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Iron-Catalyzed C−O Bond Activation for the Synthesis of Propargyl-1,2,3-triazoles and 1,1-Bis-triazoles

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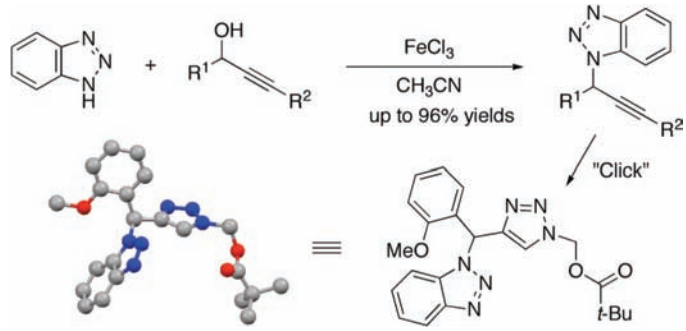
ABSTRACT



The $FeCl_3$-catalyzed triazole propargylation was developed. This transformation was suitable for a large scope of substituted propargyl alcohols, giving the corresponding propargyl triazoles in excellent yields (up to 96%). Further derivatization produced the 1,1-bis-triazoles in excellent yields and regioselectivity, which could be applied as potential transition metal ligands or new reagents.

Since the discovery of "click chemistry" at the beginning of this century,[1] 1,2,3-triazoles have become one of the most important heterocycles in medicinal,[2] material,[3] and biological[4] research. Comparing with the application as a highly efficient linkage strategy that dominated the early stage of 1,2,3-triazole research, recent efforts have been aimed at the investigation of the chemical and biological properties of this unique heterocycle.[5] Significant progress

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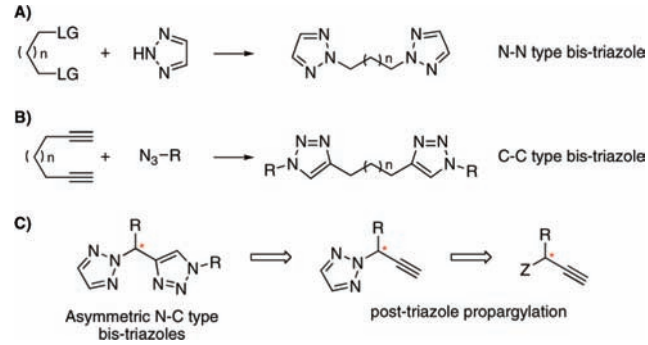
occurred in applying triazole building blocks as either bioactive components in drug discovery or special functional groups in new materials synthesis.[6] Recently, several interesting studies that utilized 1,2,3-triazoles as ligands in transition metal catalysis have been reported.[7,8] The fast growing research applications of this heterocycle necessitate the development of effective methods for the preparation of diverse 1,2,3-triazole derivatives. Herein, we report the successful use of Fe(III)-catalyzed C−O bond activation as an efficient strategy in post-triazole propargylation and its application for the preparation of asymmetric N−C type 1,1-bis-triazole compounds.

Our interest in studying 1,2,3-triazole compounds was initiated by the recent success of Lewis base-catalyzed nitroalkene activation.[9] With this method, various 4,5-disubstituted NH-triazoles were prepared in good yields.[10] Moreover, the post-triazole N-2 functionalization was developed,[11] where alkylation, arylation, and vinylation of 1,2,3-triazoles have been successfully achieved with good yields and regioselectivity.

During the last two years, our group has been working on the investigation of 1,2,3-triazole derivatives as ligands in transition metal catalysis.[8] These triazole compounds have shown significant influence on the metal catalyst reactivity by serving as effective nitrogen σ-donor. To further extend our studies of triazole-metal coordination, we aimed at the bis-triazole compounds as potential interesting bidentate ligands to coordinate with transition metal cations. Considering the substitution pattern, the bis-triazole compounds could be summarized as three different classes: N−N type,[12] C−C type,[13] and N−C type (Scheme 1).

Scheme 1. Three Different Types of Bis-triazole Compounds



While the N−N and C−C type bis-triazoles have been successfully synthesized from either post-triazole alkylation[11a] or click chemistry (Scheme 1, A and B), the N−C type bis-triazoles have not been reported. These unsymmetrical N−C type bis-triazoles, especially the 1,1-bis-triazoles, are particularly interesting because of the presence of the stereocenter. A brief synthetic design of this type of compounds is shown in Scheme 1C, where the two triazole moieties are introduced by click chemistry and post-triazole propargylation sequentially. Although the retrosynthesis design looked straightforward, the actual preparation was much more challenging than we expected (*vide infra*), especially the post-triazole propargylation.

In general, the propargylation could be challenging since the nucleophiles would potentially attack the propargyl position as well as the triple bonds, to give corresponding allene intermediates that further convert into other products (such as Meyer−Schuster rearrangement).[14,15] Therefore, the performance of this transformation usually depends on the nature of the substrates (i.e., the stability of leaving groups and steric hindrance of alkynes). With simple propargyl bromide **2a**, effective triazole propargylation could be achieved in excellent yields (Scheme 2A). However, the direct substitution failed to work for substituted alkynes. For example, reaction between triazole **1a** and propargyl acetate **2b** gave no reaction with Cs_2CO_3 as the base. Treating the substrates under harsher conditions (DMSO and strong base) led to the formation of complex reaction mixtures with no desired propargyl triazole **3b** observed (Scheme 2B). Moreover, attempts in converting propargyl alcohol **4a** into

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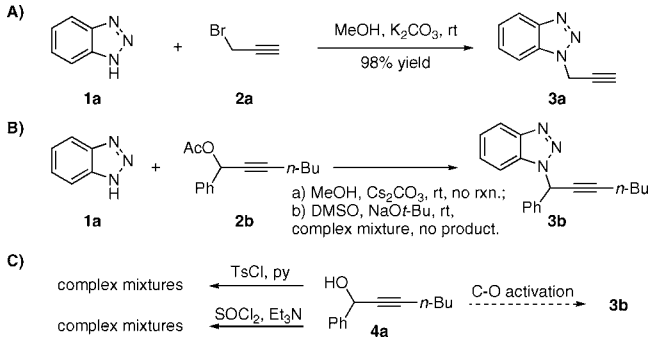
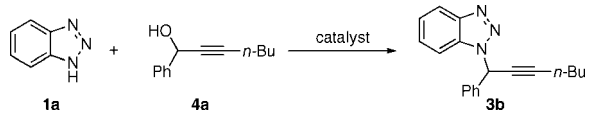
Scheme 2. Challenges in Triazole Propargylation



propargyl tolsylate or halide also failed, which was likely caused by the undesired side reactions associated with propargyl carbon cations.

We therefore deduced that one practical synthesis of propargyl triazoles could likely occur from the effective C−O bond activation of a propargyl alcohol (Scheme 2C). A series of different commonly used Lewis acid catalysts were then investigated in promoting the propargylation of triazole **1a** and propargyl alcohol **4a**. The results are summarized in Table 1. Although significant decomposition of **4a** occurred with most of the Lewis acid catalysts, we observed that $FeCl_3$ was an effective catalyst in promoting this transformation and gave the desired product **3b** in good yield (entry 1). Further screening revealed MeCN as the optimal solvent (entries 14−20) and effective conversion was accomplished even with decreased catalyst loading (entries 23 and 24). With this optimal condition in hand, different triazoles and propargyl alcohols were evaluated to investigate the reaction substrate scope. The results are shown in Figure 1.

Table 1. Catalyst Screening[a]



	catalyst	loading (%)	solvn	temp (°C)	time (h)	convn (%)[b]	yield (%)[c]	N1:N2[c]
1	$FeCl_3$	20	DCE	60	17	100	90	8:1
2	$Cu(OAc)_2$	20	DCE	60	17	57	<5	
3	CuI	20	DCE	60	17	22	<5	
4	$PdCl_2$	20	DCE	60	17	13	<5	
5	$RuCl_3$	20	DCE	60	17	69	49	1.1:1
6	$IrCl_3$	20	DCE	60	17	96	65	2:1
7	$Co(OAc)_2$	20	DCE	60	17	28	<5	
8	$LaCl_3$	20	DCE	60	17	21	<5	
9	$CeCl_3$	20	DCE	60	17	30	<5	
10	$Ti(O\text{-}iPr)_4$	20	DCE	60	17	52	<5	
11	$AlCl_3$	20	DCE	60	17	26	<5	
12	TfOH	20	DCE	60	17	100	35	1.5:1
13	H_3PO_4	20	DCE	60	17	73	9	1:1
14	$FeCl_3$	20	THF	60	7	90	70	6:1
15	$FeCl_3$	20	Toluene	60	7	100	40	2:1
16	$FeCl_3$	20	MeOH	60	7	60	44	7:1
17	$FeCl_3$	20	$MeNO_2$	60	7	90	<5	
18	$FeCl_3$	20	DMF	60	7	<5	<5	
19	$FeCl_3$	20	DMSO	60	7	<5	<5	
20	$FeCl_3$	20	MeCN	60	7	91	85	10:1
21	$FeCl_3$	20	MeCN	rt	12	62	50	9:1
22	$FeCl_3$	20	MeCN	90	5	100	93	11:1
23	$FeCl_3$	10	MeCN	90	10	100	90	10:1
24	$FeCl_3$	5	MeCN	90	12	90	82	9:1

[a] Standard reaction condition: 1 equiv of propargyl alcohols, 1.2 equiv of triazoles, and 0.2 equiv of catalyst were mixed in corresponding solvents. [b] Conversions were determined based on the consumption of **4a**. [c] Yields determined by NMR with 1,3,5-trimethoxybenzene as internal standard, and ratios determined by NMR of crude reaction mixtures.

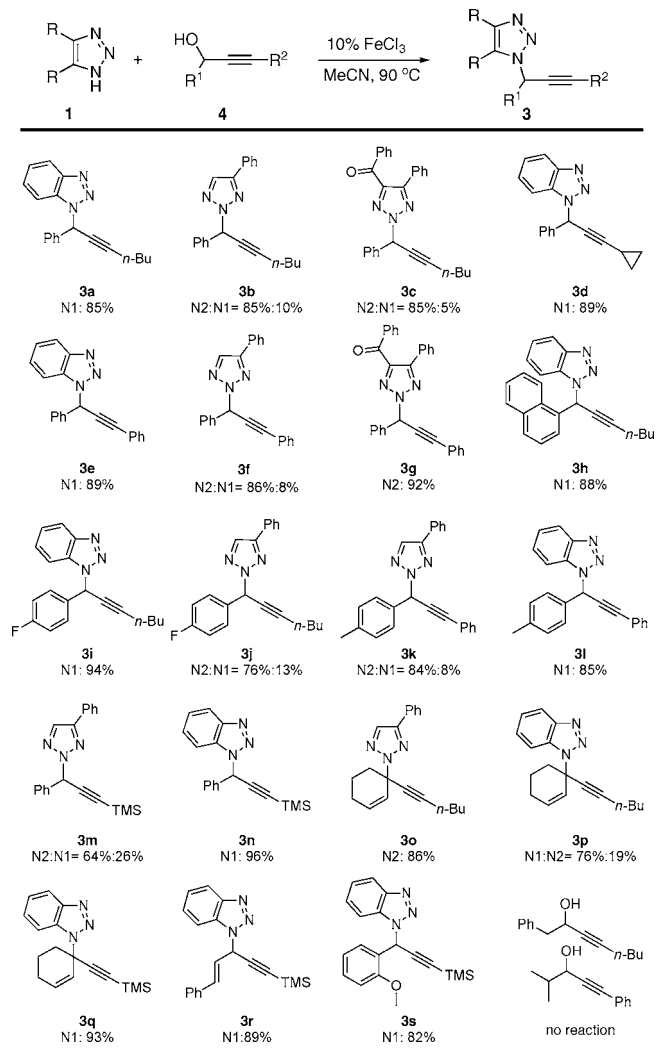


Figure 1. Reaction substrate scope. Yields were determined by NMR with 1,3,5-trimethoxybenzene as internal standard, and ratios determined by NMR of crude reaction mixtures. The N-2 **3f** structure was confirmed by X-ray crystallography.

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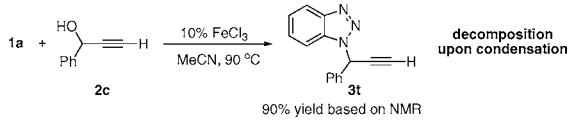
As shown in Figure 1, this Fe(III)-catalyzed propargylation was suitable for various different propargyl alcohols, which further enriched the available methods for effective post-triazole functionalization. Similar to our previously reported strategy,[11a] the regioselectivity of 1,2,3-triazole strongly depends on the nature of triazole substrates. For example, the benzotriazole gave N-1 substitutions and dominant N-2 isomers were obtained when keto-modified 4,5-disubstituted triazoles were applied (i.e., **3c**, **3g**). Meanwhile, the C-4 phenyl triazole gave a mixture of both N-1 and N-2 isomers with roughly 4:1 ratio, favoring the N-2 isomer.

The substituted groups on the propargyl position were critical for this transformation. The reaction generally worked well with aromatic substituted propargyl alcohols, except substrates with strong electron withdrawing groups (the *p*-nitrobenzene gave no reaction). No reactions were observed with aliphatic substituted propargyl alcohols. Impressively, the reaction proceeded smoothly with vinyl-substituted substrate (such as **3r**), giving the corresponding triazole substituted enynes in excellent yields. Notably, Nazarov cyclization products were not observed in these reactions, which highlighted the rather mild conditions of the reported method.

Excellent yields were generally received for internal alkynes with different substituted groups, including alkyl, aryl, TMS, and cyclopropyl. The reaction was also suitable for terminal alkyne and gave the corresponding propargyl triazoles in good yields based on NMR (Scheme 3).

Scheme 3. Unexpected Decomposition of Terminal Alkyne Substrates



Surprisingly, these substrates were not stable upon concentration and gave complex reaction mixtures. This interesting transformation is currently under investigation.

The unexpected decomposition of terminal alkyne **3t** raised serious concerns regarding the designated click chemistry for the introduction of the second triazole rings. Fortunately, the reactions between TMS-alkynes and corresponding azides gave the desired bis-triazoles (**5a**−**h**) without the TMS deprotection step in excellent yields under standard "click chemistry" condition (Figure 2).[16]

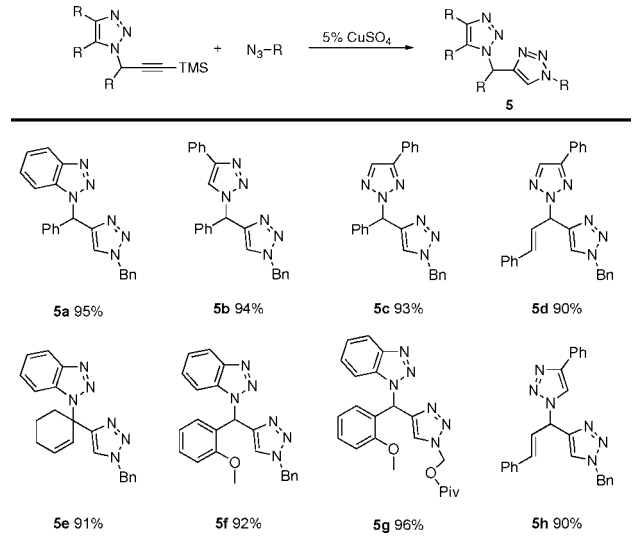


Figure 2. Synthesis of unsymmetrical N−C type bis-triazoles. Isolated yields for all cases. Condition: 0.05 equiv of $CuSO_4$, 0.1 equiv of sodium ascorbate, *t*-BuOH-H_2O (1:1), rt, 12 h. Structure **5g** was confirmed by X-ray crystallography.

In conclusion, a highly efficient $FeCl_3$-catalyzed post-triazole propargylation was developed, giving the desired propargyl triazole in excellent yields. Application of this strategy led to the synthesis of unsymmetrical 1,1-bis-triazoles. This study not only gave another efficient post-triazole functionalization strategy for the preparation of diverse triazole analogues, but also provided entry to a new class of bis-triazole compounds as bidentate ligands. Application of these bis-triazole ligands in transition metal coordination is currently under development in our group.

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Note Added after ASAP Publication. Some yields were missing from Figure 2 in the version published ASAP July 9, 2010; the correct version reposted on July 13, 2010.

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

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