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Iridium-Catalyzed Cycloaddition of Azides and 1-Bromoalkynes at Room Temperature

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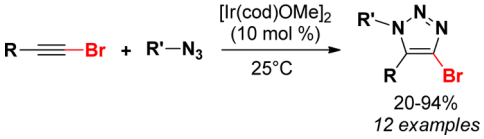
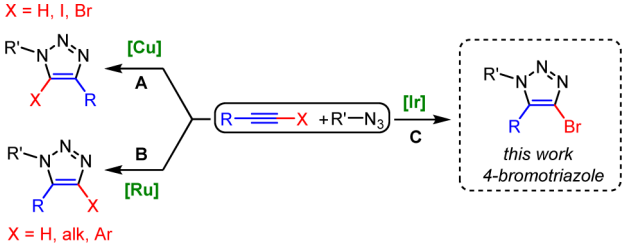
ABSTRACT



Iridium dimer complexes were found to catalyze the [3 + 2] cycloaddition reaction of azides with bromoalkynes, yielding 1,5-disubstituted 4-bromo-1,2,3-triazoles in reasonable to excellent yields under mild conditions. The reaction offers a direct route to new 1,4,5-trisubstituted triazoles.

In addition to their high value as synthetic intermediates,[1] 1,2,3-triazoles have found widespread applications in agricultural and medicinal chemistry.[2] Since the discovery of Cu(I)-catalyzed azide−alkyne cycloaddition (CuAAC), a tremendous number of 1,4-disubstituted triazoles have been synthesized for various applications. Extensions of this powerful reaction have then been successfully developed to give straightforward access to halogeno-substituted triazoles that would serve as suitable precursors to trisubstituted triazoles (Scheme 1A). Thus, the Cu(I)-catalyzed cycloaddition of azides with iodoalkynes, leading to flexible 5-iodotriazoles, was first disclosed by Fokin et al.[3] and then by Zhu et al.[4] To circumvent the lack of stability of iodoalkynes, both teams developed an alkyne iodination−cycloaddition one-pot sequence. The presence of an iodo substituent was then successfully exploited using Suzuki-type coupling to synthesize fully substituted triazoles.

Scheme 1. Metal-Catalyzed Routes to Trisubstituted Triazoles



In comparison with iodoalkynes, bromoalkynes are advantageous due to their higher stability and their easier preparation and handling. However, their reactivity toward the Cu-catalyzed [3 + 2] cycloaddition reaction with azides appeared to be much lower than that observed with iodoalkynes. As a matter of fact, only one report describes the formation of 5-bromotriazoles in a regioselective manner using a catalytic mixture of Cu(I) and Cu(II).[5] On the

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(4) Brotherton, W. S.; Clarck, R. J.; Zhu, L. *J. Org. Chem.* **2012**, *77*, 6443.

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10.1021/ol402008u

other hand, ruthenium complexes have been employed to catalyze the cycloaddition of azides and internal alkynes, leading to 1,4,5-trisubstituted triazoles (Scheme 1B).[6] This reaction delivers fully substituted triazole heterocycles in good yields, but it is marred by the need for alkynes to contain "push-pull" triple bonds or strong H-donors to direct their regioselectivity.[7] It is important to note that Ru-catalyzed cycloaddition of bromoalkynes has not yet been described. A complementary process allowing the regioselective formation of 1,5-disubstituted bromotriazoles is therefore highly desirable.

Using a high-throughput screening approach for reaction discovery, we recently showed that $[Ir(cod)Cl]_2$ is able to promote a 1,3-dipolar cycloaddition of azides with bromoalkynes, leading to 1,5-disubstituted 4-bromotriazoles in low yields. On the basis of this preliminary result, we describe here our attempts to optimize this unprecedented Ir-catalyzed transformation and to study its scope (Scheme 1C).

Using benzyl azide **1a** and bromoalkyne **2a** as model substrates, we first investigated the influence of a series of iridium complexes on the reaction (Table 1).

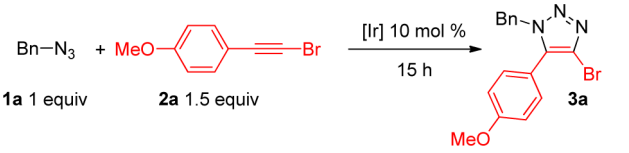
The use of a dimeric iridium complex is crucial, as only a small amount of cycloadduct was formed with a monomeric species (Table 1, entries 2 and 3). No reaction took place in the absence of Ir catalyst even at high temperature (Table 1, entry 1). Among the dimeric iridium species, $[Ir(cod)OMe]_2$ was found to be the most powerful, leading to the regioselective formation of the 4-bromo-1,5-triazole **3a** in 61% isolated yield in CH_2Cl_2 at room temperature (Table 1, entry 6). Addition of phosphines or N-based ligands was detrimental to the reaction efficiency. Changing the solvent or temperature resulted in lower yields and degradation of bromoalkyne **2a**. No trace of 5-bromo-1,4-triazole regioisomer was detected under all tested conditions described in Table 1.

The reaction was found to be quite selective for bromoalkyne substrates (Table 2). Chloroalkynes were indeed almost unreactive toward the iridium complex, and iodoalkynes underwent degradation under the reaction conditions (Table 2, entries 1 and 3).

Polarized disubstituted alkynes such as aryl propiolates were also unreactive in the reaction (Table 2, entry 5). Interestingly, terminal alkynes reacted with opposite regioselectivity under the reaction conditions, affording pure 1,4-disubstituted triazoles in low yields (Table 2, entry 4).

We next probed the scope of azides and bromoalkynes using $[Ir(cod)OMe]_2$ under the optimized conditions (Scheme 2). Successful attempts proceeded at ambient temperature and delivered regioselectively the desired 4-bromo-1,5-triazoles after overnight reaction in reasonable to excellent yields. With regard to the dipole partner, reactions of alkyl azides were most efficient, whereas the

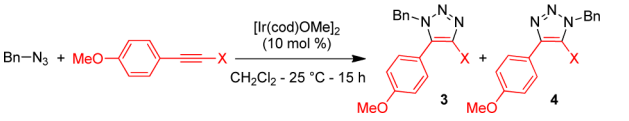
Table 1. Optimization of the Reaction[a]



entry	catalyst	conditions	yield of **3a** (%)[b]
1	none	110 °C, toluene	0
2	$[Ir(cod)(PPh_2Me)_2]PF_6$	25 °C, CH_2Cl_2	3
3	Ir(cod)(acac)	25 °C, CH_2Cl_2	6
4	$[Ir(cod)Cl]_2$	25 °C, CH_2Cl_2	10
5	$[Ir(cod)OPh]_2$	25 °C, CH_2Cl_2	17
6	**$[Ir(cod)OMe]_2$**	**25 °C, CH_2Cl_2**	**61**
7	$[Ir(cod)OMe]_2$	25 °C, toluene	19
8	$[Ir(cod)OMe]_2$	25 °C, dioxane	16
9	$[Ir(cod)OMe]_2$	25 °C, MeCN	24
10	$[Ir(cod)OMe]_2$	25 °C, MeOH	trace
11	$[Ir(cod)OMe]_2$	40 °C, CH_2Cl_2	18
12	$[Ir(cod)OMe]_2$	25 °C, DCE	37
13	$[Ir(cod)OMe]_2$	25 °C, $CHCl_3$	33

[a] Conditions: inert atmosphere and substrates at 0.2 M. [b] Isolated yields.

Table 2. Alkyne Scope of the Ir-Catalyzed Cycloaddition with Azides[a]



entry	X	yield of **3** (%)[b]	**3/4**
1	Cl	10	100/0
2	**Br**	**71**	**100/0**
3	I	0	
4	H	10	0/100
5	CO_2Me	0	

[a] Conditions: inert atmosphere and substrates at 0.2 M; 1.5 equiv of alkyne was used. [b] NMR yield.

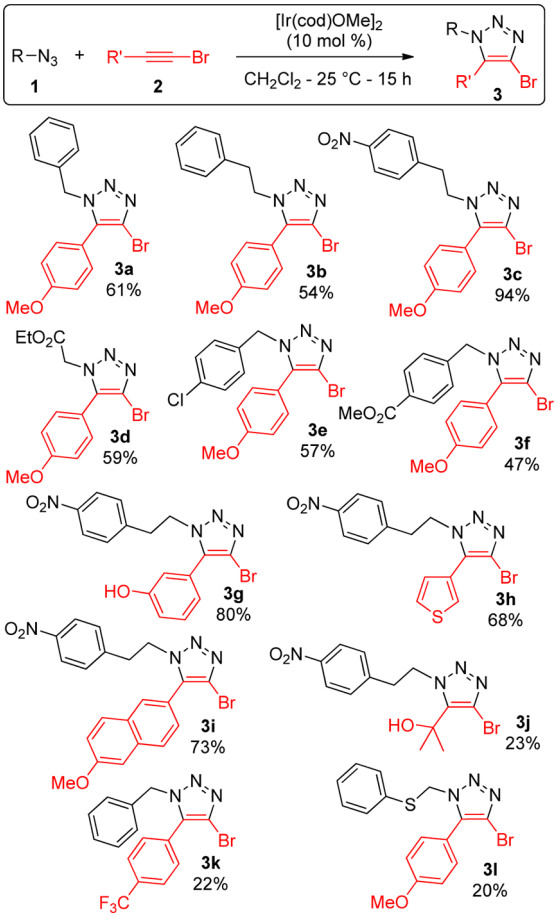
use of aromatic azides led to only traces of the corresponding cycloadducts (data not shown). The electronic features of the alkyne component appeared to have a considerable effect on the reaction. As evidenced by compounds **3c** (94% yield), **3g** (80% yield), and **3k** (22% yield), electron-rich arylalkynes demonstrated the best dipolarophile abilities, although electron-poor bromoalkynes gave the corresponding 4-bromotriazoles in poor yields. The reaction was compatible with sulfur-containing substrates (**3h**,**l**) but was found sensitive to steric hindrance, as no reaction was observed with 1-azidoadamantane and product **3j** was obtained in only 23% yield from 2-methyl-3-butyn-2-ol.

Remarkably, the reaction appeared tolerant to unprotected phenol (**3g**, 80% yield), although 12% of the 5-bromo isomer was recovered in this particular case.

(6) (a) Zhang, L.; Chen, X.; Xue, P.; Sun, H. H. Y.; Williams, I. D.; Sharpless, K. B.; Fokin, V. V.; Jia, G. *J. Am. Chem. Soc.* **2005**, *127*, 15998. (b) Majireck, M. M.; Weinreb, S. M. *J. Org. Chem.* **2006**, *71*, 8680. (c) Rasmussen, L. K.; Boren, B. C.; Fokin, V. V. *Org. Lett.* **2007**, *9*, 5337.

(7) Boren, B. C.; Narayan, S.; Rasmussen, L. K.; Zhang, L.; Zhao, H.; Lin, Z.; Jia, G.; Fokin, V. V. *J. Am. Chem. Soc.* **2008**, *130*, 8923.

Scheme 2. Regioselective Formation of 1,5-Disubstituted 4-Bromotriazoles **3** through the Ir-Catalyzed Cycloaddition Reaction



No trace of 5-bromo regioisomer was observed by crude NMR analysis of other reactions. The structures of compounds **3** were assigned by comparison to published analytical data and further proven by the X-ray crystallography of the representative product **3c** (Figure 1).

We then tried to apply this new Ir-catalyzed reaction to the preparation of 1,4,5-trisubstituted triazoles **5** by forming the 4-bromotriazole and immediately employing Pd-catalyzed Suzuki type reactions with appropriate arylboronic acids (Scheme 3). The 4-bromotriazole products were partially purified by filtration through silica gel to remove iridium salts prior to the Pd-coupling step.

This simple two-step procedure allowed the formation of fully substituted triazoles in moderate to good global yields (Scheme 3).

Although the mechanistic underpinnings for this Ir-catalyzed reaction would need a specific study, we propose a tentative hypothesis. The low reactivity and the reverse regioselectivity observed with terminal alkynes (Table 2) suggest that the reactions do not proceed through transitional debromination of bromoalkynes. The reaction may thus be initiated by electrophilic activation of the alkyne by the Ir^{I} complex, leading to the formation of the π-alkynyl

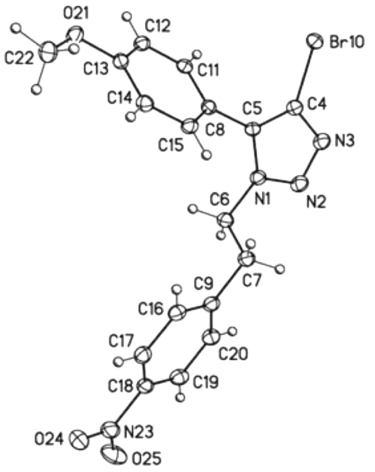
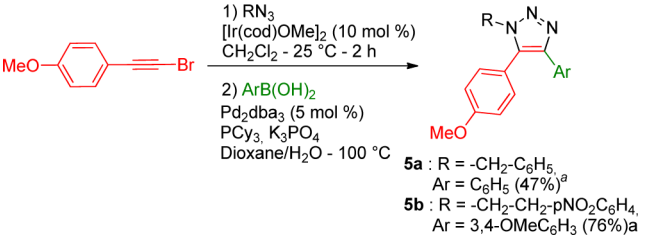


Figure 1. X-ray structure of **3c**.

Scheme 3. Two-Step Synthesis of Trisubstituted Triazoles by Ir-Catalyzed [3 + 2] Cycloaddition Followed by Pd-Catalyzed Suzuki Coupling Reactions[a]



[a] Overall isolated yields.

complex **A** (Scheme 4).[8] Unlike the mechanism described for CuAAC,[9] where the azide terminal nitrogen atom becomes an electrophilic center after coordination with copper, subsequent complexation of the azide partner by Ir may lead to anti-nucleophilic attack of the N-3′ atom of the azide moiety to the C-1 atom of the π-coordinated triple bond, resulting in the formation of the stabilized Ir carbenoid **B**. Such azide behavior was recently proposed as a key step in a samarium-catalyzed cycloaddition of alkynes with azides leading to 1,5-disubstituted 1,2,3-triazoles.[10] Given the regioselective outcome of this Ir-catalyzed [3 + 2] cycloaddition, the other alternative would consist of the attack of the N-1′ atom of the azide at the C-2 atom of the triple bond. This combination would lead to the nonstabilized iridium carbenoid **B′** and therefore is thought to be less probable. Intermediate **B** can then undergo a "Cope-like"

(8) For similar examples, see: (a) Genin, E.; Antoniotti, S.; Michelet, V.; Genet, J.-P. *Angew. Chem. Int. Ed.* **2005**, *44*, 4949. (b) Beller, M.; Seayad, J.; Tillack, A.; Jiao, H. *Angew. Chem. Int. Ed.* **2004**, *43*, 3368.

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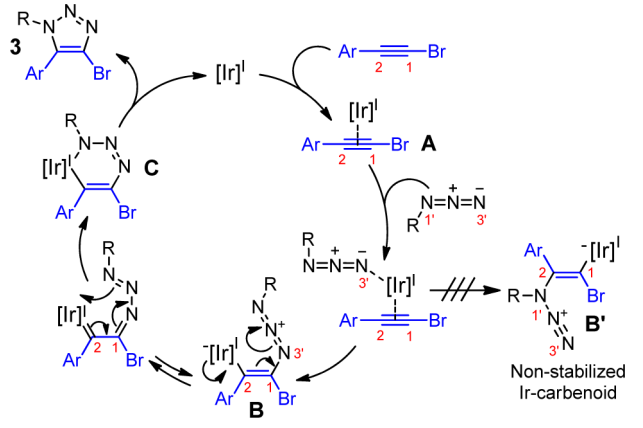
Scheme 4. Postulated Mechanism



cyclization to yield metallacycle **C**,[11] which would finally deliver 4-bromo-1,5-triazole **3** upon iridium C–N reductive elimination.

(11) Crabtree et al. previously proposed a "Cope-like" cyclization of an Ir carbenoid species in the context of iridium hydride catalyzed intramolecular oxygen transfer from nitro groups to alkyne triple bonds: Li, X.; Incarvito, C. D.; Vogel, T.; Crabtree, R. H. *Organometallics* **2005**, *24*, 3066.

In conclusion, we have developed an unprecedented Ir-catalyzed [3 + 2] cycloaddition of bromoalkynes with azides, offering a direct and regioselective route to 4-bromo-1,5-triazoles. Post-functionalization of 4-bromotriazoles smoothly afforded fully substituted heterocycles. Despite some limitations in terms of alkyne substrate scope, this new reaction represents a valuable complement to CuAAC and RuAAC reactions, offering complete control over the placement of substituents around the triazole heterocycle core.

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Supporting Information Available. Text and figures giving experimental procedures for synthesis and full characterization data for compounds; ^{1}H NMR and ^{13}C NMR spectra of products **3**, and the crystal structure of product **3c**. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.