ORGANIC LETTERS

2010
Vol. 12, No. 9
2056−2059

Palladium-Catalyzed Dehydrogenative Direct Arylations of 1,2,3-Triazoles

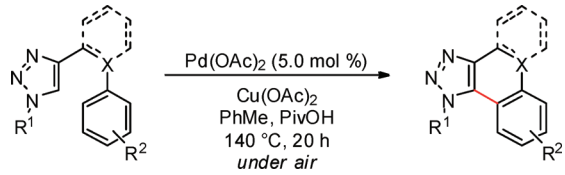
Lutz Ackermann,* Rajkumar Jeyachandran, Harish K. Potukuchi, Petr Novák, and Lea Büttner

Institut fuer Organische und Biomolekulare Chemie, Georg-August-Universitaet, Tammannstrasse 2, 37077 Goettingen, Germany

lutz.ackermann@chemie.uni-goettingen.de

Received March 5, 2010

ABSTRACT



Palladium-catalyzed intramolecular dehydrogenative direct arylations of 1,2,3-triazoles were accomplished under ambient pressure of air, which set the stage for a modular synthesis of annulated phenanthrenes through a reaction sequence comprising two distinct catalytic C−H bond functionalization reactions.

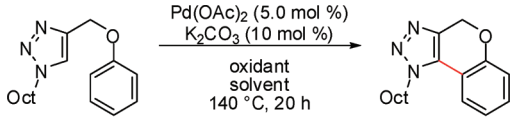
The outstanding chemo- and regioselectivities of the catalyzed Huisgen 1,3-dipolar-cycloaddition reaction[1] between azides and alkynes have resulted in its widespread application to inter alia material sciences or pharmaceutical and agrochemical industries.[2] Particularly, copper-catalyzed azide−alkyne cycloadditions (CuAAC) have proven most useful for the construction of 1,4-disubstituted 1,2,3-triazoles.[3] On the contrary, the regioselective preparation of fully decorated 1,2,3-triazoles employing internal alkynes continues to be more challenging, and was thus far largely limited to the use of 1-bromo-[4] or 1-iodoalkynes[5] as dipolarophiles.[6,7] A more atom-economical approach is, however, represented by recently developed palladium-[8] or copper-catalyzed[9] direct arylations[10] of 1,2,3-triazoles through regioselective C−H bond functionalizations.[11] While these reactions proceeded in a highly regioselective fashion, they unfortunately required aryl (pseudo)halides as prefunctionalized arylating reagents. During studies on intramolecular direct arylations of 1,2,3-triazoles,[8c] we thus became interested in developing unprecedented oxidative[10,12] direct arylations[13] of these heteroarenes with unfunctionalized arenes. Herein, we wish to report on these studies, which further enabled a modular synthesis of heteroannulated phenanthrenes through a reaction sequence involving two distinct C−H bond arylations.

At the outset, we probed representative protocols for transition metal-catalyzed dehydrogenative biaryl syntheses.

(1) Huisgen, R. *Angew. Chem.* **1963**, *75*, 604–637.
(2) Select recent reviews: (a) Nandivada, H.; Jiang, X.; Lahann, J. *Adv. Mater.* **2007**, *19*, 2197–2208. (b) Angell, Y. L.; Burgess, K. *Chem. Soc. Rev.* **2007**, *36*, 1674–1689. (c) Fournier, D.; Hoogenboom, R.; Schubert, U. S. *Chem. Soc. Rev.* **2007**, *36*, 1369–1380. (d) Moses, J. E.; Moorhouse, A. D. *Chem. Soc. Rev.* **2007**, *36*, 1249–1262. (e) Lutz, J.-F. *Angew. Chem., Int. Ed.* **2007**, *46*, 1018–1025. (f) Dondoni, A. *Chem. Asian J.* **2007**, *2*, 700–708. (g) Qin, A.; Lam, J. W. Y.; Tang, B. Z. *Chem. Soc. Rev.* **2010**, DOI: 10.1039/b909064a. (h) El-Sagheer, A. H.; Brown, T. *Chem. Soc. Rev.* **2010**, *39*, 1388−1405. (i) Hänni,K. D.; Leigh, D. A. *Chem. Soc. Rev.* **2010**, *39*, 1240−1251. (j) Kappe, C. O.; Van der Eycken, E. *Chem. Soc. Rev.* **2010**, *39*, 1280−1290.
(3) (a) Tornoe, C. W.; Christensen, C.; Meldal, M. *J. Org. Chem.* **2002**, *67*, 3057–3064. (b) Rostovtsev, V. V.; Green, L. G.; Fokin, V. V.; Sharpless, K. B. *Angew. Chem., Int. Ed.* **2002**, *41*, 2596–2599.
(4) Kuijpers, B. H. M.; Dijkmans, G. C. T.; Groothuys, S.; Quaedflieg, P. J. L. M.; Blaauw, R. H.; van Delft, F. L.; Rutjes, F. P. J. T. *Synlett* **2005**, 3059–3062.
(5) Hein, J. E.; Tripp, J. C.; Krasnova, L. B.; Sharpless, K. B.; Fokin, V. V. *Angew. Chem., Int. Ed.* **2009**, *48*, 8018–8021.
(6) Spiteri, C.; Moses, J. E. *Angew. Chem., Int. Ed.* **2010**, *49*, 31–33.
(7) For a recent example of the use of stoichiometrically metalated alkynes, see: Zhou, Y.; Lecourt, T.; Micouin, L. *Angew. Chem., Int. Ed.* DOI: 10.1002/anie.200907016 and references cited therein.
(8) (a) Chuprakov, S.; Chernyak, N.; Dudnik, A. S.; Gevorgyan, V. *Org. Lett.* **2007**, *9*, 2333–2336. (b) Iwasaki, M.; Yorimitsu, H.; Oshima, K. *Chem. Asian J.* **2007**, *2*, 1430–1435. (c) Ackermann, L.; Vicente, R.; Born, R. *Adv. Synth. Catal.* **2008**, *350*, 741–748. (d) Ackermann, L.; Althammer, A.; Fenner, S. *Angew. Chem., Int. Ed.* **2009**, *48*, 201–204. (e) Ackermann, L.; Vicente, R. *Org. Lett.* **2009**, *11*, 4922–4925.

10.1021/ol1005517 © 2010 American Chemical Society
Published on Web 03/31/2010

Table 1. Optimization of Dehydrogenative Arylation[a]

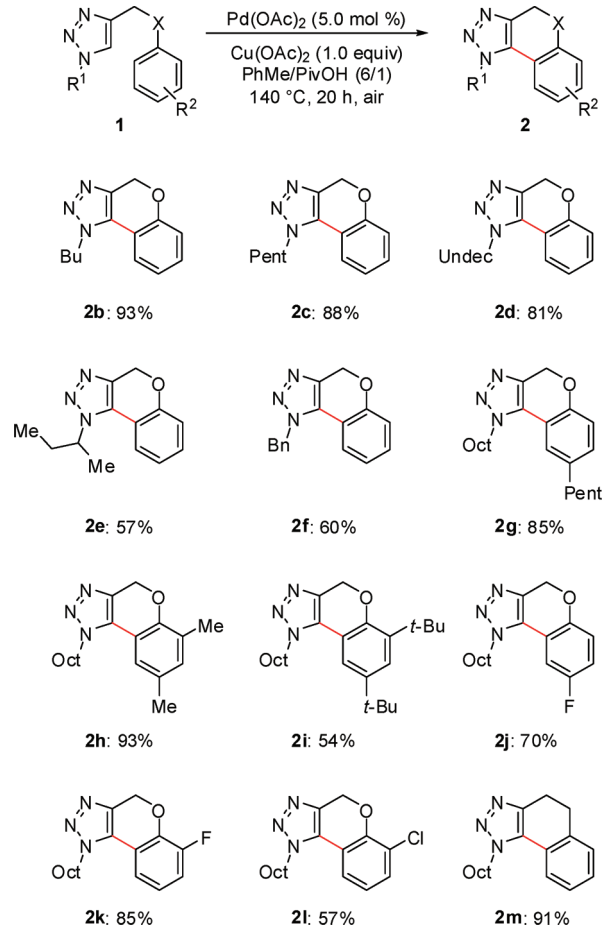


entry	oxidant (equiv)	solvent (ratio)	temp [°C]	isolated yield (%)
1	air	PivOH	120	14[b]
2	$Cu(OAc)_2$ (1.2)	PivOH	120	27
3	$Cu(OAc)_2$ (2.0)	xylene	120	–
4	$FeCl_3$ (2.0)	PivOH	120	–
5	AgOAc (1.2)	PivOH	120	59
6	$Cu(OAc)_2$ (1.2)	dioxane/PivOH (6/1)	120	24[b,c]
7	$Cu(OAc)_2$ (1.0)	PhMe/PivOH (6/1)	120	72[b,c]
8	$Cu(OAc)_2$ (1.0)	PhMe/PivOH (6/1)	140	93[c]
9	$Cu(OAc)_2$ (1.0)	PhMe/PivOH (6/1)	140	94[d]
10	$Cu(OAc)_2$ (1.0)	PhMe/PivOH (6/1)	140	96[c,d]
11	$Cu(OAc)_2$ (1.0)	PhMe/PivOH (6/1)	140	–[c–e]

[a] Reaction conditions: **1a** (1.00 mmol), $Pd(OAc)_2$ (5.0 mol %), K_2CO_3 (10 mol %), oxidant (1.0–2.0 mmol), solvent (3.0–3.5 mL), N_2, 20 h. [b] GC yield. [c] Under air. [d] Without K_2CO_3. [e] Without $Pd(OAc)_2$.

Unfortunately, reaction conditions for palladium-catalyzed arylations with air as sacrificial oxidant[14] only provided unsatisfactory low conversions (Table 1, entry 1). However, among a variety of terminal oxidants, $Cu(OAc)_2$ or AgOAc enabled more effective oxidative arylations (entries 2–5), particularly when using a solvent system consisting of toluene and pivalic acid (entries 6–9). Importantly, high yields of isolated product **2a** could be obtained at ambient pressure of air, and the use of molecular oxygen[13] was not mandatory (entry 10). Notably, the dehydrogenative coupling did not occur in the absence of a palladium catalyst (entry 11).

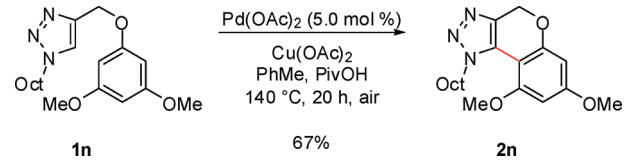
Scheme 1. Cyclodehydrogenative arylations of 1,2,3-Triazoles **1**



With an optimized catalytic system in hand, we explored its scope in dehydrogenation arylations of 1,2,3-triazoles **1** (Scheme 1). Hence, diversely decorated products **2b–m** were regioselectively formed in high yields, even when bearing halo-substituents (**2j–l**).

Remarkably, the catalytic system also proved applicable to the synthesis of sterically hindered tetra-ortho-substituted biaryl **2n** (Scheme 2).

Scheme 2. Synthesis of Tetra-ortho-Substituted Biheteroaryl **2n**



As to the mechanism, intramolecular competition experiments highlighted that the less sterically hindered site on

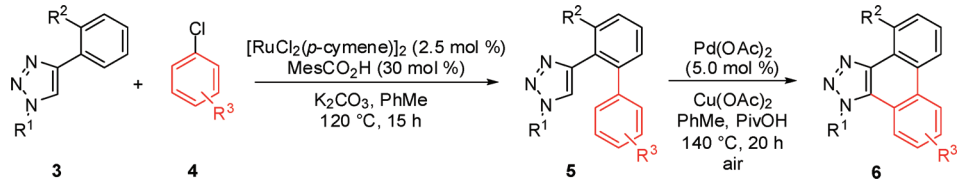
(9) (a) Ackermann, L.; Potukuchi, H. K.; Landsberg, D.; Vicente, R. *Org. Lett.* **2008**, *10*, 3081–3084. (b) For a similar subsequent report, see: Fukuzawa, S.-I.; Shimizu, E.; Ogata, K. *Heterocycles* **2009**, *78*, 645–655.

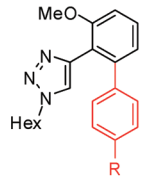
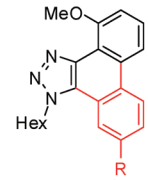
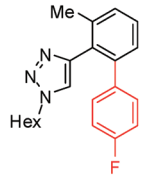
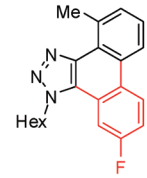
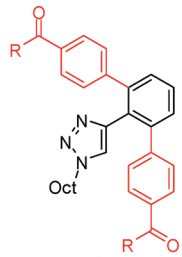
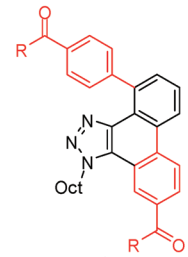
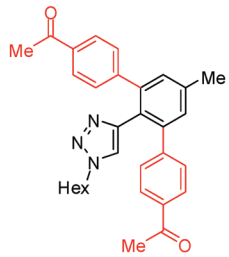
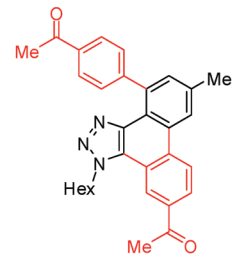
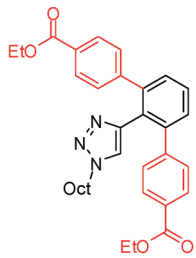
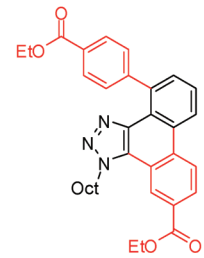
(10) Recent reviews: (a) Sun, C.-L.; Li, B.-J.; Shi, Z.-J. *Chem. Commun.* **2010**, 677–685. (b) Lyons, T. W.; Sanford, M. S. *Chem. Rev.* **2010**, *110*, 1147–1169. (c) Ackermann, L.; Vicente, R.; Kapdi, A. *Angew. Chem., Int. Ed* **2009**, *48*, 9792–9826. (d) Chen, X.; Engle, K. M.; Wang, D.-H.; Yu, J.-Q. *Angew. Chem., Int. Ed.* **2009**, *48*, 5094–5115. (e) Thansandote, P.; Lautens, M. *Chem.–Eur. J.* **2009**, *15*, 5874–5883. (f) Daugulis, O.; Do, H.-Q.; Shabashov, D. *Acc. Chem. Res.* **2009**, *42*, 1074–1086. (g) Kakiuchi, F.; Kochi, T. *Synthesis* **2008**, 3013–3039. (h) Lewis, J. C.; Bergman, R. G.; Ellman, J. A. *Acc. Chem. Res.* **2008**, *41*, 1013–1025. (i) Satoh, T.; Miura, M. *Chem. Lett.* **2007**, *36*, 200–205. (j) Alberico, D.; Scott, M. E.; Lautens, M. *Chem. Rev.* **2007**, *107*, 174–238. (k) Seregin, I. V.; Gevorgyan, V. *Chem. Soc. Rev.* **2007**, *36*, 1173–1193. (l) Campeau, L.-C.; Stuart, D. R.; Fagnou, K. *Aldrichim. Acta* **2007**, *40*, 35–41. (m) Ackermann, L. *Synlett* **2007**, 507–526. (n) Pascual, S.; de Mendoza, P.; Echavarren, A. M. *Org. Biomol. Chem.* **2007**, *5*, 2727–2734.

(11) For ruthenium-catalyzed direct arylations of *N*-aryl-substituted 1,2,3-triazoles, see: (a) Ackermann, L.; Vicente, R.; Althammer, A. *Org. Lett.* **2008**, *10*, 2299–2302. (b) Ackermann, L.; Born, R.; Vicente, R. *ChemSusChem* **2009**, *2*, 546–549.

(12) For representative recent examples of palladium-catalyzed dehydrogenative arylations for bi(hetero)aryl syntheses, see: (a) Xi, P.; Yang, F.; Qin, S.; Zhao, D.; Lan, J.; Gao, G.; Hu, C.; You, J. *J. Am. Chem. Soc.* **2010**, *132*, 1822–1824. (b) Liang, Z.; hao, J.; Zhang, Y. *J. Org. Chem.* **2010**, *75*, 170–177. (c) Hull, K. L.; Sanford, M. S. *J. Am. Chem. Soc.* **2009**, *131*, 9651–9653. (d) Watanabe, T.; Oishi, S.; Fujii, N.; Ohno, H. *J. Org. Chem.* **2009**, *74*, 4720–4726. (e) Cho, S. H.; Hwang, S. J.; Chang, S. *J. Am. Chem. Soc.* **2008**, *130*, 9254–9256. (f) Brasche, G.; Garcia-Fortanet, J.; Buchwald, S. L. *Org. Lett.* **2008**, *10*, 2207–2210. (g) Voutchkova, A.; Coplin, A.; Leadbeater, N. E.; Crabtree, R. H. *Chem. Commun.* **2008**, 6312–6314. (h) Li, B.-J.; Tian, S.-L.; Fang, Z.; Shi, Z.-J. *Angew. Chem., Int. Ed.* **2008**, *47*, 1115–1118. (i) Stuart, D. R.; Villemure, E.; Fagnou, K. *J. Am. Chem. Soc.* **2007**, *129*, 12072–12073. (j) Dwight, T. A.; Rue, N. R.; Charyk, D.; Josselyn, R.; DeBoef, B. *Org. Lett.* **2007**, *9*, 3137–3139. (k) Stuart, D. R.; Fagnou, K. *Science* **2007**, *316*, 1172–1175. (l) Li, R.; Jiang, L.; Lu, W. *Organometallics* **2006**, *25*, 5973–5975, and references cited therein.

Table 2. Sequential Catalytic Direct Arylations for the Synthesis of Phenanthrenes **6**[a]



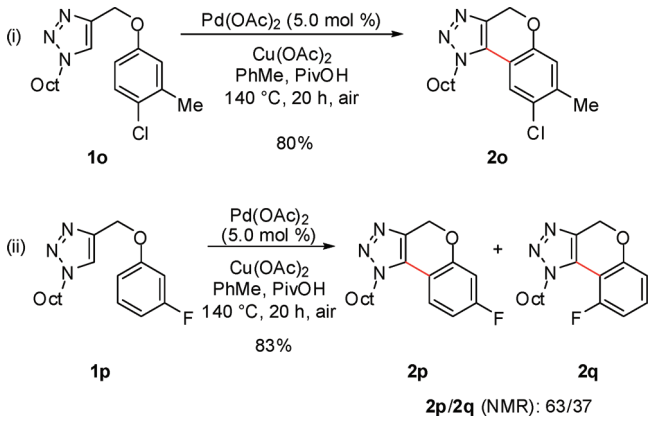
entry	5	isolated yield	6	isolated yield
1	 R = Me: **5a**	74%	 R = Me: **6a**	71%
2	R = CO_2Et: **5b**	67%	R = CO_2Et: **6b**	68%
3	 **5c**	89%	 **6c**	66%
4	 R = Ph: **5d**	78%	 R = Ph: **6d**	68%
5	R = Me: **5e**	71%	R = Me: **6e**	72%
6	 **5f**	66%	 **6f**	65%
7	 **5g**	64%	 **6g**	96%

[a] Reaction conditions: (a) **3** (1.00 mmol), **4** (1.50−3.00 mmol), $[RuCl_2(p\text{-cymene})]_2$ (2.5 mol %), $MesCO_2H$ (30 mol %), K_2CO_3 (2.00 mmol), PhMe (4.0 mL), 120 °C, 15 h; (b) **5** (0.50 mmol), $Pd(OAc)_2$ (5.0 mol %), $Cu(OAc)_2$ (0.50 mmol), PivOH (250 mg), PhMe (1.5 mL), 140 °C, 20 h, under air.

arene **1o** was preferentially functionalized (Scheme 3i). Moreover, the less acidic[15] C−H bond on arene **1p** was predominantly heteroarylated (ii), thereby rendering a base-assisted metalation less likely to be operative here.

Finally, we devised a modular sequential synthesis of heteroannulated phenanthrenes **6** consisting of two mechanistically distinct direct C−H bond functionalizations (Table 2). Thus, a novel ruthenium-catalyzed directed arylation[11,16]

Scheme 3. Intramolecular Competition Experiments



of 4-aryl-substituted 1,2,3-triazoles set the stage for efficient cyclodehydrogenative arylations, yielding differently substituted phenanthro[9,10-*d*]triazoles **6**. Notably, this multicatalytic approach to π-conjugated heteroarenes **6** tolerated a variety of valuable functional groups, such as (enolizable) ketones or esters (entries 2 and 4−7).

In summary, we reported on the development of unprecedented dehydrogenative arylations of 1,2,3-triazoles. Specifically, a palladium catalyst enabled highly efficient cyclodehydrogenative biheteroaryl formations under ambient pressure of air. The broad scope of this method was furthermore illustrated with a modular synthesis of π-conjugated heteroannulated phenanthrenes.

Acknowledgment. Support by the DFG and the DAAD (fellowship to H.K.P.) is gratefully acknowledged.

Supporting Information Available: Experimental procedures, characterization data, and ^{1}H and ^{13}C NMR spectra for new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

OL1005517

(13) (a) During the preparation of this manuscript, Jiang and co-workers reported on Fujiwara−Moritani alkenylations of triazoles with terminal, activated alkenes under 8 atm of O_2: Jiang, H.; Feng, Z.; Wang, A.; Liu, X.; Chen, Z. *Eur. J. Org. Chem.* **2010**, 1227–1230. (b) For representative select reports on palladium-catalyzed oxidative alkenylations, see: Wang, D.-H.; Engle, K. M.; Shi, B.-F.; Yu, J.-Q. *Science* **2010**, *327*, 315–319. (c) Boele, M. D. K.; van Strijdonck, G. P. F.; de Vries, A. H. M.; Kamer, P. C. J.; de Vries, J. G.; van Leeuwen, P.W. N. M. *J. Am. Chem. Soc.* **2002**, *124*, 1586–1587. (d) Jia, C.; Kitamura, T.; Fujiwara, Y. *Acc. Chem. Res.* **2001**, *34*, 633–639.

(14) Liegault, B.; Lee, D.; Huestis, M. P.; Stuart, D. R.; Fagnou, K. *J. Org. Chem.* **2008**, *73*, 5022–5028.

(15) Shen, K.; Fu, Y.; Li, J.-N.; Liu, L.; Guo, Q.-X. *Tetrahedron* **2007**, *63*, 1568–1576.

(16) Reviews: (a) Ackermann, L.; Vicente, R. *Top. Curr. Chem.* DOI: 10.1007/128_2009_9. (b) Ackermann, L.; Born, R.; Spatz, J. H.; Althammer, A.; Gschrei, C. J. *Pure Appl. Chem.* **2006**, *78*, 209–214.