ORGANIC LETTERS

2008
Vol. 10, No. 14
3081−3084

Copper-Catalyzed “Click” Reaction/ Direct Arylation Sequence: Modular Syntheses of 1,2,3-Triazoles

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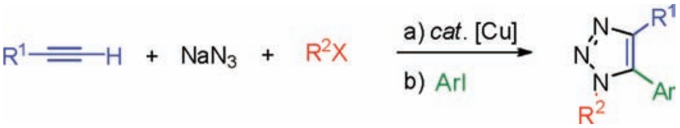
Received May 9, 2008

ABSTRACT



Inexpensive copper catalysts enabled modular one-pot multicomponent syntheses of fully decorated triazoles through a sustainable “click” reaction/direct arylation sequence.

The remarkable efficiency and selectivity accomplished with copper catalysts[1,2] in Huisgen cycloadditions of organic azides with alkynes[3] resulted in its application in various research areas, ranging from bioorganic and medicinal chemistry to material sciences.[4] This “click” reaction proceeded highly regioselectively when using terminal alkynes, thereby providing 1,4-disubstituted 1,2,3-triazoles **2** as the sole products. On the contrary, [3 + 2] cycloadditions of the corresponding internal alkynes for the synthesis of fully decorated 1,2,3-triazoles **4** were found either not generally applicable or gave rise to mixtures of regioisomers.[5]

Catalytic C−H-bond functionalizations are attractive because of their ecologically and economically benign nature. Among these, regioselective direct arylations of (hetero)arenes represent a valuable alternative to traditional cross-couplings with stoichiometric amounts of organometallic reagents.[6] The overall efficiency of this strategy was significantly improved by its combination with mechanistically distinct processes within sustainable one-pot reactions. Unfortunately, this approach proved thus far restricted to the use of catalysts based on relatively expensive transition metals, such as palladium[7] or ruthenium.[8]

As part of our program on the development of sustainable C−H-bond functionalizations,[9] we wished to explore the

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10.1021/ol801078r CCC: $40.75

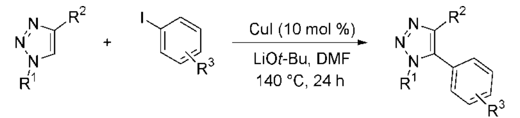
application of less expensive copper complexes[10] to direct arylation-based[11] sequential catalyzes. During these studies, we observed that a single copper precursor sequentially enabled two sustainable catalytic transformations, namely atom-economical "click" reactions and novel C−H-bond functionalizations of 1,2,3-triazoles.[12,13] Herein, we report on this approach, which allowed for modular syntheses of fully substituted 1,2,3-triazoles **4** through a chemo- and regioselective one-pot, four-component coupling (Scheme 1).

Scheme 1. Copper-Catalyzed Sequential Synthesis of Triazoles

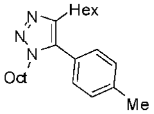
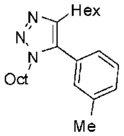
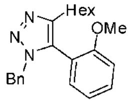
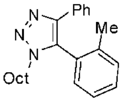
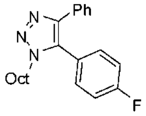
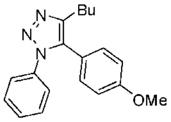
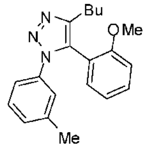
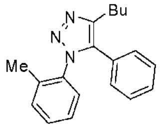
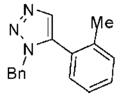
To probe the viability of the envisioned sequential catalytic protocol, we first tested copper-catalyzed direct arylations of 1,4-disubstituted 1,2,3-triazoles **2** (Table 1). Triazoles **2** displaying electron-donating alkyl-substituents on the heteroarenes were efficiently converted with a variety of substituted aryl iodides **3** (entries 1−9). Pronucleophiles with aryl groups at either position of the heterocycle were regioselectively functionalized at the electron-rich triazole moieties (entries 4−8). Notably, the copper-catalyzed direct arylation of a monosubstituted 1,2,3-triazole proceeded also exclusively at position C-5, yielding triazole **4i** exclusively (entry 9).

With an effective protocol for copper-catalyzed direct arylations of triazoles **2** in hand, we tested its application to the one-pot sequential synthesis of fully[14] substituted triazoles **4**. At the outset, we chose preformed alkyl-substituted azides as starting materials for the initial catalytic "click" reaction (Table 2).

Table 1. Copper-Catalyzed Direct Arylations of Triazoles **2**[a]



2 **3** **4**

entry	R^1	R^2	4		yield
1	Oct	Hex		**4a**	74%
2	Oct	Hex		**4b**	72%
3	Bn	Hex		**4c**	86%
4	Oct	Ph		**4d**	98%
5	Oct	Ph		**4e**	73%
6	Ph	Bu		**4f**	71%
7	3-MeC$_6$H$_4$	Bu		**4g**	92%
8	2-MeC$_6$H$_4$	Bu		**4h**	92%
9	Bn	H		**4i**	93%

[a] Reaction conditions: **2** (1.00 mmol), **3** (3.00 mmol), CuI (10 mol %), LiO-*t*-Bu (2.00 mmol), DMF (3.0 mL), 140 °C, 24 h; yields of isolated product.

Importantly, these studies revealed that a single inexpensive copper catalyst could be employed for two mechanistically distinct reactions, providing triazoles **4** in high yields. This protocol proved broadly applicable, allowing for the use of alkyl- (entry 1) as well as aryl-substituted alkynes (entries 2−9). Further, electrophiles with either electron-donating (entries 1−5) or electron-withdrawing (entries 6−9) substituents were successfully converted, even when more sterically demanding (entries 1−4, and 9).

Subsequently, we probed a modular synthesis of *N*-aryltriazoles **4** through a chemoselective coupling of four

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(9) Ackermann, L. *Synlett* **2007**, 507–526.

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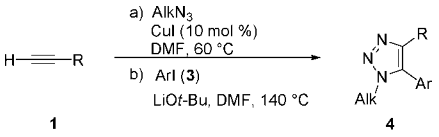
(11) For the elegant development of copper-catalyzed direct arylations, see: (a) Do, H.-Q.; Daugulis, O. *J. Am. Chem. Soc.* **2007**, *129*, 12404–12405. (b) Do, H.-Q.; Daugulis, O. *J. Am. Chem. Soc.* **2008**, *130*, 1128–1129. (c) For the use of stoichiometric amounts of copper in direct arylations, see: Yoshizumi, T.; Tsurugi, H.; Satoh, T.; Miura, M. *Tetrahedron Lett.* **2008**, *49*, 1598–1600.

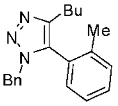
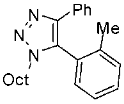
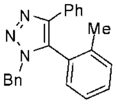
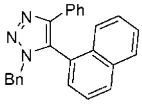
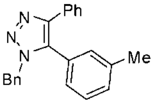
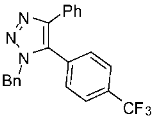
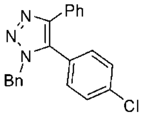
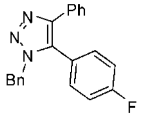
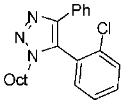
(12) For palladium-catalyzed direct arylations of 1,2,3-triazoles **2**, see: (a) Chuprakov, S.; Chernyak, N.; Dudnik, A. S.; Gevorgyan, V. *Org. Lett.* **2007**, *9*, 2333–2336. (b) Iwasaki, M.; Yorimitsu, H.; Oshima, K. *Chem. Asian J.* **2007**, *2*, 1430–1435. (c) Ackermann, L.; Vicente, R.; Born, R. *Adv. Synth. Catal.* **2008**, *350*, 741–748.

(13) Ruthenium-catalyzed direct arylations of 1,2,3-triazoles **2**: Ackermann, L.; Vicente, R.; Althammer, A. *Org. Lett.* **2008**, *10*, 2299–2305.

(14) One-pot syntheses of 1,4-*disubstituted* 1,2,3-triazoles **2** from in situ generated azides were reported: (a) Feldman, A. K.; Colasson, B.; Fokin, V. V. *Org. Lett.* **2004**, *6*, 3897–3899. (b) Kacprzak, K. *Synlett* **2005**, 943–946. (c) Andersen, J.; Bolvig, S.; Liang, X. *Synlett* **2005**, 2941–2947.

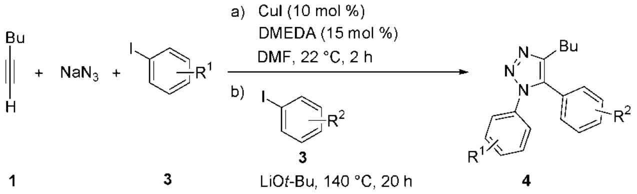
Table 2. Sequential Copper-Catalyzed Synthesis of Triazoles **4**[a]

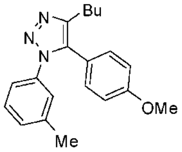
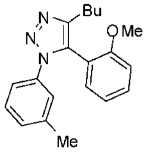
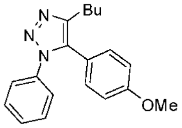
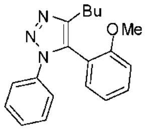
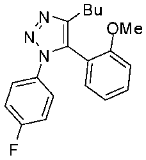
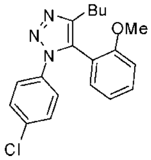


entry	R	Alk	4		yield
1	Bu	Bn		**4j**	67%
2	Ph	Oct		**4d**	69%
3	Ph	Bn		**4k**	70%
4[b]	Ph	Bn		**4l**	84%
5	Ph	Bn		**4m**	61%
6[b]	Ph	Bn		**4n**	69%
7[b]	Ph	Bn		**4o**	80%
8[b]	Ph	Bn		**4p**	79%
9[b]	Ph	Oct		**4q**	63%

[a] Reaction conditions: (a) **1** (1.00 mmol), AlkN$_3$ (1.00 mmol), CuI (10 mol %), DMF (3 mL), 60 °C, 4 h; (b) **3** (3.00 mmol), LiO-*t*-Bu (2.00 mmol), DMF (2.0 mL), 140 °C, 20 h; yields of isolated product. [b] **3** (3.00 mmol), CuI (10−30 mol %), LiO-*t*-Bu (2.00 mmol), DMF (2.0 mL), 140 °C, 20 h.

Table 3. Sequential Copper-Catalyzed Four-Component Synthesis[a]



entry	R^1	R^2	4		yield
1	3-Me	4-MeO		**4r**	70%
2	3-Me	2-MeO		**4g**	81%
3	H	4-MeO		**4f**	73%
4	H	2-MeO		**4s**	74%
5	4-F	2-MeO		**4t**	70%
6	4-Cl	2-MeO		**4u**	67%

[a] Reaction conditions: (a) **1** (1.00 mmol), **3** (1.00 mmol), NaN$_3$ (1.05 mmol), CuI (10 mol %), DMEDA (15 mol %), DMF (3.0 mL), 22 °C, 2 h; (b) **3** (3.00 mmol), LiO-*t*-Bu (2.00 mmol), DMF (2.0 mL), 140 °C, 20 h; yields of isolated product. DMEDA = *N*,*N*′-dimethylethylenediamine.

components. A copper catalyst modified with *N*,*N*′-dimethylethylenediamine (DMEDA) as stabilizing ligand yielded disubstituted triazoles **2** efficiently. Importantly, their regioselective direct arylations were also achieved with the same copper catalyst (Table 3).[15] Therefore, a variety of triazoles **4** were obtained, displaying both electron-rich (entries 1−4) as well as functionalized electron-deficient (entries 5 and 6) aryl-substituents. It is noteworthy that this four-component one-pot synthesis involved the formation of one C−C- and three C−N-bonds in a highly selective fashion.

In conclusion, a novel copper-catalyzed direct arylation of 1,4-disubstituted triazoles **2** set the stage for the development of a modular one-pot approach to diversely substituted 1,2,3-triazoles **4**. The unprecedented direct arylation-based

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(15) **Representative Procedure (Table 3, Entry 2).** A suspension of CuI (19 mg, 0.10 mmol, 10 mol %) and NaN$_3$ (69 mg, 1.05 mmol) in DMF (3 mL) was treated with 1-hexyne (82 mg, 1.00 mmol), 3-iodobenzene (204 mg, 1.00 mmol), and *N*,*N*′-dimethylethylenediamine (13 mg, 0.15 mmol, 15 mol %) and was stirred under N$_2$ at ambient temperature for 2 h. Then, LiO-*t*-Bu (160 mg, 2.00 mmol), 2-iodoanisole (702 mg, 3.00 mmol), and DMF (2.0 mL) were added, and the resulting suspension was stirred under N$_2$ at 140 °C for 20 h. At ambient temperature, Et$_2$O (50 mL) and H$_2$O (50 mL) were added, and the separated aqueous layer was extracted with Et$_2$O (2 × 75 mL). The combined organic layers were washed with satd aq NH$_4$Cl (50 mL), H$_2$O (50 mL), and brine (50 mL), dried over Na$_2$SO$_4$, and concentrated in vacuum. The remaining residue was purified by column chromatography on silica gel (*n*-hexane/EtOAc 12/1 → 10/1) to yield **4g** as an off-white solid (260 mg, 81%).

sequential copper-catalysis combined atom-economical “click” reactions with sustainable C−H-bond functionalizations, enabling the chemoselective coupling of up to four components through the formation of one C−C- and three C−N-bonds.

Acknowledgment. Support by the DFG, the DAAD (fellowship to H.K.), the Alexander-von-Humboldt foundation (fellowship to R.V.), and the Fonds der Chemischen Industrie is gratefully acknowledged.

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

OL801078R