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Nickel-Catalyzed Borylation of Aryl and Benzyl 2-Pyridyl Ethers: A Method for Converting a Robust *ortho*-Directing Group

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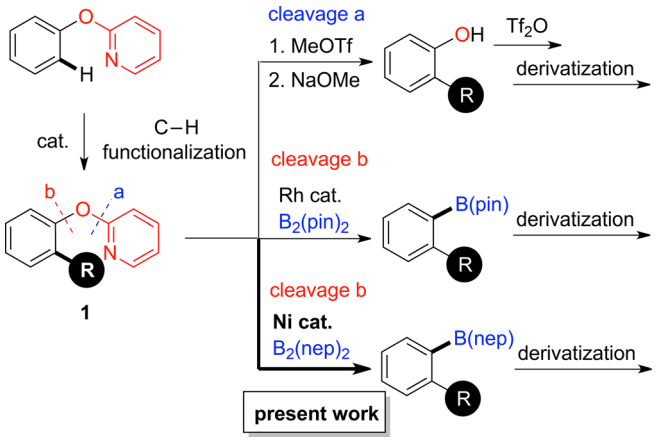
Abstract: The nickel-catalyzed borylation of aryl 2-pyridyl ethers *via* the loss of a 2-pyridyloxy group is described. This method allows a 2-pyridyloxy group to be used as a convertible directing group in C–H bond functionalization reactions. The nickel catalyst can also borylate arylmethyl 2-pyridyl ethers, in which the stereochemistry at the benzylic position is retained in the case of chiral secondary benzylic substrates.

Keywords: borylation; C–O activation; cross-coupling; directing group; nickel catalyst

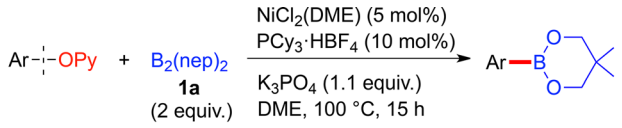


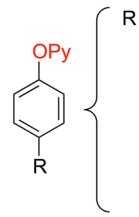
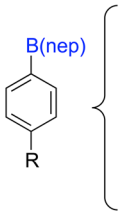
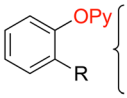
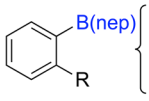
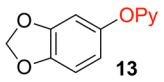
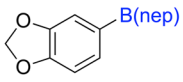
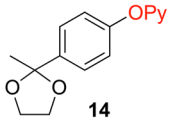
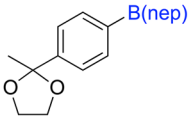
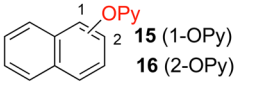
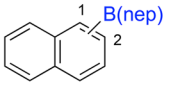
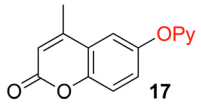
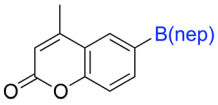
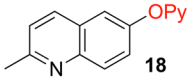
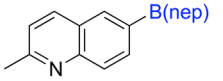
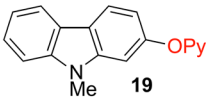
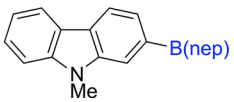
Scheme 1. The 2-pyridyloxy group as a convertible directing group for *ortho* C–H bond functionalization reactions.

The use of a directing group is a powerful strategy for achieving the regioselective functionalization of C–H bonds.[1] A 2-pyridyloxy (OPy) group has served as a useful directing group, partly because of the strong coordinating ability of its sp^2-hybridized nitrogen atom and its stability under various synthetic conditions.[2] Despite its robustness, the removal of the pyridine ring in OPy proceeds through a two-step sequence involving N-methylation with MeOTf, followed by the cleavage of the resulting C(pyridinium)–O bond by a strong base such as NaOMe (Scheme 1, *top*).[2b] We previously reported on a new catalytic method for the conversion of an OPy group, namely, the rhodium-catalyzed borylation of aryl 2-pyridyl ethers with $B_2(pin)_2$ (Scheme 1, *middle*).[3,4] This rhodium-catalyzed protocol has the following advantages: (i) a high functional group compatibility that is enabled by the neutral conditions employed and the fact that strong alkylating reagents are not needed, (ii) the OPy group can be converted into a boryl group in one step, and (iii) the resulting boryl group can be directly used for further elaboration. Herein, we report on the development of a nickel catalyst that promotes the borylation of 2-pyridyl ethers (Scheme 1, *bottom*). The use of a nickel catalyst not only makes the process less expensive but also allows the scope of the reaction to be expanded to secondary benzylic ether substrates that are inapplicable when the previous rhodium system is used.

We initiated our study by examining the reaction of $B_2(nep)_2$ (**1a**, nep: neopentylglycolate) and the aryl 2-pyridiyl ether **2** in the presence of a nickel catalyst.[5,6,7] After optimization, the expected borylation product **2a** was obtained in 80% isolated yield under the conditions using $NiCl_2(DME)$ (DME: 1,2-dimethoxyethane) as a catalyst, $PCy_3{\cdot}HBF_4$ as a ligand, K_3PO_4 as a base in DME at 100 °C for 15 h (Table 1, entry 1). Several other electron-rich ligands including PBu_3 (34%), IMes·HCl [59%, IMes = 1,3-bis(2,4,6-trimethylphenyl)imidazol-2-ylidene], IPr·HCl [78%,

Table 1. Nickel-catalyzed borylation of aryl 2-pyridyl ethers.[a]



Entry	2-Pyridyl Ether	Product	Isolated Yield [%]
1–8	 R = *t*-Bu (**2**), Ph (**3**), NMe_2 (**4**), OMe (**5**), OPh (**6**), F (**7**), CF_3 (**8**), CO_2Et (**9**)		**2a**: 80, **3a**: 68, **4a**: 55, **5a**: 75, **6a**: 77, **7a**: 64, **8a**: 81, **9a**: 70
9–11[b]	 R = F (**10**), CO_2Et (**11**), Ph (**12**)		**10a**: 71, **11a**: 68, **12a**: 56[c]
12	 **13**		**13a**: 86
13	 **14**		**14a**: 80
14, 15	 **15** (1-OPy), **16** (2-OPy)		**15a**: 54, **16a**: 62
16	 **17**		**17a**: 60
17	 **18**		**18a**: 73
18	 **19**		**19a**: 83

[a] *Reaction conditions:* 2-pyridyl ether (0.50 mmol), **1a** (1.0 mmol), $NiCl_2$(DME) (0.025 mmol), PCy_3·HBF_4 (0.050 mmol) and K_3PO_4 (0.55 mmol) in DME (1.0 mL) at 100 °C for 15 h.

[b] $Ni(cod)_2$ (0.025 mmol) and PCy_3 (0.050 mmol) were used instead of $NiCl_2$(DME) and PCy_3·HBF_4.

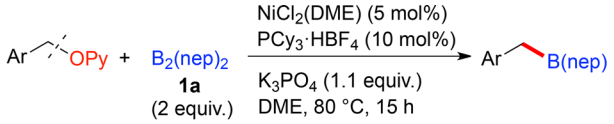
[c] The yield was determined by NMR because **12a** could not be separated from the unreacted **1a**.

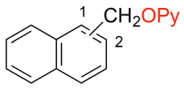
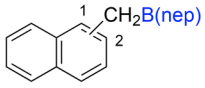
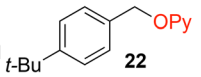
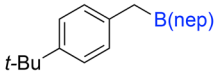
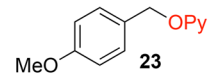
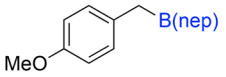
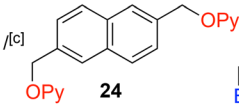
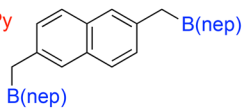
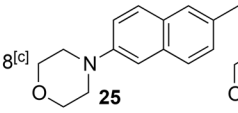
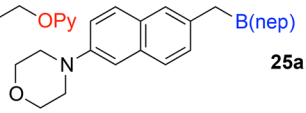
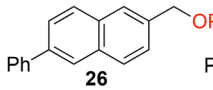
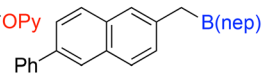
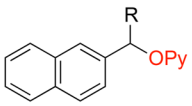
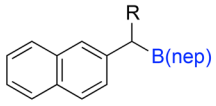
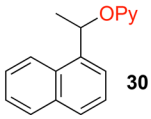
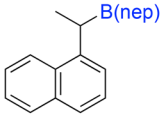
IPr = 1,3-bis(2,6-diisopropylphenyl)imidazol-2-ylidene] also afforded **2a**, while PPh_3 was completely ineffective. The use of $B_2(pin)_2$ (**1b**, pin = pinacolate) instead of **1a** significantly decreased the yield of **2a** (19%). The corresponding 4-pyridyl ether did not undergo borylation under these conditions, indicating that the presence of a 2-pyridyl moiety is essential for the activation of the C(aryl)–O bond.[8] Various functional groups are tolerated in these nickel-catalyzed conditions and includes amines (entry 3), ethers (entries 4 and 5), fluorides (entries 6, 7 and 9), esters (entries 8 and 10) and acetals (entries 12 and 13). Importantly, substituents at the *ortho* position are acceptable, allowing for this borylation to occur at a sterically congested position (entries 9–11). π-Extended (entries 14 and 15) and heteroaromatic substrates such as coumarin (entry 16), quinoline (entry 17) and carbazole (entry 18) were also applicable to this borylation. Low-valent nickel catalysts in conjunction with an electron-rich ligand have been reported to promote the cleavage of various C(aryl)–O bonds.[5] Nevertheless, an OPy group is activated with complete chemoselectivity in the presence of other C(aryl)–O bonds (entries 4, 5, 12 and 16), indicating that an OPy group significantly accelerates the C–O bond activation event.

In view of several reports on C(benzyl)–O bond activation using nickel catalysts,[5,9,10,11] we next turned our attention to the nickel-catalyzed borylation of arylmethyl 2-pyridyl ethers. In these cases, the present nickel system was found to be able to successfully activate an OPy group at the benzylic position. For example, the 1-naphthylmethyl 2-pyridyl ether (**20**) afforded the corresponding borylated product **20a** in 80% NMR yield, although the isolated yield of **20a** was decreased to 68% and a protodeboronation compound (1-methylnaphthalene) was also produced in 19% (entry 1, Table 2). Benzyl ethers were less reactive than naphthyl ethers[5] and required the use of the stronger σ-donor 1,3-dicyclohexylimidazol-2-ylidene (ICy) as a ligand to achieve an efficient reaction (entries 3–6). It is noteworthy that this protocol can also be used for borylation of *secondary* benzylic ethers. The reaction of 2-naphthylmethyl ethers bearing a methyl group at the benzylic position, i.e., **27**, gave the corresponding secondary benzylic boronic ester **27a** in 71% isolated yield (entry 10). While a substrate bearing an *n*-butyl group could also be borylated with comparable efficiency, the yield was decreased significantly (30%) when a bulkier isopropyl-substituted substrate **29** was used with a protodeboronation product being formed (46%). The formation of this undesired side product was suppressed by using (±)-BINAP as a ligand to form the borylated product **29a** in 68% yield (entry 12). When a phenyl group was introduced at the benzylic position, the borylated product was formed in 16% with the formation of a protodeboronation product (66%, see the Supporting Information for details).

The reaction of secondary benzylic substrates provided us with an opportunity to examine the stereospecificity of this borylation using a chiral substrate. Although a range of stereospecific cross-coupling processes using chiral secondary benzylic electrophiles have been reported to date, nearly all of the examples

Table 2. Nickel-catalyzed borylation of arylmethyl 2-pyridyl ethers.[a]



Entry	2-Pyridyl Ether	Product	Isolated Yield [%]
1	**20** (1-CH_2OPy)		**20a**: 68
2	**21** (2-CH_2OPy)		**21a**: 67
3	 **22**		**22a**: 37
4[b]			**22a**: 63
5	 **23**		**23a**: 40
6[b]			**23a**: 75
7[c]	 **24**		**24a**: 70
8[c]	 **25**		**25a**: 71
9[c]	 **26**		**26a**: 60
10	**27** (R = Me)		**27a**: 71
11	**28** (R = *n*-Bu)		**28a**: 66
12[d]	**29** (R = *i*-Pr)		**29a**: 68
13	 **30**		**30a**: 65

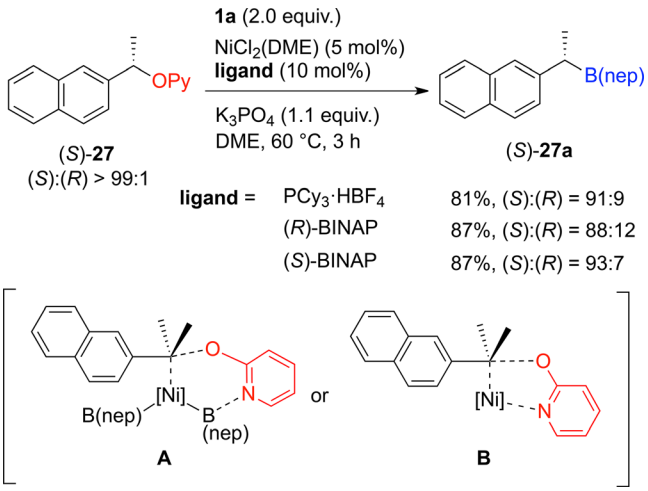
[a] *Reaction conditions:* 2-pyridyl ether (0.50 mmol), **1a** (1.0 mmol), $NiCl_2$(DME) (0.025 mmol), PCy_3·HBF_4 (0.050 mmol) and K_3PO_4 (0.55 mmol) in DME (1.0 mL) at 80 °C for 15 h.

[b] ICy·HCl (0.050 mmol) was used instead of PCy_3·HBF_4.

[c] Run for 24 h.

[d] (±)-BINAP (0.025 mmol) was used instead of PCy_3·HBF_4.

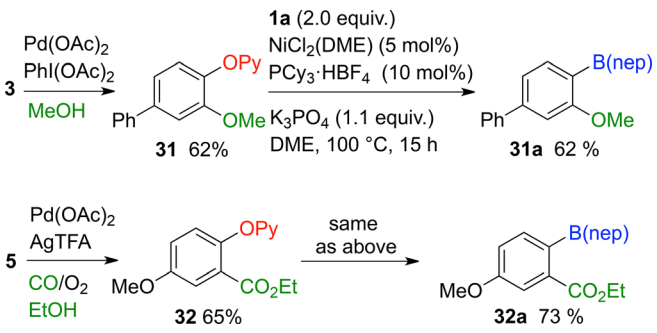
involve the overall inversion of the benzylic stereocenter, in which the reaction proceeds through an S_N2-type oxidative addition with inversion followed by stereoretentive transmetalation and reductive elimination.[9,12] A notable exception is the nickel-catalyzed cross-coupling of chiral secondary benzylic carbamates with arylboronic esters with retention of the benzylic configuration.[13] The stereospecificity of our



Scheme 2. Stereoretentive borylation of (*S*)-**27**.

benzylic borylation reaction was examined using (*S*)-**27** as the substrate and PCy_3 as the ligand (Scheme 2). As a result, (*S*)-**27a** was obtained as the major isomer. The use of (*S*)- and (*R*)-BINAP also afforded (*S*)-**27a** with a good level of selectivity, in which the sense and magnitude of the specificity was not affected significantly by the absolute configuration of the BINAP. These results indicate that the initial C(benzyl)–O bond cleavage proceeds with retention of the configuration possibly *via* transition state **A** or **B**, in which the coordination of a pyridine nitrogen directs the nickel center to attack from the same side as the leaving OPy group. Unlike in the cases of aryl 2-pyridyl ethers, IMes and IPr ligands were ineffective for the borylation of arylmethyl 2-pyridyl ethers (0% yield in both cases).

The sequential OPy-directed *ortho* C–H functionalization and borylative removal of the directing group is demonstrated (Scheme 3). One of the advantages of using a pyridine-based directing group is its stability under oxidative conditions, which allows it to be used in oxidative *ortho* C–H transformations. For example, the pyridyl ether **3** readily underwent palladium-catalyzed oxidative *ortho* methoxylation to form



Scheme 3. 2-Pyridyloxy group-directed C–H functionalization and its borylative removal.

31,[2j] which can subsequently be converted to the boron derivative **31a** *via* the loss of an OPy group under our nickel-catalyzed conditions. Similarly, the *ortho* ethoxycarbonylation of **5**,[2i] followed by our borylation successfully delivered polyfunctionalized phenylboronic ester **32a**.

In summary, we report on the use of a nickel system that can catalyze the borylation of aryl and arylmethyl 2-pyridyl ethers *via* the cleavage of C(aryl)–O bonds. Given the utility of the OPy group as a directing group in C–H functionalization reactions,[2] the present method broadens the synthetic utility of the C–H functionalized products to a considerable extent by allowing the OPy group to be converted into a versatile boryl group. This nickel system can also be used to borylate more challenging secondary benzylic substrates, in which case, the reaction proceeds with retention of configuration at the benzylic stereocenter. This stereochemical course of the reaction is complementary to the vast majority of stereospecific processes of chiral benzylic electrophiles, which proceed with net inversion.[9,12] Further studies directed to developing catalytic processes involving boryl-metal species are currently underway in our laboratories.

Experimental Section

Typical Procedure

$NiCl_2$(DME) (5.5 mg, 0.025 mmol), $PCy_3{\cdot}HBF_4$ (18 mg, 0.050 mmol), **2** (114 mg, 0.50 mmol), **1a** (226 mg, 1.0 mmol), K_3PO_4 (117 mg, 0.55 mmol), and DME (1.0 mL) were added to a 5-mL screw-capped vial in air. The vial was then flushed with nitrogen and the cap was closed. The mixture was stirred at 100 °C for 15 h followed by cooling to room temperature. The resulting mixture was filtered through a Celite pad (eluting with AcOEt). The filtrate was analyzed by NMR using $C_2H_2Cl_4$ as an internal standard (88% NMR yield). The filtrate was concentrated under vacuum and purified by flash column chromatography over silica gel (eluting with hexane/AcOEt = 10/1) to give **2a** as a white solid; yield: 98 mg (80%).

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References

[1] Selected reviews: a) D. A. Colby, R. G. Bergman, J. A. Ellman, *Chem. Rev.* **2010**, *110*, 624; b) O. Daugulis, H.-Q. Do, D. Shabashov, *Acc. Chem. Res.* **2009**, *42*, 1074; c) T. W. Lyons, M. S. Sanford, *Chem. Rev.* **2010**, *110*, 1147; d) P. Sehnal, R. J. K. Taylor, I. J. S. Fairlamb, *Chem. Rev.* **2010**, *110*, 824; e) X. Chen, K. M. Engle, D.-H. Wang, J.-Q. Yu, *Angew. Chem.* **2009**, *121*, 5196; *Angew. Chem. Int. Ed.* **2009**, *48*, 5094; f) K. M. Engle, T.-S. Mei, M. Wasa, J.-Q. Yu, *Acc. Chem. Res.* **2012**, *45*, 788; g) L.-M. Xu, B.-J. Li, Z. Yang, Z.-J. Shi, *Chem. Soc. Rev.* **2010**, *39*, 712; h) P. B. Arockiam, C. Bruneau, P. H. Dixneuf, *Chem. Rev.* **2012**, *112*, 5879; i) G. Rouquet, N. Chatani, *Angew. Chem.* **2013**, *125*, 11942; *Angew. Chem. Int. Ed.* **2013**, *52*, 11726; j) J. Wencel-Delord, F. Glorius, *Nat. Chem.* **2013**, *5*, 369; k) S. De Sarkar, W. Liu, S. I. Kozhushkov, L. Ackermann, *Adv. Synth. Catal.* **2014**, *356*, 1461; l) N. Yoshikai, *Bull. Chem. Soc. Jpn.* **2014**, *87*, 843; m) M. Miura, T. Satoh, K. Hirano, *Bull. Chem. Soc. Jpn.* **2014**, *87*, 751; n) A. Ros, R. Fernandez, J. M. Lassaletta, *Chem. Soc. Rev.* **2014**, *43*, 3229; o) L. C. M. Castro, N. Chatani, *Chem. Lett.* **2015**, *44*, 410.

[2] a) F. Kakiuchi, K. Igi, M. Matsumoto, T. Hayamizu, N. Chatani, S. Murai, *Chem. Lett.* **2002**, *31*, 396; b) J.-H. Chu, P.-S. Lin, M.-J. Wu, *Organometallics* **2010**, *29*, 4058; c) L. Ackermann, E. Diers, A. Manvar, *Org. Lett.* **2012**, *14*, 1154; d) L. Niu, H. Yang, R. Wang, H. Fu, *Org. Lett.* **2012**, *14*, 2618; e) M. Kim, S. Sharma, J. Park, M. Kim, Y. Choi, Y. Jeon, J. H. Kwak, I. S. Kim, *Tetrahedron* **2013**, *69*, 6552; f) W. Ma, L. Ackermann, *Chem. Eur. J.* **2013**, *19*, 13925; g) J. Yao, R. Feng, Z. Wu, Z. Liu, Y. Zhang, *Adv. Synth. Catal.* **2013**, *355*, 1517; h) B. Liu, H.-Z. Jiang, B.-F. Shi, *J. Org. Chem.* **2014**, *79*, 1521; i) B. Liu, H.-Z. Jiang, B.-F. Shi, *Org. Biomol. Chem.* **2014**, *12*, 2538; j) C. Zhang, P. Sun, *J. Org. Chem.* **2014**, *79*, 8457; k) W. Zhang, J. Zhang, S. Ren, Y. Liu, *J. Org. Chem.* **2014**, *79*, 11508; l) Y. Xu, P. Liu, S.-L. Li, P. Sun, *J. Org. Chem.* **2015**, *80*, 1269; m) Y.-F. Liang, X. Li, X. Wang, Y. Yan, P. Feng, N. Jiao, *ACS Catal.* **2015**, *5*, 1956; n) S.-J. Lou, Q. Chen, Y.-F. Wang, D.-Q. Xu, X.-H. Du, J.-Q. He, Y.-J. Mao, Z.-Y. Xu, *ACS Catal.* **2015**, *5*, 2846; o) A. J. Borah, G. Yan, L. Wang, *Eur. J. Org. Chem.* **2015**, 4782.

[3] H. Kinuta, M. Tobisu, N. Chatani, *J. Am. Chem. Soc.* **2015**, *137*, 1593.

[4] Related rhodium-catalyzed inert C(aryl)–O bond transformations: a) H. Kinuta, J. Hasegawa, M. Tobisu, N. Chatani, *Chem. Lett.* **2015**, *44*, 366; b) K. Nakamura, K. Yasui, M. Tobisu, N. Chatani, *Tetrahedron* **2015**, *71*, 4484.

[5] Selected reviews on nickel-catalyzed inert C(aryl)–O bond transformations: a) B. M. Rosen, K. W. Quasdorf, D. A. Wilson, N. Zhang, A.-M. Resmerita, N. K. Garg, V. Percec, *Chem. Rev.* **2011**, *111*, 1346; b) D.-G. Yu, B.-J. Li, Z.-J. Shi, *Acc. Chem. Res.* **2010**, *43*, 1486; c) B.-J. Li, D.-G. Yu, C.-L. Sun, Z.-J. Shi, *Chem. Eur. J.* **2011**, *17*, 1728; d) M. Tobisu, N. Chatani, *Top. Organomet. Chem.* **2013**, *44*, 35; e) J. Cornella, C. Zarate, R. Martin, *Chem. Soc. Rev.* **2014**, *43*, 8081; f) M. Tobisu, N. Chatani, *Acc. Chem. Res.* **2015**, *48*, 1717.

[6] Nickel-catalyzed borylation of inert bonds: a) K. Huang, D.-G. Yu, S.-F. Zheng, Z.-H. Wu, Z.-J. Shi, *Chem. Eur. J.* **2011**, *17*, 786; b) M. Tobisu, K. Nakamura, N. Chatani, *J. Am. Chem. Soc.* **2014**, *136*, 5587;

c) T. Furukawa, M. Tobisu, N. Chatani, *Chem. Commun.* **2015**, *51*, 6508; d) H. Zhang, S. Hagihara, K. Itami, *Chem. Lett.* **2015**, *44*, 779; e) C. Zarate, R. Manzano, R. Martin, *J. Am. Chem. Soc.* **2015**, *137*, 6754; f) K. Nakamura, M. Tobisu, N. Chatani, *Org. Lett.* **2015**, *17*, 6142; g) X.-W. Liu, J. Echavarren, C. Zarate, R. Martin, *J. Am. Chem. Soc.* **2015**, *137*, 12470; h) T. Niwa, H. Ochiai, Y. Watanabe, T. Hosoya, *J. Am. Chem. Soc.* **2015**, *137*, 14313; i) H. Zhang, S. Hagihara, K. Itami, *Chem. Eur. J.* **2015**, *21*, 16796; j) J. Hu, H. Sun, W. Cai, X. Pu, Y. Zhang, Z. Shi, *J. Org. Chem.* **2016**, *81*, 14; k) C. H. Basch, K. M. Cobb, M. P. Watson, *Org. Lett.* **2016**, *18*, 136.

[7] Nickel-catalyzed cross-coupling of triazinyl ehters: a) X.-J. Li, J.-L. Zhang, Y. Geng, Z. Jin, *J. Org. Chem.* **2013**, *78*, 5078; b) N. Iranpoor, F. Panahi, *Adv. Synth. Catal.* **2014**, *356*, 3067; c) N. Iranpoor, F. Panahi, *Org. Lett.* **2015**, *17*, 214: d) N. Iranpoor, F. Panahi, F. Jamedi, *J. Organomet. Chem.* **2015**, *781*, 6.

[8] Instead, 4-*tert*-butylphenol was obtained in 75% *via* C(pyridyl)–O bond cleavage. See the Supporting Information for details.

[9] E. J. Tollefson, L. E. Hanna, E. R. Jarvo, *Acc. Chem. Res.* **2015**, *48*, 2344.

[10] Catalytic borylation of inter benzylic C–O bonds: Z.-C. Cao, F.-X. Luo, W.-J. Shi, Z.-J. Shi, *Org. Chem. Front.* **2015**, *2*, 1505. See also ref.[6c,d]

[11] Our contribution to C(benzlic)–O activation under nickel cataysis: M. Tobisu, A. Yasutome, H. Kinuta, K. Nakamura, N. Chatani, *Org. Lett.* **2014**, *16*, 5572.

[12] A. H. Cherney, N. T. Kadunce, S. E. Reisman, *Chem. Rev.* **2015**, *115*, 9587.

[13] a) M. R. Harris, L. E. Hanna, M. A. Greene, C. E. Moore, E. R. Jarvo, *J. Am. Chem. Soc.* **2013**, *135*, 3303; b) Q. Zhou, H. D. Srinivas, S. Dasgupta, M. P. Watson, *J. Am. Chem. Soc.* **2013**, *135*, 3307.

6 Nickel-Catalyzed Borylation of Aryl and Benzyl 2-Pyridyl Ethers: A Method for Converting a Robust *ortho*-Directing Group

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