Cobalt-catalyzed C(sp²)-H/C(sp³)-H coupling via directed C-H activation and 1,5-hydrogen atom transfer

Sun, Qiao; Yoshikai, Naohiko

2017

Sun, Q., & Yoshikai, N. (2018). Cobalt-catalyzed C(sp²)-H/C(sp³)-H coupling via directed C-H activation and 1,5-hydrogen atom transfer. *Organic Chemistry Frontiers*, 5(4), 582-585.
doi:10.1039/C7QO00906B

<https://hdl.handle.net/10356/90289>

<https://doi.org/10.1039/C7QO00906B>

© 2018 the Partner Organisations. All rights reserved. This paper was published in *Organic Chemistry Frontiers* and is made available with permission of the Partner Organisations.

Downloaded on 26 Apr 2023 12:58:32 SGT

Cobalt-catalyzed C(sp²)-H/C(sp³)-H coupling via directed C-H activation and 1,5-hydrogen atom transfer

Received 00th January 20xx,
Accepted 00th January 20xx

Qiao Sun^a and Naohiko Yoshikai^{*a}

DOI: 10.1039/x0xx00000x

www.rsc.org/

A cobalt-catalyzed C(sp²)-H/C(sp³)-H coupling reaction between an aryl imine and a 2-bromobenzyl-protected secondary amine is reported. Promoted by a combination of a cobalt-N-heterocyclic carbene catalyst and a Grignard reagent, the reaction allows for the introduction of α -aminoalkyl groups into the *ortho* position of the imine at a mild temperature. The cobalt catalyst is proposed to play key roles in two distinct modes of C-H cleavage, i.e., directed C-H metalation and 1,5-hydrogen atom transfer (HAT).

Catalytic C-H bond functionalization has evolved to offer a number of C-C and C-heteroatom bond-forming methods, thus playing an integral part in current synthetic chemistry.¹ Notable among various approaches to selective C-H functionalization are transition metal-mediated directed C-H activation and 1,5-hydrogen atom transfer (HAT). The former approach allows regioselective activation of C(sp²)-H and C(sp³)-H bonds in the proximity of heteroatom directing groups, which has been practiced using a series of late transition metal catalysts.² The latter approach, while long known in radical chemistry (e.g., Hofmann-Löffler-Freytag reaction), has gained renewed interest as it enables remote functionalization of unactivated C(sp³)-H bonds triggered by metal or photoredox catalyst-mediated generation of reactive carbon or heteroatom radicals.³⁻⁵ To our knowledge, these mechanistically distinct C-H activation modes have not been employed simultaneously to achieve a C-C bond formation. Herein, we report on the development of a cobalt-catalyzed C(sp²)-H/C(sp³)-H coupling reaction that features a merger of directed C-H activation and 1,5-HAT.

Over the last years, Nakamura, Ackermann, and our group have developed low-valent cobalt-catalyzed directed arene C(sp²)-H functionalization (e.g., alkylation and arylation) reactions using organic halides and pseudohalides (Scheme

1a).⁶⁻¹² These reactions are commonly assumed to involve a low-valent organocobalt species generated from a cobalt precatalyst and a Grignard reagent, which undergoes directed C(sp²)-H metalation to form a cobaltacycle intermediate **I**.¹³ Mechanistic studies on some of the reactions implied that **I** would undergo a single electron transfer (SET) to the organic halide to generate an oxidized cobaltacycle **II** and an organic radical (R•), followed by C-C coupling.¹⁴ We hypothesized that, if the radical were capable of 1,5-HAT, the resulting C(sp³) radical would undergo C-C coupling with the cobaltacycle. On the basis of this hypothesis, we have developed a cobalt-catalyzed cross-coupling reaction between an aryl imine and a 2-bromobenzyl-protected secondary amine, where a C(sp²)-C(sp³) bond is selectively formed between the *ortho*-position of the imine and the α -position of the amine (Scheme 1b).

(a) Cobalt-catalyzed directed C-H/electrophile coupling

(b) This work

Scheme 1. Cobalt-catalyzed directed arene C-H functionalization.

The present study commenced with screening of conditions for the reaction between acetophenone *N*-PMP (*p*-methoxyphenyl) imine **1a** (0.3 mmol) and *N*-(2-bromobenzyl)pyrrolidine **2a** (0.6 mmol). The reaction performed under our previous conditions for the direct

^a Division of Chemistry and Biological Chemistry, School of Physical and Mathematical Sciences, Nanyang Technological University. E-mail: nyoshikai@ntu.edu.sg

^b † Footnotes relating to the title and/or authors should appear here.

^c Electronic Supplementary Information (ESI) available: [details of any supplementary information available should be included here]. See DOI: 10.1039/x0xx00000x

arylation with aryl chloride,^{8a} i.e., in the presence of CoBr₂ (10 mol %), IMes•HCl (10 mol %), and *t*-BuCH₂MgBr (2 equiv) in THF at room temperature, afforded the desired alkylation product **3aa** in 7% yield (Table 1, entry 1). The use of IPr•HCl or SIPr•HCl instead of IMes•HCl led to a slight but noticeable increase in the yield of **3aa** (entries 2 and 3), whereas phosphine ligands such as PPh₃ and dppe were entirely ineffective (data not shown). With SIPr•HCl, the reaction was further improved by replacing *t*-BuCH₂MgBr by secondary acyclic Grignard reagent such as *i*-PrMgBr or *sec*-BuMgBr, the latter affording **3aa** in 30% yield (entries 4 and 5). On the other hand, cycloalkyl Grignard reagents proved detrimental (entries 6 and 7). Upon further screening, mixed solvent systems, THF/DME (1:1) in particular, further improved the yield of **3aa** to near 50% (entries 8–10). When the reaction was performed using **1a** in excess (2 equiv) at 0 °C, the yield of **3aa** based on **2a** reached 55% (entry 11). Unfortunately, the reaction could not be further improved beyond this level despite intensive further screening. Note that replacement of CoBr₂ with NiBr₂ or FeBr₂ under otherwise identical conditions resulted in none or only trace of **3aa** (entries 12 and 13). Note also that replacement of the 2-bromobenzyl group of **2a** with 2-iodobenzyl or 2-chlorobenzyl group largely shut down the desired reaction.

Table 1. Optimization of reaction conditions^a

Entry	Ligand	RMgX	Solvent	Yield [%] ^b
1	IMes•HCl	<i>t</i> -BuCH ₂ MgBr	THF	7
2	IPr•HCl	<i>t</i> -BuCH ₂ MgBr	THF	13
3	SIPr•HCl	<i>t</i> -BuCH ₂ MgBr	THF	17
4	SIPr•HCl	<i>i</i> -PrMgBr	THF	23
5	SIPr•HCl	<i>sec</i> -BuMgBr	THF	30
6	SIPr•HCl	<i>c</i> -C ₅ H ₉ MgBr	THF	5
7	SIPr•HCl	CyMgCl	THF	8
8	SIPr•HCl	<i>sec</i> -BuMgBr ^c	THF/Et ₂ O ^d	34
9	SIPr•HCl	<i>sec</i> -BuMgBr ^c	THF/DME ^d	47
10	SIPr•HCl	<i>sec</i> -BuMgBr ^c	THF/Toluene ^d	42
11 ^e	SIPr•HCl	<i>sec</i> -BuMgBr	THF/DME ^d	55
12 ^{e,f}	SIPr•HCl	<i>sec</i> -BuMgBr	THF/DME ^d	0
13 ^{e,g}	SIPr•HCl	<i>sec</i> -BuMgBr	THF/DME ^d	6

^a The reaction was performed using 0.3 mmol of **1a** (*c* = 0.3 M) and 0.6 mmol of **2a**. ^b Determined by ¹H NMR using 1,1,2,2-tetrachloroethane as an internal standard. ^c The amount of *sec*-BuMgBr was 2.2 equiv. ^d The ratio of the solvents was 1:1. ^e The reaction was performed using 0.4 mmol of **1a** and 0.2 mmol of **2a** (*c* = 0.2 M) at 0 °C. ^f NiBr₂ was used instead of CoBr₂. ^g FeBr₂ was used instead of CoBr₂.

Figure 1. Byproducts detected in the coupling of **1a** and **2a**.

During the above optimization study, the desired product **3aa** was persistently accompanied by byproducts **4–8** (up to ca. 5% yield for **4**, **5**, and **8** and up to ca. 20% yield for **6** and **7**) shown in Figure 1 (see Table S1 for detail). These byproducts can be attributed to ortho C–H arylation of **1a** with the bromoaryl moiety of **2a** (**4**),^{7,8} ortho C–H alkylation of **1a** with the Grignard reagent (**5**),¹⁵ cross-coupling between the Grignard reagent and **2a** (**6**),¹⁶ hydrodehalogenation of **2a** (**7**), and reduction of **1a** (**8**). These competing side reactions, which interrupt the desired catalytic cycle (vide infra) at different steps, underlines the challenge in selectively achieving the C(sp²)–H/C(sp³)–H coupling.

With the optimal reaction conditions (Table 1, entry 11), we explored the scope of aryl imines (Table 2). A series of *para*-substituted acetophenone imines took part in the reaction with **2a** to afford the desired alkylation products **3ba–3ga** in moderate yields. The presence of methoxy or trifluoromethyl group at the *para* position was detrimental to the reaction (see **3fa** and **3ga**). The reactions of *meta*-trifluoromethyl- and *meta*-chloro-substituted imines took place regioselectively at the less hindered ortho position, affording the corresponding products **3ha** and **3ia** in respectable yields. On the other hand, *meta*-fluoroacetophenone imine underwent regioselective alkylation at the proximity of the fluorine atom, presumably due to the secondary directing effect. Though sluggish, propiophenone imine and tetralone imine also took part in the present alkylation reaction (see **3ka** and **3la**). Note that the synthesis of **3aa** could be performed on a 5 mmol scale, albeit with a decrease in the yield from 49% to 37%.

Table 2. Scope of Aryl Imines^a

^a The reaction was performed on a 0.2 mmol scale under the conditions in Table 1, entry 11. ^b The yield of a 5 mmol-scale reaction is shown in parentheses. ^c The reaction time was 24 h.

Next, we examined the reaction of different *N*-(2-bromobenzyl)amine substrates, using *meta*-trifluoromethylacetophenone imine **1h** as the reaction partner (Table 3). Amine substrates derived from six-membered cyclic amines, such as piperidine, morpholine, and tetrahydroquinoline, reacted much more sluggishly compared with the pyrrolidine derivative **2a** (see **3hb–3hd**). By contrast, azepane-derived substrate smoothly participated in the reaction to afford the alkylation product **3he** in 64% yield. Furthermore, substrates derived from acyclic amines such as diethylamine and dibutylamine also furnished the desired products **3hf** and **3hg** in moderate yields.

Table 3. Reaction of different amines (^BBn = 2-bromobenzyl)^a

^a The reaction was performed on a 0.2 mmol scale under the conditions in Table 1, entry 11.

To illustrate the possible use of the present alkylation products, we performed a two-step transformation of **3aa** into a spirocyclic compound **10** (Scheme 2). Thus, diazotization of the acetyl group of **3aa** afforded the diazoketone derivative **9**. Subsequently, rhodium-catalyzed decomposition of **9** resulted in selective C–H insertion into the tertiary C–H bond.

Scheme 2. Product transformation to a spirocycle.

A proposed catalytic cycle of the present $\text{C}(\text{sp}^2)\text{--H}/\text{C}(\text{sp}^3)\text{--H}$ coupling reaction is shown in Scheme 3. An organocobalt species **A** would undergo cyclometalation of the aryl imine to form a cobaltacycle intermediate **B**. SET from **B** to *N*-(2-bromobenzyl)amine would result in a pair of oxidized cobaltacycle and aryl radical (**C**),¹⁴ which would then undergo 1,5-HAT to generate more stable α -aminoradical (**D**). Aryl–alkyl coupling of the intermediate **D** would furnish the alkylation product, and transmetalation between the cobalt bromide species **E** and the Grignard reagent would regenerate the species **A**. Note that the addition of a radical scavenger (1 equiv) to the coupling reaction between **1a** and **2a** significantly reduced the yield of **3aa** (22% and 28% yields with TEMPO and 1,1-diphenylethylene, respectively), which would support the involvement of the radical intermediates. As suggested from the byproducts (Figure 1), several side reactions can interrupt the catalytic cycle. The intermediate **C** may undergo aryl–aryl coupling to form the biaryl **4**. The intermediate **C** or **D** may undergo transmetalation with the Grignard reagent, which may lead to the byproduct **5**. Furthermore, the species **A** may react with *N*-(2-bromobenzyl)amine to give the cross-coupling and reduction products (**6**, **7**). The formation of the reduced imine **8** may be mediated by the Grignard reagent or cobalt hydride derived from the species **A**.

In summary, we have demonstrated a cobalt-catalyzed $\text{C}(\text{sp}^2)\text{--H/C}(\text{sp}^3)\text{--H}$ coupling reaction between aryl imines and *N*-(2-bromobenzyl)amines, which involves two distinct modes of C–H bond cleavage, i.e., directed C–H activation and 1,5-HAT. The reaction allows *ortho* C–H functionalization with α -aminoalkyl groups, for which the corresponding halide precursors are not readily available. The success of the present reaction may be attributed to the ability of low-valent cobalt species to engage in both inner-sphere C–H activation and single electron transfer, while other transition metals such as iron may also be endowed with similar attributes.^{3a,17} Further studies on the merger of transition metal- and radical-mediated C–H bond cleavages are underway.

This work was supported by the Ministry of Education (Singapore) and Nanyang Technological University (RG3/15, RG114/15, and MOE2016-T2-2-043).

‡ Footnotes relating to the main text should appear here. These might include comments relevant to but not central to the matter under discussion, limited experimental and spectral data, and crystallographic data.

- 1 (a) W. R. Gutekunst and P. S. Baran, *Chem. Soc. Rev.*, 2011, **40**, 1976; (b) J. Yamaguchi, A. D. Yamaguchi and K. Itami, *Angew. Chem., Int. Ed.*, 2012, **51**, 8960; (c) J. Wencel-Delord and F. Glorius, *Nat. Chem.*, 2013, **5**, 369; (d) Y. Segawa, T. Maekawa and K. Itami, *Angew. Chem., Int. Ed.*, 2015, **54**, 66.
- 2 For selected reviews, see: (a) D. A. Colby, R. G. Bergman and J. A. Ellman, *Chem. Rev.*, 2010, **110**, 624; (b) T. W. Lyons and

- Please do not adjust margins

- 13 H.-F. Klein, S. Camadanli, R. Beck, D. Leukel and U. Flörke, *Angew. Chem., Int. Ed.*, 2005, **44**, 975.
- 14 For selected references, see: (a) H. Yorimitsu and K. Oshima, *Pure Appl. Chem.*, 2006, **78**, 441; (b) K. Wakabayashi, H. Yorimitsu and K. Oshima, *J. Am. Chem. Soc.*, 2001, **123**, 5374; (c) W. Affo, H. Ohmiya, T. Fujioka, Y. Ikeda, T. Nakamura, H. Yorimitsu, K. Oshima, Y. Imamura, T. Mizuta and K. Miyoshi, *J. Am. Chem. Soc.*, 2006, **128**, 8068; (d) T. Kobayashi, H. Ohmiya, H. Yorimitsu and K. Oshima, *J. Am. Chem. Soc.*, 2008, **130**, 11276.
- 15 (a) Q. Chen, L. Ilies, N. Yoshikai and E. Nakamura, *Org. Lett.*, 2011, **13**, 3232; (b) B. Li, Z.-H. Wu, Y.-F. Gu, C.-L. Sun, B.-Q. Wang and Z.-J. Shi, *Angew. Chem., Int. Ed.*, 2011, **50**, 1109.
- 16 (a) G. Cahiez and A. Moyeux, *Chem. Rev.*, 2010, **110**, 1435; (b) C. Gosmini, J. M. Begouin and A. Moncomble, *Chem. Commun.*, 2008, 3221; (c) W. Hess, J. Treutwein and G. Hilt, *Synthesis* 2008, 3537; (d) P. Röse and G. Hilt, *Synthesis* 2016, **48**, 463.
- 17 (a) R. Shang, L. Ilies and E. Nakamura, *Chem. Rev.*, 2017, **117**, 9086; (b) C.-L. Sun, B.-J. Li and Z.-J. Shi, *Chem. Rev.*, 2011, **111**, 1293.