

Catalytic C–H Functionalisation | Hot Paper |

Ru-Catalysed C–H Arylation of Indoles and Pyrroles with Boronic Acids: Scope and Mechanistic Studies

Carina Sollert,^[a] Karthik Devaraj,^[a] Andreas Orthaber,^[b] Paul J. Gates,^[c] and Lukasz T. Pilarski^{*[a]}

Abstract: The Ru-catalysed C2–H arylation of indoles and pyrroles by using boronic acids under oxidative conditions is reported. This reaction can be applied to tryptophan derivatives and tolerates a wide range of functional groups on both coupling partners, including bromides and iodides, which can be further derivatised selectively. New indole-

based ruthenacyclic complexes are described and investigated as possible intermediates in the reaction. Mechanistic studies suggest the on-cycle intermediates do not possess a *para*-cymene ligand and that the on-cycle metalation occurs through an electrophilic attack by the Ru centre.

Introduction

Transition metal-catalysed C–H activation has received enormous attention in recent years as a viable synthetic strategy; it offers previously impossible transformations, new selectivities and shortened routes in the preparation of organic molecules.^[1,2] The importance of indole and pyrrole units in bioactive molecules has fuelled continued efforts to develop new approaches to their selective C–H functionalisation.^[3] For instance, the 2-arylindole unit appears in several natural products,^[4] potential microtubulin polymerisation inhibitors, and molecules of interest for their antifungal and antimicrobial properties.^[5] To date, indole and pyrrole C–H arylation has been developed most extensively by using aryl halide^[6] and hypervalent iodine^[7] electrophiles. Meanwhile, the complementary method in which anionic coupling partners^[8] and an external oxidant are employed has received less attention. The dehydrogenative coupling of two (hetero)arene C–H units^[9] represents, in principle, the most atom economical and desirable

of these approaches. However, at present, the conjunction of two selective, compatible C–H activation processes often presents regioselectivity/scope limitations, the need for a large excess of one coupling partner, harsh conditions, and/or expensive additives. In this context, organoboronates^[10] are an attractive alternative for oxidative direct arylation reactions,^[11–14] by offering low cost, diversity, and ease of activation, amongst other advantages.

In Ru-catalysed C–H functionalisation reactions, which have attracted considerable recent interest (Figure 1),^[15,16] the use of boronates has remained rare. Ru⁰-catalysed C–H arylation reac-

[a] C. Sollert, K. Devaraj, Dr. L. T. Pilarski
Department of Chemistry–BMC, Uppsala University
Box 576, 75-123 Uppsala (Sweden)
Fax: (+46) 18-471-38-18
E-mail: lukasz.pilarski@kemi.uu.se

[b] Dr. A. Orthaber
Department of Chemistry–Ångström, Uppsala University
Box 523, 75-120 Uppsala (Sweden)

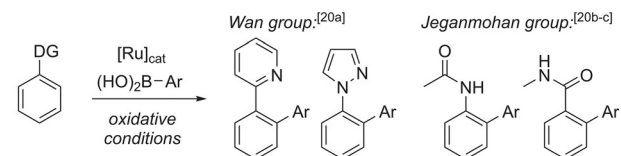
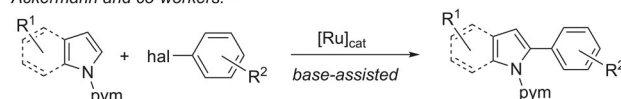
[c] Dr. P. J. Gates
School of Chemistry, University of Bristol, Cantock's Close
Clifton, Bristol, BS8 1TS (UK)

Supporting information for this article is available on the WWW under <http://dx.doi.org/10.1002/chem.201405931>.

© 2015 The Authors. Published by Wiley-VCH Verlag GmbH & Co. KGaA. This is an open access article under the terms of the Creative Commons Attribution Non-Commercial NoDerivs License, which permits use, distribution and reproduction in any medium, provided the original work is properly cited and is not used for commercial purposes.

Selected previous work:

Ackermann and co-workers:^[6f]



Prabhu^[21b] and Wang^[21c] groups:

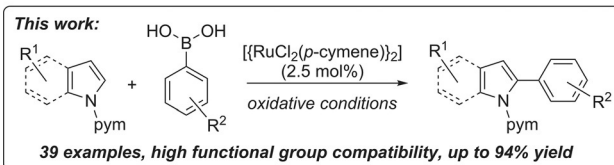
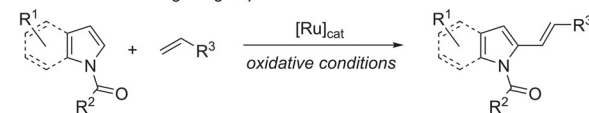


Figure 1. Selected Ru-catalysed C–H transformations relating to this study. Pym = 2-pyrimidyl.

tions developed by the groups of Kakiuchi,^[17] and later Sames^[18] and Schnürch,^[19] require protected boronates. Unprotected boronic acids have been used in Ru^{II}-catalysed C–H arylation reactions with only a handful of substrates^[20] and virtually no accompanying mechanistic investigation, despite a recent surge in the development of various related oxidative transformations.^[21] In addition, the use of aryl halides by Ackermann and Lygin^[6f] under carboxylate-assisted conditions^[22] stands as the only example to date of Ru-catalysed indole or pyrrole C–H arylation.^[23]

Herein, we report the use of unprotected, diversely functionalised arylboronic acids in the Ru-catalysed C2–H arylation of indoles and pyrroles. We also describe the synthesis of new ruthenacyclic complexes and examine their role in the reaction, which is of direct relevance to commonly proposed mechanisms.

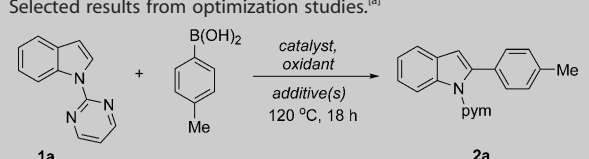
Results and Discussion

Reaction optimisation

We undertook our investigation with indole derivative **1a** as the test-bed substrate. Sames and co-workers^[18] and Ackermann and Lygin^[6r,24] pioneered the use of pyrimidine as a versatile, removable directing group^[25] for catalytic C–H functionalisation. A number of groups have since described the use of this species in both the synthesis^[24,26] and derivatisation of indoles and pyrroles by using various metals.^[27–32]

In our initial experiments, we isolated **2a** in 37% yield from the coupling of **1a** and 4-tolylboronic acid with 2.5 mol% $[\{\text{RuCl}_2(p\text{-cymene})\}_2]$ and 1.5 equivalents of Ag_2O in THF (Table 1, entry 1). Replacement of the oxidant with $\text{Cu}(\text{OAc})_2 \cdot \text{H}_2\text{O}$ (1 equiv) improved the yield to 64% and including water raised the yield further to 86% (Table 1, entry 3). A combination of substoichiometric amounts of $\text{Cu}(\text{OAc})_2 \cdot \text{H}_2\text{O}$ (0.5 equiv) and O_2 proved less effective (Table 1, entry 4). As an additive, AgSbF_6 proved superior to AgBF_4 , AgPF_6 , and KPF_6 . The addition of organic or inorganic bases, including carboxylates and carbonates (see Table 1, entry 5 and Table S5 in the Supporting Information),^[33] was detrimental to the catalysis, whereas HOAc (up to 4 equiv) had no effect on the yield.^[34] Replacement of the catalyst precursor with $[\text{Ru}(\text{OAc})_2(p\text{-cymene})]$ (5 mol%) or the more expensive $[\{\text{RhCp}^*\text{Cl}_2\}_2]$ (2.5 mol%; $\text{Cp}^* = 1,2,3,4,5\text{-pentamethylcyclopentadienyl}$) gave lower yields (Table 1, entries 9 and 10, respectively). As solvent, *i*PrOH proved slightly superior to the THF/ H_2O system (Table 1, entries 7 and 8), presumably due to the formation of alkoxyboronates in situ, giving improved nucleophile solubility and slower protodeborylation.^[10] Accordingly, *i*PrOH was selected as the default solvent for the rest of our exploration of the reaction scope. All the arylation reactions occurred exclusively at C2. The desired reaction was not observed if the Ru catalyst, oxidant, or silver additive were excluded. Under the same conditions, arylation did not occur with indoles bearing oxygen-based directing groups, nor with a variety of other substrates commonly used in Ru-catalysed C–H arylation reactions (see the Supporting Information for further details). Thus, the pyrimidyl group seemed uniquely privileged under the conditions we explored.

Table 1. Selected results from optimization studies.^[a]

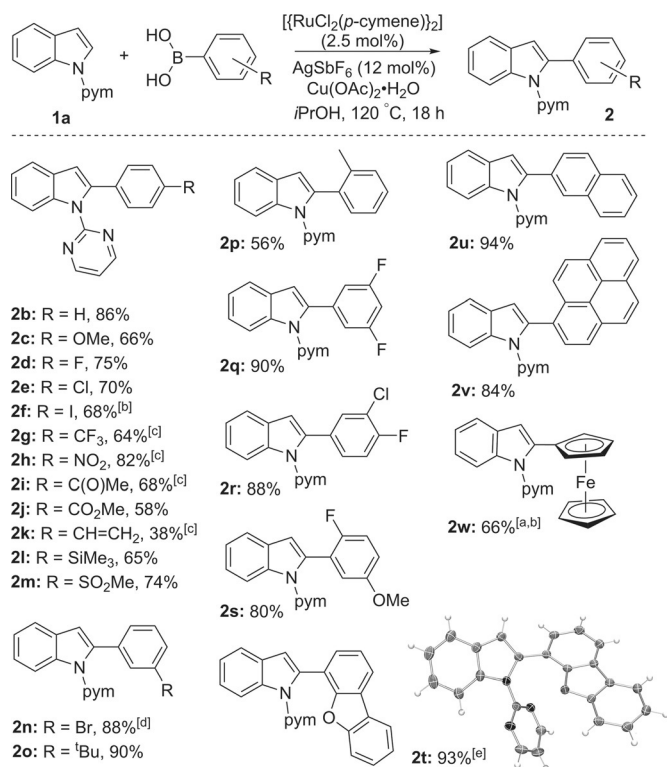


Entry	Catalyst [mol %]	Oxidant [equiv]	Additives [equiv]	Solvent	Yield ^[b] [%]
1	$[\{\text{RuCl}_2(p\text{-cymene})\}_2]$ (2.5)	Ag_2O (1.5)	AgSbF_6 (0.12)	THF	37 ^[c]
2	$[\{\text{RuCl}_2(p\text{-cymene})\}_2]$ (2.5)	$\text{Cu}(\text{OAc})_2 \cdot \text{H}_2\text{O}$ (1)	AgSbF_6 (0.12)	THF	64
3	$[\{\text{RuCl}_2(p\text{-cymene})\}_2]$ (2.5)	$\text{Cu}(\text{OAc})_2 \cdot \text{H}_2\text{O}$ (1)	AgSbF_6 (0.12)	THF	86
4	$[\{\text{RuCl}_2(p\text{-cymene})\}_2]$ (2.5)	$\text{Cu}(\text{OAc})_2 \cdot \text{H}_2\text{O}$ (0.5) O_2 (balloon)	AgSbF_6 (0.12) H_2O (3.7)	THF	56
5	$[\{\text{RuCl}_2(p\text{-cymene})\}_2]$ (2.5)	$\text{Cu}(\text{OAc})_2 \cdot \text{H}_2\text{O}$ (1)	AgSbF_6 (0.12) KOAc (1.0) H_2O (3.7)	THF	0
6	$[\{\text{RuCl}_2(p\text{-cymene})\}_2]$ (2.5)	$\text{Cu}(\text{OAc})_2 \cdot \text{H}_2\text{O}$ (1)	AgOAc (0.12) H_2O (3.7)	THF	0
7	$[\{\text{RuCl}_2(p\text{-cymene})\}_2]$ (2.5)	$\text{Cu}(\text{OCOCF}_3)_2$ (1)	AgSbF_6 (0.12)	<i>i</i> PrOH	89
8	$[\{\text{RuCl}_2(p\text{-cymene})\}_2]$ (2.5)	$\text{Cu}(\text{OAc})_2 \cdot \text{H}_2\text{O}$ (1)	AgSbF_6 (0.12)	<i>i</i> PrOH	98
9	$[\text{Ru}(\text{OAc})_2(p\text{-cymene})]$ (5)	$\text{Cu}(\text{OAc})_2 \cdot \text{H}_2\text{O}$ (1)	AgSbF_6 (0.12)	THF	53
10	$[\{\text{Cp}^*\text{RhCl}_2\}_2]$ (2.5)	$\text{Cu}(\text{OAc})_2 \cdot \text{H}_2\text{O}$ (1)	AgSbF_6 (0.12) H_2O (3.7)	THF	52

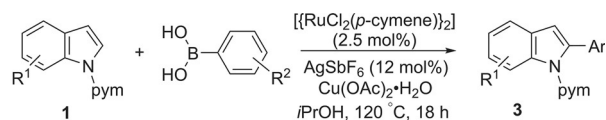
[a] **1a** (0.15 mmol), boronic acid (0.45 mmol), solvent (0.5 mL). [b] Yield was determined by ¹H NMR spectroscopic analysis with respect to 1,3,5-trimethoxybenzene (0.05 mmol), which was added after the end of the reaction. [c] Yield of the isolated product.

Substrate scope

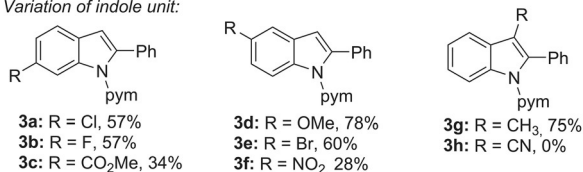
The reaction showed high tolerance towards a wide range of arylboronic acids, including those bearing nitro (**2h**), ketone (**2i**), alkenyl (**2k**), silyl (**2l**), sulfonyl (**2m**), ferrocenyl (**2w**), and halogen groups (Scheme 1). Tolerance of aryl iodides (**2f**) is both rare and complementary to their frequent use as oxidants/electrophiles in C–H arylation reactions. To the best of our knowledge, this C–H arylation of indoles is the first in which the C–I functionality is preserved. Reactions with 4-trifluoromethyl- and 4-acetylphenylboronic acids gave higher yields when *i*PrOH was replaced with the THF/ H_2O solvent system. Protected boronic acids,^[10,35] such as their pinacol boronate (-Bpin), *N*-methyliminodiacetyl boryl (-Bmida),^[36] or potassium trifluoroborate (- BF_3K)^[37] derivatives, were not effective under our conditions. This outcome is in line with the requirement for their prior hydrolysis and the rate acceleration observed under acidic conditions in related C–H arylation reactions.^[34] Various substituted indoles also selectively underwent the C–H arylation reaction (Scheme 2). Good yields were obtained with bromide and iodide groups on either or both coupling



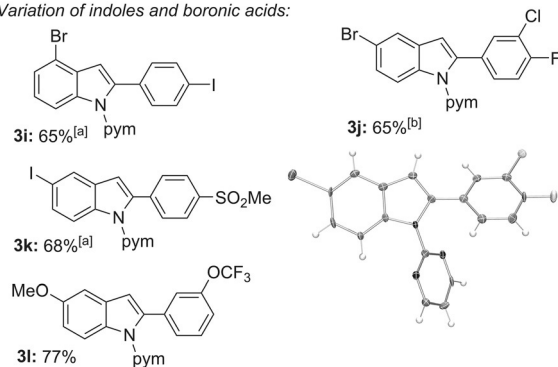
Scheme 1. Scope of the boronic acids in the Ru-catalysed indole C2–H arylation reaction (the yields given are for the isolated products). Conditions: **1a** (0.5 mmol), boronic acid (1.5 mmol), $[(\text{RuCl}_2(p\text{-cymene}))_2]$ (2.5 mol%), AgSbF_6 (12 mol%), $\text{Cu}(\text{OAc})_2 \cdot \text{H}_2\text{O}$ (0.5 mmol), and *i*PrOH (1.5 mL). [a] 2 mmol boronic acid was used. [b] $t = 4$ h, $T = 100^\circ\text{C}$. [c] Solvent system: THF (1.5 mL + 3.7 equiv water). [d] $t = 3$ h. [e] The crystal structure ellipsoids are shown at 50% probability.



Variation of indole unit:



Variation of indoles and boronic acids:

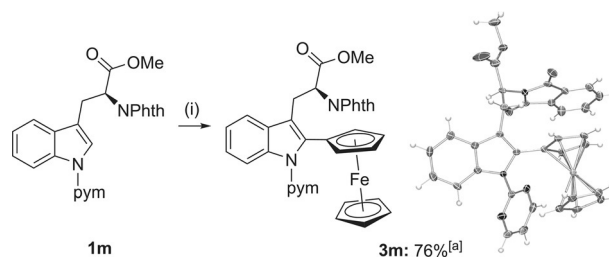


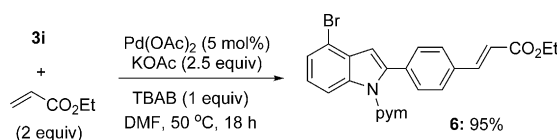
Scheme 4. Arylation of pyrrole derivatives. Reagents: **4** (0.5 mmol), boronic acid (1.5 mmol), $[(\text{RuCl}_2(p\text{-cymene}))_2]$ (2.5 mol%), AgSbF_6 (12 mol%), $\text{Cu}(\text{OAc})_2 \cdot \text{H}_2\text{O}$ (0.5 mmol), *i*PrOH (1.5 mL).

partners (Scheme 2; **3e** and **3i–k**). The 3-methylindole derivative **3g** was obtained in 75% yield, despite the proximate steric bulk, whereas indoles with 6-methoxycarbonyl (**3c**), 5-nitro (**3f**), and 3-cyano (**3h**) groups gave worse performance, hinting at the importance of the nucleophilicity of the indole unit. The protocol could further be extended to the phthaloyl-protected tryptophan derivative **1m**^[38] (Scheme 3). In addition to standard analysis by NMR spectroscopy and mass spectrometry, products **2t**, **3j**, and **3m** were characterised by X-ray crystallography studies.

Pyrroles also proved amenable to the arylation reaction with various boronic acids (Scheme 4). Substrate **4a** ($R^1 = \text{H}$) gave a separable mixture of mono- (**5a**) and diphenylated (**5a'**) products in a combined yield of 42%. The 2-ethylpyrrole derivatives **4b–d** afforded good-to-excellent yields, with arylation occurring exclusively at C2 for both electron-poor and electron-rich boronic acids to give products **5b–d**. 2-Methoxycarbonyl-substituted pyrrole **5e** was not formed, which is consistent with the nucleophilicity requirements of the indole substrates.

The iodide group of **3i** underwent selective and efficient Heck alkenylation, highlighting the potential for derivatisation





Scheme 5. Selective derivatisation of the aryl halide functionality. TBAB = tetrabutylammonium bromide.

of the newly installed aryl group whilst retaining an electrophilic coupling substrate on the indole (Scheme 5).

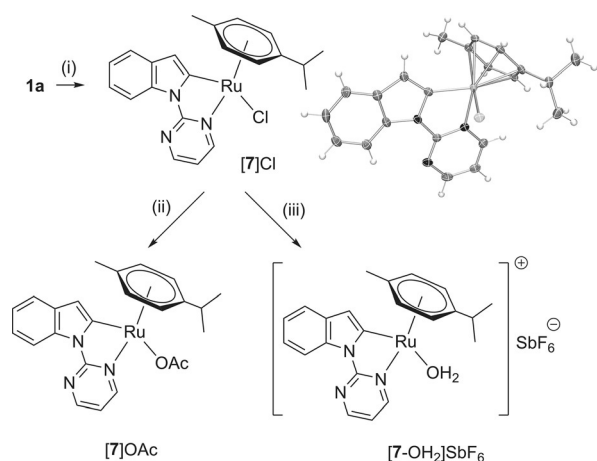
Mechanistic Considerations

Investigation of putative ruthenacyclic intermediates

We prepared the previously unreported complexes **[7]Cl**, **[7]OAc**, and **[7-OH₂]₂SbF₆** (Scheme 6)^[40] to probe the potential role of ruthenacyclic intermediates.^[15a,22,39] In addition to standard ¹H and ¹³C NMR spectroscopy and mass spectrometry, complex **[7]Cl** was characterised by means of X-Ray crystallography (see the Supporting Information for further details).

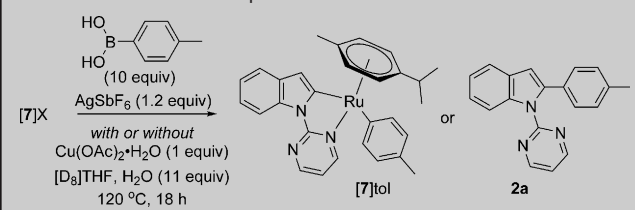
Replacing $[\{\text{RuCl}_2(p\text{-cymene})\}_2]$ with **[7]Cl**, **[7]OAc**, or **[7-OH₂]₂SbF₆** gave 86, 60, and 40% spectroscopic yields of **2b**, respectively, under the standard reaction conditions shown in Scheme 1. Thus, species **7** are either catalytically active or are converted into catalytically active species in situ (see below).

Species **[7]tol** was not observed on exposure of **[7]Cl**, **[7]OAc**, or **[7-OH₂]₂SbF₆** to 4-tolylboronic acid with or without $\text{Cu}(\text{OAc})_2 \cdot \text{H}_2\text{O}$ present (Table 2). Product **2a** formed in the absence of $\text{Cu}(\text{OAc})_2 \cdot \text{H}_2\text{O}$ from both **[7]OAc** and **[7-OH₂]₂SbF₆** (15% and trace yields, respectively), indicating that transmetalation and reductive elimination are possible for Ru^{II} species. These results complement the finding by Lan and co-workers that a Rh^{III}Cp* analogue of **[7]Cl** underwent transmetalation



Scheme 6. Preparation of ruthenacycles **[7]Cl**, **[7]OAc**, and **[7-OH₂]₂SbF₆**. Conditions: (i) $[\{\text{RuCl}_2(p\text{-cymene})\}_2]$ (0.5 equiv), MeOH, RT, 24 h, 78%; (ii) AgOAc (2.5 equiv), MTBE, RT, 24 h, 80%; (iii) AgSbF₆ (1.1 equiv), H₂O (6.9 equiv), [D₈]THF, RT. ORTEP representation of complex **[7]Cl**. Ellipsoids are drawn at the 50% probability level with the MeOH solvate omitted for clarity. MTBE = methyl *tert*-butyl ether.

Table 2. Transmetalation experiments.



Entry	Complex	Cu(OAc) ₂ ·H ₂ O	[7]tol	2a
1	[7]Cl	yes	–	–
2	[7]Cl	no	–	–
3	[7]OAc	yes	–	traces
4	[7]OAc	no	– ^[a]	15%
5	[7-OH₂]₂SbF₆	yes	–	traces
6	[7-OH₂]₂SbF₆	no	–	traces

[a] A symmetrical complex of the type $[\text{Ru}(p\text{-cymene})\text{X}_2]$ was observed by ¹H NMR spectroscopic analysis at the end of the reaction.^[41]

and reductive elimination with benzothiophene in the absence of an oxidant.^[9g] Traces of **2a** were also observed for both **[7]OAc** and **[7-OH₂]₂SbF₆** in the presence of $\text{Cu}(\text{OAc})_2 \cdot \text{H}_2\text{O}$. An intractable mixture of indole-containing species constituted the mass balance of these reactions.

Hydrogen–deuterium exchange studies

Compound **1a** gave no H/D exchange at either C2 or C3 in the presence of D₂O, catalytic $[\{\text{RuCl}_2(p\text{-cymene})\}_2]$, and AgSbF₆ (Table 3, entry 1) at 23 °C, although the ¹H NMR spectrum of the reaction mixture revealed the complete conversion of the catalyst precursor to ruthenacycle **[7-OD₂]₂SbF₆**. Substrate **1a** underwent significant C3–H/D and modest C2–H/D exchange when the same experiment was performed at 60 °C, again with the quantitative formation of **[7-OD₂]₂SbF₆** (Table 3, entry 2). On heating to 80 °C, only traces of **[7-OD₂]₂SbF₆** were observed, with the concomitant formation of uncoordinated *para*-cymene and 64% deuterium incorporation at C3 (Table 3, entry 3). On heating to 100 °C, no **[7-OD₂]₂SbF₆** remained and

Table 3. Hydrogen–deuterium exchange studies.

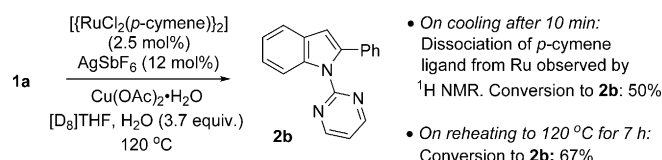
Entry	[7-OD₂]₂SbF₆	T [°C]	C2–H/C2–D	C3–H/C3–D
1	yes	23	100:0	100:0
2 ^[a]	yes	60	94:6	69:31
3	traces ^[b]	80	85:15	36:64
4	no ^[b]	100	75:25	32:68
5 ^[a]	no	120	40:60	41:59
6 ^[c]	–	120	85:15	32:68
7 ^[d]	–	120	100:0	100:0

[a] Average of two runs. [b] Free *para*-cymene observed by ¹H NMR spectroscopic analysis. [c] $[\{\text{RuCl}_2(p\text{-cymene})\}_2]$ was excluded. [d] $[\{\text{RuCl}_2(p\text{-cymene})\}_2]$ and AgSbF₆ were excluded.

uncoordinated *para*-cymene was observed, but C–H/D exchange increased only incrementally (Table 3, entry 4). Finally, heating to 120 °C gave no observable Ru–cymene complexes, with **1a** showing 60% C2–H/D exchange (Table 3, entry 5). Thus, the greatest degree of reversible C2–H activation occurred after complete loss of *para*-cymene from the Ru centre. When $[\{\text{RuCl}_2(p\text{-cymene})\}_2]$ was excluded from the reaction mixture, 15% C2–H/D and 68% C3–H/D exchange was observed at 120 °C. Kanai and co-workers found that simple Lewis acids, such as $\text{Sc}(\text{OTf})_3$, promote similar levels of C3-selective exchange for **1a**,^[29f] which we attribute to the presence of Ag^+ ions in our reaction (Table 3, entries 6 and 7). Analogous experiments with *N*-acetylindole or 1-(pyrimidin-2-yl)benzimidazole did not give C2–H/D exchange, which is consistent with the requirement for nucleophilicity of the heteroarene and the inability of the acetyl group to effect C2 arylation under our catalytic conditions (see Figure S1 in the Supporting Information).

Importance of the *para*-cymene ligand

Cymene-ligated Ru complexes have frequently been invoked as catalytic intermediates in C–H functionalisation reactions. For the phenylation of **1a** under our conditions, complete loss of the cymene ligand from the Ru coordination sphere could be confirmed by ¹H NMR spectroscopic analysis on cooling the reaction mixture to room temperature after just 10 minutes (Scheme 7). Conversion into **2b** was 50% at this point. The reaction mixture was reheated to 120 °C for a further 7 hours, after which the conversion into **2b** increased to 67%, with cymene remaining uncoordinated.



Scheme 7. The catalytic phenylation of **1a** continued despite the loss of the *para*-cymene ligand from the Ru centre.

Discussion of the mechanism

We suggest that although initial ruthenation of the indole–pyrimidine unit occurs easily under our conditions, $[\text{7-OH}_2]\text{SbF}_6$ acts as a precursor rather than as a true catalytic intermediate. The inferior performance of several other transition-metal salts in our optimisation studies (see Table S2 in the Supporting Information) may indicate that the formation of such ruthenacycles at the beginning of the reaction—but prior to the catalysis—is advantageous. Facile exchange of the *para*-cymene ligand in ruthenacycles in the presence of excess nitrogen donors is well documented. For example, Jutand and co-workers reported that complexes of the type $[\text{Ru}\{\kappa^2\text{-C,N-(2-phenylpyridine)}\}(\text{MeCN})_2]\text{OPiv}$ (OPiv = dimethylpropanoate) formed easily in the presence of excess MeCN, but were catalytically inactive in the arylation of phenylpyridines with aryl halides.^[34]

We propose that under our catalytic conditions the pyrimidine groups of substrates **1** or **4** displace the *para*-cymene ligand of cyclometalated species **7** and on-cycle intermediates may have more than one pyrimidyl heteroarene ligand in the ruthenium coordination sphere. Thus, **1** or **4** could act as spectator ligands in the cycle prior to their own C2 ruthenation. This outcome would be consistent with the poor performance of complexes $[\text{7}]\text{Cl}$, $[\text{7}]\text{OAc}$, and $[\text{7-OH}_2]\text{SbF}_6$ in attempts to induce transmetalation and reductive elimination in the absence of unmetalated substrates **1** (Table 2). It is also in agreement with the need for a sufficiently strongly σ -donating directing group, hence why oxygen-based directing groups^[42] proved ineffective.

With respect to the on-cycle C–H activation, the following observations suggest electrophilic attack by the ruthenium centre on the heteroarene: 1) the significant increase in efficiency when silver additives are used, 2) higher yields with electron-rich substrates, 3) failure of 1-(pyrimidin-2-yl)benzimidazole to undergo C–H/D exchange or C2 arylation, 4) that using Ag_2O as an oxidant gives **2a** in a moderate yield (Table 1, entry 1) in the absence of carboxylates, 5) that C–H ruthenation of **1a** occurred in the absence of carboxylates during H/D exchange experiments (Table 3), suggesting the plausibility of an analogous on-cycle ruthenation reaction. In addition, KOAc had a detrimental effect on the catalysis (Table 1, entry 5) and no significant effect on the rate of C2–H/D exchange, whereas $\text{Cu}(\text{OAc})_2$ inhibited the rate of C2–H/D exchange (see Table S7 in the Supporting Information).

Therefore, our proposed mechanism is complementary to the carboxylate-assisted Ru-catalysed C–H functionalisation reactions^[22] studied in depth by the groups of Ackermann^[43] and Dixneuf,^[34] in which aryl halide coupling partners were used. This mechanism also agrees with recent mechanistic proposals for related reactions in which electrophilic cationic Ru^{II} intermediates have been suggested.^[44]

Conclusion

We have developed an oxidative, Ru-catalysed C2–H selective arylation reaction of indoles and pyrroles with boronic acids as the aryl source. The reaction shows high functional-group tolerance for both coupling partners, including halides, thus preserving the scope of the reaction for selective subsequent manipulation of the products. *para*-Cymene-ligated ruthenacycles give, at best, poor yields in attempts at transmetalation, but lose the *para*-cymene ligand under our catalytic conditions; therefore, these complexes are unlikely on-cyclic intermediates. Efforts to broaden this methodology to other transformations and substrates are ongoing in our laboratory.

Experimental Section

General arylation procedure

$[\{\text{RuCl}_2(p\text{-cymene})\}_2]$ (7.6 mg, 0.013 mmol, 2.5 mol%), substrate **1** or **4** (0.5 mmol), boronic acid (1.5 mmol), $\text{Cu}(\text{OAc})_2\cdot\text{H}_2\text{O}$ (100 mg, 0.50 mmol), and AgSbF_6 (21 mg, 0.06 mmol, 12 mol%) were added

to a microwave vial (20 mL) equipped with a magnetic stirrer bar. The vial was evacuated and backfilled with argon. *i*PrOH (1.5 mL) was added by syringe, the vial sealed, and the mixture heated to 120 °C for 18 h with vigorous stirring. The reaction mixture was cooled to room temperature and loaded directly onto silica gel. The product was isolated by flash column chromatography (eluent = EtOAc/pentane).

Acknowledgements

We are grateful to the Swedish Research Council (Vetenskapsrådet) for generous funding and Dr. Emilien Demory (Uppsala University) for help with the preparation of the starting materials. We also thank Professor Lars Engman, Dr. Eszter Borbas, and Dr. Johanna Larsson for proofreading of the manuscript.

Keywords: catalysis · C–H activation · heterocycles · reaction mechanisms · ruthenium

- [1] *Handbook of C–H Transformations: Applications in Organic Synthesis* (Ed.: G. Dyker), Wiley-VCH, Weinheim, **2005**.
- [2] For selected reviews, see: a) J. Wencel-Delord, F. Glorius, *Nat. Chem.* **2013**, *5*, 369–375; b) L. G. Mercier, M. Leclerc, *Acc. Chem. Res.* **2013**, *46*, 1597–1605; c) J. Yamaguchi, A. D. Yamaguchi, K. Itami, *Angew. Chem.* **2012**, *124*, 9092–9142; *Angew. Chem. Int. Ed.* **2012**, *51*, 8960–9009; d) T. Brückl, R. D. Baxter, Y. Ishihara, P. S. Baran, *Acc. Chem. Res.* **2012**, *45*, 826–839; e) D. Y. K. Chen, S. W. Youn, *Chem. Eur. J.* **2012**, *18*, 9452–9474.
- [3] a) L. Ackermann, R. Vicente, A. R. Kapdi, *Angew. Chem.* **2009**, *121*, 9976–10011; *Angew. Chem. Int. Ed.* **2009**, *48*, 9792–9826; b) M. Bandini, A. Eichholzer, *Angew. Chem.* **2009**, *121*, 9786–9824; *Angew. Chem. Int. Ed.* **2009**, *48*, 9608–9644; c) E. M. Beck, M. J. Gaunt, *Top. Curr. Chem.* **2010**, *292*, 85–121; d) G. Broggini, E. M. Beccalli, A. Fasana, S. Gazzola, *Beilstein J. Org. Chem.* **2012**, *8*, 1730–1746; e) N. Lebrasseur, I. Larrosa in *Advances in Heterocyclic Chemistry, Vol. 105* (Ed. K. Alan), Academic Press, **2012**, Chapter 4, pp. 309–351.
- [4] M. Ishikura, K. Yamada, *Nat. Prod. Rep.* **2009**, *26*, 803–852.
- [5] a) B. L. Flynn, E. Hamel, M. K. Jung, *J. Med. Chem.* **2002**, *45*, 2670–2673; b) R. Gastpar, M. Goldbrunner, D. Marko, E. von Angerer, *J. Med. Chem.* **1998**, *41*, 4965–4972; c) N. Kaushik, N. Kaushik, P. Attri, N. Kumar, C. Kim, A. Verma, E. Choi, *Molecules* **2013**, *18*, 6620–6662.
- [6] For Pd-catalysed examples, see: a) J. Feng, G. Lu, M. Lv, C. Cai, *J. Organomet. Chem.* **2014**, *761*, 28–31; b) S. Preciado, L. Mendive-Tapia, F. Albericio, R. Lavilla, *J. Org. Chem.* **2013**, *78*, 8129–8135; c) S. Islam, I. Larrosa, *Chem. Eur. J.* **2013**, *19*, 15093–15096; d) K.-J. Wu, L.-X. Dai, S.-L. You, *Org. Lett.* **2012**, *14*, 3772–3775; e) L.-L. Sun, Z.-Y. Liao, R.-Y. Tang, C.-L. Deng, X.-G. Zhang, *J. Org. Chem.* **2012**, *77*, 2850–2856; f) L. Wang, W.-b. Yi, C. Cai, *Chem. Commun.* **2011**, *47*, 806–808; g) E. T. Nadres, A. Lazareva, O. Daugulis, *J. Org. Chem.* **2011**, *76*, 471–483; h) L. Joucla, N. Batail, L. Djakovitch, *Adv. Synth. Catal.* **2010**, *352*, 2929–2936; i) J. Roger, H. Doucet, *Adv. Synth. Catal.* **2009**, *351*, 1977–1990; j) N. Lebrasseur, I. Larrosa, *J. Am. Chem. Soc.* **2008**, *130*, 2926–2927; k) X. Wang, D. V. Gribkov, D. Sames, *J. Org. Chem.* **2007**, *72*, 1476–1479; l) B. B. Touré, B. S. Lane, D. Sames, *Org. Lett.* **2006**, *8*, 1979–1982; m) B. S. Lane, M. A. Brown, D. Sames, *J. Am. Chem. Soc.* **2005**, *127*, 8050–8057; n) B. S. Lane, D. Sames, *Org. Lett.* **2004**, *6*, 2897–2900; for a Rh-catalysed example, see: o) X. Wang, B. S. Lane, D. Sames, *J. Am. Chem. Soc.* **2005**, *127*, 4996–4997; for Ru-catalysed examples, see: p) L. A. Adrio, J. Gimeno, C. Vicent, *Chem. Commun.* **2013**, *48*, 8320–8322; q) B. Li, C. B. Bheeter, C. Darcel, P. H. Dixneuf, *ACS Catal.* **2011**, *1*, 1221–1224; r) L. Ackermann, A. V. Lygin, *Org. Lett.* **2011**, *13*, 3332–3335; for a Cu-catalysed example, see: s) H.-Q. Do, O. Daugulis, *Chem. Commun.* **2009**, 6433–6435.
- [7] a) A. M. Wagner, M. S. Sanford, *Org. Lett.* **2011**, *13*, 288–291; b) R. J. Phipps, N. P. Grimster, M. J. Gaunt, *J. Am. Chem. Soc.* **2008**, *130*, 8172–8174; c) N. R. Deprez, D. Kalyani, A. Krause, M. S. Sanford, *J. Am. Chem. Soc.* **2006**, *128*, 4972–4973.
- [8] For examples using silanes, see: a) M.-Z. Lu, P. Lu, Y.-H. Xu, T.-P. Loh, *Org. Lett.* **2014**, *16*, 2614–2617; b) Z. Liang, B. Yao, Y. Zhang, *Org. Lett.* **2010**, *12*, 3185–3187; for a decarbonylative approach, see: c) L. Zhang, X. Xue, C. Xu, Y. Pan, G. Zhang, L. Xu, H. Li, Z. Shi, *ChemCatChem* **2014**, *6*, 3069–3074; for desulfurative approaches, see: d) T. Miao, P. Li, G.-W. Wang, L. Wang, *Chem. Asian J.* **2013**, *8*, 3185–3190; e) M. Wu, J. Luo, F. Xiao, S. Zhang, G.-J. Deng, H.-A. Luo, *Adv. Synth. Catal.* **2012**, *354*, 335–340.
- [9] For selected reviews, see: a) S. A. Girard, T. Knauber, C.-J. Li, *Angew. Chem.* **2014**, *126*, 76–103; *Angew. Chem. Int. Ed.* **2014**, *53*, 74–100; b) D.-G. Yu, B.-J. Li, Z.-J. Shi, *Tetrahedron* **2012**, *68*, 5130–5136; c) J. Wencel-Delord, C. Nimphius, F. W. Patureau, F. Glorius, *Angew. Chem.* **2012**, *124*, 2290–2294; *Angew. Chem. Int. Ed.* **2012**, *51*, 2247–2251; d) D. Zhao, J. You, C. Hu, *Chem. Eur. J.* **2011**, *17*, 5466–5492; e) C. S. Yeung, V. M. Dong, *Chem. Rev.* **2011**, *111*, 1215–1292; f) S. H. Cho, J. Y. Kim, J. Kwak, S. Chang, *Chem. Soc. Rev.* **2011**, *40*, 5068–5083; for Rh-catalysed examples with indoles, see: g) X. Qin, H. Liu, D. Qin, Q. Wu, J. You, D. Zhao, Q. Guo, X. Huang, J. Lan, *Chem. Sci.* **2013**, *4*, 1964–1969; for Pd-catalysed examples with indoles, see: h) D. G. Pintori, M. F. Greaney, *J. Am. Chem. Soc.* **2011**, *133*, 1209–1211; i) X. Gong, G. Song, H. Zhang, X. Li, *Org. Lett.* **2011**, *13*, 1766–1769; j) S. Potavathi, K. C. Pereira, S. I. Gorelsky, A. Pike, A. P. LeBris, B. DeBoef, *J. Am. Chem. Soc.* **2010**, *132*, 14676–14681; k) S. Potavathi, A. S. Dumas, T. A. Dwight, G. R. Naumiec, J. M. Hammann, B. DeBoef, *Tetrahedron Lett.* **2008**, *49*, 4050–4053; l) D. R. Stuart, E. Villemure, K. Fagnou, *J. Am. Chem. Soc.* **2007**, *129*, 12072–12073; m) D. R. Stuart, K. Fagnou, *Science* **2007**, *316*, 1172–1175; n) T. Itahara, *J. Org. Chem.* **1985**, *50*, 5272–5275; o) T. Itahara, *J. Chem. Soc. Chem. Commun.* **1981**, 254–255; p) A. N. Campbell, E. B. Meyer, S. S. Stahl, *Chem. Commun.* **2011**, *47*, 10257–10259; q) C.-L. Sun, B.-J. Li, Z.-J. Shi, *Chem. Commun.* **2010**, *46*, 677–685; for a Cu-catalysed example with indoles, see: r) M. Nishino, K. Hirano, T. Satoh, M. Miura, *Angew. Chem.* **2012**, *124*, 7099–7103; *Angew. Chem. Int. Ed.* **2012**, *51*, 6993–6997.
- [10] D. G. Hall in *Structure, Properties, and Preparation of Boronic Acid Derivatives, Vol. 1*, Wiley-VCH, Weinheim, **2011**, pp. 1–133.
- [11] For Pd-catalysed examples using indole substrates, see: a) S. Kirchberg, R. Fröhlich, A. Studer, *Angew. Chem.* **2009**, *121*, 4299–4302; *Angew. Chem. Int. Ed.* **2009**, *48*, 4235–4238; b) R. Y. Nimje, M. V. Leskinen, P. M. Pihko, *Angew. Chem.* **2013**, *125*, 4918–4922; *Angew. Chem. Int. Ed.* **2013**, *52*, 4818–4822; c) S.-D. Yang, C.-L. Sun, Z. Fang, B.-J. Li, Y.-Z. Li, Z.-J. Shi, *Angew. Chem.* **2008**, *120*, 1495–1498; *Angew. Chem. Int. Ed.* **2008**, *47*, 1473–1476; d) L. Zhang, P. Li, C. Liu, J. Yang, M. Wang, L. Wang, *Catal. Sci. Technol.* **2014**, *4*, 1979–1988; e) L. Yang, L. Luo, S. Zhang, X. Su, J. Lan, C.-T. Chen, J. You, *Chem. Commun.* **2010**, *46*, 3938–3940; f) Y. Huang, T. Ma, P. Huang, D. Wu, Z. Lin, R. Cao, *ChemCatChem* **2013**, *5*, 1877–1883; g) J. Ruiz-Rodríguez, F. Albericio, R. Lavilla, *Chem. Eur. J.* **2010**, *16*, 1124–1127; h) J. Zhao, Y. Zhang, K. Cheng, *J. Org. Chem.* **2008**, *73*, 7428–7431; i) P. Kannaboina, K. Anilkumar, S. Aravinda, R. A. Vishwakarma, P. Das, *Org. Lett.* **2013**, *15*, 5718–5721.
- [12] For other Pd-catalysed examples, see: a) S. Kirchberg, S. Tani, K. Ueda, J. Yamaguchi, A. Studer, K. Itami, *Angew. Chem.* **2011**, *123*, 2435–2439; *Angew. Chem. Int. Ed.* **2011**, *50*, 2387–2391; b) M. Koley, N. Dastbaravard, M. Schnürch, M. D. Mihovilovic, *ChemCatChem* **2012**, *4*, 1345–1352; c) J. Guan, G.-J. Wu, F.-S. Han, *Chem. Eur. J.* **2014**, *20*, 3301–3305; d) R. Joncour, N. Susperregui, N. Pinaud, K. Miqueu, E. Fouquet, J.-M. Sotiropoulos, F.-X. Felpin, *Chem. Eur. J.* **2013**, *19*, 9291–9296; e) S. Ranjit, X. Liu, *Chem. Eur. J.* **2011**, *17*, 1105–1108; f) K. M. Engle, P. S. Thuy-Boun, M. Dang, J.-Q. Yu, *J. Am. Chem. Soc.* **2011**, *133*, 18183–18193; g) X. Meng, S. Kim, *J. Org. Chem.* **2013**, *78*, 11247–11254; h) X. Chen, C. E. Goodhue, J.-Q. Yu, *J. Am. Chem. Soc.* **2006**, *128*, 12634–12635; i) R. Giri, N. Maugel, J.-J. Li, D.-H. Wang, S. P. Breazzano, L. B. Saunders, J.-Q. Yu, *J. Am. Chem. Soc.* **2007**, *129*, 3510–3511; j) T. Nishikata, A. R. Abela, S. Huang, B. H. Lipshutz, *J. Am. Chem. Soc.* **2010**, *132*, 4978–4979; k) P. S. Thuy-Boun, G. Villa, D. Dang, P. Richardson, S. Su, J.-Q. Yu, *J. Am. Chem. Soc.* **2013**, *135*, 17508–17513; l) D.-H. Wang, M. Wasa, R. Giri, J.-Q. Yu, *J. Am. Chem. Soc.* **2008**, *130*, 7190–7191; m) K. S. L. Chan, M. Wasa, L. Chu, B. N. Laforteza, M. Miura, J.-Q. Yu, *Nat. Chem.* **2014**, *6*, 146–150; n) Y. Wei, J. Kan, M. Wang, W. Su, M. Hong, *Org. Lett.* **2009**, *11*, 3346–3349; o) J. Feng, G. Lu, M. Lv, C. Cai, *Synlett* **2013**, *24*, 2153–2159; p) J.-H. Chu, S.-L. Tsai, M.-J. Wu, *Synthesis* **2009**, 3757–3764; q) J.-H. Chu, C.-C.

- Wu, D.-H. Chang, Y.-M. Lee, M.-J. Wu, *Organometallics* **2013**, *32*, 272–282.
- [13] For a Rh-catalysed example with indoles, see: J. Zheng, Y. Zhang, S. Cui, *Org. Lett.* **2014**, *16*, 3560–3563.
- [14] For Cu-catalysed examples, see: a) I. Ban, T. Sudo, T. Taniguchi, K. Itami, *Org. Lett.* **2008**, *10*, 3607–3609; b) O. Baslé, C.-J. Li, *Org. Lett.* **2008**, *10*, 3661–3663; c) M. Shang, S.-Z. Sun, H.-X. Dai, J.-Q. Yu, *Org. Lett.* **2014**, *16*, 5666.
- [15] a) P. B. Arockiam, C. Bruneau, P. H. Dixneuf, *Chem. Rev.* **2012**, *112*, 5879–5918; b) P. M. Liu, C. G. Frost, *Org. Lett.* **2013**, *15*, 5862–5865; c) V. P. Mehta, J.-A. García-López, M. F. Greaney, *Angew. Chem. Int. Ed.* **2014**, *53*, 1529–1533.
- [16] For Ru-catalysed C–H functionalisation with unusual *meta* selectivity, see: a) N. Hofmann, L. Ackermann, *J. Am. Chem. Soc.* **2013**, *135*, 5877–5884; b) O. Saidi, J. Marafie, A. E. W. Ledger, P. M. Liu, M. F. Mahon, G. Kociok-Köhn, M. K. Whittlesey, C. G. Frost, *J. Am. Chem. Soc.* **2011**, *133*, 19298–19301; c) W. R. Reynolds, P. M. Liu, G. Kociok-Köhn, C. G. Frost, *Synlett* **2013**, *24*, 2687–2690.
- [17] a) F. Kakiuchi, S. Kan, K. Igi, N. Chatani, S. Murai, *J. Am. Chem. Soc.* **2003**, *125*, 1698–1699; b) F. Kakiuchi, Y. Matsuura, S. Kan, N. Chatani, *J. Am. Chem. Soc.* **2005**, *127*, 5936–5945.
- [18] S. J. Pastine, D. V. Gribkov, D. Sames, *J. Am. Chem. Soc.* **2006**, *128*, 14220–14221.
- [19] a) M. Schwarz, N. Dastbaravardeh, K. Kirchner, M. Schnürch, M. Mihovilovic, *Monatsh. Chem.* **2013**, *144*, 539–552; b) N. Dastbaravardeh, M. Schnürch, M. D. Mihovilovic, *Org. Lett.* **2012**, *14*, 1930–1933; c) N. Dastbaravardeh, K. Kirchner, M. Schnürch, M. D. Mihovilovic, *J. Org. Chem.* **2013**, *78*, 658–672.
- [20] a) H. Li, W. Wei, Y. Xu, C. Zhang, X. Wan, *Chem. Commun.* **2011**, *47*, 1497–1499; b) R. K. Chinnagolla, M. Jeganmohan, *Org. Lett.* **2012**, *14*, 5246–5249; c) R. K. Chinnagolla, M. Jeganmohan, *Chem. Commun.* **2014**, *50*, 2442–2444; d) H. Li, Y. Xu, E. Shi, W. Wei, X. Suo, X. Wan, *Chem. Commun.* **2011**, *47*, 7880–7882.
- [21] For selected recent examples, see: a) L. Ackermann, L. Wang, A. V. Lygin, *Chem. Sci.* **2012**, *3*, 177–180; b) V. Lanke, K. R. Prabhu, *Org. Lett.* **2013**, *15*, 2818–2821; c) B. Li, J. Ma, W. Xie, H. Song, S. Xu, B. Wang, *J. Org. Chem.* **2013**, *78*, 9345–9353; d) L.-Q. Zhang, S. Yang, X. Huang, J. You, F. Song, *Chem. Commun.* **2013**, *49*, 8830–8832; e) T. Ueyama, S. Mochida, T. Fukutani, K. Hirano, T. Satoh, M. Miura, *Org. Lett.* **2011**, *13*, 706–708; f) V. Lanke, K. Ramaiah Prabhu, *Org. Lett.* **2013**, *15*, 6262–6265; g) M. C. Reddy, M. Jeganmohan, *Org. Lett.* **2014**, *16*, 4866–4869; h) M.-L. Louillat, A. Biafora, F. Legros, F. W. Patureau, *Angew. Chem.* **2014**, *126*, 3573–3577; *Angew. Chem. Int. Ed.* **2014**, *53*, 3505–3509; i) K. S. Singh, P. H. Dixneuf, *Organometallics* **2012**, *31*, 7320–7323; j) J. Li, C. Kornhaas, L. Ackermann, *Chem. Commun.* **2012**, *48*, 11343–11345; k) A. Biafora, F. W. Patureau, *Synlett* **2014**, *25*, 2525–2530.
- [22] For a review of the role of carboxylates in C–H functionalisation, see: L. Ackermann, *Chem. Rev.* **2011**, *111*, 1315–1345.
- [23] A single, low-yielding Ru⁰-catalysed example has recently been reported: Y. Zhao, V. Snieckus, *Adv. Synth. Catal.* **2014**, *356*, 1527–1532.
- [24] L. Ackermann, A. V. Lygin, *Org. Lett.* **2012**, *14*, 764–767.
- [25] For reviews on removable directing groups, see: a) G. Rousseau, B. Breit, *Angew. Chem.* **2011**, *123*, 2498–2543; *Angew. Chem. Int. Ed.* **2011**, *50*, 2450–2494; b) C. Wang, Y. Huang, *Synlett* **2013**, *24*, 145–149.
- [26] a) J. Chen, Q. Pang, Y. Sun, X. Li, *J. Org. Chem.* **2011**, *76*, 3523–3526; b) W. Song, L. Ackermann, *Chem. Commun.* **2013**, *49*, 6638–6640.
- [27] Cu-catalysed examples: a) X. Kou, M. Zhao, X. Qiao, Y. Zhu, X. Tong, Z. Shen, *Chem. Eur. J.* **2013**, *19*, 16880–16886; b) M. Nishino, K. Hirano, T. Satoh, M. Miura, *Angew. Chem.* **2012**, *124*, 7099–7103; *Angew. Chem. Int. Ed.* **2012**, *51*, 6993–6997; c) R. Odani, M. Nishino, K. Hirano, T. Satoh, M. Miura, *Heterocycles* **2014**, *88*, 595–602; d) C. Pan, H. Jin, P. Xu, X. Liu, Y. Cheng, C. Zhu, *J. Org. Chem.* **2013**, *78*, 9494–9498; e) H. Xu, X. Qiao, S. Yang, Z. Shen, *J. Org. Chem.* **2014**, *79*, 4414–4422.
- [28] Pd-catalysed examples: a) C. Pan, H. Jin, X. Liu, Y. Cheng, C. Zhu, *Chem. Commun.* **2013**, *49*, 2933–2935; b) Z. Wang, F. Song, Y. Zhao, Y. Huang, L. Yang, D. Zhao, J. Lan, J. You, *Chem. Eur. J.* **2012**, *18*, 16616–16620; c) S. Xu, X. Huang, X. Hong, B. Xu, *Org. Lett.* **2012**, *14*, 4614–4617; d) X.-B. Yan, Y.-W. Shen, D.-Q. Chen, P. Gao, Y.-X. Li, X.-R. Song, X.-Y. Liu, Y.-M. Liang, *Tetrahedron* **2014**, *70*, 7490–7495; e) W. Zhou, P. Li, Y. Zhang, L. Wang, *Adv. Synth. Catal.* **2013**, *355*, 2343–2352.
- [29] Co-catalysed examples: a) Z. Ding, N. Yoshikai, *Beilstein J. Org. Chem.* **2012**, *8*, 1536–1542; b) Z. Ding, N. Yoshikai, *Angew. Chem.* **2012**, *124*, 4776–4779; *Angew. Chem. Int. Ed.* **2012**, *51*, 4698–4701; c) B. Punjji, W. Song, G. A. Shevchenko, L. Ackermann, *Chem. Eur. J.* **2013**, *19*, 10605–10610; d) W. Song, L. Ackermann, *Angew. Chem.* **2012**, *124*, 8376–8379; *Angew. Chem. Int. Ed.* **2012**, *51*, 8251–8254; e) B. Sun, T. Yoshino, S. Matsunaga, M. Kanai, *Adv. Synth. Catal.* **2014**, *356*, 1491–1495; f) T. Yoshino, H. Ikemoto, S. Matsunaga, M. Kanai, *Chem. Eur. J.* **2013**, *19*, 9142–9146.
- [30] Rh-catalysed examples: a) B. Gong, J. Shi, X. Wang, Y. Yan, Q. Li, Y. Meng, H. E. Xu, W. Yi, *Adv. Synth. Catal.* **2014**, *356*, 137–143; b) X. Hong, H. Wang, G. Qian, Q. Tan, B. Xu, *J. Org. Chem.* **2014**, *79*, 3228–3237; c) K. Parthasarathy, A. R. Azcargorta, Y. Cheng, C. Bolm, *Org. Lett.* **2014**, *16*, 2538–2541; d) V. P. Reddy, R. Qiu, T. Iwasaki, N. Kambe, *Org. Lett.* **2013**, *15*, 1290–1293; e) J. Ryu, K. Shin, S. H. Park, J. Y. Kim, S. Chang, *Angew. Chem.* **2012**, *124*, 10042–10046; *Angew. Chem. Int. Ed.* **2012**, *51*, 9904–9908; f) J. Shi, G. Zhao, X. Wang, H. E. Xu, W. Yi, *Org. Biomol. Chem.* **2014**, *12*, 6831–6836; g) J. Shi, B. Zhou, Y. Yang, Y. Li, *Org. Biomol. Chem.* **2012**, *10*, 8953–8955; h) Z. Shi, M. Bouladakis-Arapinis, F. Glorius, *Chem. Commun.* **2013**, *49*, 6489–6491; i) H. Wang, N. Schroeder, F. Glorius, *Angew. Chem.* **2013**, *125*, 5495–5499; *Angew. Chem. Int. Ed.* **2013**, *52*, 5386–5389; j) F. Xie, Z. Qi, S. Yu, X. Li, *J. Am. Chem. Soc.* **2014**, *136*, 4780–4787; k) S. Yu, X. Li, *Org. Lett.* **2014**, *16*, 1200–1203; l) M. Nonoyama, K. Nakajima, *Polyhedron* **1998**, *18*, 533–543; m) J. Qi, L. Huang, Z. Wang, H. Jiang, *Org. Biomol. Chem.* **2013**, *11*, 8009–8013; see also refs. [8a, 8c, 9g].
- [31] For a Ru-catalysed example, see: J. Pospech, A. Tlili, A. Spannenberg, H. Neumann, M. Beller, *Chem. Eur. J.* **2014**, *20*, 3135–3141. See also refs. [6f] and [30m].
- [32] For a metal-free functionalisation, see: H.-H. Liu, Y. Wang, G. Deng, L. Yang, *Adv. Synth. Catal.* **2013**, *355*, 3369–3374.
- [33] I. Özdemir, S. Demir, B. Çetinkaya, C. Gourlaouen, F. Maseras, C. Bruneau, P. H. Dixneuf, *J. Am. Chem. Soc.* **2008**, *130*, 1156–1157.
- [34] For studies on the effect of HOAc in related C–H arylation reactions with aryl halides, see: a) I. Fabre, N. von Wolff, G. Le Duc, E. Ferrer Flegeau, C. Bruneau, P. H. Dixneuf, A. Jutand, *Chem. Eur. J.* **2013**, *19*, 7595–7604; b) E. Ferrer Flegeau, C. Bruneau, P. H. Dixneuf, A. Jutand, *J. Am. Chem. Soc.* **2011**, *133*, 10161–10170.
- [35] A. J. Lennox, G. C. Lloyd-Jones, *Chem. Soc. Rev.* **2014**, *43*, 412–443.
- [36] a) G. R. Dick, D. M. Knapp, E. P. Gillis, M. D. Burke, *Org. Lett.* **2010**, *12*, 2314–2317; b) E. P. Gillis, M. D. Burke, *J. Am. Chem. Soc.* **2007**, *129*, 6716–6717; c) E. P. Gillis, M. D. Burke, *J. Am. Chem. Soc.* **2008**, *130*, 14084–14085; d) E. P. Gillis, M. D. Burke, *Aldrichimica Acta* **2009**, *42*, 17–27; e) D. M. Knapp, E. P. Gillis, M. D. Burke, *J. Am. Chem. Soc.* **2009**, *131*, 6961–6963; f) S. J. Lee, K. C. Gray, J. S. Paek, M. D. Burke, *J. Am. Chem. Soc.* **2008**, *130*, 466–468; g) E. M. Woerly, J. Roy, M. D. Burke, *Nat. Chem.* **2014**, *6*, 484–491.
- [37] G. A. Molander, N. Ellis, *Acc. Chem. Res.* **2007**, *40*, 275–286.
- [38] The *N*-Boc-protected analogue of **1m** did not give the desired arylated product; for a review of amino acid protecting groups, see: A. Idro-Llobet, M. Álvarez, F. Alberico, *Chem. Rev.* **2009**, *109*, 2455–2504.
- [39] B. Li, T. Roisnel, C. Darcel, P. H. Dixneuf, *Dalton Trans.* **2012**, *41*, 10934–10937.
- [40] For recently reported Rh and Pd analogues, see refs. [9g] and [30l], respectively; the synthesis of an indolyl ruthenacycle with an oxygen-based directing group has recently been reported as unsuccessful, see ref. [21c].
- [41] D. A. Tocher, R. O. Gould, T. A. Stephenson, M. A. Bennett, J. P. Ennett, T. W. Matheson, L. Sawyer, V. K. Shah, *J. Chem. Soc. Dalton Trans.* **1983**, 1571–1581.
- [42] S. De Sarkar, W. Liu, S. I. Kozhushkov, L. Ackermann, *Adv. Synth. Catal.* **2014**, *356*, 1461–1479.
- [43] L. Ackermann, R. n. Vicente, H. K. Potukuchi, V. Pirovano, *Org. Lett.* **2010**, *12*, 5032–5035.
- [44] For two recent representative examples, see ref. [21i] and W. Liu, L. Ackermann, *Chem. Commun.* **2014**, *50*, 1878–1881.

Received: November 3, 2014

Published online on February 17, 2015