C–H Bond Functionalization

DOI: 10.1002/anie.200902458

Ruthenium-Catalyzed Regioselective Direct Alkylation of Arenes with Unactivated Alkyl Halides through C–H Bond Cleavage**

Lutz Ackermann, Petr Novák, Rubén Vicente, and Nora Hofmann*

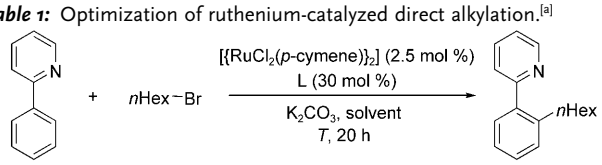
Direct arylation of arenes by C–H bond cleavage, which is attractive because of its ecologically and economically benign nature, is an increasingly viable alternative to conventional cross-coupling reactions with stoichiometric amounts of organometallic reagents.[1,2] However, while the development of stabilizing ligands allowed for the use of unactivated alkyl halides in traditional cross-coupling chemistry,[3–5] generally applicable methodologies for intermolecular[6] regioselective direct alkylations of arenes[7] with alkyl halides[8] by C–H bond cleavage have proven elusive.

Recently, we reported on the beneficial effect of carboxylic acids[9] as additives in ruthenium-catalyzed direct arylation[10,11] with aryl bromides, chlorides, or tosylates.[12] Given the significantly improved activity of the in situ generated catalytic system, we became interested in exploring its use for unprecedented ruthenium-catalyzed direct alkylations[13] with unactivated alkyl halides[14,15] as electrophiles. Herein, we report our findings on the development of such C–H bond functionalization reactions, which allowed for the efficient conversion of primary and secondary alkyl halides and proved applicable to neopentyl-substituted electrophiles.

At the outset of our studies, we probed various additives in the ruthenium-catalyzed direct alkylation of 2-pyridyl benzene (**1a**), employing unactivated alkyl bromide **2a** in NMP as solvent (Table 1). Different phosphines did not significantly affect the outcome of the envisioned reaction (Table 1, entries 1–4). On the contrary, more promising results were obtained when catalytic amounts of carboxylic acids were used as additives (Table 1, entries 5–9). The alkyl-substituted, sterically hindered acid 1-$AdCO_2H$ gave the best results (Table 1, entry 9).

Reactions performed in toluene[16] as solvent proceeded less efficiently (Table 1, entry 10), and other solvents, such as THF, 1,4-dioxane, DMSO, or *N*,*N*-dimethylacetamide, gave considerably lower yields of desired product **3a**. As an economically attractive alternative, $RuCl_3 \cdot n\,H_2O$[17] could be employed as catalyst precursor (Table 1, entry 11).[18] Importantly, direct alkylation of pyridine derivative **1a** could be performed at reaction temperatures as low as 60 °C with comparable efficiencies (Table 1, entries 13–15). Finally, the use of independently prepared carboxylic ester 1-$AdCO_2$-(*n*Hex) clearly indicated that its formation was not relevant to the generation of the catalytically active ruthenium species (Table 1, entry 16).

Table 1: Optimization of ruthenium-catalyzed direct alkylation.[a]



1a **2a** **3a**

Entry	L	Solvent	*T* [°C]	Yield [%]
1	–	NMP	120	–[b]
2	–	NMP	120	13
3	PPh_3	NMP	120	21
4	PCy_3	NMP	120	23
5	$MesCO_2H$	NMP	120	33
6	$MeCO_2H$	NMP	120	45
7	$nPrCO_2H$	NMP	120	53
8	$iPrCO_2H$	NMP	120	61
9	1-$AdCO_2H$	NMP	120	69
10	1-$AdCO_2H$	toluene	120	51
11	1-$AdCO_2H$	NMP	120	49[c]
12	1-$AdCO_2H$	NMP	100	68
13	1-$AdCO_2H$	NMP	80	68
14	1-$AdCO_2H$	NMP	60	73
15	1-$AdCO_2H$	NMP	23	17
16	1-$AdCO_2$(*n*Hex)	NMP	100	–

[a] Reaction conditions: **1a** (1.0 mmol), **2a** (3.0 mmol), [{$RuCl_2$(*p*-cymene)}$_2$] (2.5 mol%), L (30 mol%), K_2CO_3 (2.0 mmol), solvent (4.0 mL), 20 h, yield of isolated product. NMP = *N*-methylpyrrolidinone; Ad = adamantyl. [b] In the absence of [{$RuCl_2$(*p*-cymene)}$_2$]. [c] $RuCl_3 \cdot n\,H_2O$ (5.0 mol%) instead of [{$RuCl_2$(*p*-cymene)}$_2$].

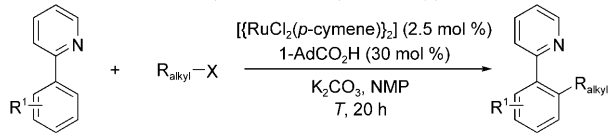
We then explored the scope of the optimized catalytic system in the direct alkylation of pyridine derivatives **1** (Table 2). A variety of unactivated alkyl bromides bearing β-hydrogen atoms enabled regioselective direct alkylations (Table 2, entries 1–8). While an alkyl iodide also led to an acceptable yield of product **3a** (Table 2, entry 9), the corresponding alkyl chloride turned out to be a more challenging substrate (Table 2, entry 10). Notably, our in situ generated catalytic system was not limited to the use of primary alkyl halides but also enabled the conversion of sterically more congested secondary alkyl halides, albeit with lower yield (Table 2, entry 11). Importantly, neopentyl bromide also served as starting material for a direct alkylation (Table 2, entry 12), which indicated that mechanisms relying on either a

[*] Prof. Dr. L. Ackermann, P. Novák, R. Vicente, N. Hofmann
Institut für Organische und Biomolekulare Chemie
Georg-August-Universität
Tammannstrasse 2, 37077 Göttingen (Germany)
Fax: (+49) 551-39-6777
E-mail: lutz.ackermann@chemie.uni-goettingen.de
Homepage: http://www.org.chemie.uni-goettingen.de/ackermann/

[**] Support by the DFG and the Alexander-von-Humboldt foundation (fellowship to R.V.) is gratefully acknowledged.

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/anie.200902458.

Table 2: Ruthenium-catalyzed direct alkylation of pyridine derivatives **1**.[a]



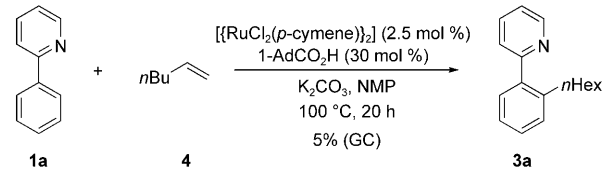
1 **2** **3**

Entry	R_{alkyl}—X	*T* [°C]	**3**	R^1	Yield [%]
1	*n*Bu—Br	100	**3b**	H	74
2	*n*Pent—Br	60	**3c**	H	69
3	*n*Oct—Br	60	**3d**	H	80
4	*n*Dec—Br	100	**3e**	H	81
5	*n*Dodec—Br	60	**3f**	H	78
6	*n*Tetradec—Br	100	**3g**	H	80
7	*n*Hex—Br	100	**3h**	4-Me	52
8	*n*Hex—Br	100	**3i**	4-MeO	53
9	*n*Hex—I	100	**3a**	H	61
10	*n*Hex—Cl	100	**3a**	H	31[b]
11		100	**3j**	H	51
12		100	**3k**	H	57

[a] Reaction conditions: **1** (1.0 mmol), **2** (3.0 mmol), [{$RuCl_2$(*p*-cymene)}$_2$] (2.5 mol%), 1-$AdCO_2H$ (30 mol%), K_2CO_3 (2.0–3.2 mmol), NMP (4.0 mL), 20 h, yield of isolated product. [b] GC analysis.

simple nucleophilic substitution or electrophilic aromatic substitution (Friedel–Crafts reaction) are not operative.

Furthermore, a mechanism involving initial β-elimination of HX from the alkyl halide, along with a subsequent ruthenium-catalyzed hydroarylation,[14] could be ruled out, as alkene **4** yielded only trace amounts of pyridine derivative **3a** under otherwise identical reaction conditions (Scheme 1).[19]



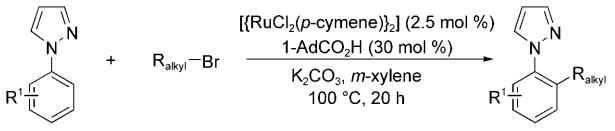
1a **4** **3a**

Scheme 1. Attempted alkylation with alkene **4**.

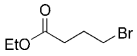
The catalytic system was not restricted to pyridine derivatives as pronucleophilic substrates. Indeed, efficient alkylation of pyrazole derivatives was also viable (Table 3). Interestingly, initial optimization studies showed that aromatic solvent *meta*-xylene[16] enabled more efficient and selective C–H bond functionalization. Thus, various primary (Table 3, entries 1–8) and secondary (Table 3, entry 9) alkyl bromides could be converted, including one functionalized derivative (Table 3, entry 6) and neopentyl bromide (Table 3, entries 7 and 8). Moreover, direct alkylation with a *meta*-substituted arene proceeded with high regioselectivity at the sterically less hindered *ortho*-position, thereby yielding pyrazole derivative **6h** as the sole product (Table 3, entry 8).

Remarkably, a comparable reactivity profile was observed when using ketimine **7a** as substrate. Thus, chemo- and regioselective alkylations occurred, and subsequent reduction yielded secondary amines **8a** and **8b** (Scheme 2).[20]

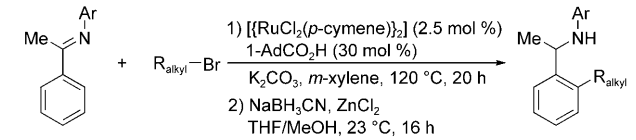
Table 3: Ruthenium-catalyzed direct alkylation of pyrazole derivatives **5**.[a]



5 **2** **6**

Entry	R_{alkyl}—Br	**6**	R^1	Yield [%]
1	*n*Pent—Br	**6a**	H	89
2	*n*Dec—Br	**6b**	H	87
3	*n*Undec—Br	**6c**	H	87
4	*n*Dodec—Br	**6d**	H	92
5	*n*Tetradec—Br	**6e**	H	91
6		**6f**	H	75
7		**6g**	H	58
8		**6h**	5-Me	56
9		**6i**	H	43

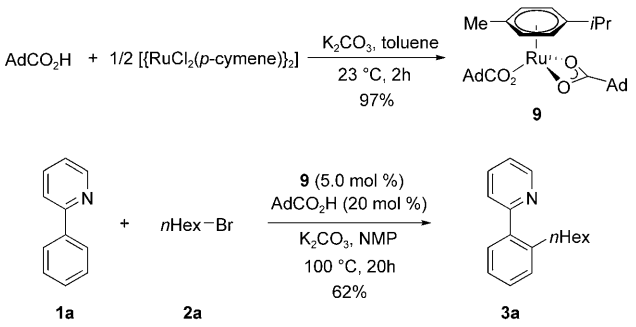
[a] Reaction conditions: **5** (1.0 mmol), **2** (3.0 mmol), [{$RuCl_2$(*p*-cymene)}$_2$] (2.5 mol%), 1-$AdCO_2H$ (30 mol%), K_2CO_3 (2.0–3.2 mmol), *meta*-xylene (4.0 mL), 20 h, yield of isolated product.



7a **2**

Scheme 2. Ruthenium-catalyzed direct alkylation of ketimine **7a**.

Finally, we became interested in probing the nature of the catalytically active species. Under the optimized reaction conditions of catalytic C–H bond functionalization, ruthenium(II) carboxylate complex **9** was formed quantitatively, even at ambient temperature.[19] Importantly, well-defined complex **9** displayed a catalytic activity comparable to that observed when using the in situ generated system (Scheme 3 vs. Table 1, entry 12).



1a **2a** **3a**

Scheme 3. Synthesis of ruthenium complex **9** and its use in catalytic direct alkylation.

In summary, we report the development of the first ruthenium-catalyzed direct alkylation of arenes with unactivated alkyl halides bearing β-hydrogen atoms. A catalytic system derived from carboxylic acid 1-$AdCO_2H$ enabled regioselective intermolecular alkylation of pyridine, pyrazole, or ketimine derivatives with primary as well as secondary alkyl halides, and the method proved amenable to the use of neopentyl bromide as electrophile. Additionally, a ruthenium(II) carboxylate complex was identified as being catalytically competent.

Experimental Section

Representative procedure for ruthenium-catalyzed direct alkylation: **3a** (Table 1, entry 12): A suspension of [{$RuCl_2$(*p*-cymene)}$_2$] (15.4 mg, 0.025 mmol, 2.5 mol%), 1-$AdCO_2H$ (54.1 mg, 0.30 mmol, 30 mol%), K_2CO_3 (276 mg, 2.00 mmol), **1a** (155 mg, 1.00 mmol), and 1-bromo-*n*-hexane (495 mg, 3.00 mmol) in NMP (4 mL) was stirred for 20 h at 100 °C under N_2. EtOAc (50 mL) and H_2O (50 mL) were added to the cold reaction mixture. The aqueous phase was extracted with EtOAc (2 × 50 mL). The combined organic layers were washed with H_2O (50 mL) and brine (50 mL), dried over Na_2SO_4, and concentrated in vacuo. The remaining residue was purified by column chromatography on silica gel (*n*-hexane/EtOAc 15:1) to yield **3a** (163 mg, 68%) as a colorless oil.

Received: May 8, 2009
Published online: July 11, 2009

Keywords: alkyl halides · alkylation · arenes · C–H bond functionalization · ruthenium

[1] L. Ackermann, *Modern Arylation Methods*, Wiley-VCH, Weinheim, **2009**.

[2] Recent reviews: a) F. Kakiuchi, T. Kochi, *Synthesis* **2008**, 3013 – 3039; b) B.-J. Li, S.-D. Yang, Z.-J. Shi, *Synlett* **2008**, 949 – 957; c) J. C. Lewis, R. G. Bergman, J. A. Ellman, *Acc. Chem. Res.* **2008**, *41*, 1013 – 1025; d) T. Satoh, M. Miura, *Top. Organomet. Chem.* **2007**, *24*, 61 – 84; e) L. Ackermann, *Top. Organomet. Chem.* **2007**, *24*, 35 – 60; f) D. Alberico, M. E. Scott, M. Lautens, *Chem. Rev.* **2007**, *107*, 174 – 238; g) I. V. Seregin, V. Gevorgyan, *Chem. Soc. Rev.* **2007**, *36*, 1173 – 1193; h) S. Pascual, P. de Mendoza, A. M. Echavarren, *Org. Biomol. Chem.* **2007**, *5*, 2727 – 2734; i) L.-C. Campeau, D. R. Stuart, K. Fagnou, *Aldrichimica Acta* **2007**, *40*, 35 – 41; j) L. Ackermann, *Synlett* **2007**, 507 – 526; k) O. Daugulis, V. G. Zaitsev, D. Shabashov, Q. N. Pham, A. Lazareva, *Synlett* **2006**, 3382 – 3388; l) J.-Q. Yu, R. Giri, X. Chen, *Org. Biomol. Chem.* **2006**, *4*, 4041 – 4047.

[3] For early examples, see: a) T. Ishiyama, S. Abe, N. Miyaura, A. Suzuki, *Chem. Lett.* **1992**, 691 – 694; b) A. Devasagayaraj, T. Stuedemann, P. Knochel, *Angew. Chem.* **1995**, *107*, 2952 – 2954; *Angew. Chem. Int. Ed. Engl.* **1995**, *34*, 2723 – 2725.

[4] For representative examples, see: a) S. W. Smith, G. C. Fu, *Angew. Chem.* **2008**, *120*, 9474 – 9476; *Angew. Chem. Int. Ed.* **2008**, *47*, 9334 – 9336; b) J. Terao, H. Todo, S. A. Begum, H. Kuniyasu, N. Kambe, *Angew. Chem.* **2007**, *119*, 2132 – 2135; *Angew. Chem. Int. Ed.* **2007**, *46*, 2086 – 2089; c) R. B. Bedford, M. Betham, D. W. Bruce, S. A. Davis, R. M. Frost, M. Hird, *Chem. Commun.* **2006**, 1398 – 1400; d) A. C. Frisch, N. Shaikh, A. Zapf, M. Beller, *Angew. Chem.* **2002**, *114*, 4218 – 4221; *Angew. Chem. Int. Ed.* **2002**, *41*, 4056 – 4059, and references therein.

[5] For reviews, see: a) M. Nakamura, S. Ito in *Modern Arylation Methods* (Ed.: L. Ackermann), Wiley-VCH, Weinheim, **2009**, pp. 155 – 181; b) A. Rudolph, M. Lautens, *Angew. Chem.* **2009**, *121*, 2694 – 2708; *Angew. Chem. Int. Ed.* **2009**, *48*, 2656 – 2670; c) J. Terao, N. Kambe, *Acc. Chem. Res.* **2008**, *41*, 1545 – 1554; d) B. D. Sherry, A. Fürstner, *Acc. Chem. Res.* **2008**, *41*, 1500 – 1511; e) A. C. Frisch, M. Beller, *Angew. Chem.* **2005**, *117*, 680 – 695; *Angew. Chem. Int. Ed.* **2005**, *44*, 674 – 688; f) M. R. Netherton, G. C. Fu, *Adv. Synth. Catal.* **2004**, *346*, 1525 – 1532.

[6] For palladium-catalyzed intramolecular alkylations with activated alkyl halides, see: α-chloroacetanilides: a) E. J. Hennessy, S. L. Buchwald, *J. Am. Chem. Soc.* **2003**, *125*, 12084 – 12085; benzyl halides: b) S. J. Hwang, S. H. Cho, S. Chang, *J. Am. Chem. Soc.* **2008**, *130*, 16158 – 16159.

[7] For reviews on palladium-catalyzed sequential reactions involving alkylations using norbornene, see: a) M. Catellani, E. Motti, N. Della Ca, *Acc. Chem. Res.* **2008**, *41*, 1512 – 1522; b) Ref. [2f]; c) M. Catellani, *Synlett* **2003**, 298 – 313; d) for a recent example of palladium-catalyzed alkylations of one heteroarene with two alkyl halides, see: C. Verrier, C. Hoarau, F. Marsais, *Org. Biomol. Chem.* **2009**, *7*, 647 – 650.

[8] For palladium-catalyzed direct alkylations with stoichiometric amounts of organometallic reagents, see: X. Chen, J.-J. Li, X.-S. Hao, C. E. Goodhue, J.-Q. Yu, *J. Am. Chem. Soc.* **2006**, *128*, 78 – 79.

[9] Pivalic acid was used in palladium-catalyzed direct arylations: a) M. Lafrance, K. Fagnou, *J. Am. Chem. Soc.* **2006**, *128*, 16496 – 16497; b) M. Lafrance, S. I. Gorelsky, K. Fagnou, *J. Am. Chem. Soc.* **2007**, *129*, 14570 – 14571; examples from our laboratories: c) L. Ackermann, R. Vicente, R. Born, *Adv. Synth. Catal.* **2008**, *350*, 741 – 748; d) L. Ackermann, A. Althammer, S. Fenner, *Angew. Chem.* **2009**, *121*, 207 – 210; *Angew. Chem. Int. Ed.* **2009**, *48*, 201 – 204; reviews: e) M. Miura, T. Sato, in *Modern Arylation Methods* (Ed.: L. Ackermann), Wiley-VCH, Weinheim, **2009**, pp. 335 – 361; f) P. de Mendoza, A. M. Echavarren in *Modern Arylation Methods* (Ed.: L. Ackermann), Wiley-VCH, Weinheim, **2009**, pp. 363 – 400.

[10] L. Ackermann, R. Vicente in *Modern Arylation Methods* (Ed.: L. Ackermann), Wiley-VCH, Weinheim, **2009**, pp. 311 – 399.

[11] For selected examples of ruthenium-catalyzed direct arylations, see: a) L. Ackermann, M. Mulzer, *Org. Lett.* **2008**, *10*, 5043 – 5045; b) I. Özdemir, S. Demir, B. Cetinkaya, C. Gourlaouen, F. Maseras, C. Bruneau, P. H. Dixneuf, *J. Am. Chem. Soc.* **2008**, *130*, 1156 – 1157; c) S. Oi, R. Funayama, T. Hattori, Y. Inoue, *Tetrahedron* **2008**, *64*, 6051 – 6059; d) L. Ackermann, R. Born, P. Álvarez-Bercedo, *Angew. Chem.* **2007**, *119*, 6482 – 6485; *Angew. Chem. Int. Ed.* **2007**, *46*, 6364 – 6367; e) L. Ackermann, A. Althammer, R. Born, *Angew. Chem.* **2006**, *118*, 2681 – 2685; *Angew. Chem. Int. Ed.* **2006**, *45*, 2619 – 2622; f) L. Ackermann, *Org. Lett.* **2005**, *7*, 3123 – 3125; g) F. Kakiuchi, Y. Matsuura, S. Kan, N. Chatani, *J. Am. Chem. Soc.* **2005**, *127*, 5936 – 5945; h) S. Oi, E. Aizawa, Y. Ogino, Y. Inoue, *J. Org. Chem.* **2005**, *70*, 3113 – 3119, and references therein.

[12] L. Ackermann, R. Vicente, A. Althammer, *Org. Lett.* **2008**, *10*, 2299 – 2302.

[13] Recently, ruthenium-catalyzed amino- and alkoxycarbonylations were reported: T. Kochi, S. Urano, H. Seki, E. Mizushima, M. Sato, F. Kakiuchi, *J. Am. Chem. Soc.* **2009**, *131*, 2792 – 2793.

[14] For reviews on elegantly developed ruthenium-catalyzed hydroarylations of alkenes, see: a) F. Kakiuchi, S. Murai, *Acc. Chem. Res.* **2002**, *35*, 826 – 834; b) F. Kakiuchi, N. Chatani in *Ruthenium Catalysts and Fine Chemistry* (Ed.: C. Bruneau, P. H. Dixneuf), Springer, Berlin, **2004**, pp. 45 – 79; c) F. Kakiuchi, N. Chatani in *Ruthenium in Organic Synthesis* (Ed.: S.-I. Murahashi), Wiley-VCH, Weinheim, **2004**, pp. 219 – 255.

[15] For oxidative alkylations with cycloalkanes using four equivalents of peroxides, see: G. Deng, L. Zhao, C.-J. Li, *Angew. Chem.* **2008**, *120*, 6374 – 6378; *Angew. Chem. Int. Ed.* **2008**, *47*, 6278 – 6282.

[16] Products originating from nondirected alkylations of aromatic solvents were not detected.
[17] a) L. Ackermann, A. Althammer, R. Born, *Tetrahedron* **2008**, *64*, 6115–6124; b) L. Ackermann, A. Althammer, R. Born, *Synlett* **2007**, 2833–2836.
[18] Anhydrous $RuCl_3$ and $[RuCl_2(PPh_3)_3]$ yielded 12% and 16% of product **3a**, respectively, under otherwise identical reaction conditions.
[19] A potential reaction mechanism could involve cyclometalation, along with subsequent oxidative addition of the alkyl halide to a ruthenacycle.
[20] *N*,*N*-Dimethylbenzylamine yielded no products of direct alkylation.
[21] The molecular structure of the corresponding ruthenium(II) carboxylate complex derived from carboxylic acid $MesCO_2H$ was established by X-ray diffraction analysis: L. Ackermann, R. Vicente, C. Schulzke, unpublished results.

