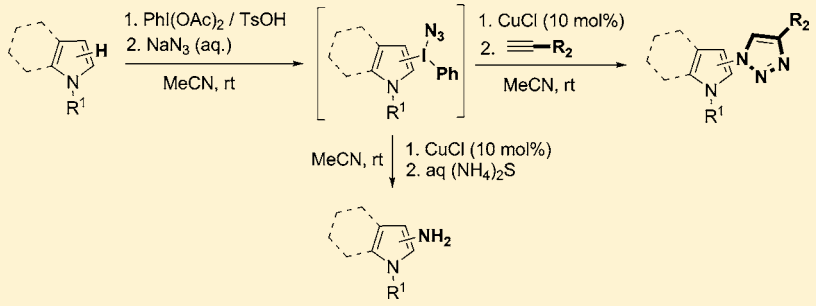
JACS
JOURNAL OF THE AMERICAN CHEMICAL SOCIETY
Article
pubs.acs.org/JACS

Indirect C–H Azidation of Heterocycles via Copper-Catalyzed Regioselective Fragmentation of Unsymmetrical λ^3-Iodanes

Dmitrijs Lubriks, Igors Sokolovs, and Edgars Suna*

Latvian Institute of Organic Synthesis, Aizkraukles 21, LV-1006 Riga, Latvia

Supporting Information



ABSTRACT: A C–H bond of electron-rich heterocycles is transformed into a C–N bond in a reaction sequence comprising the formation of heteroaryl(phenyl)iodonium azides and their in situ regioselective fragmentation to heteroaryl azides. A Cu(I) catalyst ensures complete regiocontrol in the fragmentation step and catalyzes the subsequent 1,3-dipolar cycloaddition of the formed azido heterocycles with acetylenes. The heteroaryl azides can also be conveniently reduced to heteroarylamines by aqueous ammonium sulfide. The overall C–H to C–N transformation is a mild and operationally simple one-pot sequential multistep process.

INTRODUCTION

Symmetrical diaryliodonium salts have found numerous applications as electrophilic arylating reagents in both transition-metal-catalyzed and metal-free reactions with carbon and heteroatom nucleophiles.[1] Unsymmetrical diaryliodonium salts, however, are less frequently employed, because the presence of two different aromatic moieties in λ^3-iodanes can potentially lead to the formation of product mixtures in the reactions with nucleophiles. Nevertheless, regiocontrol can be achieved by differentiation of electronic and steric properties of aromatic moieties. Thus, a nucleophile would preferentially react with the more electron-deficient and/or sterically hindered *ortho*-substituted aromatic ring of unsymmetrical diaryliodonium salts (Figure 1).[2] In the meantime, regioselective reaction of nucleophiles with electron-rich aromatic or heteroaromatic moieties of unsymmetrical diaryl-λ^3-iodanes is a challenging task. We envisioned, however, that the desired regioselectivity of nucleophile attack can be ensured by a transition-metal catalyst, because in the catalytic cross-coupling reactions electron-rich[3] and/or less sterically hindered[4] aryl moieties are selectively transferred from unsymmetrical iodonium salts to the transition metal (Figure 1).

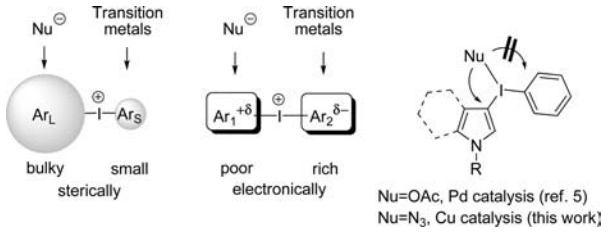


Figure 1. Regioselectivity in the reactions of nonsymmetrical iodonium salts.

We have recently demonstrated that the regioselectivity of acetoxylation of heteroaryl(phenyl)iodonium acetates can be directed to the more electron-rich heteroaryl moiety by a Pd(II) catalyst.[5] We reasoned that use of other counterions instead of acetate would provide straightforward access to differently substituted heterocycles by the transition-metal-catalyzed regioselective fragmentation of unsymmetrical heteroaryliodonium species. Herein we report a one-pot sequential procedure for C–H to C–N transformation in electron-rich heterocycles (pyrroles, pyrrolopyridines, thienopyrroles, pyrrolopyrimidines, and uracil) comprising in situ preparation of heteroaryl(phenyl)iodonium azides and their Cu-catalyzed conversion to heteroaryl azides. The formed azides are not sufficiently stable to be isolated; however, they can be in situ reduced to heteroaromatic amines. The developed one-pot four-step C–H to C–N transformation sequence is a mild and convenient alternative to the transition-metal-catalyzed direct C–H amination of arenes[6] and heteroarenes,[7,8] which usually requires elevated temperatures to proceed. The in situ formed heteroaryl azides can also undergo Cu-catalyzed azide–alkyne cycloaddition to furnish 1,2,3-triazoles,[9] thus allowing for the

Received: June 8, 2012
Published: August 22, 2012

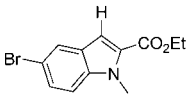
dx.doi.org/10.1021/ja305574k | J. Am. Chem. Soc. 2012, 134, 15436–15442

direct ligation of heterocycles to biomolecular frameworks via a triazole linker, an approach that is widely used in bioconjugate chemistry[10] for labeling and modification of oligonucleotides[11] and peptidomimetics.[12] The developed C−H azidation/1,3-dipolar cycloaddition sequence is suitable also for use in discovery of lead compounds by target-directed synthesis[13] as well as in the design of novel peptidomimetics.[14] Furthermore, 1,2,3-triazoles can be employed for synthesis of other heterocyclic systems.[15]

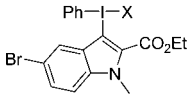
RESULTS AND DISCUSSION

At the outset of the investigation, we examined the regioselectivity of fragmentation of indolyl(phenyl)iodonium azide **3a**. The iodonium salt **3a** was synthesized by the reaction of indole **1a** with a mixture of $PhI(OAc)_2$ and TsOH,[16] followed by exchange of tosylate anion for azide in the intermediate **2a**. The formed iodonium azide **3a** was unstable, and in the crystalline form it slowly decomposed to iodoindole **5a** even at −18 °C. Nevertheless, the indolyl azide **3a** as well as its pyrrole analogue **3h** could be characterized, and their structures were confirmed by X-ray crystallographic analysis (Table 1).[17] In the crystal lattice azides **3a,h** exist in a

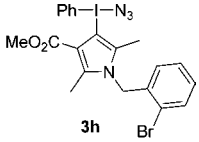
Table 1. Selected Crystallographic Parameters for Iodonium Azides 3a,h



1a



2a: X=OTs
3a: X=N_3



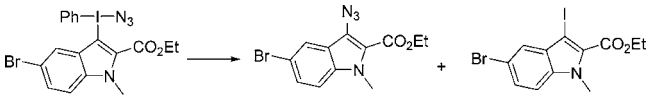
3h

λ^3-iodane	N_3−I−C(Het) angle (deg)	I−N_3 distance (Å)	I−C(Ph) distance (Å)	I−C(Het) distance (Å)
3a	174.1	2.813	2.112	2.083
3h	177.3	2.837	2.129	2.064

characteristic slightly distorted T-shaped geometry with the heterocycle in the equatorial position and Ph moiety and azide anion in axial positions (for selected crystallographic parameters see Table 1). Notably, I−N bonds in the azides **3a,h** are considerably longer than hypervalent I−N bonds in structurally related azidobenziodoxole[18] (2.182 Å) and polymeric iodine azide (2.26−2.30 Å).[19] Furthermore, the distance between the hypervalent iodine in **3h** and the azide anion (2.837 Å, Table 1) is much longer than that between the iodine of the phenyl(pyrrolyl)iodonium moiety of **3h** and the acetate anion (2.592 Å).[5] Apparently, the long hypervalent I−N bond possesses partial ionic character,[20] which accounts for the low stability of iodonium azides **3a,h**.

In MeCN and CH_2Cl_2 solutions at room temperature the iodonium azide **3a** spontaneously decomposed to 3-iodoindole **5a** and phenyl azide (see Table 2, entries 1 and 2). Importantly, the desired indolyl azide **4a** was not formed in MeCN and CH_2Cl_2. The regioselectivity of the noncatalyzed fragmentation of iodonium salt **3a** apparently is controlled by electronic factors, as evidenced by the delivery of the azide nucleophile to the relatively more electron-deficient phenyl ring rather than to the electron-rich indole moiety of **3a**.[21] Notably, λ^3-iodane **3a** was stable in DMSO (entry 3) at room temperature. The addition of $Pd(OAc)_2$ (5 mol %) did not alter the course of the reaction (entries 4 and 5), whereas Cu salts completely reversed the fragmentation regioselectivity, and the iodonium

Table 2. Fragmentation of Indolyliodonium Azide 3a



3a **4a** **5a**

entry	catalyst (concn, mol %)	solvent	time	conversion[a,b] %	**4a**:**5a** ratio[b]
1	none	MeCN	60 h	35[c]	1:99
2	none	CH_2Cl_2	3 h	70	1:99
3	none	DMSO	3 h	<5	
4	$Pd(OAc)_2$ (5)	MeCN	24 h	32	1:5
5	$Pd(OAc)_2$ (5)	CH_2Cl_2	3 h	35	1:99
6	$Cu(OTf)_2$ (10)	CH_2Cl_2	3 h	60	9:1
7	CuOTf·PhH (10)	CH_2Cl_2	30 min	100	9:1
8	CuOTf·PhH (10)	MeCN	30 min	87	9:1
9	CuOTf·PhH (10)	toluene	30 min	85	4:1
10	CuOTf·PhH (10)	THF	30 min	60	5:1
11	CuOTf·PhH (10)	DMSO	30 min	45	9:1
12	CuCl (10)	CH_2Cl_2	5 min	100	9:1
13	CuCl (10)	MeCN	5 min	100	12:1
14	CuCl (10)	DMSO	30 min	78	12:1
15	CuCl (10)	MeCN−DMSO (1:1)	15 min	85	10:1
16	TfOH (200)	CH_2Cl_2	3 h	23	1:99
17	$Zn(OTf)_2$ (10)	CH_2Cl_2	3 h	27	1:99
18	$Sc(OTf)_3$ (10)	CH_2Cl_2	3 h	20	1:99
19	$(Ph_3P)AuCl$ (10)	CH_2Cl_2	3 h	45	1:99

[a]Reactions at room temperature. [b]Determined by LC−MS assay. [c]Conversion of 100% (**4a**:**5a** = 1:99) after 30 min at 80 °C.

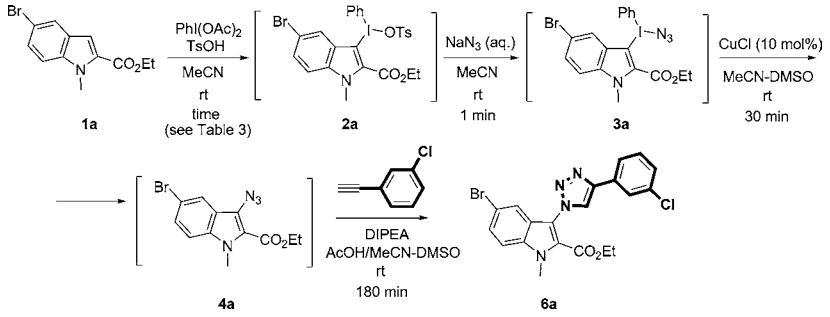
azide **3a** was smoothly converted to the desired indolyl azide **4a** (entries 6−15).

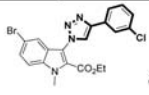
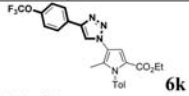
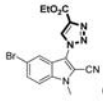
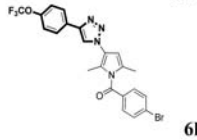
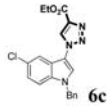
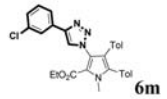
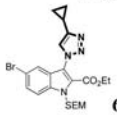
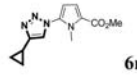
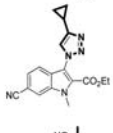
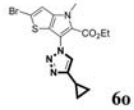
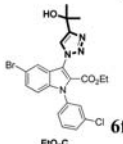
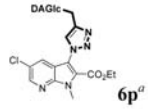
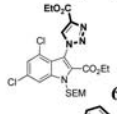
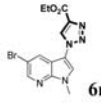
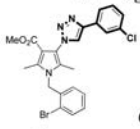
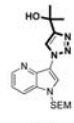
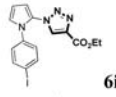
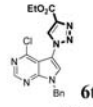
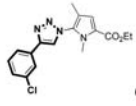
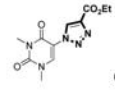
Copper catalysts considerably decreased the reaction time, with CuCl and CuOTf in CH_2Cl_2 being the most efficient (entries 7 and 12). Interestingly, both Cu(I) and Cu(II) salts can be used; however, the Cu(I) species ensured faster reaction (entry 7 vs entry 6). Other solvents either retarded the reaction (entries 10, 11, and 14) or deteriorated the regioselectivity (entries 9 and 10). It should be noted that the conversion of **3a** was faster in CH_2Cl_2 compared to MeCN (entry 2 vs entry 1 and entry 7 vs entry 8). Lewis acids such as $(Ph_3P)AuCl$, $Zn(OTf)_2$, and $Sc(OTf)_3$ as well as TfOH were completely inefficient as catalysts (entries 16−19). Consequently, CuCl (10 mol %) was chosen for all subsequent experiments.

The observed high regioselectivity of the Cu(I)-catalyzed fragmentation of iodonium salt **3a** to azide **4a** (**4a**:**5a** = 9:1) in CH_2Cl_2 is slightly lower than the regioselectivity of the alternative noncatalyzed formation of **5a** from **3a** (**4a**:**5a** = 1:99). The determined initial rates of the noncatalyzed fragmentation of **3a** to iodide **5a** in CH_2Cl_2 (rate coefficient $k = 9 \times 10^{-5}$ s^{-1}, CH_2Cl_2-d_2, 23 °C, and reaction half-life $t_{1/2}$ = 128 min) evidence that spontaneous fragmentation of iodonium azide **3a** delivers ca. 10% **5a** within the first 10 min. By this time, the CuOTf-catalyzed conversion of **3a** to azide **4a** in CH_2Cl_2 is almost 90%.[22] Consequently, the regioselectivity of the Cu-catalyzed conversion of **3a** to **4a** is

dx.doi.org/10.1021/ja305574k | J. Am. Chem. Soc. 2012, 134, 15436−15442

Table 3. Sequential One-Pot Synthesis of Heteroaryl Azides 4a–u and Triazoles 6a–u



entry	product	time	yield (%)[c]	entry	product	time	yield (%)[c]
1	 **6a**	30 min	90	11	 **6k**	10 min	65
2	 **6b**	18 h	71	12	 **6l**	30 min	65
3	 **6c**	5 min	65	13	 **6m**	30 min	73
4	 **6d**	3 h	71	14	 **6n**	5 min	59
5	 **6e**	3 h	75	15	 **6o**	30 min	75
6	 **6f**	3 h	73	16	 **6p**[a]	30 min	62
7	 **6g**	18 h	72	17	 **6r**	5 min	70
8	 **6h**	10 min	64	18	 **6s**	72 h[b]	42
9	 **6i**	5 min	53	19	 **6t**	10 min	47
10	 **6j**	5 min	55	20	 **6u**	18 h	65

[a]DAGlc (diacetone-D-glucose). [b]A 2.2 equiv amount of TsOH–H_2O. [c]Yields were calculated on the basis of the starting heterocycle **1a–u**.

compromised by the competing noncatalyzed fragmentation to **5a**, and this observation renders CH_2Cl_2 inferior as a solvent compared to alternatives such as MeCN and DMSO (entry 2 vs entries 1 and 3, Table 2). The noncatalyzed fragmentation of **3a** in MeCN is considerably less pronounced, and azide **3a** is virtually stable in DMSO. Therefore, MeCN and DMSO are solvents of choice for CuCl-catalyzed fragmentation of iodonium azides (entries 13–15, Table 2).

The formed indolyl azide **4a** decomposed during attempted purification; however, it can be employed in further transformations without isolation. Thus, addition of substituted acetylene directly to azide **4a** and CuCl in the presence of DIPEA and AcOH[23] resulted in the clean formation of 1,4-disubstituted 1,2,3-triazole **6a** as a sole regioisomer.[24] Hence, CuCl catalyzed both the in situ formation of indolyl azide **4a** and its subsequent 1,3-dipolar cycloaddition with (3-chlorophenyl)acetylene (Table 3).[9]

dx.doi.org/10.1021/ja305574k | J. Am. Chem. Soc. 2012, 134, 15436–15442

A series of heterocycles was subsequently subjected to an azidation−cycloaddition sequence to show the scope of the developed methodology. All heterocycles that can form iodonium salts in the reaction with a mixture of $PhI(OAc)_2$ and TsOH are suitable substrates,[25] including indoles[26] **1a−g**, pyrroles[27] **1h−n**, thieno[3,2-*b*]pyrrole **1o**, pyrrolo[2,3-*b*]-pyridines **1p**,**r**, pyrrolo[3,2-*b*]pyridine **1s**, pyrrolo[2,3-*d*]-pyrimidine **1t**, and uracil[28] **1u** (Table 3). In general, the regioselectivity of heteroaryliodonium salt formation is consistent with that of S_EAr reactions. Thus, λ^3-iodanes are formed at the β-position of indoles **1a−g** and fused pyrroles **1o−t** at the α-position of pyrroles **1i**,**j**,**n** and at the fifth position of uracil **1u** (Table 3). In 2,5-disubstituted pyrroles **1h**,**k−m**, however, iodonium salts were formed at the β-position. Importantly, the reaction conditions are compatible with the presence of iodine, bromine, and chlorine, thus rendering feasible their further functionalization. *N*-Alkyl, *N*-aryl, *N*-benzoyl, and *N*-benzyl substituents as well as *N*-SEM protecting groups are tolerated (Table 3).

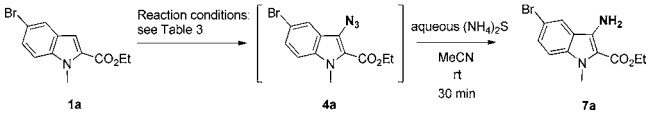
The formed heteroaryl azides **4a−u** could also be converted to the corresponding heteroaromatic amines **7a−u** by the in situ reduction with aqueous $(NH_4)_2S$ at room temperature within 30 min (see Table 4). Other reducing agents such as Ph_3P are equally efficient; however, the use of $(NH_4)_2S$ in the reduction generates less waste, requiring simple extractive workup to obtain crude products **7a−u**. In general, the one-pot three-step azidation−reduction sequence allows for amination of heteroaryl C−H bonds under mild conditions and in high overall yields.

Additional experiments have been carried out to determine the oxidation state of copper species responsible for the catalytic azidation of heterocycles. The considerably faster formation of **4a** in the presence of Cu(I) ions compared to Cu(II) counterparts (entry 7 vs entry 6, Table 2) suggests that Cu(I) salts are catalytically active species. This assumption was supported by the observed inhibition of **4a** formation by neocuproin (2 equiv with respect to CuOTf; see Figure 2). Neocuproin, a highly specific chelating agent for Cu(I) ions, forms a stable bright orange-colored complex of formula $Cu^{I}(neocuproin)_2$,[29] thus acting as an inhibitor of Cu(I)-catalyzed reactions.[30]

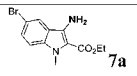
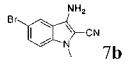
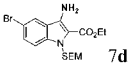
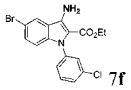
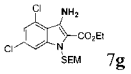
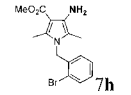
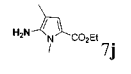
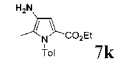
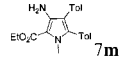
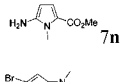
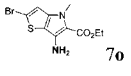
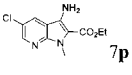
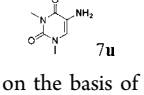
Kinetic studies demonstrated that the CuOTf-catalyzed conversion of **3a** to **4a** in DMSO-d_6 is first-order in CuOTf in the range of 0.25−5 mol % at 25 °C (Figure 3). This indicates that Cu(I) salts are involved in the rate-limiting step of the catalytic cycle. The decomposition of **3a** to **4a** was found to be zeroth-order with respect to the N_3 anion (Figure 4), suggesting that the formation of azide **4a** presumably is an intramolecular process. Finally, a radical inhibition test was also performed to verify the possibility of **3a** fragmentation via the radical chain pathway. Accordingly, the addition of radical scavengers such as 1,1-diphenylethylene[31] and 2,6-di-*tert*-butyl-4-methylphenol[6a] (both 200 mol % with respect to Cu(I)) did not affect the rate of CuOTf-catalyzed **3a** to **4a** conversion in CH_2Cl_2-d_2. Furthermore, we did not observe indole **1a**, which could form by a proton abstraction from solvent by indolyl radical during the decomposition of **3a**. All these data point against the involvement of free radical intermediates.[32]

A working mechanism for the Cu-catalyzed formation of heteroaryl azides is outlined in Scheme 1. Oxidative addition of iodonium azide **I** to Cu(I) salts would generate Cu(III) species **II**.[33] Complex **II** can directly collapse into azide **III** via the highly regioselective coupling of the heterocycle with the azide,

Table 4. Sequential Azidation−Reduction Sequence for One-Pot Synthesis of Heteroarylamines 7a−u



1a 4a 7a

entry	product	yield (%)[a]
1	 7a	84
2	 7b	80
3	 7d	82
4	 7f	84
5	 7g	79
6	 7h	65
7	 7j	60
8	 7k	62
9	 7m	72
10	 7n	53
11	 7o	66
12	 7p	75
13	 7u	50

[a]Yields were calculated on the basis of the starting heterocycle **1a−u**.

and the regioselectivity of azide attack presumably is ensured by the formation of a transient π-complex between the highly electrophilic Cu(III) species and electron-rich heterocycle.[34] Alternatively, complex **II** can undergo regioselective trans-formation to PhI and heteroarylcopper(III) species **IV**,[35] followed by reductive elimination of **III** and regeneration of Cu(I) species.

To verify the role of putative π-Cu(III) complex **II** in the control of the regioselectivity of azide formation, we envisioned the in situ preparation of a π-complex between a suitable π-acidic transition metal and electron-rich heterocycle moiety of unsymmetrical λ^3-iodane **3a**. Among various transition metals, Os(II) species are known to form well-defined and stable η^2-complexes with pyrroles.[36] We examined the fragmentation of iodonium azide **3a** in the presence of 10 mol % Os-

dx.doi.org/10.1021/ja305574k | J. Am. Chem. Soc. 2012, 134, 15436−15442

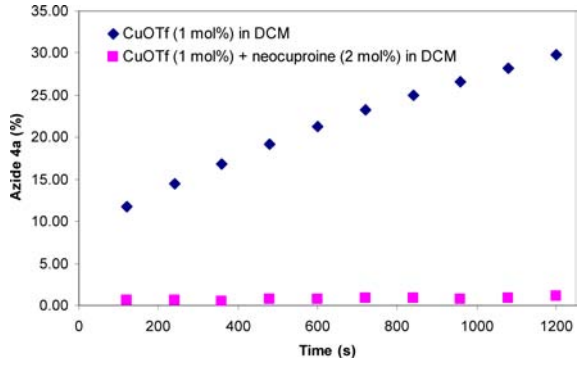


Figure 2. Inhibition of the CuOTf-catalyzed **3a** to **4a** conversion by neocuproin.

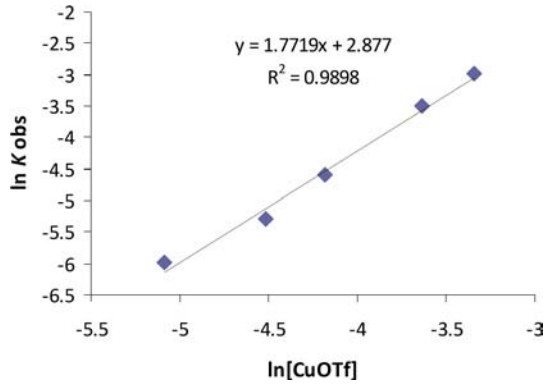


Figure 3. Initial rates vs concentration of CuOTf in DMSO-d_6.

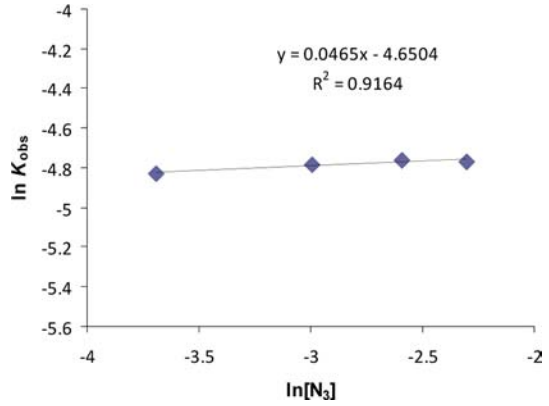


Figure 4. Initial rates vs concentration of azide ion in DMSO-d_6.

$[NH_3]_5(OTf)_3$ in CH_2Cl_2. Notably, indolyl azide **4a** was formed regioselectively (**4a**:**5a** = 7:3) within 30 min as a major product (30% conversion). This result is in sharp contrast to the opposite regioselectivity in the noncatalyzed decomposition of **3a** to **5a** in the presence of representative Lewis acids (entries 4, 5, and 17−19, Table 2). Possibly, π-complexation of a pyrrole ring to the Os(III) facilitates the substitution of the iodonium group by an azide nucleophile in transient complex **V** (Scheme 1); however, additional experiments are needed to support such a scenario.[37,38] The involvement of Cu(I) complex **V** (M = Cu(I)) to activate the heterocycle toward azide attack seems less likely because of insufficient electrophilicity of the Cu(I) species. Finally, Lewis acid activation of hypervalent iodonium species by Cu(I) or Cu(III) salts was shown to be kinetically insensitive to the concentration of copper species,[6a] an observation that contradicts our results.

CONCLUSIONS

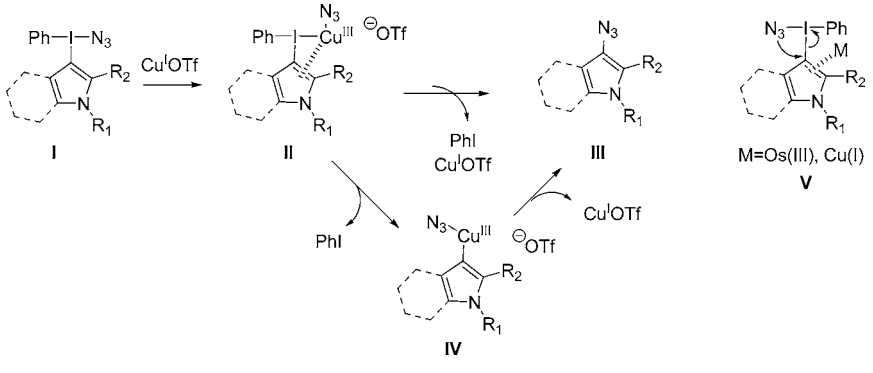
In summary, a rapid and versatile approach to heteroaryl azides via C−H to C−N bond transformation has been developed. The one-pot sequential procedure comprises formation of heteroaryl(phenyl)iodonium azides, followed by Cu(I)-catalyzed fragmentation to heteroaryl azides. The regioselectivity of the fragmentation is controlled by Cu(I) salts. The formed heteroaryl azides can be in situ reduced to heteroarylamines. Alternatively, the heteroaryl azides can undergo Cu-catalyzed click chemistry with a range of acetylenes to furnish 1,2,3-triazoles. The developed procedure is suitable for a variety of electron-rich heterocycles such as pyrroles, indoles, thienopyrroles, pyrrolopyridines, pyrrolopyrimidines, and uracil. Further studies to expand the scope of nucleophiles in the Cu-catalyzed regioselective fragmentation of heteroaryl(phenyl)iodonium salts are ongoing in our laboratory.

EXPERIMENTAL SECTION

Preparation of Iodonium Azides 3a and 3h. *Caution: Azides **3a,h** are thermally unstable and possess high thermal hazard potential.[39] Therefore, care must be taken during handling of azides **3a,h**, and a small scale is strongly encouraged.*

Ethyl 3-[(Azido)(phenyl)-λ^3-iodanyl]-1,5-dimethyl-1*H*-indole-2-carboxylate (3a). To a solution of $PhI(OAc)_2$ (509 mg, 1.58 mmol, 1.05 equiv) in CH_2Cl_2 (10 mL) was added $TsOH{\cdot}H_2O$ (342 mg, 1.80 mmol, 1.2 equiv), and the resulting suspension was stirred for 5 min at room temperature. Then a solution of indole **1a** (423 mg, 1.50 mmol, 1 equiv) in CH_2Cl_2 (5 mL) was added rapidly to the stirred suspension. The progress of the reaction was monitored by TLC, and within 30 min complete conversion of the starting **1a** was observed. The reaction was then poured into a solution of NaN_3 (146

Scheme 1. Working Mechanism for Azidation of Heterocycles



dx.doi.org/10.1021/ja305574k | J. Am. Chem. Soc. 2012, 134, 15436−15442

mg, 2.25 mmol, 1.5 equiv) in water (50 mL) and extracted with CH_2Cl_2 (3 × 30 mL). Organic layers were combined, dried over Na_2SO_4, filtered, and concentrated. The solid residue was washed with diethyl ether to afford **3a** as a white powder (727 mg, 92% yield): analytical TLC on silica gel, 20:80:5 MeOH/CH_2Cl_2/AcOH, R_f = 0.56. Pure material was obtained by crystallization from CH_2Cl_2/diethyl ether: mp 102−103 °C dec; IR (film, cm^{-1}) 1999 (N═N═N), 1716 (C═O); ^1H NMR (400 MHz, DMSO-d_6, ppm) δ 8.13−8.07 (3H, m), 7.73 (1H, d, J = 9.0 Hz), 7.60 (1H, dd, J = 9.0, 1.6 Hz), 7.55−7.50 (1H, m), 7.45−7.40 (2H, m), 4.51 (2H, q, J = 7.1 Hz), 4.07 (3H, s), 1.43 (3H, t, J = 7.1 Hz); ^{13}C NMR (100.6 MHz, DMSO-d_6, ppm) δ 159.1, 137.0, 133.9, 131.3, 131.2, 131.0, 129.1, 128.6, 123.5, 115.9, 114.6, 62.4, 33.5, 14.0; HRMS-ESI (m/z) calcd for $C_{18}H_{16}NO_2BrI$ $[M - N_3]^+$ 483.9409, found 483.9419.

Methyl 4-[(Azido)(phenyl)-λ^3-iodanyl]-1-(2-bromobenzyl)-2,5-dimethyl-1*H*-pyrrole-3-carboxylate (3h). The same procedure was used as for **3a**. Accordingly, 3-[1-(2-bromobenzyl)-4-(methoxycarbonyl)-2,5-dimethyl-1*H*-pyrrole (**1h**; 482 mg, 1.50 mmol) was converted to iodonium azide **3h**. Purification of the crude **3h** by washing with diethyl ether afforded product as a white powder (723 mg, 85% yield): analytical TLC on silica gel, 20:80:5 MeOH/CH_2Cl_2/AcOH, R_f = 0.54. Pure material was obtained by crystallization from CH_2Cl_2/diethyl ether: mp 96−97 °C dec; IR (film, cm^{-1}) 2002 (N═N═N), 1696 (C═O); ^1H NMR (400 MHz, DMSO-d_6, ppm) δ 7.95−7.91 (2H, m), 7.73−7.68 (1H, m), 7.61−7.55 (1H, m), 7.50−7.45 (2H, m), 7.29−7.24 (2H, m), 6.19−6.14 (1H, m), 5.30 (2H, s), 3.80 (3H, s), 2.43 (3H, s), 2.37 (3H, s); ^{13}C NMR (100.6 MHz, DMSO-d_6, ppm) δ 162.3, 138.2, 137.5, 134.9, 133.5, 133.0, 131.2, 131.0, 129.7, 128.4, 126.1, 121.1, 110.4, 109.6, 51.3, 48.5, 12.6, 11.8; HRMS-ESI (m/z) calcd for $C_{21}H_{20}NO_2BrI$ $[M - N_3]^+$ 523.9722, found 523.9734.

Experimental Procedures for Substituted 1,2,3-Triazoles 6a−u. To a solution of $PhI(OAc)_2$ (0.53 mmol, 1.05 equiv) in MeCN (1.5 mL) was added $TsOH·H_2O$ (0.60 mmol, 1.2 equiv), and the resulting suspension was stirred for 5 min at room temperature. Then a solution of heterocycle **1a−u** (0.50 mmol, 1 equiv) in MeCN (1 mL) was added to the stirred suspension, and the progress of the reaction was monitored by TLC (disappearance of the starting material spot; mobile phase petroleum ether:EtOAc = 3:1; the formed heteroaryliodonium salt does not migrate from the application point). Immediately upon full conversion of the starting **1a−u** (see Table 3 for the appropriate time), a solution of NaN_3 (0.75 mmol, 1.5 equiv) in water (500 μL) was added (*decomposition of the formed iodonium salt begins if the addition of NaN_3 is delayed*), followed by DMSO (2.5 mL) and solid CuCl (5 mg, 10 mol %; *CuCl must be added immediately after NaN_3 to avoid the noncatalyzed decomposition of iodonium azide*), whereupon the color of the reaction mixture changed to brown. After the reaction mixture was stirred for 30 min at room temperature, acetylene (0.75 mmol, 1.5 equiv), DIPEA (1.00 mmol, 2 equiv), and AcOH (1.00 mmol, 2 equiv) were added, and stirring was continued for 3 h at room temperature. The reaction mixture was poured into 50 mL of water and 25 mL of saturated $NaHCO_3$ and extracted with DCM (3 × 30 mL). The organic extracts were combined, dried over Na_2SO_4, filtered, and evaporated. The residue was purified by column chromatography on silica gel.

Experimental Procedures for Heteroarylamines 7a−u. To a solution of $PhI(OAc)_2$ (0.53 mmol, 1.05 equiv) in MeCN (4 mL) was added $TsOH·H_2O$ (0.60 mmol, 1.2 equiv), and the resulting suspension was stirred for 5 min at room temperature. Then a solution of heterocycle **1a−u** (0.50 mmol, 1 equiv) in MeCN (1 mL) was added to the stirred suspension, and the progress of the reaction was monitored by TLC (disappearance of the starting material spot; mobile phase petroleum ether:EtOAc = 3:1; the formed heteroaryliodonium salt does not migrate from the application point). Immediately upon full conversion of the starting **1a−u** (see Table 3 for the appropriate time), a solution of NaN_3 (0.75 mmol, 1.5 equiv) in water (500 μL) was added (*decomposition of the formed iodonium salt begins if the addition of NaN_3 is delayed*), followed by solid CuCl (5 mg, 10 mol %; *CuCl must be added immediately after NaN_3 to avoid the noncatalyzed decomposition of iodonium azide*), whereupon the color of the reaction mixture changed to brown. After the reaction mixture was stirred for 30 min at room temperature, aqueous $(NH_4)_2S$ (40−48 wt % solution in water, Aldrich, 1.25 mmol, 200 μL, 2.5 equiv) was added. After being stirring for another 30 min at room temperature, the reaction mixture was poured into a mixture of water (50 mL) and saturated aqueous $NaHCO_3$ (25 mL) and extracted with CH_2Cl_2 (3 × 30 mL). The organic extracts were combined, dried over Na_2SO_4, filtered, and evaporated. The residue was purified by column chromatography on silica gel.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Experimental procedures, product characterization data, ^1H and ^{13}C NMR spectra, X-ray crystallographic data for iodonium azides **3a** and **3h** (CIF), and details of the kinetic experiments. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

edgars@osi.lv

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

This work was supported by the European Regional Development Fund (Grant 2DP/2.1.1.1.0/10/APIA/VIAA/066). We thank Dr. S. Belyakov for X-ray crystallographic analysis and Dr. J. Zicans for DSC analysis. We also thank Prof. S. Cornaja for helpful discussions.

■ REFERENCES

(1) (a) Merritt, E. A.; Olofsson, B. *Angew. Chem., Int. Ed.* **2009**, *48*, 9052. (b) Zhdankin, V. V.; Stang, P. J. *Chem. Rev.* **2008**, *108*, 5299.

(2) (a) Oh, C. H.; Kim, J. S.; Jung, H. H. *J. Org. Chem.* **1999**, *64*, 1338. (b) Shah, A.; Pike, V. W.; Widdowson, D. A. *J. Chem. Soc., Perkin Trans. 1* **1998**, 2043. (c) Ross, T. L.; Ermert, J.; Hocke, C.; Coenen, H. H. *J. Am. Chem. Soc.* **2007**, *129*, 8018. (d) Lancer, K. M.; Wiegand, G. H. *J. Org. Chem.* **1976**, *41*, 3360. (e) Petersen, T. B.; Khan, R.; Olofsson, B. *Org. Lett.* **2011**, *13*, 3462. (f) Grushin, V. V.; Demkina, I. I.; Tolstaya, T. P. *J. Chem. Soc., Perkin Trans. 2* **1992**, 505. (g) Dohi, T.; Ito, M.; Yamaoka, N.; Morimoto, K.; Fujioka, H.; Kita, Y. *Angew. Chem., Int. Ed.* **2010**, *49*, 3334.

(3) Deprez, N. R.; Sanford, M. S. *Inorg. Chem.* **2007**, *46*, 1924.

(4) The presence of a bulky mesityl group in iodonium salts [MesIAr]X ensured the selective transfer of the smaller Ar group in Pd-catalyzed arylations: (a) Kalyani, D.; Deprez, N. R.; Desai, L. V.; Sanford, M. S. *J. Am. Chem. Soc.* **2005**, *127*, 7330. (b) Deprez, N. R.; Sanford, M. S. *J. Am. Chem. Soc.* **2009**, *131*, 11234. (c) For the use of a nontransferable 2,4,6-triisopropylphenyl group in Cu(II)-catalyzed arylation of indoles, see: Phipps, R. J.; Grimster, N. P.; Gaunt, M. J. *J. Am. Chem. Soc.* **2008**, *130*, 8172.

(5) Lubriks, D.; Sokolovs, I.; Suna, E. *Org. Lett.* **2011**, *13*, 4324.

(6) (a) Cho, S. H.; Yoon, J.; Chang, S. *J. Am. Chem. Soc.* **2011**, *133*, 5996. (b) John, A.; Nicholas, K. M. *J. Org. Chem.* **2011**, *76*, 4158. (c) Cen, X.; Hao, X.-S.; Goodhue, C. E.; Yu, J.-Q. *J. Am. Chem. Soc.* **2006**, *128*, 6790. For selected Pd-catalyzed C−H activation/C−N bond formation examples, see: (d) Yoo, E. J.; Ma, S.; Mei, T.-S.; Chan, K. S. L.; Yu, J.-Q. *J. Am. Chem. Soc.* **2011**, *133*, 7652. (e) Vickers, C. J.; Mei, T.-S.; Yu, J.-Q. *Org. Lett.* **2010**, *12*, 2511. (f) Mei, T.-S.; Wang, X.; Yu, J.-Q. *J. Am. Chem. Soc.* **2009**, *131*, 10806. (g) Jordan-Hore, J. A.; Johansson, C. C. C.; Gulias, M.; Beck, E. M.; Gaunt, M. J. *J. Am. Chem. Soc.* **2008**, *130*, 16184. (h) Wasa, M.; Yu, J.-Q. *J. Am. Chem. Soc.* **2008**, *130*, 14058. (i) Uemura, T.; Imoto, S.; Chatani, N. *Chem. Lett.* **2006**, *35*, 842. (j) Thu, H.-Y.; Yu, W.-Y.; Che, C.-M. *J. Am. Chem. Soc.* **2006**, *128*, 9048. (k) Tsang, W. C. P.; Zheng, N.; Buchwald, S. L. *J. Am.*

Chem. Soc. **2005**, *127*, 14560. For rhodium-catalyzed C−H aminations, see: (l) Kim, J. Y.; Park, S. H.; Ryu, J.; Cho, S. H.; Kim, S. H.; Chang, S. *J. Am. Chem. Soc.* **2012**, *134*, 9110. (m) Grohmann, C.; Wang, H.; Glorius, F. *Org. Lett.* **2012**, *14*, 656.

(7) (a) Wang, X.; Jin, Y.; Zhao, Y.; Zhu, L.; Fu, H. *Org. Lett.* **2012**, *14*, 452. (b) Guo, S.; Qian, B.; Xie, Y.; Xia, C.; Huang, H. *Org. Lett.* **2011**, *13*, 522. (c) Matsuda, N.; Hirano, K.; Satoh, T.; Miura, M. *Org. Lett.* **2011**, *13*, 2860. (d) Miyasaka, M.; Hirano, K.; Satoh, T.; Kowalczyk, R.; Bolm, C.; Miura, M. *Org. Lett.* **2011**, *13*, 359. (e) Li, Y.; Xie, Y.; Zhang, R.; Jin, K.; Wang, X.; Duan, C. *J. Org. Chem.* **2011**, *76*, 5444. (f) Armstrong, A.; Collins, J. C. *Angew. Chem., Int. Ed.* **2010**, *49*, 2282. (g) Kim, J. Y.; Cho, S. H.; Joseph, J.; Chang, S. *Angew. Chem., Int. Ed.* **2010**, *49*, 9899. (h) Monguchi, D.; Fujiwara, T.; Furukawa, H.; Mori, A. *Org. Lett.* **2009**, *11*, 1607. (i) Wang, Q.; Schreiber, S. L. *Org. Lett.* **2009**, *11*, 5178. (j) Cho, S. H.; Kim, J. Y.; Lee, S. Y.; Chang, S. *Angew. Chem., Int. Ed.* **2009**, *48*, 9127.

(8) For reviews on C−H activation/functionalization of heterocycles, see: (a) Cho, S. H.; Kim, J. Y.; Kwak, J.; Chang, S. *Chem. Soc. Rev.* **2011**, *40*, 5068. (b) Beck, E. M.; Gaunt, M. J. *Top. Curr. Chem.* **2010**, *292*, 85. (c) Ackermann, L.; Vicente, R.; Kapdi, A. R. *Angew. Chem., Int. Ed.* **2009**, *48*, 9792. (d) Xiao, C.; Engle, K. M.; Wang, D.-H.; Yu, J.-Q. *Angew. Chem., Int. Ed.* **2009**, *48*, 5094. (e) Seregin, I. V.; Gevorgyan, V. *Chem. Soc. Rev.* **2007**, *36*, 1173.

(9) (a) Hein, J. E.; Fokin, V. V. *Chem. Soc. Rev.* **2010**, *39*, 1302. (b) Meldal, M.; Tornøe, C. W. *Chem. Rev.* **2008**, *108*, 2952.

(10) Breinbauer, R.; Köhn, M. *ChemBioChem* **2003**, *4*, 1147.

(11) El-Sagheer, A. H.; Brown, T. *Chem. Soc. Rev.* **2010**, *39*, 1388.

(12) Holub, J. M.; Kirshenbaum, K. *Chem. Soc. Rev.* **2010**, *39*, 1325.

(13) (a) Mamidyala, S. K.; Finn, M. G. *Chem. Soc. Rev.* **2010**, *39*, 1252. (b) Hu, X.; Manetsch, R. *Chem. Soc. Rev.* **2010**, *39*, 1316.

(14) Angell, Y. L.; Burgess, K. *Chem. Soc. Rev.* **2007**, *36*, 1674.

(15) Chattopadhyay, B.; Gevorgyan, V. *Angew. Chem., Int. Ed.* **2012**, *51*, 862.

(16) (a) Neiland, O.; Karele, B. *J. Org. Chem. USSR (Engl. Transl.)* **1970**, *6*, 889. (b) Koser, G. F.; Wettach, R. H.; Troup, J. M.; Frenz, B. A. *J. Org. Chem.* **1976**, *41*, 3609.

(17) To the best of our knowledge, the X-ray structure of diaryl(azido)-λ^3-iodanes has never been reported in the literature.

(18) Zhdankin, V. V.; Krasutsky, A. P.; Kuehl, C. J.; Simonsen, A. J.; Woodward, J. K.; Mismash, B.; Bolz, J. T. *J. Am. Chem. Soc.* **1996**, *118*, 5192.

(19) Buzek, P.; Klapötke, T. M.; von Ragué Schleyer, P.; Tornieporth-Oetting, I. C.; White, P. S. *Angew. Chem., Int. Ed.* **1993**, *32*, 275.

(20) A 2.758 Å distance between the iodonium cation and fluorine of a weekly nucleophilic PF_6^+ anion in $[C_6F_5(C_6H_5)I][PF_6]$ has been reported; see: Frohn, H.; Hirschberg, M. E.; Boese, R.; Bläser, D.; Flörke, U. *Z. Anorg. Allg. Chem.* **2008**, *634*, 2539.

(21) (a) Lubinkowski, J. J.; Gomez, M.; Calderon, J. L.; McEwen, W. E. *J. Org. Chem.* **1978**, *43*, 2432. (b) Wang, B.; Graskemper, J. W.; Qin, L.; DiMagno, S. G. *Angew. Chem., Int. Ed.* **2010**, *49*, 4079.

(22) For the initial rates of **3a** to **5a**, see the Supporting Information. We could not determine the rate coefficient for the CuCl-catalyzed fragmentation of **3a** in CH_2Cl_2-d_2 because of the extremely fast reaction (~70% conversion after 2 min).

(23) Shao, C.; Wang, X.; Zhang, Q.; Luo, S.; Zhao, J.; Hu, Y. *J. Org. Chem.* **2011**, *76*, 6832.

(24) Kumar, D.; Reddy, V. *Synthesis* **2010**, 1687.

(25) Neilands, O. *Chem. Heterocycl. Compd. (N. Y., NY, U. S.)* **2003**, *39*, 1555.

(26) Karele, B. Y.; Treigute, L. E.; Kalnin', S. V.; Grinberga, I. P.; Neiland, O. Y. *Chem. Heterocycl. Compd. (N. Y., NY, U. S.)* **1974**, *10*, 189.

(27) Vanag, G. Y.; Neiland, O. Y. *Dokl. Akad. Nauk SSSR* **1961**, *141*, 872.

(28) Karele, B. Y.; Kalnin', S. V.; Grinberga, I. P.; Neiland, O. Y. *Chem. Heterocycl. Compd. (N. Y., NY, U. S.)* **1973**, *9*, 510.

(29) Davies, G.; Loose, D. J. *Inorg. Chem.* **1976**, *15*, 694.

(30) Structurally related cuproine has been used as a specific inhibitor of Cu(I)-catalyzed reactions; see: (a) Caserio, M. C.; Glusker, D. L.; Roberts, J. D. *J. Am. Chem. Soc.* **1959**, *81*, 336−342. (b) Lockhart, T. P. *J. Am. Chem. Soc.* **1983**, *105*, 1940.

(31) Barton, D. H. R.; Finet, J.-P.; Giannotti, C.; Halley, F. *J. Chem. Soc., Perkin Trans. 1* **1987**, 241.

(32) A radical pathway has been proposed for α-azidation of silyl enol ethers with hypervalent iodonium azides: (a) Magnus, P.; Lacour, J.; Evans, P. A.; Roe, M. B.; Hulme, C. *J. Am. Chem. Soc.* **1996**, *118*, 3406. (b) Magnus, P.; Roe, M. B.; Hulme, C. *J. Chem. Soc., Chem. Commun.* **1995**, 263.

(33) Related Cu(III) complexes have been proposed: (a) Ochiai, M. In *Hypervalent Iodine Chemistry*; Wirth, T., Ed.; Springer: Berlin, Heidelberg, 2003; Vol. *224*, pp 5−68. (b) Lee, J. M.; Park, E. J.; Cho, S. H.; Chang, S. *J. Am. Chem. Soc.* **2008**, *130*, 7824. (c) Beringer, F. M.; Bodlaender, P. *J. Org. Chem.* **1969**, *34*, 1981.

(34) A related π-Cu^{III} complex has been recently suggested in the copper-catalyzed arylation of indoles with diaryl-λ^3-iodanes: Zhu, S.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2012**, *134*, 10815. A π-Cu^{III} complex has also been proposed in α-arylation and α-vinylation of aldehydes: Allen, A. E.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2011**, *133*, 4260. Skucas, E.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2012**, *134*, 9090. See also: Seayad, J.; Seayad, A. M.; Chai, C. L. L. *Org. Lett.* **2010**, *12*, 1412.

(35) Formation of arylcopper(III) species that form Cu(I) salts and diaryl-λ^3-iodanes has been proposed: (a) Phipps, R. J.; Grimster, N. P.; Gaunt, M. J. *J. Am. Chem. Soc.* **2008**, *130*, 8172. (b) Phipps, R. J.; Gaunt, M. J. *Science* **2009**, *323*, 1593. (c) Phipps, R. J.; McMurray, L.; Ritter, S.; Duong, H. A.; Gaunt, M. J. *J. Am. Chem. Soc.* **2012**, *134*, 10773. (d) Harvey, J. S.; Simonovich, S. P.; Jamison, C. R.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2011**, *133*, 13782. (e) Reference 30b. For studies of the mechanism of Cu-catalyzed aryl halide activation, see: Strieter, E. R.; Bhayana, B.; Buchwald, S. L. *J. Am. Chem. Soc.* **2009**, *131*, 78 and references therein.. For a well-defined arylcopper(III) species, see: King, A. E.; Huffman, L. M.; Casitas, A.; Costas, M.; Ribas, X.; Stahl, S. S. *J. Am. Chem. Soc.* **2010**, *132*, 12068.

(36) (a) Cordone, R.; Harman, W. D.; Taube, H. *J. Am. Chem. Soc.* **1989**, *111*, 5969. (b) Hodges, L. M.; Gonzalez, J.; Koontz, J. I.; Myers, W. H.; Harman, W. D. *J. Org. Chem.* **1995**, *60*, 2125. (c) Myers, W. H.; Sabat, M.; Harman, W. D. *J. Am. Chem. Soc.* **1991**, *113*, 6682. (d) Valahovic, M. T.; Myers, W. H.; Harman, W. D. *Organometallics* **2002**, *21*, 4581.

(37) Formation of a Cu(I)−acetylene π-complex was proposed to rationalize the regioselective attack of nucleophiles on the acetylene moiety of alkynyl(phenyl)iodonium salts: (a) Stang, P. J.; Surber, B. W. *J. Am. Chem. Soc.* **1985**, *107*, 1452. (b) Stang, P. J.; Surber, B. W.; Chen, Z. C.; Roberts, K. A.; Anderson, A. G. *J. Am. Chem. Soc.* **1987**, *109*, 228. For the related Au(I)−acetylene π-complexes, see: (c) Brand, J. P.; Chevalley, C.; Scopelliti, R.; Waser, J. *Chem.—Eur. J* **2012**, *18*, 5655. (d) Brand, J. P.; Charpentier, J.; Waser, J. *Angew. Chem., Int. Ed.* **2009**, *48*, 9346.

(38) Control experiments supported the importance of electronic effects in the regiocontrol of the Cu-catalyzed fragmentation of iodonium azide **3a**. Thus, replacement of the Ph group in **3a** with an electron-poor 4-$NO_2C_6H_4$ moiety altered the regioselectivity of azide attack and favored the formation of aryl azide 4-$NO_2C_6H_4N_3$ (**4a**:**5a** = 1:1 in MeCN and **4a**:**5a** = 1:3 in DCM). In the meantime, substitution of the Ph ring with a more electron-rich mesityl moiety in **3a** did not change the fragmentation regioselectivity (**4a**:**5a** = 9:1 in MeCN). Likewise, CuOTf-catalyzed decomposition of **3a** possessing a 4-$MeOC_6H_4$ moiety instead of a Ph ring afforded **4a**, albeit with diminished regioselectivity (**4a**:**5a** = 4:1 in DCM).

(39) The decomposition of indolyl azide **3a** was investigated by differential scanning calorimetry (DSC) and thermogravimetry methods. The DSC analysis of **3a** (heating rate 5 K/min) showed two exotherms: from 100 to 120 °C with a heat release of 122.0 J/g and from 212 to 263 °C with a heat release of 1842.7 J/g. The total decomposition enthalpy of 1964.7 J/g points toward a high thermal hazard potential for iodonium azide **3a**.