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Splitting a Substrate into Three Parts: Gold-Catalyzed Nitrogenation of Alkynes by C–C and C≡C Bond Cleavage

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Dedicated to Professor Xuelong Hou on the occasion of his 60th birthday

Abstract: A gold-catalyzed nitrogenation of alkynes for the synthesis of carbamides and amino tetrazoles through C-C and C=C bond cleavages is described. A diverse set of functionalized carbamide and amino tetrazole derivatives were selectively constructed under mild conditions. The chemoselectivity can be easily switched by the selection of the acid additives. The reaction is characterized by its broad substrate scope, direct construction of high value products, easy operation under air, and mild conditions at room temperature. This chemistry provides a way to transform alkynes by splitting the substrate into three parts.

As very common, readily available, and reactive functional molecules, alkynes have been widely used in organic transformations.^[1] Transition-metal-catalyzed unstrained C-C bond cleavage represents an attractive but challenging strategy in organic synthesis to discover new transformations.^[2] In the past decades, significant progress has been made on the direct transformation of alkynes through C=C triple bond cleavage, including the alkyne metathesis,^[3] oxidation,^[4] and nitrogenation reactions.^[5] In these cases, the original alkyne structure was split and located in two kinds of products (Scheme 1 a). Recently, the groups of Echavarren^[6] and Jiao^[7] have successfully realized the direct transformation of alkynes to tetrazoles^[6] and amides^[7] through C-C single bond cleavage, in which the alkyne structure was split into two parts but, interestingly, located in one product molecule (Scheme 1b).

Encouraged by these improvements, the discovery of new alkyne transformations through C–C bond cleavage is still attractive but very challenging. Herein, we describe a Aucatalyzed nitrogenation of alkynes for the synthesis of

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Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/anie.201508347. a) Oxidation of alkynes to carboxylic acids or metathesis by C=C bond cleavage.

$$Ar \stackrel{ \clubsuit}{\longrightarrow} R \xrightarrow{C = C \ cleavage \ of \ alkyne} \qquad Ar \stackrel{ \clubsuit r \quad \circledast OOH + R - @OOH \\ or \\ Ar \stackrel{ \clubsuit r \quad \ref{algorithm}}{\longrightarrow} R' ; \ Ar \stackrel{ \clubsuit r \quad \ref{algorithm}}{\longrightarrow} N$$

b) Split alkynes to 2 parts located in one product by C-C bond cleavage.

c) Split alkynes to 3 parts located in one product by C-C and C=C cleavages



Scheme 1. The transformation of alkynes through C-C bond cleavage.

carbamides and amino tetrazoles through both C–C and C=C bond cleavages (Scheme 1 c). In this chemistry: 1) The original alkyne structure was split into three parts and reassembled in one product molecule. To our knowledge, this is the first example of the direct transformation of alkynes through both C–C single bond and C=C triple bond cleavage in one step; 2) The chemoselectivity can be easily controlled by the reaction conditions. Therefore, the desired carbamides and amino tetrazoles could be easily switched by the selection of the acid additives; 3) The reaction is characterized by the transformation of alkynes, the direct construction of high value products, easy operation under air, and mild conditions at room temperature.

Gold catalysts have proven to be one of the most effective catalysts for alkyne activation.^[8,9] During the Au-catalyzed amide synthesis,^[7] trace amount of carbamides and amino tetrazoles were detected in some cases. We therefore started the investigation by probing the nitrogenation of phenyl-1-hexyne (**1a**) with TMSN₃ in the presence of Au- and Ag-catalysts (Table 1). Interestingly, we found that the reaction was significantly influenced by which acid was used. HOAc and TFA (trifluoroacetic acid) failed to facilitate the transformation. To our delight, in the presence of PTSA (*p*-toluenesulfonic acid, $pK_a = -2.8$ in water), the desired multiple nitrogenation and hydration products carbamide **2a** and amino tetrazole **3a** were obtained in yields of 21% and 13%, respectively (entry 1). The efficiency and selectivity of this protocol were improved by changing PTSA to MSA

(Ph)-	1 ●●● [_] Bu	10 mol% catalyst acid, TMSN ₃ → Ph ^N → ^N → ⁿ Bu			u _ Ph			
	1a	air, sol [,] r.t., 2	vent 4h	0 2a		HN 3a	ⁿ Bu	
entry	catalyst		acid (p <i>K</i> _a)	additive	solvent	Yield	[%] ^[b]	
	(10 mol%)					_	-	
						2 a	3 a	
1	1 PPh ₃ AuCl/Ag ₂ CO ₃		PTSA	H_2O	DCE	21	13	
			(-2.8 ^[c])					
2	PPh₃AuCl/A	g ₂ CO ₃	MSA	H ₂ O	DCE	37	< 5	
			(-2.6 ^[c])					
3	(4-CF ₃ -Ph) ₃ P	AuCl	MSA	H ₂ O	DCE	28	< 5	
	/Ag ₂ CO ₃							
4	PPh₃AuNTf		MSA	H ₂ O	DCE	33	0	
5	PPh₃AuCl/Ag	gF	MSA	H ₂ O	DCE	42	< 5	
6	PPh₃AuCl/Ag	gSbF₀	MSA	H ₂ O	DCE	36	< 5	
7	PPh₃AuCl		MSA	H ₂ O	DCE	< 5	0	
8	AgF		MSA	H ₂ O	DCE	< 5	0	
9	none		MSA	H ₂ O	DCE	< 5	0	
10	PPh₃AuCl/A§	gF	MSA	H ₂ O	DCM	29	< 5	
11	PPh₃AuCl/A§	gF	MSA	H_2O	TCE	58	< 5	
12	PPh₃AuCl/Ag	gF	MSA ^[d]	H₂O	TCE	67	< 5	
13	PPh ₃ AuCl/Ag	gF	TfOH	-	DCE	< 5	48	
			(-14 ^[c] ,					
			-11.4 ^[e])					
14	PPh₃AuCl/Ag	gF	H(NTf)₂	-	DCE	< 5	36	
	, ,	-	(-11.9 ^[e])					
15	PPh₃AuCl/AgF		TfOH	-	TCE	< 5	55	
16	PPh₃AuCl/AgF		TfOH ^[f]	-	TCE	< 5	66	

[a] Reaction conditions: **1a** (0.5 mmol), catalyst (0.05 mmol), TMSN₃ (2.0 mmol), additive (1.0 mmol) and acid (2.5 mmol) in solvent (2 mL) at room temperature for 24 h under air. Amide byproducts^[7] were detected in some cases. [b] Yields of isolated products. [c] pK_a value of acid in water. [d] MSA (2.5 mmol) and TMSN₃ (2.0 mmol) were added in two portion in six hours. [e] pK_a value of acid in 1,2-dichloroethane. [f] TfOH (2.5 mmol) and TMSN₃ (2.0 mmol) were added in two portion in six hours. TFA=trifluoroacetic acid, PTSA=*p*-toluenesulfonic acid, MSA=methanesulfonic acid.

(methanesulfonic acid, $pK_a = -2.6$ in water), providing 37 % yield of **2a** with trace amount of **3a** formation (entry 2). Moreover, evaluation of a number of different gold catalysts revealed that PPh₃AuCl was more efficient than others (entries 3,4; see the Supporting Information). Next, we determined that the choice of silver salt had a slight influence on the reaction outcome (entries 5,6; see the Supporting Information). In comparison, AgF turned out to be more effective at mediating this transformation. The required participation of both the gold catalyst and silver salt was confirmed in control tests (entries 7-9). The choice of solvent significantly influenced the transformation, with TCE proving to be the optimal reaction medium (entries 10,11; see the Supporting Information). Finally, we found that the addition of MSA and TMSN₃ in two portions provided slightly higher yields, delivering carbamide 2a in 67% yield and with a good selectivity with the formation of a trace amount of 3a (entry 12). In the following investigations, two superacids $(pK_a < -12 \text{ in water})$ were employed to change the selectivity of the transformation (entries 13, 14). Fortunately, when TfOH ($pK_a = -14$ in water and -11.4 in DCE) or H(NTf)₂ $(pK_a = -11.9 \text{ in DCE})$ were added, the reaction generated **3a** in the yields of 48 % and 36 % respectively, probably owing to the nucleophilicity of water being inhibited by strong acids. Furthermore, we found that TCE is also the best medium for this process, while solvents such as MeCN or PhMe are also competent (entry 15, 55 % yield; see the Supporting Information). Similarly, adding TfOH and TMSN₃ in two portions led to a higher yield of amino tetrazoles with good chemoselectivity (entry 16, 66 %). Control experiments demonstrated that the reactions in the absence of Au catalyst did not work (Supporting Information). Although the yields for the preparation of amino tetrazoles and carbamides are moderate, considering that both C–C and C=C bond are cleaved and nitrogen and/or oxygen atoms are incorporated, the efficiency for each step is high and acceptable.

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With optimal reaction conditions for the transformation of alkynes to carbamides in hand, we explored the generality of this reaction. As shown in Table 2, a broad range of





[a] Reaction conditions: see entry 12, Table 1. [b] Yield of isolated products.

differently substituted alkynes, bearing both electron-donating and halo-substitutents at the aromatic ring, reacted with TMSN₃ and H₂O to form a series of carbamide molecules. Electron-rich substrates were suitable for the reaction with relatively high yields (**2b** and **2c**). Substituents at the *meta*position were tolerated for this transformation (**2f** and **2g**).

Encouraged by these results with internal alkynes, we then investigated the nitrogenation and hydration reaction with a range of terminal alkynes (Table 3). To our delight, although amide and amino tetrazole byproducts were detected in some cases, it was noteworthy that the substituted phenylacetylenes gave the desired products in the presence of TfOH in good efficiencies (Table 3). Compared with MSA, the usage of TfOH showed higher efficiencies for terminal alkynes. As shown in Table 3, electron-donating groups, such as -Me (**2**k) **Communications**





[a] Reaction conditions: 1 (0.5 mmol), PPh₃AuCl (0.05 mmol), AgF (0.05 mmol), TMSN₃ (2.0 mmol), H₂O (1.0 mmol) and TfOH (2.5 mmol) in TCE (2 mL) at room temperature for 24 hour under air. Amide byproducts^[7] were detected in some cases [b] Yield of isolated products.

and -OMe, (2j), increase the overall efficiency. Notably, this transformation readily generated halogen-substituted carbamides (2l and 2m), offering an opportunity for subsequent cross-coupling, thereby facilitating expedient synthesis of complex carbamide derivatives. Substituents at *meta*- and *ortho*-positions also led to the desired products (2n-q).

We next focused on expanding the scope of alkynes for the amino tetrazole preparation. As illustrated in Table 4, this protocol for amino tetrazoles generically proceeded at room temperature in good yields with an extensive range of phenyl and alkyl substituted acetylenes (Table 4). With respect to the aryl side, substrates with electron-donating substituents at the *para*-position led to good yields (**3b**-**3e**). Moreover, *meta*-substituted substrates were also accommodated by these conditions (**3f** and **3g**). Unfortunately, sterically encumbered substrates, such as alkynes with *ortho*-substituted phenyls, failed to offer the desired products. In terms of the alkyl side, phenyl was tolerated, furnishing amino tetrazoles in a good yield (**3h**).

To gain insight into the mechanism, a proposed intermediate vinyl azide **4** was tested under the standard conditions, resulting in carbamide **2i** in a yield of 65% (Scheme 2a). Besides, in the absence of PPh₃AuCl and AgF, a 62% yield of **2i** was obtained, showing that the catalyst was not necessary in this step of the transformation. To further explore this reaction, another probable intermediate carbodiimide **5** was synthesized and submitted to these transformations (Scheme 2b). In the case of MSA and H₂O, an 86% yield of **2a** was generated from the hydration of **5**. Similarly, nitrogenation of **5** occurred in the presence of TfOH and TMSN₃, providing an 87% yield of **3a**. Moreover, addition of the gold catalyst had no obvious effect on either of the reactions.

Compound 2a failed to be transformed into 3a in the presence of TMSN₃ and TfOH (Scheme 2c). The above

Table 4: Substrate scope of alkynes to amino tetrazoles.^[a,b]



[a] Reaction conditions: 1 (0.5 mmol), PPh₃AuCl (0.05 mmol), AgF (0.05 mmol), TMSN₃ (2.0 mmol) and HOTf (2.5 mmol) in TCE (2 mL) at room temperature for 24 h under air. [b] Yield of isolated product.

a) Mechanistic studies of key intermidiate vinyl azide

b) Sulfoacid controlled nitrogenation or hydration of carbodiimide

c) Transformation of carbamide 2a to amino tetrazole 3a

Scheme 2. Mechanistic studies of cascade reactions.

results strongly suggest that sulfoacid plays an important role in the reaction mechanism, where the reaction results could be controlled by the presence and strength of the sulfoacid.

On the basis of the above results, a plausible mechanism was proposed (Scheme 3). Initially, the alkyne is activated by cationic gold(I) generated in situ from the gold catalyst and silver salt. Subsequent nucleophilic attack of TMSN₃ on intermediate **A** led to alkenyl azide **B**. Further protonation of **B** generated azide cation intermediate **C**, which could be transformed to intermediate **D** through an acid-catalyzed rearrangement process.^[10] Next, cation **D** was attacked by TMSN₃ once again, producing imino azide **E**. The nucleophilic attack of water was prevented in this step probably owing to the protonation of H₂O to H₃O⁺ by strong or super acids. The subsequent protonation of **E** took place in the presence of sulfuric acid to form α -amino azide carbocation **F**,



Scheme 3. Proposed Mechanism.

which would be converted to **G** or carbodiimide **H** by rearrangement and loss of a proton. Finally, nucleophilic attack by H_3O^+ led to the desired carbamide product **2** through the tautomerization of the intermediate **I**.^[11] Alternatively, 1,3-dipolar cycloaddition with azide led to the desired amino tetrazole product **3**.^[12]

In conclusion, we have developed an efficient goldcatalyzed double carbon-carbon bond cleavage (both of C–C and C=C bond are cleaved) of alkynes for the direct synthesis of amino tetrazoles and carbamides. The original alkyne structure was split into three parts and reassembled in one product molecule. The transformation, mild conditions, and high-value products make this protocol very practical and attractive. The chemoselectivity can be easily switched by the selection of the acid additives. Further applications and mechanistic studies of the applications are ongoing in our laboratory.

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Keywords: carbamides · C–C bond cleavage · gold · rearrangements · tetrazoles

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