



# Cobalt-catalyzed *peri*-selective alkoxylation of 1-naphthylamine derivatives

Jiao-Na Han, Cong Du, Xinju Zhu, Zheng-Long Wang, Yue Zhu, Zhao-Yang Chu, Jun-Long Niu\* and Mao-Ping Song\*

## Letter

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### Address:

College of Chemistry and Molecular Engineering, Zhengzhou University, Zhengzhou 450001, People's Republic of China

### Email:

Jun-Long Niu\* - niujunlong@zzu.edu.cn; Mao-Ping Song\* - mpsong@zzu.edu.cn

\* Corresponding author

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## Abstract

A cobalt-catalyzed C(sp<sup>2</sup>)–H alkoxylation of 1-naphthylamine derivatives has been disclosed, which represents an efficient approach to synthesize aryl ethers with broad functional group tolerance. It is noteworthy that secondary alcohols, such as hexafluoroisopropanol, isopropanol, isobutanol, and isopentanol, were well tolerated under the current catalytic system. Moreover, a series of biologically relevant fluorine-aryl ethers were easily obtained under mild reaction conditions after the removal of the directing group.

## Introduction

Aryl ethers are common structural units present in many natural products, functional materials, and pharmaceuticals [1]. Consequently, a variety of strategies have emerged to access them, including Pd-catalyzed and Cu-catalyzed coupling reactions (Buchwald–Harting couplings and Ullmann reactions) [2–4]. However, these classic methods always possess some limitations such as preactivated starting materials, poor regioselectivities, and tedious steps [5]. Therefore, it is desirable to develop an effective strategy to achieve this transformation [6,7].

Over the past few decades, transition-metal-catalyzed C–H activation to form C–C or C–heteroatom bonds has attracted more attention [8–13]. In particular, the formation of C–O bonds is

widely used in the syntheses of pharmaceuticals and functional materials [14–17]. The direct hydroxylation [18,19] and acetoxylation [20–22] have been developed rapidly in recent years. By contrast, alkoxylation or phenoxylation confronts great challenges because alkanols or phenols are easily converted into the corresponding aldehydes, ketones, or carboxylic acids [7,23–25]. Recently, Gooßen [26,27], Sanford [28], Song, [29,30] and others [31–42] have successfully reported alkoxylation reactions with the auxiliary of directing groups. However, the transition-metal-catalyzed C–H alkoxylation is still largely limited to palladium- [28,33–40] or copper- [26,27,29,41,42] catalyzed systems. Recently, the inexpensive cobalt catalysts have received significant attention because of their unique and

versatile activities in the C–H functionalizations [43–51]. In 2015, the cobalt-catalyzed alkoxylation of aromatic (and olefinic) carboxamides with primary alcohols was first reported by the Niu and Song group (Figure 1a) [30]. Successively, Ackermann realized the electrochemical cobalt-catalyzed alkoxylation via a similar process (Figure 1b) [32]. However, cobalt-catalyzed directed coupling of arenes with secondary alcohols has not been reported so far. Herein, we explored a simple and facile protocol for cobalt-catalyzed picolinamide-directed alkoxylation of 1-naphthylamine derivatives with alcohols (Figure 1c).

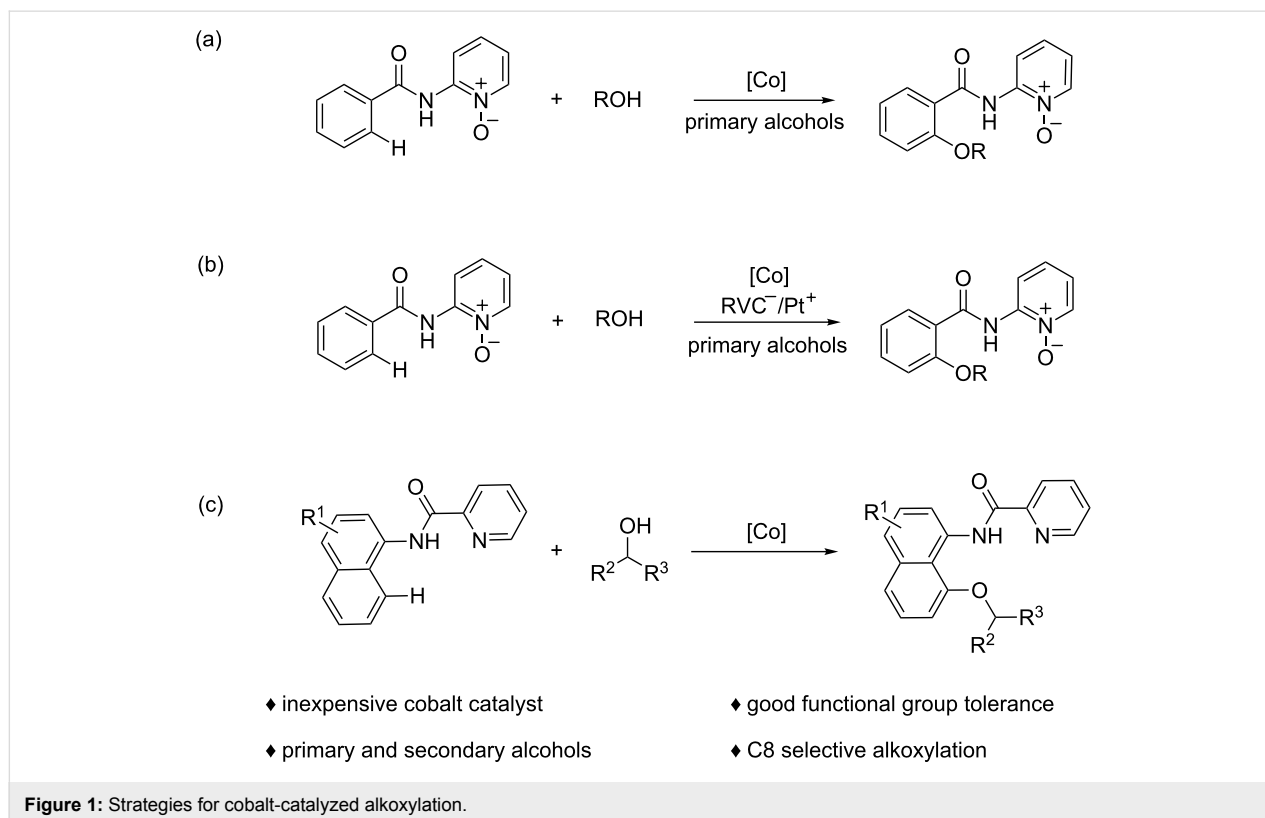
## Results and Discussion

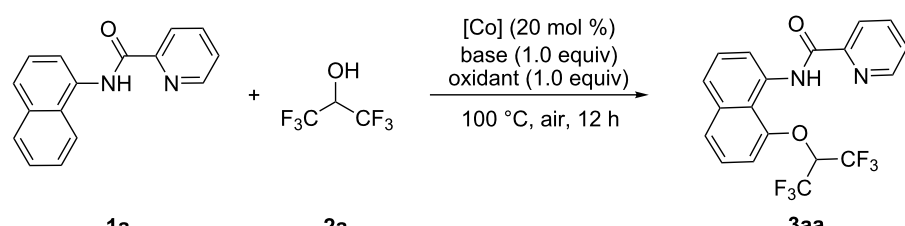
Initially, *N*-(naphthalen-1-yl)picolinamide (**1a**) and hexafluoroisopropanol (HFIP, **2a**) were chosen as the model substrates to optimize the alkoxylation reaction (Table 1, see more in Tables S1–S5 in Supporting Information File 1). To our delight, the desired product **3aa** was obtained in 66% yield when using  $\text{Co}(\text{OAc})_2 \cdot 4\text{H}_2\text{O}$  as catalyst and  $\text{Ag}_2\text{CO}_3$  as oxidant (Table 1, entry 1). Other cobalt salts such as  $\text{CoF}_3$  and  $\text{CoF}_2$  were also employed as metal catalysts for C8 alkoxylation of **1a**, and  $\text{CoF}_2$  was proved to be the optimal catalyst, affording **3aa** in 71% yield (Table 1, entries 2 and 3). Subsequently, various bases such as  $\text{Na}_2\text{CO}_3$ ,  $\text{K}_2\text{CO}_3$ , and  $\text{Cs}_2\text{CO}_3$  were screened (Table 1, entries 4–6), which indicated that  $\text{Cs}_2\text{CO}_3$  was most effective and the alkoxylation product **3aa** could be isolated in

82% yield. Next, the effect of oxidants on the reactivity was investigated, and  $\text{Ag}_2\text{CO}_3$  showed a superior result compared with alternative oxidants (Table 1, entries 6–8). Moreover, DCE and HFIP as co-solvents demonstrated higher reactivity, resulting in a slightly increased yield in 84% (Table 1, entries 9–11). Finally, variation of the reaction temperature did not promote the reaction efficiency.

With the established alkoxylation protocol in hand, the substrate scope of 1-naphthylamine derivatives was explored as shown in Scheme 1. Halogenated naphthylamines could afford the target products in 86–88% yields (**3ba–3ca**). Nitro- (**1d**) and benzene-sulfonyl- (**1e**) substituted naphthylamines were found to proceed smoothly via this strategy (61–64%). In addition, a disubstituted naphthylamine provided the alkoxylation product in 47% yield (**3fa**). Moreover, a *Boc* amino group at C5 of the substrate **1g** was also compatible with the transformation (33%). When a methoxy group was located at the C7 site of the naphthylamine, sterically hindered product **3ha** was obtained in 81%. Besides, some benzylamine derivatives (*N*-(1-phenylethyl)picolinamide and *N*-benzhydrylpicolinamide) were attempted. However, no desired product could be detected.

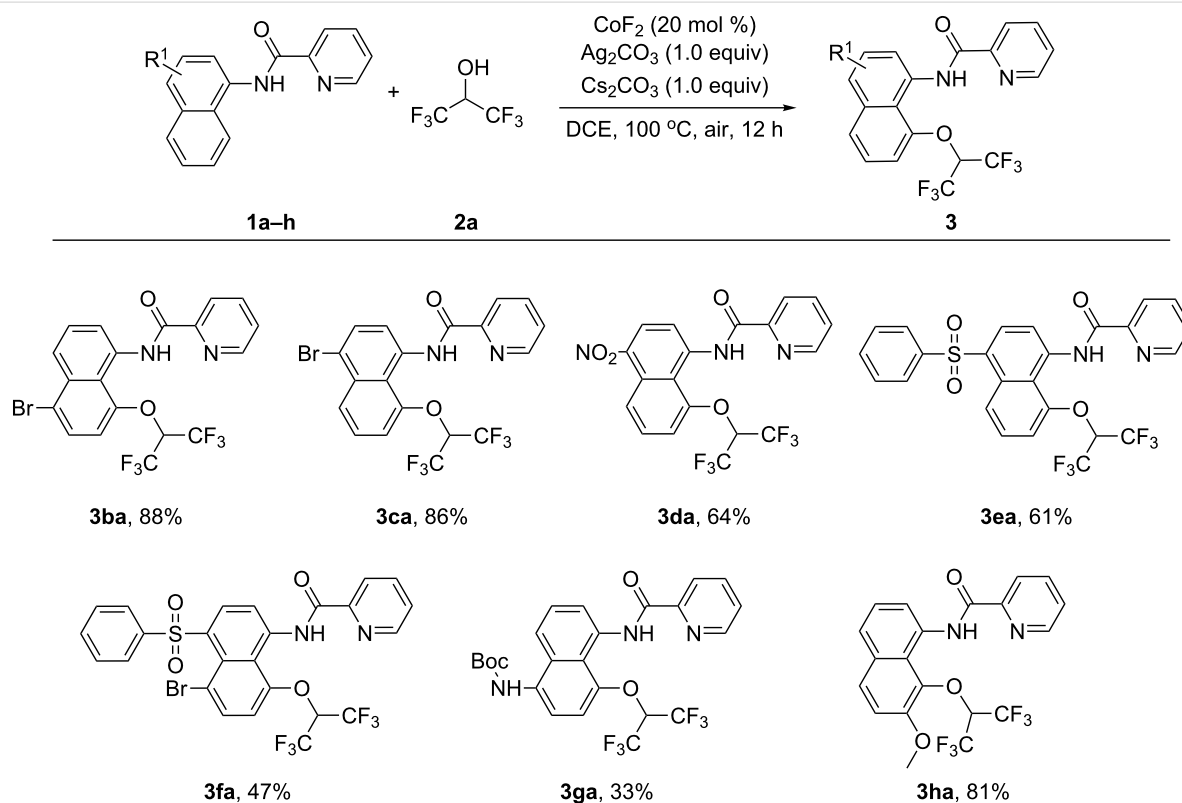
Next, the substrate scope of alcohols was investigated. As shown in Scheme 2, both primary and secondary alcohols were compatible with the slightly modified optimized conditions. A



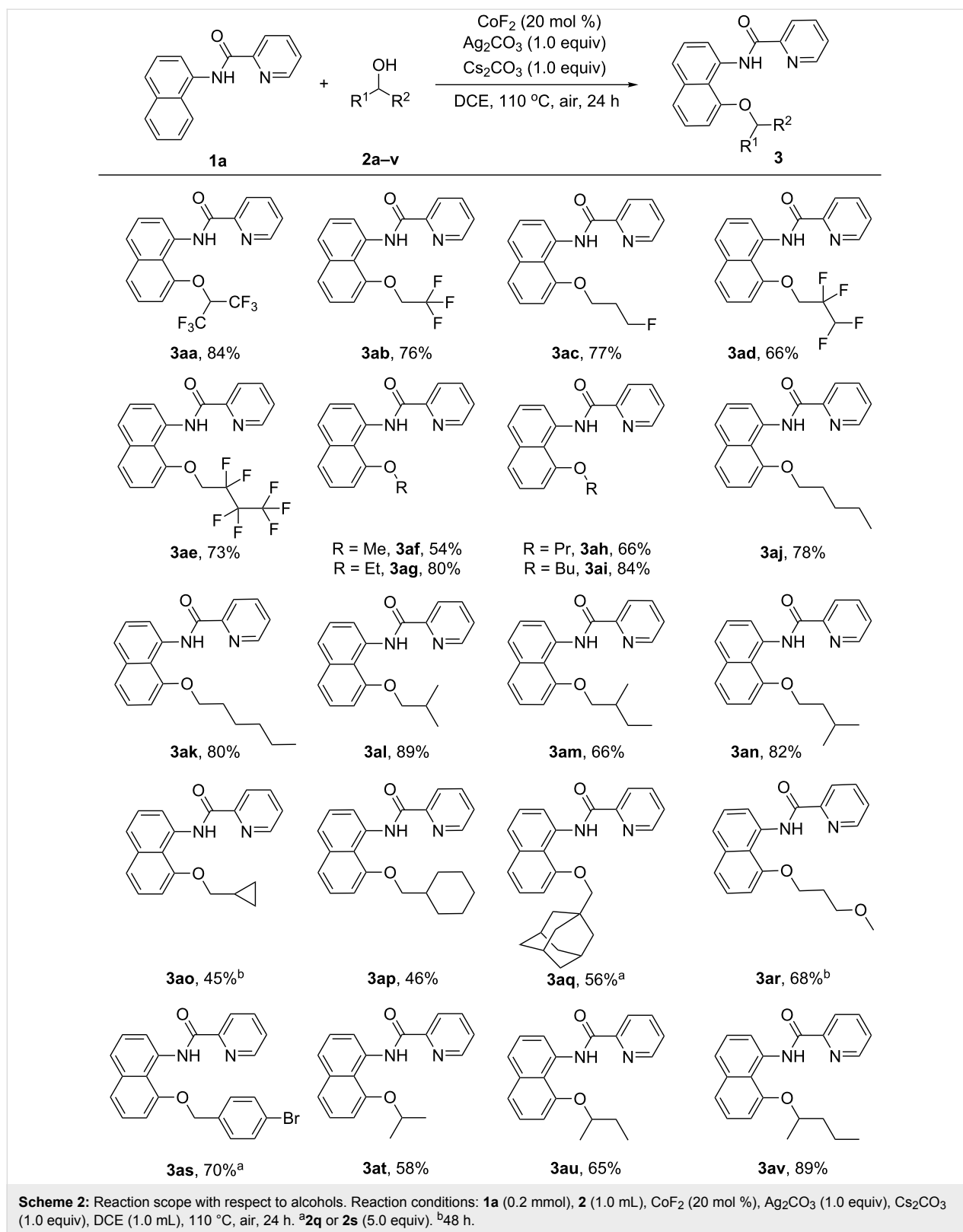
**Table 1:** Optimization of the reaction conditions.<sup>a</sup>


entry	catalyst	base	oxidant	yield (%)
1	Co(OAc) <sub>2</sub> ·4H <sub>2</sub> O	<i>t</i> -AmONa	Ag <sub>2</sub> CO <sub>3</sub>	66
2	CoF <sub>3</sub>	<i>t</i> -AmONa	Ag <sub>2</sub> CO <sub>3</sub>	60
3	CoF <sub>2</sub>	<i>t</i> -AmONa	Ag <sub>2</sub> CO <sub>3</sub>	71
4	CoF <sub>2</sub>	Na <sub>2</sub> CO <sub>3</sub>	Ag <sub>2</sub> CO <sub>3</sub>	58
5	CoF <sub>2</sub>	K <sub>2</sub> CO <sub>3</sub>	Ag <sub>2</sub> CO <sub>3</sub>	67
6	CoF <sub>2</sub>	Cs <sub>2</sub> CO <sub>3</sub>	Ag <sub>2</sub> CO <sub>3</sub>	82
7	CoF <sub>2</sub>	Cs <sub>2</sub> CO <sub>3</sub>	AgNO <sub>3</sub>	11
8	CoF <sub>2</sub>	Cs <sub>2</sub> CO <sub>3</sub>	Ag <sub>2</sub> O	32
9 <sup>b</sup>	CoF <sub>2</sub>	Cs <sub>2</sub> CO <sub>3</sub>	Ag <sub>2</sub> CO <sub>3</sub>	84
10 <sup>c</sup>	CoF <sub>2</sub>	Cs <sub>2</sub> CO <sub>3</sub>	Ag <sub>2</sub> CO <sub>3</sub>	80
11 <sup>d</sup>	CoF <sub>2</sub>	Cs <sub>2</sub> CO <sub>3</sub>	Ag <sub>2</sub> CO <sub>3</sub>	77

<sup>a</sup>Reaction conditions: **1a** (0.2 mmol), **2a** (1.0 mL), Co-catalyst (20 mol %), oxidant (1.0 equiv), base (1.0 equiv), 100 °C, air, 12 h. <sup>b</sup>DCE (1.0 mL) as co-solvent. <sup>c</sup>PhCF<sub>3</sub> (1.0 mL) as co-solvent. <sup>d</sup>PhF (1.0 mL) as co-solvent. DCE = 1,2-dichloroethane.



**Scheme 1:** Reaction scope with respect to *N*-(naphthalen-1-yl)picolinamide derivatives. Reaction conditions: **1** (0.2 mmol), **2a** (1.0 mL), CoF<sub>2</sub> (20 mol %), Ag<sub>2</sub>CO<sub>3</sub> (1.0 equiv), Cs<sub>2</sub>CO<sub>3</sub> (1.0 equiv), DCE (1.0 mL), 100 °C, air, 12 h.



variety of fluoro-substituted alcohols **2a–e** proceeded smoothly to afford the corresponding products in moderate to good yields (66–84%). Simple primary alkyl alcohols were well tolerated to

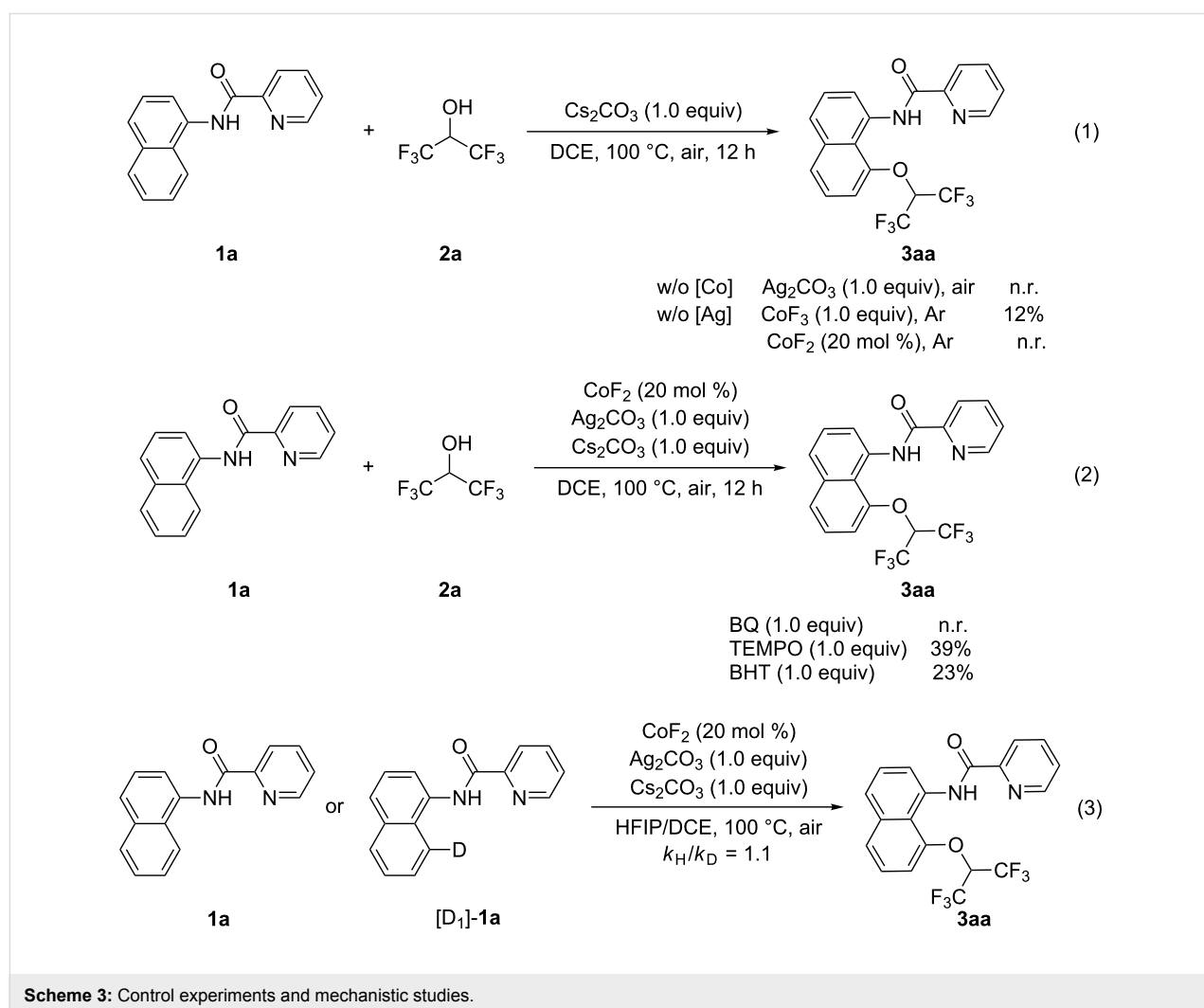
provide the desired products in 54–84% yields (**3af–ak**). Also, the branched alcohols **2l**, **2m**, and **2n** were employed to afford the corresponding products in 66–89% yields. Cyclopropyl-

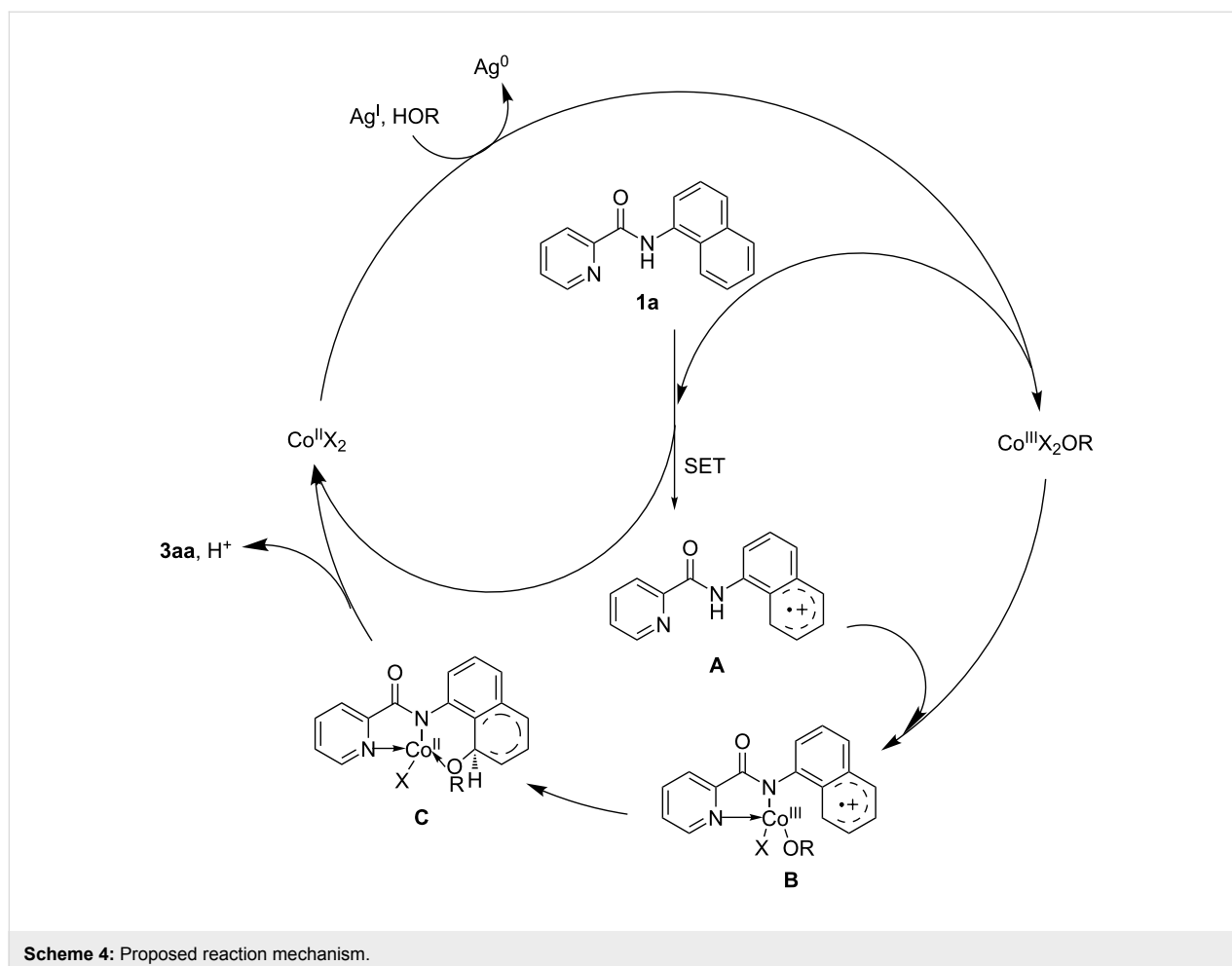
methanol (**2o**), cyclohexylmethanol (**2p**), and adamantanemethanol (**2q**) were compatible with the transformation (45–56%). Moreover, an aliphatic ether and benzyl alcohol were proved to be effective coupling partners to provide **3ar** and **3as** in 68% and 70% yields, respectively. Compared with Co-catalyzed alkoxylation of arenes with primary alcohols [30,31], HFIP (**2a**), isopropanol (**2t**), isobutanol (**2u**), and isopentanol (**2v**) could all proceed smoothly to deliver the alkoxyated products in 58–89% yields. Furthermore, we attempted some tertiary alcohols (*tert*-butanol and 2-methyl-2-butanol). However, no desired product could be detected.

In order to study the reaction mechanism, a series of control experiments were carried out (Scheme 3, see more details in Supporting Information File 1). In the absence of cobalt salt, no product was obtained under the standard reaction conditions. Under an argon atmosphere and without  $\text{Ag}_2\text{CO}_3$ , the product was isolated in 12% yield when a stoichiometric amount of  $\text{CoF}_3$  was introduced, whereas no product was obtained in the

presence of  $\text{CoF}_2$  (Scheme 3, reaction 1). These results imply that the reaction should initiate from a  $\text{Co}^{\text{III}}$  species. The addition of a radical quencher, benzoquinone (BQ), suppressed the formation of product **3aa**. When 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO) or 2,6-di-*tert*-butyl-4-methylphenol (BHT) was added under the standard reaction conditions, a significantly reduced yield (39% or 23%) was obtained (Scheme 3, reaction 2). These facts suggest that a radical approach may be involved in the reaction. Moreover, in the parallel experiments, a KIE value of 1.1 was observed between **1a** or  $[\text{D}_1]$ -**1a** with **2a**, which indicates that Co-catalyzed C–H bond cleavage should not be the rate determining step (Scheme 3, reaction 3).

On the basis of the above studies and previous literature [30,31,46,47], a plausible reaction mechanism for cobalt-catalyzed alkoxylation was proposed. As shown in Scheme 4, initially,  $\text{Co}^{\text{II}}\text{X}_2$  could be oxidized to  $\text{Co}^{\text{III}}\text{X}_2\text{OR}$  in the presence of a silver salt and an alcohol. Based on the experiments and the density functional theory calculations (DFT) [30,31],



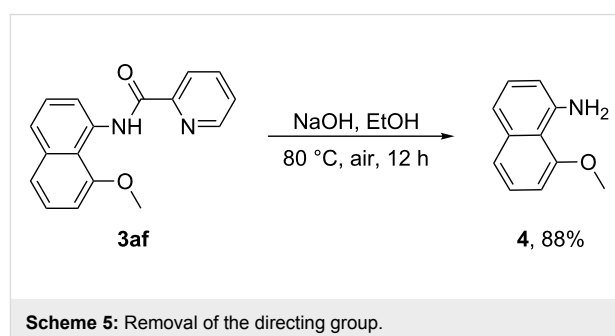


the C–H activation most possibly proceeded via a single-electron transfer (SET) path compared to a concerted metalation-deprotonation (CMD) path. Followed by an intermolecular SET process, the cation-radical intermediate **A** was generated, which coordinates with a  $\text{Co}^{\text{III}}$  species to provide the intermediate **B**. Subsequently, the transfer of ligand OR from the coordinated  $\text{Co}^{\text{III}}$  to the naphthalene ring led to the formation of intermediate **C**. Finally, the alkoxyated product **3aa** was released accompanied with the deprotonation and the  $\text{Co}^{\text{II}}$  species was transformed into the  $\text{Co}^{\text{III}}$  species by re-oxidation.

The current alkoxylation methodology also exhibited potential applications. When treated with NaOH at 80 °C, the picolinic acid directing group could be easily removed, and the corresponding **4** was obtained in 88% yield (Scheme 5).

## Conclusion

In summary, a cobalt-catalyzed C8 alkoxylation of naphthylamine derivatives with both primary and secondary alcohols was developed. This protocol is characterized by mild reaction conditions, broad substrate scope, and good functional group



tolerance. Moreover, the excellent compatibility of fluorine-substituted alcohols (for instance, HFIP, trifluoroethanol, and 3-fluoropropanol etc.) shows that this strategy is highly valuable for the syntheses of biologically relevant fluorine-aryl ethers after the removal of the directing group. The above studies of the mechanism indicate that this reaction undergoes a SET process and cobalt salt is the actual catalyst. Overall, this protocol provides a new insight into the cobalt-catalyzed alkoxylation of naphthylamine derivatives. Further exploration of this strategy to aliphatic substrates is currently in progress.

## Supporting Information

### Supporting Information File 1

Experimental details and characterization data of new compounds, and X-ray crystal structure details for **3aa**.

[<https://www.beilstein-journals.org/bjoc/content/supplementary/1860-5397-14-183-S1.pdf>]

### Supporting Information File 2

Crystallographic information file for compound **3aa**.

[<https://www.beilstein-journals.org/bjoc/content/supplementary/1860-5397-14-183-S2.cif>]

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## ORCID® IDs

Jun-Long Niu - <https://orcid.org/0000-0001-8012-4676>

Mao-Ping Song - <https://orcid.org/0000-0003-3883-2622>

## References

- Enthaler, S.; Company, A. *Chem. Soc. Rev.* **2011**, *40*, 4912–4924. doi:10.1039/c1cs15085e
- Altman, R. A.; Shafir, A.; Choi, A.; Lichtor, P. A.; Buchwald, S. L. *J. Org. Chem.* **2008**, *73*, 284–286. doi:10.1021/jo702024p
- Hartwig, J. F. *Nature* **2008**, *455*, 314–322. doi:10.1038/nature07369
- Monnier, F.; Taillefer, M. *Angew. Chem., Int. Ed.* **2009**, *48*, 6954–6971. doi:10.1002/anie.200804497
- Bruice, T. C. *J. Am. Chem. Soc.* **1957**, *79*, 702–705. doi:10.1021/ja01560a055
- Beccalli, E. M.; Brogini, G.; Martinelli, M.; Sottocornola, S. *Chem. Rev.* **2007**, *107*, 5318–5365. doi:10.1021/cr0680006f
- Chen, X.; Hao, X.-S.; Goodhue, C. E.; Yu, J.-Q. *J. Am. Chem. Soc.* **2006**, *128*, 6790–6791. doi:10.1021/ja061715q
- Colby, D. A.; Bergman, R. G.; Ellman, J. A. *Chem. Rev.* **2010**, *110*, 624–655. doi:10.1021/cr900005n
- Xiao, B.; Gong, T.-J.; Liu, Z.-J.; Liu, J.-H.; Luo, D.-F.; Xu, J.; Liu, L. *J. Am. Chem. Soc.* **2011**, *133*, 9250–9253. doi:10.1021/ja203335u
- Wei, Y.; Yoshikai, N. *Org. Lett.* **2011**, *13*, 5504–5507. doi:10.1021/ol202229w
- John, A.; Nicholas, K. M. *J. Org. Chem.* **2011**, *76*, 4158–4162. doi:10.1021/jo200409h
- Zhao, J.; Wang, Y.; He, Y.; Liu, L.; Zhu, Q. *Org. Lett.* **2012**, *14*, 1078–1081. doi:10.1021/ol203442a
- Zhang, C.; Feng, P.; Jiao, N. *J. Am. Chem. Soc.* **2013**, *135*, 15257–15262. doi:10.1021/ja4085463
- Huang, R.; Huang, Y.; Lin, X.; Rong, M.; Weng, Z. *Angew. Chem., Int. Ed.* **2015**, *54*, 5736–5739. doi:10.1002/anie.201501257
- Shan, G.; Yang, X.; Zong, Y.; Rao, Y. *Angew. Chem., Int. Ed.* **2013**, *52*, 13606–13610. doi:10.1002/anie.201307090
- Yan, Y.; Feng, P.; Zheng, Q.-Z.; Liang, Y.-F.; Lu, J.-F.; Cui, Y.; Jiao, N. *Angew. Chem., Int. Ed.* **2013**, *52*, 5827–5831. doi:10.1002/anie.201300957
- Krylov, I. B.; Vil', V. A.; Terent'ev, A. O. *Beilstein J. Org. Chem.* **2015**, *11*, 92–146. doi:10.3762/bjoc.11.13
- Zhang, Y.-H.; Yu, J.-Q. *J. Am. Chem. Soc.* **2009**, *131*, 14654–14655. doi:10.1021/ja907198n
- Li, X.; Liu, Y.-H.; Gu, W.-J.; Li, B.; Chen, F.-J.; Shi, B.-F. *Org. Lett.* **2014**, *16*, 3904–3907. doi:10.1021/ol5016064
- Dick, A. R.; Hull, K. L.; Sanford, M. S. *J. Am. Chem. Soc.* **2004**, *126*, 2300–2301. doi:10.1021/ja031543m
- Cheng, X.-F.; Li, Y.; Su, Y.-M.; Yin, F.; Wang, J.-Y.; Sheng, J.; Vora, H. U.; Wang, X.-S.; Yu, J.-Q. *J. Am. Chem. Soc.* **2013**, *135*, 1236–1239. doi:10.1021/ja311259x
- Emmert, M. H.; Cook, A. K.; Xie, Y. J.; Sanford, M. S. *Angew. Chem., Int. Ed.* **2011**, *50*, 9409–9412. doi:10.1002/anie.201103327
- Hoover, J. M.; Ryland, B. L.; Stahl, S. S. *J. Am. Chem. Soc.* **2013**, *135*, 2357–2367. doi:10.1021/ja3117203
- Kumpulainen, E. T. T.; Koskinen, A. M. P. *Chem. – Eur. J.* **2009**, *15*, 10901–10911. doi:10.1002/chem.200901245
- Okada, T.; Asawa, T.; Sugiyama, Y.; Kiriwara, M.; Iwai, T.; Kimura, Y. *Synlett* **2014**, 25, 596–598. doi:10.1055/s-0033-1340483
- Bhadra, S.; Dzik, W. I.; Gooßen, L. J. *Angew. Chem., Int. Ed.* **2013**, *52*, 2959–2962. doi:10.1002/anie.201208755
- Bhadra, S.; Matheis, C.; Katayev, D.; Gooßen, L. J. *Angew. Chem., Int. Ed.* **2013**, *52*, 9279–9283. doi:10.1002/anie.201303702
- Desai, L. V.; Malik, H. A.; Sanford, M. S. *Org. Lett.* **2006**, *8*, 1141–1144. doi:10.1021/ol0530272
- Zhang, L.-B.; Hao, X.-Q.; Zhang, S.-K.; Liu, K.; Ren, B.; Gong, J.-F.; Niu, J.-L.; Song, M.-P. *J. Org. Chem.* **2014**, *79*, 10399–10409. doi:10.1021/jo502005j
- Zhang, L.-B.; Hao, X.-Q.; Zhang, S.-K.; Liu, Z.-J.; Zheng, X.-X.; Gong, J.-F.; Niu, J.-L.; Song, M.-P. *Angew. Chem., Int. Ed.* **2015**, *54*, 272–275. doi:10.1002/anie.201409751
- Guo, X.-K.; Zhang, L.-B.; Wei, D.; Niu, J.-L. *Chem. Sci.* **2015**, *6*, 7059–7071. doi:10.1039/C5SC01807B
- Saueremann, N.; Meyer, T. H.; Tian, C.; Ackermann, L. *J. Am. Chem. Soc.* **2017**, *139*, 18452–18455. doi:10.1021/jacs.7b11025
- Wang, G.-W.; Yuan, T.-T. *J. Org. Chem.* **2010**, *75*, 476–479. doi:10.1021/jo902139b
- Jiang, T.-S.; Wang, G.-W. *J. Org. Chem.* **2012**, *77*, 9504–9509. doi:10.1021/jo301964m
- Li, W.; Sun, P. *J. Org. Chem.* **2012**, *77*, 8362–8366. doi:10.1021/jo301384r
- Kolle, S.; Batra, S. *Org. Biomol. Chem.* **2015**, *13*, 10376–10385. doi:10.1039/C5OB01500F
- Zheng, Y.-W.; Ye, P.; Chen, B.; Meng, Q.-Y.; Feng, K.; Wang, W.; Wu, L.-Z.; Tung, C.-H. *Org. Lett.* **2017**, *19*, 2206–2209. doi:10.1021/acs.orglett.7b00463
- Yin, Z.; Jiang, X.; Sun, P. *J. Org. Chem.* **2013**, *78*, 10002–10007. doi:10.1021/jo401623j
- Shi, S.; Kuang, C. *J. Org. Chem.* **2014**, *79*, 6105–6112. doi:10.1021/jo5008306
- Li, S.; Zhu, W.; Gao, F.; Li, C.; Wang, J.; Liu, H. *J. Org. Chem.* **2017**, *82*, 126–134. doi:10.1021/acs.joc.6b02257
- Yin, X.-S.; Li, Y.-C.; Yuan, J.; Gu, W.-J.; Shi, B.-F. *Org. Chem. Front.* **2015**, *2*, 119–123. doi:10.1039/C4QO00276H

42. Lu, W.; Xu, H.; Shen, Z. *Org. Biomol. Chem.* **2017**, *15*, 1261–1267. doi:10.1039/C6OB02582J
43. Yoshikai, N. *Bull. Chem. Soc. Jpn.* **2014**, *87*, 843–857. doi:10.1246/bcsj.20140149
44. Fallon, B. J.; Derat, E.; Amatore, M.; Aubert, C.; Chemla, F.; Ferreira, F.; Perez-Luna, A.; Petit, M. *J. Am. Chem. Soc.* **2015**, *137*, 2448–2451. doi:10.1021/ja512728f
45. Moselage, M.; Li, J.; Ackermann, L. *ACS Catal.* **2016**, *6*, 498–525. doi:10.1021/acscatal.5b02344
46. Wei, D.; Zhu, X.; Niu, J.-L.; Song, M.-P. *ChemCatChem* **2016**, *8*, 1242–1263. doi:10.1002/cctc.201600040
47. Tan, G.; He, S.; Huang, X.; Liao, X.; Cheng, Y.; You, J. *Angew. Chem., Int. Ed.* **2016**, *55*, 10414–10418. doi:10.1002/anie.201604580
48. Kalsi, D.; Barsu, N.; Sundararaju, B. *Chem. – Eur. J.* **2018**, *24*, 2360–2364. doi:10.1002/chem.201705710
49. Du, C.; Li, P.-X.; Zhu, X.; Suo, J.-F.; Niu, J.-L.; Song, M.-P. *Angew. Chem., Int. Ed.* **2016**, *55*, 13571–13575. doi:10.1002/anie.201607719
50. Zhang, J.; Chen, H.; Lin, C.; Liu, Z.; Wang, C.; Zhang, Y. *J. Am. Chem. Soc.* **2015**, *137*, 12990–12996. doi:10.1021/jacs.5b07424
51. Wang, Y.; Du, C.; Wang, Y.; Guo, X.; Fang, L.; Song, M.-P.; Niu, J.-L.; Wei, D. *Adv. Synth. Catal.* **2018**, *360*, 2668–2677. doi:10.1002/adsc.201800036

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