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# Carboxylate-Assisted Ruthenium-Catalyzed Direct Alkylations of Ketimines

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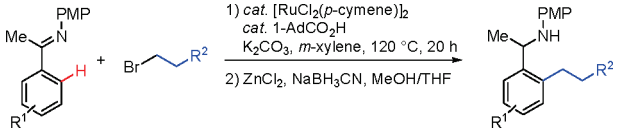
## ABSTRACT




**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 $\beta$-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.

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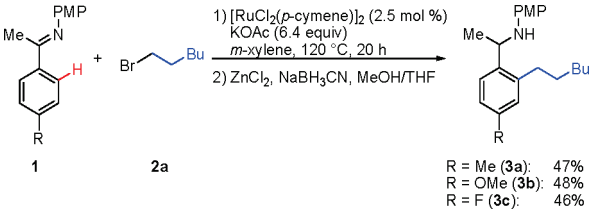
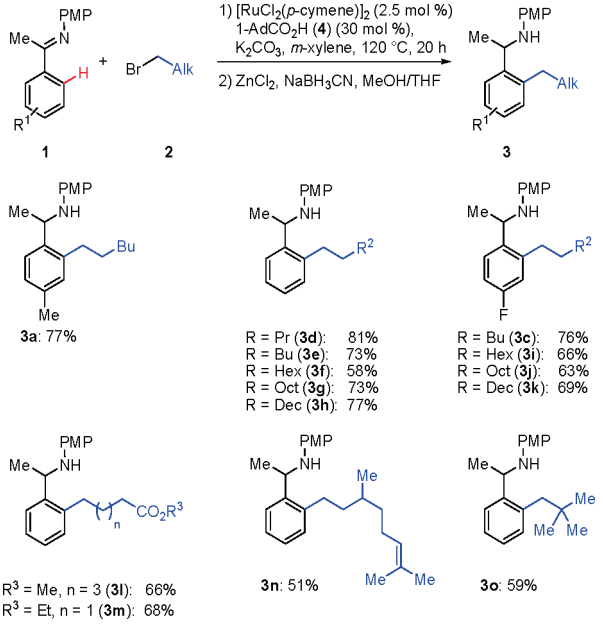
additional sterically hindered carboxylate as a cocatalyst (Scheme 1).

**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**.

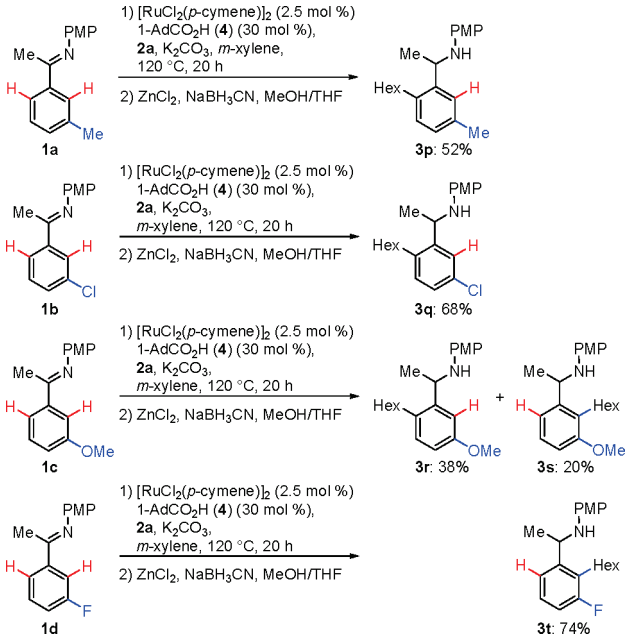
**Scheme 2.** Direct Alkylations with Acid **4** as a Cocatalyst




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**.

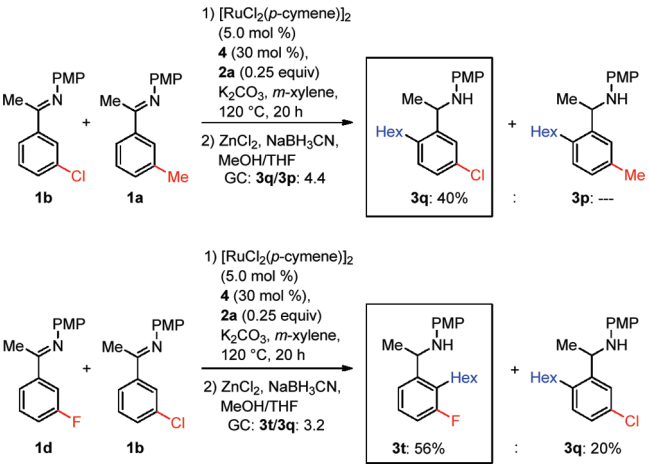
(9) (a) Shen, K.; Fu, Y.; Li, J.-N.; Liu, L.; Guo, Q.-X. *Tetrahedron* **2007**, *63*, 1568–1576. (b) Clot, E.; Mégret, C.; Eisenstein, O.; Perutz, R. N. *J. Am. Chem. Soc.* **2009**, *131*, 7817–7827. (c) Preliminary experiments on ruthenium-catalyzed direct arylations revealed that C−H bond functionalizations 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]

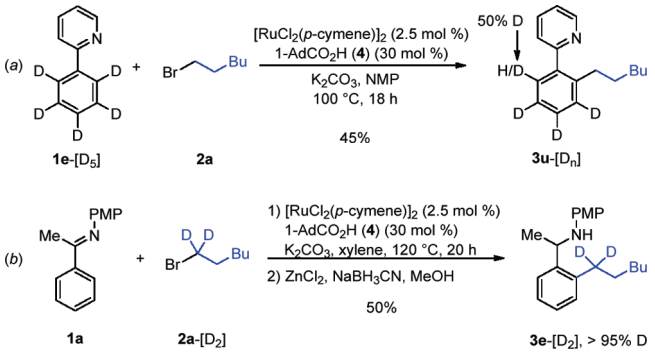
**Scheme 4.** Intermolecular Competition Experiments




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]

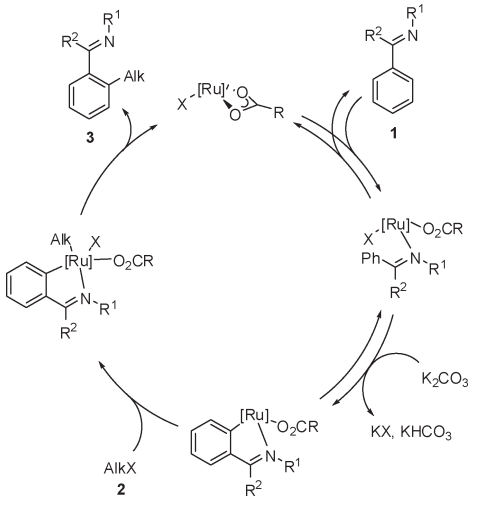
(10) Analysis of the crude reaction mixture by GC-MS showed the mass balance to be mainly unreacted starting material **1**.

**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



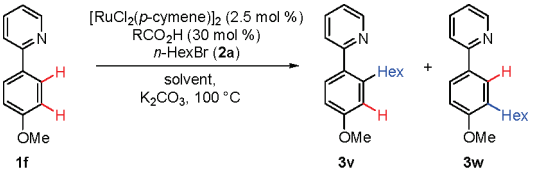

Based on these mechanistic studies, we propose the catalytic cycle depicted in Scheme 6, which involves an initial reversible cyclometalation, along with a subsequent activation of alkyl halide **2** and a reductive elimination.

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




| | 3v | 3w |
|---|---|---|
| 1-AdCO$_2$H (**4**), NMP: | 53% | --- |
| MesCO$_2$H, NMP: | 48% | --- |
| MesCO$_2$H, H$_2$O: | 45% | 7% |
| MesCO$_2$H, neat: | 40% | 6% |

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.

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**Supporting Information Available.** Experimental procedures, characterization data, and $^1$H 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.