DOI: 10.1002/chem.201001887

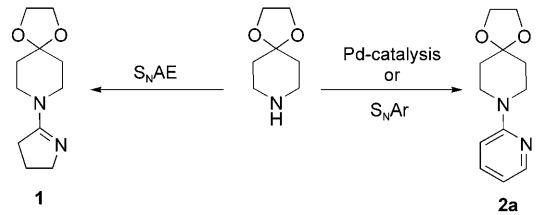
C-2 Arylation of Piperidines through Directed Transition-Metal-Catalyzed sp^3 C–H Activation

Hana Prokopcová,[a] Sheba D. Bergman,[a] Karel Aelvoet,[a] Veerle Smout,[a] Wouter Herrebout,[b] Benjamin Van der Veken,[b] Lieven Meerpoel,[c] and Bert U. W. Maes*[a]

In memory of Keith Fagnou

The development of transition-metal-catalyzed methods for the direct functionalization of C–H bonds has attracted much attention during the past decade.[1] While the direct functionalization of sp^2 C–H bonds is an active field of research,[2] the corresponding knowledge on sp^3 C–H bonds is still limited and remains one of the current challenges in organic chemistry.[3] Within the area of sp^3 C–H activation, the transformation of a C–H bond in the α-position to the nitrogen atom of saturated cyclic amines is of particular importance,[4] since such heterocyclic motifs can be found in an impressive number of natural products and marketed drugs.[5] The intermolecular, direct transition-metal-catalyzed functionalization of saturated cyclic amines adjacent to nitrogen offers a simple and efficient synthetic approach towards valuable building blocks. To the best of our knowledge, only six articles are hitherto published on this topic, wherein the main focus is on five-membered cyclic substrates.[6,7a] In 2006, Sames and co-workers reported the first direct arylation of saturated cyclic amines through transition-metal-catalyzed sp^3 C–H activation, involving arylboronate esters as a coupling partner.[7a] Pyrrolidines were successfully arylated adjacent to nitrogen by using a Ru-catalyzed C-H activation process, directed by a pyrroline group and mediated by ketone (used also as a solvent). The authors suggested that the key role of the ketone (pinacolone) is to allow a transmetalation by transforming the initially formed metal hydride species into a metal alkoxide intermediate.[7b] The pyrroline directing group could be removed by treatment of the α-arylated pyrrolidines with NH_2NH_2/AcOH. One example of a piperidine substrate also appeared in this work, which was C-2 *p*-methoxyphenylated in moderate yield (38%).[7a] The six-membered piperidine ring is inherently less reactive than its five-membered analogue (pyrrolidine) due to its chair conformation.[8] Consequently, there are very few examples in the literature of direct functionalization of piperidines by means of a transition-metal-catalyzed, sp^3 C–H activation process.[6c,d,7a] We report here a novel method for the direct C-2 arylation of piperidines with arylboronate esters, resulting from a mechanistic study of the transmetalation step of the catalytic cycle.

As part of our interest in C-2 functionalized 4-substituted piperidines, we first applied the conditions described by Sames and co-workers[7a] to 1-(pyrrolin-2-yl)-4-piperidinone ethylene ketal (Scheme 1, **1**). Unfortunately, the reaction of **1** with phenylboronic acid pinacol ester resulted in a low conversion to the arylated product, and directing group in-



Scheme 1. 4-Piperidinone ethylene ketal bearing a pyrroline or pyridine directing group: substrates designed to explore the C-2 arylation process.

[a] Dr. H. Prokopcová, Dr. S. D. Bergman, Dr. K. Aelvoet, V. Smout, Prof. Dr. B. U. W. Maes
Organic Synthesis, University of Antwerp
Groenenborgerlaan 171, 2020 Antwerp (Belgium)
Fax: (+32) 32653233
E-mail: bert.maes@ua.ac.be

[b] Prof. Dr. W. Herrebout, Prof. Dr. B. Van der Veken
Cryospectroscopy, University of Antwerp
Groenenborgerlaan 171, 2020 Antwerp (Belgium)

[c] Dr. L. Meerpoel
Johnson & Johnson Pharmaceutical Research & Development
A Division of Janssen Pharmaceutica N.V.
Turnhoutseweg 30, 2340 Beerse (Belgium)

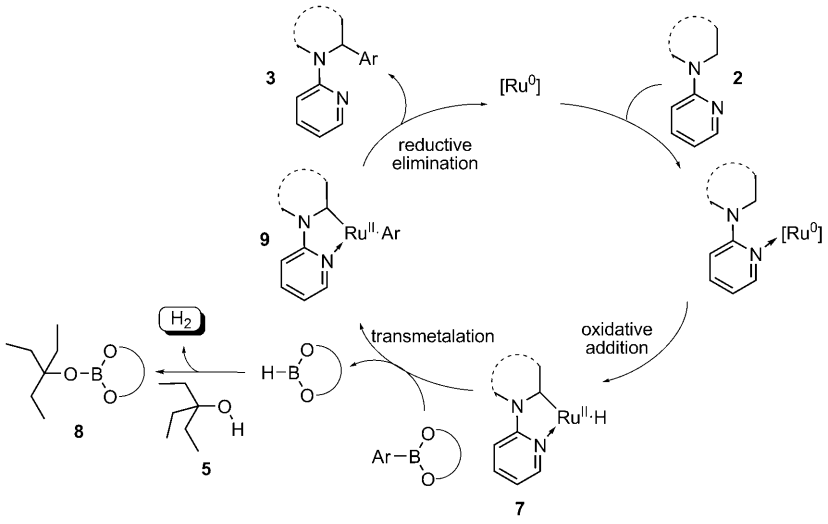
Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/chem.201001887.

 © 2010 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim View this journal online at wileyonlinelibrary.com

stability was observed (see Supporting Information). We therefore decided to use pyridine as a directing group (Scheme 1, **2a**). Pyridine is known as an effective and very stable directing group in C–H activation processes,[9] but has always been considered a nonremovable group when attached to nitrogen.[6b–d] However, our preliminary results showed that subjecting **2a** to Pd-catalyzed hydrogenation followed by NH_2NH_2/AcOH treatment smoothly delivered 4-piperidinone ethylene ketal.

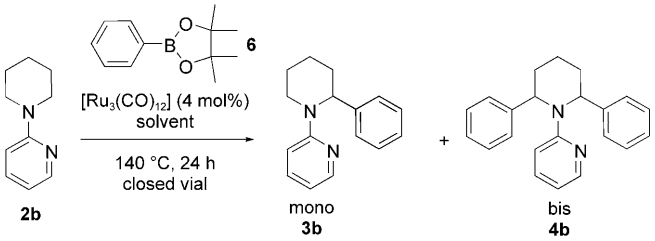
In a first attempt to obtain higher conversions, we examined a variety of ketones using 1-(pyridin-2-yl)-4-piperidinone ethylene ketal (**2a**) as substrate. With pinacolone, only 15% conversion of **2a** was obtained. Interestingly, when acetophenones were applied as solvent, significantly better conversions were reached ($\leq$49%, see Supporting Information). A similar reactivity pattern was observed when C-4 unsubstituted 1-(pyridin-2-yl)piperidine (**2b**) was used as substrate. These results were not in accordance with the previously reported mechanism,[7a] since we observed that ketones with nearly similar pK_E's (pinacolone, pK_E=8.76 and acetophenones, p$K_E\approx$8; pK_E: keto–enol equilibrium constant)[10,11] gave rise to very different conversions. The question arose whether applying the ketone as solvent was essential for the reaction to proceed.[7b]

We selected unsubstituted **2b** as a substrate to test a variety of solvents and, surprisingly, when the reaction was performed in *t*BuOH, 61% conversion was achieved (Table 1, entry 1). Reaction in 1,2-dichloroethane (ε=10.9), with similar dielectric constant as *t*BuOH (ε=10.4), resulted in only 15% conversion (entry 2). In 3-ethyl-3-pentanol (**5**; entry 3), the same reactivity as in *t*BuOH was observed, whereas in *t*BuOMe, the conversion to the arylated product was very low (entry 4). These results indicate that a free hydroxyl group is beneficial for the direct arylation process. As a full conversion of **2b** was still not achieved, we assumed that this might be caused by catalyst deactivation during the course of the reaction. Indeed, when fresh catalyst was added to the reaction mixture of **2b** with phenylboronic acid pinacol ester (**6**) after 24 h, the reaction conversion increased further to 83%. We hypothesized that, if the reaction proceeds through a direct transmetalation of the Ru^{II}–H intermediate **7** (Scheme 2) with boronate ester **6**, the resulting pinacolborane species has to be scavenged in order to avoid catalyst poisoning, for example, by oxidative addition.[12] Then, the role of *t*BuOH is to scavenge the pinacolborane, with formation of the corresponding *tert*-butylborate and H_2. Up to this point, all reactions were carried out in closed vials at 140°C, so the in situ created H_2 could be responsible for the loss of catalytic activity (oxidative addition of H_2)[13] (Table 1, entry 1). In order to release the presumed in situ formed H_2-gas, we decided to perform the reaction of 1-(pyridin-2-yl)piperidine (**2b**) with phenylboronic acid pinacol ester (**6**) in an open vial under reflux conditions. We chose the higher boiling 3-ethyl-3-pentanol (**5**) (b.p.=140–143°C) as solvent to maintain the temperature around 140°C. In accordance with our hypothesis, we found that the conversion could be further increased. Moreover, a Raman spectroscopy measurement confirmed that H_2 is formed during the reaction (see Supporting Information).[14] Additionally, an independent model experiment showed that upon heating of pinacolborane with alcohol **5**, 1,1-diethylpropylborate (**8**) and H_2 were formed (see Supporting Infor-



Scheme 2. Proposed mechanism for the direct C-2 arylation of saturated cyclic amines.

Table 1. The effect of different solvents on the direct C-2 arylation of 1-(pyridin-2-yl)piperidine (**2b**).[a]



	Solvent	GC-FID[b] **2b**/**3b**/**4b** [%]
1	*t*BuOH	39/47/14
2	1,2-dichloroethane	85/15/0
3	3-ethyl-3-pentanol (**5**)	41/45/14
4	*t*BuOMe	81/19/0

[a] The reactions were performed on a 0.5 mmol scale, using $[Ru_3(CO)_{12}]$ (4 mol%), phenylboronic acid pinacol ester (3 equiv), and solvent (6 equiv) at 140°C for 24 h. [b] Uncorrected GC-FID conversions; the bis product **4b** is a mixture of diastereoisomers.

 © 2010 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim

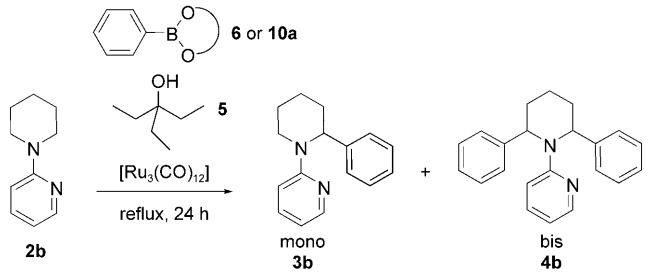
mation). Compound **8** was also detected in the reaction mixture of substrate **2b** with boronate ester **6**. The occurrence of a mechanism involving a reaction of Ru^{II}–H intermediate **7** with alcohol **5**, yielding Ru^{II}–OR and H_2, could be excluded based on an experiment of **2b** with **6** in the absence of alcohol,[15] as **3b** and **4b** were still formed, supporting our direct transmetalation hypothesis. Raman spectroscopy confirmed that H_2 is also formed in the absence of alcohol. A lower conversion of **2b** was obtained in comparison with the experiment in the presence of **5**.

The proposed catalytic cycle of our new direct arylation process is presented in Scheme 2. The mechanism involves the initial complexation of Ru^0 to pyridine, promoting the oxidative addition of the sp^3 C–H bond adjacent to the piperidine nitrogen to Ru^0, with formation of a Ru^{II}–H species **7** (Scheme 2). Subsequently, transmetalation of **7** with the arylboronate ester yields dialkoxyborane and Ru^{II}–Ar species **9**. Reductive elimination of **9** finally gives **3**, and the Ru^0 catalyst is regenerated. The dialkoxyborane is destroyed by reaction with alcohol **5** delivering H_2.

Further optimization showed that one equivalent of 3-ethyl-3-pentanol (**5**) could be taken as a standard (Table 2, entries 1–3). During our research, we experienced some purification problems caused by remaining phenylboronic acid pinacol ester (**6**). This could easily be solved by exchange of pinacol ester **6** for its neopentylglycol equivalent **10a** (Table 2, entry 4). Ultimately, we found that the reaction proceeded most effectively by heating **2b** with three equivalents of phenylboronic acid neopentylglycol ester (**10a**) and 6 mol% of $[Ru_3(CO)_{12}]$ in one equivalent of 3-ethyl-3-pentanol (**5**) at reflux for 24 h (Table 2, entry 5). In this way, we obtained 97% total conversion (46% mono-**3b**, 51% bis-**4b**) and 76% isolated yield (38% mono-**3b**, 38% bis-**4b**). A further increase of the amount of boronate ester and catalyst favors the formation of bis **4b** which is then obtained as the major product (Table 2, entry 6).

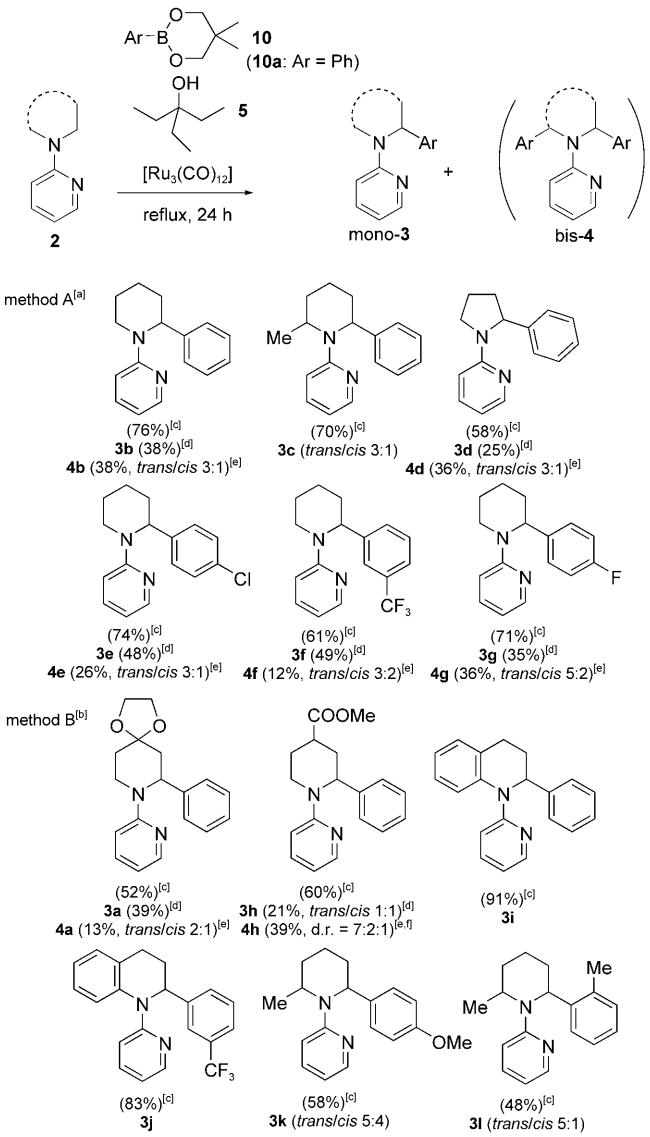
With the optimized conditions in hand (method A, Scheme 3), we explored the scope of our C-2 arylation method. Some of the substrates needed four equivalents of arylboronate ester **10** and 8 mol% of $[Ru_3(CO)_{12}]$ in order to reach full conversion of starting material (method B,

Table 2. Model reaction used to identify the optimal reaction conditions.[a]



	6 or 10a	6 or 10a [equiv]	$[Ru_3(CO)_{12}]$ [mol%]	5 [equiv]	GC-FID[b] 2b/3b/4b [%]	Total yield[c] (3b/4b) [%]
1	**6**	3	4	3	17/51/32	–
2	**6**	3	4	2	19/52/29	–
3	**6**	3	4	1	13/51/36	–
4	**10a**	3	4	1	10/49/41	63 (39/24)
5	**10a**	3	6	1	3/46/51	76 (38/38)
6	**10a**	4	8	1	0/14/86	71 (11/60)

[a] The reactions were performed on a 0.5 mmol scale, using $[Ru_3(CO)_{12}]$ as a catalyst, phenylboronate ester **6** or **10a**, and 3-ethyl-3-pentanol at 140 °C for 24 h. [b] Uncorrected GC-FID conversions; the bis product **4b** is a mixture of diastereoisomers. [c] Total isolated yield; isolation performed on a 1.0 mmol scale.

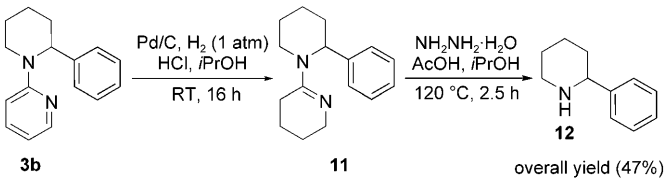


Scheme 3. C-2 arylation reaction of piperidine, pyrrolidine and tetrahydroquinoline substrates with a variety of arylboronate esters under optimized conditions. For simplicity, only the structures of mono-arylated products are represented. [a] Reaction conditions, method A: the reactions were performed in duplicate on a 0.5 mmol scale, using $[Ru_3(CO)_{12}]$ (6 mol%), arylboronic acid neopentylglycol ester (**10**; 3 equiv), and 3-ethyl-3-pentanol (**5**; 1 equiv) at reflux for 24 h. [b] Reaction conditions, method B: the reactions were performed in duplicate on a 0.5 mmol scale, using $[Ru_3(CO)_{12}]$ (8 mol%), arylboronic acid neopentylglycol ester (**10**; 4 equiv), and 3-ethyl-3-pentanol (**5**; 1 equiv) at reflux for 24 h. [c] Total isolated yield; isolation performed on a 1.0 mmol scale. [d] **3a–l** represent mono isolated yields. [e] **4a–l** represent bis isolated yields. [f] See the Supporting Information.

 © 2010 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim

Scheme 3). 1-(Pyridin-2-yl)piperidine (**2b**) was successfully functionalized at the C-2-position with phenylboronic acid neopentylglycol ester **10a** (Scheme 3, **3b**/**4b**), as well as with arylboronate esters **10** bearing electron-withdrawing substituents in the *meta*- or *para*-position (**3e**–**g**/**4e**–**g**). The coupling of α-methyl-1-(pyridin-2-yl)piperidine with different arylboronate esters smoothly yielded the C-2 arylated products (**3c**, **3k**, and **3l**), indicating that also substituted piperidines can be applied as substrates in this direct transition-metal-catalyzed arylation. To our delight, not only were alkyl substituents well tolerated, as good isolated yields were also obtained for the C-2 phenylation of 1-(pyridin-2-yl)piperidine containing a ketal or ester group in the 4-position (**3a**/**4a**, **3h**/**4h**). To the best of our knowledge, these are the first examples of direct functionalization by means of transition-metal-catalyzed sp^3 C–H activation performed on piperidines bearing substituents other than simple alkyl groups. Interestingly, moderate to high yields were also obtained when pyrrolidine or tetrahydroquinoline were used as substrate (**3d**/**4d**, **3i**, **3j**).

As mentioned above, our preliminary results indicated that the pyridine directing group can be efficiently removed. Indeed, when the C-2-phenylated product **3b** was subjected to a Pd-catalyzed hydrogenation and subsequent NH_2NH_2/AcOH treatment, this delivered the corresponding deprotected product **12** in 47% yield (Scheme 4). The crude 1-



Scheme 4. Removal of the pyridine directing group.

(3,4,5,6-tetrahydropyridin-2-yl)piperidine (**11**) was not purified, but just filtered over dicalite before NH_2NH_2/AcOH was added. This is a novel procedure for the removal of a *N*-pyridin-2-yl group from an amine.

In conclusion, we developed a method for the direct arylation of substituted piperidines, which can also be applied to other saturated cyclic amines. The Ru-catalyzed C-2 arylation process proceeds smoothly with a variety of arylboronate esters under reflux and in the presence of a tertiary alcohol. The pyridine directing group could be introduced and removed in a straightforward manner. The development of this new arylation method stems from a better understanding of the transmetalation step of the catalytic cycle. The removal of the dialkoxyborane formed during this process is critical, as it poisons the catalyst. New and more profound insights into the exact mechanism of direct sp^3 C–H functionalization are important to overcome the current limitations in this area and to stimulate future research towards selective methods applicable to complex molecules.

Experimental Section

Two 10 mL vials were each charged with saturated cyclic amine **2** (0.5 mmol), $[Ru_3(CO)_{12}]$ (6–8 mol%), arylboronic acid neopentylglycol ester **10** (3–4 equiv), and 3-ethyl-3-pentanol (**5**) (58 mg, 0.5 mmol, 1 equiv). The vials were flushed with argon and fitted with a condenser. The reaction mixtures were then heated to reflux—the temperature of the oil bath being set at 153 °C—under magnetic stirring for 24 h (Ar atmosphere). After this time, the reaction mixtures were cooled down and both combined into a flask using CH_2Cl_2, and the volatiles were removed under reduced pressure. A commercially available ruthenium scavenger (Siliabond® DMT, Silicycle, 1.5–2 g) was added to the residue, along with CH_2Cl_2 (100 mL). The resulting suspension was stirred at RT for 16 h. Subsequently, the solids were removed by filtration through Celite, the pad was washed with distilled CH_2Cl_2 (5×20 mL), and the combined filtrate was evaporated to dryness. The residue was purified by reversed-phase flash chromatography. The desired fractions were combined and evaporated to dryness to deliver the reaction products **3** and **4**.

Acknowledgements

This work was financially supported by the University of Antwerp (IOF and BOF), the Fund for Scientific Research-Flanders (FWO-Flanders), the Hercules foundation, and J&J PRD. The authors would like to thank Gaston Diels for valuable remarks.

Keywords: C–H activation · hydrogen · homogeneous catalysis · piperidines · ruthenium

[1] For general reviews about direct functionalization through C–H bond activation, see: a) A. E. Shilov, G. B. Shulpin, *Chem. Rev.* **1997**, *97*, 2879–2932; b) J. A. Labinger, J. E. Bergaw, *Nature* **2002**, *417*, 507–514; c) K. Godula, D. Sames, *Science* **2006**, *312*, 67–72; d) R. G. Bergman, *Nature* **2007**, *446*, 391–393.

[2] For examples of reviews about direct functionalization through sp^2 C–H activation, see: a) G. Dyker, *Angew. Chem.* **1999**, *111*, 1808–1822; *Angew. Chem. Int. Ed.* **1999**, *38*, 1698–1712; b) F. Kakiuchi, N. Chatani, *Adv. Synth. Catal.* **2003**, *345*, 1077–1101; c) F. Kakiuchi, T. Kochi, *Synthesis* **2008**, 3013–3039; d) J. C. Lewis, R. G. Bergman, J. A. Ellman, *Acc. Chem. Res.* **2008**, *41*, 1013–1025; e) P. Thansandote, M. Lautens, *Chem. Eur. J.* **2009**, *15*, 5874–5883; f) L. Ackermann, R. Vicente, A. R. Kapdi, *Angew. Chem.* **2009**, *121*, 9976–10011; *Angew. Chem. Int. Ed.* **2009**, *48*, 9792–9826; g) X. Chen, K. M. Engle, D.-H. Wang, J.-Q. Yu, *Angew. Chem.* **2009**, *121*, 5196–5217; *Angew. Chem. Int. Ed.* **2009**, *48*, 5094–5115; h) D. A. Colby, R. G. Bergman, J. A. Ellman, *Chem. Rev.* **2010**, *110*, 624–655; i) T. W. Lyons, M. S. Sanford, *Chem. Rev.* **2010**, *110*, 1147–1169.

[3] For general reviews about direct functionalization through sp^3 C–H activation, see: a) R. Jazzar, J. Hitce, A. Renaudat, J. Sofack-Kreutzer, O. Baudoin, *Chem. Eur. J.* **2010**, *16*, 2654–2672; b) F. Bellina, R. Rossi, *Chem. Rev.* **2010**, *110*, 1082–1146.

[4] For a general review, see: K. R. Campos, *Chem. Soc. Rev.* **2007**, *36*, 1069–1084.

[5] For selected examples, see: a) L. Patel, C. Lindley, *Expert Opin. Pharmacother.* **2003**, *4*, 2279–2296; b) G. A. M. Giardina, S. Gagliardi, M. Martinelli, *IDrugs* **2003**, *6*, 758–772; c) M. Gerspacher, *Prog. Med. Chem.* **2005**, *43*, 49–103; d) P. S. Watson, B. Jiang, K. Harrison, N. Asakawa, P. K. Welch, M. Covington, N. C. Stowell, E. A. Wadman, P. Davies, K. A. Solomon, R. C. Newton, G. L. Trainor, S. M. Friedman, C. P. Decicco, S. S. Ko, *Bioorg. Med. Chem. Lett.* **2006**, *16*, 5695–5699; e) J. D. Scott, J. Weinstein, M. W. Miller, A. W. Stamford, E. J. Gilbert, Y. Xia, W. J. Greenlee, W. Li, PCT Int. Appl., **2007**, WO2007 084319 (A2); f) J. Ackermann, K. Bleicher, G.

 © 2010 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim

Ceccarelli, M. Simona, O. Chomienne, P. Mattei, T. Schulz-Gasch, PCT Int. Appl., **2007**, WO2007063012 (A1); g) J. P. Michael, *Nat. Prod. Rep.* **2008**, *25*, 139–165.

[6] For direct alkylation and alkanoylation through sp^3 C–H activation in saturated cyclic amines, see: a) Y. Ishii, N. Chatani, F. Kakiuchi, S. Murai, *Tetrahedron Lett.* **1997**, *38*, 7565–7568; b) Y. Ishii, N. Chatani, F. Kakiuchi, S. Murai, *Organometallics* **1997**, *16*, 3615–3622; c) N. Chatani, T. Asaumi, T. Ikeda, S. Yorimitsu, Y. Ishii, F. Kakiuchi, S. Murai, *J. Am. Chem. Soc.* **2000**, *122*, 12882–12883; d) N. Chatani, T. Asaumi, S. Yorimitsu, T. Ikeda, F. Kakiuchi, S. Murai, *J. Am. Chem. Soc.* **2001**, *123*, 10935–10941; e) C. S. Yi, S. Y. Yun, *Organometallics* **2004**, *23*, 5392–5395.

[7] a) S. J. Pastine, D. V. Gribkov, D. Sames, *J. Am. Chem. Soc.* **2006**, *128*, 14220–14221; b) direct C-2 *p*-methoxyphenylation of 1-(pyrrolin-2-yl)piperidine reported by Sames:[7a] Raman spectroscopy indicates that pinacolyl alcohol is formed via Ru-catalyzed hydrogenation of pinacolone and not through a Ru-alkoxide intermediate (see the Supporting Information).

[8] H. M. L. Davies, R. E. J. Beckwith, *Chem. Rev.* **2003**, *103*, 2861–2903.

[9] L. Ackermann, *Top. Organomet. Chem.* **2007**, *24*, 35–60.

[10] F. Kakiuchi, Y. Matsuura, S. Kan, N. Chatani, *J. Am. Chem. Soc.* **2005**, *127*, 5936–5945.

[11] a) J. P. Guthrie, J. Cossar, A. Klym, *Can. J. Chem.* **1987**, *65*, 2154–2159; b) J. R. Keeffe, A. J. Kresge, N. P. Schepp, *J. Am. Chem. Soc.* **1990**, *112*, 4862–4868.

[12] For a review about C–H activation/C–B bond formation by means of oxidative addition of a dialkoxyborane species to transition metals, see: T. Ishiyama, N. Miyaura, *J. Organomet. Chem.* **2003**, *680*, 3–11.

[13] a) R. H. Crabtree, *Acc. Chem. Res.* **1990**, *23*, 95–101; b) D. M. Heinekey, W. J. Oldham, Jr., *Chem. Rev.* **1993**, *93*, 913–926.

[14] H_2-gas formation during transition-metal-catalyzed C–H functionalization processes was previously described for C–B bond forming reactions, see: I. A. I. Mkhalid, J. H. Barnard, T. B. Marder, J. M. Murphy, J. F. Hartwig, *Chem. Rev.* **2010**, *110*, 890–931.

[15] An experiment of **2b** with **6** in more acidic perfluoro-*t*BuOH (under reaction conditions described in Table 2) delivered only traces of product **3b** and no **4b**. This further indicates that formation of H_2 does not occur through protonation of Ru^{II}–H species **7** with alcohol.[10] Interference of an acid-base equilibrium hampering catalysis cannot be excluded in this case.

Received: July 5, 2010
Published online: October 27, 2010

 © 2010 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim