ORGANIC LETTERS

XXXX
Vol. XX, No. XX
000–000

# Hydroxyl-Directed Ruthenium-Catalyzed C−H Bond Functionalization: Versatile Access to Fluorescent Pyrans

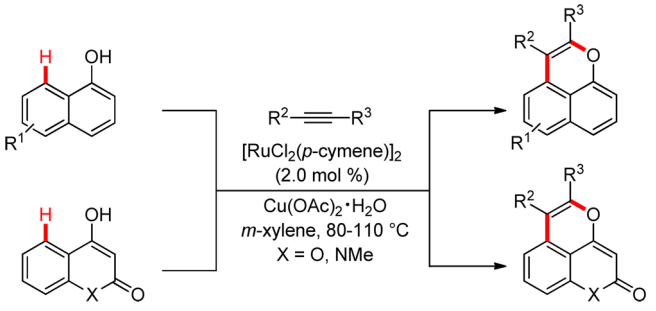
**Vedhagiri S. Thirunavukkarasu, Margherita Donati, and Lutz Ackermann***

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

*Lutz.Ackermann@chemie.uni-goettingen.de*

**Received May 19, 2012**

## ABSTRACT




**Hydroxyl-assisted oxidative annulations of alkynes were accomplished with an inexpensive ruthenium(II) complex, delivering fluorescent pyrans *via* highly site selective as well as chemo- and regioselective C−H/O−H bond functionalizations.**

Oxidative C−H bond functionalizations[1] provide step-economical access to important bioactive heteroarenes, the vast majority of which have thus far been prepared with the aid of palladium or rhodium catalysts.[2] A significant recent advance in direct C−H bond functionalizations was represented by the development of palladium and rhodium catalysts that proved applicable to hydroxyl groups as versatile Lewis basic directing groups.[3] While rather inexpensive[4] ruthenium complexes have very recently emerged as powerful catalysts for oxidative annulations of alkynes *via* C−H/N−H or C−H/C−O bond cleavages,[5−9] ruthenium-catalyzed oxidative[10] C−H bond functionalizations utilizing ubiquitous hydroxyl groups have unfortunately as of yet proven elusive. Within our program on catalyzed direct C−H bond transformations for a streamlining of organic synthesis,[11] we consequently became interested in exploring the possibility of controlling site selectivity in oxidative C−H bond functionalizations through hydroxyl assistance. To this end, we employed naphthols **1** as substrates, which were only recently utilized by Miura, Satoh and co-workers in elegant rhodium-catalyzed couplings, however, unfortunately solely with symmetrical alkynes.[12] Considering the importance of unsymmetrically

(1) Recent illustrative reviews on C−H bond functionalizations: (a) Engle, K. M.; Mei, T.-S.; Wasa, M.; Yu, J.-Q. *Acc. Chem. Res.* **2012**, DOI: 10.1021/ar200185g. (b) Hickman, A. J.; Sanford, M. S. *Nature* **2012**, *484*, 177–185. (c) Yeung, C. S.; Dong, V. M. *Chem. Rev.* **2011**, *111*, 1215–1292. (d) McMurray, L.; O'Hara, F.; Gaunt, M. J. *Chem. Soc. Rev.* **2011**, *40*, 1885–1898. (e) Wencel-Delord, J.; Dröge, T.; Liu, F.; Glorius, F. *Chem. Soc. Rev.* **2011**, *40*, 4740–4761. (f) Ackermann, L.; Potukuchi, H. K. *Org. Biomol. Chem.* **2010**, *8*, 4503–4513. (g) Daugulis, O. *Top. Curr. Chem.* **2010**, *292*, 57–84. (h) Sun, C.-L.; Li, B.-J.; Shi, Z.-J. *Chem. Commun.* **2010**, *46*, 677–685. (i) Colby, D. A.; Bergman, R. G.; Ellman, J. A. *Chem. Rev.* **2010**, *110*, 624–655. (j) Fagnou, K. *Top. Curr. Chem.* **2010**, *292*, 35–56. (k) Boutadla, Y.; Davies, D. L.; Macgregor, S. A.; Poblador-Bahamonde, A. I. *Dalton Trans.* **2009**, 5820–5831. (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 and references cited therein.

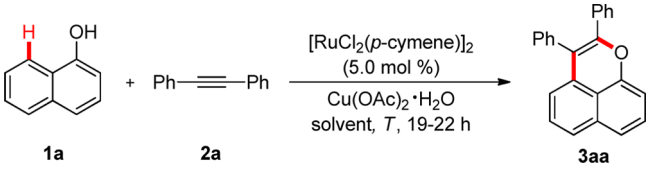
(2) For representative recent reviews, see: (a) Zhu, C.; Wang, R.; Falck, J. R. *Chem. Asian J.* **2012**, DOI: 10.1002/asia.201200035. (b) Song, G.; Wang, F.; Li, X. *Chem. Soc. Rev.* **2012**, *41*, 3651–3678. (c) Satoh, T.; Miura, M. *Chem.—Eur. J.* **2010**, *16*, 11212–11222. For selected recent examples, see: (d) Duttwyler, S.; Lu, C.; Rheingold, A. L.; Bergman, R. G.; Ellman, J. A. *J. Am. Chem. Soc.* **2012**, *134*, 4064–4067. (e) Muralirajan, K.; Parthasarathy, K.; Cheng, C.-H. *Angew. Chem., Int. Ed.* **2011**, *50*, 4169–4172. (f) Hyster, T. K.; Rovis, T. *Chem. Sci.* **2011**, *2*, 1606–1610. (g) Huestis, M. P.; Chan, L.; Stuart, D. R.; Fagnou, K. *Angew. Chem., Int. Ed.* **2011**, *50*, 1338–1341. (h) Shiota, H.; Ano, Y.; Aihara, Y.; Fukumoto, Y.; Chatani, N. *J. Am. Chem. Soc.* **2011**, *133*, 14952–14955. (i) Patureau, F. W.; Besset, T.; Kuhl, N.; Glorius, F. *J. Am. Chem. Soc.* **2011**, *133*, 2154–2156. (j) Shi, Z.; Ding, S.; Cui, Y.; Jiao, N. *Angew. Chem., Int. Ed.* **2009**, *48*, 7895–7898. (k) Umeda, N.; Tsurugi, H.; Satoh, T.; Miura, M. *Angew. Chem., Int. Ed.* **2008**, *47*, 4019–4022. (l) Ueura, K.; Satoh, T.; Miura, M. *Org. Lett.* **2007**, *9*, 1407–1409 and references cited therein.

10.1021/ol301387t 

substituted naphtha[1,8-*bc*]pyrans as key structural motifs of bioactive compounds[13] and in optoelectronics,[14] we particularly became attracted by the use of unsymmetrical alkynes for oxidative annulations with inexpensive ruthenium catalysts.

At the outset, we probed various reaction conditions for the envisioned oxidative annulation of alkyne **2a** by α-naphthol (**1a**) (Table 1). Among a set of representative solvents, *t*-AmOH, 1,4-dioxane, and toluene furnished promising results, while optimal yields were obtained with *m*-xylene (entries 1−11). Interestingly, an increase of the reaction temperature led to a decreased yield of the desired product **3aa** (entries 11 and 12), and an aerobic oxidative annulation under an atmosphere of ambient air proved viable (entries 13−15). Furthermore, $CuBr_2$ could be utilized as the oxidant, provided that NaOAc was present as an additive (entries 16−19), hence highlighting carboxylate assistance to be of key importance.[15,16]

**Table 1.** Hydroxyl Assistance for Oxidative Annulation[a]




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

| entry | solvent | oxidant | *T* (°C) | yield (%) |
|---|---|---|---|---|
| 1 | DMSO | $Cu(OAc)_2 \cdot H_2O$ | 80 | – |
| 2 | NMP | $Cu(OAc)_2 \cdot H_2O$ | 80 | – |
| 3 | DCE | $Cu(OAc)_2 \cdot H_2O$ | 80 | 18 |
| 4 | $H_2O$ | $Cu(OAc)_2 \cdot H_2O$ | 80 | 11 |
| 5 | AcOH | $Cu(OAc)_2 \cdot H_2O$ | 80 | 5 |
| 6 | DMF | $Cu(OAc)_2 \cdot H_2O$ | 80 | 26 |
| 7 | DME | $Cu(OAc)_2 \cdot H_2O$ | 80 | 33 |
| 8 | *t*-AmOH | $Cu(OAc)_2 \cdot H_2O$ | 80 | 59 |
| 9 | 1,4-dioxane | $Cu(OAc)_2 \cdot H_2O$ | 80 | 42 |
| 10 | PhMe | $Cu(OAc)_2 \cdot H_2O$ | 80 | 66 |
| 11 | *m*-xylene | $Cu(OAc)_2 \cdot H_2O$ | 80 | 89 |
| 12 | *m*-xylene | $Cu(OAc)_2 \cdot H_2O$ | 110 | 55 |
| 13 | *m*-xylene | $Cu(OAc)_2 \cdot H_2O$ | 80 | –[b] |
| 14 | *m*-xylene | $Cu(OAc)_2 \cdot H_2O$ | 80 | –[c] |
| 15 | *m*-xylene | $Cu(OAc)_2 \cdot H_2O$ (20 mol %) | 80 | 45[d] |
| 16 | *m*-xylene | $CuBr_2$ | 80 | – |
| 17 | *m*-xylene | $CuBr_2$/NaOAc[e] | 80 | 41 |
| 18 | ***m*-xylene** | **$Cu(OAc)_2 \cdot H_2O$** | **80** | **89**[f] |
| 19 | *m*-xylene | $Cu(OAc)_2 \cdot H_2O$ | 80 | 74[g] |

[a] Reaction conditions: **1a** (1.0 mmol), **2a** (0.5 mmol), oxidant (1.0 mmol), $[RuCl_2(p\text{-cymene})]_2$ (5.0 mol %), solvent (3.0 mL); isolated yields. [b] Without $[RuCl_2(p\text{-cymene})]_2$. [c] Without $Cu(OAc)_2 \cdot H_2O$. [d] Under air (1 atm), GC-conversion. [e] NaOAc (1.5 mmol). [f] $[RuCl_2(p\text{-cymene})]_2$ (2.0 mol %). [g] **1a** (0.5 mmol), **2a** (1.0 mmol).

With an optimized catalytic system in hand, we tested its scope in the oxidative annulation of alkynes **2** by naphthol derivatives **1** (Scheme 1). The ruthenium(II) catalyst allowed for the efficient conversion of decorated substrates **1** and displayed a remarkable tolerance of valuable electrophilic

(3) For pertinent examples, see: (a) Simmons, E. M.; Hartwig, J. F. *Nature* **2012**, *483*, 70–73. (b) Lu, Y.; Leow, D.; Wang, X.; Engle, K. M.; Yu, J.-Q. *Chem. Sci.* **2011**, *2*, 967–971. (c) Wei, Y.; Yoshikai, N. *Org. Lett.* **2011**, *13*, 5504–5507. (d) Xiao, B.; Gong, T.-J.; Liu, Z.-J.; Liu, J.-H.; Luo, D.-F.; Xu, J.; Liu, L. *J. Am. Chem. Soc.* **2011**, *133*, 9250–9253. (e) Wang, X.; Lu, Y.; Dai, H.-X.; Yu, J.-Q. *J. Am. Chem. Soc.* **2010**, *132*, 12203–12205. (f) Morimoto, K.; Hirano, K.; Satoh, T.; Miura, M. *J. Org. Chem.* **2011**, *76*, 9548–9551. (g) Lewis, J. C.; Wu, J.; Bergman, R. G.; Ellman, J. A. *Organometallics* **2005**, *24*, 5737–5746. (h) Bedford, R. B.; Coles, S. J.; Hursthouse, M. B.; Limmert, M. E. *Angew. Chem., Int. Ed.* **2003**, *42*, 112–114. (i) Kawamura, Y.; Satoh, T.; Miura, M.; Nomura, M. *Chem. Lett.* **1999**, 961–962. (j) Satoh, T.; Kawamura, Y.; Miura, M.; Nomura, M. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 1740–1742 and references cited therein.

(4) $[\{Cp^*RhCl_2\}_2]$: € 638 versus $[\{RuCl_2(p\text{-cymene})\}_2]$: € 77 (2.0 g, Sigma−Aldrich, 19.05.2012).

(5) Amides: (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) Hashimoto, Y.; Ueyama, T.; Fukutani, T.; Hirano, K.; Satoh, T.; Miura, M. *Chem. Lett.* **2011**, *40*, 1165–1166.

(6) Acids: (a) Ackermann, L.; Pospech, J. *Org. Lett.* **2011**, *13*, 4153–4155. (b) Ackermann, L.; Pospech, J.; Graczyk, K.; Rauch, K. *Org. Lett.* **2012**, *14*, 930–933. (c) Chinnagolla, R. K.; Jeganmohan, M. *Chem. Commun.* **2012**, *48*, 2030–2032. See also: (d) Ueyama, T.; Mochida, S.; Fukutani, T.; Hirano, K.; Satoh, T.; Miura, M. *Org. Lett.* **2011**, *13*, 706–708. (e) Ketones: Chinnagolla, R. K.; Jeganmohan, M. *Eur. J. Org. Chem.* **2012**, 417–423.

(7) (a) (*NH*)-Azoles: Ackermann, L.; Wang, L.; Lygin, A. V. *Chem. Sci.* **2012**, *3*, 177–180. (b) Anilides: Ackermann, L.; Lygin, A. V. *Org. Lett.* **2012**, *14*, 764–767.

(8) *N*-Methoxybenzamides: (a) Ackermann, L.; Fenner, S. *Org. Lett.* **2011**, *13*, 6548–6551. (b) Li, B.; Ma, J.; Wang, N.; Feng, H.; Xu, S.; Wang, B. *Org. Lett.* **2012**, *14*, 736–739.

(9) Selected oxidative alkenylations: (a) Ackermann, L.; Wang, L.; Wolfram, R.; Lygin, A. V. *Org. Lett.* **2012**, *14*, 728–731. (b) Arockiam, P. B.; Fischmeister, C.; Bruneau, C.; Dixneuf, P. H. *Green Chem.* **2011**, *13*, 3075–3078. (c) Hashimoto, Y.; Hirano, K.; Satoh, T.; Kakiuchi, F.; Miura, M. *Org. Lett.* **2012**, *14*, 2058–2061. (d) Kwon, K.-H.; Lee, D. W.; Yi, C. S. *Organometallics* **2010**, *29*, 5748–5750. (e) Weissman, H.; Song, X.; Milstein, D. *J. Am. Chem. Soc.* **2001**, *123*, 337–338 and references cited therein.

(10) For recent dehydrative (non-oxidative) direct alkylations, see: Lee, D.-H.; Kwon, K.-H.; Yi, C. S. *J. Am. Chem. Soc.* **2012**, *134*, 7325–7328.

(11) Recent reviews: (a) Ackermann, L. *Pure Appl. Chem.* **2010**, *82*, 1403–1413. (b) Ackermann, L. *Isr. J. Chem.* **2010**, *50*, 652–663. (c) Ackermann, L.; Vicente, R. *Top. Curr. Chem.* **2010**, *292*, 211–229.

(12) Mochida, S.; Shimizu, M.; Hirano, K.; Satoh, T.; Miura, M. *Chem.—Asian J.* **2010**, *5*, 847–851.

(13) Representative examples: (a) Shin, D.-Y.; Kim, S. N.; Chae, J.-H.; Hyun, S.-S.; Seo, S.-Y.; Lee, Y.-S.; Lee, K.-O.; Kim, S.-H.; Lee, Y.-S.; Jeong, J. M.; Choi, N.-S.; Suh, Y.-G. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 4519–4523. (b) Suh, Y.-G.; Shin, D.-Y.; Min, K.-H.; Hyun, S.-S.; Jung, J.-K.; Seo, S.-Y. *Chem. Commun.* **2000**, 1203–1204.

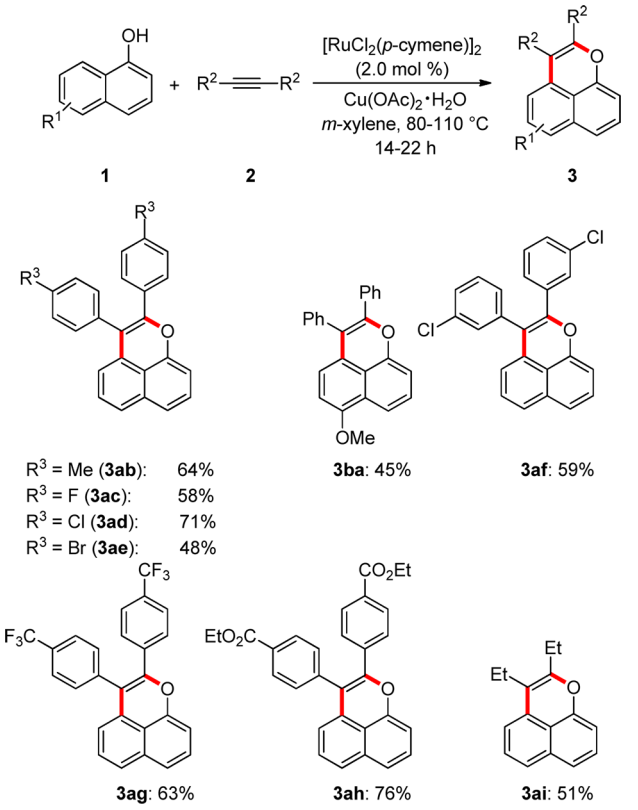
(14) Selected examples: (a) Tyson, D. S.; Fabrizio, E. F.; Panzner, M. J.; Kinder, J. D.; Buisson, J.-P.; Christensen, J. B.; Meador, M. A. *J. Photochem. Photobiol. A* **2005**, *172*, 97–107. (b) Christensen, J. B.; Johannsen, I.; Bechgaard, K. *J. Org. Chem.* **1991**, *56*, 7055–7058.

(15) Examples of carboxylate-assisted ruthenium-catalyzed arylations and alkylations: (a) Ackermann, L.; Pospech, J.; Potukuchi, H. K. *Org. Lett.* **2012**, *14*, 2146–2149. (b) Ackermann, L.; Diers, E.; Manvar, A. *Org. Lett.* **2012**, *14*, 1154–1157. (c) Ackermann, L.; Lygin, A. *Org. Lett.* **2011**, *13*, 3332–3335. (d) Ouellet, S. G.; Roy, A.; Molinaro, C.; Angelaud, R.; Marcoux, J.-F.; O'Shea, P. D.; Davies, I. W. *J. Org. Chem.* **2011**, *76*, 1436–1439. (e) Ackermann, L.; Vicente, R.; Potukuchi, H. K.; Pirovano, V. *Org. Lett.* **2010**, *12*, 5032–5035. (f) Arockiam, P.; Poirier, V.; Fischmeister, C.; Bruneau, C.; Dixneuf, P. H. *Green Chem.* **2009**, *11*, 1871–1875. (g) Ackermann, L.; Vicente, R. *Org. Lett.* **2009**, *11*, 4922–4925. (h) Ackermann, L.; Novák, P. *Org. Lett.* **2009**, *11*, 4966–4969. (i) Ackermann, L.; Vicente, R.; Althammer, A. *Org. Lett.* **2008**, *10*, 2299–2302.

(16) A review: (a) Ackermann, L. *Chem. Rev.* **2011**, *111*, 1315–1345. Examples of acetate-assisted stoichiometric cyclometalations: (b) Duff, J. M.; Shaw, B. L. *J. Chem. Soc., Dalton Trans.* **1972**, 2219–2225. (c) Davies, D. L.; Al-Duaij, O.; Fawcett, J.; Giardiello, M.; Hilton, S. T.; Russell, D. R. *Dalton Trans.* **2003**, 4132–4138.

functional groups, such as chloro, bromo, or ester substituents. The catalytic system was not restricted to tolan derivatives but proved applicable to the conversion of dialkyl alkyne **2i** as well,[17] thereby furnishing desired product **3ai**.

**Scheme 1.** Ruthenium-Catalyzed Annulation with Naphthols **1**



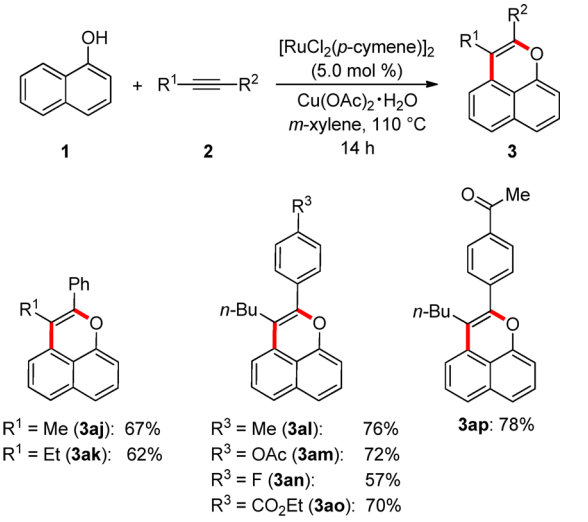

Given the importance of unsymmetrically substituted naphtha[1,8-*bc*]pyrans **3** in bioactive compounds and functional materials, we subsequently tested differently substituted alkynes **2** in the oxidative annulation (Scheme 2). Fortunately, the ruthenium(II) catalyst delivered the desired products **3aj**–**3ap** with high chemical yields and excellent regioselectivities. Interestingly, the novel annulated pyrans **3** and **5** showed remarkable fluorescence in a range of 430–560 nm.

The catalytic system was not limited to C–H bond functionalizations on naphthol derivatives **1**. Indeed, highly effective annulations of alkynes **2** also proved viable with 4-hydroxycoumarin **4** (Scheme 3). The ruthenium(II) catalyst showed a useful functional group tolerance and led to excellent regioselectivities with unsymmetrical alkynes **2**. Additionally, 4-hydroxy-substituted quinolin-2-one **6** was found to be a suitable substrate, which allowed for the step-economical preparation of annulated product **7aa**.

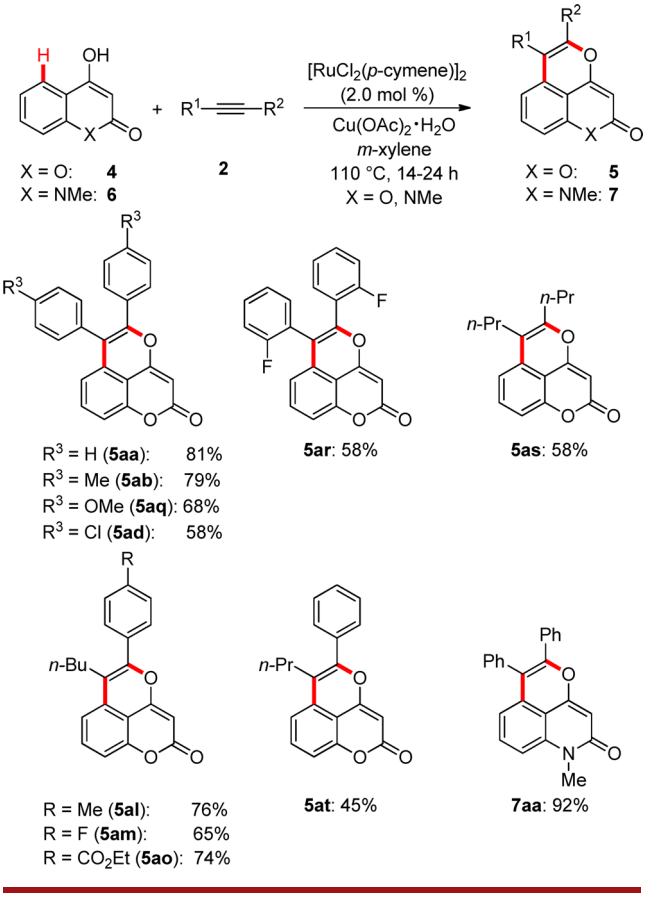
Given the high catalytic efficacy and excellent site selectivity and regioselectivity of our ruthenium catalyst, we became interested in its mode of action. To this end, we performed intermolecular competition experiments between differently substituted acetylenes, which revealed electron-deficient alkynes to be preferentially converted (Scheme 4 and the Supporting Information).

(17) Terminal alkyne 1-octyne provided thus far only unsatisfactory results.

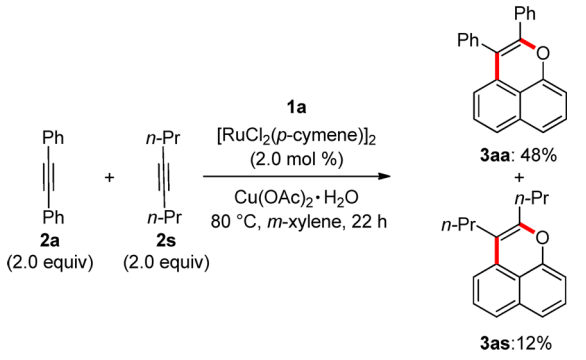
**Scheme 2.** Scope with Unsymmetrical Alkynes **2**




**Scheme 3.** Annulation with Coumarin **4** and Quinolin-2-one **6**

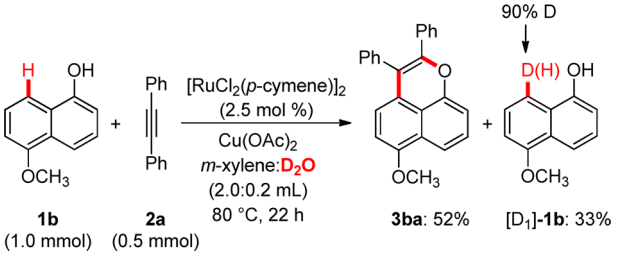


**Scheme 4.** Competition Experiment with Alkynes **2**




Furthermore, a catalytic C−H bond transformation in the presence of $D_2O$ employing an excess of substrate **1b** resulted in a significant D/H exchange in the *peri*-position of the recovered starting material [$D_1$]-**1b** (Scheme 5), thereby providing evidence for a reversible C−H bond ruthenation step.

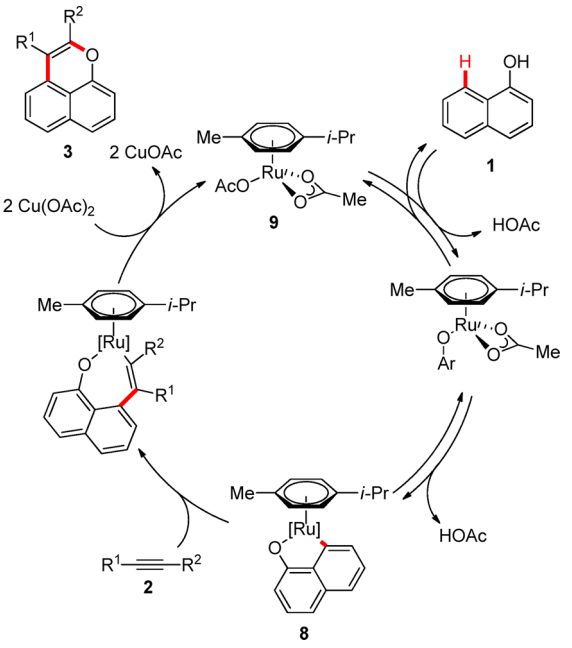
**Scheme 5.** Hydroxyl-Directed C−H Bond Functionalization with $D_2O$




Based on our mechanistic studies we propose a catalytic cycle involving initial reversible cycloruthenation to form complex **8** (Scheme 6). Subsequent migratory insertion of alkyne **2** and reductive elimination furnish desired product **3**, while reoxidation regenerates the catalytically active species [$Ru(O_2CMe)_2$(*p*-cymene)] (**9**).

In summary, we have reported on the first ruthenium-catalyzed oxidative C−H bond functionalization through

**Scheme 6.** Proposed Mechanism




hydroxyl assistance. Thus, a ruthenium(II) catalyst allowed for the efficient annulation of alkynes by naphthols to yield fluorescent annulated pyrans and gave step-economical access to diversely decorated coumarins and quinolin-2-ones with ample scope. Mechanistic studies provided evidence for a carboxylate-assisted reversible C−H bond ruthenation.

**Acknowledgment.** We thank Prof. Dr. Ulf Diederichsen (Georg-August-Universität Göttingen) for providing access to a fluorescence spectrometer. Support by the Alexander von Humboldt Foundation (fellowship to V.S.T.) is gratefully acknowledged.

**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.

The authors declare no competing financial interest.