C–H Activation

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Direct Cross-Coupling of C–H Bonds with Grignard Reagents through Cobalt Catalysis**

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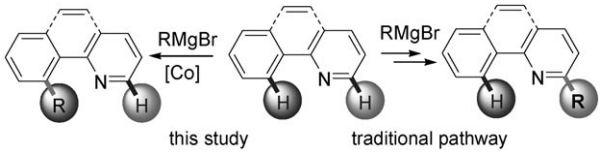
Many methods have recently been developed to construct C–C bonds through direct C–H transformations.[1] Among these methods, various transition metals have been shown to be effective in the last two decades.[2,3] The first-row transition-metal catalysts, such as iron complexes,[4,5] have drawn much attention recently as a result of their ready availability, low cost, relatively low toxicity, and unique catalytic abilities. Cases where the catalytic direct C–H transformation is mediated by Co catalysis are very rare.[6] On the other hand, various organometallic reagents have been successfully used to facilitate such transformations.[7] However, much more active Grignard reagents have never been successfully applied as an intermolecular coupling partner with C–H bonds. Herein, we demonstrated the first successful example of cobalt-catalyzed direct C–H transformation with both aryl and alkyl Grignard reagents as nucleophiles to facilitate C–C bond formation.

In other studies, the directing group orientation was considered useful to control the regioselectivity in C–H activation.[8] Among different anchoring groups, nitrogen-contained groups were frequently used owing to their good compatibility with transition metals and synthetic applications.[5g,h,7h,9] Initially, we chose the benzo[*h*]quinoline (**1a**) as the substrate to explore the reactivity of Grignard reagents in the presence of transition-metal catalysts. However, in the absence of any catalyst, the direct nucleophilic attack of pyridine derivatives at the 2-position by Grignard reagents is a big challenge (traditional pathway, Scheme 1).[10] For instance, even much less active organozinc reagents promote such a reaction through nickel catalysis.[7k] We propose that the presence of a suitable transition-metal catalyst and lowering the reaction temperature might be the good strategy to decrease the reactivity of RMgBr toward the direct addition to pyridine derivatives.



Scheme 1. New catalytic pathway beyond the traditional nucleophilic addition of RMgBr in the presence of a Co catalyst.

After many trials to achieve the goal, the desired cross-coupling finally took place smoothly with $Co(acac)_3$ as a catalyst in the presence of TMEDA and DCB in THF at room temperature (Table 1, entry 1).[11] Certainly, no desired product **3aa** was formed in the absence of catalyst, under otherwise identical conditions with Grignard reagents.

Next, the reactivity of various Grignard reagents was investigated (Table 1). Phenyl Grignard reagents bearing different substituents provided the desired products in moderate to excellent yields. The steric effect was important in influencing the reaction outcome. Thus, increase of the steric hindrance dramatically decreased the yield (compare Table 1, entries 2, 3, and 4). Meanwhile, further increase of steric hindrance completely inhibited the transformation (Table 1, entry 14). Importantly, the functional groups MeO (Table 1, entries 8 and 9), F (Table 1, entry 11), and Cl (Table 1, entry 12) are compatible. These findings offer the opportunity for the orthogonal coupling to afford more complicated molecules.

This direct cross-coupling can be extended to alkyl Grignard reagents for the constructions of $C(sp^2)$–$C(sp^3)$ bonds. Interestingly, MeMgBr showed the best reactivity and the desired methylated product **3aq** was isolated in an excellent yield (Table 1, entry 17). However, other alkyl Grignard reagents gave much lower yields and only linear products were obtained (Table 1, entries 18–21). Unfortunately, under the same conditions, vinylMgBr completely failed to facilitate this cross-coupling reaction (Table 1, entry 22).

Moreover, different benzo[*h*]quinoline compounds were investigated (Scheme 2). We found that this transformation was very sensitive to steric effects. When either a Ph or Me group was introduced at the 2-position, the coupling was completely inhibited and only the starting material was recovered (**3ba** and **3ca**). If the substituent was introduced at the 9-position, the cross-coupling indeed took place while

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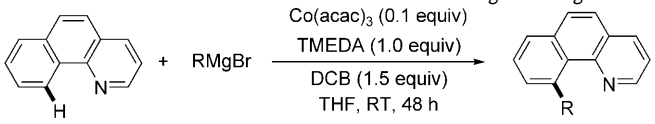
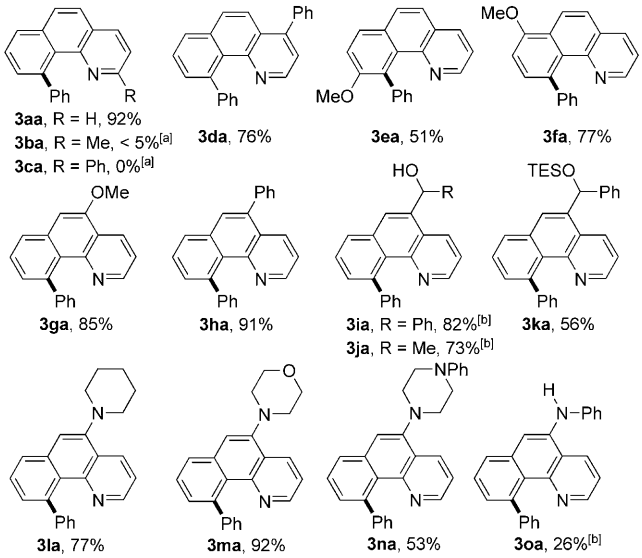
Table 1: Direct functionalization of **1a** with various Grignard reagents.[a]



Entry	R (**2**)	Product (**3**)	Yield [%][b]
1	Ph (**2a**)	**3aa**	92
2	2-tolyl (**2b**)	**3ab**	41
3	3-tolyl (**2c**)	**3ac**	93
4	4-tolyl (**2d**)	**3ad**	75
5	4-*t*BuC$_6$H$_4$ (**2e**)	**3ae**	75
6	4-C$_6$H$_5$C$_6$H$_4$ (**2f**)	**3af**	68
7	4-vinylC$_6$H$_4$ (**2g**)	**3ag**	82
8	3-MeOC$_6$H$_4$ (**2h**)	**3ah**	93
9	4-MeOC$_6$H$_4$ (**2i**)	**3ai**	88
10	4-Me$_2$NC$_6$H$_4$ (**2j**)	**3aj**	63
11	4-FC$_6$H$_4$ (**2k**)	**3ak**	76
12	4-ClC$_6$H$_4$ (**2l**)	**3al**	66
13	3,5-Me$_2$C$_6$H$_3$ (**2m**)	**3am**	85
14	2,4,6-Me$_3$C$_6$H$_2$ (**2n**)	**3an**	< 5
15	1-naphthyl (**2o**)	**3ao**	71
16	2-naphthyl (**2p**)	**3ap**	70
17	Me (**2q**)	**3aq**	83
18	Et (**2r**)	**3ar**	54
19	*n*-hexyl (**2s**)	**3as**	40
20	*n*-octyl (**2t**)	**3at**	19
21	benzyl (**2u**)	**3au**	42
22	vinyl (**2v**)	**3av**	0

[a] Reaction conditions: 0.28 mmol of **1a**, 1.12 mmol of Grignard reagent, 0.028 mmol of Co(acac)$_3$, 0.28 mmol of TMEDA, 0.42 mmol of 2,3-dichlorobutane. [b] Yield of isolated product. acac = acetylacetonate, DCB = 2,3-dichlorobutane, THF = tetrahydrofuran, TMEDA = *N*,*N*,*N*′,*N*′-tetramethylethylenediamine.

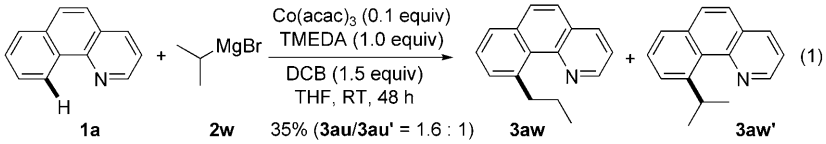


Scheme 2. Direct functionalization of C–H bond with different substrates. Reaction conditions: 0.28 mmol of substrate, 1.12 mmol of PhMgBr, 0.028 mmol of Co(acac)$_3$, 0.28 mmol of TMEDA, 0.42 mmol of 2,3-dichlorobutane, RT, 48 h. Reported yield is of isolated product. [a] Product was detected by GC analysis with *n*-dodecane as an internal standard. [b] Carried out using 1.68 mmol of PhMgBr and 0.56 mmol of 2,3-dichlorobutane. TES = triethylsilyl.

the yield was also low (**3ea**). To our satisfaction, the substituents at other positions did not affect the yield and the desired products were obtained in good to excellent yields (**3da**, **3fa**–**3na**). Notably, various groups survived under the reaction condition. A free hydroxy group and a silyl protected ether survived well (**3ia**–**3ka**). Furthermore, a tertiary amino group did not affect the yield (**3la**–**3na**), while the secondary amine dramatically lowered the yield (**3oa**).

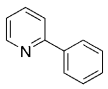
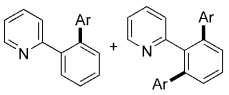
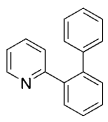
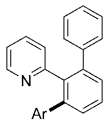
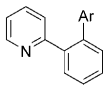
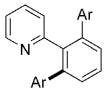
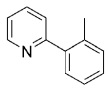
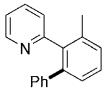
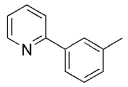
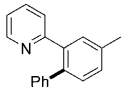
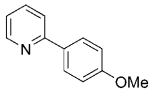
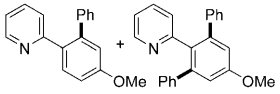
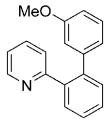
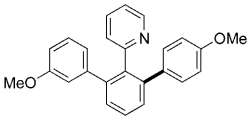
2-Phenylpyridine derivatives were also suitable for this transformation (Table 2). When 2-phenylpyridine was the substrate, the direct arylation took place and afforded monoarylated and diarylated products as a mixture in good yield (Table 2, entries 1, 3, and 5). To our delight, diarylated products could be selectively produced by simply lengthening the reaction time or increasing the amount of Grignard reagents (Table 2, entries 2, 4, and 6). Meanwhile, when one of the *ortho* positions or *meta* positions was blocked, only a single product was obtained in moderate to good yields (Table 2, entries 7–13, and 15). Moreover, the mixture of mono- and di-arylated products was also obtained when the *para*-substituted substrate was applied (Table 2, entry 14).

Further investigations unveiled the mechanistic pathway of this unprecedented transformation.[11] In previous reports a radical process was generally proposed.[6a–c] We first tested our developed process in the presence of radical scavengers. To our surprise, the reaction ran very smoothly even in the presence of two equivalents of TEMPO (2,2,6,6-tetramethyl-1-piperidinyloxy, free radical). When 1,1-diphenylethylene was added to the reaction mixture, the radical addition product was not observed. On the other hand, the dimerization of starting materials (10,10′-bibenzo[*h*]quinoline) was not detected. Thus, the radical process was tentatively ruled out. Interestingly, with the use of *i*PrMgBr as a reagent, a mixture of the products with both linear and branched alkylation was isolated in a ratio of 1.6:1 [Eq. (1)]. Therefore, we hypothesize that both R–Co and H–Co species exist in the catalytic system. Moreover, starting from 10-[D]benzo[*h*]quinoline, the amount of 6-[D]2-methoxylnaphthylene is almost equal to that of the desired coupling product [Eq. (2)]. Finally, the intermolecular isotopic studies indicated that the cleavage of the C–H bond was not involved in the rate determining step [Eq. (3); yield determined by ^{1}H NMR spectroscopy].

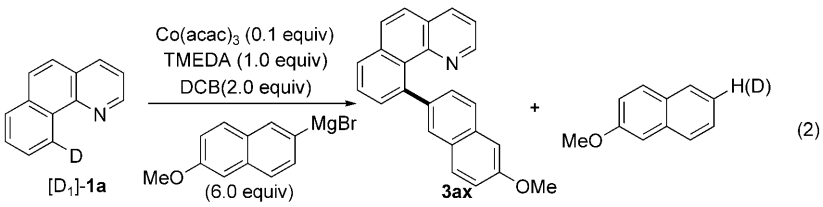


Thus, we propose the catalytic cycle shown in Scheme 3. In the presence of TMEDA and Grignard reagents, the catalytic active species **5** is produced followed by reductive elimination of the Co^{III} intermediate **4**. Species **5** could further undergo oxidative addition with benzo[*h*]quinoline (**1a**) to

Table 2: Direct functionalization with different 2-phenylpyridinyl substrates.[a]

Entry	Substrate	Product(s)	Yield of monosubstituted, disubstituted products [%][b]
1			30, 35 (Ar = Ph)
2			–, 62[c] (Ar = Ph)
3			17, 49 (Ar = 4-MeOC$_6$H$_4$)
4			–, 63[d] (Ar = 4-MeOC$_6$H$_4$)
5			10, 55 (Ar = 3-MeOC$_6$H$_4$)
6			–, 64[d] (Ar = 3-MeOC$_6$H$_4$)
7			68, – (Ar = Ph)
8			64, – (Ar = 4-MeOC$_6$H$_4$)
9			59, – (Ar = 3-MeOC$_6$H$_4$)
10			70, – (Ar = 4-MeOC$_6$H$_4$)
11			74, – (Ar = 3-MeOC$_6$H$_4$)
12			40, –
13			38, –
14			8, 52
15			63, –

[a] Reaction conditions: 0.28 mmol of substrate, 1.68 mmol of Grignard reagent, 1.12 mmol of LiCl, 0.028 mmol of Co(acac)$_3$, 0.28 mmol of TMEDA, 0.56 mmol of 2,3-dichlorobutane, RT, 48 h. [b] Yield of isolated monoarylated product and (if applicable) the diarylated product. [c] Carried out with 8.0 equiv of ArMgBr, 3.0 equiv of 2,3-dichlorobutane, 72 h. [d] Carried out with 6.0 equiv of ArMgBr, 2.0 equiv of 2,3-dichlorobutane, 72 h.



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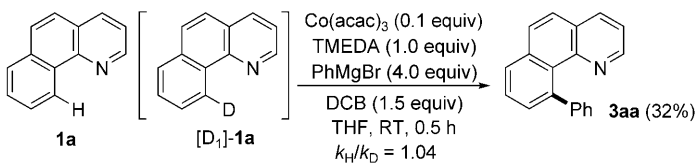


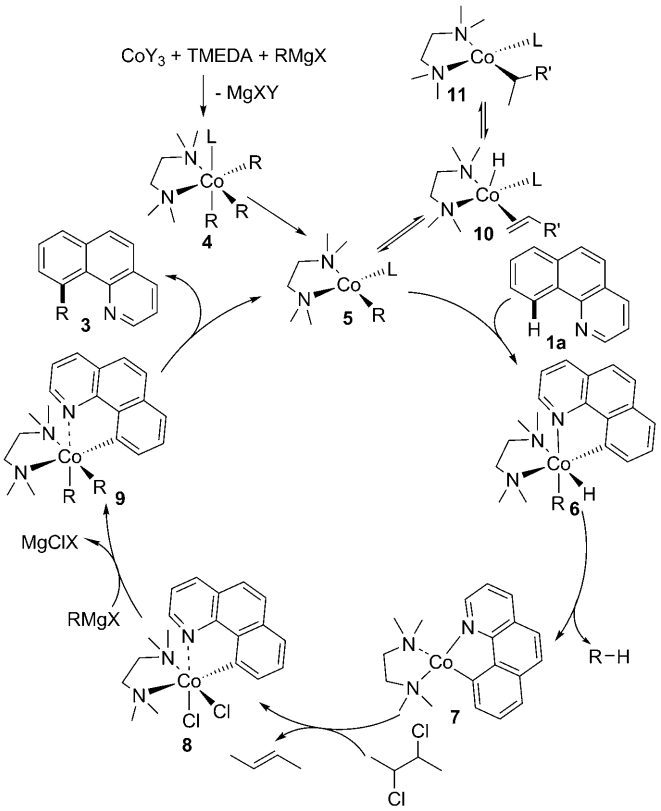
(3)

generate a new Co^{III} species **6**. After the reductive elimination to generate the by-product R–H with the sacrifice of 1 equivalent of RMgX, the Co^{I} complex **7** that is produced is oxidized by 2,3-butyldichloride to produce the Co^{III} species **8**. With the double transmetalations, the new Co^{III} complex **9** is produced. After subsequent reductive elimination to generate the desire coupling product **3**, the Co^{I} species **5** is regenerated to facilitate the catalytic cycle. If the β-hydrogen atom is present and the steric hindrance increases in the Grignard reagents, for example when using *i*PrMgBr, β-hydride elimination produces the Co–H species **10**, which undergoes the insertion in the reverse direction to generate the isomerized intermediate **5**. By following the same coupling catalytic pathway, the propylation was observed.

In summary, we have reported the first highly regioselective cobalt-catalyzed C–H transformation of benzo[*h*]quilonine and phenylpyridine derivatives with Grignard reagents at room temperature. An unprecedented reactivity of Grignard reagents with pyridine derivatives was presented. Various substituents on the heterocycles were compatible under these mild reaction conditions. In addition to aryl Grignard reagents, alkyl Grignard reagents also showed good to excellent reactivity. To date, this is the only successful example that applies Grignard reagents as the coupling partners in direct C–H functionalization. Based on our preliminary studies, the radical process was excluded and a new catalytic pathway via an oxidative addition is now highly preferred. Further studies to explore this new method and clearly understand the reaction pathway are underway.

Experimental Section

Typical procedure for cobalt-catalyzed arylation of benzo[*h*]quinoline with an aryl Grignard reagent (Table 1, entry 1): Phenylmagnesium bromide (1.12 mL, 1.00 M, 1.12 mmol) in a solution of THF, TMEDA (33 mg, 0.28 mmol), and 2,3-dichlorobutane (53 mg, 0.42 mmol) were added to a Schlenk tube containing benzo[*h*]quinoline (50 mg, 0.28 mmol) and Co(acac)$_3$ (10 mg, 0.028 mmol) at RT. The reaction mixture was stirred at RT for 48 h and then quenched by the addition of saturated aqueous solution of NaHCO$_3$ (5 mL). After extraction with ethyl acetate (10 × 3 mL), the organic layer was dried over MgSO$_4$ and concentrated under reduced pressure. The crude residue was purified by column chromatography on silica gel (eluent: first *n*-hexane to



Scheme 3. Plausible catalytic pathway for direct C–H functionalization with RMgX through Co catalysis.

remove the biphenyl, then toluene) to afford the product as a white solid (65.7 mg, 92% yield).

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[11] See the Supporting Information for details.

