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N-2-Selective gold-catalyzed alkylation of 1-sulfonyl-1,2,3-triazoles†

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An efficient new method was developed to synthesise *N*-2-alkyl-1,2,3-triazoles via gold catalyzed alkylation of 1-sulfonyl-1,2,3-triazoles with vinyl ethers. Only *N*-2-isomers were obtained in these reactions. The sulfonyl group in the 1-sulfonyl-1,2,3-triazoles acted as the leaving group, which was trapped by H₂O in this reaction.

1,2,3-Triazoles have found widespread applications in biological science,¹ material science² and medicinal chemistry.³ More recently, they also have been utilized as ligands in transition-metal coordination,⁴ and this catalytic system provided an efficient strategy for many challenging transformations.⁵ Because of the importance of this structural motif, many practical synthetic methods have been developed. Both thermal and Cu(I)/Ru(II)-catalyzed condensations of alkynes and azides provide an excellent approach to *N*-1/*N*-3-substituted triazoles,⁶ whereas the regioselective synthesis of *N*-2-substituted 1,2,3-triazoles remains a challenging issue. Considerable recent efforts have been made toward the preparation of *N*-2-aryl⁷ and *N*-2-allyl-1,2,3-triazoles⁸ with high *N*-2-selectivity. Despite these achievements, however, a general method for the preparation of *N*-2-alkyl-1,2,3-triazoles is lacking.

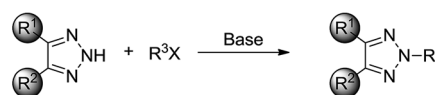
The current main approach to *N*-2-alkyl-1,2,3-triazoles by the conversion of alkyl halides with bulky C-4- and C-5-disubstituted NH-1,2,3-triazoles limits its broader utility by the substrate's steric requirements (Scheme 1a).⁹ Recently, Chen's group reported a highly regioselective *N*-2 alkylation of NH-1,2,3-triazoles through NIS-mediated iodofunctionalization with olefins (Scheme 1b, eqn (1)).^{10a} Our interest in developing a new strategy for the synthesis of *N*-2-alkyl-1,2,3-triazoles was initiated by the recent success of TsOH mediated addition of 1-sulfonyl-1,2,3-triazole to olefins (Scheme 1b, eqn (2)).^{10b} This new strategy incorporated a labile *N*-1-substituent and the mechanism was based on a carbocation intermediate. Based on these results, we want to expand this reaction to metal catalyzed transformation.

The activation of unsaturated C–C bonds by gold complexes has led to a range of attractive and useful strategies for a variety of organic transformations due to their low toxicity and increased stability to moisture and air,¹¹ whereas employing 1-sulfonyl-1,2,3-triazoles as the nucleophiles in gold catalyzed

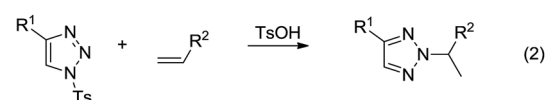
olefins conversion has never been explored before. In the previous studies, *N*-2-alkyl-substituted triazole derivatives possess a broad spectrum of antiherpetic, antiarrhythmic and antiviral activities.¹² Therefore, efficient synthetic methods for the synthesis of *N*-2-alkyl triazoles are highly desirable. In this paper, we will report the first example of gold-catalyzed *N*-2 alkylation of 1-sulfonyl-1,2,3-triazoles with electronic-rich vinyl ethers (Scheme 1c).

The initial experiments were performed with 4-phenyl-1-sulfonyl-1,2,3-triazole **1a** and vinyl ether **2a** in the presence of IPrAuCl (5 mol%) and AgOTf (5 mol%) in 1,2-dichloroethane (DCE) at 80 °C. To our delight, the desired *N*-2-alkyl-1,2,3-triazole **3a** was obtained in 53% yield and no *N*-1-coupling adduct was detected (Table 1, entry 1). In order to optimize the reaction condition, silver salts screening was first performed, in which, IPrAuCl/AgNTf₂ was found to be the best silver combination (Table 1, entry 2). The catalyst's ligands were then evaluated.

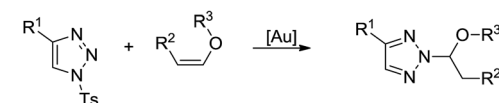
(a) Shi and Wang group: Bulky groups on C-4 and C-5 directed *N*-2 alkylation. [9]



(b) Chen group: NIS/TsOH mediated *N*-2 alkylation. [10]



(c) This work: gold catalyzed *N*-2 alkylation.

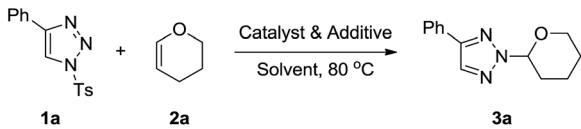


Scheme 1 Strategy for selective *N*-2 alkylation.

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Table 1 Screening of the optimal conditions^a


Entry	Catalyst (mol%)	Solv./additive (equiv.)	Time (h)	Yield ^b (%)
1	IPrAuCl/AgOTf (5)	DCE	6.5	53
2	IPrAuCl/AgNTf ₂ (5)	DCE	6.5	61
3	IPrAuCl/AgSbF ₆ (5)	DCE	6.5	39
4	Ph ₃ PAuCl/AgNTf ₂ (5)	DCE	6	32
5	JohnphosAuCl/AgNTf ₂ (5)	DCE	6	14
6	IPrAuCl/AgNTf ₂ (5)	DCE/H ₂ O (2)	6	98
7	IPrAuCl/AgNTf ₂ (5)	THF/H ₂ O (2)	6.5	17
8	IPrAuCl/AgNTf ₂ (5)	CHCl ₃ /H ₂ O (2)	6.5	45
9	IPrAuCl/AgNTf ₂ (5)	Toluene/H ₂ O (2)	24	NR
10	IPrAuCl/AgNTf ₂ (5)	DCM/H ₂ O (2)	10	56
11 ^c	IPrAuCl/AgNTf ₂ (5)	DCE/H ₂ O (2)	6	51
12	IPrAuCl/AgNTf ₂ (2)	DCE/H ₂ O (2)	8	47
13 ^d	IPrAuCl/AgNTf ₂ (5)	DCE	24	NR
14	IPrAuCl (5)	DCE/H ₂ O (2)	24	NR
15	AgNTf ₂ (5)	DCE/H ₂ O (2)	24	NR

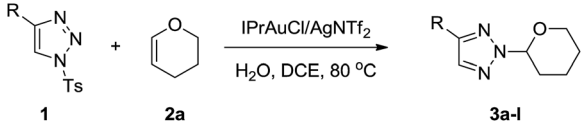
^a Unless noted, all reactions were carried out at 0.5 mmol scale in 3 mL of solvent with the addition of 5 mol% catalyst at 80 °C (1a/2a) = 1/5.

^b Isolated yields. ^c 3 equiv. of compound 2a were added. ^d 100 mg 4 Å MS was added.

With Ph₃PAuCl only half of the yield was obtained while JohnphosAuCl was not favored for this transformation, affording 3a in only 14% yield after 6 h (Table 1, entries 4, 5). According to the previous report of Chen's group,^{10b} the trace amount of water is auxiliary to capture the leaving Ts group. Therefore, 2 equiv. of water was added to the reaction and 3a's yield was improved to 98% (Table 1, entry 6). Further solvent optimization identified DCE to be the best reaction medium (Table 1, entry 6). Variation of the number of equivalents of 2a from 5.0 to 3.0 lowered the conversion of 3a to 51% (Table 1, entry 11), which indicates that the excess of vinyl ether probably is necessary due to the high tendency of vinyl ethers to undergo cationic polymerization initiated by gold(I).¹³ Reducing the catalyst loading to 2 mol% led to a reduced reaction yield to 47% after 8 hours (Table 1, entry 12). Addition of 4 Å molecular sieves to remove the residual moisture inhibited this reaction which indicated that H₂O was necessary for this N-2 alkylation reaction (Table 1, entry 13). The control experiments employing IPrAuCl and AgNTf₂ separately gave no desired products (Table 1, entries 14, 15).

With the optimized reaction conditions in hand, we examined the scope of this transformation by synthesizing a series of N-2-alkyl-1,2,3-triazoles. As shown in Table 2, various 4-aryl-substituted 1-sulfonyl-1,2,3-triazoles were explored by using vinyl ether 2a as the reactants. First, 4-phenyl-substituted 1-sulfonyl-1,2,3-triazole 1a could afford the desired N-2-alkyl-1,2,3-triazole 3a in 98% yield. 4-Alkyl and 4-methoxy phenyl substituted 1-sulfonyl-1,2,3-triazoles gave 3b–e in 74–91% yield (Table 2, entries 2–5). 4-Halogen phenyl substituted 1-sulfonyl-1,2,3-triazoles were also well tolerated, although 4-bromo phenyl substituted 1-sulfonyl-1,2,3-triazole 1g gave the corresponding

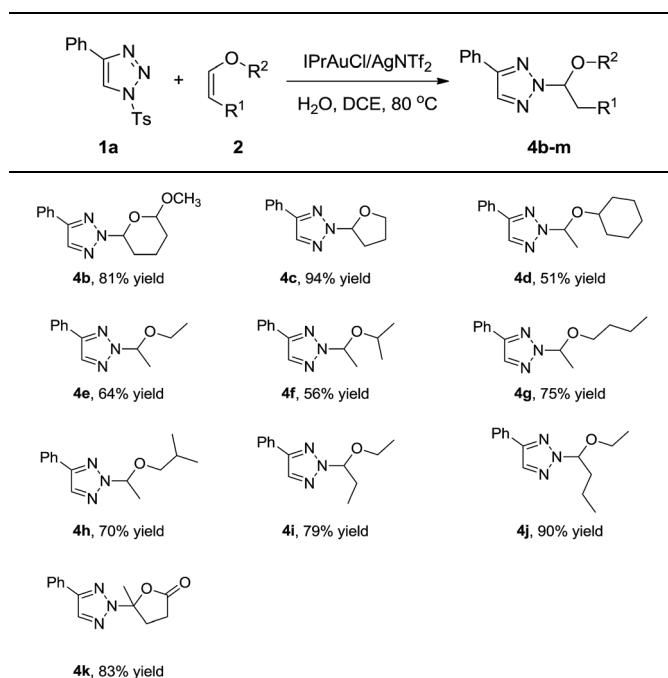
product 3g in 57% yield (Table 2, entries 6–8). 2-Fluoro and 3-fluoro phenyl substituted 1-sulfonyl-1,2,3-triazoles were also tested, giving 3i and 3j in 73% and 87% yield, respectively (Table 2, entries 9 and 10). The reaction of 2-thienyl and 3-thienyl substituted 1-sulfonyl-1,2,3-triazoles 1k and 1l went smoothly,

Table 2 Substrate scope of 1-sulfonyl-1,2,3-triazoles (1)^a


Entry	Substrate 1	R	Product 3	Yield ^b (%)
1	1a	Phenyl	3a	98
2	1b	4-MeC ₆ H ₄	3b	74
3	1c	4-PrC ₆ H ₄	3c	84
4	1d	4- ^t BuC ₆ H ₄	3d	86
5	1e	4-MeOC ₆ H ₄	3e	91
6	1f	4-ClC ₆ H ₄	3f	77
7	1g	4-BrC ₆ H ₄	3g	57
8	1h	4-FC ₆ H ₄	3h	99
9	1i	2-FC ₆ H ₄	3i	73
10	1j	3-FC ₆ H ₄	3j	87
11	1k	2-Thienyl	3k	63
12	1l	3-Thienyl	3l	70
13	1m	ⁿ Bu	3m	0
14	1n	Cyclopentyl	3n	0

^a Reaction conditions: 1 (0.5 mmol), 2a (2.5 mmol), H₂O (1 mmol), IPrAuCl/AgNTf₂ (5 mol%), DCE (3 mL), 80 °C. ^b Yield of isolated product.

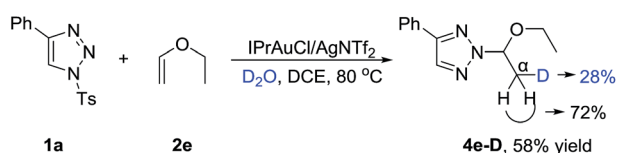


Table 3 Substrate scope of vinyl ether (2)^a

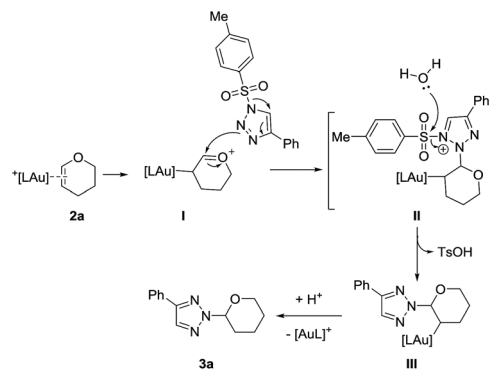
^a Reaction conditions: **1a** (0.5 mmol), **2** (2.5 mmol), H₂O (1 mmol), IPrAuCl/AgNTf₂ (5 mol%), DCE (3 mL), 80 °C.

affording **3k** and **3l** in moderate yields (Table 2, entries 11 and 12). However, no conversion was observed for 4-alkyl-substituted 1-sulfonyl-1,2,3-triazoles, probably owing to the alkyl substituent can't stabilize the intermediate **II** in Scheme 3 (Table 2, entries 13 and 14). Then, *N*-2-alkyl reactions of 4-phenyl-substituted 1-sulfonyl-1,2,3-triazole **1a** with various vinyl ether were explored. As shown in Table 3, cyclic vinyl ethers worked very well. 2-Methoxy-3,4-dihydro-2*H*-pyran **2b** gave **4b** in 81% yield, while 2,3-dihydrofuran **2c** afforded **4c** in 94% yield. Next, we investigated the linear vinyl ether's reactions. We found that mono-substituted and 1,2-disubstituted linear vinyl ether could be employed in this reaction and gave the desired products in moderate to good yields. Moreover, this reaction was also efficient with alpha-angelica lactone, giving **4k** in 83% yield. The structure of **4k** was determined according to the literature of Chen.^{10b} However, 1,1-disubstituted vinyl ether **2l**, styrene **2m**, 4-*tert*-butyl substituted styrene **2n** did not work in this transformation may be due to the larger steric effects and lower complexation with gold(I).

To gain more insight into the mechanism of this reaction, deuterium-labeling experiments were conducted. When H₂O



Scheme 2 Deuterium-labeling experiments.



Scheme 3 Proposed reaction mechanism.

was replaced by 2.0 equiv. of D₂O in the model reaction, the *N*-2-alkyl-1,2,3-triazole product **4e-D** was isolated in 58% yield. The incorporation of deuterium at the α-position of **4e-D** in a 28% ratio suggested that H₂O was necessary for this *N*-2 alkylation reaction (Scheme 2).¹⁴ The incorporation of deuterium at the α-position of **4e-D** was lowered in 5% yield may be due to the trace amount of water in the reaction system.

On the basis of previous work^{10b} and our deuterium-labeling experiments, a plausible¹⁵ catalytic cycle is proposed in Scheme 3. Complexation of the cationic gold catalyst with vinyl ether **2a** generated intermediate **I**, which is then attacked by the internal nitrogen of the 1-sulfonyl-1,2,3-triazole substrate **1a** to give the intermediate **II**. Then the activated sulfur–N bond is hydrolyzed to form the alkyl gold intermediate **III**, which subsequently undergoes protodeauration¹⁶ to give the final *N*-2-alkyl-1,2,3-triazole **3a** and regenerated the cationic gold catalyst.

In summary, a highly efficient gold-catalyzed *N*-2-selective alkylation was developed, giving the desired *N*-2-alkyl-1,2,3-triazoles in good yields. The sulfonyl group in the 1-sulfonyl-1,2,3-triazoles acted as the leaving group, which was trapped by H₂O in this reaction. Notably, only *N*-2-isomers were obtained in these reactions. With the continuously growing interest in *N*-2-substituted 1,2,3-triazoles, we are currently studying the *N*-2-selective arylation, alkenylation, and allylation using this strategy and the results will be reported in due course.

Acknowledgements

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