

Ruthenium-Catalyzed Alkyne Annulations with Substituted 1*H*-Pyrazoles by C–H/N–H Bond Functionalizations

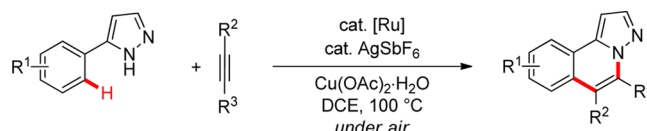
Wenbo Ma, Karolina Graczyk, and Lutz Ackermann*

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

Lutz.Ackermann@chemie.uni-goettingen.de

Received November 9, 2012

ABSTRACT



Cationic ruthenium(II) complexes allowed for highly efficient oxidative annulations of aryl- and alkyl-substituted alkynes by 5-aryl-1*H*-pyrazoles. The C–H/N–H bond functionalization strategy furthermore proved applicable to the high-yielding activation of heteroaryl as well as alkenyl C–H bonds.

Oxidative metal-catalyzed C–H bond functionalization reactions¹ have emerged as versatile tools for the step-economical assembly and functionalization of heterocycles.² Particularly, domino reactions³ that involve the sequential functionalization of C–H and N–H bonds are highly desirable, which have as of yet mostly relied on the use of Cp*-rhodium complexes.⁴ Conversely, significantly less

expensive ruthenium(II) complexes were only very recently identified as catalysts for annulations of alkenes⁵ and alkynes *via* oxidative C–H bond functionalizations of arenes.⁶ As part of our research program on the streamlining

(1) Recent reviews: (a) Neufeldt, S. R.; Sanford, M. S. *Acc. Chem. Res.* **2012**, *45*, 936–946. (b) Engle, K. M.; Mei, T.-S.; Wasa, M.; Yu, J.-Q. *Acc. Chem. Res.* **2012**, *45*, 788–802. (c) Arockiam, P. B.; Bruneau, C.; Dixneuf, P. H. *Chem. Rev.* **2012**, *112*, 5879–5918. (d) Ackermann, L.; Potukuchi, H. K. *Org. Biomol. Chem.* **2010**, *8*, 4503–4513. (e) Daugulis, O. *Top. Curr. Chem.* **2010**, *292*, 57–84. (f) Colby, D. A.; Bergman, R. G.; Ellman, J. A. *Chem. Rev.* **2010**, *110*, 624–655. (g) Ackermann, L.; Vicente, R.; Kapdi, A. *Angew. Chem., Int. Ed.* **2009**, *48*, 9792–9826 and references cited therein.

(2) Selected reviews: (a) Mei, T.-S.; Kou, L.; Ma, S.; Engle, K. M.; Yu, J.-Q. *Synthesis* **2012**, *44*, 1778–1791. (b) Thansandote, P.; Lautens, M. *Chem.—Eur. J.* **2009**, *15*, 5874–5883. (c) Seregin, I. V.; Gevorgyan, V. *Chem. Soc. Rev.* **2007**, *36*, 1173–1193.

(3) Tietze, L. F.; Brasche, G.; Gericke, K. M. *Domino Reactions in Organic Synthesis*; Wiley-VCH: Weinheim, 2006.

(4) Reviews: (a) Song, G.; Wang, F.; Li, X. *Chem. Soc. Rev.* **2012**, *41*, 3651–3678. (b) Patureau, F. W.; Wencel-Delord, J.; Glorius, F. *Aldrichimica Acta* **2012**, *45*, 31–41. (c) Wencel-Delord, J.; Droge, T.; Liu, F.; Glorius, F. *Chem. Soc. Rev.* **2011**, *40*, 4740–4761. (d) Satoh, T.; Miura, M. *Chem.—Eur. J.* **2010**, *16*, 11212–11222 and references cited therein. Selected examples: (e) Umeda, N.; Hirano, K.; Satoh, T.; Shibata, N.; Sato, H.; Miura, M. *J. Org. Chem.* **2011**, *76*, 13–24. (f) Patureau, F. W.; Besset, T.; Glorius, F. *Angew. Chem., Int. Ed.* **2011**, *50*, 1064–1067. (g) Stuart, D. R.; Bertrand-Laperle, M.; Burgess, K. M. N.; Fagnou, K. *J. Am. Chem. Soc.* **2008**, *130*, 16474–16475. (h) Ueura, K.; Satoh, T.; Miura, M. *J. Org. Chem.* **2007**, *72*, 5362–5367.

(5) Selected examples: (a) Li, J.; Kornhaass, C.; Ackermann, L. *Chem. Commun.* **2012**, *48*, 11343–11345. (b) Li, B.; Devaraj, K.; Darcel, C.; Dixneuf, P. H. *Green Chem.* **2012**, *14*, 2706–2709. (c) Li, B.; Ma, J.; Wang, N.; Feng, H.; Xu, S.; Wang, B. *Org. Lett.* **2012**, *14*, 736–739. (d) Hashimoto, Y.; Orloff, T.; Hirano, K.; Satoh, T.; Bolm, C.; Miura, M. *Chem. Lett.* **2012**, *41*, 151–153. (e) Graczyk, K.; Ma, W.; Ackermann, L. *Org. Lett.* **2012**, *14*, 4110–4113. (f) Kishor, P.; Jeganmohan, M. *Org. Lett.* **2012**, *14*, 1134–1137. (g) Hashimoto, Y.; Ueyama, T.; Fukutani, T.; Hirano, K.; Satoh, T.; Miura, M. *Chem. Lett.* **2011**, *40*, 1165–1166. (h) Ackermann, L.; Pospech, J. *Org. Lett.* **2011**, *13*, 4153–4155. (i) Ueyama, T.; Mochida, S.; Fukutani, T.; Hirano, K.; Satoh, T.; Miura, M. *Org. Lett.* **2011**, *13*, 706–708. (j) A review: Kozhushkov, S. I.; Ackermann, L. *Chem. Sci.* **2013**, DOI:10.1039/C2SC21524A, and references cited therein.

(6) Illustrative examples: (a) Zhao, P.; Wang, F.; Han, K.; Li, X. *Org. Lett.* **2012**, *14*, 5506–5509. (b) Kornhaass, C.; Li, J.; Ackermann, L. *J. Org. Chem.* **2012**, *77*, 9190–9198. (c) Li, B.; Feng, H.; Wang, N.; Ma, J.; Song, H.; Xu, S.; Wang, B. *Chem.—Eur. J.* **2012**, *18*, 12873–12879. (d) Parthasarathy, K.; Senthilkumar, N.; Jayakumar, J.; Cheng, C.-H. *Org. Lett.* **2012**, *14*, 3478–3481. (e) Thirunavukkarasu, V. S.; Donati, M.; Ackermann, L. *Org. Lett.* **2012**, *14*, 3416–3419. (f) Chinnagolla, R. K.; Jeganmohan, M. *Chem. Commun.* **2012**, *48*, 2030–2032. (g) Ackermann, L.; Pospech, J.; Graczyk, K.; Rauch, K. *Org. Lett.* **2012**, *14*, 930–933. (h) Ackermann, L.; Lygin, A. V. *Org. Lett.* **2012**, *14*, 764–767. (i) Ackermann, L.; Wang, L.; Lygin, A. V. *Chem. Sci.* **2012**, *3*, 177–180. (j) Li, B.; Feng, H.; Xu, S.; Wang, B. *Chem.—Eur. J.* **2011**, *17*, 12573–12577. (k) Ackermann, L.; Fenner, S. *Org. Lett.* **2011**, *13*, 6548–6551. (l) Ackermann, L.; Lygin, A. V.; Hofmann, N. *Org. Lett.* **2011**, *13*, 3278–3281. (m) Ackermann, L.; Lygin, A. V.; Hofmann, N. *Angew. Chem., Int. Ed.* **2011**, *50*, 6379–6382. See also: (n) Ackermann, L.; Novák, P.; Vicente, R.; Pirovano, V.; Potukuchi, H. K. *Synthesis* **2010**, 2245–2253.

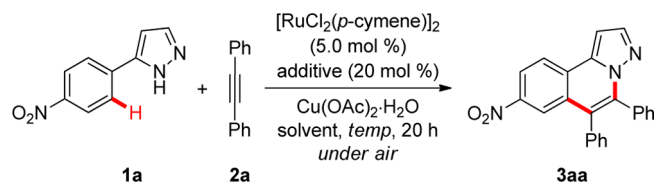
of organic synthesis through sustainable C–H bond functionalizations,⁷ we became attracted to developing ruthenium-catalyzed oxidative C–H/N–H bond functionalizations with easily accessible 1*H*-pyrazoles, because of their key importance in organic synthesis, medicinal chemistry and material science.⁸ Compared to a recently reported process that utilized rhodium complex [Cp*RhCl₂]₂,⁹ beneficial features of our ruthenium(II) catalyst are not limited to the significantly reduced catalyst costs. Indeed, our catalytic system also displayed a considerably improved substrate scope, which among others allowed for high-yielding transformations of heteroaryl C–H bonds as well as for the unprecedented use of alkenyl-substituted pyrazoles and dialkyl alkynes.

We commenced our studies by exploring representative cocatalytic additives in the envisioned ruthenium(II)-catalyzed oxidative annulation of alkyne **2a** by 5-aryl-pyrazole **1a** (Table 1). Cationic complexes *in situ* derived from silver(I) salts proved to be most effective, with optimal results being obtained with AgSbF₆ (entries 1–9). Importantly, the C–H bond functionalization did not occur in the absence of a ruthenium catalyst (entry 10). Likewise, the desired oxidative annulation was not accomplished with CuBr₂ in lieu of Cu(OAc)₂·H₂O as the terminal oxidant, thereby indicating the importance of carboxylate assistance (entry 11).¹⁰ Different protic and aprotic solvents were tested, which revealed DCE to be the reaction

medium of choice (entries 8 and 12–17). Intriguingly, the cationic ruthenium(II) catalyst was found to be remarkably robust in that the C–H bond functionalizations did not require inert reaction conditions, and proceeded effectively under a most user-friendly atmosphere of ambient air.¹¹

With an optimized catalytic system in hand, we probed its versatility in the oxidative annulation of alkynes **2** utilizing differently decorated 5-aryl-pyrazoles **1** (Scheme 1). We were pleased to find that the catalyst was widely applicable, and, thus, proved to be tolerant of various important functional groups, such as nitro, chloro, cyano, or amino substituents. Moreover, the oxidative functionalizations of *meta*-substituted arenes **1h** and **1i** proceeded with excellent site selectivities at the less sterically encumbered C–H bonds. The cationic ruthenium(II) catalyst was not restricted to the use of tolane derivatives **2a–2e** but efficiently converted alkyl-substituted alkyne **2f** as well. Given the importance of indoles as key structural motifs in

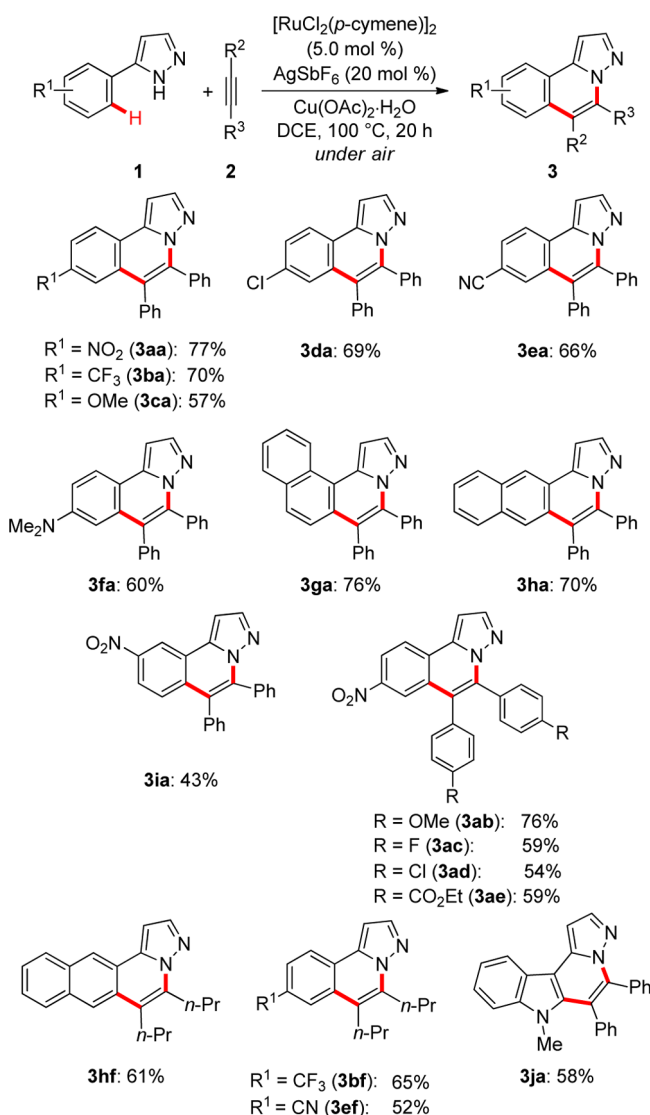
Table 1. Optimization of C–H/N–H Bond Functionalization^a



entry	additive	solvent	temp (°C)	yield (%)
1	–	DCE	100	13
2	NaOAc	DCE	100	19
3	CsOAc	DCE	100	6
4	KO ₂ CMes	DCE	100	16
5	KPF ₆	DCE	100	30
6	AgSO ₃ CF ₃	DCE	100	38
7	AgBF ₄	DCE	100	46
8	AgSbF₆	DCE	100	78
9	AgSbF₆	DCE	100	77^b
10	AgSbF ₆	DCE	100	— ^c
11	AgSbF ₆	DCE	100	— ^d
12	AgSbF ₆	NMP	120	—
13	AgSbF ₆	DMF	120	—
14	AgSbF ₆	<i>o</i> -xylene	120	12
15	AgSbF ₆	1,4-dioxane	120	17
16	AgSbF ₆	<i>t</i> -AmOH	120	41
17	AgSbF ₆	H ₂ O	120	13

^a Reaction conditions: **1a** (0.5 mmol), **2a** (1.0 mmol), Cu(OAc)₂·H₂O (1.0 mmol), [RuCl₂(*p*-cymene)]₂ (5.0 mol %), solvent (2.0 mL), and additive (20 mol %); isolated yields. ^b Cu(OAc)₂·H₂O (0.5 mmol). ^c CuBr₂ as the oxidant. ^d Without [RuCl₂(*p*-cymene)]₂.

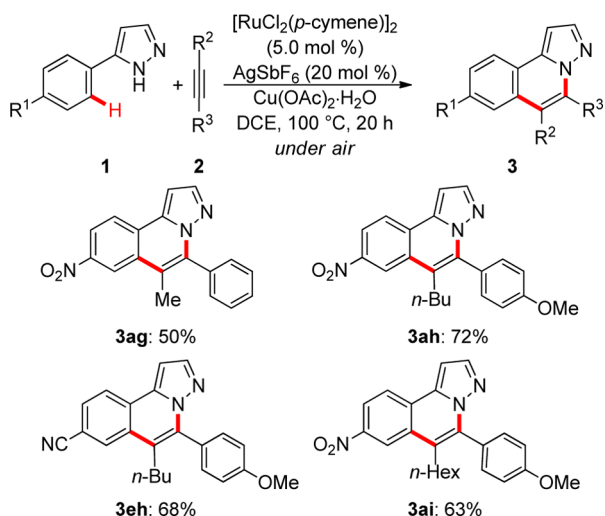
Scheme 1. Scope of Oxidative Annulation of Alkynes **2**



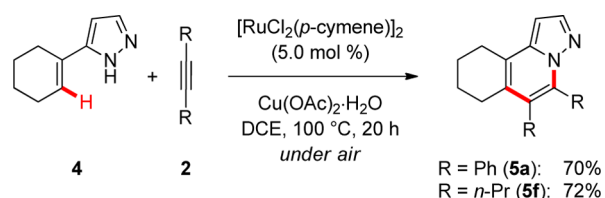
bioactive molecules,¹² we were pleased to observe that the catalytic system allowed for the step-economical synthesis of annulated indole **3ja** as well. Note that attempts to activate heteroaryl C–H bonds by a rhodium(III) catalyst unfortunately met with limited success and only resulted in unsatisfactorily low yields.⁹

Importantly, oxidative annulations with unsymmetrically substituted alkynes **2** occurred with excellent regioselectivities, thereby furnishing the regioisomers **3ag–3ai** and **3eh** in high isolated yields (Scheme 2). Generally, arenes **1** bearing electron-withdrawing substituents were found to be significantly more reactive (*vide infra*).

Scheme 2. Oxidative Annulations of Unsymmetrical Alkynes **2**



Scheme 3. Alkenyl C–H Bond Functionalizations



The ruthenium(II) catalyst also enabled first C–H/N–H bond functionalizations with alkenyl-substituted

(7) Recent reviews: (a) Kozhushkov, S. I.; Potukuchi, H. K.; Ackermann, L. *Catal. Sci. Technol.* **2013**, DOI: 10.1039/C2CY20505J. (b) Ackermann, L. *Isr. J. Chem.* **2010**, *50*, 652–663. (c) Ackermann, L. *Pure Appl. Chem.* **2010**, *82*, 1403–1413.

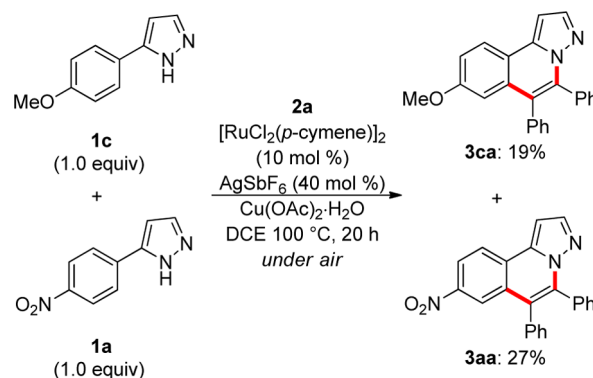
(8) Selected reviews: (a) Janin, Y. L. *Chem. Rev.* **2012**, *112*, 3924–3958. (b) Elguero, J.; Silva, A. M. S.; Tomé, A. C. In *Modern Heterocyclic Chemistry*; Alvarez-Builla, J.; Vaquero, J. J.; Barluenga, J., Eds.; Wiley-VCH: Weinheim, 2011; Vol. 2, pp 635–725. (c) Fustero, S.; Sanchez-Rosello, M.; Barrio, P.; Simon-Fuentes, A. *Chem. Rev.* **2011**, *111*, 6984–7034 and references cited therein.

(9) Li, X.; Zhao, M. *J. Org. Chem.* **2011**, *76*, 8530–8536.

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

(11) Catalytic reactions were conducted under atmospheric pressure open to air.

Scheme 4. Competition Experiments with Arenes **1**

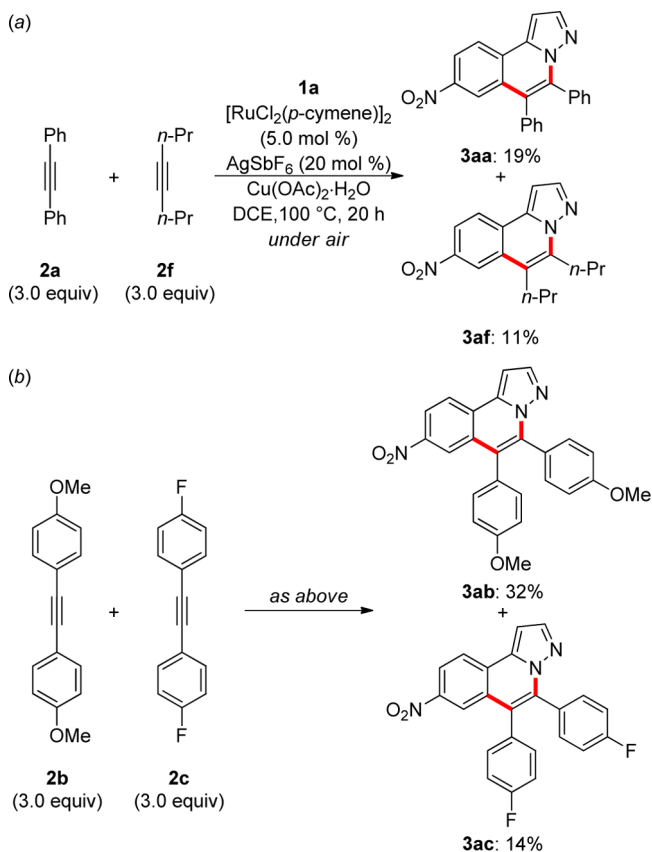


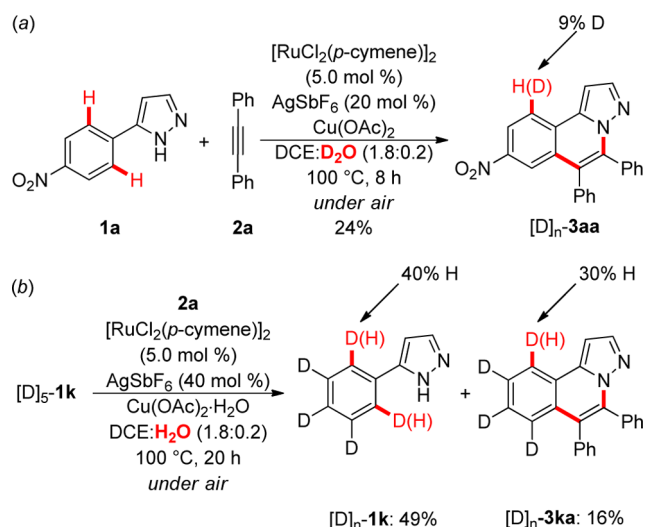
1*H*-pyrazole **4** (Scheme 3). Again, aryl- and alkyl-substituted alkynes **2** were found to be suitable substrates.

In consideration of the remarkably broad substrate scope displayed by the ruthenium(II) catalyst, we performed mechanistic studies to delineate its mode of action. To this end, intermolecular competition experiments showed electron-deficient arene **1a** to be preferentially functionalized (Scheme 4), a notable difference to the recently reported rhodium-catalyzed annulation process.⁹

Competition experiments between differently decorated alkynes **2** highlighted aryl alkynes to be more reactive

Scheme 5. Competition Experiments with Alkynes **2**



Scheme 6. Studies with D₂O and Substrate [D]₅-**1k**

(Scheme 5a), particularly when bearing electron-donating substituents (Scheme 5b).

(12) Selected reviews: (a) Cacchi, S.; Fabrizi, G.; Goggiamani, A. *Org. React.* **2012**, 76, 281–534. (b) Krüger, K.; Tillack, A.; Beller, M. *Adv. Synth. Catal.* **2008**, 350, 2153–2167. (c) Ackermann, L. *Synlett* **2007**, 507–526. (d) Humphrey, G. R.; Kuethe, J. T. *Chem. Rev.* **2006**, 106, 2875–2911 and references cited therein.

Finally, reactions conducted with D₂O as the additive or with isotopically labeled substrate [D]₅-**1k** revealed a significant H/D scrambling, being hence indicative of a reversible C–H bond metalation step (Scheme 6).

In summary, we have reported on the first ruthenium-catalyzed oxidative alkyne annulations by 1*H*-pyrazoles. Thus, a ruthenium complex allowed for C–H/N–H functionalizations of aryl-, heteroaryl-, and alkenyl-substituted 1*H*-pyrazoles with ample substrate scope and set the stage for the oxidative annulation of aryl- and alkyl-alkynes with excellent chemo- and regioselectivities. Detailed mechanistic studies provided strong support for a reversible C–H bond metalation step with the cationic ruthenium(II) catalyst.

Acknowledgment. Support by the Chinese Scholarship Council (fellowship to W.M.) and the European Research Council under the European Community's Seventh Framework Program (FP7 2007–2013)/ERC Grant Agreement No. 307535 is gratefully acknowledged.

Supporting Information Available. Experimental procedures, characterization data, and ¹H and ¹³C 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.