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Efficient Synthesis of *N*-2-Aryl-1,2,3-Triazole Fluorophores via Post-Triazole Arylation

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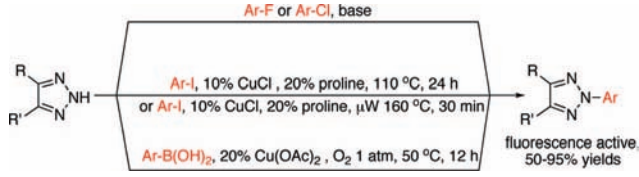
ABSTRACT



Efficient post-triazole regioselective N-2 arylation was developed from C-4, C-5 disubstituted-1,2,3-NH-triazoles. Three different approaches had been investigated, including S_NAr, Cu(I) catalyzed aryl amidation and Cu(II) mediated boronic acid coupling. The N-2-aryl triazoles were successfully synthesized with excellent yields. The structures were characterized by X-ray crystallography and some N-2-triazole products gave strong fluorescence with various emission controlled by the C-5 groups.

Initiated by the remarkable discovery of Cu-catalyzed-azide-alkyne-cycloaddition (CuAAC, also referred as "click chemistry"), the 1,2,3-triazole has become one of the most important heterocycles in current chemistry research.[1] Within the last five years, the applications of this building block have been extended into various research fields, as diverse as biological science,[2] material chemistry[3] and medicinal chemistry.[4] One important group of triazole derivatives is the N-2-aryl triazoles, where the two aromatic rings adopt coplanar conformation. With the characteristic electron density distribution, these bis-aromatic compounds give unique photonic properties. One example is the commercially available o-hydroxyphenyl benzotriazoles (such as Tinuvin P), which has been applied as an efficient light absorber to prevent polymer degradation from light radiation.[5]

It has been well documented that the N-2 substitution is one major challenge for triazole derivatization. The application of substituted azide in click-chemistry gives only N-1 products. The higher electron density on the two terminal nitrogens allows them to have a better nucleophilic position

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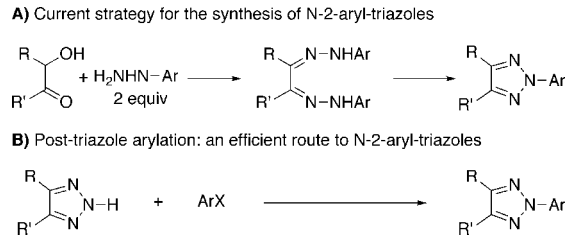
and gives dominant N-1 products for most or reported post-triazole derivatization. Recently, Sharpless and Fokin have made good progress toward the N-2 alkyl substituted triazoles.[6] As they pointed out, the N-2-substituted triazoles are thermodynamically more stable with less steric hindrance. Therefore, N-2-substitution will be the major products when dynamic equilibrium of the substituted triazole products exists. However, for the N-2 aryl and nonexchangeable N-2 alkyl triazoles, which could be of more important triazole derivatives with better stability, the selective N-2 substitution is difficult since the regioselectivity is under kinetic control and N-1 is the preferred nucleophilic site.

Our group has recently reported the synthesis of 4,5-disubstituted-NH-traizoles through Lewis base catalyzed process.[7] With these compounds in hand, recently, we reported a successful post-triazole N-2 alkylation through substrate conformation control.[8] Encouraged by these results, we wondered if this strategy could be further extended into the regioselective N-2-arylation (Scheme 1B). Currently, the

Scheme 1. N-2-aryl-1,2,3-triazole Synthesis

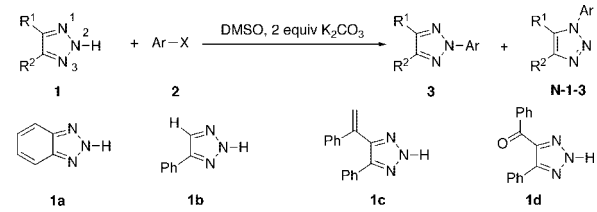


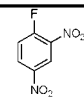
general approach for N-2-aryl triazole is from the hydrazine/α-hydoxyketone condensation[9] as shown in Scheme 1A. The need of various aryl hydrazines and α-hydoxyketones as starting materials significantly limited the application of this method and only specific N-2 aryl triazole can be prepared with good yields. Therefore, an effective regioselective N-2 arylation approach will be of great importance for the triazole related research.[10] Herein, we report an efficient Cu catalyzed regioselective N-2 arylation through post-triazole aryl amidation and their photonic emissions.

To evaluate the regioselectivity, the S_NAr substitution was first studied with a variety of 1,2,3-triazoles. The results are listed in Table 1.

Because the arylation products **3** are stable (no C−N bond exchange under the reaction condition), the S_NAr reaction then provided direct measurement of C-4 and C-5 groups influence on the regioselectivity. As shown above, benzotriazole **1a** gave modest selectivity with N-1 as the major product. The application of 4-phenyl group in **1b** improved the selectivity, giving N-2 arylation as the major product, though with poor selectivity.

Table 1. Post-Triazole Arylation via S_NAr Reactions[a]



	triazoles	Ar-X	temp (°C)	time (h)	convn (%)[b]	yield (%)[c]	N-2:N-1
1	**1a**	 **2a**	rt	2	100	**3a**: 92	1:3
2	**1b**		rt	2	100	**3b**: 90	1.7:1[d]
3	**1c**		rt	2	100	**3c**: 95	6:1
4	**1d**		rt	2	100	**3d**: 95	Only N-2
5	**1c**	 **2b**: X = F; R = NO_2	80	1	100	**3e**: 92	10:1
6	**1c**	**2c**: X = Cl; R = NO_2	80	30	90	**3e**: 85	10:1
7	**1c**	**2d**: X = F; R = CN	80	30	66	**3f**: 62	10:1
8	**1c**	**2b**: X = Cl; R = CN	80	30	0	-	-

[a] **1**:**2** = 1:1.5, c = 0.2 M. [b] Based on the consumption of **1** by NMR. [c] Isolated yields of all isomers. [d] Structure of **N-1-3b** was determined by X-ray crystallography.

To our pleasure, application of 4,5-disubstituted triazole **1c** and **1d** gave excellent regioselectivity with N-2 as the dominant products. As reported previously,[8] the selectivity was driven by the conformation control of the C-4 and C-5 substitute groups. However, at higher temperature, the selectivity should be only driven by the steric effect. To our pleasure, increasing reaction temperature gave improved N-2 selectivity (entries 5−7), which suggested that the regioselectivity of post-triazole arylation could be achieved at higher temperature. Notably, as a good nucleophile, triazole can also react with less electron-deficient substrates to form the corresponding N-2 arylation products (entries 5−7). Encouraged by excellent regioselectivity of S_NAr reactions, we then explored the possible coupling strategy for aromatic systems with higher electron density.

Although an increasing number of copper catalyzed N-aryl halide coupling reactions have been reported recently, the reaction mechanism remains unclear.[11] The most likely mechanism involves a Cu(I) oxidative addition to Cu(III) intermediate followed by reductive elimination, which was proposed by Buchwald, Hartwig and Stahl.[12] Hartwig and co-workers also suggested that oxidative addition of carbon-halogen bond likely occur in the catalytic cycles with strong ligand effects.[12b] Based on these remarkable works, we rationalized that NH-triazoles might be another suitable nitrogen source for copper mediated aryl halide amidation. Reactions between NH-triazole **1a** and phenyl iodide were carried out with the focus on the ligand effect for optimal performance (Table 2).

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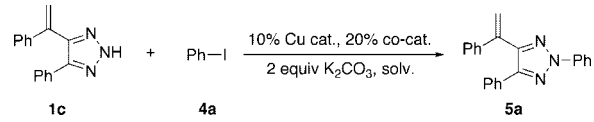
Table 2. Screening of the Reactions for Coupling with PhI[a]



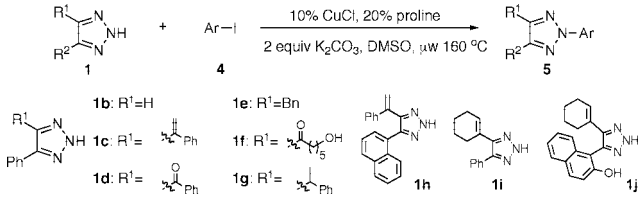
1c 4a 5a

	Cu cat	co-cat.[c]	solvent	temp (°C)	time (h)	convn (%)[d]	yield (%)[d]
1	CuI	–	DMSO	110	24	low	0
2	CuI	proline	DMSO	110	24	100	71
3	CuCl	proline	DMSO	110	24	100	88
4	other[b] Cu cat.	proline	DMSO	110	24	<92	<79
5	CuCl	proline	other solvents[b]	110	24	<85	<74
6	CuCl	proline	DMSO	μw 160	0.5	98	92
7	CuCl	glycine	DMSO	μw 160	0.5	trace	trace
8	CuCl	Me-Gly	DMSO	μw 160	0.5	60	30
9	CuCl	DMG	DMSO	μw 160	0.5	98	86
10	CuCl	EDA	DMSO	μw 160	0.5	53	29
11	CuCl	DMEDA	DMSO	μw 160	0.5	70	47
12	CuCl	TMEDA	DMSO	μw 160	0.5	trace	trace
13	CuCl	DACH	DMSO	μw 160	0.5	53	44

[a] **1c**:**4a** = 1:1.5, c = 0.2 M. [b] See Supporting Information. [c] See ref 13. [d] Based on the ^{1}H NMR with 1,3,5-trimethoxybenzene as internal standard.

Among all the tested reactions, the coupling product **5a** were not formed, if no ligands were applied as co-catalysts. Although different nitrogen containing ligands have been reported as ligands for Cu mediated amidation, proline was identified as the best ligand for this transformation. To our satisfaction, excellent regioselectivity was received with N-2 arylation as the dominant product. Both Cu(I) and Cu(II) could effectively promote the reaction (entries 2−4) and CuCl in DMSO were identified as the optimal condition.

Table 3. Substrate Scope for Cu Catalyzed Triazole Amidation[a]



	ArI	yield (%)[b]		ArI	yield (%)[b]
1a	**4a**	**5b**: 8[c]	**1f**	**4a**	**5f**: 60
1b	**4a**	**5c**: 68[d]	**1g**	**4a**	**5g**: 85
1c	**4a**	**5a**: 87	**1h**	**4a**	**5h**: 87
1d	**4a**	**5d**: 85[e]	**1i**	**4a**	**5i**: 80
1e	**4a**	**5e**: 85	**1j**	**4a**	**5j**: 45[e,f]
1c	**4b**: R = *p*-Me	**5k**: 86	**1c**	 **4h**	**5r**: 70
1d	**4c**: R = *p*-NO_2	**5l**: 88			
1c	**4d**: R = *p*-OMe	**5m**: 74	**1c**	 **4i**	**5s**:70
1i	**4e**: R = *o*-Me	**5n**: 70	**1d**		**5t**:60
1c	**4f**: R = *p*-I	**5o**: 67[e,g]			
1c	 **4g**	**5p**: 88	**1c**	 **4j**	**5u**: 70[e]
1d		**5q**: 83[e]			

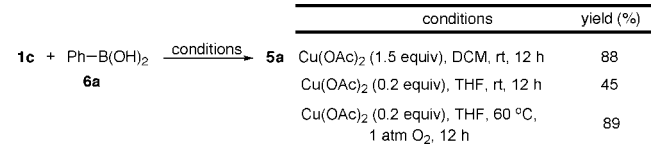
[a] **1**:**4** = 1:1.5, c = 0.2 M. [b] Isolated yield. [c] N-1-**5b** 60% yield. [d] N-1-**5c** 11% yield. [e] Structure determined by X-ray crystallography. [f] N-3-**5j** 40% yield. [g] Diamidation product **5v** was formed in 10%.

Application of microwave initiation significantly shortened the reaction time, giving N-2 phenyl **5a** in excellent yield. The substrate scope is listed in Table 3.

As shown in Table 3, benzotriazole **1a** gave the N-1 arylation as the dominant product with only 8% N-2 product isolated. The N-2 selectivity was increased while 4-phenyl substituted **1b** was applied, giving 60% N-2 isomer with another 15% N-1 isomer and only trace amount of N-3 isomer. Dramatic difference was observed when 4,5-disubstituted triazoles were used, where, as expected, in all cases only N-2 isomers were isolated with excellent yields. The substrate scope of this transformation covered different substituted groups on C-5 position and various aryl iodides. Application of aryl bromides resulted in significant decrease of reaction conversion and yield. Notably, the substrate **1j** gave 45% of desired N-2 arylation product **5j** and 40% of N-3-arylation product (structures were determined by X-ray diffraction), which suggested the Cu-chelation between phenol oxygen and triazole-N-3 position. The fact that the steric disfavored N-3 arylation product was obtained strongly supported the Cu(III) reductive elimination mechanism, proposed previously by other groups based on their mechanistic studies.

The strong dependence on ligands of this transformation initiated our interest in evaluating trans-metalation as an alternative path to further extend the substrate scope. Thus,

Scheme 2. Copper Catalyzed Transmetalation



the reactions between the triazoles and boronic acids were investigated (Scheme 2).

To our pleasure,transmetalation indeed produced the desired N-2 arylation product under milder conditions. With triazole **1c**, the N-2 isomer was the only product isolated (**1a** and **1b** gave less than 40% N-2 isomers). Screening of reaction conditions gave THF as the best solvent (see other conditions in the Supporting Information). The turnover of the copper catalyst can also be effectively achieved with the assistance of oxygen gas. We then focused on applying this strategy for the synthesis of N-2 aryl substrates that were difficult to be prepared from aryliodide amidation. The results are summarized in Figure 1.

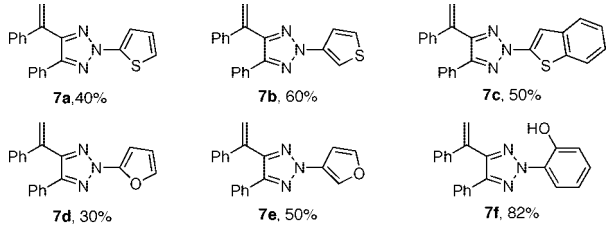


Figure 1. Products from coupling with arylboronic acid. Reaction conditions: **1c**/boronic acid = 1:1.5, c = 0.1 M, THF, 0.2 equiv $Cu(OAc)_2$, 2 equiv. pyridine, O_2 1 atm, 50 °C, 24 h.

Finally, with a series of new N-2 aryl triazoles in hand, the photonic properties were studied. To our excitement, besides the strong UV absorptions, the new triazole derivatives produce strong photonic luminescence and their emission pattern depends on the substituted groups.

The importance of fluorescence active molecules has been well documented in various research fields.[14] As shown in the Figure 2A, the N-2-aryl group is crucial for photonic emission (the emission of N-1 aryl analogues is significantly weaker). More importantly, the 4,5-substituted triazoles provided significant increase of the emission compared to benzotriazole derivatives (Figure 2B). More detailed studies regarding the photonic properties of these newly discovered PL molecules are currently under investigation in our group and will be reported in due course. This new group of fluorophores just provided other examples for the importance of reported regioselective post-triazole arylation for the preparation of N-2 aryl triazoles.

In conclusion, the first regioselective post triazole-arylation was developed through substrate controlled N-arylation. The importance of ligand effect in the copper mediated coupling

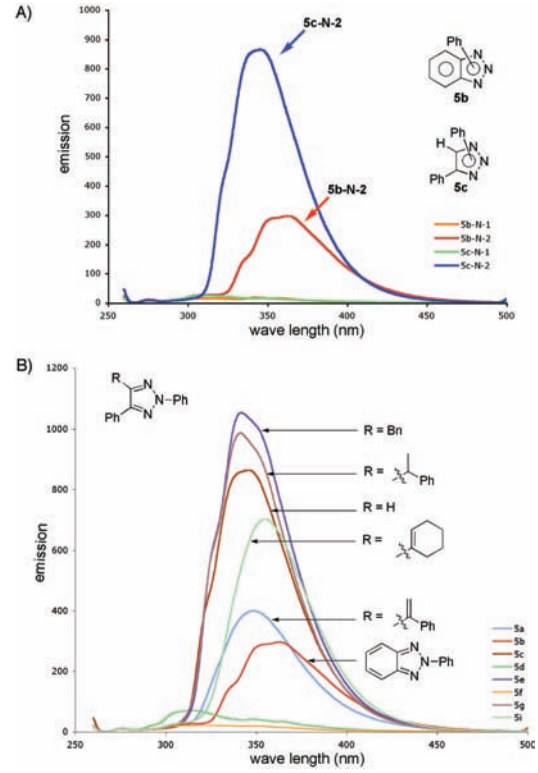


Figure 2. Photonic luminescence of selected N-aryl triazoles: samples were measured in CH_3OH, c = 10 μM; λ_{ex} = 254 nm.

with aryl iodide was observed and optimal condition allowed the formation of N-2 aryl products in excellent yields. Alternative approaches, including S_NAr and boronic acid transmetalations, had also been proved effective with excellent regioselectivity. Moreover, the newly prepared N-2 aryl products gave interesting photonic luminescent emission, which re-emphasized the significance of the N-2-aryl-triazoles and reported methodologies. Considering the extremely fast growth of the 1,2,3-triazole related research, we believe that the reported synthesis and photonic investigation will benefit the researchers in various fields.

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Supporting Information Available: Experimental details, spectrographic data, and XRD information. This material is available free of charge via the Internet at http://pubs.acs.org.

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(13) Me-Gly: *N*-methyl glycine; DMG: *N*,*N*-dimethyl glycine; EDA: ethylenediamine; DMEDA: *N*,*N*′-dimethylethylenediamine; TMEDA: *N*,*N*,*N*′,*N*′-tetramethylethylenediamine; DACH: trans-diaminocyclohexane.

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