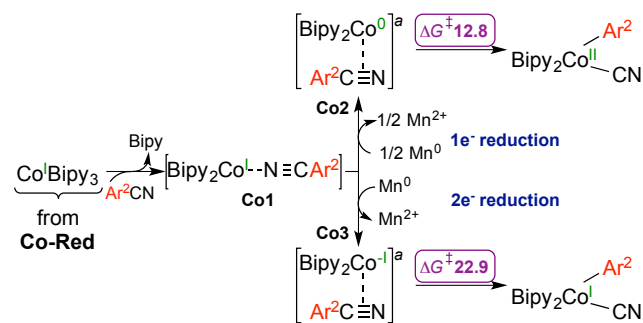


^aYields determined by GC using *n*-pentadecane as internal standard.

Therefore, all these results led us to consider an initiation phase comprised of (i) formation of $[\text{Co}^{\text{I}}\text{Bipy}_2(\text{PhCN})]$ **Co1**, by substitution of one 2,2'-bipyridine of $\text{Co}^{\text{I}}\text{Bipy}_3$ arising from **Co-Red**, by one benzonitrile and (ii) reduction of the resulting complex by Mn, prior to the insertion into the $\text{C}(sp^2)\text{-CN}$ bond (Scheme 5). Besides, the presence of this initiation phase would be in agreement with the relatively low conversion of **1** with **Co-Red** in the presence of Mn (Scheme 4) and the longer induction period needed to activate **1** than **2**, which has been observed on the plot of the time dependence for the reaction progress (Figure S3). Of note, since the cyclic voltammogram of **B** displayed a 2-electron reduction wave, we investigated the possible involvement of formal Co^0 (**Co2**) or formal Co^{-1} (**Co3**) spe-

cies for the insertion into the $\text{C}(sp^2)\text{-CN}$ bond of benzonitrile **1**.

Scheme 5. Computational data for the involvement of formal cobalt(0)^a or cobalt(-I)^a species in the initiation phase for the insertion into the $\text{C}(sp^2)\text{-CN}$ bond of **1**.

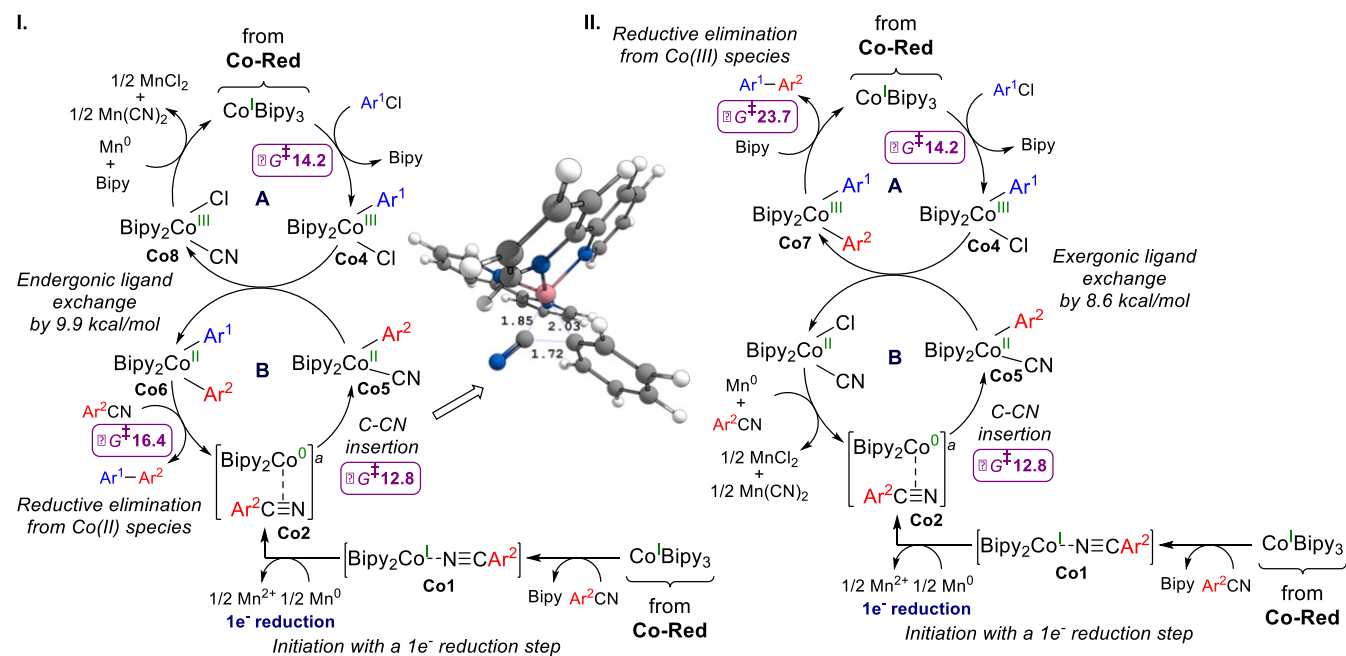


^aOxidation states are indicative as it is known that 2,2'-bipyridine is a redox non-innocent ligand that can bear the charge repartition.

As showed in Scheme 5, primary DFT calculations suggested that both species could be accounted for the insertion into the $\text{C}(sp^2)\text{-CN}$ bond, but with a quite higher free energy of activation computed for **Co3** (22.9 kcal/mol) than for **Co2** (12.8 kcal/mol) (see Schemes S20 and S21 for further details).

As a consequence, we propose the two following catalytic cycles depicted in Scheme 6. In both cases, first, $\text{CoBr}_2\text{Bipy}_2$ is reduced by Mn to afford $\text{Co}^{\text{I}}\text{Bipy}_3$ after ligand redistribution (Equation 1). On one hand, insertion into C-Cl bond occurs to give **Co4** (cycles **I-A** and **II-A**). On the other hand, substitution of one 2,2'-bipyridine by one benzonitrile leads to the complex **Co1**, which can then undergo reduction by one electron from Mn to afford complex **Co2** (Initiation). This is driven by subsequent insertion into the $\text{C}(sp^2)\text{-CN}$ bond, allowing **Co5**, with a free energy of activation of 12.8 kcal/mol when $\text{Ar}^2 = \text{Ph}$. After that, two different ligand exchanges might take place between complexes **Co4** and **Co5**. Indeed, the two aryl ligands could be carried either by a Co^{II} species (**Co6**) (Scheme 6, **I**) or a Co^{III} species (**Co7**) (Scheme 6, **II**), that then, would each ultimately undergo irreversible reductive elimination to afford the biaryl product. These two steps, for one and the other possibilities, were evaluated by DFT calculations with **1** and **2** as model substrates. Ligand exchange to form **Co6** is endergonic by 9.9 kcal/mol. The following reductive elimination requires 16.4 kcal/mol of free energy of activation and is exergonic by 18.8 kcal/mol (see Scheme S18). On the other hand, the exchange to generate **Co7** is now exergonic by 8.6 kcal/mol, but the consecutive reductive elimination step necessitates 23.7 kcal/mol of free energy of activation, which is higher than the one computed in the mechanism **I** (see Scheme S19). Therefore, even though more experiments would still be needed to fully rule out other mechanistic cycles, all those considerations led us to favor the proposed mechanism **I**. Finally then, to close the catalytic cycle **I**, irreversible reductive elimination occurs from Co^{II} species **Co6** to afford the biaryl product and

Scheme 6. Simplified proposed catalytic cycles with ΔG^\ddagger_{323} of the corresponding insertion/reductive elimination steps (kcal/mol) for $\text{Ar}^1 = 4\text{-MeCO}_2\text{C}_6\text{H}_4$ and $\text{Ar}^2 = \text{Ph}$, and geometry of the C-CN bond activation TS with selected distances in Å (see S8.2 for full details on DFT calculations). I. Reductive elimination occurs on a cobalt(II) species in cycle B; II. Reductive elimination occurs on a cobalt(III) species in cycle A.



^aOxidation state is indicative as it is known that 2,2'-bipyridine is a redox non-innocent ligand that can bear the charge repartition regenerate formal Co^0 species able to activate benzonitrile derivatives again (cycle **B**), whereas reduction of **Co8** by Mn and re-coordination of 2,2'-bipyridine ligand regenerates $\text{Co}^{\text{I}}\text{Bipy}_3$ (cycle **I-A**).

Conclusion

In conclusion, we have developed a simple cobalt-catalyzed cross-electrophile coupling between benzonitrile derivatives and aryl halides under mild conditions. The use of AlMe_3 Lewis acid boosts the reactivity of benzonitrile derivatives and promotes cross-selectivity without overly affecting functional group tolerance. Furthermore, we believe this work brings major insights into the understanding of this type of reactivity and the mechanism of cobalt-catalyzed cross-electrophile couplings. On one hand, X-Ray structure determination of unusual **Co-Red** species has revealed an original reduction/ligand redistribution from $\text{CoBr}_2\text{Bipy}_2$ pre-catalyst by Mn, which, associated with catalytic and stoichiometric experiments, indicated a $\text{Co}^{\text{I}}\text{Bipy}_3$ active species towards aryl halides. On the other hand, stoichiometric studies combined with cyclic voltammetry experiments suggested the involvement of a new cobalt complex induced by replacement of 2,2'-bipyridine ligand by benzonitrile derivative. This latter can then be further reduced by 1 or 2e⁻ into formal Co^0 or Co^{-1} species and insert into the $\text{C}(sp^2)\text{-CN}$ bond, which allowed us to propose a mechanism involving two low-valent cobalt complexes of different oxidation states. DFT calculations shed light on the feasibility of the mechanisms with either formal Co^0 or Co^{-1} active species for benzonitrile derivatives, but supported the thermodynamically more favora-

ble mechanism with formal Co^0 species and subsequent reductive elimination from Co^{II} instead of Co^{III} species. Work is still ongoing in our laboratory to get a deeper mechanistic insight and a better understanding of the activation of $\text{C}(sp^2)\text{-CN}$ bond by cobalt complexes in order to develop new reactivities.

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Notes

The authors declare no competing financial interest.

ASSOCIATED CONTENT

The Supporting Information is available free of charge via the Internet at <http://pubs.acs.org>.

Reaction optimization tables, mechanistic and stoichiometric studies, synthetic procedures, cyclic voltammetry, DFT calculations and characterization data NMR spectra

X-Ray data for **Co-Red**

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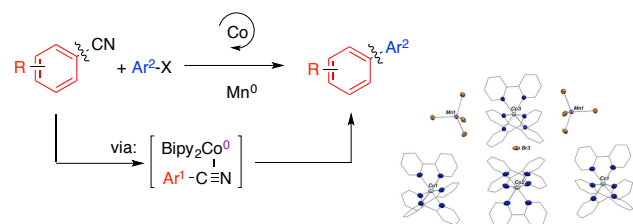
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For Table of Contents Only



- *Co-catalyzed C-CN activation*
 - *mild cross-electrophile coupling*
 - *low-valent Co species X-Ray structure*
 - *two low-valent Co species mechanism*
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