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Highly efficient synthesis of vinyl substituted triazoles by Au(I) catalyzed alkyne activation

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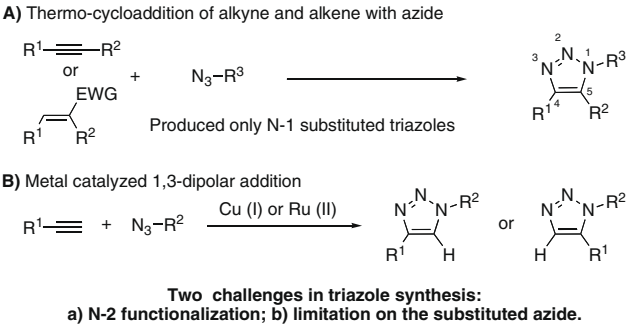
ABSTRACT

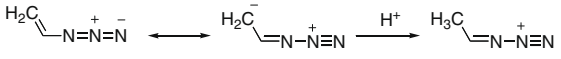
Au(I) catalyzed 1,2,3-triazole addition to non-activated alkyne was reported. A large group of substituted NH-1,2,3-triazoles were suitable for this transformation along with both internal and terminal alkynes. The N-1 and N-2 vinyl substituted 1,2,3-triazoles were prepared in up to 98% yield with as low as 0.2% catalyst loading, thereby providing a new protocol for the synthesis of potentially biological-active vinyl-triazole building blocks.

With the discovery of the Cu-catalyzed azide-alkyne 1,3-dipolar cycloaddition (CuAAC, often referred as 'click-chemistry') at the beginning of this century, 1,2,3-triazoles have become one of the most important heterocycles in chemical and biological researches.[1] Within the last five years, the importance of this heterocyclic building block has been continuously demonstrated in research fields from material science[2] and chemical biology[3] to medicinal chemistry.[4] Suggested by the numerous reports in literature, one great advantage of the 1,2,3-triazoles is its bio-compatibility, which allowed the application of click chemistry in both in vitro and in vivo studies.[5] Compared to the dominant studies regarding the application of the CuAAC reaction as a biocompatible coupling strategy, recently, more efforts have been focused on the investigation of the triazole motif itself as a biologically active building block for new drug discovery. Therefore, a significant growing need was generated for effective synthetic methods in preparing diverse functionalized triazole analogues.

As one extremely efficient synthetic method, the Cu catalyzed 'click chemistry' possesses some potential limitation: (a) with the application of substituted azides, the CuAAC gives N-1 substituted triazoles as the dominant products; (b) the usage of the substituted azide makes the products heavily rely on the availability of alkyl/aryl azides. Recently, Sharpless and Fokin reported the effective synthesis of N-2 alkyl triazole through substitutent dynamic equilibrium.[6] Meanwhile, our group reported the regio-selective N-2 alkylation[7] and arylation[8] through post NH-triazole functionalization. Herein, we report the Au(I) catalyzed NH-triazole addition to alkynes with excellent yields and stereoselectivity (trans-addition). To the best of our knowledge, this is the first successful example in achieving vinyl substituted 1,2,3-triazoles through alkyne addition, which will surely benefit medicinal chemistry researches that targets the application of 1,2,3-triazole building blocks as potential drug candidates.



Scheme 1. General approach in the preparation of 1,2,3-triazoles.



Scheme 2. Vinyl azide: challenging substrate for dipolar cycloaddition due to the existence of equilibrium.

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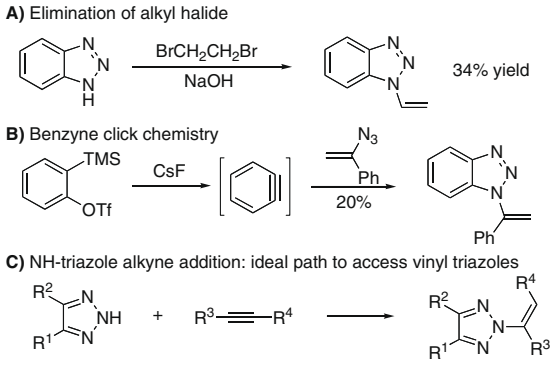
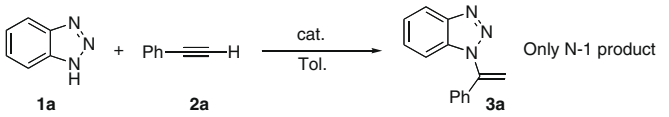


Scheme 3. Synthesis of vinyl triazole.

As indicated in Scheme 1, the two most general approaches in the preparation of 1,2,3-triazoles are the cycloaddition of alkyne/alkene with substituted azides through either thermo condition or metal catalyzed 1,3-dipolar additions. Although the metal catalyzed dipolar addition significantly improved the reaction efficiency, giving the N-1 substituted triazoles in excellent yields, one challenge in this approach is the limitation on the substituted azides. For example, the metal catalyzed dipolar addition between alkynes and vinyl-substituted azides has never been reported in literature,[9] possibly due to the poor stability (high energy material) and existence of different resonance structures (Scheme 2). As a result, the preparation of vinyl-triazole was very challenging.

Driven by the growing interest in triazole research, some methods regarding the synthesis of vinyl-triazoles have been recently reported. The two most general methods reported in literature were through the elimination of alkyl halide[10] and the cyclization of vinyl azides with highly reactive benzyne intermediate[11] (Scheme 3).

Table 1
Screening of catalyst for triazole-alkyne addition[a]



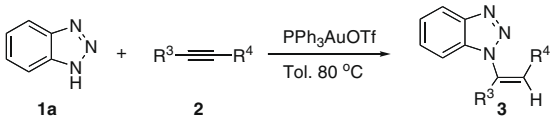
1a 2a 3a

	Catalyst	Loading (%)	Temp (°C)	Time (h)	Yields[b] (%)
1	AuCl	5	80	6	82
2	$AuCl_3$	5	80	6	88
3	PPh_3AuOTf	5	rt	12	15
4	PPh_3AuOTf	5	50	20	60
5	PPh_3AuOTf	5	80	5	>99%
6	PPh_3AuOTf	1	80	6	96
7	PPh_3AuOTf	0.2	80	12	92
8	CuI	5	80	12	N.R.
9	$Cu(OAc)_2$	5	80	12	N.R.
10	$Sc(OTf)_2$	5	80	12	<5%
11	HOTf	5	80	12	10
12	$In(OTf)_3$	5	80	12	68%
13	$La(OTf)_3$	5	80	12	N.R.
14	AgOTf	5	80	12	20
15	$Pd(OAc)_2$	5	80	12	N.R.

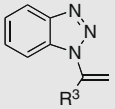
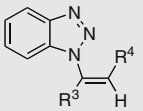
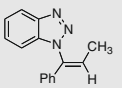
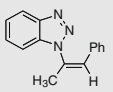
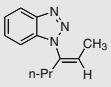
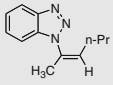
[a] Reactions were carried out by dissolving **1a** (1.0 equiv), **2a** (1.5 equiv) and catalyst in toluene (0.2 M).
[b] Determined by NMR.

For the elimination approach, significant amounts of bis-triazole byproducts were usually formed and the substrate scope was very limited. The benzyne click chemistry provided an interesting alternative strategy in preparing triazoles, however, again, vinyl azides suffered from poor yields and limited substrate scope. Therefore, efficient synthetic routes to access vinyl-triazoles are highly desirable. Considering the strong nucleophilicity of NH-triazole, and more importantly, the easy access to this building block based on our recently reported cascade synthesis,[12] we wondered whether the NH-triazole alkyne addition could be achieved as a new strategy

Table 2
Substituted scope of alkynes in the Au(I) catalyzed triazole addition[a]

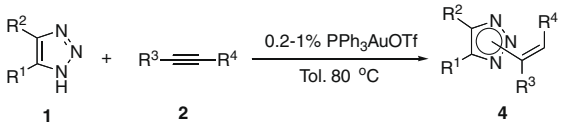


1a 2 3

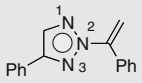
Alkyne	Product		Cat. (%)	Time (h)	Yield[b] (%)
p-Me-Ph—≡—H *p*-F-Ph—≡—H n-Bu—≡—H		**3b**: R^3 = *p*-Me-Ph **3c**: R^3 = *p*-F-Ph **3d**: R^3 = *n*-Bu	0.2 0.2 0.2	12 10 12	94 96 90
Ph—≡—Ph n-Pr—≡—n-Pr TMS—≡—CH_3		**3e**: $R^3 = R^4$ = Ph **3f**: $R^3 = R^4$ = *n*-Pr **3g**: R^3 = CH_3, R^4 = H	1.0 1.0 1.0	30 20 12	70 83 82
Ph—≡—CH_3	 **3h:** 1:1 of the two regio isomer		1.0	20	84
n-Pr—≡—CH_3	 **3i:** 1:1 of the two regio isomer		1.0	20	81

[a] Reactions were carried out by dissolving **1a** (1.0 equiv), **2** (1.5 equiv) and PPh_3AuOTf in toluene (0.2 M) and heating at 80 °C.
[b] Isolated yields.

Table 3
Substituted scope of different NH-triazoles[a]

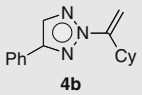


1 2 4



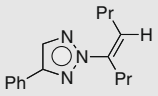
4a

0.2% cat., 91% yield N1:N2:N3 = 22:78:0[b]



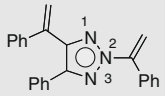
4b

0.2% cat., 87% yield N1:N2:N3 = 20:80:0



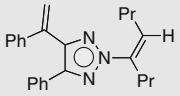
4c

1.0% cat., 81% yield N1:N2:N3 = 18:82:0



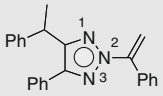
4d

0.2% cat., 90% yield N1:N2:N3 = 24:71:5



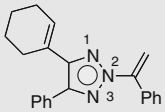
4e

1.0% cat., 85% yield N1:N2:N3 = 22:78:0



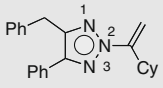
4f

0.2% cat., 88% yield N1:N2:N3 = 20:80:0



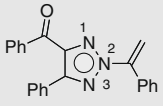
4g

0.2% cat., 87% yield N1:N2:N3 = 29:71:0



4h

0.2% cat., 93% yield N1:N2:N3 = 18:82:0



4i

0.2% cat., 84% yield N1:N2:N3 = 0:100:0

[a] Reactions were carried out by dissolving **1a** (1.0 equiv), **2** (1.5 equiv) and PPh_3AuOTf in toluene (0.2 M) and heating at 80 °C.
[b] Ratio of the products were determined by NMR.

for the synthesis of vinyl triazoles with high efficiency and a much better substrate scope. The reaction between benzotriazole **1a** and terminal alkyne **1b** were then performed in the presence of various promoters. The results are summarized in Table 1.

Reaction at room temperature gave either very low yields or no reaction at all for all catalysts tested due to the slow reaction rate or lack of reactivity. By increasing the reaction temperature, the Au complexes were identified as the best catalysts in activating the alkyne. With 5% loading of PPh_3AuOTf at 80 °C, the desired vinyl triazole **3a** was obtained in quantitative yield (entry 5). The reaction gave excellent regio selectivity, where, only the N-1 substituted Markovnikov's product was observed. Although some other catalysts, such as $In(OTf)_3$, indicated modest reactivity, the superior efficiency of the Au(I) catalysts made them an ideal catalytic system for this transformation. Different alkynes were then applied to the reaction to investigate the substrate scope. The results are summarized in Table 2.

As indicated in Table 2, the transformation was suitable for a variety of substituted alkynes. The terminal alkynes gave higher than 90% yields of only the Markovnikov's products even with only 0.2% catalyst loading. Impressively, the reaction also worked very well with internal alkynes, which are usually challenging substrates to be activated by metal catalysts. With 1% catalyst loading, the desired addition products were prepared in good yields. Notably, although the regio-selectivity of the asymmetric alkynes was poor (**3h**, **3i**), the reaction reached excellent double-bond selectivity and *only the trans addition products were formed* in all cases. The double-bond stereochemistry was confirmed by NOE experiments. Meanwhile, both alkyl and aryl substituted alkynes were suitable for this reaction. With this highly efficient catalytic triazole addition strategy, we then investigated the N-selectivity with different NH-triazoles as shown in Table 3.

As shown in Table 3, all NH-triazoles are suitable for this reaction, giving the alkyne addition products in excellent yields. Only trans additions were observed, giving exclusive single double-bond isomers. The substituents on the triazoles showed a strong influence on the N-regio-selectivity, where most C-4-phenyl substituted triazoles gave N-2 isomers as the major products. Increasing the steric hindrance on the C-4 and C-5 position did not show a dramatic difference towards the regio-selectivity. However, application of carbonyl-substituted NH-triazole led to the formation of a single N-2 isomer, similar to the results that we reported recently regarding the post N-2 alkylation[7] and N-2 arylation[8] of NH-triazoles. Considering the great efficiency, excellent stereo-selectivity of double bonds, broad substrate scope and controllable triazole nitrogen regio selectivity, it is our belief that the reported method would provide a good strategy for the preparation of various vinyl-triazoles and thereby benefiting researches involving 1,2,3-triazoles as building blocks.

Acknowledgements

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Supplementary data

Detailed experimental procedures and spectral data for all new compounds are provided. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.bmcl.2009.03.096.

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