

# Ruthenium-Catalyzed C–H/N–O Bond Functionalization: Green Isoquinolone Syntheses in Water

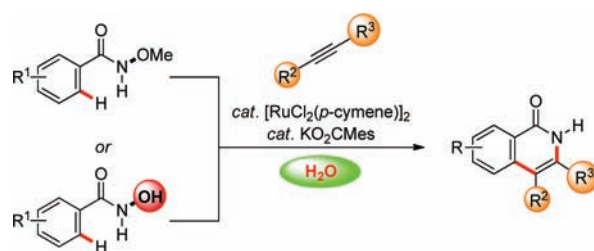
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Received October 24, 2011

## ABSTRACT



Ruthenium-catalyzed isoquinolone syntheses with ample scope were accomplished through carboxylate assistance in environmentally benign water as a reaction medium. The high chemoselectivity of the ruthenium(II) carboxylate complex also set the stage for the direct use of free hydroxamic acids for annulations of alkynes.

Oxidative transition-metal-catalyzed annulations of alkynes by C–H bond cleavages<sup>1</sup> are increasingly viable tools for atom- and step-economical syntheses of bioactive heterocycles.<sup>2,3</sup> These transformations usually require

stoichiometric amounts of external, mostly metallic oxidants, which results in the generation of undesired waste.<sup>2,3</sup> Notable recent progress was accomplished by Guimond, Fagnou and co-workers through the use of hydroxamic acid esters<sup>4</sup> as valuable substrates for rhodium-catalyzed annulations of alkynes in MeOH as the solvent.<sup>5</sup> Thus, the N–O bond of *N*-methoxybenzamides served as a handle

(1) Select recent reviews on metal-catalyzed C–H bond functionalizations: (a) Hartwig, J. F. *Chem. Soc. Rev.* **2011**, *40*, 1992–2002. (b) Willis, M. C. *Chem. Rev.* **2010**, *110*, 725–748. (c) Ackermann, L.; Potukuchi, H. K. *Org. Biomol. Chem.* **2010**, *8*, 4503–4513. (d) Daugulis, O. *Top. Curr. Chem.* **2010**, *292*, 57–84. (e) Sun, C.-L.; Li, B.-J.; Shi, Z.-J. *Chem. Commun.* **2010**, *46*, 677–685. (f) Colby, D. A.; Bergman, R. G.; Ellman, J. A. *Chem. Rev.* **2010**, *110*, 624–655. (g) Fagnou, K. *Top. Curr. Chem.* **2010**, *292*, 35–56. (h) Jazzar, R.; Hitce, J.; Renaudat, A.; Sofack-Kreutzer, J.; Baudoin, O. *Chem.—Eur. J.* **2010**, *16*, 2654–2672. (i) Lyons, T. W.; Sanford, M. S. *Chem. Rev.* **2010**, *110*, 1147–1169. (j) Dudnik, A. S.; Gevorgyan, V. *Angew. Chem., Int. Ed.* **2010**, *49*, 2096–2098. (k) Giri, R.; Shi, B.-F.; Engle, K. M.; Mauge, N.; Yu, J.-Q. *Chem. Soc. Rev.* **2009**, *38*, 3242–3272. (l) Bellina, F.; Rossi, R. *Tetrahedron* **2009**, *65*, 10269–10310. (m) Ackermann, L.; Vicente, R.; Kapdi, A. *Angew. Chem., Int. Ed.* **2009**, *48*, 9792–9826. (n) Thansandote, P.; Lautens, M. *Chem.—Eur. J.* **2009**, *15*, 5874–5883. (o) Kakiuchi, F.; Kochi, T. *Synthesis* **2008**, 3013–3039. (p) Satoh, T.; Miura, M. *Chem. Lett.* **2007**, *36*, 200–205. (q) Alberico, D.; Scott, M. E.; Lautens, M. *Chem. Rev.* **2007**, *107*, 174–238 and references cited therein.

(2) Representative recent reviews on oxidative C–H bond functionalizations: (a) Cho, S. H.; Kim, J. Y.; Kwak, J.; Chang, S. *Chem. Soc. Rev.* **2011**, *40*, 5068–5083. (b) Yeung, C. S.; Dong, V. M. *Chem. Rev.* **2011**, *111*, 1215–1292. (c) Chao, L.; Hua, Z.; Wei, S.; Aiwen, L. *Chem. Rev.* **2011**, *111*, 1780–1824. (d) Yoo, W.-J.; Li, C.-J. *Top. Curr. Chem.* **2010**, *292*, 281–302 and references cited therein.

(3) A review: Satoh, T.; Miura, M. *Chem.—Eur. J.* **2010**, *16*, 11212–11222.

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(6) For recent reviews on transition-metal-catalyzed coupling reactions in or on water, see: (a) Li, C.-J. *Handbook Of Green Chemistry: Reactions In Water*; Wiley-VCH: Weinheim, 2010; Vol. 5. (b) Li, C.-J. *Acc. Chem. Res.* **2010**, *43*, 581–590. (c) Lipshutz, B. H.; Abela, A. R.; Boskovic, Z. V.; Nishikata, T.; Duplais, C.; Krasovskiy, A. *Top. Catal.* **2010**, *53*, 985–990. (d) Butler, R. N.; Coyne, A. G. *Chem. Rev.* **2010**, *110*, 6302–6337. (e) Herreras, C. I.; Yao, X.; Li, Z.; Li, C.-J. *Chem. Rev.* **2007**, *107*, 2546–2562 and references cited therein.

for the reoxidation of rhodium(I) intermediates, thereby preventing the use of additional external oxidants.

Water is a nonflammable, nontoxic, green solvent,<sup>6</sup> which has attracted considerable recent attention as a reaction medium for sustainable C–H bond functionalizations.<sup>7</sup> Given our interest in employing water as a user-friendly solvent for catalyzed C–H bond transformations,<sup>8,9</sup> we thus became attracted by devising first metal-catalyzed direct annulations<sup>10</sup> of alkynes by benzamides in water,<sup>11</sup> on which we report herein. Intriguingly, the remarkable chemoselectivity of the optimized ruthenium(II) carboxylate catalyst allowed for the use of *N*-methoxybenzamides as well as more atom-economical free hydroxamic acids for syntheses of isoquinolones, indispensable structural motifs in bioactive compounds of importance to medicinal chemistry.<sup>12</sup>

At the outset of our studies, we probed the effect of a set of cocatalytic additives for the envisioned coupling of *N*-methoxybenzamide (**1a**) with alkyne **2a** in water as green solvent (Table 1). Unfortunately, the use of KPF<sub>6</sub> did not provide a satisfactory rate acceleration (entries 1 and 2). Yet, among different carboxylate additives, sterically hindered KO<sub>2</sub>CMes provided optimal yields of the desired product **3aa** (entries 3–7). Furthermore, it is noteworthy that water compared favorably with respect to representative organic solvents (entries 7–12).

With optimized reaction conditions in hand, we explored the scope of the ruthenium-catalyzed annulation of alkynes **2** by differently substituted *N*-methoxybenzamides **1** with water as a reaction medium (Scheme 1).

Notably, the catalytic system proved broadly applicable, thus enabling the efficient conversion of both electron-rich arenes **1b–1d** as well as electron-deficient derivatives **1e–1h** displaying valuable functionalities, such as nitro- or halo-substituents.

Moreover, alkyl-substituted alkynes **2** were converted with high catalytic efficacy as well (Scheme 2), while

(7) Select examples of palladium-catalyzed C–H bond functionalizations in or on water: (a) Ohnmacht, S. A.; Culshaw, A. J.; Greaney, M. F. *Org. Lett.* **2010**, *12*, 224–226. (b) Nishikata, T.; Lipshutz, B. H. *Org. Lett.* **2010**, *12*, 1972–1975. (c) Nishikata, T.; Abela, A. R.; Lipshutz, B. H. *Angew. Chem., Int. Ed.* **2010**, *49*, 781–784. (d) Ohnmacht, S. A.; Mamone, P.; Culshaw, A. J.; Greaney, M. F. *Chem. Commun.* **2008**, 1241–1243. (e) Turner, G.; Morris, J. A.; Greaney, M. F. *Angew. Chem., Int. Ed.* **2007**, *46*, 7996–8000 and references cited therein.

(8) (a) Ackermann, L.; Pospech, J. *Org. Lett.* **2011**, *13*, 4153–4155. (b) Ackermann, L.; Hofmann, N.; Vicente, R. *Org. Lett.* **2011**, *13*, 1875–1877. (c) Ackermann, L. *Org. Lett.* **2005**, *7*, 3123–c. A review: (d) Ackermann, L. *Chem. Commun.* **2010**, *46*, 4866–4877.

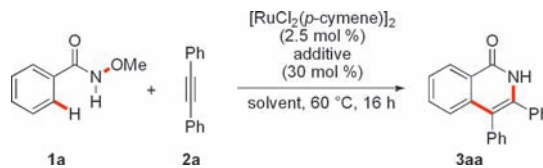
(9) See also: Arockiam, P. B.; Fischmeister, C.; Bruneau, C.; Dixneuf, P. H. *Angew. Chem., Int. Ed.* **2010**, *49*, 6629–6632 and references cited therein.

(10) For ruthenium-catalyzed oxidative annulations of alkynes with stoichiometric or cocatalytic amounts of external oxidants, see: (a) Ackermann, L.; Lygin, A. V.; Hofmann, N. *Angew. Chem., Int. Ed.* **2011**, *50*, 6379–6382. (b) Ackermann, L.; Lygin, A. V.; Hofmann, N. *Org. Lett.* **2011**, *13*, 3278–3281. (c) Ackermann, L.; Wang, L.; Lygin, A. V. *Chem. Sci.* **2011**, *2*, DOI:10.1039/C1SC00619C.

(11) During the preparation of our manuscript a ruthenium-catalyzed annulation with hydroxamic acid esters in MeOH as the solvent was reported: Li, B.; Feng, H.; Xu, S.; Wang, B. *Chem.—Eur. J.* **2011**, *17*, DOI: 10.1002/chem.201102445.

(12) (a) Eicher, T.; Hauptmann, S. *The Chemistry of Heterocycles*, 2nd ed.; Wiley-VCH: Weinheim, 2003. (b) Joule, J. A.; Mills, K. *Heterocyclic Chemistry*, 4th ed.; Blackwell Science Ltd.: Oxford, 2000, and references cited therein.

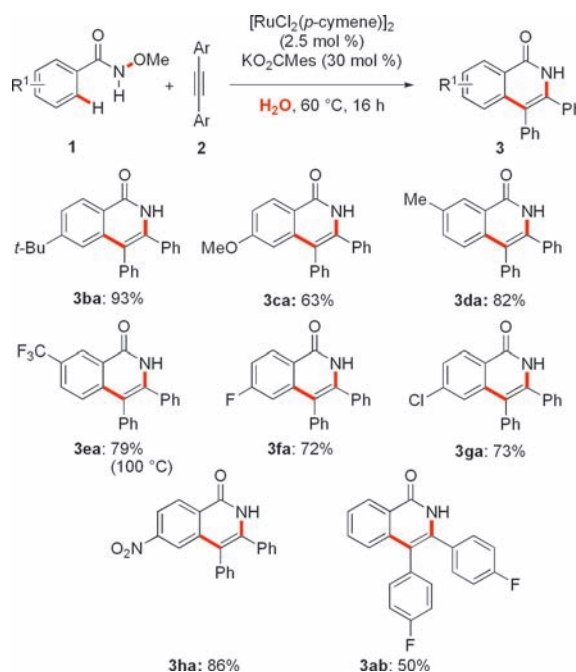
**Table 1.** Optimization of Isoquinolone Synthesis<sup>a</sup>



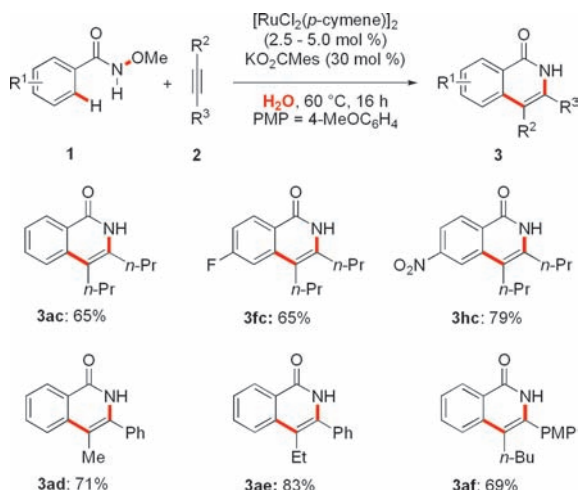
entry	additive	solvent	yield
1	—	H <sub>2</sub> O	17%
2	KPF <sub>6</sub>	H <sub>2</sub> O	25%
3	KOAc	H <sub>2</sub> O	11%
4	NaOAc	H <sub>2</sub> O	17%
5	CsOAc	H <sub>2</sub> O	46% <sup>b</sup>
6	KOPiv	H <sub>2</sub> O	58%
7	KO <sub>2</sub> CMes	H <sub>2</sub> O	81%
8	KO <sub>2</sub> CMes	<i>t</i> -AmOH	19%
9	KO <sub>2</sub> CMes	MeOH	65%
10	KO <sub>2</sub> CMes	DMF	3%
11	KO <sub>2</sub> CMes	PhMe	26% <sup>b</sup>
12	KO <sub>2</sub> CMes (10 mol %)	H <sub>2</sub> O	76%

<sup>a</sup> Reaction conditions: **1a** (0.5 mmol), **2a** (1.0 mmol), [RuCl<sub>2</sub>(*p*-cymene)]<sub>2</sub> (2.5 mol %), additive (30 mol %), solvent (2.0 mL), 16 h; isolated yields. <sup>b</sup> GC-conversion.

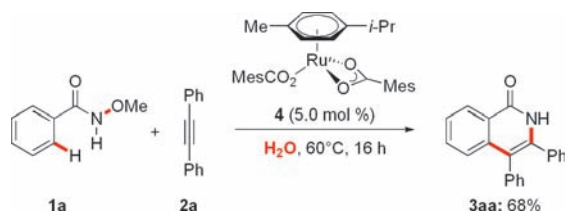
**Scheme 1.** Scope of C–H/N–O Bond Functionalization in Water



unsymmetrical alkynes **2d–2f** provided the desired products **3ad–3af** with excellent regioselectivities.

**Scheme 2.** Reaction Scope with Alkyl-Alkynes **2** in Water

As to the catalyst's working mode it is noteworthy that well-defined ruthenium(II) carboxylate complex **4**<sup>13</sup> displayed an efficacy comparable to the one observed when using the *in situ* generated catalytic system (Scheme 3).

**Scheme 3.** Well-Defined Complex **4** As Catalyst

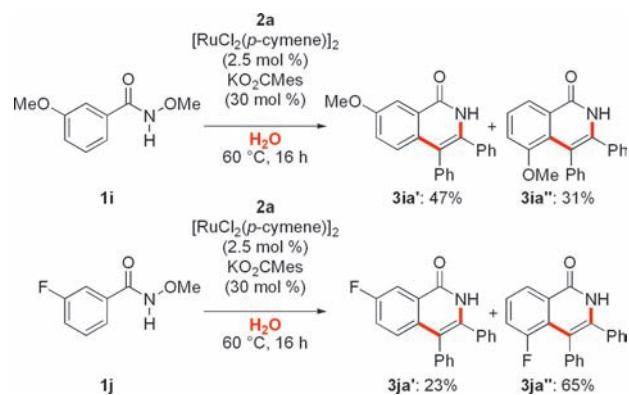
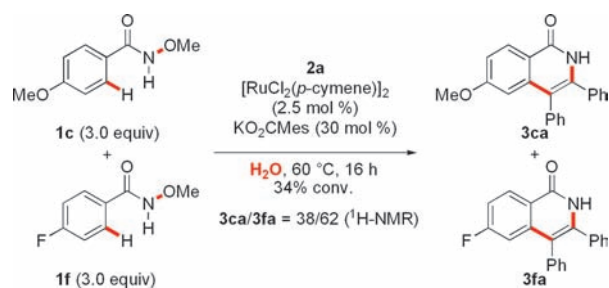
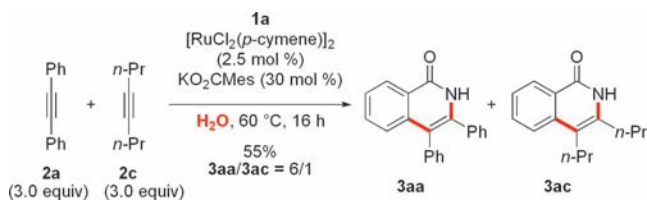
Intramolecular competition experiments with substrates **1i** and **1j** bearing heteroatom-containing substituents in the *meta*-position occurred with a significantly altered site selectivity (Scheme 4) as compared to a *meta*-methyl-substituted *N*-methoxybenzamide (**1d**) (**3da**, Scheme 1). This observation can be rationalized with the key cyclo-ruthenation step depending on the kinetic C–H bond acidity.<sup>14</sup>

Additionally, intermolecular competition experiments indicated electron-deficient arenes to be preferentially functionalized (Scheme 5), hence rendering an electrophilic activation manifold less likely to be operative.

Intermolecular competition experiments between differently substituted alkynes **2a** and **2c** revealed toluene (**2a**) to be predominantly reacted (Scheme 6).

(13) (a) Ackermann, L.; Novák, P.; Vicente, R.; Hofmann, N. *Angew. Chem., Int. Ed.* **2009**, *48*, 6045–6048. (b) Ackermann, L.; Vicente, R.; Potukuchi, H. K.; Pirovano, V. *Org. Lett.* **2010**, *12*, 5032–5035.

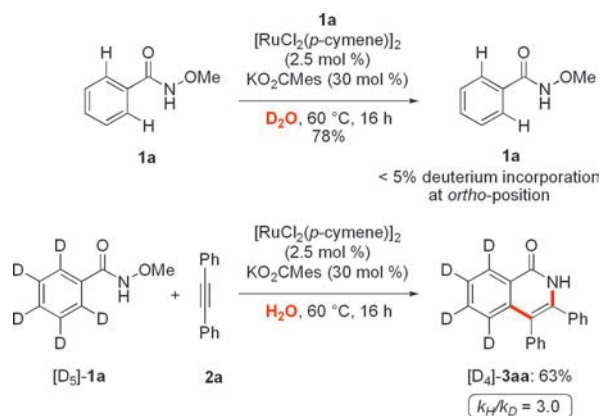
(14) Ackermann, L. *Chem. Rev.* **2011**, *111*, 1315–1345.

**Scheme 4.** Site Selectivity with *Meta*-Substituted Arenes**Scheme 5.** Intermolecular Competition Experiment**Scheme 6.** Competition Experiment between Alkynes **2a** and **2c**

Further, annulations with differently substituted diaryl-alkynes highlighted electron-deficient derivatives to be converted with higher relative reaction rates.<sup>15</sup>

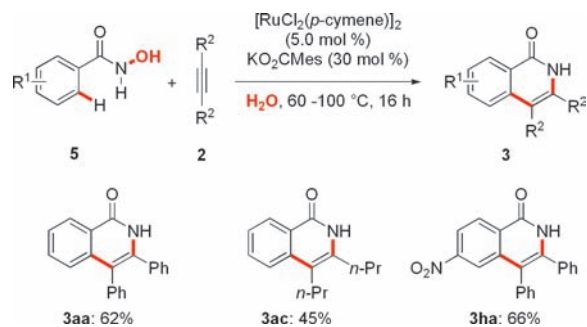
Experiments with isotopically labeled solvent and substrate [D<sub>5</sub>]-**1a** were suggestive of an irreversible C–H bond metalation (Scheme 7), which constitutes a notable difference to rhodium-catalyzed C–H bond functionalizations with *N*-methoxybenzamides.<sup>5b</sup> Moreover, the kinetic isotope effect (KIE) was determined to be  $k_H/k_D \approx 3.0$ ,<sup>15</sup> which can be rationalized with a working mode involving carboxylate-assisted ruthenation as the rate-limiting step.

(15) See the Supporting Information for further details.

**Scheme 7.** Studies with D<sub>2</sub>O and Labeled Substrate [D<sub>5</sub>]-1a

Finally, we were intrigued by the possibility of directly using significantly more atom-economical free hydroxamic acids **5** for ruthenium-catalyzed annulations of alkynes by C–H/N–O bond cleavages. Thus, we were pleased to observe that isoquinolones **3** were efficiently accessible from user-friendly acids **5** in water (Scheme 8), thereby further illustrating the remarkable robustness of the inexpensive ruthenium catalyst.

In summary, we have reported on first catalyzed annulations of alkynes by benzamides through C–H bond cleavages with water as a green reaction medium. Thus, carboxylate assistance set the stage for a broadly applicable ruthenium-catalyzed isoquinolone synthesis from

**Scheme 8.** Free Hydroxamic Acids **5** as Substrates

*N*-methoxybenzamides. Moreover, the extraordinary robustness and chemoselectivity of the ruthenium(II) carboxylate catalyst allowed for the direct use of free hydroxamic acids in annulations of alkynes. Further applications of inexpensive ruthenium complexes to catalyzed oxidative C–H bond functionalizations are ongoing in our laboratories and will be reported in due course.

**Acknowledgment.** Support by the DFG is gratefully acknowledged.

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