CHEMISTRY
A EUROPEAN JOURNAL

ChemPubSoc
Europe

DOI: 10.1002/chem.201204438

Ruthenium-Catalyzed α-(Hetero)Arylation of Saturated Cyclic Amines: Reaction Scope and Mechanism

Aldo Peschiulli,[a] Veerle Smout,[a] Thomas E. Storr,[a] Emily A. Mitchell,[a] Zdeněk Eliáš,[a] Wouter Herrebout,[b] Didier Berthelot,[c] Lieven Meerpoel,[c] and Bert U. W. Maes*[a]

Abstract: Transition-metal-catalyzed sp^3 C–H activation has emerged as a powerful approach to functionalize saturated cyclic amines. Our group recently disclosed a direct catalytic arylation reaction of piperidines at the α position to the nitrogen atom. 1-(Pyridin-2-yl)piperidine could be smoothly α-arylated if treated with an arylboronic ester in the presence of a catalytic amount of $[Ru_3(CO)_{12}]$ and one equivalent of 3-ethyl-3-pentanol. A systematic study on the substrate and reagent scope of this transformation is disclosed in this paper. The effect of substitution on both the piperidine ring and the arylboronic ester has been investigated. Smaller (pyrrolidine) and larger (azepane) saturated ring systems, as well as benzoannulated derivatives, were found to be compatible substrates with the α-arylation protocol. The successful use of a variety of heteroarylboronic esters as coupling partners further proved the power of this direct functionalization method. Mechanistic studies have allowed for a better understanding of the catalytic cycle of this remarkable transformation featuring an unprecedented direct transmetalation on a Ru^{II}–H species.

Keywords: C–H activation · homogeneous catalysis · hydrogen · nitrogen heterocycles · ruthenium

Introduction

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 the C–H bond in the α position to the nitrogen atom of saturated cyclic amines is of particular importance because such heterocyclic motifs can be found in a number of natural products and marketed drugs (Figure 1).[4]

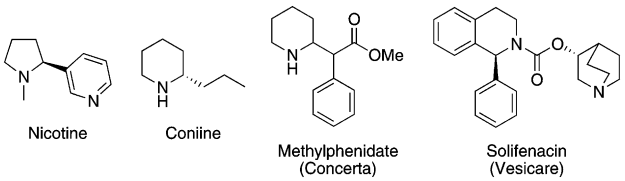


Figure 1. Examples of biologically active α-substituted saturated cyclic amines.

A number of methods exist for the direct α-functionalization of saturated cyclic amines, which have been reviewed by Campos[5] and Maes and co-workers.[6] Major research efforts have focused on the low-temperature organolithium-mediated α-deprotonation and subsequent functionalization of *N*-(*tert*-butoxycarbonyl)-protected pyrrolidines and, more recently, *N*-(*tert*-butoxycarbonyl)piperidines.[7] Besides protocols proceeding via an α-anionic species, α-cationic intermediates have also received a great deal of attention.[6] With some notable exceptions,[8] these oxidative procedures, based on the formation of an electrophilic iminium ion from a given cyclic amine, have been mainly employed for the functionalization of the benzylic position of *N*-substituted tetrahydroisoquinolines.[9] Lately, a number of reports describing the generation of α-amino radical intermediates and their subsequent reaction with a range of radicophiles have also been published.[10] These direct α-functionalization procedures, however, all require a stoichiometric reagent to activate the cyclic amine.

Transition-metal-catalyzed sp^3 C–H activation represents an elegant alternative synthetic approach to the direct functionalization of saturated cyclic amines involving stoichiometric reagents. Nevertheless, only a limited number of reports where the main focus is on five-membered cyclic sub-

[a] Dr. A. Peschiulli, V. Smout, Dr. T. E. Storr, Dr. E. A. Mitchell, Z. Eliáš, 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

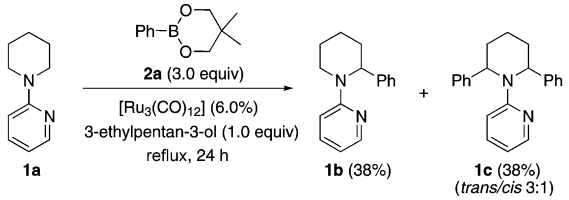
[b] Prof. Dr. W. Herrebout
Cryospectroscopy, University of Antwerp
Groenenborgerlaan 171, 2020 Antwerp (Belgium)

[c] Dr. D. Berthelot, Dr. L. Meerpoel
Janssen 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.201204438.

strates have appeared in the literature.[11–13] This is remarkable, given the importance of such cyclic amines in medicinal chemistry. A pioneering study appeared in 2001, in which Murai and co-workers reported a method for the α-functionalization of cyclic amines through transition-metal-catalyzed coupling of the sp^3 C–H bonds adjacent to the nitrogen atom with unfunctionalized alkenes.[12d] The process is catalyzed by $[Ru_3(CO)_{12}]$ and the presence of a pyridine directing group[14] on the nitrogen atom was found to be essential for the reaction to proceed. A number of alkenes were successfully employed to bring about the alkylation of pyrrolidine, with α,α′-dialkylated derivatives being obtained as the major reaction products as a mixture of diastereoisomers. With ethene as the alkene, the substrate scope of the reaction could also be extended to six- and seven-membered cyclic amines. However, when we applied the described alkylation protocol to other alkenes (for example, 1-hexene) and less reactive substrates (for example, piperidine and substituted derivatives thereof), we failed to isolate the anticipated C2-functionalized products in synthetically useful yields.[15] This is due to the chair conformation of the six-membered piperidine ring being inherently less reactive than the five-membered ring counterpart.[16] Only recently, our group has succeeded in developing novel reaction conditions that allow the efficient ruthenium-catalyzed sp^3 C–H alkylation of piperidines that is not possible under the original conditions of Murai and co-workers.[15]

The first direct arylation reaction of saturated cyclic amines through transition-metal-catalyzed sp^3 C–H activation was disclosed by Sames and co-workers in 2006.[13] The protocol is based upon the direct arylation of aromatic ketones developed by Kakiuchi et al.[17] Pyrrolidines were successfully arylated adjacent to the nitrogen atom by using a Ru-catalyzed C–H activation process and employing arylboronic esters as the coupling partners. The process is directed by a pyrroline group on the nitrogen atom and mediated by a ketone, which also acts as a solvent. The methodology was successfully applied to a small set of 2-substituted pyrrolidines to produce 2,5-difunctionalized derivatives in excellent yields as a mixture of diastereomers. One example of a piperidine substrate also appeared in this work, which was *p*-methoxyphenylated, but the anticipated product could only be isolated in a moderate yield (38%). Similarly, as observed in the direct alkylation reaction, we previously disclosed in a communication that the reaction conditions reported by Sames and co-workers[13] for the C2 arylation of pyrrolidines cannot be directly applied to the six-membered analogues with the same efficiency and we therefore developed suitable reaction conditions for these substrates.[18] Substrate instability (directing-group cleavage) and low conversion values were observed when using pyrroline as the directing group in the arylation reaction of piperidine derivatives. Hence, pyridine, already known as an effective and stable directing group in C–H activation processes,[12d,19] was found to provide optimal results. Although the presence of a ketone in the reaction mixture was found to be not necessary, the addition of a tertiary alcohol was discovered to be beneficial. Moreover, the execution of the reaction in an 'open vial' was identified as a crucial parameter to avoid catalyst poisoning and to obtain high conversion levels.[20] As shown in Scheme 1 for the phenylation of 1-(pyridin-2-yl)piperidine (**1a**), the reaction proceeds most effectively by heating **1a** with three equivalents of phenylboronic acid ne-



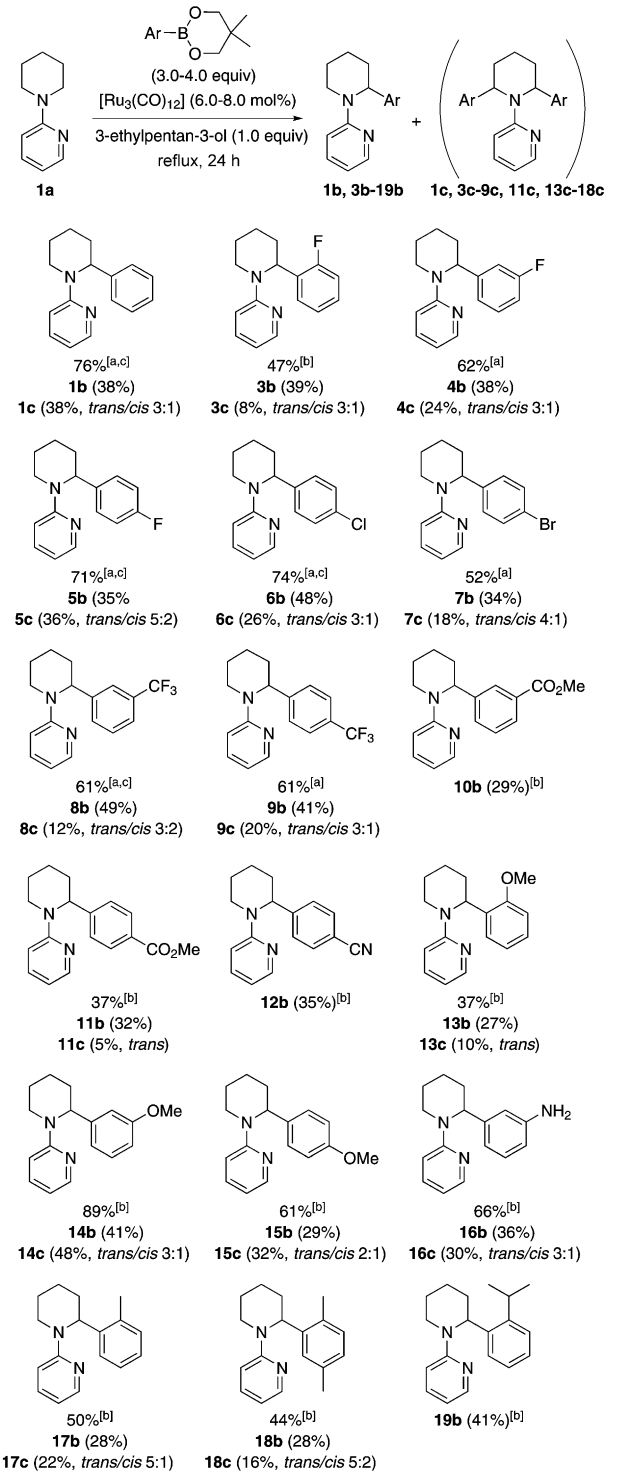
Scheme 1. Direct α-phenylation of 1-(pyridin-2-yl)piperidine (**1a**) under optimized reaction conditions.

opentylglycol ester (**2a**) in the presence of 6 mol% of $[Ru_3(CO)_{12}]$ and one equivalent of 3-ethylpentan-3-ol at reflux temperature for 24 h. Under these conditions, we obtained the functionalized products **1b** and **1c**, readily separated by column chromatography, in 76% yield (38% of **1b** and 38% of **1c**). A further increase in the amount of boronic ester (4 equiv) and catalyst (8 mol%) favors the formation of diarylated **1c**, which is then obtained as the major product in 60% yield.[18] A protocol to smoothly and efficiently remove the pyridine directing group, which is generally considered to be unremovable from a tertiary amine, was also developed for **1b** as a model compound.[18]

With the optimal reaction conditions in hand, we set out to explore the substrate and reagent scope of our novel catalytic method for the direct C2 arylation of piperidines with arylboronic esters and we wish to disclose the results of our study herein. Substitutions in both the piperidine substrate and the arylboronic reagent were investigated. The applicability of the protocol on structurally related cyclic amines, involving other ring sizes and benzoannulation, and the use of heteroarylboronic esters were also examined. In addition, more evidence supporting the previously reported mechanistic proposal will be disclosed herein.[18]

Results and Discussion

Substrate scope: Firstly, the influence of the substitution pattern in the phenylboronic ester was systematically investigated and our findings are summarized in Scheme 2. A variety of arylboronic esters with different electronic and steric features were coupled with 1-(pyridin-2-yl)piperidine (**1a**) in the presence of a catalytic amount of $[Ru_3(CO)_{12}]$ (6–8 mol%) and one equivalent of alcohol. Piperidine **1a** was successfully C2 functionalized with arylboronic esters bearing electron-withdrawing substituents in the *meta* or *para* position. The anticipated mono- and diarylated products, readily separated by column chromatography, were obtained in good total yields (**4**–**9**, up to 74%). Notably, halo-

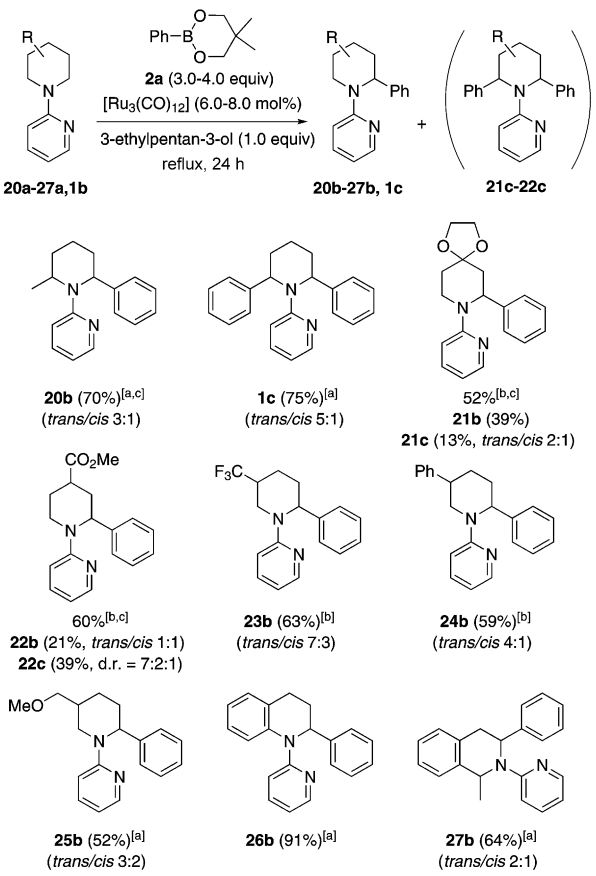


Scheme 2. Direct α-arylation of 1-(pyridin-2-yl)piperidine (**1a**) with a variety of arylboronic esters. For simplicity, only the structures of the monoarylated products are represented. All reactions were performed in duplicate on a 0.5 mmol scale in an 'open vial' equipped with a reflux condenser and under an argon atmosphere (ref. [20]). Isolation was performed on two combined reactions. [a] $[Ru_3(CO)_{12}]$: 6 mol%; arylboronic acid neopentylglycol ester: 3.0 equiv. [b] $[Ru_3(CO)_{12}]$: 8 mol%; arylboronic acid neopentylglycol ester: 4.0 equiv. [c] Compound previously reported; see ref. [18].

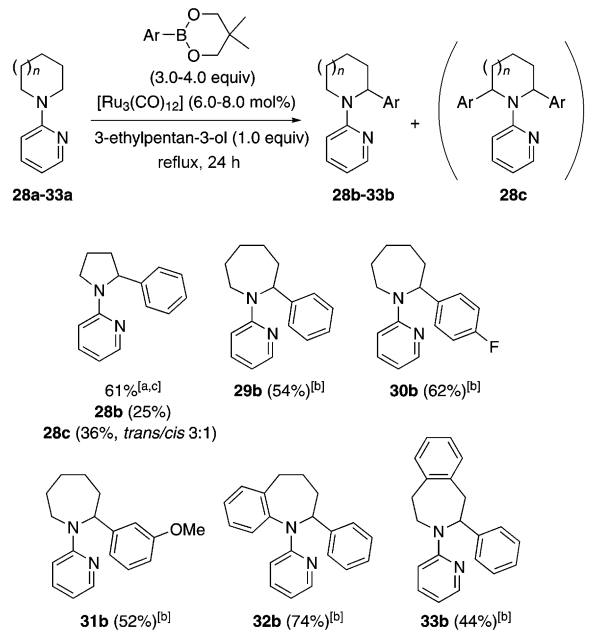
gens are well tolerated, which allows for further functionalization through Pd-catalyzed cross-coupling reactions. Reduced yields were observed in the cases of benzenes substituted with functionalities with strong electron-withdrawing properties, such as an ester or a cyano group (**10**–**12**, 29–37%). With electron-rich arylboronic esters, the total yields of the C2-functionalized piperidine products were particularly satisfying in the case of *meta* and *para* substitution (**14**–**16**, 61–89%). Remarkably, aniline derivatives can be used in the reaction without protecting the amino group. Generally, lower yields were observed in the case of *ortho*-substituted phenylboronic esters. Products **3**, **13**, **17**, and **18**, possessing 2-fluoro, 2-methoxy, and 2-methyl substituents, respectively, were isolated in 37–50% yields. Sterically hindered *ortho*-substituted phenylboronic esters are also tolerated, as demonstrated by the synthesis of the α-isopropylphenyl derivative **19b**, but a lower yield (41%) was obtained, in accordance with the results with other 2-substituted derivatives. No product formation occurred in the case of *ortho* substitution with highly electron-withdrawing functional groups, such as an ester or a trifluoromethyl group.

Importantly, the scope of the reaction is not limited to 1-(pyridin-2-yl)piperidine (**1a**) and the protocol could be successfully extended to the functionalization of C-substituted piperidine derivatives (Scheme 3). Phenylation of 2-methyl-1-(pyridin-2-yl)piperidine yielded product **20b** as a mixture of diastereomers (*trans*/*cis* 3:1) in 70% yield. From 2-phenyl-1-(pyridin-2-yl)piperidine (**1b**), the 2,6-diphenylated product **1c** could be obtained in 75% yield (*trans/cis* 5:1). To our delight, not only alkyl/aryl substituents were tolerated, but good isolated yields were also obtained for the direct phenylation of 1-(pyridin-2-yl)piperidines containing a ketal or ester group in the C4 position (products **21** and **22**, respectively). Interestingly, when applied to C3-substituted piperidines, the reaction was found to be completely regioselective. Derivatives possessing a trifluoromethyl, phenyl, or methoxymethyl substituent in the C3 position all underwent smooth arylation at the sterically less hindered α-position, with the resulting 2,5-disubstituted piperidines (**23b**–**25b**) being isolated in 52–63% yield. As is the case with C2-substituted piperidines, preferential formation of the *trans* diastereomer of the reaction product also occurred with C3 substituted piperidines.

The effect of benzoannulation was also studied. Excellent product yields resulted from the phenylation of 1-(pyridin-2-yl)-1,2,3,4-tetrahydroquinoline (to give **26b**, 91% yield). The corresponding tetrahydroisoquinoline derivative was also tested under optimized conditions and provided unexpected results in terms of regioselectivity. GC-MS analysis of the crude reaction mixture indicated the formation of high amounts of the 1,3-diphenylated product together with the two possible monophenylated products (at the C1 and C3 positions) in an approximately 1:1 ratio. This is surprising because the C1 position is benzylic and therefore is expected to be much more reactive than the C3 position. A reduction in the amount of boronic ester to 1.5 equivalents did not suppress the formation of the C3-phenylated regioisom-



Scheme 3. Direct α-phenylation reaction of substituted piperidine derivatives (**1b**, **20a**–**25a**) and benzoannulated analogues (**26a** and **27a**). For simplicity, only the structures of the monophenylated products are represented. All reactions were performed in duplicate on a 0.5 mmol scale in an 'open vial' equipped with a reflux condenser and under an argon atmosphere (ref. [20]). Isolation was performed on two combined reactions. [a] $[Ru_3(CO)_{12}]$: 6 mol%; phenylboronic acid neopentylglycol ester: 3.0 equiv. [b] $[Ru_3(CO)_{12}]$: 8 mol%; phenylboronic acid neopentylglycol ester: 4.0 equiv. [c] Compound previously reported; see ref. [18].

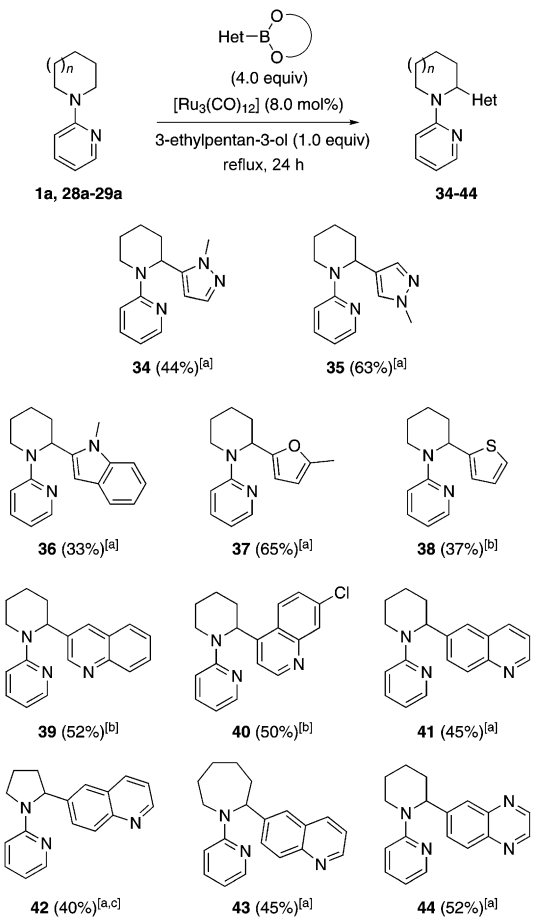


Scheme 4. Direct α-arylation reaction of 2-(pyrrolidin-1-yl)pyridine (**28a**), 1-(pyridin-2-yl)azepane (**29a**), and its benzoannulated analogues (**32a** and **33a**). For simplicity, only the structures of the monoarylated products are represented. All reactions were performed in duplicate on a 0.5 mmol scale in an 'open vial' equipped with a reflux condenser and under an argon atmosphere (ref. [20]). Isolation was performed on two combined reactions. [a] $[Ru_3(CO)_{12}]$: 6 mol%; phenylboronic acid neopentylglycol ester: 3.0 equiv. [b] $[Ru_3(CO)_{12}]$: 8 mol%; arylboronic acid neopentylglycol ester: 4.0 equiv. [c] Compound previously reported; see ref. [18].

er, which encouraged us to investigate the outcome of the reaction in the case of substrates already bearing a substituent in the benzylic position. Taking into account the fact that 1-substituted 1,2,3,4-tetrahydroisoquinolines can be readily obtained through iminium ion generation,[6] our protocol could offer a convenient synthetic route to 3-arylated 1-substituted 1,2,3,4-tetrahydroisoquinolines. Indeed, with 1-methyl-2-(pyridin-2-yl)-1,2,3,4-tetrahydroisoquinoline (**27a**) as the substrate, the reaction proceeded cleanly and produced a high yield of the C3-phenylated product (**27b**, 64% yield, *trans*/*cis* 2:1).

The compatibility of our Ru-catalyzed direct arylation protocol with smaller (azetidine and pyrrolidine) and larger (azepane) saturated ring systems was also tested (Scheme 4). Although only traces of the desired phenylated product were detected in the case of 2-(azetidin-1-yl)pyridine (uncorrected GC-FID conversion: 5%), both five- and seven-membered-ring analogues of piperidine could be transformed into the anticipated functionalized products in synthetically attractive yields. 2-(Pyrrolidin-1-yl)pyridine (**28a**) proved reactive, with the 2,5-diphenyl derivative (**28c**) being isolated as the major product of the reaction in 36% yield (*trans*/*cis* 3:1). For 1-(pyridin-2-yl)azepane (**29a**), the best conversion values were observed in the presence of an increased catalyst loading (8 mol%) and the formation of the difunctionalized product was found to be marginal even under these forcing conditions. Electronic effects on the arylboronic ester were found to have little impact on the outcome of the reaction (**29b**–**31b**, 52–62% yield). The use of benzoannulated analogues of azepane (**32a** and **33a**) was also successful.

Heteroaryl motifs are regarded as privileged scaffolds in medicinal chemistry[21] and a general method allowing the direct C2 heteroarylation of piperidine and related cyclic amines is therefore of high importance. The use of heteroaryl donors has been limitedly explored by Sames and coworkers in the context of the pyrrolidine ring system, for which, remarkably, pyridine-derived boronic esters were found to be suitable reagents despite the basic sp^2 nitrogen atom.[13] No examples of direct C2 functionalization of the (less reactive) piperidine derivatives with heteroarene donors have appeared in the literature. We therefore became interested in evaluating a representative set of heteroarylboronic esters under our optimized reaction conditions. As summarized in Scheme 5, both six- and five-membered heteroarenes were found to be compatible with our



Scheme 5. Direct α-heteroarylation reaction of 1-(pyridin-2-yl)piperidine (**1a**) and its five- and seven-membered ring analogues (**28a** and **29a**). All reactions were performed in duplicate on a 0.5 mmol scale in an 'open vial' equipped with a reflux condenser and under an argon atmosphere (ref. [20]). Isolation was performed on two combined reactions. [a] The heteroarylboronic acid pinacol ester was used. [b] The heteroarylboronic acid neopentylglycol ester was used. [c] Three equivalents of heteroarylboronic acid pinacol ester were used.

C–H activation protocol and, in general, moderate to good yields of the desired monofunctionalized reaction products were obtained. Firstly, five-membered heteroarene donors were studied. The methodology proved particularly successful for the coupling of regioisomeric 1-methylpyrazolylboronic acid esters (to give **34** and **35**, 44 and 63% yield). Disappointingly, very little product formation was observed if the pinacol ester of *N*-methylpyrrol-2-ylboronic acid was employed as the heteroaryl donor (uncorrected GC-FID conversion: 7%). Replacement of the *N*-methyl group for an *N*-tosyl group resulted in no reaction product being formed. Interestingly, *N*-methylindole-2-boronic acid pinacol ester, the benzoannulated derivative of *N*-methylpyrrole, gave a moderate yield of the anticipated C2-substituted piperidine derivative (**36**, 33% yield). The protocol could be applied to oxygen- and sulphur-containing heteroarene reagents (**37** and **38**, 65 and 37% yield). Next, the coupling of six-membered heteroarene reagents with piperidines was studied. Unfortunately, the use of pyridine-derived boronic esters (2-, 3-, and 4-pyridylboronic acid pinacol esters were all screened under optimized conditions) proved unsuccessful in our protocol. However, as observed for *N*-methylpyrrole, benzoannulation of the pyridine reagents provided good results. Both quinolin-3-yl- and quinolin-4-ylboronic acid neopentylglycol esters smoothly coupled with **1a**. In the latter case, an additional halogen atom was present in the core, which made the reaction even more challenging (**40**, 50% yield). Coupling through the arene ring of the quinoline system was also possible, as exemplified by the synthesis of **41** (45% yield). Quinolin-6-ylboronic acid neopentylglycol ester reagent was subsequently also selected to test the scope for heteroarylation with smaller (pyrrolidine) and larger (azepane) ring analogues of piperidine (to give **42** and **43**). Finally, direct heteroarylation of **1a** with an aza analogue of quinoline, quinoxalin-6-ylboronic acid pinacol ester, was investigated and the anticipated product (**44**) was isolated in 52% yield. Remarkably, no bis-functionalized products are observed during the isolation of monoheteroarylated products

Reaction mechanism: In our previous communication, a proposal for the mechanism of the direct α-arylation of cyclic amines was disclosed (Figure 2).[18] It involves complexation of a Ru^0 species to the pyridine and subsequent directed oxidative addition of an α-sp^3 C–H bond next to the nitrogen atom to the Ru^0 species. The resulting Ru^{II}–H species **C** undergoes transmetalation with the arylboronic ester **F** to yield the Ru^{II}–Ar species **D** and dialkoxyborane **G**. Reductive elimination finally gives the α-arylated reaction product **E** and regenerates the Ru^0 species to make the process catalytic. The dialkoxyborane side product formed in the catalysis is a poison for the catalyst because it can oxidatively add to the Ru^0 species (with the formation of **H**), thereby removing the catalyst from the catalytic cycle.[22] The role of the alcohol reagent (3-ethyl-3-pentanol in Figure 2) is to destroy **G** with the formation of trialkoxyborane **I** and hydrogen gas.[23] The use of an 'open vial' for the reaction is crucial, otherwise H_2 cannot escape and will oxidatively add to the Ru^0 species (to form **J**), which would also lead to catalyst poisoning (Figure 2).[24]

The direct reaction of a transition-metal hydride with an arylboronic ester is not known, so additional experiments were performed to support the direct transmetalation of **C**. Notably, trialkoxyborane **45** could be detected with GC-MS in the reaction mixture of substrate **1a** with pinacolboronic ester **2b** (Scheme 6). Scavenging of the gas formed during this direct arylation reaction revealed that hydrogen gas is indeed formed (Raman spectroscopy of H_2: 4163.3 (w), 4157.4 (s), 4145.7 (w) and 4128.4 cm^{-1} (w)). Moreover, in an independent experiment, heating of 4,4,5,5-tetramethyl-1,3,2-dioxaborolane (**46**) with 3-ethyl-3-pentanol at 150°C yielded trialkoxyborane **45** and H_2, in accordance with our mechanistic proposal (Scheme 7). The occurrence of a mechanism involving a protonation reaction of Ru^{II}–H species **C** with the alcohol, yielding an Ru^{II}–OR species (allow-

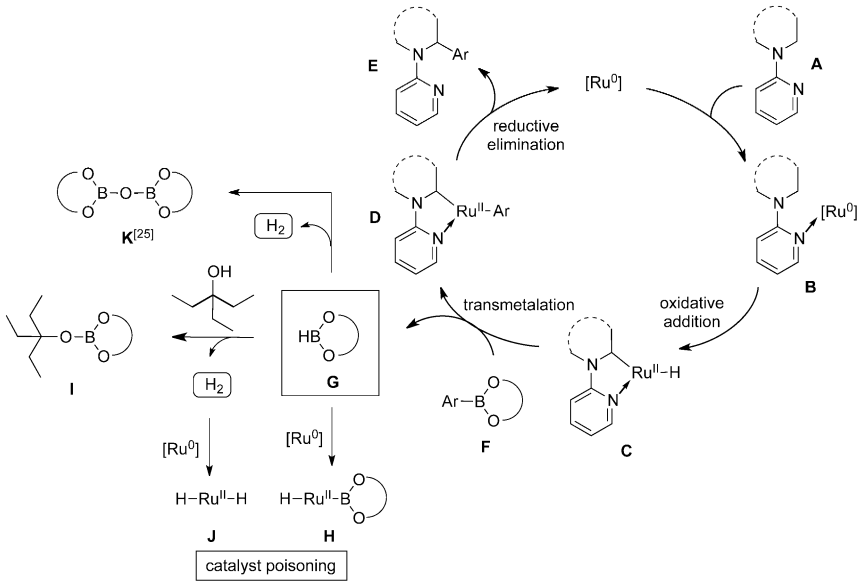
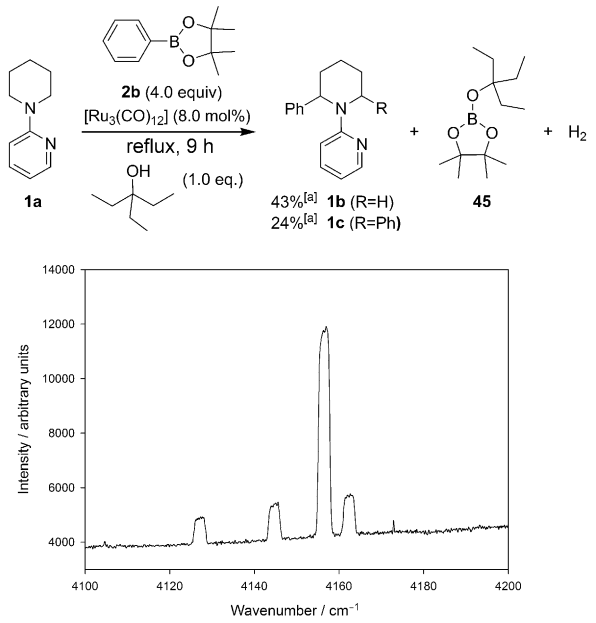


Figure 2. Proposed mechanism for the direct α-arylation of saturated cyclic amines and catalyst poisoning pathways.

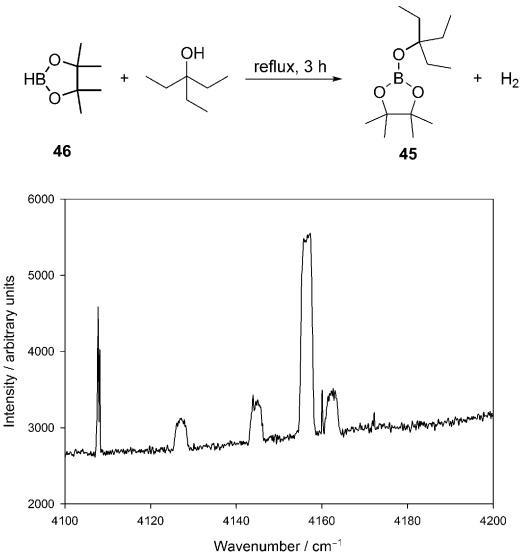


Scheme 6. Ru-catalyzed direct arylation of 1-(pyridin-2-yl)piperidine (**1a**) with phenylboronic acid pinacol ester (**2b**) in the presence of 3-ethyl-3-pentanol (in an 'open vial'). Raman spectroscopy shows H_2 gas and GC-MS analysis reveals the formation of 2-(1,1-diethylpropoxy)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (**45**). [a] GC-FID corrected conversion values by using 1,3,5-trimethoxybenzene (TMB) as an internal standard.

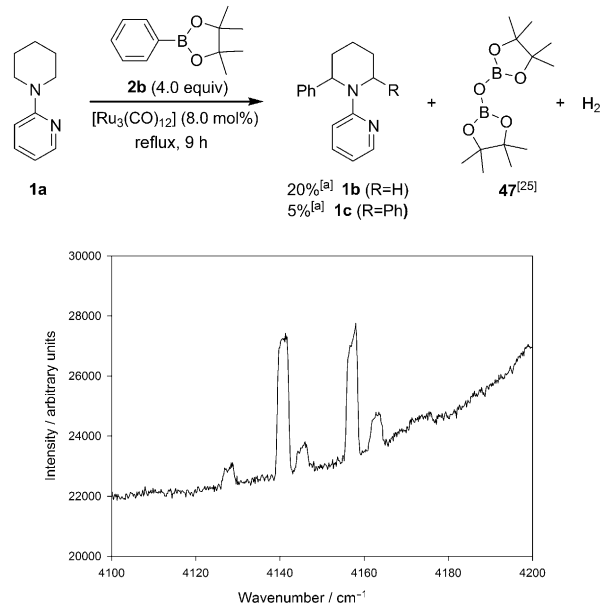
ing for a classical transmetalation) and H_2, could be excluded on the basis of a reaction of **1a** with boronic ester **2b** in the absence of alcohol, because arylated products **1b** and **1c** were still formed, albeit in lower amounts (Scheme 8). Raman spectroscopy indicated that hydrogen gas is also formed in the absence of the alcohol. In this case, 2,2′-oxybis(4,4,5,5-tetramethyl-1,3,2-dioxaborolane) (**47**) was observed by both GC-MS and ^{11}B NMR analysis in the crude reaction mixture (see the Supporting Information). Bis boryloxide **47** formation from pinacolborane (**46**) is well documented in the literature.[26]

To prove the poisoning effect of the H_2 gas, the arylation reaction of 1-(pyridin-2-yl)piperidine (**1a**) was executed in a pressure-cap-sealed vessel. As expected, conversion values into **1b** and **1c** dropped significantly (Scheme 9). In agreement with this, the direct arylation reaction in a pressure-cap-sealed vessel under a H_2 atmosphere (created with a balloon) gave even lower amounts of the desired phenylated products (14% **1b** and 1% **1c**). GC-MS analysis also revealed formation of trialkoxyborane **45** in these reactions (Scheme 9).

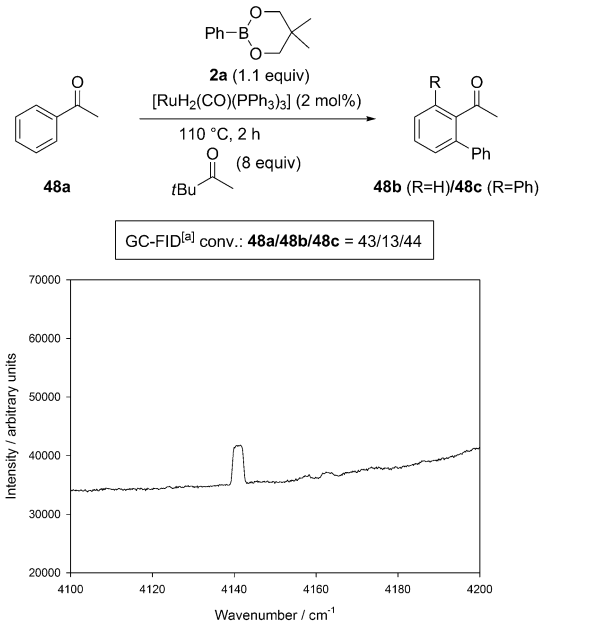
The unprecedented direct transmetalation on Ru^{II}–H species **C**, yielding Ru^{II}–Ar, prompted us to check whether other Ru-catalyzed direct arylation reactions follow the original mechanistic proposal[17] or occur through an alternative pathway, as discovered by us. With this goal in mind, we tested the Ru-catalyzed α-arylation protocol of aromatic ketones, reported by Kakiuchi et al., for H_2 formation (Scheme 10).[17] Kakiuchi and co-workers proposed a pathway for this transformation that is based on the insertion of



Scheme 7. Reaction of 4,4,5,5-tetramethyl-1,3,2-dioxaborolane (**46**) with 3-ethyl-3-pentanol. Raman spectroscopy shows H_2 gas and GC-MS analysis reveals the formation of 2-(1,1-diethylpropoxy)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (**45**).



Scheme 8. Ru-catalyzed direct arylation of 1-(pyridin-2-yl)piperidine (**1a**) with phenylboronic acid pinacol ester (**2b**) in the absence of alcohol (in an 'open vial'). Raman spectroscopy shows H_2 gas and GC-MS analysis reveals the formation of 2,2′-oxybis(4,4,5,5-tetramethyl-1,3,2-dioxaborolane) (**47**). [a] GC-FID corrected conversion values by using TMB as an internal standard.



Scheme 10. Ru-catalyzed α-phenylation of acetophenone (**48a**) under the reaction conditions reported by Kakiuchi and co-workers. Raman spectroscopy shows no H_2 gas and GC-MS analysis reveals the formation of pinacolyl alcohol. [a] Uncorrected GC-FID conversion values.

pinacolone into the Ru^{II}–H species (**49**) to deliver intermediate **50** (Figure 3). Interestingly, H_2 formation was not observed in the phenylation of acetophenone (**48a**) (Scheme 10), which supports the suggestion that the mechanism observed indeed occurs through ketone insertion followed by a classical transmetalation to deliver the Ru^{II}–Ar species. Next, we tested the direct arylation protocol of pyrrolidines developed by Sames and co-workers for H_2 formation.[13] The development of this protocol is based on the work of Kakiuchi and it was reported to proceed through a similar reaction mechanism (Figure 4). Unexpectedly, we found that H_2 gas was formed in the phenylation of 2-phenyl-1-(3,4-dihydro-2*H*-pyrrol-5-yl)pyrrolidine (**52a**) (Scheme 11). Pinacolyl alcohol was also formed, based on GC-MS analysis of the crude reaction mixture. The alcohol can be formed directly through ketone insertion into an Ru^{II}–H species or indirectly through Ru-catalyzed hydrogenation of the ketone (reagent and solvent) by the hydrogen gas formed (the reported experiments are performed in closed vessel).[27] Our experiment therefore supports the fact that direct arylation, at least partially, occurs through direct transmetalation on the Ru^{II}–H species with the arylboronic ester in this literature protocol. However, a combination of the two reaction mechanisms cannot be excluded because ketone insertion also generates alcohol. Importantly, our Raman measurements point to

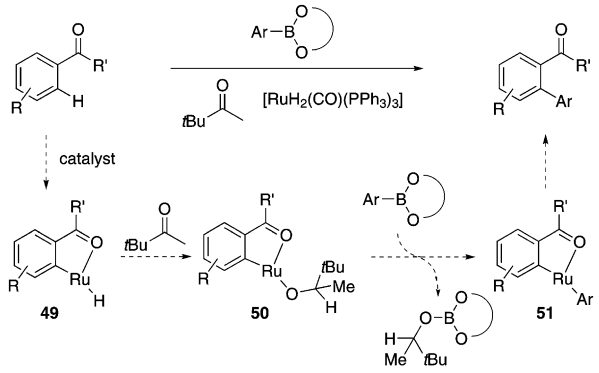
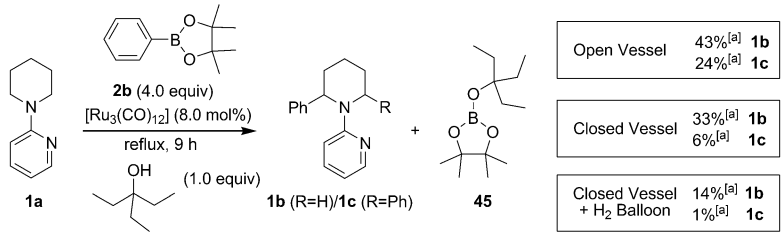


Figure 3. Proposed mechanism for the direct sp^2 C–H arylation of aromatic ketones developed by Kakiuchi et al.[17]



Scheme 9. Ru-catalyzed direct arylation of 1-(pyridin-2-yl)piperidine (**1a**) with phenylboronic acid pinacol ester (**2b**) in an 'open vessel' (ref. [20]), in a closed vessel, and in a closed vessel under a H_2 atmosphere. GC-MS analysis reveals the formation of 2-(1,1-diethylpropoxy)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (**45**). [a] GC-FID corrected conversion values by using TMB as an internal standard.

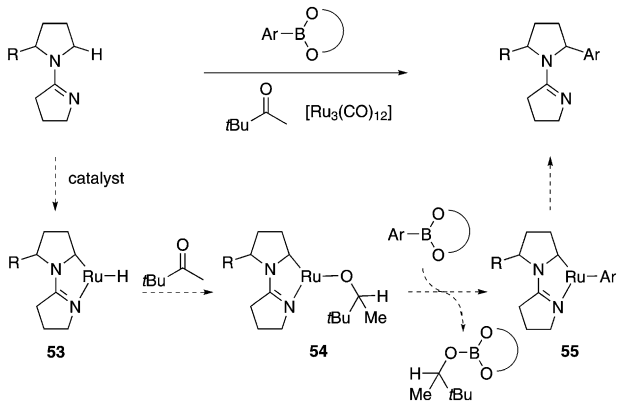
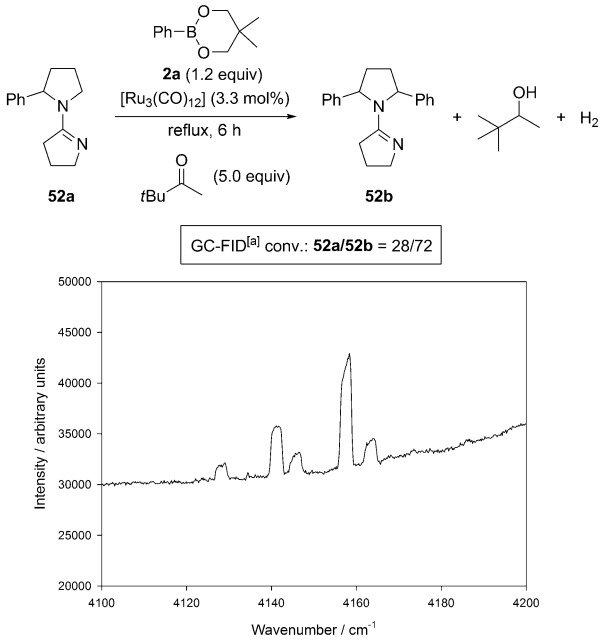


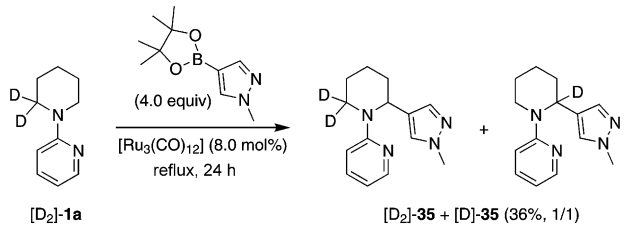
Figure 4. Proposed mechanism for the direct sp^3 C–H arylation of pyrrolidines developed by Sames and co-workers.[13]



Scheme 11. Phenylation of 2-phenylpyrrolidine **52a** under the reaction conditions reported by Sames and co-workers. Raman spectroscopy shows H_2 gas and GC-MS analysis reveals the formation of pinacolyl alcohol. [a] Uncorrected GC-FID conversion values.

distinct reaction mechanisms for Ru-catalyzed direct arylation of sp^2 C–H versus sp^3 C–H bonds.

The cleavage of an sp^3 C–H bond is generally more difficult than that of an sp^2 C–H bond, so we decided to perform an intramolecular primary kinetic isotope effect (KIE) experiment on 2,2-dideutero-1-(pyridin-2-yl)piperidine ([D_2]-**1a**) because this gives information on the kinetic relevance of the C–H bond activation process in our direct arylation reaction (Scheme 12).[28] For this experiment, the optimal reaction conditions in the absence of alcohol were used, in order to avoid a possible undesired background deuterium–hydrogen exchange. We also selected a boronic ester that does not give 2,6-difunctionalization because a second arylation reaction also hampers interpretation of the result. Remarkably, this experiment revealed no KIE, which indicates that the C–H bond activation step is actually a facile process in our substrates (Scheme 12). This is in accordance with the phenylation of 1-(pyridin-2-yl)-1,2,3,4-tetrahydroisoquinoline, in which no selectivity between the benzylic C1 position and the 'unactivated' C3 position was observed and with hydrogen–deuterium exchange experiments with [Ru_3CO_{12}] in [D_8]-2-propanol reported by Murai and co-workers on 1-(pyridin-2-yl)pyrrolidine.[12d] To support the feasibility of a C–H oxidative addition step, as proposed in our catalytic cycle (Figure 2), stoichiometric quantities of both [Ru_3CO_{12}] and 1-(pyridin-2-yl)piperidine (**1a**) were combined in mesitylene and heated at 150 °C for 20 min under an argon atmosphere. The resulting crude mixture was subsequently analyzed by ^{1}H NMR spectroscopy, which revealed the presence of a ruthenium hydride species ($\delta = -17.8$ ppm).[29,30] The absence of a KIE and the stoichiometric oxidative addition experiment support C–H activation through oxidative addition and a rate-limiting transmetalation step in the developed direct arylation reaction.



Scheme 12. Intramolecular KIE experiment: The heteroarylation reaction of 2,2-dideutero-1-(pyridin-2-yl)piperidine ([D_2]-**1a**).

Conclusion

In conclusion, we have fully explored the scope of our previously disclosed direct arylation method for the C2 (hetero)arylation of 1-(pyridin-2-yl)piperidine and C2-, C3-, and C4-substituted derivatives. The process also allows the functionalization of other structurally related saturated cyclic amines (pyrrolidines, azepanes, and benzoannulated derivatives). The direct arylation involves the use of a catalytic amount of [$Ru_3(CO)_{12}$], a (hetero)arylboronic acid ester as a (hetero)arene donor, and a tertiary alcohol as a dialkoxyborane scavenger. The development of this new (hetero)arylation method stems from a better understanding of the transmetalation step of the catalytic cycle. Removal of the dialkoxyborane formed during this process is critical because otherwise the catalyst would be poisoned. In the presence of the tertiary alcohol, the dialkoxyborane is transformed into a trialkoxyborane and hydrogen gas, the latter necessitating an 'open vial' to avoid oxidative addition of hydrogen, which would poison the catalyst. Our results indicate that direct Ru-catalyzed arylation of sp^3 C–H bonds occurs through a distinct reaction mechanism to that of the corresponding sp^2 C–H bond arylation process. Moreover, the sp^3

C–H bond activation step is remarkably facile. Such insights are crucial to further develop the field of direct sp^3 C–H bond functionalizations.

Experimental Section

C2 (Hetero)arylation of *N*-(pyridin-2-yl)piperidines and analogues: General procedure: Two 10 mL vials were each charged with the appropriate *N*-(pyridin-2-yl) cyclic amine (0.5 mmol) and (hetero)arylboronic ester (3.0–4.0 equiv), $[Ru_3(CO)_{12}]$ (6–8 mol%), and 3-ethyl-3-pentanol (0.5 mmol, 1 equiv). The vials were flushed with argon and equipped with a condenser fitted with a rubber septum and an argon-filled balloon. The reaction mixtures were then heated to reflux, with the temperature of the oil bath being set at 153 °C, under an argon atmosphere and with magnetic stirring for 24 h. After this time, the reaction mixtures were cooled down and combined into a 250 mL round-bottomed flask by using CH_2Cl_2. A commercially available ruthenium scavenger (2 g; Siliabond DMT, Silicycle) and CH_2Cl_2 (100 mL) were added to the residue. The resulting suspension was stirred at room temperature for 16 h (overnight). Subsequently, the solids were removed by filtration through celite, the pad was washed with CH_2Cl_2 (5×20 mL), and the combined filtrate was evaporated to dryness. The residue was purified by flash chromatography to obtain the desired (hetero)arylated product(s).

Acknowledgements

This work was financially supported by the University of Antwerp (BOF), the Hercules Foundation and Janssen Research & Development (A Division of Janssen Pharmaceutica N.V.). The authors would like to thank Dr. Hana Prokopcová, Dr. Stefan Verbeeck, Audrey Velleine, and Dr. Artem Kulago for their contribution to this work.

[1] For general reviews about direct functionalization through C–H bond activation, see: a) A. E. Shilov, G. B. Shul'pin, *Chem. Rev.* **1997**, *97*, 2879–2932; b) G. Dyker, *Angew. Chem.* **1999**, *111*, 1808–1822; *Angew. Chem. Int. Ed.* **1999**, *38*, 1698–1712; c) J. A. Labinger, J. E. Bergaw, *Nature* **2002**, *417*, 507–514; d) F. Kakiuchi, N. Chatani, *Adv. Synth. Catal.* **2003**, *345*, 1077–1101; e) K. Godula, D. Sames, *Science* **2006**, *312*, 67–72; f) R. G. Bergman, *Nature* **2007**, *446*, 391–393; g) F. Kakiuchi, T. Kochi, *Synthesis* **2008**, 3013–3039; h) P. Thansandote, M. Lautens, *Chem. Eur. J.* **2009**, *15*, 5874–5883; i) 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; j) T. W. Lyons, M. S. Sanford, *Chem. Rev.* **2010**, *110*, 1147–1169; k) J. Yamaguchi, A. D. Yamaguchi, K. Itami, *Angew. Chem.* **2012**, *124*, 9092–9142; *Angew. Chem. Int. Ed.* **2012**, *51*, 8960–9009.

[2] For general reviews about direct functionalization through sp^2 C–H bond activation, see: a) J. C. Lewis, R. G. Bergman, J. A. Ellman, *Acc. Chem. Res.* **2008**, *41*, 1013–1025; b) L. Ackermann, R. Vicente, A. R. Kapdi, *Angew. Chem.* **2009**, *121*, 9976–10011; *Angew. Chem. Int. Ed.* **2009**, *48*, 9792–9826; c) D. A. Colby, R. G. Bergman, J. A. Ellman, *Chem. Rev.* **2010**, *110*, 624–655; d) S. H. Cho, J. Y. Kim, J. Kwak, S. Chang, *Chem. Soc. Rev.* **2011**, *40*, 5068–5083; e) N. Kuhl, M. N. Hopkinson, J. Wencel-Delord, F. Glorius, *Angew. Chem.* **2012**, *124*, 10382–10401; *Angew. Chem. Int. Ed.* **2012**, *51*, 10236–10254; f) P. B. Arockiam, C. Bruneau, P. H. Dixneuf, *Chem. Rev.* **2012**, *112*, 5879–5918.

[3] For general reviews about direct functionalization through sp^3 C–H bond 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; c) O. Baudoin, *Chem. Soc. Rev.* **2011**, *40*, 4902–4911.

[4] 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.* WO2007084319 (A2), **2007**; f) J. Ackermann, K. Bleicher, G. Ceccarelli, M. Simona, O. Chomienne, P. Mattei, T. Schulz-Gasch, *PCT Int. Appl.* WO2007063012 (A1), **2007**; g) J. P. Michael, *Nat. Prod. Rep.* **2008**, *25*, 139–165.

[5] K. R. Campos, *Chem. Soc. Rev.* **2007**, *36*, 1069–1084.

[6] E. A. Mitchell, A. Peschiulli, N. Lefevre, L. Meerpoel, B. U. W. Maes, *Chem. Eur. J.* **2012**, *18*, 10092–10142.

[7] For selected examples, see: a) P. Beak, W.-K. Lee, *Tetrahedron Lett.* **1989**, *30*, 1197–1200; b) W. F. Bailey, P. Beak, S. T. Kerrick, S. Ma, K. B. Wiberg, *J. Am. Chem. Soc.* **2002**, *124*, 1889–1896; c) T. A. Johnson, D. O. Jang, B. W. Slafer, M. D. Curtis, P. Beak, *J. Am. Chem. Soc.* **2002**, *124*, 11689–11698; d) P. O'Brien, *Chem. Commun.* **2008**, 655–667; e) G. Barker, P. O'Brien, K. R. Campos, *Org. Lett.* **2010**, *12*, 4176–4179; f) M. J. McGrath, J. L. Bilke, P. O'Brien, *Chem. Commun.* **2006**, 2607–2609; g) I. Coldham, D. Leonori, *Org. Lett.* **2008**, *10*, 3923–3925; h) S. Seel, T. Thaler, K. Takatsu, C. Zhang, H. Zipse, B. F. Straub, P. Mayer, P. Knochel, *J. Am. Chem. Soc.* **2011**, *133*, 4774–4777; i) I. Coldham, S. Raimbault, P. T. Chovatia, J. J. Patel, D. Leonori, N. S. Sheikh, D. T. E. Whittaker, *Chem. Commun.* **2008**, 4174–4176; j) T. K. Beng, R. E. Gawley, *J. Am. Chem. Soc.* **2010**, *132*, 12216–12217; k) T. K. Beng, R. E. Gawley, *Org. Lett.* **2011**, *13*, 394–397.

[8] a) Y. Shen, Z. Tan, D. Chen, X. Feng, M. Li, C.-C. Guo, C. Zhu, *Tetrahedron* **2009**, *65*, 158–163; b) G. Kumaraswamy, A. N. Murthy, A. Pitchaiah, *J. Org. Chem.* **2010**, *75*, 3916–3919; c) X.-Z. Shu, Y.-F. Yang, X.-F. Xia, K.-G. Ji, X.-Y. Liu, Y.-M. Liang, *Org. Biomol. Chem.* **2010**, *8*, 4077–4079; d) N. Shankaraiah, R. A. Pilli, L. S. Santos, *Tetrahedron Lett.* **2008**, *49*, 5098–5100; e) A. G. Condie, J. C. González-Gómez, C. R. J. Stephenson, *J. Am. Chem. Soc.* **2010**, *132*, 1464–1465.

[9] For selected examples, see: a) Z. Li, P. D. MacLeod, C.-J. Li, *Tetrahedron: Asymmetry* **2006**, *17*, 590–597; b) G. Zhang, Y. Zhang, R. Wang, *Angew. Chem.* **2011**, *123*, 10613–10616; *Angew. Chem. Int. Ed.* **2011**, *50*, 10429–10432; c) H. Mitsudera, C.-J. Li, *Tetrahedron Lett.* **2011**, *52*, 1898–1900; d) D. Sureshkumar, A. Sud, M. Klussmann, *Synlett* **2009**, *10*, 1558–1561; e) O. Baslé, C.-J. Li, *Org. Lett.* **2008**, *10*, 3661–3663; f) A. Sud, D. Sureshkumar, M. Klussmann, *Chem. Commun.* **2009**, 3169–3171; g) D. P. Hari, B. König, *Org. Lett.* **2011**, *13*, 3852–3855.

[10] a) N. Yoshikai, A. Mieczkowski, A. Matsumoto, L. Ilies, E. Nakamura, *J. Am. Chem. Soc.* **2010**, *132*, 5568–5569; b) S. Kamijo, T. Hoshikawa, M. Inoue, *Org. Lett.* **2011**, *13*, 5928–5931; c) A. McNally, C. K. Prier, D. W. C. MacMillan, *Science* **2011**, *334*, 1114–1117; d) T. Yoshimitsu, K. Matsuda, H. Nagaoka, K. Tsukamoto, T. Tanaka, *Org. Lett.* **2007**, *9*, 5115–5118.

[11] For direct alkylation and arylation through sp^3 C–H activation in acyclic amines, see: a) N. Dastbaravardeh, M. Schnürch, M. D. Mihovilovic, *Org. Lett.* **2012**, *14*, 1930–1933; b) N. Dastbaravardeh, K. Kirchner, M. Schnürch, M. D. Mihovilovic, *J. Org. Chem.* **2013**, *78*, 658–672; c) S. Pan, K. Endo, T. Shibata, *Org. Lett.* **2011**, *13*, 4692–4695.

[12] 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.

[13] S. J. Pastine, D. V. Gribkov, D. Sames, *J. Am. Chem. Soc.* **2006**, *128*, 14220–14221.

[14] For a detailed review on the use of directing groups in catalysis, see: G. Rousseau, B. Breit, *Angew. Chem.* **2011**, *123*, 2498–2543; *Angew. Chem. Int. Ed.* **2011**, *50*, 2450–2494.
[15] S. D. Bergman, T. E. Storr, H. Prokopcova, K. Aelvoet, G. Diels, L. Meerpoel, B. U. W. Maes, *Chem. Eur. J.* **2012**, *18*, 10393–10398.
[16] H. M. L. Davies, R. E. J. Beckwith, *Chem. Rev.* **2003**, *103*, 2861–2903.
[17] F. Kakiuchi, Y. Matsuura, S. Kan, N. Chatani, *J. Am. Chem. Soc.* **2005**, *127*, 5936–5945.
[18] H. Prokopcová, S. D. Bergman, K. Aelvoet, V. Smout, W. Herrebout, B. Van der Veken, L. Meerpoel, B. U. W. Maes, *Chem. Eur. J.* **2010**, *16*, 13063–13067.
[19] L. Ackermann, *Top. Organomet. Chem.* **2007**, *24*, 35–60.
[20] All reactions were performed in an open vessel. An open vessel means a reflux condenser fitted with a rubber septum and maintained under an inert atmosphere with an argon-filled balloon. There is a large head-to-space volume and the balloon allows H_2 to diffuse out of the system. A reaction run under air rather than argon gave a lower conversion.
[21] a) J. A. Joule, K. Mills, *Heterocyclic Chemistry*, 4th ed., Blackwell Science, Oxford, **2000**; b) T. Eicher, S. Hauptmann, *The Chemistry of Heterocycles*, 2nd ed., Wiley-VCH, Weinheim, **2003**; c) L. D. Quin, J. Tyrell, *Fundamentals of Heterocyclic Chemistry: Importance in Nature and in the Synthesis of Pharmaceuticals*, Wiley, Hoboken, NJ, **2010**.
[22] For a review about C–H activation/C–B bond formation through oxidative addition of a dialkoxyborane species to transition metals, see: T. Ishiyama, N. Miyaura, *J. Organomet. Chem.* **2003**, *680*, 3–11.
[23] 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.
[24] 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.
[25] The source of oxygen for the formation of **K** and **47** is believed to be derived from water from either impurities or the elimination of water from a diol (pinacol or neopentanediol).
[26] a) S. Hawkeswood, D. W. Stephan, *Dalton Trans.* **2005**, *680*, 2182–2187; b) V. Montiel-Palma, M. Lumbierres, B. Donnadieu, S. Sabo-Etienne, B. Chaudret, *J. Am. Chem. Soc.* **2002**, *124*, 5624–5625; c) M. Arrowsmith, M. S. Hill, T. Hadlington, G. Kociok-Köhn, C. Weetman, *Organometallics* **2011**, *30*, 5556–5559.
[27] *Ruthenium in Organic Synthesis* (Ed.: S.-I. Murahashi), Wiley-VCH, Weinheim, **2004**.
[28] For a detailed discussion dealing with KIE in transition-metal-catalyzed C–H bond functionalization, see: E. M. Simmons, J. F. Hartwig, *Angew. Chem.* **2009**, *124*, 3120–3126; *Angew. Chem. Int. Ed.* **2012**, *51*, 3066–3072.
[29] Experimental details and the NMR spectrum for this experiment can be found in the Supporting Information.
[30] An alternative for the cleavage of the C–H bond is iminium formation through hydride abstraction; see reference [12d].

Received: December 12, 2012
Revised: April 11, 2013
Published online: June 18, 2013

