Annulations

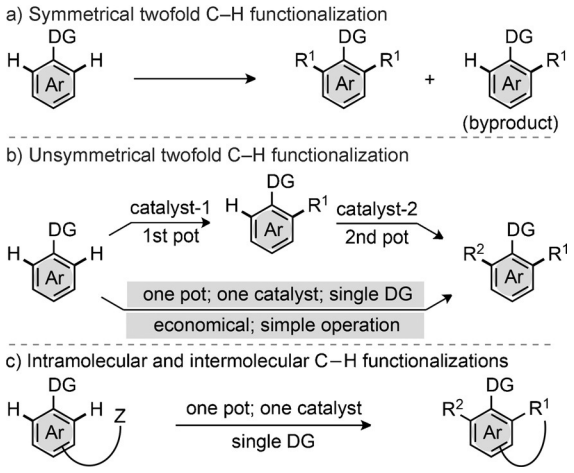
International Edition: DOI: 10.1002/anie.201600649
German Edition: DOI: 10.1002/ange.201600649

Ruthenium-Catalyzed Hydroarylation and One-Pot Twofold Unsymmetrical C–H Functionalization of Arenes

*Koushik Ghosh, Raja K. Rit, E. Ramesh, and Akhila K. Sahoo**

Abstract: *A methyl phenyl sulfoximine (MPS) is used as a directing group in the ruthenium-catalyzed intramolecular hydroarylation of alkene-tethered benzoic acid derivatives to afford dihydrobenzofurans and indolines in good to excellent yields. A one-pot, unsymmetrical, twofold C–H functionalization involving intramolecular C–C and intermolecular C–C/C–N bond formations is successfully demonstrated by using a single set of catalytic reaction conditions, which is unprecedented thus far. A novel isoquinolone-bearing dihydrobenzofuran is constructed through an unsymmetrical twofold C–H functionalization.*

Transition metal (TM) catalyzed directing group (DG)-aided functionalization of inert C–H bonds is a promising method for the step- and atom-efficient construction of versatile molecular structures from readily accessible starting materials.[1–3] Despite the growth and success of C–H activation, synthetically useful DG-promoted multiple functionalizations of arene C–H bonds are less explored, yet exceedingly attractive. In general, the steric/electronic/coordinating effect of the *ortho*-monofunctionalized product, obtained from the DG-coupled arene, hampers the efficient introduction of other functional groups to the second *ortho* C–H bond on the arene. Consequently, effective twofold C–H bond functionalization of arenes remains challenging.[4] Furthermore, the DG and catalytic conditions are highly selective for the respective bond formations, and as a consequence, unsymmetrical functionalization of C–H bonds in the presence of one catalyst is mostly unsuccessful. Moreover, the formation of numerous by-products and an incomplete reaction profile involved in each step of the transformation makes the overall process cumbersome and unproductive.[5] Notably, single DG-enabled, symmetrical double *ortho*-C–H functionalization of arenes has been thoroughly investigated (Scheme 1a).[6,7] Recently, the groups of Yu and Gevorgyan have independently disclosed elegant two-step unsymmetrical *ortho*-C–H functionalizations of arenes. The reactions proceeded well in the presence of two different catalytic systems and one DG (Scheme 1b).[5,8,9] The realization of a one-pot, unsymmetrical, twofold C–H functionalization of arenes in the presence of a single DG and single catalyst would essentially lead to highly functionalized arene derivatives in a step-efficient and byproduct-free fashion, and would therefore be considered ideal (Scheme 1b). To the best of our knowledge, no such transformations are known.



Scheme 1. Unsymmetrical twofold *ortho*-C–H functionalization.

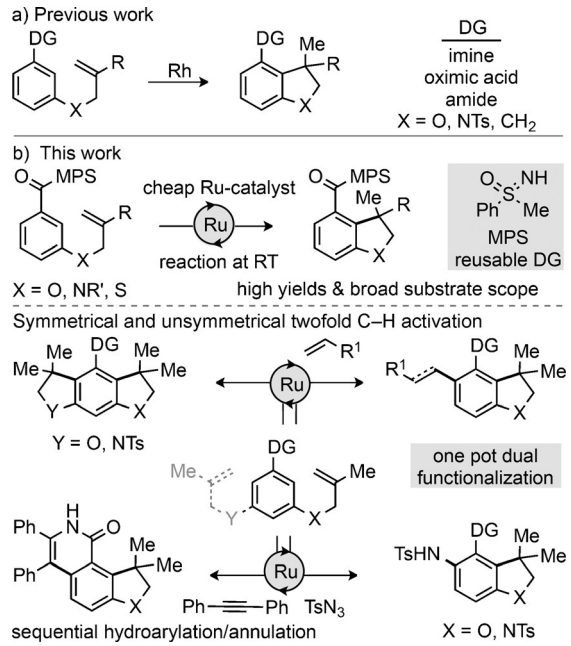
Dihydrobenzofuran skeletons are widely found in many biologically active compounds and potential drug candidates.[10] The groups of Ellman and Bergman, Rovis, Cramer, and Yoshikai have independently demonstrated the rhodium- and cobalt-catalyzed intramolecular hydroarylation of O-bearing olefin-tethered arenes for the synthesis of dihydrobenzofurans (Scheme 2a).[11–13] However, the use of air-stable and low-cost ruthenium catalysts for intramolecular hydroarylation with unactivated alkenes remains underdeveloped.[14]

We therefore devised a one-pot, unsymmetrical, twofold C–H functionalization using a rationally designed olefin-tethered substrate (Scheme 1c). The reaction involves an intramolecular *ortho*-C–H hydroarylation and intermolecular functionalization of a second *ortho*-C–H bond. Herein, we discuss the methyl phenyl sulfoximine (MPS; **1**) directed[15,16] ruthenium-catalyzed intramolecular hydroarylation of an O-tethered olefin bearing benzoic acid derivatives for the synthesis of a wide array of dihydrobenzofurans at room temperature (Scheme 2b). One-pot, symmetrical and unsymmetrical, twofold C–H functionalizations in the presence of a single catalyst were successfully investigated (Scheme 2b). A sequential hydroarylation and annulation with alkynes, through two C–H functionalizations, is also reported.

To realize the feasibility of the envisioned process sketched in Scheme 2b, the ruthenium-catalyzed intramolecular hydroarylation was explored with [3-(2-methylallyloxy)-benzoyl]methylphenyl sulfoximine (**2a**). Screening of the catalysts, additives, and bases led to the optimized reaction

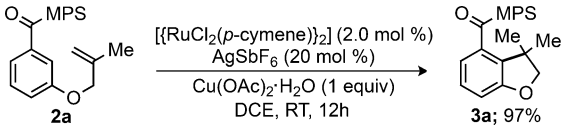
[*] K. Ghosh, R. K. Rit, E. Ramesh, Prof. Dr. A. K. Sahoo
School of Chemistry, University of Hyderabad
Gachibowli, Hyderabad, Telangana 500046 (India)
E-mail: akhilchemistry12@gmail.com

Supporting information for this article can be found under: http://dx.doi.org/10.1002/anie.201600649.



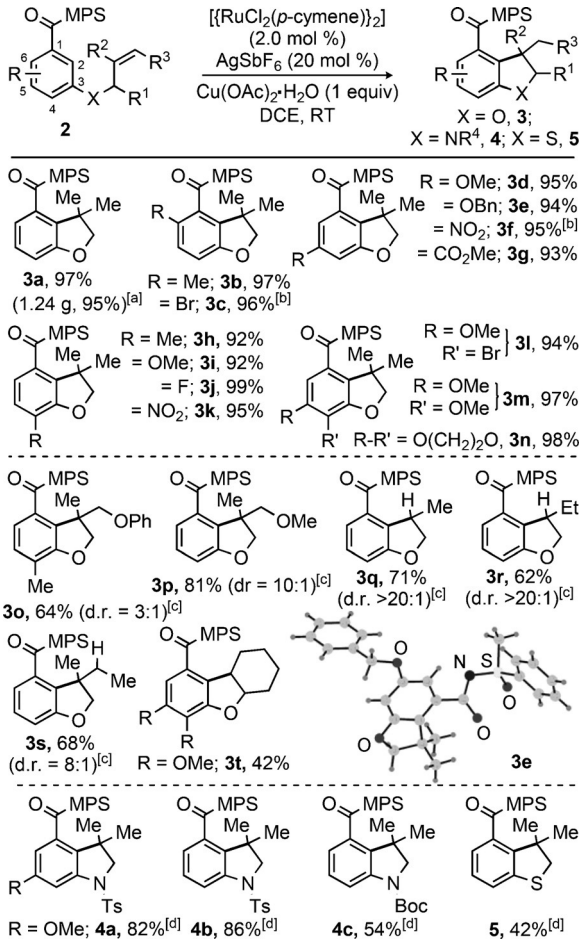
Scheme 2. Unsymmetrical twofold C–H functionalization. Ts = 4-toluenesulfonyl.

conditions, $[\{RuCl_2(p\text{-cymene})\}_2]$ (2.0 mol %), $AgSbF_6$ (20 mol %), and $Cu(OAc)_2{\cdot}H_2O$ (1.0 equiv) in $ClCH_2CH_2Cl$ (DCE) at room temperature for 12 h, to access **3a** (97 %) from **2a** [Eq. (1)].[17]



(1)

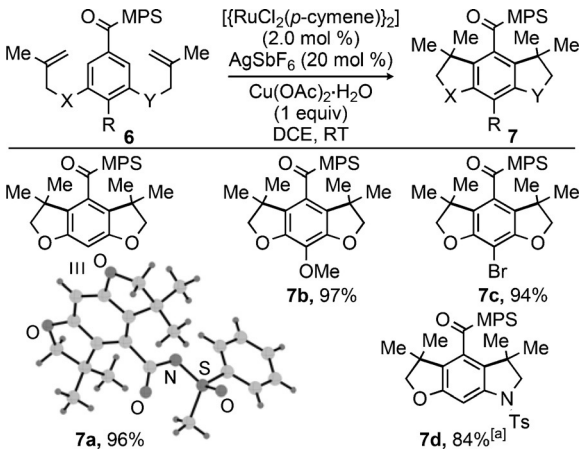
The generality of this novel ruthenium-catalyzed DG-assisted intramolecular hydroarylation is showcased in Scheme 3. The reaction of **2a** (1.3 g) with 0.5 mol % of the ruthenium catalyst at 35 °C for 6 hours furnished **3a** (1.24 g), thus the reaction is scalable. The 6-methyl- (**2b**) and 6-bromo (**2c**) bearing sterically encumbered substrates smoothly underwent hydroarylation to produce **3b** and **3c**, respectively, in excellent yields. The electron-donating and electron-withdrawing (NO_2, ester) functional groups at the 5-position of aryl moiety did not affect the reaction efficiency, thus yielding **3d–g** in excellent yields. X-ray crystallographic studies established the structure of **3e**.[18] Excellent yield of the products **3h–k** were obtained from the 4-substituted benzoic acid derivatives **2h–k**, and electronically biased (OMe/NO_2) groups did not affect the yields. Construction of the highly substituted dihydrobenzofurans **3l–n** were readily obtained. The current transformation conveniently resulted in the phenoxymethyl- and methoxymethyl-bearing (all-carbon quaternary stereocenter enabled) products **3o** (64 %, 3:1) and **3p** (81 %, 10:1), respectively.[17] The O-allyl substrate **2q** successfully underwent hydroarylation, thus delivering 71 % of **3q**.[17] Internal alkenes also participated and the dihydrobenzofuran derivatives **3r–t** were synthesized in appreciable yields.[17] The identical reactions with the N- and S-tethered substrates were facile, thus resulting the N-Tosyl/Boc-protected indolines **4a–c** (54–86 % yield) and dihydrobenzothiophene **5** (Scheme 3).



Scheme 3. Scope of the hydroarylation reaction. Reaction conditions: **2** (0.5 mmol), Ru catalyst (2.0 mol %), $AgSbF_6$ (20 mol %), and $Cu(OAc)_2{\cdot}H_2O$ (0.5 mmol) in DCE (2.0 mL) at RT for 8–16 h.
[a] 0.5 mol % the Ru catalyst (at 35 °C). [b] At 50 °C. [c] Based on NMR/HPLC analysis. [d] 4.0 mol % Ru catalyst (at 65 °C). Boc = *tert*-butoxycarbonyl.

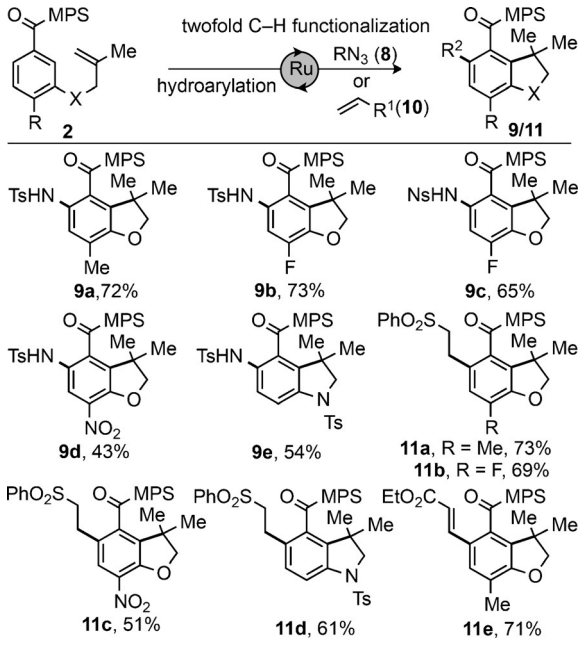
We next examined the twofold hydroarylation of the *ortho* C–H bonds with the appended olefins. Pleasingly, the dicyclization product **7a** (96 %) was exclusively formed when **6a** was exposed to the optimized reaction conditions in (Scheme 4).[18] This twofold hydroarylation with a low catalyst loading at room temperature is a distinct advantage over the rhodium-catalyzed transformations.[11b] Likewise, 4-methoxy- and 4-bromo-substituted **7b** and **7c**, respectively, were achieved in the corresponding yields of 97 % and 94 %. The dihydroarylation of **6d** proceeded smoothly to exclusively produce 84 % of **7d**. Collectively, these data reveal the potential of the MPS DG for the incorporation of two heterocycles into an arene moiety by a twofold hydroarylation.

Unsymmetrical functionalization of multiple C–H bonds creates densely functionalized scaffolds with the introduction



Scheme 4. Twofold hydroarylation reaction. Reaction conditions: **6** (0.5 mmol), Ru catalyst (2.0 mol%), $AgSbF_6$ (20 mol%), and $Cu(OAc)_2{\cdot}H_2O$ (0.5 mmol) in DCE (2.0 mL) for 10–16 h. [a] 4.0 mol% Ru catalyst (at 60°C).

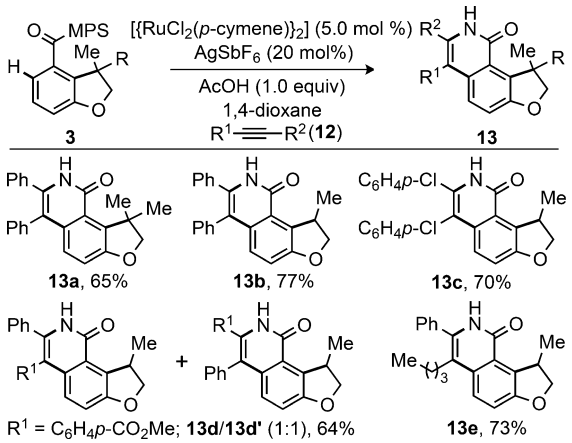
of diverse substituents. Thus, ruthenium-catalyzed intramolecular hydroarylation followed by intermolecular amidation with sulfonylazides under one set of catalytic conditions is envisioned (Scheme 5).[15a,19] Gratifyingly, the compound **9a** (72%) was isolated when **2h** was exposed to the ruthenium-catalyzed conditions in the presence of TsN_3 at room temperature, then with heating at 120°C. Likewise, the dihydrobenzofurans **9b–d** were successfully constructed. The same reaction sequences were also applied to construct the N-tethered indoline derivative **9e**.



Scheme 5. One-pot hydroarylation-amidation/alkylation/alkenylation. Reaction conditions: **2** (0.5 mmol), Ru catalyst (5.0 mol%), $AgSbF_6$ (20 mol%), $Cu(OAc)_2{\cdot}H_2O$ (0.5 mmol), and either sulfonyl azide (1.0 mmol) or alkene (1.0 mmol) in DCE (4.0 mL) at RT for 12–16 h and then heated to 120°C for 24 h.

The success of the one-pot hydroarylation amidation reaction led us to explore the unsymmetrical twofold C–C bond formations at the two *ortho* positions (Scheme 5). To our delight, the reaction of **2h** with phenyl vinyl sulfone (**10a**) under the optimized reaction conditions led directly to the 5-alkyl-substituted dihydrobenzofuran **11a** in 73% yield in a single operation.[15b,20] The presence of 4-fluoro and 4-nitro groups on the arene did not hamper the reaction, thus delivering **11b** (69%) and **11c** (51%), respectively. The steric strain of the quaternary group at the 3-position of the dihydrobenzofuran in the transition state suppresses the β-hydride elimination over proto-demetalation, and is presumably responsible for alkylation product formation.[21] The N-tethered **2v** was also effectively reacted, thus leading to the indoline derivative **11d** (61%). In contrast, the reaction of **2h** with ethyl acrylate (**10b**) gave the alkenylation product **11e**. To the best of our knowledge, the one-pot unsymmetrical functionalizations of arenes [hydroarylation/amidation, hydroarylation/olefination] under one set of catalytic conditions has not been reported previously.

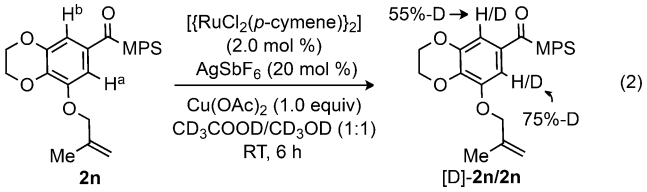
Development of a synthetic manifold for the introduction of isoquinolone motifs into (hetero)arenes is appealing, as they are widely found in the molecules of biological importance.[22] We thus envisaged the introduction of an isoquinolone scaffold into the dihydrobenzofuran skeleton (Scheme 6).[23] Gratifyingly, the reaction of **3a** and diphenyl-

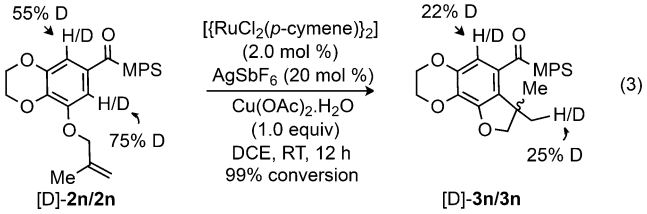


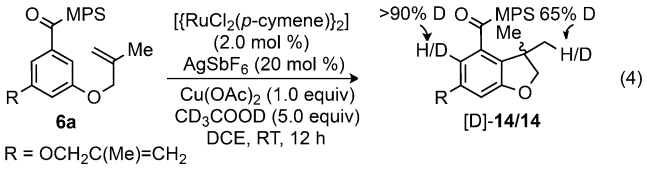
Scheme 6. Sequential hydroarylation and annulation. Reaction conditions: **3** (0.5 mmol), Ru catalyst (5.0 mol%), $AgSbF_6$ (20 mol%), and AcOH (0.5 mmol) in 1,4-dioxane (4.0 mL) at 120°C for 24 h.

acetylene (**12a**) under the catalytic ruthenium conditions delivered the dihydrofuran-fused isoquinolone **13a** in 65% yield. Likewise, annulation between **3q** and **12a** and **12b** led to **13b** (77%) and **13c** (70%), respectively. The use of the unsymmetrical diarylacetylene **12c** provided a mixture of regioisomers, **13d** and **13d′** (1:1; 64%). Whereas the reaction of **3q** with the alkyl-aryl alkyne **12d** yielded **13e**, for which NOESY studies were used to establish the structure.[17] Notably, the unsymmetrical twofold functionalization of inert C–H bonds, proceeding by hydroarylation and annulation, leads to novel N- and O-bearing heterocycles.

To gain some mechanistic insights, deuterium-labeling studies were performed. At first, the hydroarylation of **2n** in CD_3CO_2D and CD_3OD (1:1) explicitly provided H/D scrambled products [D]-**2n/2n** [Eq. (2)]. The incorporation of D into the *ortho* C–H^a bond (75%), which is sandwiched between the DG and the O-allyl moiety, over the *ortho* C–H^b bond (55%) reveals that the tethered olefin moiety helps in the activation of the *ortho* C–H^a bond in **2n**. Interestingly, hydroarylation of [D]-**2n/2n** under the optimized reaction conditions resulted in [D]-**3n/3n** [Eq. (3)]. To our surprise, a significant decrease in the deuterium population at the arene *ortho* C–H bond (22%) and incorporation of only 25% of D into the 3-methyl in [D]-**3n/3n** is observed [Eq. (3)]. Thus, cleavage of the *ortho* C–H bond, which generally involves a concerted metalation-deprotonation (CMD) pathway, is reversible.[24] Furthermore, ruthenium-catalyzed hydroarylation of **6a** in the presence of $Cu(OAc)_2$ (1.0 equiv) and CD_3CO_2D (5.0 equiv) afforded [D]-**14/14** with 65% deuterium incorporation in the 3-methyl moiety [Eq. (4)], thus indicating the involvement of protodemetalation.[12a]

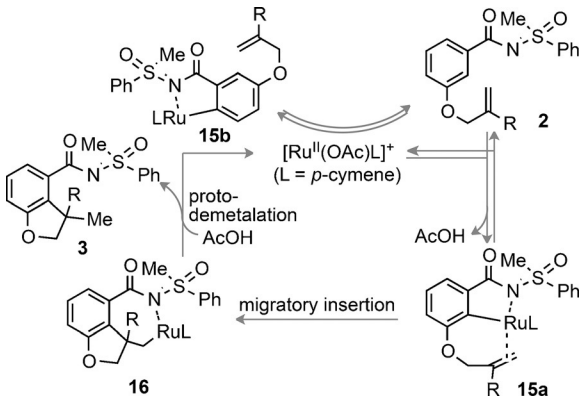






A plausible reaction pathway is outlined in Scheme 7. The active catalyst, generated from $[\{RuCl_2(p\text{-cymene})\}_2]$, $AgSbF_6$, and $Cu(OAc)_2$, coordinates to MPS and activates the *ortho* C–H bonds to produce the cyclometalated complex **15a/15b**. The additional interaction of the tethered olefin to the metal probably facilitates the activation of sterically encumbered proximal C–H bond to provide **15a** over **15b**. The migratory insertion of **15a** then leads to **16**, which upon proto-demetalation produces the desired product **3** with the regeneration of active catalyst.[12a]

In summary, a novel and efficient DG-promoted ruthenium-catalyzed hydroarylation of benzoic acid derivatives at room temperature was demonstrated for the first time. The reaction exhibits broad scope for synthesizing dihydrobenzofuran, indoline, and dihydro-benzothiophene derivatives. The unprecedented one-pot, unsymmetrical, twofold C–H functionalization of arene derivatives through hydroarylation-amidation and hydroarylation-alkylation/ alkenylation creates novel molecular scaffolds. The unsymmetrical twofold functionalization of unactivated C–H bonds involves hydroarylation and annulation (with alkynes) and leads to novel N- and O-bearing heterocycles by incorporating dihydrobenzofuran and isoquinolone motifs in a single molecule for the first time. The cleavage and recovery of the MPS group from the products makes this strategy synthetically viable.[17]



Scheme 7. Possible mechanistic pathway.

Acknowledgments

This research was supported by the CSIR (02/(0155)/13/ EMR-II). K.G., R.K.R., and E.R. thank CSIR, India, for a fellowship.

Keywords: annulations · C–H activation · heterocycles · reaction mechanisms · ruthenium

How to cite: *Angew. Chem. Int. Ed.* **2016**, *55*, 7821–7825
Angew. Chem. **2016**, *128*, 7952–7956

[1] Selected reviews on C–H activation: a) X. Chen, K. M. Engle, D.-H. Wang, J.-Q. Yu, *Angew. Chem. Int. Ed.* **2009**, *48*, 5094; *Angew. Chem.* **2009**, *121*, 5196; b) D. A. Colby, R. G. Bergman, J. A. Ellman, *Chem. Rev.* **2010**, *110*, 624; c) T. W. Lyons, M. S. Sanford, *Chem. Rev.* **2010**, *110*, 1147; d) L. C. M. Castro, N. Chatani, *Chem. Lett.* **2015**, *44*, 410; e) B. Liu, F. Hu, B.-F. Shi, *ACS Catal.* **2015**, *5*, 1863.
[2] D. Y.-K. Chen, S. W. Youn, *Chem. Eur. J.* **2012**, *18*, 9452.
[3] a) G. Rouquet, N. Chatani, *Angew. Chem. Int. Ed.* **2013**, *52*, 11726; *Angew. Chem.* **2013**, *125*, 11942; b) S. De Sarkar, W. Liu, S. I. Kozhushkov, L. Ackermann, *Adv. Synth. Catal.* **2014**, *356*, 1461; c) M. R. Yadav, R. K. Rit, M. Shankar, A. K. Sahoo, *Asian J. Org. Chem.* **2015**, *4*, 846; d) G. Rousseau, B. Breit, *Angew. Chem. Int. Ed.* **2011**, *50*, 5007; *Angew. Chem.* **2011**, *123*, 5111.
[4] M. Sonoda, F. Kakiuchi, N. Chatani, S. Murai, *Bull. Chem. Soc. Jpn.* **1997**, *70*, 3117.

[5] D. Sarkar, F. S. Melkonyan, A. V. Gulevich, V. Gevorgyan, *Angew. Chem. Int. Ed.* **2013**, *52*, 10800; *Angew. Chem.* **2013**, *125*, 11000.
[6] a) T.-S. Mei, R. Giri, N. Maugel, J.-Q. Yu, *Angew. Chem. Int. Ed.* **2008**, *47*, 5215; *Angew. Chem.* **2008**, *120*, 5293; b) P. Arockiam, V. Poirier, C. Fischmeister, C. Bruneau, P. H. Dixneuf, *Green Chem.* **2009**, *11*, 1871; c) A. V. Gulevich, F. S. Melkonyan, D. Sarkar, V. Gevorgyan, *J. Am. Chem. Soc.* **2012**, *134*, 5528; d) L. D. Tran, I. Popov, O. Daugulis, *J. Am. Chem. Soc.* **2012**, *134*, 18237; e) T. Truong, K. Klimovica, O. Daugulis, *J. Am. Chem. Soc.* **2013**, *135*, 9342; f) X.-C. Wang, Y. Hu, S. Bonacorsi, Y. Hong, R. Burrell, J.-Q. Yu, *J. Am. Chem. Soc.* **2013**, *135*, 10326; g) L. Ackermann, A. Althammer, R. Born, *Angew. Chem. Int. Ed.* **2006**, *45*, 2619; *Angew. Chem.* **2006**, *118*, 2681; h) B. Li, C. B. Bheeter, C. Darcel, P. H. Dixneuf, *ACS Catal.* **2011**, *1*, 1221; i) A. Bechtoldt, C. Tirler, K. Raghuvanshi, S. Warratz, C. Kornhaaß, L. Ackermann, *Angew. Chem. Int. Ed.* **2016**, *55*, 264; *Angew. Chem.* **2016**, *128*, 272.
[7] a) N. Umeda, K. Hirano, T. Satoh, M. Miura, *J. Org. Chem.* **2009**, *74*, 7094; b) K. M. Engle, D.-H. Wang, J.-Q. Yu, *Angew. Chem. Int. Ed.* **2010**, *49*, 6169; *Angew. Chem.* **2010**, *122*, 6305; c) A. Deb, S. Bag, R. Kancherla, D. Maiti, *J. Am. Chem. Soc.* **2014**, *136*, 13602.
[8] a) H. Wang, G. Li, K. M. Engle, J.-Q. Yu, H. M. L. Davies, *J. Am. Chem. Soc.* **2013**, *135*, 6774; b) B. R. Rosen, L. R. Simke, P. S. Thuy-Boun, D. D. Dixon, J.-Q. Yu, P. S. Baran, *Angew. Chem. Int. Ed.* **2013**, *52*, 7317; *Angew. Chem.* **2013**, *125*, 7458; c) D. Sarkar, A. V. Gulevich, F. S. Melkonyan, V. Gevorgyan, *ACS Catal.* **2015**, *5*, 6792.
[9] a) H. J. Kim, M. J. Ajitha, Y. Lee, J. Ryu, J. Kim, Y. Lee, Y. Jung, S. Chang, *J. Am. Chem. Soc.* **2014**, *136*, 1132; b) S.-Y. Zhang, Q. Li, G. He, W. A. Nack, G. Chen, *J. Am. Chem. Soc.* **2015**, *137*, 531.
[10] a) G. Zammit, M. Erman, S. Wang-Weigand, S. Sainati, J. Zhang, T. Roth, *J. Clin. Sleep Med.* **2007**, *3*, 495.
[11] a) R. K. Thalji, K. A. Ahrendt, R. G. Bergman, J. A. Ellman, *J. Am. Chem. Soc.* **2001**, *123*, 9692; b) K. A. Ahrendt, R. G. Bergman, J. A. Ellman, *Org. Lett.* **2003**, *5*, 1301; c) R. K. Thalji, J. A. Ellman, R. G. Bergman, *J. Am. Chem. Soc.* **2004**, *126*, 7192; d) S. J. O'Malley, K. L. Tan, A. Watzke, R. G. Bergman, J. A. Ellman, *J. Am. Chem. Soc.* **2005**, *127*, 13496.
[12] a) T. A. Davis, T. K. Hyster, T. Rovis, *Angew. Chem. Int. Ed.* **2013**, *52*, 14181; *Angew. Chem.* **2013**, *125*, 14431; b) B. Ye, P. A. Donets, N. Cramer, *Angew. Chem. Int. Ed.* **2014**, *53*, 507; *Angew. Chem.* **2014**, *126*, 517.
[13] Z. Ding, N. Yoshikai, *Angew. Chem. Int. Ed.* **2013**, *52*, 8574; *Angew. Chem.* **2013**, *125*, 8736.
[14] a) P. B. Arockiam, C. Bruneau, P. H. Dixneuf, *Chem. Rev.* **2012**, *112*, 5879; b) L. Ackermann, *Acc. Chem. Res.* **2014**, *47*, 281; c) L. Ackermann, R. Born, P. Álvarez-Bercedo, *Angew. Chem. Int. Ed.* **2007**, *46*, 6364; *Angew. Chem.* **2007**, *119*, 6482.
[15] a) M. R. Yadav, R. K. Rit, A. K. Sahoo, *Org. Lett.* **2013**, *15*, 1638; b) M. R. Yadav, R. K. Rit, M. Shankar, A. K. Sahoo, *J. Org. Chem.* **2014**, *79*, 6123.
[16] K. Parthasarathy, C. Bolm, *Chem. Eur. J.* **2014**, *20*, 4896.
[17] See the Supporting Information.
[18] CCDC 1447800 (**3e**) and 1447993 (**7a**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre.
[19] a) M. Bhanuchandra, M. R. Yadav, R. K. Rit, M. R. Kuram, A. K. Sahoo, *Chem. Commun.* **2013**, *49*, 5225; b) J. Kim, J. Kim, S. Chang, *Chem. Eur. J.* **2013**, *19*, 7328; c) Q.-Z. Zheng, Y.-F. Liang, C. Qin, N. Jiao, *Chem. Commun.* **2013**, *49*, 5654.
[20] a) P. Kishor, M. Jeganmohan, *Org. Lett.* **2011**, *13*, 6144; b) G. Rouquet, N. Chatani, *Chem. Sci.* **2013**, *4*, 2201; c) M. Schinkel, I. Marek, L. Ackermann, *Angew. Chem. Int. Ed.* **2013**, *52*, 3977; *Angew. Chem.* **2013**, *125*, 4069; d) B. Li, K. Devaraj, C. Darcel, P. H. Dixneuf, *Green Chem.* **2012**, *14*, 2706; e) W. Ma, L. Ackermann, *Chem. Eur. J.* **2013**, *19*, 13925.
[21] a) D.-H. Wang, K. M. Engle, B.-F. Shi, J.-Q. Yu, *Science* **2010**, *327*, 315; b) H. Wang, N. Schröder, F. Glorius, *Angew. Chem. Int. Ed.* **2013**, *52*, 5386; *Angew. Chem.* **2013**, *125*, 5495.
[22] H. A. Paine, et al., *Bioorg. Med. Chem.* **2015**, *23*, 5891.
[23] a) L. Ackermann, A. V. Lygin, N. Hofmann, *Angew. Chem. Int. Ed.* **2011**, *50*, 6379; *Angew. Chem.* **2011**, *123*, 6503; b) L. Ackermann, S. Fenner, *Org. Lett.* **2011**, *13*, 6548; c) B. Li, H. Feng, S. Xu, B. Wang, *Chem. Eur. J.* **2011**, *17*, 12573.
[24] F. Kakiuchi, H. Ohtaki, M. Sonoda, N. Chatani, *Chem. Lett.* **2001**, 918.

Received: January 21, 2016
Published online: March 23, 2016

