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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.

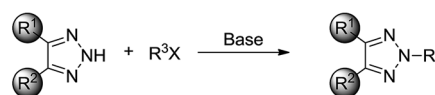
The current main approach to *N*-2-alkyl-1,2,3-triazoles by the conversion of alkyl halides with bulky C-4- and C-5-disubstituted NH-1,2,3-triazoles limits its broader utility by the substrate's steric requirements (Scheme 1a).⁹ Recently, Chen's group reported a highly regioselective *N*-2 alkylation 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

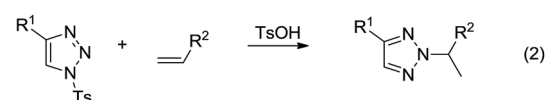
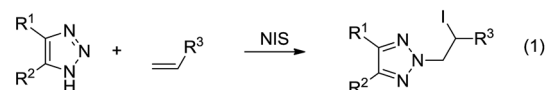
olefins conversion has never been explored before. In the previous studies, *N*-2-alkyl-substituted triazole derivatives possess a broad spectrum of antiherpetic, antiarrhythmic and antiviral activities.¹² Therefore, efficient synthetic methods for the synthesis of *N*-2-alkyl triazoles are highly desirable. 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.

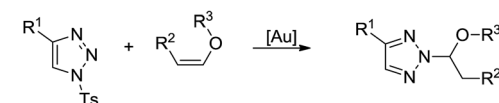
(a) Shi and Wang group: Bulky groups on C-4 and C-5 directed *N*-2 alkylation. [9]



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



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

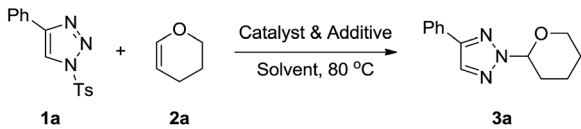


Scheme 1 Strategy for selective *N*-2 alkylation.

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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 |

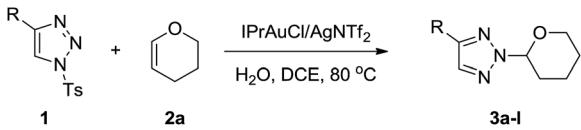
^a Unless noted, all reactions were carried out at 0.5 mmol scale in 3 mL of solvent with the addition of 5 mol% catalyst at 80 °C (**1a/2a**) = 1/5.

^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

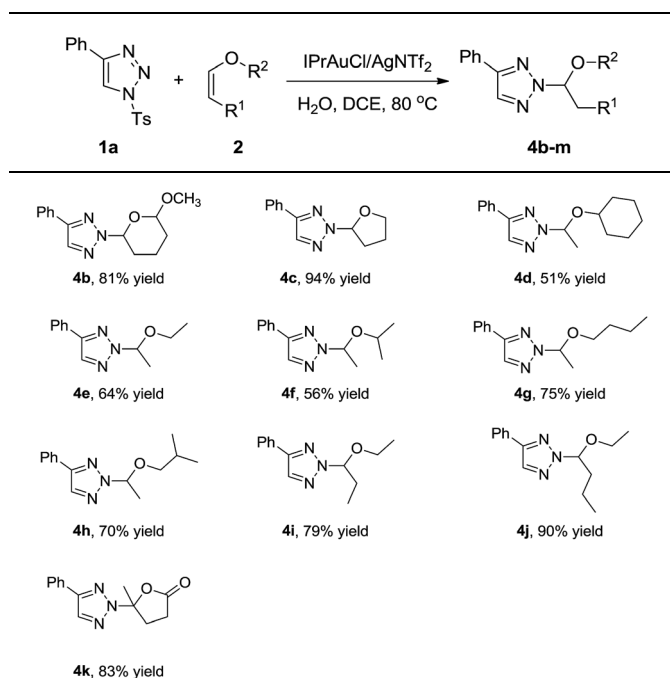
product **3g** in 57% yield (Table 2, entries 6–8). 2-Fluoro and 3-fluoro phenyl substituted 1-sulfonyl-1,2,3-triazoles were also tested, giving **3i** and **3j** in 73% and 87% yield, respectively (Table 2, entries 9 and 10). The reaction of 2-thienyl and 3-thienyl substituted 1-sulfonyl-1,2,3-triazoles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

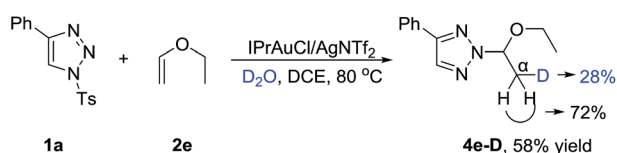


Table 3 Substrate scope of vinyl ether (2)^a

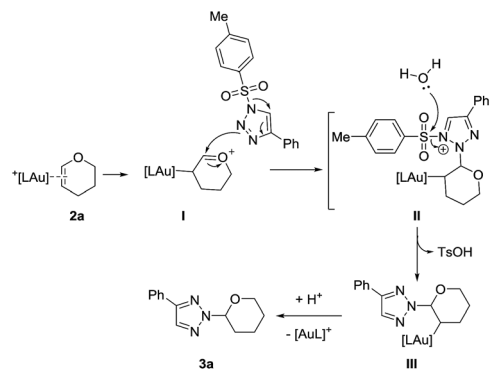
^a Reaction conditions: **1a** (0.5 mmol), **2** (2.5 mmol), H₂O (1 mmol), IPrAuCl/AgNTf₂ (5 mol%), DCE (3 mL), 80 °C.

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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