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

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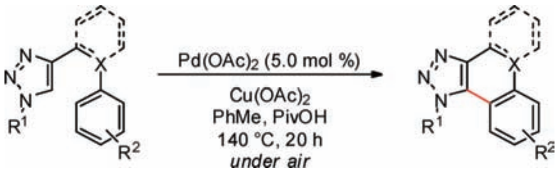
ABSTRACT



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.

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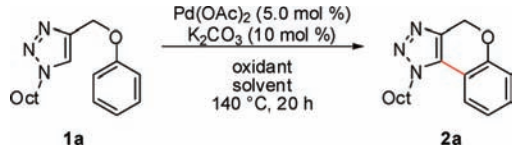
10.1021/ol1005517

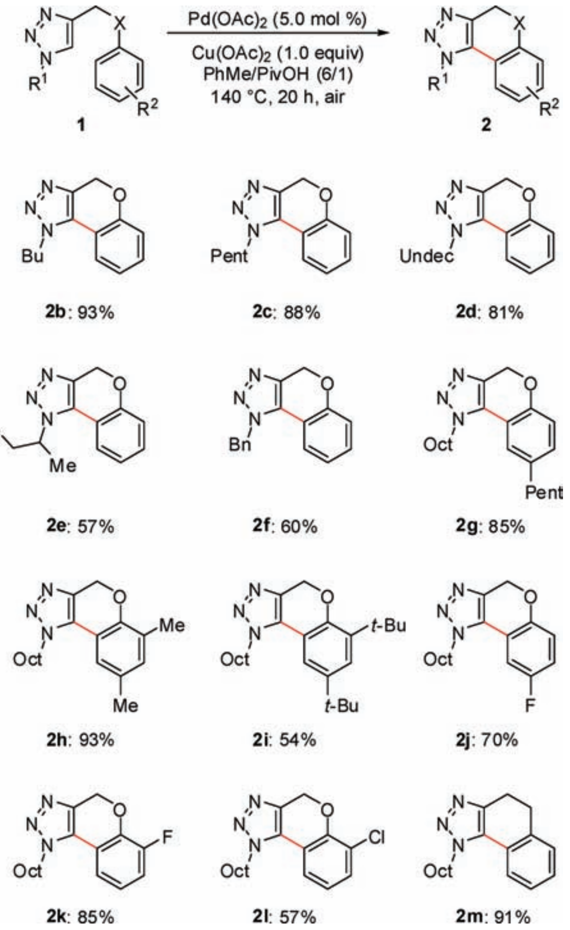
Table 1. Optimization of Dehydrogenative Arylation[a]



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 $Pd(OAc)_2$.

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

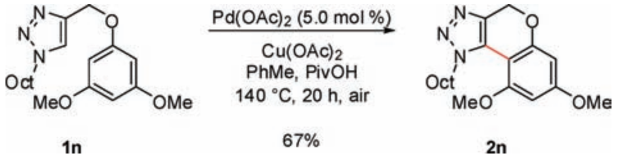


Unfortunately, reaction conditions for palladium-catalyzed arylations with air as sacrificial oxidant[14] only provided unsatisfactory low conversions (Table 1, entry 1). However, among a variety of terminal oxidants, $Cu(OAc)_2$ or AgOAc enabled more effective oxidative arylations (entries 2−5), particularly 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).

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

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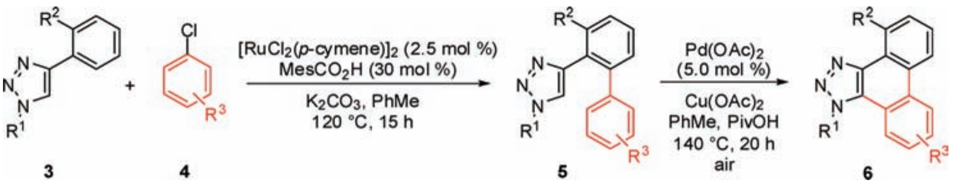
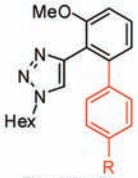
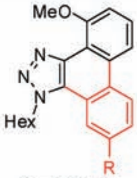
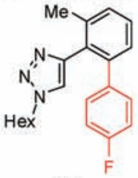
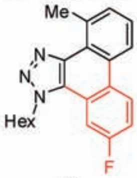
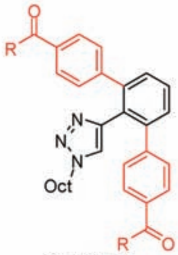
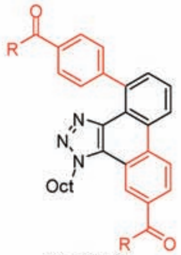
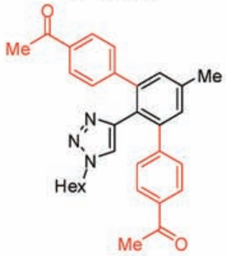
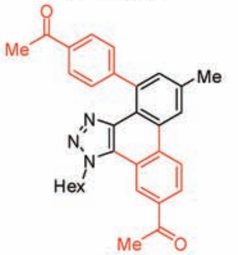
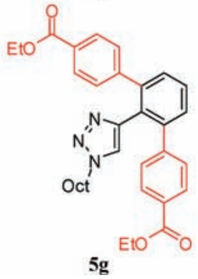
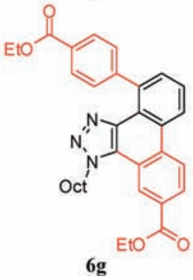
Table 2. Sequential Catalytic Direct Arylations for the Synthesis of Phenanthrenes **6**[a]



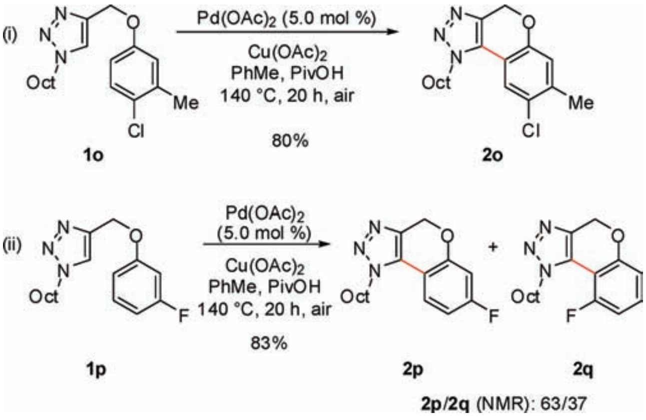
entry	5	isolated yield	6	isolated yield
1	 R = Me: **5a**	74%	 R = Me: **6a**	71%
2	R = CO_2Et: **5b**	67%	R = CO_2Et: **6b**	68%
3	 **5c**	89%	 **6c**	66%
4	 R = Ph: **5d**	78%	 R = Ph: **6d**	68%
5	R = Me: **5e**	71%	R = Me: **6e**	72%
6	 **5f**	66%	 **6f**	65%
7	 **5g**	64%	 **6g**	96%

[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.

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(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.

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

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