ORGANIC LETTERS

2011
Vol. 13, No. 7
1875–1877

Carboxylate-Assisted Ruthenium-Catalyzed Direct Alkylations of Ketimines

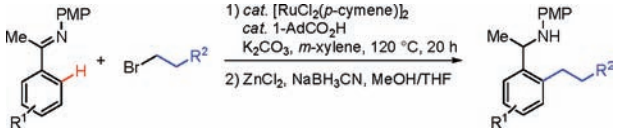
Lutz Ackermann,* Nora Hofmann, and Rubén Vicente

Institut für Organische und Biomolekulare Chemie, Georg-August-Universität, Tammannstrasse 2, 37077 Göttingen, Germany

Lutz.Ackermann@chemie.uni-goettingen.de

Received February 8, 2011

ABSTRACT



The mechanism of carboxylate-assisted ruthenium(II)-catalyzed direct alkylations of ketimines with unactivated alkyl halides was probed through experimental studies. The remarkable chemoselectivity of the broadly applicable catalyst also enabled direct alkylations among others on H_2O or under solvent-free reaction conditions.

Transition-metal-catalyzed direct C−H bond[1] alkylations of arenes under basic reaction conditions have recently been developed as sustainable alternatives to traditional cross-coupling reactions between organometallic reagents and alkyl halides.[2] Particularly, ruthenium catalysts[3] enabled C−H bond functionalizations with challenging unactivated alkyl halides bearing β-hydrogens.[4,5] Despite this recent progress, mechanistic studies on ruthenium-catalyzed direct alkylations[6] have unfortunately thus far not been reported. As a consequence, we explored the working mode of ruthenium(II) carboxylate complexes in direct C−H bond functionalizations focusing particularly on ketimines[7] as substrates, because of their importance as key intermediates in organic synthesis. Herein, we wish to report on our findings, which include first direct alkylations on H_2O or under solvent-free reaction conditions.

At the outset of our studies, we tested various phosphine ligand-free[8] reaction conditions for direct alkylations of ketimines. Among a variety of stoichiometric bases, KOAc gave promising results in the absence of an

(1) Select recent reviews on metal-catalyzed C−H bond functionalizations: (a) Ackermann, L.; Potukuchi, H. K. *Org. Biomol. Chem.* **2010**, *8*, 4503–4513. (b) Daugulis, O. *Top. Curr. Chem.* **2010**, *292*, 57–84. (c) Sun, C.-L.; Li, B.-J.; Shi, Z.-J. *Chem. Commun.* **2010**, *46*, 677–685. (d) Colby, D. A.; Bergman, R. G.; Ellman, J. A. *Chem. Rev.* **2010**, *110*, 624–655. (e) Fagnou, K. *Top. Curr. Chem.* **2010**, *292*, 35–56. (f) Satoh, T.; Miura, M. *Chem.—Eur. J.* **2010**, *16*, 11212–11222. (g) Jazzar, R.; Hitce, J.; Renaudat, A.; Sofack-Kreutzer, J.; Baudoin, O. *Chem.—Eur. J.* **2010**, *16*, 2654–2672. (h) Lei, A.; Liu, W.; Liu, C.; Chen, M. *Dalton Trans.* **2010**, *39*, 10352–10361. (i) Lyons, T. W.; Sanford, M. S. *Chem. Rev.* **2010**, *110*, 1147–1169. (j) Kulkarni, A. A.; Daugulis, O. *Synthesis* **2009**, 4087–4109. (k) Bellina, F.; Rossi, R. *Tetrahedron* **2009**, *65*, 10269–10310. (l) Ackermann, L.; Vicente, R.; Kapdi, A. *Angew. Chem., Int. Ed* **2009**, *48*, 9792–9826. (m) Thansandote, P.; Lautens, M. *Chem.—Eur. J.* **2009**, *15*, 5874–5883. (n) Kakiuchi, F.; Kochi, T. *Synthesis* **2008**, 3013–3039. (o) Satoh, T.; Miura, M. *Chem. Lett.* **2007**, *36*, 200–205. (p) Ackermann, L. *Synlett* **2007**, 507–526. (q) Alberico, D.; Scott, M. E.; Lautens, M. *Chem. Rev.* **2007**, *107*, 174–238 and references cited therein.

(2) Ackermann, L. *Chem. Commun.* **2010**, *46*, 4866–4877.

(3) (a) Ackermann, L.; Vicente, R. *Top. Curr. Chem.* **2010**, *292*, 211–229. (b) Ackermann, L. *Pure Appl. Chem.* **2010**, *82*, 1403–1413.

(4) (a) Ackermann, L.; Novák, P.; Vicente, R.; Hofmann, N. *Angew. Chem., Int. Ed.* **2009**, *48*, 6045–6048. (b) Ackermann, L.; Novák, P. *Org. Lett.* **2009**, *11*, 4966–4969.

(5) For examples of nickel- or palladium-catalyzed direct alkylations of (hetero)arenes, see: (a) Yao, T.; Hirano, K.; Satoh, T.; Miura, M. *Chem.—Eur. J.* **2010**, *16*, 12307–12311. (b) Shabashov, D.; Daugulis, O. *J. Am. Chem. Soc.* **2010**, *132*, 3965–3972. (c) Vechorkin, O.; Proust, V.; Hu, X. *Angew. Chem., Int. Ed.* **2010**, *49*, 3061–3064. (d) Ackermann, L.; Barfüsser, S.; Pospech, J. *Org. Lett.* **2010**, *12*, 724–726. (e) Lapointe, D.; Fagnou, K. *Org. Lett.* **2009**, *11*, 4160–4163. (f) Zhang, Y.-H.; Shi, B.-F.; Yu, J.-Q. *Angew. Chem., Int. Ed.* **2009**, *48*, 6097–6100. (g) Rudolph, A.; Rackelmann, N.; Lautens, M. *Angew. Chem., Int. Ed.* **2007**, *46*, 1485–1488 and references cited therein.

(6) For experimental mechanistic studies on ruthenium-catalyzed direct arylations, see: Ackermann, L.; Vicente, R.; Potukuchi, H. K.; Pirovano,
V. *Org. Lett.* **2010**, *12*, 5032–5035.

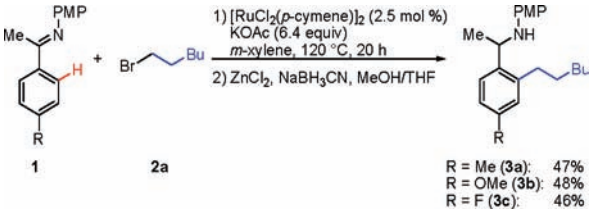
(7) For representative recent examples of direct arylations with imines, see: (a) Tredwell, M. J.; Gulias, M.; Gaunt Bremeyer, N.; Johansson, C. C. C.; Collins, B. S. L.; Gaunt, M. J. *Angw. Chem., Int. Ed.* **2011**, *50*, 1076–1079. (b) Gao, K.; Yoshikai, N. *J. Am. Chem. Soc.* **2011**, *133*, 400–402. (c) Yoshikai, N.; Matsumoto, A.; Norinder, J.; Nakamura, E. *Angew. Chem, Int. Ed.* **2009**, *48*, 2925–2928. (d) Ackermann, L.; Althammer, A.; Born, R. *Tetrahedron* **2008**, *64*, 6115–6124. (e) Oi, S.; Ogino, Y.; Fukita, S.; Inoue, Y. *Org. Lett.* **2002**, *4*, 1783–1785 and references cited therein.

(8) For early direct arylations in the absence of phosphine additives, see: Ackermann, L.; Althammer, A.; Born, R. *Synlett* **2007**, 2833–2836.

10.1021/ol200366n
Published on Web 03/09/2011

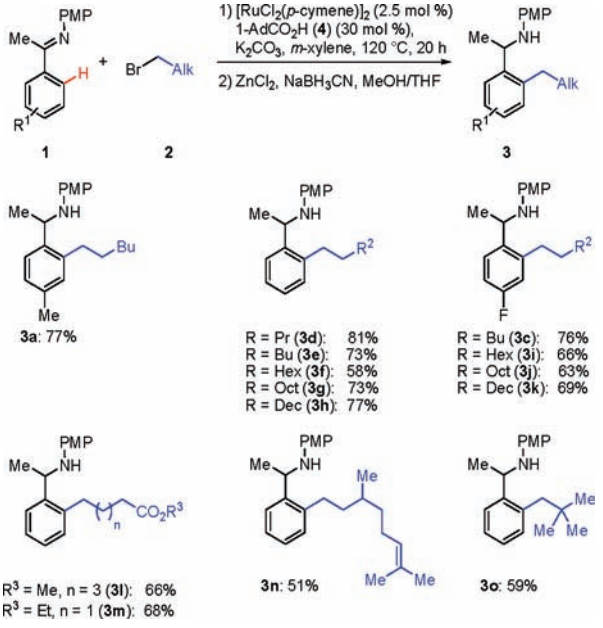
additional sterically hindered carboxylate as a cocatalyst (Scheme 1).

Scheme 1. Direct Alkylations with KOAc as the Base



However, the efficacy of this catalytic system proved to be inferior to the one of a ruthenium catalyst derived from sterically hindered carboxylic acid **4**, as illustrated by the syntheses of alkylated products **3a** and **3c** (Scheme 2). Notably, the carboxylate-assisted C−H bond functionalization proved broadly applicable and allowed for the direct introduction of the neopentyl group to give access to compound **3o**.

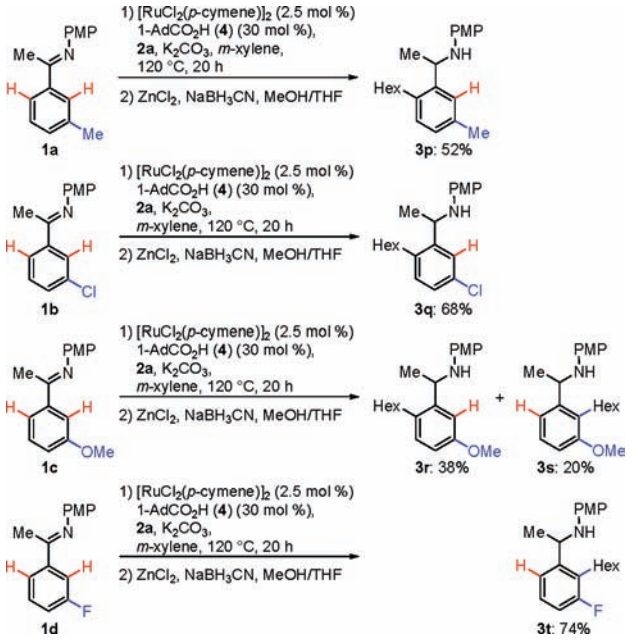
Scheme 2. Direct Alkylations with Acid **4** as a Cocatalyst



Given the broad scope of these carboxylate-assisted C−H bond functionalizations, and since mechanistic studies on ruthenium-catalyzed direct alkylations have thus far proven elusive, we subsequently performed intramolecular competition experiments with *meta*-substituted arenes **1**.

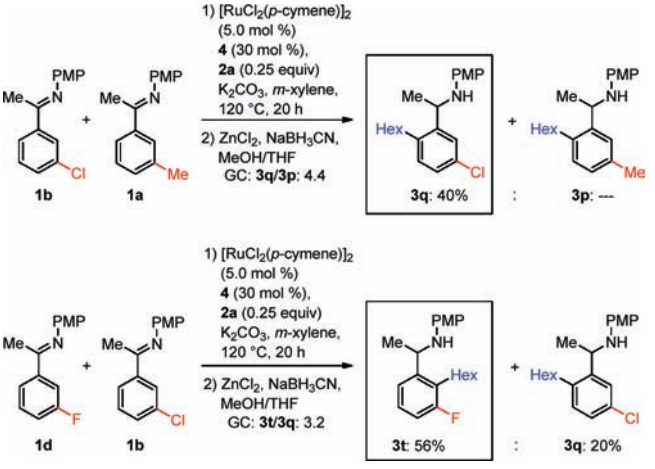
(9) (a) Shen, K.; Fu, Y.; Li, J.-N.; Liu, L.; Guo, Q.-X. *Tetrahedron* **2007**, *63*, 1568–1576. (b) Clot, E.; Mégret, C.; Eisenstein, O.; Perutz, R. N. *J. Am. Chem. Soc.* **2009**, *131*, 7817–7827. (c) Preliminary experiments on ruthenium-catalyzed direct arylations revealed that C−H bond functionalizations with 2-{*meta*-(trifluoromethyl)phenyl}pyridine are controlled by steric interactions, thus yielding the 6-arylated products.

Scheme 3. Intramolecular Competition Experiments



These transformations were largely controlled by steric interactions (Scheme 3). However, the presence of a *meta*-substituent displaying an electronegative heteroatom led to the formation of compound **3s** as a byproduct and the selective generation of arene **3t** as the sole product.[9,10]

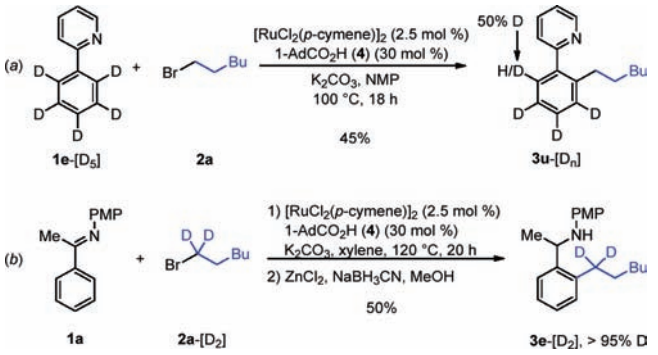
Scheme 4. Intermolecular Competition Experiments



Intermolecular competition experiments clearly highlighted electron-deficient arenes to be functionalized preferentially (Scheme 4). Interestingly, this reactivity profile contrasts with previously made observations in ruthenium-catalyzed direct arylations.[6]

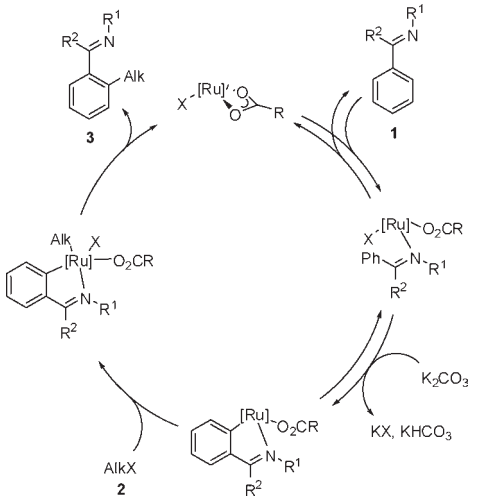
(10) Analysis of the crude reaction mixture by GC-MS showed the mass balance to be mainly unreacted starting material **1**.

Scheme 5. Direct Alkylations with Isotopically Labeled Starting Materials



Experiments with isotopically labeled starting materials revealed a D/H-exchange reaction (Scheme 5a). Further, potential mechanisms involving the formation of ruthenium alkylidenes were shown unlikely to be operative, since the transformation of substrate **2a**-[D_2] occurred without the detectable loss of its isotopic labels (*b*).

Scheme 6. Proposed Mechanism of Ruthenium-Catalyzed Direct Alkylations



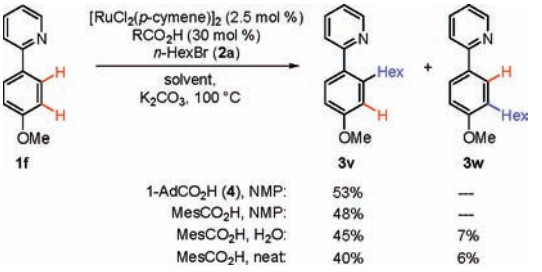
Based on these mechanistic studies, we propose the catalytic cycle depicted in Scheme 6, which involves an initial reversible cyclometalation, along with a subsequent activation of alkyl halide **2** and a reductive elimination.

Previously, we studied ruthenium-catalyzed direct C−H bond functionalizations in the presence of H_2O.[11]

(11) For ruthenium-catalyzed direct *arylations* in the presence of H_2O, see: (a) Ackermann, L. *Org. Lett.* **2005**, *7*, 3123–3125. See also: (b) Arockiam, P. B.; Fischmeister, C.; Bruneau, C.; Dixneuf, P. H. *Angew. Chem., Int. Ed.* **2010**, *49*, 6629–6632.

Given the increased hydrolytic stability of pyridine directing groups, we thus probed unprecedented ruthenium-catalyzed direct alkylations with substrate **1f** on H_2O. Interestingly, when using $MesCO_2H$ as a cocatalyst we observed the formation of byproduct **3w** being functionalized in the *meta*-position[12] with respect to the 2-pyridyl substituent (Scheme 7). Notably, compound **3w** was also generated under solvent-free[13] reaction conditions.

Scheme 7. *Meta*-Selectivity in Direct Alkylations



In summary, we have reported on broadly applicable ruthenium-catalyzed direct alkylations of ketimines through carboxylate assistance. Mechanistic studies revealed these reactions to proceed through an initial cyclometalation, and a subsequent activation of the alkyl halide. Notably, electron-deficient arenes were preferentially functionalized, thereby supporting a nonelectrophilic C−H bond metalation event. The catalytic system displayed an excellent chemoselectivity, which was exploited for first direct alkylations on H_2O or under solvent-free reaction conditions.

Acknowledgment. Support by the State of Lower Saxony within the CaSuS (Catalysis for Sustainable Synthesis) PhD program (fellowship to N.H.) and the DFG is gratefully acknowledged. Further, we thank Dr. S. I. Kozhushkov for preliminary experiments and Dipl.-Chem. R. Machinek for 2D-NMR experiments (both Georg-August-Universität).

Supporting Information Available. Experimental procedures, characterization data, and ^1H and ^{13}C NMR spectra for new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

(12) For examples of *meta*-selective C−H bond functionalizations, see: (a) Duong, H. A.; Gilligan, R. E.; Cooke, M. L.; Phipps, R. J.; Gaunt, M. J. *Angew. Chem., Int. Ed.* **2011**, *50*, 463–466. (b) Phipps, R. J.; Gaunt, M. J. *Science* **2009**, *323*, 1593–1597. (c) Yue, W.; Li, Y.; Jiang, W.; Zhen, Y.; Wang, Z. *Org. Lett.* **2009**, *11*, 5430–5433. (d) Zhang, Y.-H.; Shi, B.-F.; Yu, J.-Q. *J. Am. Chem. Soc.* **2009**, *131*, 5072–5074 and references cited therein.

(13) For recent examples of palladium-catalyzed direct arylations in the absence of solvent, see: (a) Bedford, R. B.; Mitchell, C. J.; Webster, R. L. *Chem. Commun.* **2010**, *46*, 3095–3097. (b) Bedford, R. B.; Engelhart, J. U.; Haddow, M. F.; Mitchell, C. J.; Webster, R. L. *Dalton Trans* **2010**, *39*, 10464–10472.