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

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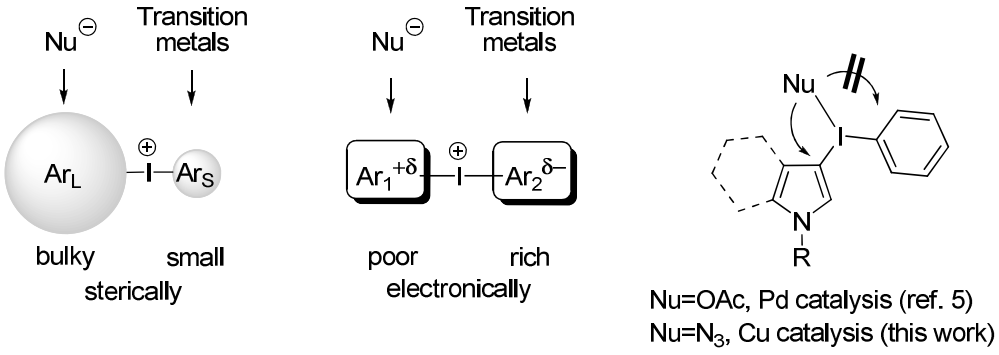
Abstract. C–H Bond of electron-rich heterocycles is transformed into a C–N bond in a reaction sequence comprising the formation of heteroaryl(phenyl)iodonium azides and their *in situ* regioselective fragmentation to heteroaryl azides. Cu(I) Catalyst ensures complete regiocontrol in the fragmentation 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 heteroaryl amines by aqueous ammonium sulfide. The overall C–H to C–N transformation is mild and operationally simple one-pot sequential multi-step process.

Introduction.

Symmetrical diaryliodonium salts have found numerous applications as electrophilic arylating reagents both in the 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 products mixtures in the reactions with nucleophiles. Nevertheless, the regiocontrol can be achieved by differentiation of electronic and steric properties of aromatic moieties. Thus, 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 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 non-symmetrical iodonium salts.

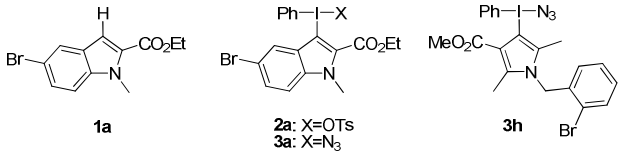


We have recently demonstrated that the regioselectivity of acetoxylation of heteroaryl(phenyl)iodonium acetates can be directed to the more electron rich heteroaryl moiety by Pd(II) catalyst.[5] We reasoned that use of other counter ions instead of acetate would provide a straightforward access to differently 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, pyrrolo-pyridines, thieno-pyrroles, pyrrolo-pyrimidines and uracil) comprising *in situ* preparation of heteroaryl(phenyl)iodonium azides and their Cu–catalyzed conversion to heteroarylazides. 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 heteroarylazides can also undergo Cu–catalyzed azide-alkyne cycloaddition to furnish 1,2,3-triazoles,[9] thus allowing for the direct ligation of heterocycles to biomolecular frameworks via 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 the 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 iodo-indole **5a** even at –18 ^{o}C. Nevertheless, the indolyl azide **3a** as well as its pyrrole analogue **3h** could be characterized and their structure was confirmed by X-ray crystallographic analysis (Table 1).[17] In the crystal lattice azides **3a,h** exist in a characteristic slightly distorted T-shaped geometry with 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 hypervalent iodine in **3h** and azide anion (2.837 Å, Table 1) is much longer than that between the iodine of the phenyl(pyrrolyl)iodonium moiety of **3h** and 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**.

Table 1. Selected crystallographic parameters for iodonium azides **3a,h**.

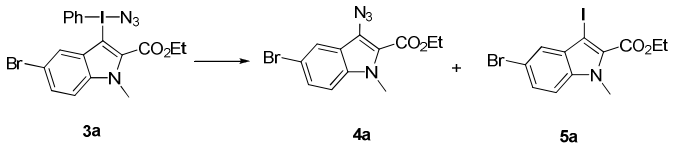


1a **2a**: X=OTs **3a**: X=N_3 **3h**

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

In MeCN and CH_2Cl_2 solutions at room temperature the iodonium azide **3a** spontaneously decomposed to 3-iodoindole **5a** and phenylazide (see Table 2, entries 1,2). Importantly, the desired indolylazide **4a** was not formed in MeCN and CH_2Cl_2. The regioselectivity of the non-catalyzed 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 4,5), whereas Cu salts completely reversed the fragmentation regioselectivity, and the iodonium azide **3a** was smoothly converted to the desired indolylazide **4a** (entries 6–15).

Table 2. Fragmentation of indolyliodonium azide **3a**.



entry	catalyst (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	30min	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] 100% Conversion (**4a**:**5a**=1:99) after 30 min at 80 °C

Copper catalysts decreased considerably the reaction time with CuCl and CuOTf in CH_2Cl_2 being the most efficient (entries 7,12). Interestingly, both Cu(I) and Cu(II) salts can be used, however the Cu(I) species ensured faster reaction (entry 7 vs. 6). Other solvents either retarded the reaction (entries 10,11,14) or deteriorated the regioselectivity (entries 9,10). It should be noted that the conversion of **3a** was faster in CH_2Cl_2 compared to MeCN (entries 2 vs. 1 and 7 vs. 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 non-catalyzed formation of **5a** from **3a** (**4a**:**5a**=1:99). The determined initial rates of the non-catalyzed fragmentation of **3a** to iodide **5a** in CH_2Cl_2 (rate coefficient $k=9\bullet10^{-5}$ s^{-1}, CH_2Cl_2–d_2, 23 ^{o}C and reaction half-life $t_{1/2}$=128 min) evidences that spontaneous fragmentation of iodonium azide **3a** delivers ca. 10% of **5a** within the first 10 minutes. 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 compromised by the competing non-catalyzed 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. 1,3, Table 2). The non-catalyzed 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 indolylazide **4a** decomposed during attempted purification, however it can be employed in further transformations without the isolation. Thus, addition of substituted acetylene directly to the 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 indolylazide **4a** and its subsequent 1,3-dipolar cycloaddition with 3-chlorophenylacetylene (Table 3).[9]

A series of heterocycles was subsequently subjected to 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*]pyrroles **1o**, pyrrolo[2,3-*b*]pyridines **1p,r**, pyrrolo[3,2-*b*]pyridines **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 5th position of uracil **1u** (Table 3). In 2,5-disubstituted pyrroles **1h**,**k–m**, however, iodonium salts were formed at 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, *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 product **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. 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 the first order in CuOTf in the range of 0.25–5 mol % at 25 ^{o}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 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* 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 points against the involvement of free-radical intermediates.[32]

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

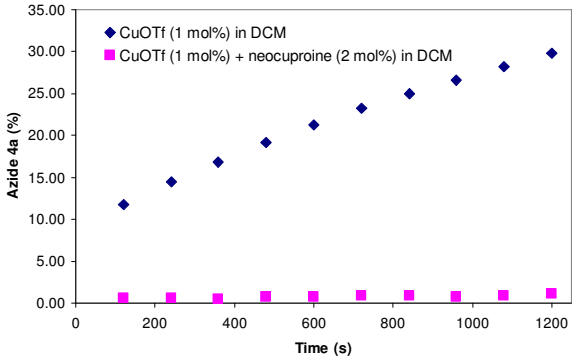


Figure 3. Plot of initial rates vs. concentration of CuOTf in DMSO-d_6.

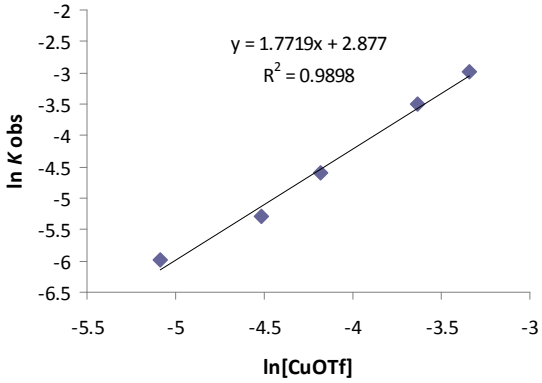


Figure 4. Plot of initial rates vs. concentration of azide ion in DMSO-d_6.

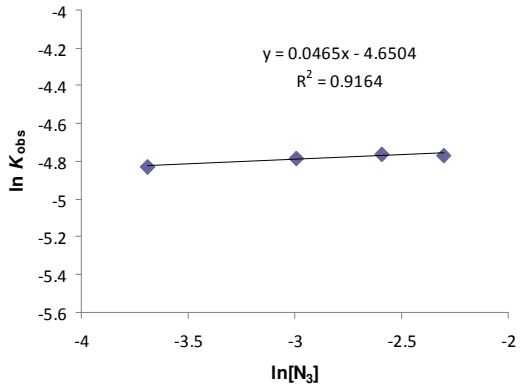
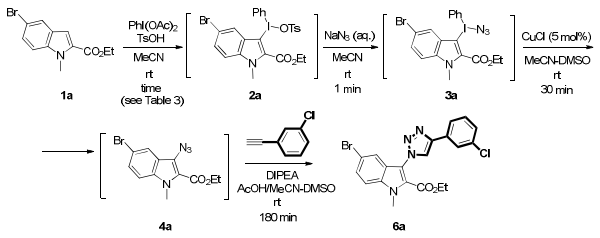
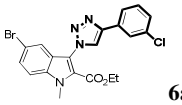
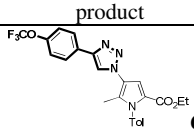
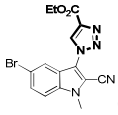
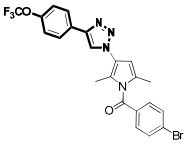
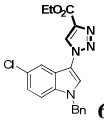
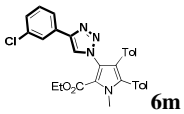
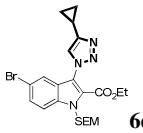
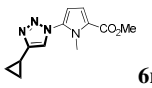
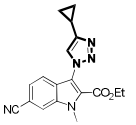
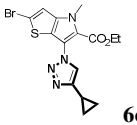
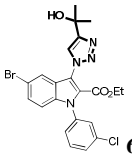
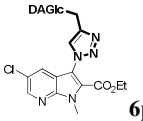
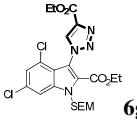
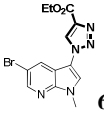
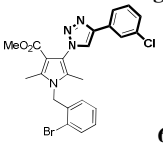
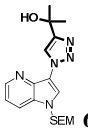
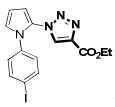
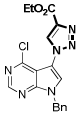
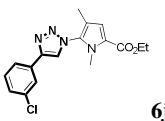
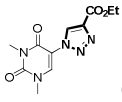


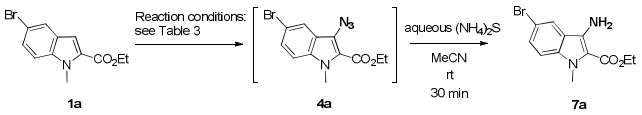
Table 3. Sequential one-pot synthesis of heteroaryl azides **4a–u** and triazoles **6a–u**.

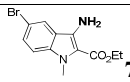
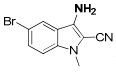
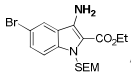
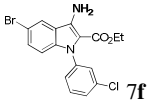
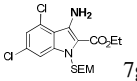
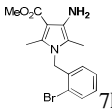
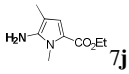
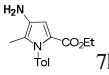
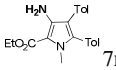
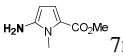
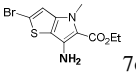
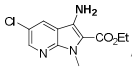


entry	product	time	yield (%)[c]	entry	product	time	yield (%)[c]
1	 **6a**	30 min	90	11	 **6k**	10 min	65
2	 **6b**	18 h	71	12	 **6l**	30 min	65
3	 **6c**	5 min	65	13	 **6m**	30 min	73
4	 **6d**	3 h	71	14	 **6n**	5 min	59
5	 **6e**	3 h	75	15	 **6o**	30 min	75
6	 **6f**	3 h	73	16	 **6p**[a]	30 min	62
7	 **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] 2.2 equiv. of TsOH-H_2O; [c] Yields were calculated based on the starting heterocycle **1a–u**

Table 4. Sequential azidation-reduction sequence for one-pot synthesis of heteroaryl amines **7a–u**.

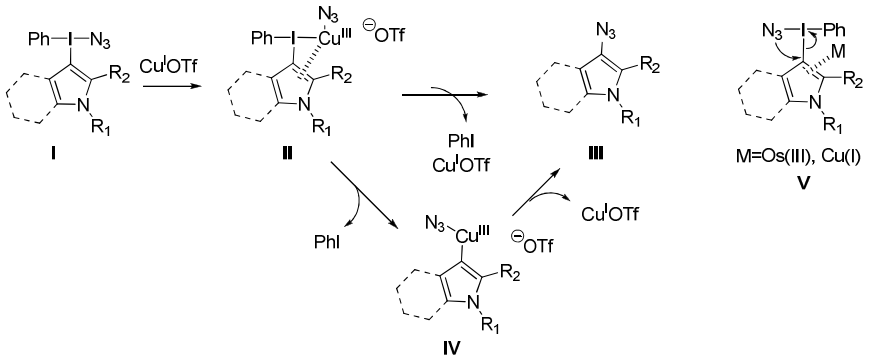


entry	product	yield (%)[a]
1	 **7a**	84
2	 **7b**	80
3	 **7d**	82
4	 **7f**	84
5	 **7g**	79
6	 **7h**	65
7	 **7j**	60
8	 **7k**	62
9	 **7m**	72
10	 **7n**	53
11	 **7o**	66
12	 **7p**	75
13	 **7u**	50

[a] Yields were calculated based on the starting heterocycle **1a–u**

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] The complex **II** can directly collapse into azide **III** *via* the highly regioselective coupling of heterocycle with azide, and the regioselectivity of azide attack presumably is ensured by the formation of transient π–complex between the highly electrophilic Cu(III) species and electron-rich heterocycle.[34] Alternatively, complex **II** can undergo regioselective transformation to PhI and heteroaryl–Cu(III) **IV** species,[35] followed by reductive elimination of **III** and regeneration of Cu(I) species.

Scheme 1. Working mechanism for azidation of heterocycles.



To verify the role of putative π-Cu(III) complex **II** in the control of regioselectivity of the 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 transitions 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% of $Os[NH_3]_5(OTf)_3$ in CH_2Cl_2. Notably, the indolylazide **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 non-catalyzed decomposition of

3a to **5a** in the presence of representative Lewis acids (entries 4,5,17–19, Table 2). Possibly, π-complexation of pyrrole ring to the Os(III) facilitates the substitution of iodonium group by 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 heterocycle towards azide attack seems less likely because of insufficient electrophilicity of 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 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 heteroaryl amines. 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, thieno-pyrroles, pyrrolo–pyridines, pyrrolo–pyrimidines 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.

Experiment Section

Preparation of Iodonium Azides 3a and 3h.

Hazard Warning: 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 small scale is strongly encouraged.

Ethyl 3-[(azido)(phenyl)-λ^3-iodanyl]-1,5-dimethyl-1H-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 $TsOH\bullet H_2O$ (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 the solution of NaN_3 (146 mg, 2.25 mmol, 1.5 equiv) in water (50 mL) and extracted with CH_2Cl_2 (3x30 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, Rf=0.56. Pure material was obtained by crystallization from CH_2Cl_2/diethylether: mp 102-103 ^oC (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, pmm) 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-1H-pyrrole-3-carboxylate (3h). The same procedure was used as for **3a**. Accordingly, 3-[1-(2-bromobenzyl)-4-(methoxycarbonyl)-2,5-dimethyl-1H-pyrrole **1h** (482 mg, 1.50 mmol) was converted to iodonium azide **3h**. Purification of the crude **3h** by washing with diethylether afforded product as a white powder (723 mg, 85% yield); analytical TLC on silica gel, 20:80:5 MeOH/CH_2Cl_2/AcOH, Rf=0.54. Pure material was obtained by crystallization from CH_2Cl_2/diethylether: mp 96-97 ^oC (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, pmm) 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 $TsOH\bullet H_2O$ (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 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 with DMSO (2.5 mL), and solid CuCl (5 mg, 10 mol%;

CuCl must be added immediately after NaN_3 in order to avoid the non-catalyzed decomposition of iodonium azide) whereupon the color of reaction changed to brown. After stirring 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. Reaction mixture was poured into 50 mL of water and 25 mL of saturated $NaHCO_3$, extracted with DCM (3x30 mL). 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 $TsOH \bullet H_2O$ (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 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 with solid CuCl (5 mg, 10 mol%; *CuCl must be added immediately after NaN_3 in order to avoid the non-catalyzed decomposition of iodonium azide*) whereupon the color of reaction changed to brown. After stirring 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 stirring for another 30 min at room temperature the reaction was poured into a mixture of water (50 mL) and saturated

aqueous $NaHCO_3$ (25 mL) and extracted with CH_2Cl_2 (3x30 mL). 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, products characterization data, copies of ^{1}H and ^{13}C NMR spectra, X-ray crystallographic data for iodonium azides **3a** and **3h** (CIF files) and details of kinetic experiments. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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(39) The decomposition of indolyl azide **3a** was investigated by differential scanning calorimetry (DSC) and thermogravimetry (TG) methods. The DSC analysis of

3a (heating rate 5 K/min) showed two exotherms: from 100 ^{o}C to 120 ^{o}C with a heat release of 122.0 J/g and from 212 ^{o}C to 263 ^{o}C with a heat release of 1842.7 J/g. The total decomposition enthalpy of 1964.7 J/g points toward high thermal hazard potential for iodonium azide **3a**.

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