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Ruthenium-Catalyzed Hydroarylations of Methylenecyclopropanes: Mild C−H Bond Functionalizations with Conservation of Cyclopropane Rings

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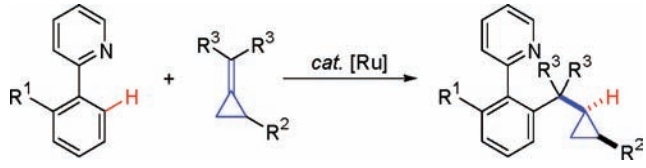
ABSTRACT



Ring conservation was observed in the first catalytic intermolecular hydroarylation of methylenecyclopropanes via C−H bond functionalization, a remarkable reactivity mode for a transformation proceeding through (cyclopropylcarbinyl)metal intermediates.

Transition-metal-catalyzed additions of arenes to C−C multiple bonds, hydroarylation reactions, have received considerable attention as an ecologically and economically benign approach to the direct functionalization[1] of aromatic C−H bonds. Consequently, a number of valuable protocols for intermolecular hydroarylations of alkenes, alkynes, and allenes have been developed,[2] with ruthenium-catalyzed[3] directed[4] C−H bond functionalizations being among the most powerful strategies.[5,6]

The chemistry of highly strained methylenecyclopropanes[7] is attractive because their enhanced reactivities allow to probe fundamental concepts in organic chemistry and enable the development of efficient synthetic methodologies. In particular, (transition) metals were found useful for the conversion of these highly strained starting materials.[8] Notably,

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(1) Recent reviews on C−H bond functionalizations, see: (a) Ackermann, L. *Top. Organomet. Chem* **2007**, *24*, 35–60. (b) Alberico, D.; Scott, M. E.; Lautens, M. *Chem. Rev.* **2007**, *107*, 174–238. (c) Stuart, D. R.; Fagnou, K. *Aldrichim. Acta* **2007**, *40*, 35–41. (d) Seregin, I. V.; Gevorgyan, V. *Chem. Soc. Rev.* **2007**, *36*, 1173–1193. (e) Ackermann, L. *Synlett* **2007**, 507–526. (f) Satoh, T.; Miura, M. *Chem. Lett.* **2007**, *36*, 200–205. (g) Catellani, M.; Motti, E.; Della Ca', N.; Ferraccioli, R. *Eur. J. Org. Chem.* **2007**, 4153–4165. (h) Daugulis, O.; Zaitsev, V. G.; Shabashov, D.; Pham, Q.-N.; Lazareva, A. *Synlett* **2006**, *20*, 3382–3388. (i) Yu, J.-Q.; Giri, R.; Chen, X. *Org. Biomol. Chem.* **2006**, *4*, 4041–4047.

(2) (a) Dyker, G., Ed. *Handbook of C-H Transformations*; Wiley-VCH: Weinheim, 2005. (b) Bandini, M.; Emer, E.; Tommasi, S.; Umani-Ronchi, A. *Eur. J. Org. Chem.* **2006**, 3527–3544. (c) Nevado, C.; Echavarren, A. M. *Synthesis* **2005**, 167–182. (d) Liu, C.; Bender, C. F.; Han, X.; Widenhoefer, R. A. *Chem. Commun.* **2007**, 3607–3618. (e) Kakiuchi, F.; Chatani, N. *Adv. Synth. Catal.* **2003**, *345*, 1077–1101. (f) Jia, C.; Kitamura, T.; Fujiwara, Y. *Acc. Chem. Res.* **2001**, *34*, 633–639, and references cited therein.

(3) Selected related intermolecular hydroarylations catalyzed by metals other than ruthenium: (a) Colby, D. A.; Bergman, R. G.; Ellman, J. A. *J. Am. Chem. Soc.* **2008**, *130*, 3645–3651. (b) Nakao, Y.; Kanyiva, K. S.; Hiyama, T. *J. Am. Chem. Soc.* **2008**, *130*, 2448–2449. (c) Lewis, J. C.; Bergman, R. G.; Ellman, J. A. *J. Am. Chem. Soc.* **2007**, *129*, 5332–5333. (d) Ueura, K.; Satoh, T.; Miura, M. *J. Org. Chem.* **2007**, *72*, 5362–5367. (e) Oxgaard, J.; Periana, R. A.; Goddard, W. A., III. *J. Am. Chem. Soc.* **2004**, *126*, 11658–11665. (f) Reetz, M. T.; Sommer, K. *Eur. J. Org. Chem.* **2003**, 3485–3496. (g) Jia, C.; Piao, D.; Oyamada, J.; Lu, W.; Kitamura, T.; Fujiwara, Y. *Science* **2000**, *287*, 1992–1995. (h) Jun, C.-H.; Hong, J.-B.; Kim, Y.-H.; Chung, K.-Y. *Angew. Chem., Int. Ed.* **2000**, *39*, 3440–3442. (i) Lenges, C. P.; Brookhart, M. *J. Am. Chem. Soc.* **1999**, *121*, 6616–6623.

(4) Kakiuchi, F. *Top. Organomet. Chem.* **2007**, *24*, 1–33.

(5) (a) Murai, S.; Kakiuchi, F.; Sekine, S.; Tanaka, Y.; Kamatani, A.; Sonoda, M.; Chatani, N. *Nature* **1993**, *366*, 529–531. (b) Kakiuchi, F.; Murai, S. *Acc. Chem. Res.* **2002**, *35*, 826–834. (c) Kakiuchi, F.; Chatani, N. In *Ruthenium in Organic Synthesis*; Murahashi, S.-I., Ed.; Wiley-VCH: Weinheim, 2004; pp 219−255, and references cited therein.

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these transformations proceeded almost exclusively via opening of at least one cyclopropane ring.[9] Herein, we report on the development of unprecedented intermolecular[10] hydroarylations of methylenecyclopropanes through C−H bond functionalizations, surprisingly occurring with conservation of all cyclopropane rings.

At the outset of our studies, we tested ruthenium-catalyzed[11] hydroarylations of methylenecyclopropane **2**, employing $[RuCl_2(cod)]_n$ as precatalyst[12] modified with a representative set of commonly used ligands (Figure 1). Due

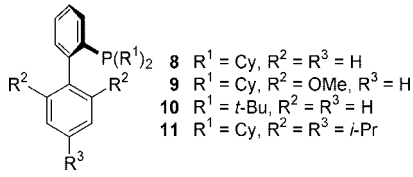


Figure 1. Ligands employed for catalytic hydroarylations.

to cyclopropane ring-opening, triaryl phosphines **4**−**6** provided rather unsatisfactory results (Table 1, entries 1−3).[13]

On the contrary, more selective catalysis was achieved with electron-rich phosphines **7**−**10** (entries 4−7), with monophosphine biphenyl ligand **11**[14] providing superior

(6) Selected additional ruthenium-catalyzed hydroarylations: (a) Foley, N. A.; Lail, M.; Lee, J. P.; Gunnoe, T. B.; Cundari, T. R.; Petersen, J. L. *J. Am. Chem. Soc.* **2007**, *129*, 6765–6781. (b) Martinez, R.; Chevalier, R.; Darses, S.; Genet, J.-P. *Angew. Chem., Int. Ed.* **2006**, *45*, 8232–8235. (c) Grellier, M.; Vendier, L.; Chaudret, B.; Albinati, A.; Rizzato, S.; Mason, S.; Sabo-Etienne, S. *J. Am. Chem. Soc.* **2005**, *127*, 17592–17593. (d) Busch, S.; Leitner, W. *Adv. Synth. Catal.* **2001**, *343*, 192–196. (e) Lewis, L. N.; Smith, J. F. *J. Am. Chem. Soc.* **1986**, *108*, 2728–2735, and references cited therein.

(7) (a) de Meijere, A.; Kozhushkov, S. I.; Schill, H. *Chem. Rev.* **2006**, *106*, 4926–4996. (b) Brandi, A.; Goti, A. *Chem. Rev.* **1998**, *98*, 589–636.

(8) Reviews on metal-promoted reactions of methylenecyclopropanes: (a) Binger, P.; Schmidt, T. In *Houben-Weyl*; de Meijere, A., Ed.; Thieme: Stuttgart, 1997; Vol. E17c, pp 2217−2294. (b) Nakamura, I.; Yamamoto, Y. *Adv. Synth. Catal.* **2002**, *344*, 111–129. (c) Rubin, M.; Rubina, M.; Gevorgyan, V. *Chem. Rev.* **2007**, *107*, 3117–3179.

(9) Only a few catalytic reactions were thus far reported, not resulting in an opening of at least one cyclopropane ring: (a) Takeuchi, D.; Anada, K.; Osakada, K. *Angew. Chem., Int. Ed.* **2004**, *43*, 1233–1235. (b) Pohlmann, T.; de Meijere, A. *Org. Lett.* **2000**, *2*, 3877–3879. (c) Tian, G.-Q.; Shi, M. *Org. Lett.* **2007**, *9*, 4917–4920. (d) Shao, L.-X.; Ming-Hui Qi, M.-H.; Shi, M. *Tetrahedron Lett.* **2008**, *49*, 165–168.

(10) A recent elegant intramolecular rhodium-catalyzed C−H bond activation with alkylidenecyclopropanes also resulted in ring opening of the cyclopropane moiety: Aïssa, C.; Fürstner, A. *J. Am. Chem. Soc.* **2007**, *129*, 14836–14837.

(11) Selected reports from our laboratories on ruthenium-catalyzed C−H bond functionalizations: (a) Ackermann, L.; Vicente, R.; Althammer, A. *Org. Lett.* **2008**, 2299–2302. (b) Ackermann, L.; Althammer, A.; Born, R. *Synlett* **2007**, 2833–2836. (c) Ackermann, L.; Born, R.; Alvarez-Bercedo, P. *Angew. Chem., Int Ed.* **2007**, *46*, 6364–6367. (d) Ackermann, L.; Althammer, A.; Born, R. *Angew. Chem., Int. Ed.* **2006**, *45*, 2619–2622. (e) Ackermann, L. *Org. Lett.* **2005**, *7*, 3123–3125.

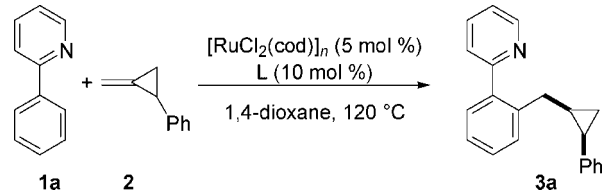
(12) Under otherwise identical reaction conditions, catalytic amounts of $[RhCl(cod)]_2$ and PPh_3 yielded quantitative ring opening of **2**, along with its polymerization, even at 50 °C reaction temperature.

(13) Here, only undesired by-products due to Diels−Alder [4 + 2] cycloadditions of 2-phenylbuta-1,4-diene were obtained (see the Supporting Information).

(14) Huang, X.; Anderson, K. W.; Zim, D.; Jiang, L.; Klapars, Buchwald, A. S. *J. Am. Chem. Soc.* **2003**, *125*, 6653–6655.

(15) de Meijere, A.; Kozhushkov, S. I.; Khlebnikov, A. F. *Top. Curr. Chem.* **2000**, *207*, 89–147.

Table 1. Ruthenium-Catalyzed Hydroarylation of **2**[a]



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

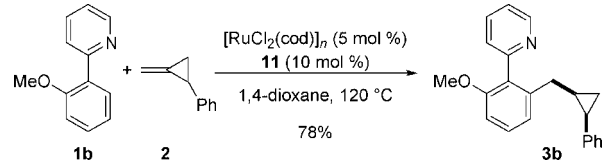
entry	L	**1a** (%)	**3a** (%)
1	PPh_3 (**4**)	97	
2	*rac*-BINAP (**5**)	97	
3	dppf (**6**)	96	
4	PCy_3 (**7**)	96	<5
5	**8**	95	<5
6	**9**	80	17
7	**10**	53	46
8	**11**	39	53
9	**11**	40	54[b]

[a] Reaction conditions: **1a** (1−2 mmol), **2** (3 equiv), $[RuCl_2(cod)]_n$ (5 mol %), L (10 mol %), 1,4-dioxane (3 mL), 120 °C, 48 h; cod = *cis*-1,4-cyclooctadiene. [b] NMP (3 mL) as solvent.

results (entries 8 and 9). Remarkably, the anti-Markovnikov addition of arene **1a** occurred with complete conservation of the three-membered ring, yielding cyclopropane derivate **3a** highly selectively.

The optimized catalyst enabled an efficient C−H bond functionalization of pyridine **1b** as well, giving rise to desired product **3b** with excellent chemo- and regioselectivity (Scheme 1).

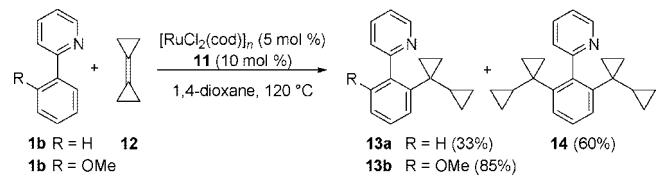
Scheme 1. Ruthenium-Catalyzed Hydroarylation with Pyridine **1b**



1b **2** **3b**

Therefore, we set out to probe the more challenging hydroarylation of bicyclopropylidene (**12**)[15] with pyridine derivatives **1a** and **1b** (Scheme 2). Under the optimized

Scheme 2. Ruthenium-Catalyzed Hydroarylation of Bicyclopropylidene **12**



1b R = H **12**
1b R = OMe

13a R = H (33%) **14** (60%)
13b R = OMe (85%)

reaction conditions, these substrates were converted into the corresponding *cis*-adducts **13a** and **13b**, as well as **14**, respectively, in high isolated yields.

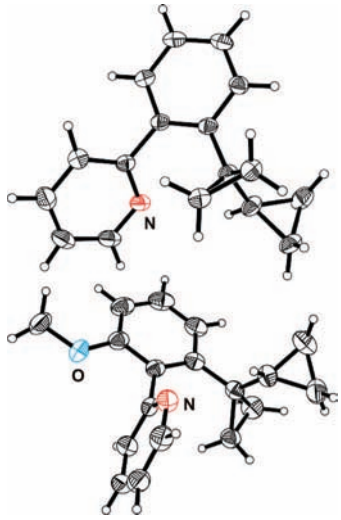


Figure 2. Molecular structures of pyridines **13a** (top) and **13b** (bottom) in the crystal.[16]

Importantly, X-ray diffraction analyses of novel products **13a**, **13b** (Figure 2), and **14** (Figure 3) revealed that all three-membered rings remained intact during the C−H bond functionalization reactions (Supporting Information).[16]

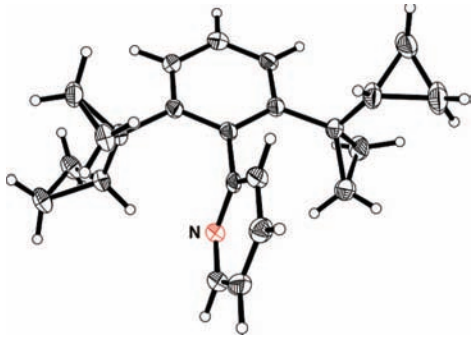
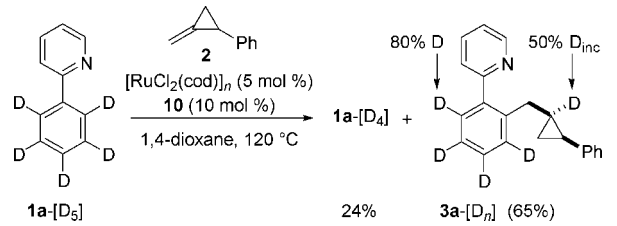


Figure 3. Molecular structure of pyridine **14** in the crystal.[16]

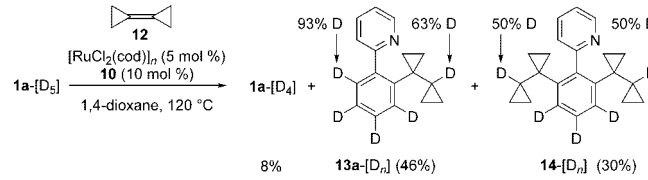
Since the high selectivity of our novel ruthenium catalyst enabled C−H bond functionalizations to occur with retention of cyclopropane moieties, we became interested in testing its working mode. Thus, we subjected deuterium labeled pyridine **1a**-[D_5] to the reaction conditions for the hydroarylation of alkene **2** (Scheme 3). Interestingly, deuterium incorporation into the cyclopropane moiety of product **3a** was found to be incomplete. Moreover, recovered starting material revealed a regioselective deuterium−proton exchange[17] at the *ortho*-position of pyridine **1a**-[D_5].

Scheme 3. Ruthenium-Catalyzed Hydroarylation of Alkene **2** with Pyridine **1a**-[D_5] (D_{inc} = ^{2}H Incorporation)



Notably, hydroarylation of bicyclopropylidene (**12**) with pyridine **1a**-[D_5] highlighted a regioselective deuterium−proton exchange as well, indicating that C−H bond activation is not rate-limiting (Scheme 4). In these deuterium−proton exchange reactions, starting materials **2** and **12**, respectively, served most likely as proton donors.[18]

Scheme 4. Ruthenium-Catalyzed Hydroarylation of Alkene **12** with Pyridine **1a**-[D_5] (D_{inc} = ^{2}H Incorporation)



Based on our observations, we propose a mechanistic rationale for ruthenium-catalyzed hydroarylations of methylelencyclopropanes depicted in Scheme 5. Coordination of the catalytically competent ruthenium complex **15**[19,20] ini-

(16) CCDC-678126 (**13a**), -688765 (**13b**), and -678125 (**14**) contain the supplementary crystallographic data for these compounds. The data can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html (or from the Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge CB21EZ, UK; fax: (+44)1223-336-033; or deposit@ccdc.cam.ac.uk).

(17) A deuterium−proton exchange was previously observed in hydroarylations of simple alkenes: (a) Kakiuchi, F.; Ohtaki, H.; Sonoda, M.; Chatani, N.; Murai, S. *Chem. Lett.* **2001**, *30*, 918–919. (b) Ie, Y.; Chatani, N.; Ogo, T.; Marshall, D. R.; Fukuyama, T.; Kakiuchi, F.; Murai, S. *J. Org. Chem.* **2000**, *65*, 1475–1488.

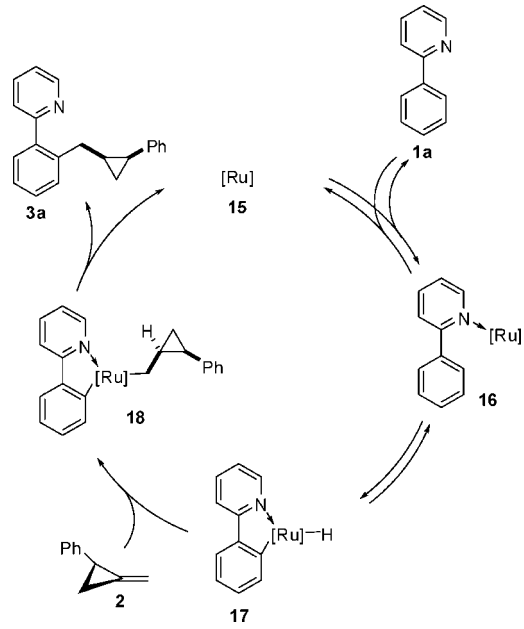
(18) When using DMF-[D_7] as solvent, proton−deuterium exchange on pyridines **1a** and **3a** was not observed under otherwise identical reaction conditions.

(19) The high selectivity obtained with monophosphine biphenyl ligand **11** is likely due to formation of arene-tethered ruthenium phosphine complexes. For the use of comparable phosphines in ruthenium catalysis, see: (a) Aikawa, K.; Kaito, I.; Mikami, K. *Chem. Lett.* **2007**, *36*, 1482–1483. (b) Faller, J. W.; Fontaine, P. P. *Organometallics* **2007**, *26*, 1738–1743, and references cited therein.

(20) The corresponding arene-tethered ruthenium phosphine complex derived from ligand **11** was isolated and unambigiously characterized: Kozhushkov, S. I.; Yufit, D. S.; Ackermann, L. Unpublished results.

(21) (a) Wendisch, D. In *Houben-Weyl*; Thieme: Stuttgart, 1971; Vol. 4/3, pp 399−405. (b) Dyker, G. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 2223–2224. (c) Nishihara, Y.; Yoda, C.; Osakada, K. *Organometallics* **2001**, *20*, 2124–2126. (d) Nüske, H.; Bräse, S.; Kozhushkov, S. I.; Noltemeyer, M.; Es-Sayed, M.; de Meijere, A. *Chem. Eur. J.* **2002**, *8*, 2350–2369. (e) Nishihara, Y.; Yoda, C.; Itazaki, M.; Osakada, K. *Bull. Chem. Soc. Jpn.* **2005**, *78*, 1469–1480. (f) Shi, M.; Wang, B.-Y.; Huang, J.-W. *J. Org. Chem.* **2005**, *70*, 5606–5610.

Scheme 5. Proposed Catalytic Cycle for Hydroarylations of Methylenecyclopropanes



tiates a rapid and *reversible* C−H bond activation, providing ruthenacycle **17**. Subsequently, cyclometalated complex **17** adds to alkene **2**. Reductive elimination from complex **18** yields the desired product **3a**, thereby regenerating the catalytically active species **15**.

The rate of the final reductive elimination in the catalytic cycle is at least of the order as the one observed for the well-known, very fast (cyclopropylmethyl)metal-to-homoallyl-metal rearrangement.[8c,21] The latter reorganization, along with a subsequent β-hydride elimination, results in the formation of buta-1,3-dienes as byproduct (see Supporting Information).[21c–f] When using **1a**-[D_5] as substrate, the generated [Ru-D] intermediate is, therefore, converted into the corresponding [Ru−H] complex, which likely accounts for the observed deuterium−proton exchange reactions.

In conclusion, we have developed the first protocol for intermolecular hydroarylations of highly strained methylenecyclopropanes via C−H bond functionalizations. Although these transformations involved (cyclopropylcarbinyl)metal intermediates, the high selectivity of our new catalytic system resulted in complete retention of the cyclopropane moieties in the products. This unique reactivity pattern is a strong testament for the mild reaction conditions of ruthenium-catalyzed C−H bond functionalizations.

Acknowledgment. Support by the DFG, the Fonds der Chemischen Industrie, EPSRC (UK), and Saltigo GmbH (Leverkusen) is gratefully acknowledged.

Supporting Information Available: Crystallographic data (CIF) for **13a**, **13b**, and **14**; experimental procedures and characterization data (^{1}H and ^{13}C NMR) for all products. This material is available free of charge via the Internet at http://pubs.acs.org.

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