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Cobalt-Catalyzed *ortho*-C−H Alkylation of 2-Arylpyridines *via* Ring-Opening of Aziridines

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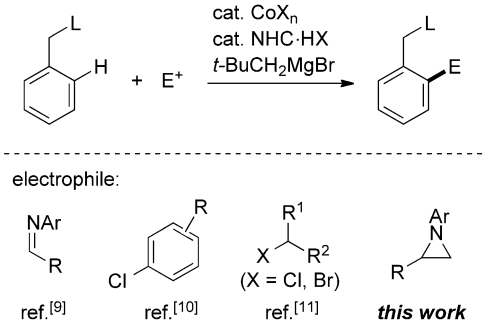
Abstract: A cobalt–N-heterocyclic carbene catalyst, in combination with neopentylmagnesium bromide, was found to promote *ortho*-C−H functionalization of 2-arylpyridines with 1,2-diarylaziridines through ring-opening alkylation. The reaction affords 1,1-diarylethanes bearing 2-amino functional groups in moderate to good yields under mild room-temperature conditions.

Keywords: aziridines; C−C bond formation; C−H functionalization; cobalt

Transition metal-catalyzed chelation-assisted C−H bond activation has attracted considerable attention as an atom- and step-economical approach to regioselective functionalization of aromatic compounds.[1] While C−H alkylation, alkenylation, and arylation reactions using alkenes, alkynes, and arylating agents (e.g., aryl halides, arylmetals, and arenes) have been extensively developed, exploration of other types of coupling partners is crucial for further expansion of the synthetic scope of this approach. In this context, recent years have witnessed remarkable progress in *ortho*-C−H functionalization reactions using carbon-based electrophiles such as alkyl halides[2,3] and those containing polar π-bonds (e.g, aldimines, aldehydes, isocyanates).[4,5] Recently, Li, Wan and co-workers added *N*-sulfonylaziridines to the repertoire of electrophiles, which served as coupling partners for Rh(III)-catalyzed *ortho*-C−H functionalization of 2-arylpyridines.[6]

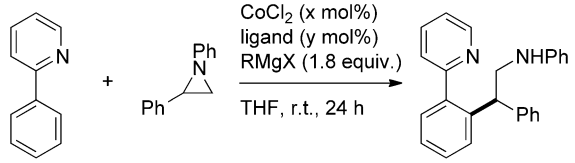
Over the past several years, our group has developed mild and cost-effective cobalt catalysts for a series of chelation-assisted C−H bond functionalization reactions, which can be classified into two types.[7] One involves insertion of unsaturated hydrocarbons such as alkynes and alkenes into the *ortho*-C−H bond,[8] and the other involves formal deprotonation of the *ortho*-C−H bond followed by electrophilic trapping. The feasibility of the latter type of reaction has been demonstrated for electrophiles such as aldimines,[9] aryl chlorides,[10] and alkyl chlorides/bromides.[11–13] Here, we report that aziridines also serve as viable electrophiles for this reaction manifold (Scheme 1). Thus, a cobalt–N-heterocyclic carbene catalyst, in combination with neopentyl-Grignard reagent, allows *ortho*-functionalization of 2-arylpyridines with 1,2-diarylaziridines *via* regioselective C−N bond cleavage, affording 1,1-diarylethanes bearing 2-amino groups.

We chose 2-phenylpyridine **1a** and 1,2-diphenylaziridine **2a** as model substrates for a screening of the reaction conditions (Table 1). A catalytic system consisting of $CoCl_2$ (10 mol%), IPr·HCl (10 mol%), and *t*-$BuCH_2MgBr$ (1.8 equiv.), which we previously used for the reaction of 2-arylpyridines and aldimines,[9] promoted the reaction of **1a** and **2a** (2 equiv.) at room temperature to afford a 1,1-diarylethane derivative **3aa** in 70% yield (entry 1). Thus, the ring-opening of the aziridine **2a** took place regioselectively at the more hindered C-2 position. Upon brief examination of the catalyst loading, the reaction stoichiometry,



Scheme 1. Cobalt–NHC-catalyzed *ortho*-functionalization of arenes with electrophiles.

Table 1. Cobalt-catalyzed *ortho*-alkylation of 2-phenylpyridine **1a** with 1,2-diphenylaziridine **2a**.[a]



1a **2a** (2 equiv.) **3aa**

Entry	x	Ligand (y)	RMgX	Yield [%][b]
1	10	IPr·HCl (10)	*t*-$BuCH_2MgBr$	70
2	5	IPr·HCl (5)	*t*-$BuCH_2MgBr$	72[c]
3	5	SIPr·HCl (5)	*t*-$BuCH_2MgBr$	29
4	5	IMes·HCl (5)	*t*-$BuCH_2MgBr$	11
5	5	PPh_3 (10)	*t*-$BuCH_2MgBr$	0
6	5	PCy_3 (10)	*t*-$BuCH_2MgBr$	0
7	5	IPr·HCl (5)	Me_3SiCH_2MgCl	0
8	5	IPr·HCl (5)	CyMgBr	6
9	5	IPr·HCl (5)	PhMgBr	0

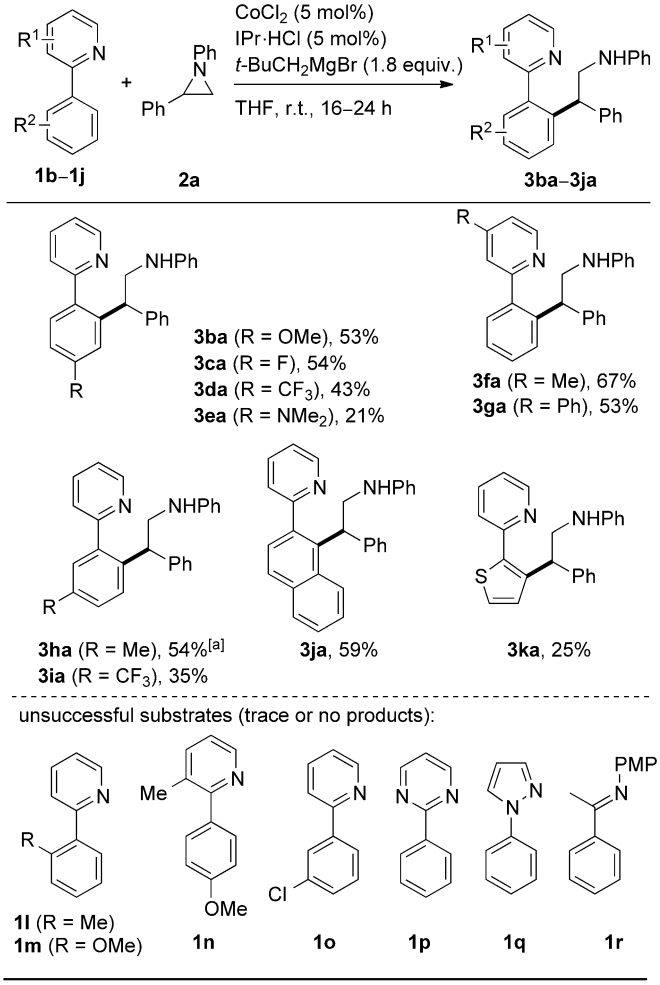
[a] The reaction was performed on a 0.3 mmol scale.
[b] Determined by ^1H NMR using 1,1,2,2-tetrachloroethane as an internal standard.
[c] Isolated yield.

and the temperature, we found that the reaction smoothly proceeded with 5 mol% each of $CoCl_2$ and IPr·HCl and 1.8 equiv. of *t*-$BuCH_2MgBr$, affording **3aa** in 72% isolated yield (entry 2). Reduction of the amount of either **2a** or *t*-$BuCH_2MgBr$ resulted in a substantial decrease in the product yield, and lower or higher temperature (0 °C or 60 °C) did not improve the reaction.

The reaction was very sensitive to the ligand and the Grignard reagent. Thus, the use of other NHC preligands such as SIPr·HCl and IMes·HCl resulted in much lower yields of **3aa** (entries 3 and 4), while PPh_3 and PCy_3 were entirely ineffective (entries 5 and 6). The catalytic activity was totally or significantly lost when *t*-$BuCH_2MgBr$ was replaced with other Grignard reagents such as Me_3SiCH_2MgCl, CyMgBr, or PhMgBr (entries 7–9).

With the reaction conditions in entry 2 of Table 1, we explored the scope of the present ring-opening alkylation reaction. First, various 2-arylpyrdine derivatives were subjected to the reaction with **2a** (Table 2). 2-Arylpyridines bearing *para*-substituents such as methoxy, fluoro, and trifluoromethyl groups on the benzene ring participated in the reaction to afford the corresponding products **3ba**–**3da** in moderate yields, while a *para*-dimethylamino group made the reaction rather sluggish (see **3ea**). Substituents on the 4-position of the pyridine ring did not interfere with the reaction (see **3fa** and **3ga**). A *meta*-methyl group on the benzene ring directed the reaction to take place preferentially at the less hindered position, affording the product **3ha** and its regioisomer in a ratio of 4:1,

Table 2. Reaction of various 2-arylpyridines with aziridine **2a**.



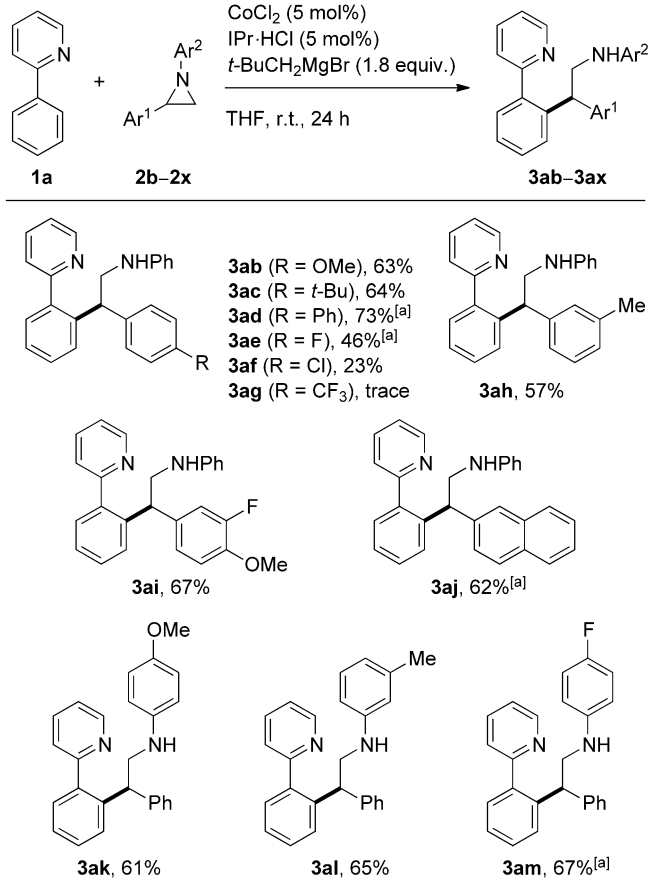
1b–1j **2a** **3ba–3ja**

[a] A mixture of regioisomers (4:1) was obtained. The major isomer is shown.

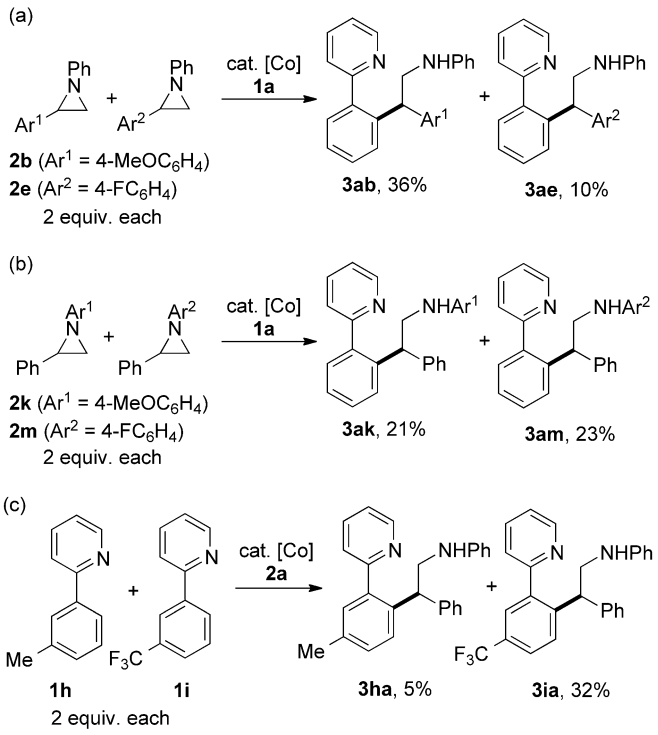
while the regioselectivity was perfect for a substrate bearing a *meta*-trifluoromethyl group (see **3ia**). In contrast, 2-(naphthalen-2-yl)pyridine reacted at the more hindered 1-position to afford the product **3ja** as a pure regioisomer. The C-3 position of 2-(thiophen-2-yl)pyridine was also alkylated albeit in a modest yield (see **3ka**). The reaction proved to be rather sensitive to steric congestion of 2-arylpyridines, because those substituted at the *ortho*-position of the benzene ring (**1l**, **1m**) or the 3-position of the pyridine ring (**1n**) afforded only trace amounts of the desired products. A substrate bearing a C–Cl bond (**1o**) also did not participate in the reaction for unknown reasons.

Attempts to use aromatic substrates other than 2-arylpyridines have been unsuccessful. Thus, only a trace amount of the desired product was detected by GC-MS in the reaction of 1-phenylpyrazole (**1q**) with **2a**, while 2-phenylpyrimidine (**1p**) and the arylimine derived from acetophenone and *p*-anisidine (**1r**) did not afford any of such products.

Table 3. Reaction of 2-phenylpyridine **1a** with various aziridines.



[a] 2 equiv. of *t*-$BuCH_2MgBr$ were used.

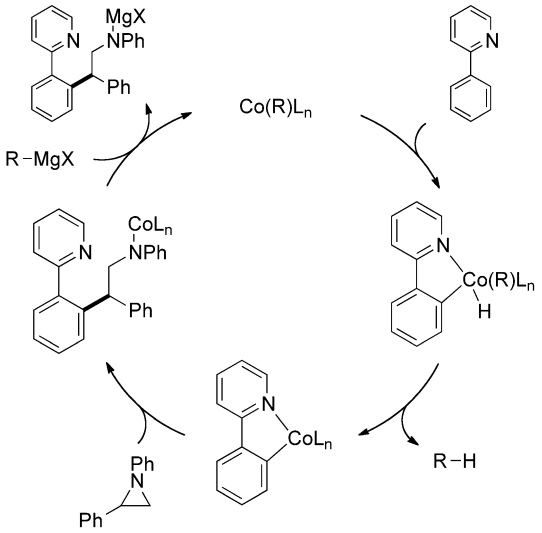


Scheme 2. Competition experiments.

Next, the reaction of 2-phenylpyridine **1a** and various aziridines was examined (Table 3). *N*-Phenylaziridines bearing a series of 2-aryl groups participated in the reaction to afford the corresponding products **3ab**–**3aj** in moderate yields. An electron-donating or neutral substituent (i.e., methoxy, *tert*-butyl, or phenyl) on the 2-aryl group was beneficial for the reaction (see **3ab**–**3ad**). In contrast, electron-withdrawing fluoro and chloro substituents made the reaction sluggish (see **3ae** and **3af**), and a trifluoromethyl group almost shut down the reaction (see **3ag**). The *N*-substituent of the aziridine could be changed to other aryl groups such as 4-methoxyphenyl, 3-tolyl, and 4-fluorophenyl groups without significant decrease in the reaction efficiency (see **3ak**–**3am**), while an *N*-methyl derivative did not give the desired product. Note also that an *N*-sulfonylaziridine, which was used for the rhodium(III)-catalyzed reaction of 2-arylpyridine,[6] did not participate in the present cobalt-catalyzed reaction.

Despite the significant development of C–C bond forming reactions with cobalt catalysts in the past decades,[14] to the best of our knowledge, aziridines have not been utilized as electrophiles for the cobalt-catalyzed cross-coupling.[15] To gain insight into the aziridine ring-opening step, competition experiments were performed (Scheme 2a, b). The reaction of **1a** with an equimolar mixture of aziridines **2b** and **2e** having 2-(4-methoxyphenyl) and 2-(4-fluorophenyl) groups, respectively, preferentially afforded the product of the former aziridine (i.e., **3ab**; Scheme 2a). This observation sounds reasonable if one invokes the development of a partial positive charge on the C-2 position during the ring-opening process. On the other hand, aziridines **2k** and **2m** bearing *N*-(4-methoxyphenyl) and *N*-(4-fluorophenyl) groups, respectively, afforded the corresponding products **3ak** and **3am** in nearly equal yields in the same type of competition (Scheme 2b). Note also that a competition of 2-arylpyridines bearing *meta*-methyl and *meta*-trifluoromethyl groups (**1h** and **1i**) resulted in predominant formation of the alkylation product of the latter (**3ia**), indicating that the cobalt catalyst prefers to activate the more acidic/electron-poor C–H bond (Scheme 2c).[13]

A putative catalytic cycle of the present ring-opening alkylation reaction is shown in Scheme 3. A low-valent alkylcobalt species generated from the cobalt salt, the NHC preligand, and the Grignard reagent undergoes oxidative addition of the *ortho*-C–H bond of 2-phenylpyridine, which is followed by reductive elimination to afford a cyclometallated intermediate.[16] This intermediate then undergoes nucleophilic



Scheme 3. A possible catalytic cycle.

attack on 1,2-diarylaziridine, resulting in ring-opening alkylation of the *ortho*-position. Possible pathways for this step may involve S_N2-type displacement, single-electron transfer-radical coupling, and oxidative addition–reductive elimination. Further mechanistic experiments, e.g., those using enantioenriched 1,2-diarylaziridines,[17] are necessary to distinguish these possibilities. Transmetallation of the resulting cobalt amide and the Grignard reagent affords the product bearing a magnesium amide moiety and regenerates the alkylcobalt species.

In summary, we have demonstrated that a cobalt–IPr catalyst, in combination with *t*-BuCH_2MgBr, efficiently promotes the *ortho*-alkylation of 2-arylpyridines through regioselective ring-opening of *N*-arylaziridines under mild conditions to afford 1,1-diarylethane derivatives in moderate to good yields. With the present study and previous studies by us and Ackermann et al.,[9–11,13] the combination of a cobalt salt, an NHC ligand, and a Grignard reagent now appears to offer versatile catalytic systems for *ortho*-C–H functionalization of arenes with electrophiles. Efforts to further expand the scope of this chemistry are currently ongoing.

Experimental Section

General Remarks

Unless otherwise noted, materials were purchased from Aldrich, Alfa Aesar, or other commercial suppliers and used as received. Anhydrous cobalt(II) chloride (>99%) was purchased from Alfa Aesar and used as received. THF was distilled over Na/benzophenone. Grignard reagents were prepared from the corresponding halides and magnesium turnings in anhydrous THF and titrated before use. 2-Arylpyridine derivatives were prepared either by nickel-catalyzed cross-coupling of 2-halopyridines and aryl-Grignard reagents[18] or by copper-catalyzed condensation of oxime acetates and α,β-unsaturated aldehydes.[19] 1,2-Diarylaziridines were prepared by Corey–Chaykovsky reaction of dimethylsulfonium methylide and the corresponding *N*-arylaldimines.[20] NMR spectra were recorded on Bruker AV-300 (300 MHz) and AV-400 (400 MHz) spectrometers, where tetramethylsilane (^{1}H) and $CDCl_3$ (^{13}C) were employed as internal standards. Gas chromatographic (GC) analysis was performed on a Shimadzu GC-2010 system equipped with an FID detector and a capillary column DB-5 (Agilent J&W, 0.25 mm i.d. × 30 m, 0.25 μm film thickness). High-resolution mass spectra (HR-MS) were recorded on a Waters Q-Tof Premier LC HR mass spectrometer.

Representative Procedure for Cobalt-Catalyzed Reaction of 2-Arylpyridine and 2-Arylaziridine

In an oven-dried Schlenk tube equipped with a magnetic stir bar were placed cobalt(II) chloride (1.9 mg, 0.015 mmol), 1,3-bis(2,6-diisopropylphenyl)imidazolium chloride (6.4 mg, 0.015 mmol), 2-phenylpyridine (**1a**, 43 μL, 0.30 mmol), 1,2-diphenylaziridine (**2a**, 117.2 mg, 0.60 mmol), and THF (0.68 mL). To the mixture was added a THF solution of neopentylmagnesium bromide (1.67 M, 0.32 mL, 0.54 mmol) dropwise at 0 °C. The resulting mixture was stirred at room temperature for 24 h, diluted with ether (1 mL), and then quenched with a saturated aqueous solution of NH_4Cl (1 mL). The aqueous layer was extracted with ethyl acetate (10 mL × 3). The combined organic layer was dried over $MgSO_4$ and concentrated under reduced pressure. The crude product was purified by silica gel chromatography (eluent: hexane/EtOAc = 10/1 to 5/1) to afford *N*-{2-phenyl-2-[2-(pyridin-2-yl)phenyl]ethyl}aniline (**3aa**) as a yellow oil; yield: 76.0 mg (72%).

Acknowledgements

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