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Versatile Pyrrole Synthesis through Ruthenium(II)-Catalyzed Alkene C–H Bond Functionalization on Enamines

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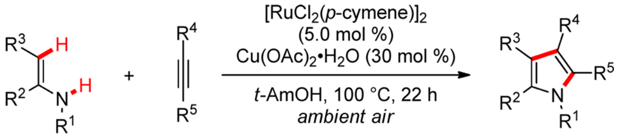
ABSTRACT



An efficient ruthenium(II) catalyst enabled broadly applicable oxidative alkyne annulations with electron-rich enamines to provide diversely decorated pyrroles, even in an aerobic fashion with air as the ideal oxidant.

Pyrroles are among the most abundant heterocycles and represent indispensable structural motifs for instance in bioactive natural products or material sciences.[1−5] Therefore, there is a continued strong demand for methods that give broad access to this important heteroaromatic scaffold. Despite significant recent advances through transition-metal catalysis, the majority of available methods for pyrrole syntheses capitalized upon preactivation of the N-containing substrates.[1] Yet, considerable recent progress was represented by Fagnou's elegant pyrrole[6] synthesis *via* rhodium-catalyzed oxidative C(sp^2)–H[7] bond functionalization[8] on enamides.[9−11] Unfortunately, the high costs of the required rhodium(III) catalyst were, among others, identified as a limitation of this approach. In contrast, significantly less expensive ruthenium(II) complexes[12,13] were only very recently identified as viable catalysts for oxidative alkyne annulations.[14] Unfortunately, these C–H/N–H bond functionalizations were hitherto restricted to electron-deficient alkenes displaying electron-withdrawing carbonyl groups. In consideration of

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(13) http://www.platinumgroupmetals.org/, November 2012: Rh: 1100, Pd: 669, and Ru: 110 US$/troy oz.

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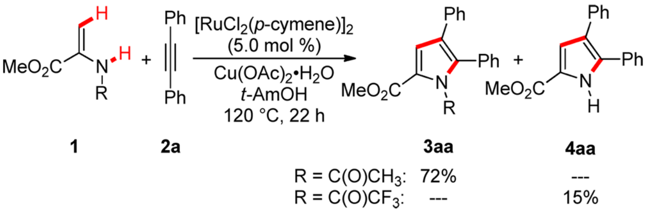
these restrictions, we hence became intrigued by developing unprecedented ruthenium(II)-catalyzed oxidative alkyne annulations with challenging electron-rich alkenes, on which we wish to report herein.

We commenced our studies by probing oxidative couplings with differently *N*-substituted enamines **1** (Scheme 1). Among a variety of starting materials **1**, solely the *N*-acetylated substrate delivered the product **3aa** in satisfactory yields, while the corresponding trifluoroacetylated starting material led to the *NH*-free product **4aa**, albeit in a diminished yield.

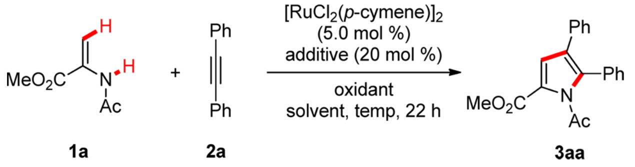
Scheme 1. Ruthenium(II)-Catalyzed Oxidative Pyrrole Synthesis



Thereafter, we tested the influence of the reaction conditions on the performance of the ruthenium(II) catalyst (Table 1). In the absence of either the ruthenium catalyst or the copper oxidant the desired product **3aa** was not formed (entries 1 and 2). The use of cocatalytic additives that form cationic ruthenium(II) catalysts did not improve the catalytic activity (entries 3–5), a feature that was also observed when employing H_2O, DMF, NMP, PhMe, or DMA in lieu of *t*-AmOH as the solvent (entries 5–10). Moreover, the use of $CuBr_2$ instead of $Cu(OAc)_2 \cdot H_2O$[15] as the sacrificial oxidant did not deliver the desired product **3aa** (entry 11).

To assess the scope of the optimized ruthenium(II) catalyst we tested its versatility in oxidative annulations of alkyne **2a** utilizing representative enamines **1** (Scheme 2). We were delighted to observe that numerous useful electrophilic functional groups were well tolerated, including ester, vinyl, bromo, cyano, and nitro substituents. Moreover, substrates **1m** and **1n** displaying heteroaromatic moieties furnished the desired pyrroles as well, while more sterically congested substrate **1o** was converted with comparable catalytic efficiency.

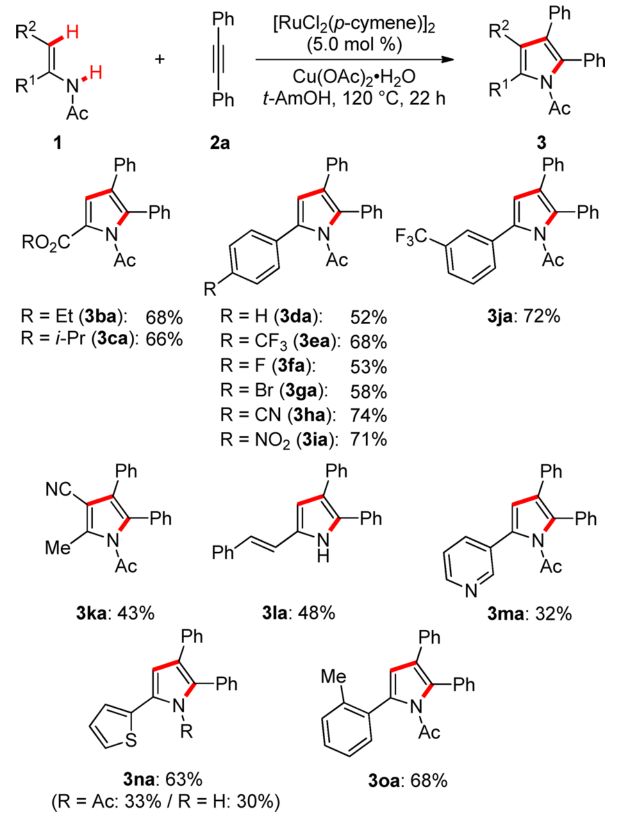
Table 1. Optimization Study for the Oxidative Pyrrole Synthesis[a]



entry	oxidant	additive	solvent	temp (°C)	yield (%)
1	–	–	*t*-AmOH	100	–
2	$Cu(OAc)_2 \cdot H_2O$	–	*t*-AmOH	100	–[b]
3	$Cu(OAc)_2 \cdot H_2O$	–	*t*-AmOH	100	70
4	$Cu(OAc)_2 \cdot H_2O$	KPF_6	*t*-AmOH	120	68
5	$Cu(OAc)_2 \cdot H_2O$	$AgSbF_6$	DCE	100	39[c]
6	$Cu(OAc)_2 \cdot H_2O$	–	H_2O	100	35
7	$Cu(OAc)_2 \cdot H_2O$	–	DMF	100	55
8	$Cu(OAc)_2 \cdot H_2O$	–	NMP	100	53
9	$Cu(OAc)_2 \cdot H_2O$	–	PhMe	100	42
10	$Cu(OAc)_2 \cdot H_2O$	–	DMA	100	63
11	$CuBr_2$	–	*t*-AmOH	100	–

[a] Reaction conditions: **1a** (0.5 mmol), **2a** (1.0 mmol), $[RuCl_2(p\text{-cymene})]_2$ (5.0 mol %), oxidant (0.5 mmol), solvent (2.0 mL), 22 h; isolated yields. [b] In the absence of $[RuCl_2(p\text{-cymene})]_2$. [c] **4aa** (19%) was also isolated.

Scheme 2. Scope of Oxidative Coupling with Enamines **1**



Thereafter, we probed different alkynes **2** in the oxidative pyrrole synthesis (Scheme 3). The optimized ruthenium

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(14) (a) Kornhaass, C.; Li, J.; Ackermann, L. *J. Org. Chem.* **2012**, *77*, 9190. (b) Zhao, P.; Wang, F.; Han, K.; Li, X. *Org. Lett.* **2012**, *14*, 5506. (c) Li, B.; Feng, H.; Wang, N.; Ma, J.; Song, H.; Xu, S.; Wang, B. *Chem.—Eur. J.* **2012**, *18*, 12873. (d) Chidipudi, S. R.; Khan, I.; Lam, H. W. *Angew. Chem., Int. Ed.* **2012**, *51*, 12115. (e) Parthasarathy, K.; Senthilkumar, N.; Jayakumar, J.; Cheng, C.-H. *Org. Lett.* **2012**, *14*, 3478. (f) Thirunavukkarasu, V. S.; Donati, M.; Ackermann, L. *Org. Lett.* **2012**, *14*, 3416. (g) Chinnagolla, R. K.; Pimparkar, S.; Jeganmohan, M. *Org. Lett.* **2012**, *14*, 3032. (h) Ackermann, L.; Lygin, A. V. *Org. Lett.* **2012**, *14*, 764. (i) Ackermann, L.; Pospech, J.; Graczyk, K.; Rauch, K. *Org. Lett.* **2012**, *14*, 930. (j) Ackermann, L.; Wang, L.; Lygin, A. V. *Chem. Sci.* **2012**, *3*, 177. (k) Li, B.; Feng, H.; Xu, S.; Wang, B. *Chem.—Eur. J.* **2011**, *17*, 12573. (l) Ackermann, L.; Lygin, A. V.; Hofmann, N. *Org. Lett.* **2011**, *13*, 3278. (m) Ackermann, L.; Fenner, S. *Org. Lett.* **2011**, *13*, 6548. (n) Ackermann, L.; Lygin, A. V.; Hofmann, N. *Angew. Chem., Int. Ed.* **2011**, *50*, 6379.

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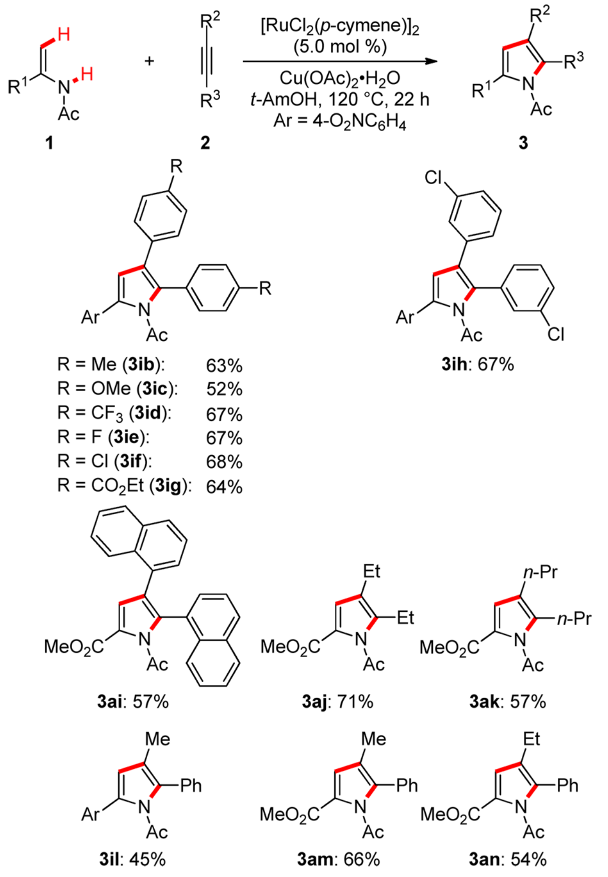
catalyst proved tolerant of functional groups in the *para*-, *meta*- and *ortho*-position of tolan, but was not restricted to aryl alkynes **2a**−**2i**. Indeed, dialkyl-substituted substrates **2j** and **2k** delivered the desired products **3aj** and **3ak**, respectively, in high yields likewise. Notably, oxidative annulations of unsymmetrical alkynes **2l**−**n** occurred with synthetically useful levels of regiocontrol, exclusively furnishing products **3il**−**3an**. This selectivity pattern is in good agreement with the one previously observed by us for a related indole synthesis.[14h]

Given the remarkable catalytic activity of the ruthenium(II) catalyst, we became interested in probing its mode of action.

Scheme 3. Scope with Substituted Alkynes **2**

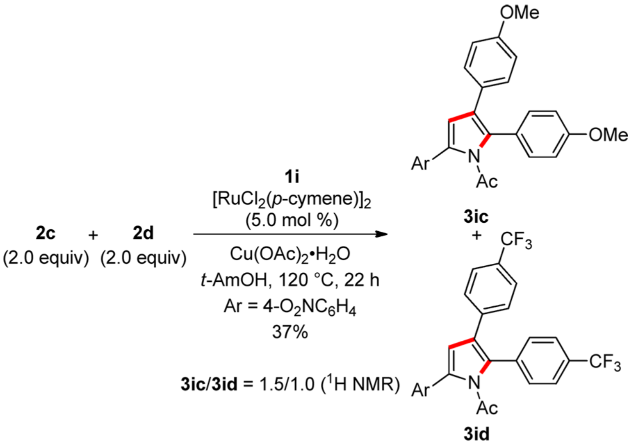


To this end, we conducted intermolecular competition experiments with alkynes **2**, which revealed more electron-rich alkyne **2c** to react preferentially (Scheme 4).

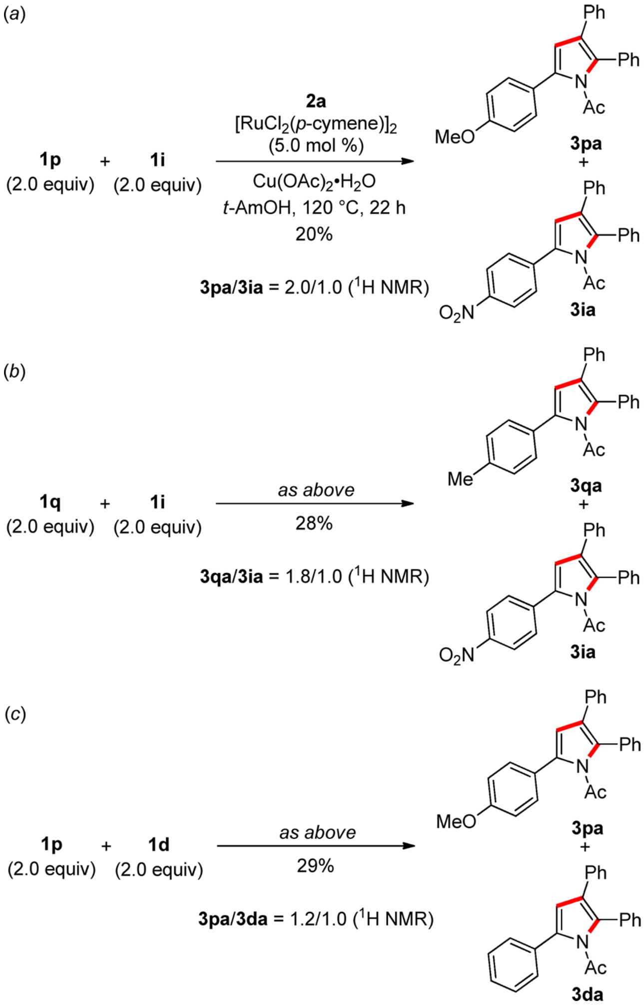
Competition experiments with differently substituted enamines **1**, in contrast, highlighted electron-donating substituents on the aryl moiety to be beneficial (Scheme 5 and the Supporting Information).[16]

Furthermore, oxidative annulations in isotopically labeled solvent [D]$_4$-MeOH unraveled the C−H bond activation on enamines **1** to be reversible in nature (Scheme 6a).

Scheme 4. Intermolecular Competition between Alkynes **2**



Scheme 5. Intermolecular Competition between Enamines **1**



Yet, the H/D scrambling was not observed in the presence of alkyne **2a** under otherwise identical reaction conditions (b). These findings can be rationalized in terms of an

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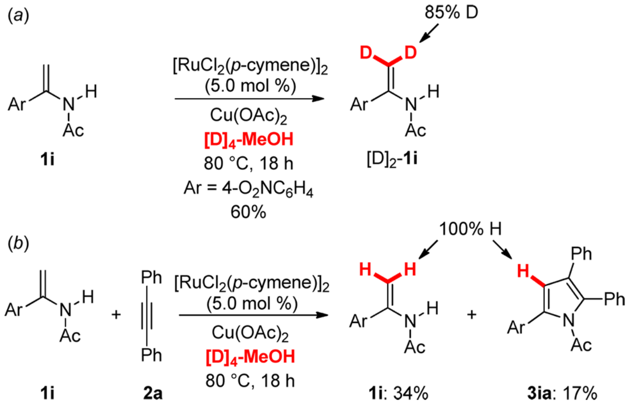
(16) In individual experiments, products **3pa** and **3qa** were obtained in 18% and 28% isolated yields, respectively.

Scheme 6. Oxidative Annulations in $[D]_4$-MeOH

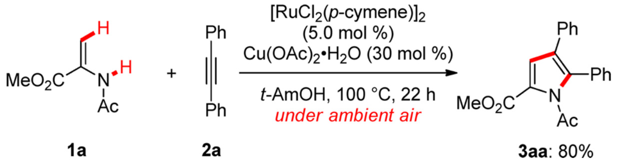


alkyne-coordinated ruthenium complex undergoing an irreversible C−H bond metalation step.

Finally, we were pleased that the C−H/N−H bond functionalization was also achieved in an aerobic fashion employing cocatalytic amounts of $Cu(OAc)_2 \cdot H_2O$ under an ambient atmosphere of air as the ideal oxidant (Scheme 7).

In summary, we have reported on the first use of rather inexpensive ruthenium catalysts for oxidative alkyne annulations utilizing electron-rich olefins. The C−H/N−H functionalization strategy set the stage for an expedient pyrrole synthesis, which was also accomplished in an aerobic manner with air as the ideal terminal oxidant.

Scheme 7. Aerobic Oxidative C−H/N−H Bond Functionalization under Air



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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.