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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 H<sub>2</sub>O in this reaction.

1,2,3-Triazoles have found widespread applications in biological science,<sup>1</sup> material science<sup>2</sup> and medicinal chemistry.<sup>3</sup> More recently, they also have been utilized as ligands in transition-metal coordination,<sup>4</sup> and this catalytic system provided an efficient strategy for many challenging transformations.<sup>5</sup> 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,<sup>6</sup> 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-aryl<sup>7</sup> and *N*-2-allyl-1,2,3-triazoles<sup>8</sup> 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.

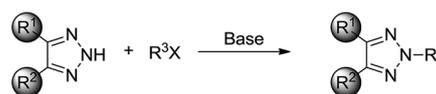
The current main approach to *N*-2-alkyl-1,2,3-triazoles by the conversion of alkyl halides with bulky C-4- and C-5-disubstituted NH-1,2,3-triazoles limits its broader utility by the substrate's steric requirements (Scheme 1a).<sup>9</sup> Recently, Chen's group reported a highly regioselective *N*-2 alkylation of NH-1,2,3-triazoles through NIS-mediated iodofunctionalization with olefins (Scheme 1b, eqn (1)).<sup>10a</sup> 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)).<sup>10b</sup> 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,<sup>11</sup> whereas employing 1-sulfonyl-1,2,3-triazoles as the nucleophiles in gold catalyzed

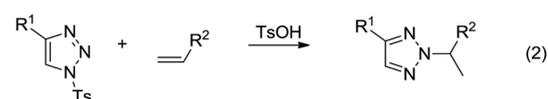
olefins conversion has never been explored before. In the previous studies, *N*-2-alkyl-substituted triazole derivatives possess a broad spectrum of antiherpetic, antiarrhythmic and antiviral activities.<sup>12</sup> Therefore, efficient synthetic methods for the synthesis of *N*-2-alkyl triazoles are 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/AgNTf<sub>2</sub> was found to be the best silver combination (Table 1, entry 2). The catalyst's ligands were then evaluated.

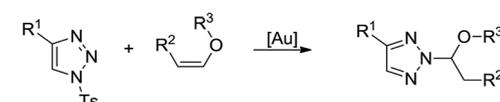
(a) Shi and Wang group: Bulky groups on C-4 and C-5 directed *N*-2 alkylation. [9]



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



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

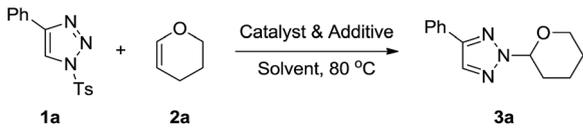


Scheme 1 Strategy for selective *N*-2 alkylation.

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Table 1 Screening of the optimal conditions<sup>a</sup>


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

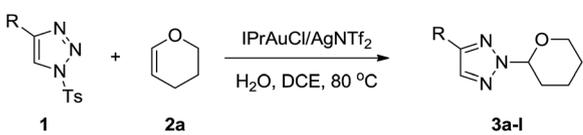
<sup>a</sup> Unless noted, all reactions were carried out at 0.5 mmol scale in 3 mL of solvent with the addition of 5 mol% catalyst at 80 °C (**1a/2a**) = 1/5.

<sup>b</sup> Isolated yields. <sup>c</sup> 3 equiv. of compound **2a** were added. <sup>d</sup> 100 mg 4 Å MS was added.

With Ph<sub>3</sub>PAuCl 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,<sup>10b</sup> 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).<sup>13</sup> 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 H<sub>2</sub>O was necessary for this N-2 alkylation reaction (Table 1, entry 13). The control experiments employing IPrAuCl and AgNTf<sub>2</sub> 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

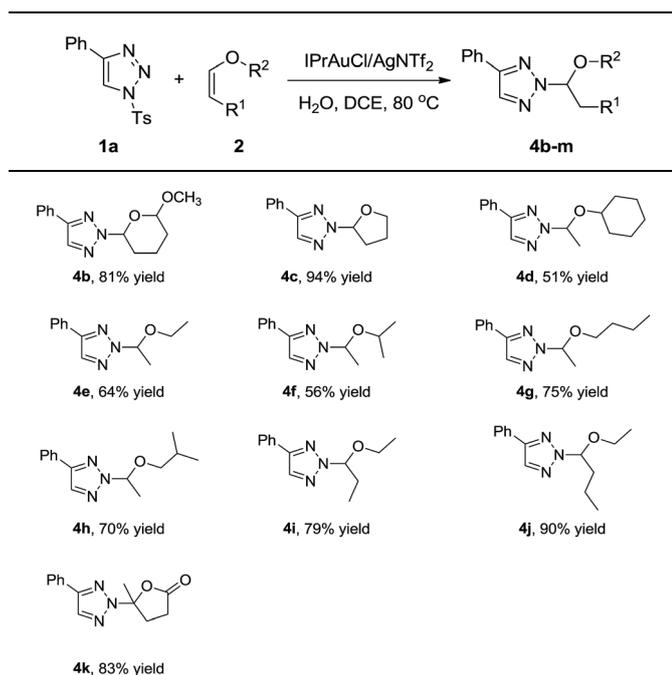
product **3g** in 57% yield (Table 2, entries 6–8). 2-Fluoro and 3-fluoro phenyl substituted 1-sulfonyl-1,2,3-triazoles were also tested, giving **3i** and **3j** in 73% and 87% yield, respectively (Table 2, entries 9 and 10). The reaction of 2-thienyl and 3-thienyl substituted 1-sulfonyl-1,2,3-triazoles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

Table 2 Substrate scope of 1-sulfonyl-1,2,3-triazoles (**1**)<sup>a</sup>


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

<sup>a</sup> Reaction conditions: **1** (0.5 mmol), **2a** (2.5 mmol), H<sub>2</sub>O (1 mmol), IPrAuCl/AgNTf<sub>2</sub> (5 mol%), DCE (3 mL), 80 °C. <sup>b</sup> Yield of isolated product.

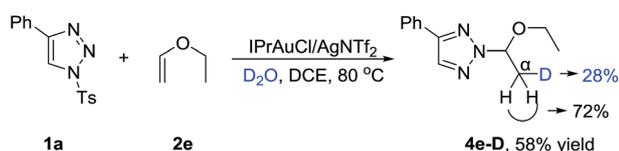


Table 3 Substrate scope of vinyl ether (2)<sup>a</sup>

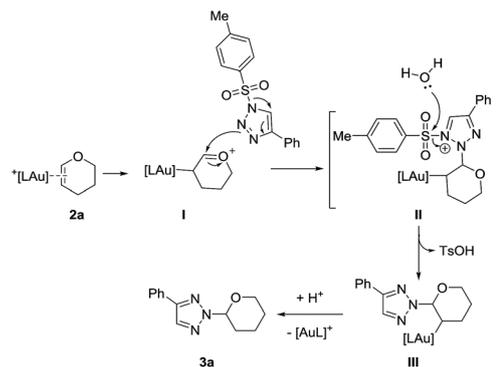
<sup>a</sup> Reaction conditions: **1a** (0.5 mmol), **2** (2.5 mmol), H<sub>2</sub>O (1 mmol), IPrAuCl/AgNTf<sub>2</sub> (5 mol%), DCE (3 mL), 80 °C.

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.<sup>10b</sup> 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 H<sub>2</sub>O



Scheme 2 Deuterium-labeling experiments.



Scheme 3 Proposed reaction mechanism.

was replaced by 2.0 equiv. of D<sub>2</sub>O 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  $\alpha$ -position of **4e-D** in a 28% ratio suggested that H<sub>2</sub>O was necessary for this *N*-2 alkylation reaction (Scheme 2).<sup>14</sup> The incorporation of deuterium at the  $\alpha$ -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<sup>10b</sup> and our deuterium-labeling experiments, a plausible<sup>15</sup> 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 protodeauration<sup>16</sup> 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 H<sub>2</sub>O 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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