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## COMMUNICATION

## Nickel-catalyzed C-O bond reduction of aryl and benzyl 2-pyridyl ethers

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

Jing Li<sup>a</sup> and Zhong-Xia Wang<sup>\*,a,b</sup>

DOI: 10.1039/x0xx00000x

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The reduction of aryl and benzyl 2-pyridyl ethers with sodium isopropoxide was carried out via nickel-catalyzed C-OPy bond cleavage, giving reductive products in reasonable to excellent yields. This method allowed the 2-pyridyloxy group to be directly removed with high efficiency, mild reaction conditions, and good compatibility of functional groups.

The use of a directing group is an effective way to realize transition-metal-catalyzed regioselective C-H functionalization.<sup>1</sup> 2-Pyridyloxy group (OPy) was one of the widely used directing groups in an aromatic system.<sup>2</sup> An important feature of this class of aromatic system is that the OPy or Py group can be removed after directing C-H functionalization. In an earlier example, the Py group was removed from a aryl 2-pyridyl ether through a two-step reaction involving N-methylation with MeOTf and then the cleavage of the resulting C(pyridinium)-O bond with MeONa.<sup>2b</sup> Recently, Chatani et al. carried out rhodium- or nickel-catalyzed borylation of aryl 2pyridyl ethers through cleavage of the C<sub>Ar</sub>-OPy bond.<sup>3</sup> More recently, we performed nickel-catalyzed conversion of the OPy group of aryl 2-pyridyl ethers into an amino group.<sup>4</sup> Although these progresses have been achieved, the methods to remove or transform OPy group are still very limited. It is significant to develop new methodology of the OPy transformation to increase the synthetic utility of the directing group.

The reductive deoxygenation of phenols and their derivatives is an important transformation in organic synthesis.<sup>5</sup> Usually, phenols could be converted into the corresponding tosylates, mesylates, or triflates and then the sulfonates were reduced in the presence of transition metal catalysts.<sup>5a,6</sup> For robust methoxy or acyloxy groups, a few of

successful examples have also been reported with reductants such as hydrogen, hydrosilanes, hydrides and isopropanol.<sup>7</sup> Alkoxides have been proved to be efficient reductants for the dehalogenation of aryl halides and deamination of aromatic and benzylic quaternary ammonium triflates.<sup>8</sup> On the basis of the excellent performance of nickel catalysts in the activation of C-O bonds and alkoxide in the reduction of C-halide and C-N bonds, we proposed that a nickel catalyst combined with an alkoxide could effect the catalytic reduction of aryl 2-pyridyl ethers.

We screened catalysts and reaction conditions using 2-(biphenyl-4-yloxy)pyridine (1a) as the model substrate (Table 1). Initially, we tried a combination of Ni(acac)<sub>2</sub> and PCy<sub>3</sub> or Nheterocyclic carbene (NHC) including IMes and IPr as the catalyst. However, the reaction of 1a with i-PrONa in dioxane at 60 °C did not give any desired product (Table 1, entries 1-3). We thought that maybe the nickel(II) precursors cannot be reduced to form active catalyst under the present reaction conditions. So we directly used Ni(0) resource, Ni(COD)2, to test the reaction. To our delight, it performed smoothly when combining with IMes or IPr, resulting in the desired products in 86% and 94% yields, respectively (Table 1, entries 4 and 5). Further tests showed that both IMes<sup>Me</sup> and SIPr also gave positive results, while ICy not (Table 1, entries 6-8). The combination of Ni(COD)<sub>2</sub> and phosphine ligands including BINAP, Dcype and PCy<sub>3</sub> was also tested. The combination of Ni(COD)<sub>2</sub> and biphosphines was nonactive, and Ni(COD)<sub>2</sub>/PCy<sub>3</sub> led to 48% product yield (Table 1, entries 9-11). It appeared that NHC ligands gave the most satisfied yields and IPr performed best. However, double the amount of the ligand making a 1:2 ratio of Ni(0) and IPr led to a significant decrease of the yield (Table 1, entry 12), indicating that excess ligand retarded the reaction and the active catalytic species seemed to be a monoligated carbene-nickel complex. Next, the solvent effect was examined. It showed that solvents had a significant influence on the reaction and THF was most suitable (Table 1, entry 13). Other solvents such as toluene, DMF and DME only showed low to moderate performance (Table 1, entries 14-16). Other alkoxides involving i-PrOLi, i-PrOK and EtONa were next

<sup>&</sup>lt;sup>a.</sup> CAS Key Laboratory of Soft Matter Chemistry, Hefei National Laboratory for Physical Sciences at Microscale and Department of Chemistry, University of Science and Technology of China, Hefei, Anhui 230026, P. R. China. E-mail: zxwang@ustc.edu.cn

<sup>&</sup>lt;sup>b.</sup> Collaborative Innovation Center of Chemical Science and Engineering, Tianjin 300072, P. R. China.

<sup>&</sup>lt;sup>+</sup> Electronic Supplementary Information (ESI) available: Experimental details of the reductive reaction, characterization data, and the copies of NMR spectra of the products. See DOI: 10.1039/x0xx00000x

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DOI: 10.1039/C7CC09668B Journal Name

Table 1 Optimization of reaction conditions<sup>a</sup>

Table 2 Scope of aryl 2-pyridyl ethers a,b



<sup>*a*</sup> Unless otherwise stated, the reactions were performed with 0.2 mmol of 2-(biphenyl-4-yloxy)pyridine and 0.6 mmol of *i*-PrONa in 1 cm<sup>3</sup> solvent according to the conditions indicated by the above equation. <sup>*b*</sup> Isolated yield. <sup>*c*</sup> *i*-PrOLi was employed to replace *i*-PrONa. <sup>*d*</sup> *i*-PrOK was employed to replace *i*-PrONa. <sup>*e*</sup> EtONa was employed to replace *i*-PrONa. <sup>*f*</sup> 1.5 equiv. of *i*-PrONa was employed. <sup>*g*</sup> The reaction was performed on a 4 mmol scale. <sup>*h*</sup> 1.5 mol% of Ni(COD)<sub>2</sub> was employed. <sup>*i*</sup> The reaction was run at 50 °C.

examined. They led to either very low product yields or no any desired product (Table1, entries 17-19). We also noticed that 1.5 equiv. of sodium isopropoxide was enough to accomplish the reaction (Table 1, entry 20). With this sodium isopropoxide loading, the reaction can be performed by employing 4 mmol **1a** and resulted in only a slightly decreased yield (86%). Finally, we attempted to run the reaction with lower catalyst loading (1.5 mol%) or lower reaction temperature. However, the product yield decreased in each case (Table 1, entries 21 and 22).

With the optimized conditions in hand, we first examined the scope of aryl 2-pyridyl ethers. Substrates **1b-1q** were found to be suitable reaction partners to get reduced products as shown in Table 2. Unactivated substrates 2-(4-(*tert*-butyl) phenoxy)pyridine (**1b**) was successfully reduced to afford **2b** in



<sup>*a*</sup> Unless otherwise stated, the reactions were performed with 0.2 mmol of aryl 2pyridyl ethers and 0.3 mmol of *i*-PrONa in THF (1 cm<sup>3</sup>) according to the conditions indicated by the above equation. <sup>*b*</sup> Isolated yield. <sup>*c*</sup> GC yield with dodecane as an internal standard. <sup>*d*</sup> The reaction was run for 3 h. <sup>*e*</sup> 5 mol% of Ni(COD)<sub>2</sub> and 3 equiv. of *i*-PrONa were employed. <sup>*f*</sup> 10 mol% of Ni(COD)<sub>2</sub> and 3 equiv. of *i*-PrONa were employed. <sup>*a*</sup> The reaction was run at 100 °C using 3 equiv. of *i*-PrONa in 1,4dioxane. <sup>*h*</sup> The reaction was run for 12 h. <sup>*i*</sup> NMR yield.

good yield. The aryl 2-pyridyl ethers with strong electrondonating groups such as PhO, BnO, and Me<sub>2</sub>N on the aryl rings (**1c-1e**) all presented excellent reactivity (90-98% product yields). The benzyloxy group in compound **1d** that could easily be reduced by catalytic hydrogenolysis stayed intact. 2-(4-Fluorophenoxy)pyridine (**1f**) resulted in an excellent yield of desired product leaving fluoro substituent untouched. Other functional groups on the aromatic rings involving alkenyl, amide, carbonyl, carbamyl and cyano groups were also well tolerated (**1h-1m**). Most of them were vulnerable under a reductive environment. Heteroaromatic substrate like 2-(pyridin-2-yloxy)quinoline (**1n**) performed smoothly with an excellent result (82% yield). Importantly, *ortho*-substituents were acceptable (**1o-1u**), allowing for the 2-pyridyloxy groups being removed after they directed C-H functionalization. The ortho-substituents included electro-donating and withdrawing ones. Some reactive groups such as F, alkenyl, and carbamyl were tolerated. *o*-Formyl group was not tolerated under current reaction conditions. However, reaction of 2-(2-(1,3dioxolan-2-yl)phenoxy)pyridine proceeded smoothly, giving the reductive product **2t** in 76% yield. Reaction of N,N-diethyl-2-(pyridin-2-yloxy)benzamide (**1u**) at 100 °C cannot form the desired product. Hence the reaction was run at 60 °C. In this case 10 mol% catalyst loading was necessary. Otherwise the starting material cannot be completely consumed.

Reductive deoxygenation of benzyl ethers is often used as a model reaction in the study of biomass transformation and has attracted considerable attention.<sup>9</sup> Ni(COD)<sub>2</sub>-IPr•HCl/*i*-PrONa system proved applicable in the reduction of benzyl 2-pyridyl ethers (Table 3). Benzyl ethers showed lower reactivity than aryl ethers in current reaction system.<sup>7c</sup> Hence more intense reaction conditions were required. Under the modified conditions the substrates containing electron-donating and electron-withdrawing substituents on the aromatic rings (3a-3c) presented reasonable reactivity and led to the desired reductive products in 57%-83% yields. The ethers with extended aromatic systems including 2-(naphthalen-2ylmethoxy)pyridine (3d) and 6-((pyridin-2-yloxy)methyl)quinoline (3e) also gave excellent reaction results. Finally, the branched benzyl ether, 2-(benzhydryloxy)pyridine (3f), was also suitable, although only with unsatisfied yield.

Table 3 Scope of benzyl 2-pyridyl ethers<sup>a,b</sup>



<sup>*a*</sup> Unless otherwise stated, the reactions were performed with 0.2 mmol of benzyl 2-pyridyl ethers and 0.6 mmol of *i*-PrONa in 1,4-dioxane ( $1 \text{ cm}^3$ ) according to the conditions indicated by the above equation. <sup>*b*</sup> Isolated yield. <sup>*c*</sup> GC yield with dodecane as an internal standard. <sup>*d*</sup> 10 mol% of Ni(COD)<sub>2</sub> was employed and run for 12 h.

It was well known that 2-pyridyloxy (OPy) group possessing strong coordination ability of its sp<sup>2</sup> nitrogen is one of the most effective directing groups which could facilitate various aromatic functionalization reactions with good efficiency and regioselectivity. The sequential OPy-directed ortho C-H functionalization and removal of the directing group were carried out to demonstrate the utility in organic synthesis. Thus, 2-phenoxypyridine was ortho-arylated under the catalysis of palladium according to the literature procedure.<sup>2b</sup> The formed compound **1q** was subsequently converted to the biaryl product **2q** through removal of the OPy group under our conditions (Scheme 1).

DOI: 10.1039/C7CC09668B

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To gain preliminary mechanistic information about this transformation, we carried out the reduction of 2-(biphenyl-4yloxy)pyridine (1a) with a deuterated sodium isopropoxide. The deuterated biphenyl product 2a-D was obtained in excellent yield with 93% deuterated (Scheme 2), which was a solid proof that the hydrogen donor actually came from sodium isopropoxide. The kinetic isotope effect (KIE) experiments were also performed separately using i-PrONa and i-PrONa-D7 as the reducing agents under identical conditions. We obtained a KIE value of 1.40, suggesting that the  $\beta$ -hydride elimination may not be the rate-determining step,<sup>10</sup> which is similar to Ni-catalyzed reduction of aryl ammonium triflates.<sup>8e</sup> As for the mechanism about the cleavage of the Ar-OPy bond, we believed that the chelation assistance of pyridine may help catalyst to exclusively break the C-OPy bond. That both 3-(biphenyl-4-yloxy)pyridine and 4-(biphenyl-4-yloxy)pyridine cannot be reduced under the same conditions supports this conjecture. Based on the abovementioned experimental facts and literature information,<sup>8b,c,e</sup> a possible catalytic cycle is outlined in Scheme 3.







Scheme 3 Proposed catalytic cycle.

In summary, we have developed an effective method of nickel-catalyzed removal of OPy group from aryl and benzyl 2-pyridyl ethers by using sodium isopropoxide as reducing agent. In both cases no products formed via  $C_{Py}$ -O bond cleavage were observed. The reaction showed a broad scope of substrates and good compatibility of functional groups, and gave mostly excellent yields. We believe that this methodology is a valuable complement to the reductive deoxygenation of phenol and benzyl alcohol derivatives and provides a subsequent conversion way for the 2-pyridyloxy directing group in the functionalization of C–H bonds. The catalytic reduction of aryl and benzyl 2-pyridyl ethers using hydrogen or hydrosilanes as mutually complementary method will be explored in the near future.

This work was supported by the National Natural Science Foundation of China (Grant No. 21772186) and the National Basic Research Program of China (Grant No. 2015CB856600). We thank Mr. Bo Yang for his help in the preparation of several substrates.

## **Conflicts of interest**

There are no conflicts to declare.

### Notes and references

- (a) D. A. Colby, R. G. Bergman and J. A. Ellman, *Chem. Rev.*, 2010, **110**, 624; (b) O. Daugulis, H.-Q. Do and D. Shabashov, *Acc. Chem. Res.*, 2009, **42**, 1074; (c) T. W. Lyons and M. S. Sanford, *Chem. Rev.*, 2010, **110**, 1147; (d) X. Chen, K. M. Engle, D.-H. Wang and J.-Q. Yu, *Angew. Chem. Int. Ed.*, 2009, **48**, 5094; (e) L.-M. Xu, B.-J. Li, Z. Yang and Z.-J. Shi, *Chem. Soc. Rev.*, 2010, **39**, 712; (f) G. Rouquet and N. Chatani, *Angew. Chem. Int. Ed.*, 2013, **52**, 11726; (g) J. Wencel-Delord and F. Glorius, *Nat. Chem.*, 2013, **5**, 369.
- 2 (a) F. Kakiuchi, K. Igi, M. Matsumoto, T. Hayamizu, N. Chatani and S. Murai, *Chem. Lett.*, 2002, **31**, 396; (b) J.-H. Chu, P.-S. Lin and M.-J. Wu, *Organometallics*, 2010, **29**, 4058; (c) L. Ackermann, E. Diers and A. Manvar, *Org. Lett.*, 2012, **14**, 1154; (d) L. Niu, H. Yang, R. Wang and H. Fu, *Org. Lett.*, 2012, **14**, 2618; (e) J. Yao, R. Feng, Z. Wu, Z. Liu and Y. Zhang, *Adv. Synth. Catal.*, 2013, **355**, 1517; (f) Y.-F. Liang; X. Li, X. Wang, Y. Yan, P. Feng and N. Jiao, *ACS Catal.*, 2015, **5**, 1956; (g) S.-J. Lou, Q. Chen, Y.-F. Wang, D.-Q. Xu, X.-H. Du, J.-Q.He, Y.-J. Mao and Z.-Y. Xu, *ACS Catal.*, 2015, **5**, 2846.
- (a) H. Kinuta, M. Tobisu and N. Chatani, *J. Am. Chem. Soc.*, 2015, **137**, 1593; (b) M. Tobisu, J. Zhao, H. Kinuta, T. Furukawa, T. Igarashi and N. Chatani, *Adv. Synth. Catal.*, 2016, **358**, 2417.
- 4 J. Li and Z.-X. Wang, Org. Lett., 2017, 19, 3723.
- 5 (a) B. M. Rosen, K. W. Quasdorf, D. A. Wilson, N. Zhang, A.-M. Resmerita, N. K. Garg and V. Percec, *Chem. Rev.*, 2011, **111**, 1346; (b) M. Tobisu and N. Chatani, *Acc. Chem. Res.*, 2015, **48**, 1717; (c) J. Cornella, C. Zarate and R. Martin, *Chem. Soc. Rev.*, 2014, **43**, 8081; (d) T. Mesganaw and N. K. Garg, *Org. Process Res. Dev.*, 2013, **17**, 29; (e) W.-J. Shi, X.-L. Li, Z.-W. Li and Z.-J. Shi, *Org. Chem. Front.*, 2016, **3**, 375.
- 6 (a) K. Sasaki, T. Kubo, M. Sakai and Y. Kuroda, *Chem. Lett.*, 1997, 617; (b) V. Kogan, *Tetrahedron Lett.*, 2006, 47, 7515; (c) B. H. Lipshutz, B. A. Frieman, T. Butler and V. Kogan, *Angew. Chem. Int. Ed.*, 2006, 45, 800; (d) A. Mori, T.

Mizusaki, T. Ikawa, T. Maegawa, Y. Monguchi and H. Sajiki, *Chem. –Eur. J.*, 2007, **13**, 1432.

- (a) M. Tobisu, K. Yamakawa, T. Shimasaki and N. Chatani, *Chem. Commun.*, 2011, **47**, 2946; (b) M. Tobisu, T. Morioka, A. Ohtsuki and N. Chatani, *Chem. Sci.*, 2015, **6**, 3410; (c) A. G. Sergeev and J. F. Hartwig, *Science*, 2011, **332**, 439; (d) A. G.
  Sergeev, J. D. Webb and J. F. Hartwig, *J. Am. Chem. Soc.*, 2012, **134**, 20226; (e) E. M. Wiensch, D. P. Todd and J.
  Montgomery, *ACS Catal.*, 2017, **7**, 5568; (f) A. Ohgi and Y.
  Nakao, *Chem. Lett.*, 2016, **45**, 45; (g) P. Álvarez-Bercedo and R. Martin, *J. Am. Chem. Soc.*, 2010, **132**, 17352; (h) J.
  Cornella, E. Gómez-Bengoa and R. Martin, *J. Am. Chem. Soc.*, 2013, **135**, 1997; (i) Y. Ren, M. Yan, J. Wang, Z. C. Zhang and K. Yao, *Angew. Chem. Int. Ed.*, 2013, **52**, 12674; (j) K. Yasui, M. Higashino, N. Chatani and M. Tobisu, *Synlett*, 2017, **28**, 2569.
- 8 (a) M. E. Cucullu, S. P. Nolan, T. R. Belderrain and R. H. Grubbs, Organometallics, 1999, 18, 1299; (b) M. S. Viciu, G. A. Grasa and S. P. Nolan, Organometallics, 2001, 20, 3607; (c) S. Kuhl, R. Schneider and Y. Fort, Adv. Synth. Catal., 2003, 345, 341; (d) C. J. E. Davies, M. J. Page, C. E. Ellul, M. F. Mahon and M. K. Whittlesey, Chem. Commun., 2010, 46, 5151; (e) Y-Q-Q Yi, W-C Yang, D-D Zhai, X-Y Zhang, S-Q Li and B-T Guan, Chem. Commun., 2016, 52, 10894.
- 9 (a) S. Gillet, M. Aguedo, L. Petitjean, A. R. C. Morais, A. M. da Costa Lopes, R. M. Łukasik and P. T. Anastas, *Green Chem.*, 2017, **19**, 4200; (b) S. K. Surmiak, C. Doerenkamp, P. Selter, M. Peterlechner, A. H. Schäfer, H. Eckert and A. Studer, *Chem. –Eur. J.*, 2017, **23**, 6019; (c) E. Paone, C. Espro, R. Pietropaolo and F. Mauriello, *Catal. Sci. Technol.*, 2016, **6**, 7937; (d) C. M. Bernt, G. Bottari, J. A. Barrett, S. L. Scott, K. Barta and P. C. Ford, *Catal. Sci. Technol.*, 2016, **6**, 2984; (e) L. Chen, J. Xin, L. Ni, H. Dong, D. Yan, X. Lu and S. Zhang, *Green Chem.*, 2016, **18**, 2341; (f) H. Fan, Y. Yang, J. Song, Q. Meng, T. Jiang, G. Yang and B. Han, *Green Chem.*, 2015, **17**, 4452; (g) X. Fan, X.-M. Cui, Y.-H. Guan, L.-A. Fu, H. Lv, K. Guo and H.-B. Zhu, *Eur. J. Org. Chem.*, 2014, 498.
- 10 J. S. M. Samec, J.-E. Backvall, P. G. Andersson and P. Brandt, *Chem. Soc. Rev.*, 2006, **35**, 237.

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Graphical content

## Nickel-catalyzed C-O bond reduction of aryl and benzyl 2-pyridyl

## ethers

Jing Li<sup>a</sup> and Zhong-Xia Wang<sup>\*,a,b</sup>

<sup>a</sup> CAS Key Laboratory of Soft Matter Chemistry, Hefei National Laboratory for Physical Sciences at Microscale and Department of Chemistry, University of Science and Technology of China, Hefei, Anhui 230026, P. R. China.

<sup>b</sup> Collaborative Innovation Center of Chemical Science and Engineering, Tianjin 300072, P. R. China.

Aryl and benzyl 2-pyridyl ethers were effectively reduced with *i*-PrONa via Ni-catalyzed C-OPy bond cleavage.

