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

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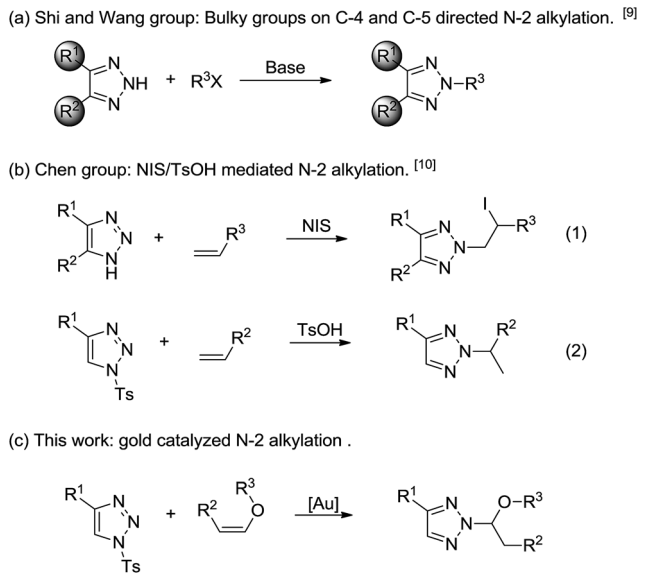
An efficient new method was developed to synthesise *N*-2-alkyl-1,2,3-trizoles *via* gold catalyzed alkylation of 1-sulfonyl-1,2,3-trizoles with vinyl ethers. Only *N*-2-isomers were obtained in these reactions. The sulfonyl group in the 1-sulfonyl-1,2,3-trizoles acted as the leaving group, which was trapped by H_2O in this reaction.

1,2,3-Triazoles have found widespread applications in biological science,[1] material science[2] 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-aryl[7] and *N*-2-allyl-1,2,3-triazoles[8] with high *N*-2-selectivity. Despite these achievements, however, a general method for the preparation of *N*-2-alkyl-1,2,3-triazols 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-trizole to olefins (Scheme 1b, eqn (2)).[10b] This new strategy incorporated a labile *N*-1-substitutents 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-trizoles with electronic-rich vinyl ethers (Scheme 1c).

The initial experiments were performed with 4-phenyl-1-sulfonyl-1,2,3-trizole **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-trizole **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/$AgNTf_2$ was found to be the best silver combination (Table 1, entry 2). The catalyst's ligands were then evaluated.



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

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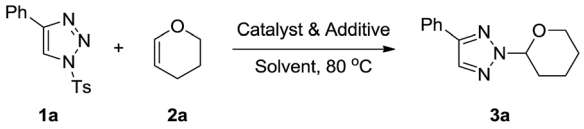
Table 1 Screening of the optimal conditions[a]



1a 2a 3a

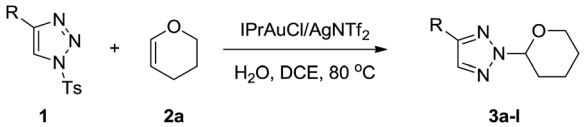
Entry	Catalyst (mol%)	Solv./additive (equiv.)	Time (h)	Yield[b] (%)
1	IPrAuCl/AgOTf (5)	DCE	6.5	53
2	IPrAuCl/$AgNTf_2$ (5)	DCE	6.5	61
3	IPrAuCl/$AgSbF_6$ (5)	DCE	6.5	39
4	$Ph_3PAuCl/AgNTf_2$ (5)	DCE	6	32
5	JohnphosAuCl/$AgNTf_2$ (5)	DCE	6	14
6	IPrAuCl/$AgNTf_2$ (5)	DCE/H_2O (2)	6	98
7	IPrAuCl/$AgNTf_2$ (5)	THF/H_2O (2)	6.5	17
8	IPrAuCl/$AgNTf_2$ (5)	$CHCl_3$/H_2O (2)	6.5	45
9	IPrAuCl/$AgNTf_2$ (5)	Toluene/H_2O (2)	24	NR
10	IPrAuCl/$AgNTf_2$ (5)	DCM/H_2O (2)	10	56
11[c]	IPrAuCl/$AgNTf_2$ (5)	DCE/H_2O (2)	6	51
12	IPrAuCl/$AgNTf_2$ (2)	DCE/H_2O (2)	8	47
13[d]	IPrAuCl/$AgNTf_2$ (5)	DCE	24	NR
14	IPrAuCl (5)	DCE/H_2O (2)	24	NR
15	$AgNTf_2$ (5)	DCE/H_2O (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 Ph_3PAuCl 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 lowed 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 H_2O was necessary for this *N*-2 alkylation reaction (Table 1, entry 13). The control experiments employing IPrAuCl and $AgNTf_2$ 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-trizoles gave **3b–e** in 74–91% yield (Table 2, entries 2–5). 4-Halogen phenyl substituted 1-sulfonyl-1,2,3-trizoles 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-trizoles (**1**)[a]

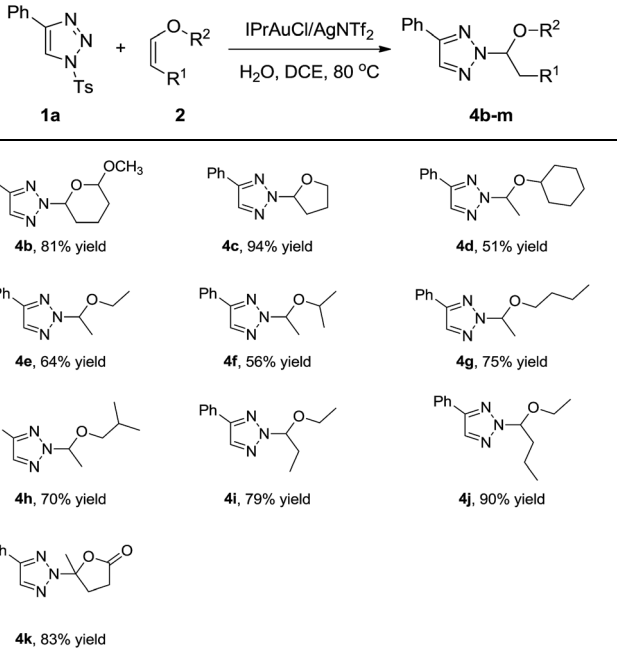


1 2a 3a-l

Entry	Substrate **1**	R	Product **3**	Yield[b] (%)
1	**1a**	Phenyl	**3a**	98
2	**1b**	4-MeC_6H_4	**3b**	74
3	**1c**	4-PrC_6H_4	**3c**	84
4	**1d**	4-$^tBuC_6H_4$	**3d**	86
5	**1e**	4-$MeOC_6H_4$	**3e**	91
6	**1f**	4-ClC_6H_4	**3f**	77
7	**1g**	4-BrC_6H_4	**3g**	57
8	**1h**	4-FC_6H_4	**3h**	99
9	**1i**	2-FC_6H_4	**3i**	73
10	**1j**	3-FC_6H_4	**3j**	87
11	**1k**	2-Thienyl	**3k**	63
12	**1l**	3-Thienyl	**3l**	70
13	**1m**	^nBu	**3m**	0
14	**1n**	Cyclopentyl	**3n**	0

[a] Reaction conditions: **1** (0.5 mmol), **2a** (2.5 mmol), H_2O (1 mmol), IPrAuCl/$AgNTf_2$ (5 mol%), DCE (3 mL), 80 °C. [b] Yield of isolated product.

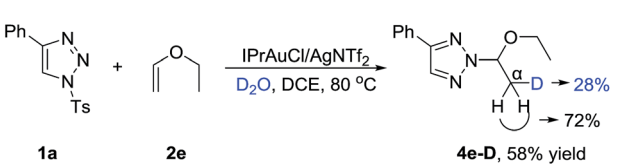
Table 3 Substrate scope of vinyl ether (2)[a]



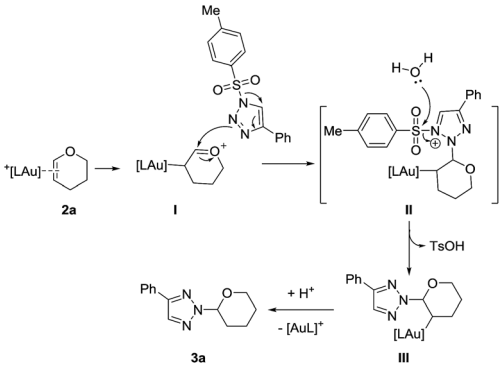
[a] Reaction conditions: **1a** (0.5 mmol), **2** (2.5 mmol), H_2O (1 mmol), IPrAuCl/$AgNTf_2$ (5 mol%), DCE (3 mL), 80 °C.

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-trizoles, 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-trizole **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 H_2O was replaced by 2.0 equiv. of D_2O in the model reaction, the *N*-2-alkyl-1,2,3-trizole 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 H_2O was necessary for this *N*-2 alkylation reaction (Scheme 2).[14] The incorporation of deuterium at the α-position of **4e-D** was lowed in 5% yield may be due to the trace amount of water in the reaction system.



Scheme 2 Deuterium-labeling experiments.



Scheme 3 Proposed reaction mechanism.

On the basis of previous work[10b] and our deuterium-labeling experiments, a plausible[15] 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[16] to give the final *N*-2-alkyl-1,2,3-trizole **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-trizoles in good yields. The sulfonyl group in the 1-sulfonyl-1,2,3-trizoles acted as the leaving group, which was trapped by H_2O 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-trizoles, we are currently studying the *N*-2-selective arylation, alkenylation, and allylation using this strategy and the results will be reported in due course.

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