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Cobalt-Catalyzed *Ortho*-Arylation of Aromatic Imines with Aryl Chlorides

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ABSTRACT

An *ortho*-arylation reaction of aromatic imines with aryl chlorides has been achieved using a cobalt–*N*-heterocyclic carbene catalyst in combination with a neopentyl Grignard reagent. The reaction takes place at room temperature to afford biaryl products in moderate to good yields.

Biaryls are key structural units in numerous functional molecules relevant to medicinal chemistry and materials science. While their syntheses have heavily relied on transition-metal-catalyzed cross-coupling between halogenated arenes and metalated arenes,[1] the past decade has witnessed significant advances in a more straightfoward and atom-economical alternative, that is, direct arylation via aromatic C–H bond activation.[2] Among several types of C–H arylation reactions, arylation of arenes bearing *ortho*-directing groups features high efficiency and perfect regiocontrol of the C–H bond activation. While the majority of catalysts for *ortho*-arylation reactions are based on palladium, rhodium, and ruthenium,[2,3] recent studies have demonstrated promising catalytic activities of inexpensive first-row transition metals.[4] Nakamura and co-workers developed iron-catalyzed oxidative arylation of 2-arylpyridines and aryl imines using arylzinc or aryl Grignard reagents in combination with a dichloroalkane oxidant, which takes place at a temperature as low as 0 °C.[5] Wang, Shi, and co-workers reported that cobalt also catalyzes a similar reaction of 2-arylpyridines with aryl Grignard reagents at room temperature (Scheme 1a).[6] Despite the inexpensive catalysts and the mild reaction conditions, the requirement of a large amount (typically 3–4 equiv) of a preformed arylmetal reagent constitutes a major drawback in these arylation reactions.[7,8] Here, we report that cobalt-catalyzed *ortho*-arylation of aryl imines can be achieved using an aryl chloride as a readily

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[1] (a) *Metal-Catalyzed Cross-Coupling Reactions*; de Meijere, A., Diederich, F., Eds.; Wiley-VCH: Weinheim, 2004. (b) *Modern Arylation Methods*; Ackermann, L., Ed.; Wiley-VCH: Weinheim, 2009.

[2] For selected reviews, see: (a) Yeung, C. S.; Dong, V. M. *Chem. Rev.* **2011**, *111*, 1215. (b) Daugulis, O. *Top. Curr. Chem.* **2010**, *292*, 57. (c) Ackermann, L.; Vicente, R. *Top. Curr. Chem.* **2010**, *292*, 211. (d) Bouffard, J.; Itami, K. *Top. Curr. Chem.* **2010**, *292*, 231. (e) Lyons, T. W.; Sanford, M. S. *Chem. Rev.* **2010**, *110*, 1147. (f) Colby, D. A.; Bergman, R. G.; Ellman, J. A. *Chem. Rev.* **2010**, *110*, 624. (g) Ackermann, L.; Vicente, R.; Kapdi, A. R. *Angew. Chem., Int. Ed.* **2009**, *48*, 9792.

[3] For latest examples of *ortho*-arylation reactions with second-row transition metal catalysts, see: (a) Wencel-Delord, J.; Nimphius, C.; Patureau, F. W.; Glorius, F. *Angew. Chem., Int. Ed.* **2012**, *51*, 2247. (b) Kalyani, D.; McMurtey, K. B.; Neufeldt, S. R.; Sanford, M. S. *J. Am. Chem. Soc.* **2011**, *133*, 18566. (c) Wang, X.; Leow, D.; Yu, J.-Q. *J. Am. Chem. Soc.* **2011**, *133*, 13864.

[4] (a) Sun, C.-L.; Li, B.-J.; Shi, Z.-J. *Chem. Rev.* **2011**, *111*, 1293. (b) Nakamura, E.; Yoshikai, N. *J. Org. Chem.* **2010**, *75*, 6061. (c) Kulkarni, A. A.; Daugulis, O. *Synthesis* **2009**, 4087.

[5] (a) Norinder, J.; Matsumoto, A.; Yoshikai, N.; Nakamura, E. *J. Am. Chem. Soc.* **2008**, *130*, 5858. (b) Yoshikai, N.; Matsumoto, A.; Norinder, J.; Nakamura, E. *Angew. Chem., Int. Ed.* **2009**, *48*, 2925. (c) Yoshikai, N.; Matsumoto, A.; Norinder, J.; Nakamura, E. *Synlett* **2010**, 313. (d) Ilies, L.; Asako, S.; Nakamura, E. *J. Am. Chem. Soc.* **2011**, *133*, 7672. (e) Yoshikai, N.; Asako, S.; Yamakawa, T.; Ilies, L.; Nakamura, E. *Chem.—Asian J.* **2011**, *6*, 3059. (f) Ilies, L.; Kobayashi, M.; Matsumoto, A.; Yoshikai, N.; Nakamura, E. *Adv. Synth. Catal.* **2012**, *354*, 593.

[6] Li, B.; Wu, Z.-H.; Gu, Y.-F.; Sun, C.-L.; Wang, B.-Q.; Shi, Z.-J. *Angew. Chem., Int. Ed.* **2011**, *50*, 1109.

[7] These reactions intrinsically require 2 equiv of the arylmetal reagent because 1 equiv of the reagent is used for the removal of the *ortho*-hydrogen atom and another 1 equiv for the arylation.

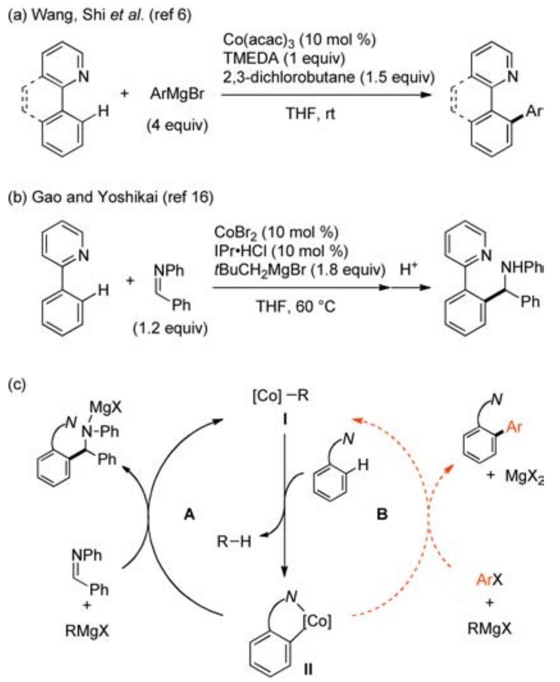
[8] Nakamura et al. demonstrated, for their iron-catalyzed reaction, that preparation of an aryl Grignard reagent can be bypassed by the direct use of an aryl bromide and metallic magnesium (see ref 5f).

[9] For direct arylation of aryl imines with aryl electrophiles, see: (a) Oi, S.; Ogino, Y.; Fukita, S.; Inoue, Y. *Org. Lett.* **2002**, *4*, 1783. (b) Ackermann, L. *Org. Lett.* **2005**, *7*, 3123. (c) Ackermann, L.; Althammer, A.; Born, R. *Tetrahedron* **2008**, *64*, 6115. (d) Kim, M.; Kwak, J.; Chang, S. *Angew. Chem., Int. Ed.* **2009**, *48*, 8935.

10.1021/ol301934y

available arylating agent under mild room-temperature conditions.[9–13]

Scheme 1

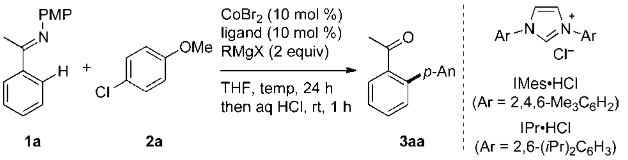


As a part of our continuing studies on cobalt-catalyzed ortho C–H bond functionalization,[14,15] we recently reported on a coupling reaction of a 2-arylpyridine derivative with an aldimine promoted by a cobalt–*N*-heterocyclic carbene catalyst and *t*BuCH$_2$MgBr (Scheme 1b).[16] A putative mechanism for this reaction involves cyclometalation of 2-arylpyridine with an alkylcobalt species **I** to give a cobaltacycle species **II** (Scheme 1c).[17] The intermediate **II** would then undergo nucleophilic attack on the aldimine, which is followed by transmetalation with the Grignard reagent to afford the addition product and regenerate the species **I** (catalytic cycle A). Based on this mechanistic assumption, we envisioned that interception of a cobaltacycle species such as **II** with an aryl electrophile would result in an *ortho*-arylation product (catalytic cycle B).[18]

With this hypothesis, we commenced our study with the reaction of acetophenone imine **1a** with 4-chloroanisole **2a** (Table 1). The Co–IPr–*t*BuCH$_2$MgBr system we used for the reaction of a 2-arylpyridine with an aldimine (Scheme 1b)[16] promoted the desired reaction to a small extent at room temperature (25 °C), affording the biaryl product **3aa** in 3% yield (entry 1). Use of IMes•HCl instead of IPr•HCl significantly enhanced the reaction efficiency to afford **3aa** in 65% yield (entry 2), which was accompanied by a byproduct arising from cross-coupling of **2a** and *t*BuCH$_2$MgBr (17% yield). No diarylation product was observed. According to the hypothetical catalytic cycle (Scheme 1c), we surmise that the cross-coupling byproduct has formed via direct reaction of the alkylcobalt species **I** and **2a**. In line with this conjecture, the use of 4-bromoanisole in place of **2a** produced the cross-coupling product as the major product, with only a trace amount of **3aa**.

The neopentyl Grignard reagent was noted to play a critical role, because other Grignard reagents such as Me$_3$SiCH$_2$MgCl, EtMgBr, *i*PrMgBr, and PhMgBr poorly promoted the reaction (entries 3–6). Further efforts to improve the Co–IMes–*t*BuCH$_2$MgBr system by modification of various reaction parameters (e.g., stoichiometry, temperature) were not fruitful. For example, the reaction at an elevated temperature (80 °C) resulted in a lower yield of **3aa** (entry 7) and an increase of the undesirable coupling product between **2a** and *t*BuCH$_2$MgBr (37%). While other ligands including mono- and bidentate phosphines and

Table 1. Screening of Reaction Conditions[a]



entry	ligand (mol %)	RMgX	temp (°C)	yield (%)[b]
1	IPr•HCl (10)	*t*BuCH$_2$MgBr	25	3
2	IMes•HCl (10)	*t*BuCH$_2$MgBr	25	65[c]
3	IMes•HCl (10)	Me$_3$SiCH$_2$MgCl	25	0
4	IMes•HCl (10)	EtMgBr	25	0
5	IMes•HCl (10)	*i*PrMgBr	25	1
6	IMes•HCl (10)	PhMgBr	25	6
7	IMes•HCl (10)	*t*BuCH$_2$MgBr	80	41
8[d]	PEt$_3$ (30)	*t*BuCH$_2$MgBr	80	63[c]
9[d]	PMe$_3$ (30)	*t*BuCH$_2$MgBr	80	35
10[d]	PPh$_3$ (30)	*t*BuCH$_2$MgBr	80	<1
11[d]	PCy$_3$ (30)	*t*BuCH$_2$MgBr	80	17

[a] Unless otherwise noted, the reaction was performed using 0.3 mmol of **1a** and 0.6 mmol of **2a**. PMP = *p*-An = 4-MeOC$_6$H$_4$. [b] Determined by GC using *n*-tridecane as an internal standard. [c] Isolated yield. [d] 0.36 mmol of **2a** was used.

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(10) For direct arylation of aryl imines with aryl nucleophiles, see ref 5 and the following: Tredwell, M. J.; Gulias, M.; Bremeyer, N. G.; Johansson, C. C. C.; Collins, B. S. L.; Gaunt, M. J. *Angew. Chem., Int. Ed.* **2011**, *50*, 1076.

(11) For cobalt-catalyzed nondirected C–H arylation reactions with aryl halides, see: (a) Liu, W.; Cao, H.; Xin, J.; Jin, L.; Lei, A. *Chem.—Eur. J.* **2011**, *17*, 3588. (b) Li, H.; Sun, C.-L.; Yu, M.; Yu, D.-G.; Li, B.-J.; Shi, Z.-J. *Chem.—Eur. J.* **2011**, *17*, 3593.

(12) For a review on mild metal-catalyzed C–H bond functionalization, see: Wencel-Delord, J.; Dröge, T.; Liu, F.; Glorius, F. *Chem. Soc. Rev.* **2011**, *40*, 4740.

(13) During submission of this manuscript, a similar cobalt-catalyzed *ortho*-arylation reaction of 2-arylpyridines and *N*-pyridylindoles with aryl sulfamates and carbamates was reported: Song, W.; Ackermann, L. *Angew. Chem., Int. Ed.* **2012**, *51*, 8251.

(14) Yoshikai, N. *Synlett* **2011**, 1047.

(15) (a) Gao, K.; Lee, P.-S.; Fujita, T.; Yoshikai, N. *J. Am. Chem. Soc.* **2010**, *132*, 12249. (b) Gao, K.; Yoshikai, N. *J. Am. Chem. Soc.* **2011**, *133*, 400. (c) Gao, K.; Yoshikai, N. *Angew. Chem., Int. Ed.* **2011**, *50*, 6888. (d) Lee, P.-S.; Fujita, T.; Yoshikai, N. *J. Am. Chem. Soc.* **2011**, *133*, 17283. (e) Ding, Z.; Yoshikai, N. *Angew. Chem., Int. Ed.* **2012**, *51*, 4698.

(16) Gao, K.; Yoshikai, N. *Chem. Commun.* **2012**, *48*, 4305.

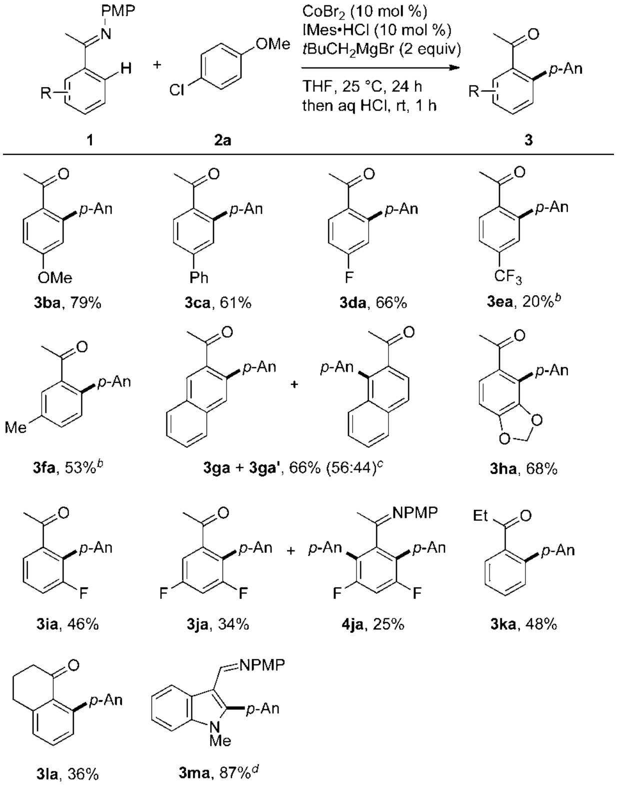
(17) Klein, H.-F.; Camadanli, S.; Beck, R.; Leukel, D.; Flörke, U. *Angew. Chem., Int. Ed.* **2005**, *44*, 975.

phenanthroline derivatives were poorly effective at 25 °C, use of PEt_3 (30 mol %) provided a comparable reaction efficiency at 80 °C, affording **3aa** in 63% yield (entry 8). Other monodentate phosphines such as PMe_3, PPh_3, and PCy_3 were much less effective (entries 9–11). Note that, in contrast to the Co–IMes system, the Co–PEt_3 system did not produce the cross-coupling byproduct.

With the Co–IMes and its alternative (i.e., Co–PEt_3) systems in hand, we first explored the scope of aromatic imines using **2a** as the arylating agent (Scheme 2). Imines bearing *para*-methoxy, phenyl, and fluoro groups smoothly participated in the reaction to afford the products **3ba**–**3da** in good yields. In contrast, an imine derived from *para*-trifluoromethyl acetophenone failed to react under the Co–IMes system, while the Co–PEt_3 system afforded the arylation product **3ea** in 20% yield. With a *meta*-methyl substituent, the less hindered position was selectively arylated (see **3fa**), while poor regioselectivity was observed for an imine derived from 2-acetonaphthone (see **3ga**). On the other hand, methylenedioxy and fluoro groups directed the reaction to take place in their proximity (see **3ha** and **3ia**), presumably because of their ability to direct the C–H metalation process by coordination or to stabilize the resulting carbon–metal bond.[15d,19–21] An imine derived from 3,5-difluoroacetophenone produced a substantial amount of the diarylation product **4ja**. In addition to the acetophenone derivatives, imines derived from propiophenone, tetralone, and indole-3-carbaldehyde were also arylated in moderate to good yields (**3ka**–**3ma**).[22]

We next explored the reaction of the imine **1a** or **1b** with a variety of aryl chlorides (Table 2). The Co–IMes system tolerated aryl chlorides bearing electronically different *para*-substituents including dimethylamino, siloxy, and fluoro groups (entries 1–6) but did not promote the reaction of *p*-chlorobenzotrifluoride at all.[23] The reaction of this highly electron-poor substrate was achieved with the Co–PEt_3 system in a moderate yield of 47% (entry 7). Under either catalytic systems, *p*-chlorothioanisole and *p*-chlorostyrene reacted rather sluggishly (entries 8 and 9), presumably because the desired reaction was inhibited by coordination of the thioether and vinyl moieties, respectively, to the catalyst. The reaction also tolerated *meta*-substituted (entries 10–12) and *ortho*-substituted aryl chlorides (entries 13–15), among which *m*-chlorobenzotrifluoride and 1-chloronaphthalene required the use of the Co–PEt_3 system (entries 12 and 15).

Scheme 2. Scope of Aryl Imines[a]



[a] The reaction was performed on a 0.3 mmol scale. [b] The reaction was performed under the Co–PEt_3 system (Table 1, entry 7). [c] The product ratio was determined by ^1H NMR. [d] The product was isolated without acidic hydrolysis.

Notably, the present cobalt catalysis allowed a twofold C–H/C–Cl coupling reaction. Thus, the reaction of **1a** (2.2 equiv) with *p*-dichlorobenzene under the Co–PEt_3 system afforded the terphenyl derivative **3aq** in a modest yield of 49% (Scheme 3).

The present *ortho*-arylation reaction represents a rare example of biaryl coupling reactions involving cobalt-mediated activation of unactivated aryl chlorides.[11a,24,25] To gain preliminary insight into the nature of the C–Cl bond activation step, we performed competition experiments using electronically different aryl chlorides (Scheme 4). The competition of chlorobenzene and an aryl chloride bearing a dimethylamino, methoxy, or fluoro group under Co–IMes catalysis resulted in the preferential reaction of the

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(18) For cobalt-catalyzed ortho C–H functionalization with *alkyl* chlorides, see: Chen, Q.; Ilies, L.; Nakamura, E. *J. Am. Chem. Soc.* **2011**, *133*, 428.

(19) (a) Ackermann, L.; Diers, E.; Manvar, A. *Org. Lett.* **2012**, *14*, 1154. (b) Ackermann, L.; Vicente, R.; Potukuchi, H. K.; Pirovano, V. *Org. Lett.* **2010**, *12*, 5032. (c) Campeau, L. C.; Parisien, M.; Jean, A.; Fagnou, K. *J. Am. Chem. Soc.* **2006**, *128*, 581. (d) Sonoda, M.; Kakiuchi, F.; Chatani, N.; Murai, S. *Bull. Chem. Soc. Jpn.* **1997**, *70*, 3117.

(20) (a) Clot, E.; Megret, C.; Eisenstein, O.; Perutz, R. N. *J. Am. Chem. Soc.* **2009**, *131*, 7817. (b) Clot, E.; Eisenstein, O.; Jasim, N.; Macgregor, S. A.; Mcgrady, J. E.; Perutz, R. N. *Acc. Chem. Res.* **2011**, *44*, 333.

(21) Deuterium-labeling experiments suggested the reversible nature of the cyclometalation process, while its detailed mechanism remains unclear (see the Supporting Information).

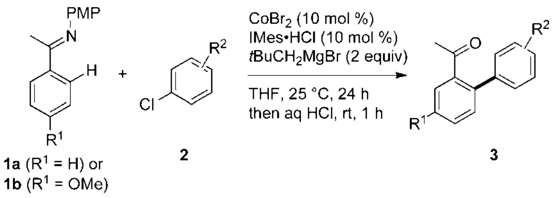
(22) Acetophenone failed to participate in the arylation reaction but underwent aldol reaction, while a small amount (3% by GC) of an arylation product was observed with *N*-methylbenzamide. For cobalt-catalyzed ortho C–H functionalization of benzamides, see ref 18 and the following: (a) Ilies, L.; Chen, Q.; Zeng, X.; Nakamura, E. *J. Am. Chem. Soc.* **2011**, *133*, 5221. (b) Chen, Q.; Ilies, L.; Yoshikai, N.; Nakamura, E. *Org. Lett.* **2011**, *13*, 3232.

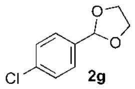
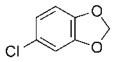
(23) The reason why the Co–IMes system was not effective remains unclear. The aryl chloride did not undergo any side reactions (e.g., cross-coupling with $tBuCH_2MgBr$) but was recovered almost completely.

(24) Hatakeyama, T.; Hashimoto, S.; Ishizuka, K.; Nakamura, M. *J. Am. Chem. Soc.* **2009**, *131*, 11949.

(25) For reviews on cobalt-catalyzed cross-coupling reactions, see: (a) Cahiez, G.; Moyeux, A. *Chem. Rev.* **2010**, *110*, 1435. (b) Hess, W.; Treutwein, J.; Hilt, G. *Synthesis* **2008**, 3537. (c) Gosmini, C.; Begouin, J. M.; Moncomble, A. *Chem. Commun.* **2008**, 3221.

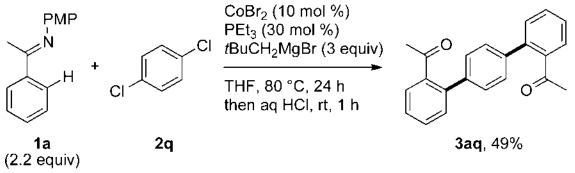
Table 2. Scope of Aryl Chlorides[a]



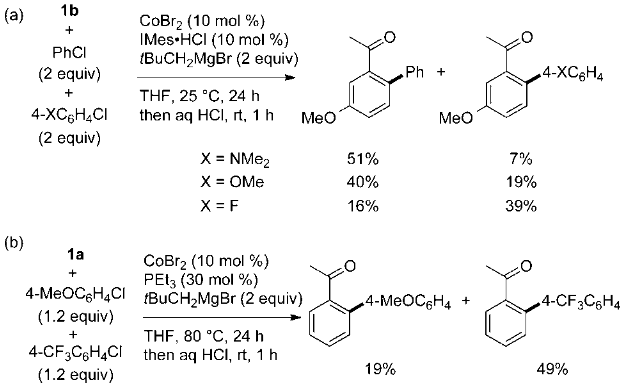
entry	imine	aryl chloride	yield (%)[b]
1	**1b**	**2b** (R^2 = H)	60
2	**1b**	**2c** (R^2 = 4-Me)	62
3	**1b**	**2d** (R^2 = 4-NMe_2)	71
4	**1b**	**2e** (R^2 = 4-OTBS)	67[c]
5	**1a**	**2f** (R^2 = 4-F)	63
6	**1b**	 **2g**	55[d]
7[e]	**1a**	**2h** (R^2 = 4-CF_3)	47
8[e]	**1a**	**2i** (R^2 = 4-SMe)	16
9	**1b**	**2j** (R^2 = 4-CH=CH_2)	2[f]
10	**1b**	**2k** (R^2 = 3-Me)	70
11	**1b**	 **2l**	63
12[e]	**1a**	**2m** (R^2 = 3-CF_3)	51
13	**1b**	**2n** (R^2 = 2-Me)	56
14	**1b**	**2o** (R^2 = 2-OMe)	54
15[e]	**1a**	**2p** (1-chloronaphthalene)	55

[a] The reaction was performed on a 0.3 mmol scale. [b] Isolated yield. [c] The siloxy group was converted to a hydroxy group by the hydrolysis. [d] The acetal moiety was converted to a formyl group by the hydrolysis. [e] The reaction was performed under the Co−PEt_3 system (Table 1, entry 7). [f] GC yield.

Scheme 3. Twofold Coupling Reaction



Scheme 4. Competition Experiments



electron-poorer aryl chloride (Scheme 4a). Likewise, the competition of *p*-chloroanisole and *p*-chlorobenzotrifluoride under the Co−PEt_3 system preferentially produced the arylation product of the latter (Scheme 4b). These results suggest higher reactivity of electron-poor aryl chlorides toward the putative cobaltacycle intermediate **II** (Scheme 1c). Note, however, that the aryl electrophile should not be too reactive as an aryl bromide, because the cross-coupling with *t*$BuCH_2MgBr$ overrides the desired direct arylation (vide supra).

In summary, we have developed Co−IMes and Co−PEt_3 catalytic systems for the *ortho*-arylation of aromatic imines with aryl chlorides. The former system allows arylation to take place at room temperature, while the latter complements some limitations of the former. Further efforts will be focused on the development of more robust and broadly applicable catalytic systems and the mechanistic investigation.

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Supporting Information Available. Experimental procedures and characterization of new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.