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Gold(I)-Catalyzed 1,3-*O*-Transposition Reactions: Ynesulfonamides to Ynamides

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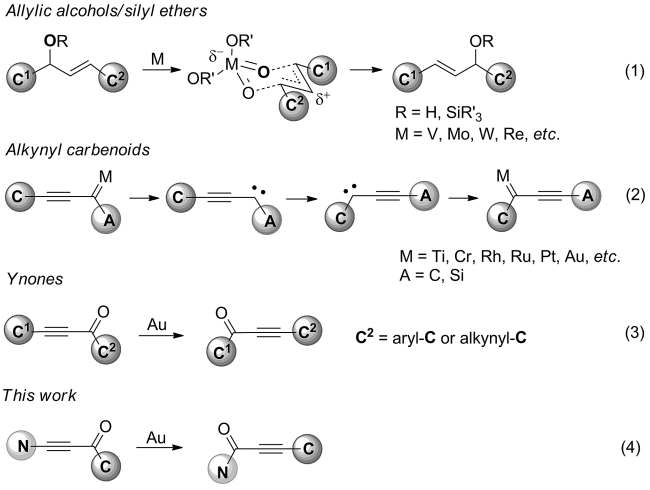
Keywords: Synthetic methods / Gold catalysis / Alkynes / Sulfonamides / Ynamides

The gold-catalyzed 1,3-*O*-transposition reaction of ynesulfonamides provides a practical synthetic protocol for the synthesis of ynamides under mild conditions. This is the first 1,3-*O*-transposition example of ynesulfonamides in which a heteroatom is attached to the alkynyl terminal. A plausible mechanism is been proposed on the basis of ^{18}O-labeling and control experiments as well as DFT calculation. By simple treatment, the obtained ynamides can easily be transformed into useful products.

Intramolecular transposition reactions are atom economical processes which have been widely reported in recent years.[1] Among them, 1,3-shift of allylic alcohols is well-studied and employed to synthesize biologically active compounds and natural products such as (–)-Galanthamine, (–)-Amphidinolide B1 and Laulimalide.[2] Moreover, transition-metal-catalyzed transposition reactions are recently attracting much more research interests especially as for these involved with a carbenoid intermediate.[3] 1,3-Transposition reactions are common reaction modes, proceeding through an unsaturated and delocalized system (such as allylic or propargylic system) under metal catalysis [Scheme 1, Equation (1)].[4] Propargylic metal carbenes can also undergo a 1,3-transposition known as a metallotropic shift [Scheme 1, Equation (2)].[5] In 2014, gold-catalyzed 1,3-transposition of ynones and diynones have been disclosed by Gevorgyan and co-workers [Scheme 1, Equation (3)].[6a] To the best of our knowledge, gold(I)-catalyzed 1,3-transposition reactions of propyne having a heteroatom at the alkynyl terminal have been rarely reported.[6] Herein, we report a novel gold-catalyzed 1,3-transposition of readily available ynesulfonamides to ynamides [Scheme 1, Equation (4)].[7] This new reaction has the advantages of mild conditions and a wide range of substrate scope. Besides, the products can further undergo an easy detosylation process to deliver useful compounds.



Scheme 1. Transition-metal-catalyzed 1,3-transposition.

During our exploration of novel reaction pathways of electron-deficient alkynes under gold catalysis, we found an entire transformation of ynesulfonamides to ynamides under gold catalysis. This reaction proceeded efficiently in the presence of gold catalyst, affording the desired ynamide in good yield within 10 min (Scheme 2). Due to the similar polarity of both substrate and product, the transformation was difficult to be monitored by TLC (silica gel: SiO_2) checking and the reaction proceeding should be traced on the basis of the crude reaction mixture's ^1H-NMR spectroscopic analysis. After mixing the starting materials **1a** with gold(I) catalyst which is generated in situ from IPrAuCl (5 mol-%) with $AgNTf_2$ (5 mol-%), the crude reaction mixture was tracked by ^1H-NMR spectra. Initially, a new signal at δ = +1.67 ppm (Me of ynamide **2a**) appeared within 30 s. After 3.0 min, the intensity of this signal increased and the intensity of the signal at δ = +2.33 ppm (Me of ynesulfonamide **1a**) decreased. Within 10 min, the signal at δ = +2.33 ppm almost disappeared and the intensity of signal at δ = +1.67 ppm reached to its maximal value (Scheme 2).

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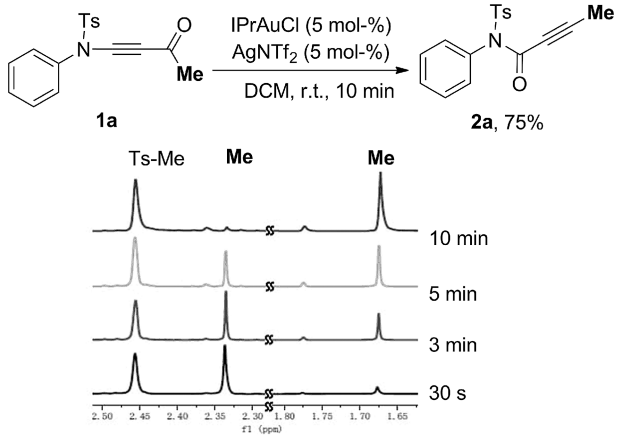
The structure of **2a** has been unambiguously assigned by X-ray diffraction. The ORTEP drawing of **2a** is shown in Supporting Information and its CIF data are also presented in Supporting Information.

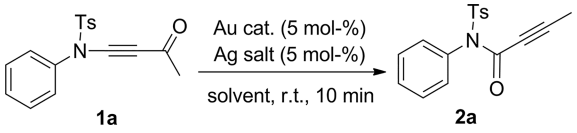


Scheme 2. Gold-catalyzed 1,3-*O*-transposition reaction.

Upon reaction condition screening, we first utilized IPrAuCl (5 mol-%) as the gold catalyst to seek out the best gold catalytic system (Table 1). After our examination of different silver salts, NTf_2^- was identified as the best coordination anion, affording **2a** in 75% NMR yield within 10 min (Table 1, entries 1–4). Then, gold catalysts with different phosphine ligands were employed (Table 1, entries 5–8). Using *t*BuXPhosAuSbF$_6$ as the catalyst produced **2a** in 82% yield within 10 min (Table 1, entry 6). Ligands *n*Bu$_3$P and Ph$_3$P gave **2a** in lower yields presumably due to the steric factor. Considering that Ag species (AgCl) generated in situ may affect the reaction outcome,[8] IPrAuNTf$_2$ was used directly to rule out the silver salt's effects, and it was found that the yield of **2a** increased to 91% NMR yield along with 90% isolated yield (Table 1, entry 9). After identification of the better gold catalyst, the screening of solvents affirmed that DCM (dichloromethane) was the better solvent because carrying out the reaction in DCE (1,2-dichloroethane), toluene and MeCN all afforded **2a** in lower yields (Table 1, entries 10–12). The reaction can be also performed in a 2.0 gram scale under the optimal conditions, giving **2a** in 88% isolated yield (Table 1, entry 13). Thus, we identified that IPrAuNTf$_2$ (5 mol-%) as gold catalyst and the reaction should be carried out in DCM. This gold-catalytic system is quite efficient for the 1,3-*O*-transposition of ynesulfonamides to ynamides.

Having the optimal reaction conditions in hand, we next investigated the scope of the reaction with respect to different ynesulfonamides. As shown in Table 2, the 1,3-*O*-transpositions proceeded smoothly to afford the desired products in moderate to excellent yields (75–93%). In general, this transformation proceeded more efficiently for electron-donating group substituted ynesulfonamides (R^1 = Ts, Mes), leading to the corresponding products in high yields, and as for electron-withdrawing group substituted ynesulfonamide (R^1 = Bs, **2b**), the yield of the desired product was slightly lower. Moreover, we also attempted to synthesize Ns-substituted ynesulfonamide (Ns = 4-nitrophenylsulfonamide), however, the substrate decomposed very rapidly probably due to that the electron deficiency caused instability during gold catalysis. Different alkyl-substituted benzene derivatives had no influences on this transforma-

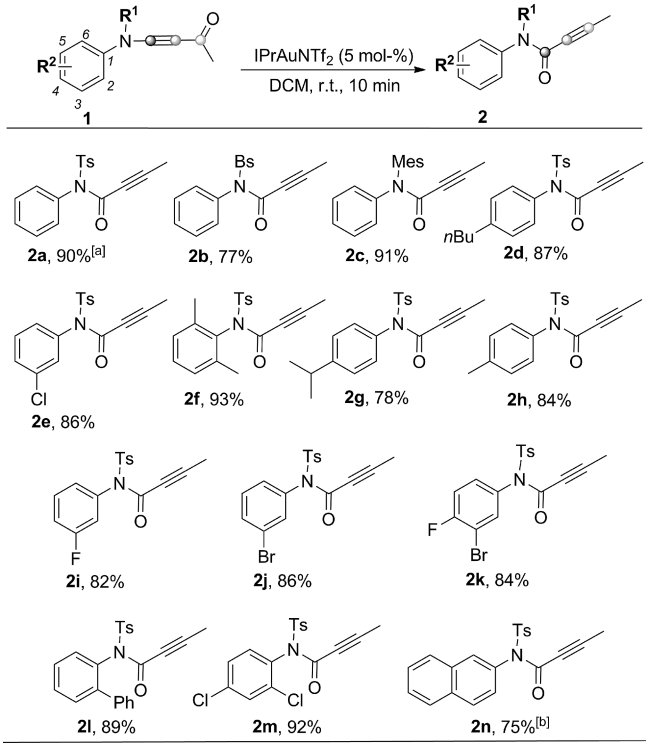
Table 1. Condition screening for the synthesis of **2a**.



Entry[a]	Au cat.	Ag salts	Solvent	Yields [%][b]
1	IPrAuCl	AgOTf	DCM	75
2	IPrAuCl	AgNTf$_2$	DCM	35
3	IPrAuCl	AgSbF$_6$	DCM	60
4	IPrAuCl	NaBArF	DCM	70
5	JohnPhosAuCl	AgNTf$_2$	DCM	57
6	*t*BuXPhosAuSbF$_6$	–	DCM	82
7	*n*Bu$_3$PAuSbF$_6$	–	DCM	66
8	PPh$_3$AuSbF$_6$	–	DCM	73
9	***IPrAuNTf$_2$***	–	***DCM***	***91 (90)***[c]
10	IPrAuNTf$_2$	–	DCE	85
11	IPrAuNTf$_2$	–	toluene	84
12	IPrAuNTf$_2$	–	MeCN	19
13	IPrAuNTf$_2$	–	DCM	(88)[d]

[a] Reactions were run as 0.1 M in solvents. [b] HPLC yields with 4-bromoanisole as an internal standard. [c] Isolated yields. [d] 2.0 gram scale, isolated yield.

Table 2. Reaction scope of ynesulfonamides **1** to ynamide products **2** with substituent at alkynyl N site.

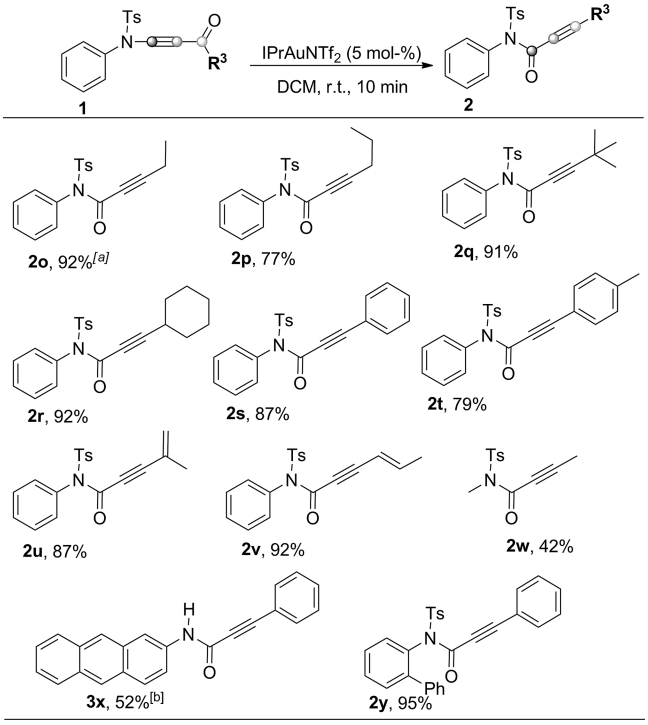


[a] Isolated yields. [b] Reaction time is 0.5 h.

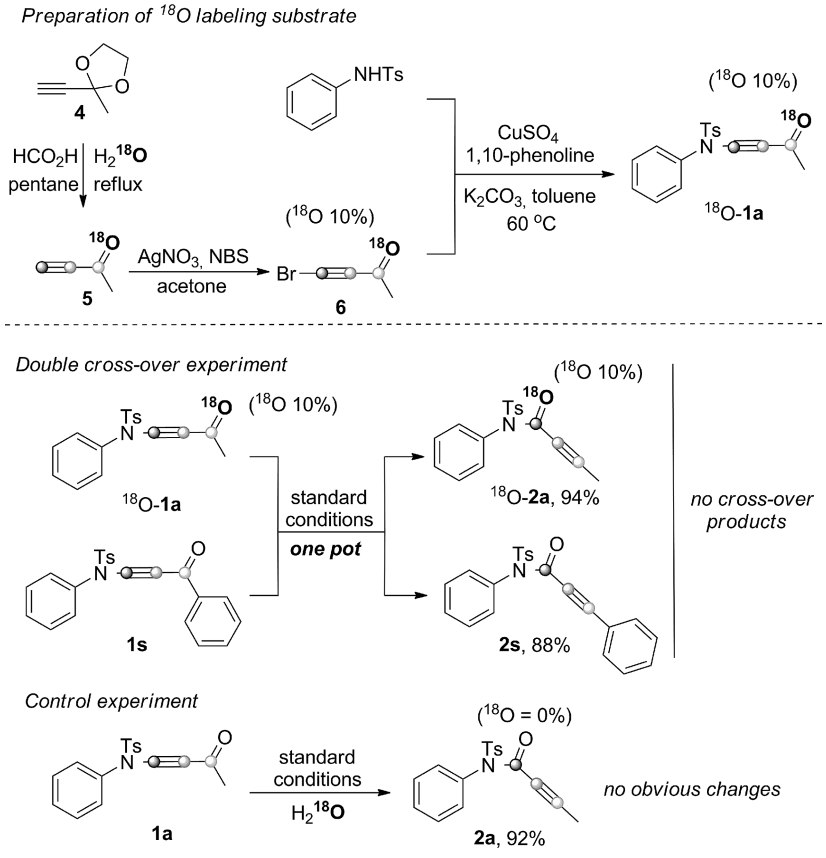
tion, all giving the desired products in good yields (**2d**, **2g** and **2h**). Sterically bulky 2,6-dimethyl-substituted ynesulfonamide afforded the corresponding product in the highest yield (**2f**, 93%). When different halogen atoms such as F, Cl or Br were presented at the benzene ring, no obvious erosion of yields was observed (**2e**, **2i** and **2j**). Even if the starting material having two halogen-atom substituents on the benzene ring, the reaction also proceeded very well, giving the desired products in good yields (for **2k** and **2m**). The substrate having phenyl substituent on the benzene ring was also tolerated, affording the desired product **2l** in 89% yield. Naphthylamine containing substrate gave the expected product **2n** in 75% yield.

We next synthesized substrates with different substituents at the carbonyl carbon terminal to examine the reaction outcome. The results are summarized in Table 3. The desired products were obtained in good yields in most cases. Alkyl-substituted products (**2o**, **2p** and **2q**) were obtained in good to excellent yields. No obvious alternation on yield was observed when cyclohexyl group was introduced at the carbonyl carbon terminal (**2r**). In the cases of aryl-substituted substrates, yields of the corresponding ynamides had a little decrease probably due to the electronic property (**2s** and **2t**). Alkenyl group substituted substrates such as 1- or 2-propenyl substituent did not affect the reaction outcome, affording the desired products **2u** and **2v** in good to excellent yields. Using **1w** as substrate, the corresponding pro-

Table 3. Reaction scope of ynesulfonamides **1** to ynamides **2** with substituent at carbonyl C site.



[a] Isolated yields. [b] After detosylation, two steps' yield.

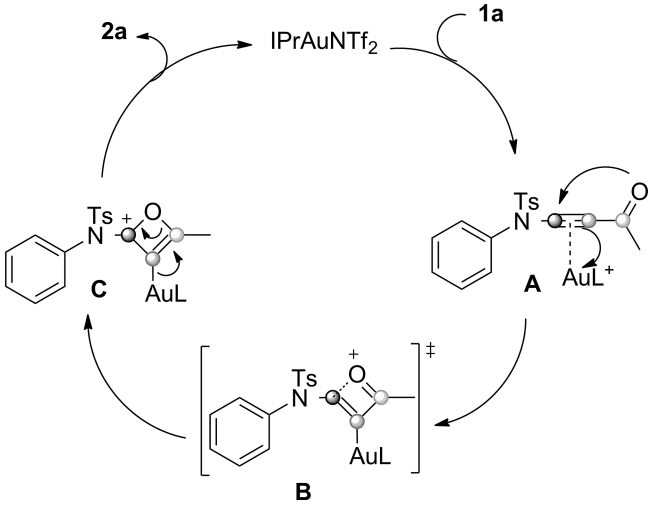


Scheme 3. Control experiments for investigation on mechanism.

duct **2w** was only obtained in 42% yield since the reaction mixture became complex quickly within 10 min. Product **2x** was unstable during purification with silica gel column chromatography, but it could be readily transformed to product **3x** through a one-pot detosylation process, which is a useful compound for photochemical study (see Scheme 6). Product **2y** is also a useful precursor of drug candidate and the detailed transformation can be seen in Scheme 6.

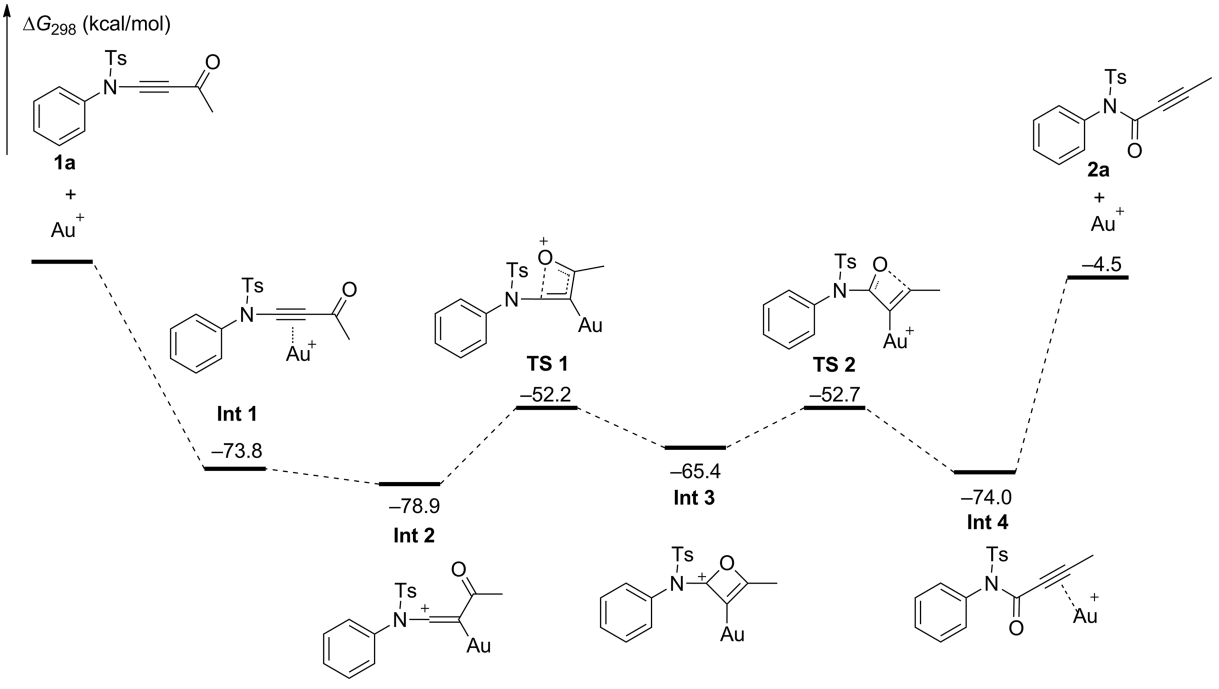
Two ^{18}O labeling experiments were conducted to clarify the O-atom-transfer process of the carbonyl group (Scheme 3). ^{18}O containing compound **6** could be readily prepared through bromination of compound **5** with NBS, which is derived from the hydrolysis of ketal **4** with $H_2{}^{18}O$ in the presence of HCO_2H. The target compound ^{18}O-**1a** was then obtained via cooper catalyzed coupling reaction. The content of ^{18}O was only 10% presumably due to that the water in situ generated from decomposition of formic acid upon heating is unavoidable. However, 10% of ^{18}O content of **1a** is good enough as compared to 0.2% of ^{18}O content in nature. The cross-over experiment was conducted with ^{18}O-**1a** and **1s** as the substrates. After the one-pot gold catalysis, no cross-over products were observed on the basis of Mass spectroscopic analysis of the reaction mixture, suggesting an intramolecular atom transferring manner (Scheme 3). Moreover, adding $H_2{}^{18}O$ into the reaction system of **1a** did not give ^{18}O containing product under the standard conditions and the desired product **2a** was given in 92% yield, indicating that the ambient water did not affect the reaction proceeding. These results firmly demonstrated that the O atom transferring process takes place through an intramolecular manner.

Based on the previous literature[6a,8] and our control experiments, a plausible mechanism for this gold-catalyzed 1,3-*O*-transposition process is outlined in Scheme 4. As for substrate **1a**, the coordination of gold(I) catalyst with alkyne gives intermediate **A**, which can initiate an intramolecular O attack to the alkyne moiety to deliver a gold stabilized carbocationic intermediate **C** via transition state **B**. Subsequent C–O bond cleavage in the intermediate **C** and dissociation of the gold catalyst generate product **2a**.



Scheme 4. A proposed mechanism.

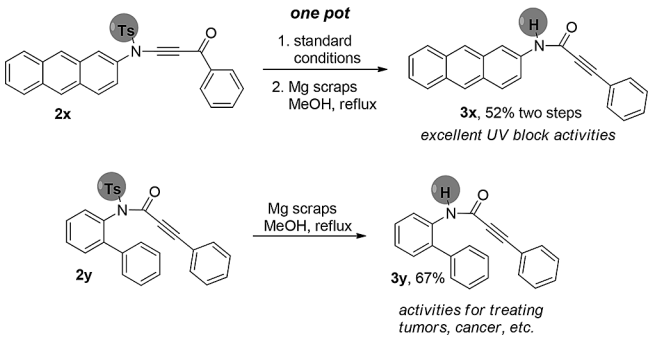
In order to understand the detailed mechanism for the formation of product **2**, we have also theoretically investigated the reaction pathway (for details, see Supporting Information). All calculations have been performed at the B3LYP/6-311+G(d,p)/SDD//B3LYP/6-31+G(d)/SDD level of theory with Gaussian 09 program. The relative energies of all intermediates and transitional states along the reac-



Scheme 5. Reaction energy profile.

tion pathways are shown in Scheme 5. Initially, the coordination of ynesulfonamide **1a** with Au^{I} catalyst generates gold complex **Int 1**. The gold complex **Int 1** is transferred to the more stable carbocationic intermediate **Int 2** without an energy barrier. Passing through transition state **TS 1** with an energy barrier of 26.7 kcal/mol, the O attacks the electrophilic carbon to give another stable carbocationic intermediate **Int 3**. Then the intermediate **Int 3** undergoes C–O bond cleavage via transition state **TS 2** with an energy barrier of 26.2 kcal/mol, generating the product complex **Int 4**. The product complex **Int 4** is finally cleaved to yield separate product **2a** with Au^{I} catalyst. Moreover, the DFT calculations show that the product **2a** is more stable than the reactant **1a** by 4.5 kcal/mol, indicating that the formation of product **2** is an exothermic process.

Due to product **2x**'s instability in silica gel column chromatography, it was transformed into stable and separable product **3x** via a one-pot detosylation process in the presence of a magnesium scraps with methanol (Scheme 6). The product **2y** could be easily transformed into detosylated derivative **3y** in good yield (Scheme 6). The compound **3x** is a useful material since it has excellent UV block activities,[9] and compound **3y** could be used as a model compound for treating tumors, cancer and hyper proliferative diseases.[10]



Scheme 6. Further transformation of products **2x** and **2y**.

In summary, we have explored a novel and efficient gold(I)-catalyzed intramolecular 1,3-*O*-transposition reaction under mild conditions. Through further transformations, two useful compounds can be easily obtained after simple treatment. This new strategy demonstrates a practical protocol for synthesis of ynamides starting from yne sulfonamides, which have a nitrogen atom tethered at alkynyl terminal. The control experiments and DFT calculation results give experimental and theoretical explanations for the proposed intramolecular 1,3-*O* atom transfer mechanism, and also show that the formation of product **2** is an exothermic process.

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[1] a) P. A. Wender, B. L. Miller, *Nature* **2009**, *460*, 197; b) P. A. Wender, F. C. Bi, G. G. Gamber, F. Gosselin, R. D. Hubbard, M. J. C. Scanio, R. Sun, T. J. Williams, L. Zhang, *Pure Appl. Chem.* **2002**, *74*, 25; c) B. M. Trost, *Acc. Chem. Res.* **2002**, *35*, 695.

[2] For a reviews, see: a) I. Volchkov, D. Lee, *Chem. Soc. Rev.* **2014**, *43*, 4381; for natural products syntheses, see: b) B. M. Trost, F. D. Toste, *J. Am. Chem. Soc.* **2000**, *122*, 11262; c) B. M. Trost, W. Tang, F. D. Toste, *J. Am. Chem. Soc.* **2005**, *127*, 14785; d) A. K. Mandal, J. S. Schneekloth, K. Kuramochi, C. M. Crews, *Org. Lett.* **2006**, *8*, 427; e) B. M. Trost, D. Amans, W. M. Seganish, C. K. Chung, *Chem. Eur. J.* **2012**, *18*, 2961. For several typical examples, see: f) S. Matsubara, K. Takai, H. Nozaki, *Tetrahedron Lett.* **1983**, *24*, 3741; g) T. Hosogai, Y. Fujita, Y. Ninagawa, T. Nishida, *Chem. Lett.* **1982**, 357; h) J. Belgacem, J. Kress, J. A. Osborn, *J. Am. Chem. Soc.* **1992**, *114*, 1501; i) J. Jacob, J. H. Espenson, J. H. Jensen, M. S. Gordon, *Organometallics* **1998**, *17*, 1835; j) G. Wang, A. Jimtaisong, R. L. Luck, *Organometallics* **2004**, *23*, 4522; k) S. Bellemin-Laponnaz, H. Gisie, J. P. Le Ny, J. A. Osborn, *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 976; *Angew. Chem.* **1997**, *109*, 1011.

[3] For a review, see: a) D. Lee, M. Kim, *Org. Biomol. Chem.* **2007**, *5*, 3418; For Au- and Pt-involved 1,3-transposition, see: b) K. Miki, K. Ohe, S. Uemura, *J. Org. Chem.* **2003**, *68*, 8505; c) S. López, E. Herrero-Gomez, P. Perez-Galan, C. Nieto-Oberhuber, A. M. Echavarren, *Angew. Chem. Int. Ed.* **2006**, *45*, 6029; *Angew. Chem.* **2006**, *118*, 6175; d) C. Nieto-Oberhuber, S. Lopez, M. P. Munoz, E. Jimenez-Nunez, E. Bunuel, D. J. Cardenas, A. M. Echavarren, *Chem. Eur. J.* **2006**, *12*, 1694; e) B. Martin-Matute, C. Nevado, D. J. Cardenas, A. M. Echavarren, *J. Am. Chem. Soc.* **2003**, *125*, 5757; f) E. J. Cho, M. Kim, D. Lee, *Org. Lett.* **2006**, *8*, 5413; g) K. Ohe, M. Fujita, H. Matsumoto, Y. Tai, K. Miki, *J. Am. Chem. Soc.* **2006**, *128*, 9270; h) D. J. Gorin, P. Dube, F. D. Toste, *J. Am. Chem. Soc.* **2006**, *128*, 14480. For other metal involved 1,3-transposition, see:; i) M. Kim, R. L. Miller, D. Lee, *J. Am. Chem. Soc.* **2005**, *127*, 12818; j) T. Takeda, S. Kuroi, M. Ozaki, A. Tsubouchi, *Org. Lett.* **2004**, *6*, 3207; k) J. Barluenga, P. García-García, D. de Sáa, M. A. Fernández-Rodríguez, R. B. de la Rúa, A. Ballesteros, E. Aguilar, M. Tomás, *Angew. Chem. Int. Ed.* **2007**, *46*, 2610; *Angew. Chem.* **2007**, *119*, 2664; l) D. B. Kimball, T. J. R. Weakley, R. Herges, M. M. Haley, *J. Am. Chem. Soc.* **2002**, *124*, 13463; m) D. B. Kimball, R. Herges, M. M. Haley, *J. Am. Chem. Soc.* **2002**, *124*, 1572.

[4] a) C. Morrill, R. H. Grubbs, *J. Am. Chem. Soc.* **2005**, *127*, 2842; b) C. Morrill, G. L. Beutner, R. H. Grubbs, *J. Org. Chem.* **2006**, *71*, 7813; c) J. Belgacem, J. Kress, J. A. Osborn, *J. Am. Chem. Soc.* **1992**, *114*, 1501; d) J. Belgacem, J. Kress, J. A. Osborn, *J. Mol. Catal.* **1994**, *86*, 267; e) P. Chabardes, E. Kuntz, J. Varagnat, *Tetrahedron* **1977**, *33*, 1775.

[5] a) M. Franck-Neumann, P. Geoffroy, J. J. Lohmann, *Tetrahedron Lett.* **1983**, *24*, 1775; b) M. Franck-Neumann, P. Geoffroy, *Tetrahedron Lett.* **1983**, *24*, 1779; c) R. A. Seburg, E. V. Patterson, J. F. Stanton, R. J. McMahon, *J. Am. Chem. Soc.* **1997**, *119*, 5847.

[6] For both ends attached to carbon atoms, see: a) R. K. Shiroodi, M. Soltani, V. Gevorgyan, *J. Am. Chem. Soc.* **2014**, *136*, 9882; b) T. Takeda, S. Kuroi, M. Ozaki, A. Tsubouchi, *Org. Lett.* **2004**, *6*, 3207; c) T. Takeda, M. Ozaki, S. Kuroi, A. Tsubouchi, *J. Org. Chem.* **2005**, *70*, 4233.

[7] For review on ynamides, see: a) K. A. DeKorver, H. Li, A. G. Lohse, R. Hayashi, Z. Lu, Y. Zhang, R. P. Hsung, *Chem. Rev.* **2010**, *110*, 5064. For gold-catalyzed of ynamide, see:; b) C. Li, L. Zhang, *Org. Lett.* **2011**, *13*, 1738; c) S. N. Karad, R.-S. Liu, *Angew. Chem. Int. Ed.* **2014**, *53*, 9072; *Angew. Chem.* **2014**, *126*, 9218; d) S. N. Karad, S. Bhunia, R.-S. Liu, *Angew. Chem. Int. Ed.* **2012**, *51*, 8722; *Angew. Chem.* **2014**, *124*, 8852.

[8] D. Wang, R. Cai, S. Sharma, J. Jirak, S. K. Thummanapelli, N. G. Akhmedov, H. Zhang, X. Liu, J. L. Petersen, X. Shi, *J. Am. Chem. Soc.* **2012**, *134*, 9012.

[9] a) Y. G. Han, I. J. Byun, B. R. Jeon, H. J. Lee, S. H. Kim, *Propiolamide-based compound with excellent UV blocking properties utilized in various devices such as display device, propiolamide-based polymer, and manufacturing method of the compound*, patent KR 2014099388 A 20140812; b) Y. G. Han, I. J. Byun, B. R. Jeon, H. J. Lee, S. H. Kim, *Ultraviolet blocking film used in* e.g. *display devices, comprising ultraviolet blocking compound (e.g. propiolamide compounds or acrylamide-based compounds), and a polymer binder*, patent KR 2014092973 A 20140725.

[10] D. J. Austin, V. A. Nguyen, D. Pupowicz, A. Deisseroth, T. Wang, E. Lerma, *Compounds and methods for treating tumors, cancer, and hyperproliferative diseases*, United States patent US 7304092 B1.

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