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C−H Bond Functionalization in the Synthesis of Fused 1,2,3-Triazoles

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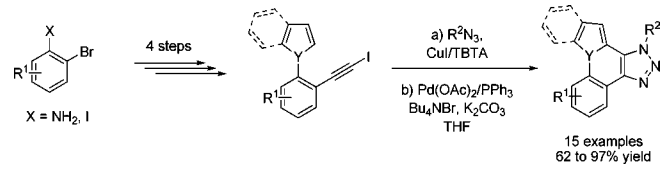
ABSTRACT



A highly modular approach to fused 1,2,3-triazoles has been developed featuring a one-pot procedure combining copper(I) catalyzed azide−alkyne cycloaddition and palladium-catalyzed C−H bond functionalization. A class of structurally unique heterocycles was synthesized in good yields.

Over the past decade, direct functionalization of C−H bonds has become a popular and sought after approach in C−C bond forming reactions.[1] Using this strategy ensures more concise and less wasteful syntheses by foregoing the steps required to make activated starting materials necessary for conventional cross-coupling reactions. Although direct arylation of heteroaromatic compounds is widespread,[1] the use of halogenated heterocycles as electrophiles in C−H functionalizing reactions is less common.[2] Herein we discuss the use of 4-iodo-1,2,3-triazoles as electrophiles in a C−H functionalization.

A common approach in the synthesis of 1,2,3-triazoles is the copper-catalyzed Huisgen cycloaddition of alkynes and azides (CuAAC). The efficacy and reliability of this reaction has demonstrated its utility in many areas of chemical science, and applications of both fused and linear triazoles in pharmaceutically relevant targets are common.[3−5] A drawback of this cycloaddition is the attenuated reactivity of disubstituted alkynes, which can limit the scope to the

(1) Reviews on C−H functionalization: (a) *Handbook of C-H Transformations*; Dyker, G., Ed.; Wiley-VCH: Weinheim, 2005. (b) Alberico, D.; Scott, M. E.; Lautens, M. *Chem. Rev.* **2007**, *107*, 174–238. (c) Thansandote, P.; Lautens, M. *Chem.—Eur. J.* **2009**, *15*, 5874–5883. (d) McGlacken, G. P.; Bateman, L. M. *Chem. Soc. Rev.* **2009**, *38*, 2447–2464. (e) Ackermann, L.; Vicente, R.; Kapdi, A. R. *Angew. Chem., Int. Ed.* **2009**, *48*, 9792–9826.

(2) Selected examples of heteroarylhalides in direct arylation: (a) Ames, D. E.; Bull, D. *Tetrahedron* **1982**, *38*, 383–387. (b) Akita, Y.; Itagaki, Y.; Takizawa, S.; Ohta, A. *Chem. Pharm. Bull.* **1989**, *37*, 1477–1480. (c) Sevignon, M.; Papillon, J.; Schulz, E.; Lemaire, M. *Tetrahedron Lett.* **1999**, *40*, 5873–5876. (d) Grigg, R.; Savic, V.; Tambyrajah, V. *Tetrahedron Lett.* **2000**, *41*, 3003–3006. (e) Zhang, Y.-M.; Razler, T.; Jackson, P. F. *Tetrahedron Lett.* **2002**, *43*, 8235–8239. (f) Masselot, D.; Charmant, J. P. H.; Gallagher, T. *J. Am. Chem. Soc.* **2006**, *128*, 694–695. (g) Masuda, N.; Tanba, S.; Sugie, A.; Monguchi, D.; Koumura, N.; Hara, K.; Mori, A. *Org. Lett.* **2009**, *11*, 2297–2300.

(3) (a) Huisgen, R. *Angew. Chem.* **1963**, *75*, 604–637. (b) Tornoe, C. W.; Christensen, C.; Meldal, M. *J. Org. Chem.* **2002**, *67*, 3057–3064. (c) Rostovtsev, V. V.; Green, L. G.; Fokin, V. V.; Sharpless, K. B. *Angew. Chem., Int. Ed.* **2002**, *41*, 2596–2599.

(4) Reviews on click reaction applications: (a) Angell, Y. L.; Burgess, K. *Chem. Soc. Rev.* **2007**, *36*, 1674–1689. (b) Nandivada, H.; Jiang, X.; Lahann, J. *Adv. Mater.* **2007**, *19*, 2197–2208. (c) Moses, J. E.; Moorhouse, A. D. *Chem. Soc. Rev.* **2007**, *36*, 1249–1262. (d) Fournier, D.; Hoogenboom, R.; Schubert, U. S. *Chem. Soc. Rev.* **2007**, *36*, 1369–1380.

(5) For selected examples of triazoles in pharmaceutically relevant targets, see: (a) Kallander, L. S.; Lu, Q.; Chen, W.; Tomaszek, T.; Yang, G.; Tew, D.; Meek, T. D.; Hofmann, G. A.; Schulz-Pritchard, C. K.; Smith, W. W.; Janson, C. A.; Ryan, M. D.; Zhang, G.-F.; Johanson, K. O.; Kirkpatrick, R. B.; Ho, T. F.; Fischer, P. W.; Mattern, M. R.; Johnson, R. K.; Hansbury, M. J.; Winkler, J. D.; Ward, K. W.; Veber, D. F.; Thompson, S. K. *J. Med. Chem.* **2005**, *48*, 5644–5647. (b) Suzuki, F.; Kuroda, T.; Nakazato, Y.; Manabe, H.; Ohmori, K.; Kitamura, S.; Ichikawa, S.; Ohno, T. *J. Med. Chem.* **1992**, *35*, 4045–4053. (c) Suzuki, F.; Kuroda, T.; Nakazato, Y.; Manabe, H.; Ohmori, K. Preparation of Imidazoquinolone Derivatives Useful for Treatment of Respiratory Disorders. Eur. Pat. Appl. EP0386722, 1990. (d) Ohtsuka, Y.; Shishikura, T.; Ogino, H.; Fushihara, K.; Kawaguchi, M.; Tsutsumi, S.; Imai, M.; Shito, K.; Tsuchiya, K. Preparation of Triazolobenzazepine and Triazolobenzothiazepine Derivatives as Allergy Inhibitors. PCT Int. Appl. WO 9518130, 1995. (e) Whiting, M.; Tripp, J. C.; Lin, Y.-C.; Lindstrom, W.; Olson, A. J.; Elder, J. H.; Sharpless, K. B.; Fokin, V. V. *J. Med. Chem.* **2006**, *49*, 7697–7710.

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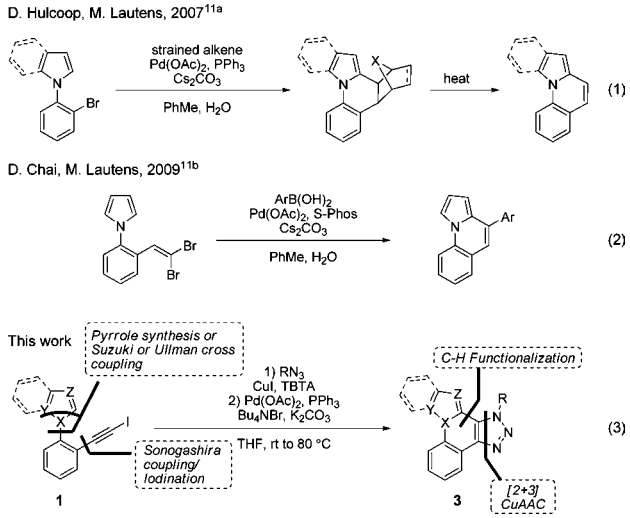
synthesis of 1,4-disubstituted triazoles.[4,6] In order to overcome this limitation several approaches have been devised: 5-bromo and 5-iodotriazoles can be accessed through either one-pot cycloaddition/halogenation[7] or cycloaddition to halogenated alkynes.[8] Alternatively 1,4-disubstituted triazoles can be functionalized through the palladium- or copper-catalyzed direct arylation with arylhalides,[9] or via a dehydrogenative intramolecular coupling recently described by the Ackermann group.[10]

Previously, we demonstrated the feasibility of six-membered ring formation by intramolecular directed arylation with alkyl- and alkenylpalladium intermediates (Scheme 1,

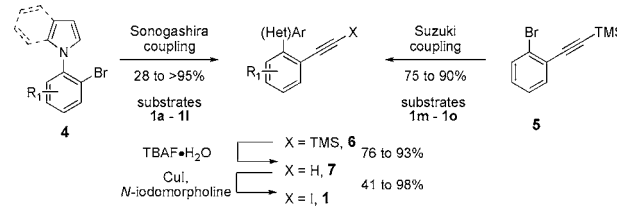
Scheme 1. Work Preceeding This Report and Proposed Retrosynthetic Analysis



eq 1 and 2).[11] We envisaged a method to synthesize fused polycyclic 1,2,3-triazoles **3** by applying this reactivity to the Huisgen cycloadducts of iodoalkynes **1** and azides (Scheme 1, eq 3). Notably, 5-halotriazoles have not been used in direct arylations prior to this report, and this strategy would complement the earlier work in this field by giving access to products with different electronics and substitution patterns.

During the course of this study, we compared several pathways for the synthesis of substrates, and the most modular and high yielding sequence is depicted in Scheme 2. The *ortho*-pyrrolyl substituted arylacetylenes could be

Scheme 2. Synthesis of Substrates

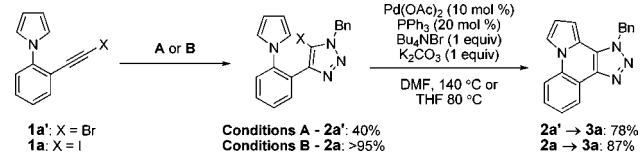


obtained through a Paal-Knorr pyrrole synthesis from bromoanilines, followed by a Sonogashira coupling of **4** with TMS-acetylene.[12] Alternatively, the *ortho*-(het)aryl phenylacetylenes were synthesized from an *ortho*-bromo phenylacetylene **5** through Suzuki or Ullmann coupling.[13,14]

The TMS protecting group in **6** was converted to the iodide **1**, through TBAF promoted desilation and iodination with catalytic copper iodide and *N*-iodomorpholine. Alternatively, benzylaldehydes can serve as precursors to these substrates through the Ramirez−Corey−Fuchs alkyne synthesis.[15] This pathway, however, proved to be less general and more laborious.

We initially examined the reactivity of bromoalkyne **1a′** (Scheme 3). Its cycloaddition with benzylazide proceeded in

Scheme 3. Preliminary Experiments on Cycloaddition and Direct Arylation[a]



[a] **Conditions A**: **1a′** (1 equiv), $Cu(OAc)_2$ (20 mol %), CuBr (20 mol %), BnN_3 (1.1 equiv), THF, 60 °C. **Conditions B**: **1a** (1 equiv), CuI (5 mol %), TBTA (5 mol %), BnN_3 (1 equiv), THF, rt, TBTA: tris((1-benzyl-1H-1,2,3-triazolyl)-methyl)amine (Table 1).

modest yield (conditions **A**) but gave a sufficient amount of **2a′** to examine the direct arylation step.[8a] Following optimization, we observed formation of the desired product **3a** in good yield under palladium/PPh_3 catalysis, however high temperature and prolonged reaction time were required to complete the reaction. At this time, a report by Fokin and co-workers on the synthesis and cycloaddition to iodoalkynes prompted us to examine iodinated substrates.[8b] Reaction of **1a**, using catalytic CuI and tris((1-benzyl-1*H*-1,2,3-triazolyl)methyl)amine (TBTA) ligand (conditions **B**), furnished the triazole intermediate **2a** in

(6) For exceptions see: (a) Hlasta, D. J.; Ackerman, J. H. *J. Org. Chem.* **1994**, *59*, 6184–6189. (b) Coats, S. J.; Link, J. S.; Gauthier, D.; Hlasta, D. J. *Org. Lett.* **2005**, *7*, 1469–1472. (c) Lõrincz, K.; Kele, P.; Novák, Z. *Synthesis* **2009**, 3527–3532. (d) Huang, J.; Macdonald, S. J. F.; Harrity, J. P. A. *Chem. Commun.* **2009**, 436–438. (e) Mehta, S.; Larock, R. C. *J. Org. Chem.* **2010**, *75*, 1652–1658.

(7) (a) Wu, Y.-M.; Deng, J.; Li, Y.; Chen, Q.-Y. *Synthesis* **2005**, 1314–1318. (b) Li, L.; Zhang, G.; Zhu, A.; Zhang, L. *J. Org. Chem.* **2008**, *73*, 3630–3633. (c) Smith, N. W.; Polenz, B. P.; Johnson, S. B.; Dzyuba, S. V. *Tetrahedron Lett.* **2010**, *51*, 550–553.

(8) (a) 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. (b) Hein, J. E.; Tripp, J. C.; Krasnova, L. B.; Sharpless, K. B.; Fokin, V. V. *Angew. Chem., Int. Ed.* **2009**, *48*, 8018–8021.

(9) (a) Chuprakov, S.; Chernyak, N.; Dudnik, A. S.; Gevorgyan, V. *Org. Lett.* **2007**, *9*, 2333–2336. (b) Basolo, L.; Beccalli, E. M.; Borsini, E.; Broggini, G.; Pellegrino, S. *Tetrahedron* **2008**, *64*, 8182–8187. (c) Ackermann, L.; Potukuchi, H. K.; Landsberg, D.; Vicente, R. *Org. Lett.* **2008**, *10*, 3081–3084. (d) Ackermann, L.; Vicente, R. *Org. Lett.* **2009**, *11*, 4922–4925.

(10) Ackermann, L.; Jeyachandran, R.; Potukuchi, H. K.; Novák, P.; Büttner, L. *Org. Lett.* **2010**, *12*, 2056–2059.

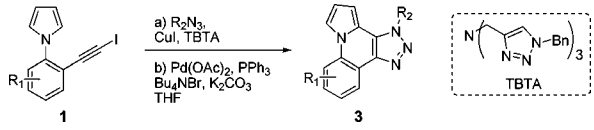
excellent yield. Significantly, the direct arylation now proceeded to give higher yield at 80 °C in THF. These milder annulation conditions showed more promise toward our goal of developing a one-pot protocol for this transformation. When we attempted to combine the [3 + 2] cycloaddition with Pd-catalyzed cyclization, the more effective protocol was to add $Pd(OAc)_2$, PPh_3, base, and tetrabutylammonium bromide as a solid to a completed CuAAC reaction and allow the annulation to proceed. The yields for the one-pot process were comparable to the two-step procedure.

With a set of optimal conditions in hand, we then examined the scope of this one-pot cycloaddition/annulation reaction (Table 1). Several different azides were reacted, and good yields were obtained with benzyl and alkyl azides (Table 1, Entries 1−5). More sterically encumbered aryl- and TMS-azides failed to yield any cycloaddition product. Notably, the palladium loading could be reduced to 1 mol % with the reaction still giving synthetically useful yield (Entry 2).

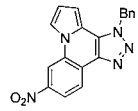
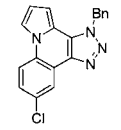
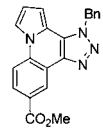
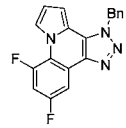
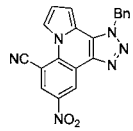
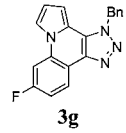
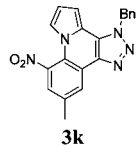
Both electron-poor and -neutral alkyne substrates reacted efficiently. Halogenated compounds could be synthesized in good yield (Entries 8−10). Ester and nitro substituents were well tolerated (Entries 11, 12), whereas the substrate bearing a cyano group gave a moderate yield (Entry 13).

We observed that several heterocyclic nucleophiles other than pyrrole reacted giving good yields (Table 2). Notably, a single isomer was observed for 3-thienyl substituted compounds (**3m**, Entry 2). A product with a phenanthroline backbone **3o** could also be accessed in high yield, illustrating

Table 1. Effects of Substitution Pattern on Reactivity in a One-Pot Reaction[a]

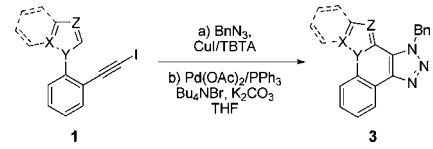


1 3

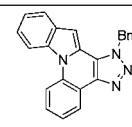
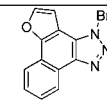
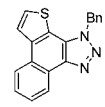
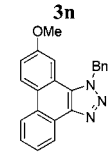
entry		yield (%)[b]	entry		yield (%)[b]
1	R_2 = Bn **3a**	94	11	 **3h**	91
2		70[c]			
3	R_2 = PMB **3b**	94			
4	R_2 = PNB **3c**	86			
5	R_2 = Hex **3d**	95[d]			
6	R_2 = TMS	-			
7	R_2 = PMP	-			
8	 **3e**	85	12	 **3i**	85
9	 **3f**	82	13	 **3j**	62
10	 **3g**	75	14	 **3k**	92

[a] Reaction conditions: iodoalkyne (0.1 mmol), azide (0.1 mmol), CuI (5 mol %) and TBTA (5 mol %) were stirred in THF at room temperature for 24 h or until full consumption of starting material was indicated by TLC. $Pd(OAc)_2$ (10 mol %), PPh_3 (20 mol %), Bu_4NBr (0.1 mmol), and K_2CO_3 (0.1 mmol) were added as a solid. [b] Isolated yields. [c] Reaction performed using 1 mol % $Pd(OAc)_2$ and 2 mol % PPh_3. [d] An additional 5 mol % of CuI and TBTA were added to the reaction after 24 h. PMB: *p*-methoxy benzyl. PNB: *p*-nitrobenzyl. PMP: *p*-methoxyphenyl.

Table 2. Effect of the Heteroaromatic and Aromatic Nucleophile on Reactivity[a]



1 3

entry		yield[b]	entry		yield[b]
1	 **3l**	62	3	 **3n**	80[c]
2	 **3m**	92[c,d]	4[e]	 **3o**	97[c]

[a] See Table 1 for representative procedure. [b] Isolated yields. [c] Additional 5 mol % of CuI and TBTA were added to the reaction after 24 h. [d] Single regioisomer is observed. [e] Control experiment shows no formation of **3o** in the absence of $Pd(OAc)_2$.

(11) (a) Hulcoop, D. G.; Lautens, M. *Org. Lett.* **2007**, *9*, 1761–1764. (b) Chai, D. I.; Lautens, M. *J. Org. Chem.* **2009**, *74*, 3054–3061. (c) Liu, Z.; Larock, R. C. *J. Org. Chem.* **2007**, *72*, 223–232. (d) Xie, C.; Zhang, Y.; Huang, Z.; Xu, P. *J. Org. Chem.* **2007**, *72*, 5431–5434.

(12) Sonogashira cross coupling: (a) Fürstner, A.; Mamane, C. *J. Org. Chem.* **2002**, *67*, 6264–6267.

(13) Suzuki cross coupling: Barder, T. E.; Walker, S. D.; Martinelli, J. R.; Buchwald, S. L. *J. Am. Chem. Soc.* **2005**, *127*, 4685–4696.

(14) Ullmann-type reactions: (a) Zhu, R.; Xing, L.; Wang, X.; Cheng, C.; Su, D.; Hu, Y. *Adv. Synth. Catal.* **2008**, *350*, 1253–1257. (b) Zhang, H.; Cai, Q.; Ma, D. *J. Org. Chem.* **2005**, *70*, 5164–5173.

(15) Corey-Fuchs alkyne synthesis: (a) Corey, E. J.; Fuchs, P. L. *Tetrahedron Lett.* **1972**, *13*, 3769–3772. (b) Ramirez, F.; Desai, N. B.; McKelvie, N. *J. Am. Chem. Soc.* **1962**, *84*, 1745–1747.

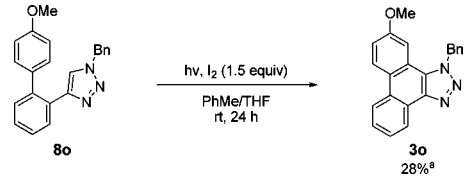
(16) We thank a reviewer for suggesting this alternative strategy to access these compounds.

(17) See supplementary information for further detail. For selected syntheses of polyaromatic compounds using an electrocyclization/oxidation sequence see: (a) Mallory, F. B.; Mallory, C. W. *Org. React.* **1984**, *30*, 1, and references therein. (b) Kovacic, P.; Jons, M. B. *Chem. Rev.* **1987**, *87*, 357–379. (c) Wadumethrige, S. H.; Rathore, R. *Org. Lett.* **2008**, *10*, 5139–5142. (d) Zhai, L.; Shukla, R.; Rathore, R. *Org. Lett.* **2009**, *11*, 3474–3477. (e) Talele, H. R.; Gohil, M. J.; Bedekar, A. V. *Bull. Chem. Soc. Jpn.* **2009**, *82*, 1182–1186.

that nonheterocyclic nucleophiles participate in this reaction (Entry 4). We observed a sluggish cycloaddition with certain substrates; however, addition of an extra 5 mol % of CuI and TBTA afforded full conversion, and the overall sequence still proceeded in excellent yields (Table 2, entries 2−4).

An alternative strategy involving a 6-π electrocyclization/oxidation of nonhalogenated triazoles may be feasible to access some of these products.[16] To compare our route with this strategy, we subjected the nonhalogenated triazole **8o** to several representative reaction conditions (Scheme 4).[17]

Scheme 4. Experiments on 6π-Electrocyclization/Oxidation Pathway



8o **3o** 28%[a]

[a] NMR yield based on 1,3,5-trimethoxybenzene as an internal standard. Other unsuccessful conditions examined: (a) DDQ (1 equiv) CH_2Cl_2: $MeSO_4H$,[17c] (b) $FeCl_3$ (3 equiv), $MeNO_2$, CH_2Cl_2.[17d]

Although most thermal/oxidative conditions did not show any starting material consumption, some product could be obtained upon irradiation of **8o** in the presence of iodine.[17e] While this approach is feasible, our work on the direct arylation of iodotriazoles provides a high-yielding method toward these targets and is an uncommon example of direct arylation of heterocyclic electrophiles.

In summary, we disclosed a concise synthesis of structurally unique polycyclic frameworks through a one-pot cycloaddition/Pd-catalyzed direct annulation strategy. This reaction is one of the first applications of 4-iodo-1,2,3-triazoles in a direct arylation. The scope of this synthetic route is general and the products are obtained in good yields. The overall modularity of this sequence is noteworthy.

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Supporting Information Available: Experimental procedures and spectroscopic characterization data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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