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Ruthenium(0)-Catalyzed sp^3 C−H Bond Arylation of Benzylic Amines Using Arylboronates

Navid Dastbaravardeh, Michael Schnürch,* and Marko D. Mihovilovic

Institute of Applied Synthetic Chemistry, Vienna University of Technology, Getreidemarkt 9/163-OC, 1060 Vienna, Austria

mschnuerch@ioc.tuwien.ac.at

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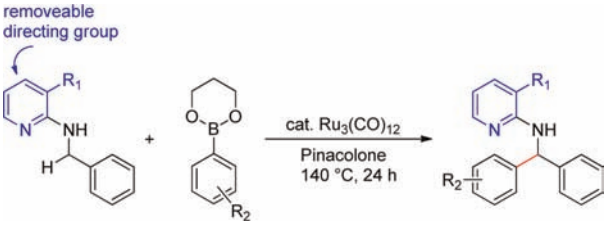
ABSTRACT



A Ru-catalyzed direct arylation of benzylic sp^3 carbons of acyclic amines with arylboronates is reported. This highly regioselective and efficient transformation can be performed with various combinations of *N*-(2-pyridyl) substituted benzylamines and arylboronates. Substitution of the pyridine directing group in the 3-position proved to be crucial in order to achieve high arylation yields. Furthermore, the pyridine directing group can be removed in high yields via a two-step protocol.

The direct catalytic cleavage of C−H bonds is highly attractive and one of the most investigated, but also most challenging, topics in modern organic synthesis. Within recent years, the field of transition metal catalyzed C−H activation reactions is rapidly expanding.[1] Especially, the field of direct functionalization of sp^2 C−H bonds has generated many interesting results in previous years.[2] On the other hand, the area of catalytic functionalization of sp^3 C−H bonds has matured to a significantly lesser extent and many challenges await to be tackled properly.[3] In 1998, the group of Jun described the first chelation assisted alkylation of benzylamine derivatives by a Ru(0) catalyst. In 2005, Kakiuchi, Chatani, and Murai reported a Ru(0)-catalyzed regioselective arylation of aromatic ketones with arylboronates,[4] followed by the discovery of the Sames group to use cyclic imine protecting groups for the arylation of pyrrolidines and piperidine (Scheme 1).[5] Recently, Maes published a pyridine directed arylation of piperidine derivatives (Scheme 1).[6] However, the last two methods

(1) For recent reviews on C−H activation, see: (a) Ackermann, L. *Chem. Rev.* **2011**, *111*, 1315–1345. (b) Yeung, C. S.; Dong, V. M. *Chem. Rev.* **2011**, *111*, 1215–1292. (c) Baudoin, O. *Chem. Soc. Rev.* **2011**, *40*, 4902–4911. (d) Cho, S. H.; Kim, J. Y.; Kwak, J.; Chang, S. *Chem. Soc. Rev.* **2011**, *40*, 5068–5083. (e) Schnürch, M.; Dastbaravardeh, N.; Ghobrial, M.; Mrozek, B.; Mihovilovic, M. D. *Curr. Org. Chem.* **2011**, *15*, 2694–2730. (f) Colby, D. A.; Bergman, R. G.; Ellman, J. A. *Chem. Rev.* **2010**, *110*, 624–655. (g) Daugulis, O. *Top. Curr. Chem.* **2010**, *292*, 57–84. (h) Fagnou, K. *Top. Curr. Chem.* **2010**, *292*, 35–56. (i) Ackermann, L.; Vicente, R.; Kapdi, A. R. *Angew. Chem., Int. Ed.* **2009**, *48*, 9792–9826. (j) McGlacken, G. P.; Bateman, L. M. *Chem. Soc. Rev.* **2009**, *38*, 2447–2464. (k) Dyker, G., Ed. *Handbook of C−H Transformations: Applications in Organic Synthesis*; Wiley: 2005; Vol. 2.

(2) For recent papers on sp^2 C−H bond functionalzation, see: (a) Ackermann, L.; Diers, E.; Manvar, A. *Org. Lett.* **2012**, *14*, 1154–1157. (b) Ackermann, L.; Pospech, J.; Graczyk, K.; Rauch, K. *Org. Lett.* **2012**, *14*, 930–933. (c) Wencel-Delord, J.; Nimphius, C.; Patureau, F. W.; Glorius, F. *Angew. Chem., Int. Ed.* **2012**, *51*, 2247–2251. (d) Tauchert, M. E.; Incarvito, C. D.; Rheingold, A. L.; Bergman, R. G.; Ellman, J. A. *J. Am. Chem. Soc.* **2012**, *134*, 1482–1485. (e) Flegeau, E. F.; Bruneau, C.; Dixneuf, P. H.; Jutand, A. *J. Am. Chem. Soc.* **2011**, *133*, 10161–10170. (f) Shiota, H.; Ano, Y.; Aihara, Y.; Fukumoto, Y.; Chatani, N. *J. Am. Chem. Soc.* **2011**, *133*, 14952–14955.

(3) For selected papers on sp^3 C−H bond functionalzation, see: (a) Sundararaju, B.; Achard, M.; Sharma, G. V. M.; Bruneau, C. *J. Am. Chem. Soc.* **2011**, *133*, 10340–10343. (b) Pan, S.; Endo, K.; Shibata, T. *Org. Lett.* **2011**, *13*, 4692–4695. (c) Ghobrial, M.; Harhammer, K.; Mihovilovic, M. D.; Schnürch, M. *Chem. Commun.* **2010**, *46*, 8836–8838. (d) Rousseaux, S.; Gorelsky, S. I.; Chung, B. K. W.; Fagnou, K. *J. Am. Chem. Soc.* **2010**, *132*, 10692–10705. (e) Jazzar, R.; Hitce, J.; Renaudat, A.; Sofack-Kreutzer, J.; Baudoin, O. *Chem.—Eur. J.* **2010**, *16*, 2654–2672. (f) Shabashov, D.; Daugulis, O. *Org. Lett.* **2005**, *7*, 3657–3659.

(4) Kakiuchi, F.; Matsuura, Y.; Kan, S.; Chatani, N. *J. Am. Chem. Soc.* **2005**, *127*, 5936–5945.

(5) Pastine, S. J.; Gribkov, D. V.; Sames, D. *J. Am. Chem. Soc.* **2006**, *128*, 14220–14221.

(6) Prokopcova, H.; Bergman, S. D.; Aelvoet, K.; Smout, V.; Herrebout, W.; Van der Veken, B.; Meerpoel, L.; Maes, B. U. W. *Chem.—Eur. J.* **2010**, *16*, 13063–13067.

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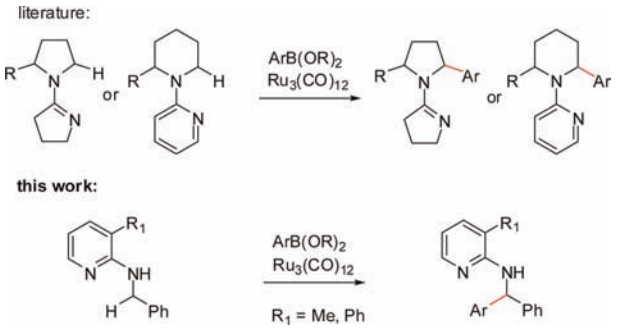
were limited to cyclic amines such as pyrrolidine or piperidine and the selectivity between mono- and bis-arylation proved to be difficult to control.

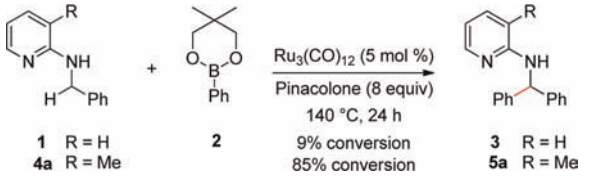
Herein, we report a Ru(0)-catalyzed arylation of acyclic C−H bonds with arylboronates directed by 3-substituted pyridin-2-yls (Scheme 1). To the best of our knowledge, this is the first chelate assisted ruthenium-catalyzed α-arylation of acyclic amines. Initially the reaction was optimized using *N*-substituted benzylamines as substrates, since it is well-known that an sp^3 C−H bond adjacent to a heteroatom or in a benzylic position is more easily activated compared to one surrounded only by carbons.[7]

Scheme 1. Direct Arylation of sp^3 C−H Bonds Adjacent to Nitrogen



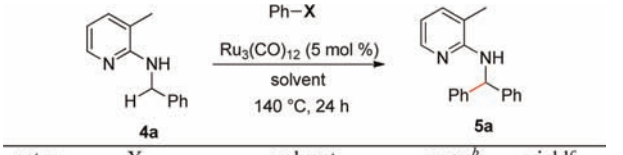
We started our investigations with pyridine as directing group for a first round of reaction parameter optimization. Using simple *N*-benzylpyridine-2-amine **1** as a starting material, only a very low conversion of 9% was obtained under the conditions reported by the Sames group using pyrrolidine substrates. Even by intensively screening different reaction parameters, we were unable to achieve a higher conversion than 9%. It was speculated that this could be attributed to a predominant conformation in which the benzylic CH_2 group points away from the pyridine nitrogen, consequently preventing a site-directing interaction and disfavoring C−H activation. By installing a sterically demanding group in the 3-position the benzylic CH_2-group should be brought into closer proximity of the pyridine nitrogen and C−H activation should be facilitated. Indeed, a much higher conversion (85%) could be achieved when a methyl group was installed at the pyridine ring in the 3-position (Scheme 2). A similar observation was made by the group of Jun.[8]

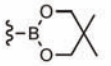
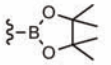
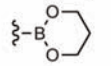
Scheme 2. Influence of a Substituent in 3-Position of Pyridine



Next, we investigated the role of the aryl donor to improve conversion. Various aryl-boron species and arylhalides were submitted to the reaction conditions. Phenylboronic acid (Table 1, entry 1) displayed low conversion, and also the addition of base (Table 1, entry 2) to quench an eventually formed acid equivalent did not improve the conversion significantly, although the yield was considerably higher. 1,3-Propanediol derived boronic ester gave the best result among the various boronic acid esters investigated (Table 1, entry 8). In addition, this ester can be hydrolyzed easily to the boronic acid upon workup which facilitates purification of the product by flash column chromatography. Aryl halides did not perform under these conditions at all (Table 1, entry 4 and 5). Furthermore, the addition of ketones increases the conversion, which is in accordance with the literature (Table 1, entry 10 and 11).[4−6]

Table 1. Assigning the Aryl Donor and Solvent as Critical Parameters for the Direct Arylation of Benylic Amine **4a**[a]



entry	X	solvent	conv[b]	yield[c]
1	$B(OH)_2$	Pinacolone	34	13
2	$B(OH)_2$[d]	Pinacolone	38	30
3	BF_3K	Pinacolone	20	13
4	Br	Pinacolone	0	0
5	I	Pinacolone	0	0
6		Pinacolone	85	67
7		Pinacolone	81	63
8	 6a	**Pinacolone**	**86**	**69 (64)**[e]
9	6a	Toluene	20	6
10	6a	Aceton/Dioxane (1:1)	82	62
11	6a	Acetophenone	80	61

[a] Reaction conditions: **4a** (0.5 mmol), Ph-X (1 mmol), $Ru_3(CO)_{12}$ (5 mol %), and solvent (0.5 mL). [b] Conversion based on GC analysis with respect to **4a** (dodecane as internal standard). [c] Yield determined by GC analysis with respect to **4a** (dodecane as internal standard). [d] Addition of K_2CO_3 (1 mmol). [e] Number in parentheses is isolated yield of **5a**.

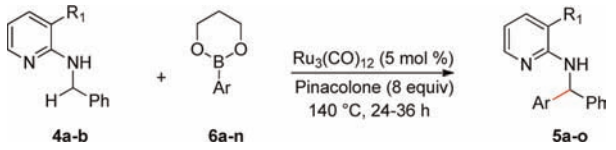
Hence, it was decided that pinacolone was to be used as the solvent and 1,3-propandiol derived boronic esters **6a**−**p** as aryl donors for all further reactions investigating the scope and limitations of the presented methodology. We found this catalytic method to be sensitive to the

(7) For selected papers on C−H bond functionalization adjacent to a heteroatom, see: (a) Kakiuchi, F.; Tsuchiya, K.; Matsumoto, M.; Mizushima, E.; Chatani, N. *J. Am. Chem. Soc.* **2004**, *126*, 12792–12793. (b) Murai, S.; Chatani, N.; Asaumi, T.; Yorimitsu, S.; Ikeda, T.; Kakiuchi, F. *J. Am. Chem. Soc.* **2001**, *123*, 10935–10941. (c) Murai, S.; Chatani, N.; Asaumi, T.; Ikeda, T.; Yorimitsu, S.; Ishii, Y.; Kakiuchi, F. *J. Am. Chem. Soc.* **2000**, *122*, 12882–12883.

(8) Jun, C.-H. *Chem. Commun.* **1998**, 1405–1406.

electronic and sterical properties of the aryl donor. Sterically demanding aryls gave significantly lower conversions, and also electron withdrawing or coordinating substituents (4-Ac, 4-CN, 4-NO_2, or 3-pyridyl) were much less tolerated compared to their neutral and electron donating counterparts. Phenyl was also tested as an alternative bulky group in the 3-position of pyridine (Table 2, entries 12–15). It was found that the arylation yield could be significantly increased compared to the corresponding methyl examples (Table 2, entries 1, 6, 7, and 9). However, in light of atom efficency, the methyl group was favored.

Table 2. Scope of Direct Arylations with Arylboronic Esters **6**[a]

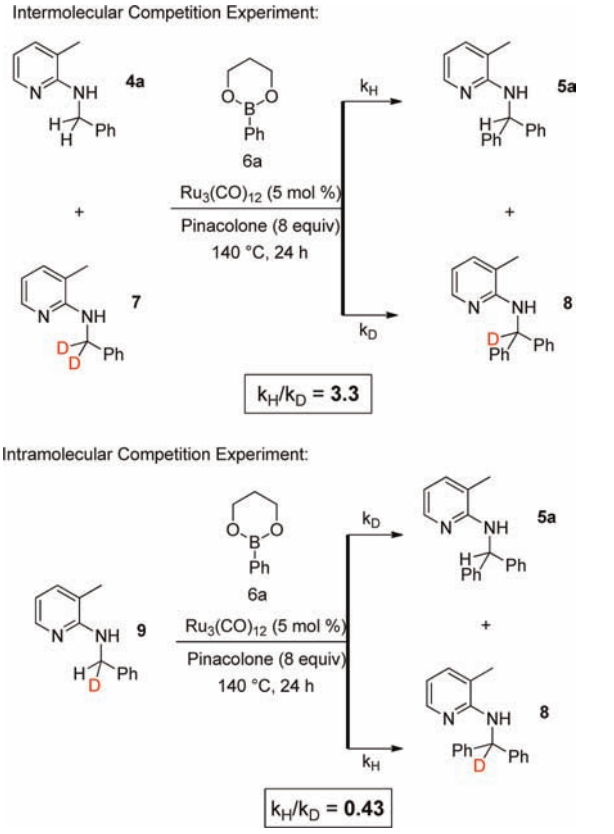


entry		R^1	Ar	conv[b]	yield[c]
1	**5a**	Me	Ph	86	64
2	**5b**	Me	2-Me-Ph	55	n.i.[d]
3	**5c**	Me	1-Naph	8	n.i.
4	**5d**	Me	3-Me-Ph	87	61
5	**5e**	Me	3-Cl-Ph	59	38
6	**5f**	Me	4-Me-Ph	88	62
7	**5g**	Me	4-t-Bu-Ph	87	64
8	**5h**	Me	4-OMe-Ph	50	39
9	**5i**	Me	4-F-Ph	89	66
10	**5j**	Me	4-Cl-Ph	49	33
11	**5k**	Me	4-CF_3-Ph	61	41
12	**5l**	Ph	Ph	100	90
13	**5m**	Ph	4-Me-Ph	100	85
14	**5n**	Ph	4-t-Bu-Ph	100	96
15	**5o**	Ph	4-F-Ph	100	72

[a] Reaction conditions: **4a**–**b** (0.5 mmol), **6a**–**x** (0.75 mmol), $Ru_3(CO)_{12}$ (5 mol %), and pinacolone (0.5 mL). [b] Conversion based on GC analysis with respect to **4a** and **4b** (dodecane as internal standard). [c] Isolated yield. [d] Mixture of products which could not be separated.

In order to determine if the C–H insertion is the rate limiting step of this arylation protocol, we carried out a kinetic isotope effect (KIE) study. An intermolecular competition experiment was set up for compounds **4a** and **7** (Scheme 3). The reaction was carried out with 1 equiv of *N*-benzyl-3-methylpyridin-2-amine **4a**, 1 equiv of the deuterated analog **7**, and 1 equiv of phenylboronic acid 1,3-propanediol ester **6a** to achieve a maximum of 50% conversion. The mixture of both products was isolated and analyzed by ^{1}H NMR. The KIE was found to be $k_H/k_D = 3.3$. This indicates that the C–H bond is of course weaker compared to the C–D bond, and hence the rate of C–H insertion is higher than the rate of C–D insertion. Interestingly, when the intramolecular KIE was investigated starting from substrate **9** an inverse KIE of 0.43 was measured. Inverse KIEs have been previously reported in C–H bond activation reactions and were attributed to a reversible C–H activation step (hence also termed *inverse equilibrium isotope effect*) eventually involving a σ-complex preceding C–H insertion.[9]

Scheme 3. Competitive Deuterium Labeling Experiments



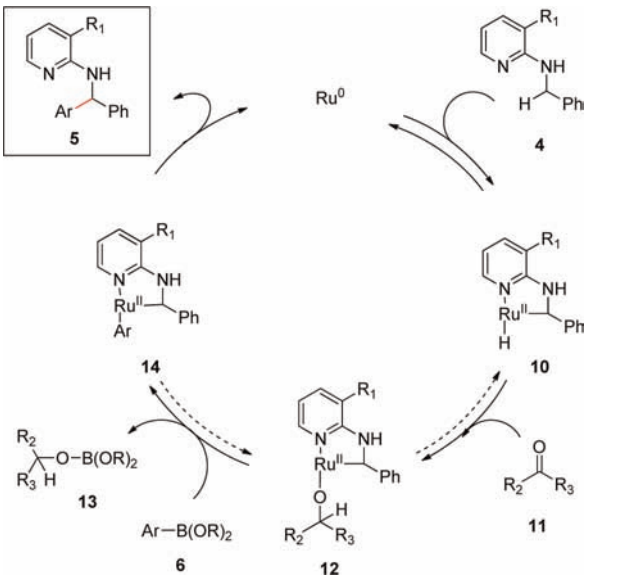
We propose the following mechanism according to the plausible hypothesis of Kakiuchi, Chatani, and Murai[4] and similarly proposed by Sames and co-workers (Scheme 4).[5] The catalytic process is initiated by coordination of ruthenium(0) to the pyridine nitrogen, followed by oxidative addition to **10**. Subsequently, the ketone is reduced to the corresponding alcohol (which could be detected by GC-MS analysis), followed by formation of a metal-alkoxy (Ru-OR) species **12**. This intermediate facilitates the transmetalation with Ar–$B(OR)_2$ to **14**. The ketone simultaneously works as a hydrogen and boron scavenger. Reductive elimination finally delivers product **5** and regenerates the catalyst. This mechanistic rationale is supported by the previous work of Sames and coauthors.[5]

For the cleavage of the directing group, we used a strategy recently reported by Studer and co-workers:[10] *N*-carbamoylation of the amino group of **5a** and subsequent *N*-methylation of the pyridyl group of **15**, followed by hydrolysis of the pyridinium salt, delivers Boc protected diphenylmethanamine **16** in high yield (Scheme 5, 84%

(9) Jones, W. D. *Acc. Chem. Res.* **2003**, *36*, 140–146 and references cited therein.

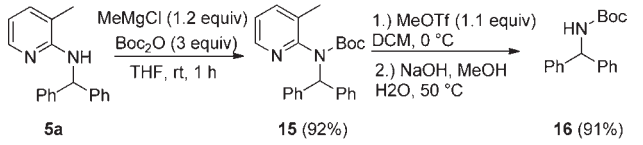
(10) Jana, K. J.; Grimme, S.; Studer, A. *Chem.—Eur. J.* **2009**, *15*, 9078–9084.

Scheme 4. Proposed Mechanism



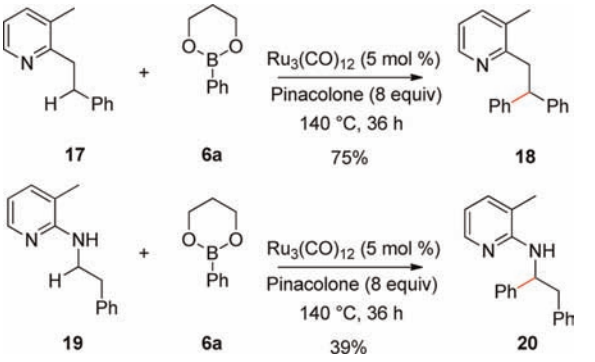
overall). *N*-Boc deprotection can then be achieved easily and often quantitatively following well established protocols.[11] However, also the Boc-protected compounds can be useful if further manipulations of the products require the protection of the amino functionality.

Scheme 5. Removal of Directing Group



Finally, we conducted a preliminary investigation if the reaction is limited to benzylamine substrates and to benzylic positions, in general. We found the NH group not to be essential; it can be replaced by a CH_2 group (**17**) without decreasing the yield significantly (Scheme 6), although a prolonged reaction time was required (36 h instead of 24 h). Notably, the reaction also works with nonbenzylic sp^3 C–H bonds as shown for compound **19**. However, the reaction required more time (48 h), and the yield decreased considerably (Scheme 6). This indicates that the activation of a CH_2 group due to its benzylic nature is more important than activation via an adjacent NH group, but not mandatory for this kind of transformation.

Scheme 6. Direct Arylation of **18** and **20**



In conclusion, acyclic sp^3 C–H bonds adjacent to a free NH group were readily arylated with various arenes via pyridine directed cyclometalation with $Ru_3(CO)_{12}$. The NH group could be replaced by CH_2 without a significant decrease in yield. A bulky group in the 3-position of the directing group was crucial for high conversions in these reactions. Finally, removal of the directing group was successfully demonstrated. Although a two-step protocol is required, deprotection is achieved in high overall yield, significantly expanding the general applicability of this approach. Mechanistic investigations were conducted and support the mechanism proposed by Kakiuchi and co-workers.

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Supporting Information Available. Full experimental details and spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.

(11) For the *N*-Boc deprotection, see: (a) Norma, J. T.; Simon, W. M.; Frost, H. N.; Ewing, M. *Tetrahedron Lett*. **2004**, *45*, 905–906. (b) Srinivasan, N.; Yurek-George, A.; Ganesan, A. *Mol. Diversity* **2005**, *9*, 291–293.