Gold Catalysis

Taking Advantage of the Ambivalent Reactivity of Ynamides in Gold Catalysis: A Rare Case of Alkyne Dimerization**

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Ynamide derivatives are easily accessible and relatively stable compounds which have proved to be useful buildings blocks for the synthesis of a large variety of nitrogen-containing molecules.^[1] Owing to the polarization of the triple bond, ynamides can be regioselectively activated by an electrophile to induce the addition of a variety of oxygen-, nitrogen-, or carbon-containing nucleophiles at the position α to the nitrogen atom (Scheme 1). Gold salts or gold complexes,

General ynamide reactivity



Scheme 1. Gold-catalyzed dimerization of ynamides. EWG = electronwithdrawing group.

which are strong alkynophilic species,^[2] are particularly efficient catalysts for such transformations, as reported in a series of recent articles.^[3,4] Following our previous work in this field,^[4] we report herein an unprecedented mode of reactivity where, in the presence of a gold(I) complex, ynamides can play the role of both the electrophilic and nucleophilic partner to produce various complex, dimerized products. The formation and the nature of the dimeric

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products appear to be dependent on the electronic nature of the substituents located on the nitrogen atom and at the alkyne terminus.

During the course of our investigations on the goldcatalyzed addition of external nucleophiles onto ynamide **1a**, we noticed the formation of a side product that could also be formed and isolated in the absence of a nucleophile. Its structure was assigned on the basis of ¹H NMR spectroscopic analysis, and was confirmed as cyclopentadiene **2a**.^[5] Different catalysts and experimental conditions were screened to optimize this transformation (Table 1).^[6] Compound **2a** was obtained in an excellent 85 % yield when **1a** was treated with

Table 1: Optimization of the catalytic system with ynamide 1 a.^[a]

	Bn N	catalyst	/Is Bn-N <i>n</i> -C ₅ H ₁₁ 2:	C ₆ H ₁₃ N ^{Bn} Ts
Entry	Catalyst (mol%)	T [°C]	<i>t</i> [h]	Yield [%] ^[b]
1	[(Ph₃P)AuNTf₂] (2) 20	0.5	85
2	$[(Ph_3P)AuNTf_2]$ (2) 40	0.5	98
3	HNTf ₂ (20)	40	2	O ^[c]
4	AgOTf (10)	40	24	4 ^[d]

[a] Reactions were carried out under argon and at a concentration of 0.1 m. [b] Yield of the isolated product. [c] Degradation occurred. [d] Yield was determined by ¹H NMR spectroscopy. Bn = benzyl, Tf = trifluoromethanesulfonyl, Ts = p-toluenesulfonyl.

2 mol % of $[(Ph_3P)AuNTf_2]^{[7]}$ in dichloromethane at 20 °C for 0.5 hour (Table 1, entry 1). The transformation was nearly quantitative (98 %) when the reaction was conducted at reflux (Table 1, entry 2). Control experiments showed that the Brønsted acid HNTf₂ did not catalyse this transformation (Table 1, entry 3), while AgOTf was almost as inefficient (Table 1, entry 4).

The formation of cyclopentadiene 2a is remarkable. To the best of our knowledge, no example of such a [3+2] cyclodimerization of an alkyne has been reported in the literature. This unprecedented transformation is not only performed under mild experimental conditions with a low loading of gold catalyst, but is also rapid and efficient.

The scope of the reaction was next investigated by screening various ynamides bearing alkyl substituents at the terminus of the alkyne. As shown in Table 2, the transformation could be applied to a series of ynamides 1a-h. The corresponding cyclopentadienes 2a-h were rapidly formed (0.5–3 h) in good to excellent yields (73–98%). The benzyl moiety (Table 2, entries 1, 2, and 6–9), as well as other

 Table 2:
 Dimerization of alkyl-substituted ynamides.

			R^2		[(Ph ₃ P).	AuNTf ₂]	(2 mol %)		
		EWG	R ³ 1a–n	_	CH ₂	Cl ₂ (0.1)	и), 40 °C	1 —11	
Entry	EWG	Su R ¹	ubstrate R ²	R ³		<i>t</i> [h]	Product		Yield $[\%]^{[a]}$
1 2 3	Ts Ts Ts	Bn Bn n-C ₄ H ₉	n-C₅H ₁₁ n-C₃H ₇ n-C₅H ₁₁	H H H	1a 1b 1c	0.5 0.5 1		2a 2b 2c	98 90 91
4 5 6 ^[b]	Ts Ts Ts	$h - C_4 H_9$	<i>n</i> -C₅H ₁₁ ∽∽OAc ∽⊂Cl	н н н	1d 1e 1f	2 3 0 5	R^{1} EWG R^{2} R^{2} R^{2}	2 d 2 e 2 f ^{(d]}	76 73 83
7 ^[b] 8 9	Ts Mbs Nos	Bn Bn Bn	$\sim NPhth$ $n-C_5H_{11}$ $n-C_5H_{11}$	H H H	1g 1h 1i	0.5 0.5 24	N-R ¹ EWG	2g 2h 2i	87 91 0
10	o≁(N≓	≕ −C ₆ H ₁₃			1j	24		2j	0
11	Ts	Bn	-C ₅ H ₁₀ - ^[e]		1k	18	R ¹ _N [_] Ts	2 k n=1	96
12	Ts	n-C ₄ H ₉	-C ₅ H ₁₀ - ^[e]		11	5		21 n=1	80
13 ^[c]	Ts	3	-C ₅ H ₁₀ - ^[e]		1 m	24		2m n=1	85
14 ^[b]	Ts	Bn	-C ₆ H ₁₂ - ^[e]		1n	24	IS	2 n n=2	79

of the unreactive Au-1j species by coordination of the gold(I) complex to the more electron-rich ynamide 1j. When 1a was treated with 1i, only the homodimer 2a was produced by the selective interaction of the more favored Au-1a gold complex (versus Au-1i) with the more nucleophilic ynamide 1a (versus 1i). Finally, no selectivity was obtained when 1a was treated with 1h, and a mixture of homodimers and cross-dimers was obtained.^[8]

A surprising but interesting divergence in reactivity was observed when using tosylynamides 1k-n that possess cycloalkyl groups at the terminus of the alkyne in the gold(I)-catalyzed reaction. In these cases, no cyclopentadiene formation was observed, and instead structurally complex tricyclic compounds 2k-n were formed in an efficient (79–96% yield) and diastereoselective manner (Table 2, entries 11–14).^[9]

[a] Yield of the isolated product. [b] 5 mol% of catalyst was used. [c] 4 mol% of catalyst was used. [d] Unstable compound. [e] R^2-R^3 = cycloalkyl. Mbs = *para*-methoxybenzenesulfonyl, Nos = *para*-nitrobenzenesulfonyl, Phth = phthalimido.

substituents were tolerated on the nitrogen atom (Table 2, entries 3-5). The reaction was also compatible with a range of functional groups, such as a halide (Table 2, entries 4 and 6), an acetate (Table 2, entry 5), and a phthalimido group (Table 2, entry 7). The nature of the electron-withdrawing group was shown to strongly affect the efficiency of the reaction. While the dimerization worked equally as well with a para-methoxybenzenesulfonyl group (91%, 0.5 h; Table 2, entry 8), no cyclopentadiene was obtained with the more electron-withdrawing para-nitrobenzenesulfonyl group (Table 2, entry 9). Also, the reaction could not be performed with a more electron-rich ynamide, which possesses an oxazolidinone moiety (Table 2, entry 10). These results highlight the necessity to have a good balance in the electronic properties of the ynamide, which should play both the roles of the electrophile and the nucleophile in the dimerization process (Scheme 2).

Ynamides containing a tosyl or a methoxybenzenesulfonyl group seem to favor the dimerization because the goldcomplexed ynamide is electrophilic enough and the ynamide is nucleophilic enough for the reaction to proceed. The unsuccessful homodimerizations of substrates **1i** and **1j** (Table 2, entries 9 and 10) could be respectively explained by the comparatively weak nucleophilic character of **1i** and the comparatively weak electrophilic character of **Au-1j**.

The tentative rationale presented in Scheme 2 is supported by the results obtained when a series of crossdimerization reactions were attempted with substrates **1a** and **1h-j** (Scheme 3). No dimer was obtained when **1j** was treated with **1i** or **1a**, as a result of the preferential formation



Scheme 2. Influence of the electronic properties of the ynamide.



Scheme 3. Investigations into cross-dimerization.

A mechanistic proposal that accounts for the divergent formation of the dimeric products **2a–h** and **2k–n** is presented in Scheme 4. The nucleophilic addition of the ynamide **3** to the gold-activated ynamide could lead to the formation of the



Scheme 4. Mechanistic proposal for dimerization of alkyl-substituted ynamides.

keteniminium intermediate **4**.^[10] A subsequent 1,5-hydride shift^[11] followed by a metalla-Nazarov reaction^[3d,12] would lead to gold carbene **5**. The cyclopentadiene can then be obtained by a 1,2-hydride shift/gold catalyst regeneration analogous to that proposed for the gold-catalyzed cyclo-isomerization of allenenes.^[13] Alternatively, gold carbene **5** could lead to the formation of a fused tricyclic compound by insertion of the gold carbene into a C–H bond of the adjacent spirocycloalkyl fragment. While such a process has already been reported to operate with seven- and eight-membered cycloalkyl rings, no example is known with a six-membered ring because the elimination of the gold fragment was shown to be more favored in this case.^[12a,14]

To extend the scope of the dimerization process, we next turned our attention to the reactivity of aryl-substituted ynamides of type **6** (Scheme 5). It was hypothesized that the resulting keteniminium intermediate **7** could be trapped by the nucleophilic pendant aryl group. Tosylynamides such as **8** proved to be unreactive under the reaction conditions used. This behavior strongly contrasts with the high reactivity of tosylynamides **1a–g** in the formation of cyclopentadienes **2a– g** (Table 2). We reasoned that the electron-withdrawing



Scheme 5. Proposed dimerization of aryl-substituted ynamides.

5092 www.angewandte.org

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character of the aryl group could lower the nucleophilicity of the ynamide **8**, thus disfavoring the dimerization process. The *N*-benzyl tosylamide moiety in **8** was therefore replaced by the less electron-withdrawing oxazolidine to compensate for the negative electronic effect of the aryl group. After optimization of the reaction conditions,^[6] we were pleased to see that the corresponding ynamide **9a** could be converted into a mixture of three products in the presence of [(John-Phos)AuSbF₆]^[15] (Table 3, entry 1).

Table 3: Dimerization of aryl-substituted ynamides.



			Combined	10	11	12
	9a (R=H)	[(JohnPhos)AuSbF ₆]	75	55	9	11
2	9a (R=H)	[(IPr)AuSbF ₆]	88	35	24	29
3	9b (R = Me)	[(JohnPhos)AuSbF ₆]	82	26	39	17
1	9c (R=OMe)	[(JohnPhos)AuSbF ₆]	57	9	32	16
5	9d (R = F)	[(JohnPhos)AuSbF ₆]	76	12	28	36

[a] Yield of the isolated product. IPr = 1,3-bis(2,6-diisopropylphenyl)imidazol-2-ylidene.

Naphthalene **10a** was isolated as the major product (55% yield) along with minor amounts of azulene **11a** (9% yield) and enyne **12a** (11% yield; Table 3, entry 1).^[16] The use of [(IPr)AuSbF₆] as the catalyst (5 mol%) led to an improvement of the combined yield (88%) with increased formation of **11a** and **12a** (Table 3, entry 2).^[17] Notably, the reaction required a higher temperature (toluene, 100°C), a longer reaction time (24 h), and a higher catalyst loading (5 mol%) than for the cyclopentadiene formation. The transformation was also attempted with aryl-substituted ynamides (Table 3, entry 3–5) using [(JohnPhos)AuSbF₆] as the catalyst.^[18] The presence of a methyl or a methoxy group on the phenyl ring favored the formation of the azulene compound (**11**), while a preference for the formation of the enyne (**12**) was observed in the presence of an electron-withdrawing fluorine atom.

A mechanistic proposal for the formation of the three products is shown in Scheme 6. The naphthalenes **10** and the



Angew. Chem. Int. Ed. 2011, 50, 5090-5094



Scheme 6. Mechanistic proposal for the dimerization of aryl-substituted ynamides.

azulenes 11 might be produced by the interception of the keteniminium species 13 by the pendant aromatic ring. Compound 10 might be formed by the direct formation of the C-C bond at the ortho position of the aromatic ring (path A) or through a spirocyclization/rearrangement sequence (path B). The spiro intermediate 14 might be in equilibrium with the fused tricyclic cationic species 15, which could give 16 (path C). Species 16 could then produce azulene 11 after the elimination of the cationic gold fragment. The spirocyclization pathway leading to 11 should be favored by the presence of aryl substituents that help stabilize the cationic charge on intermediate 14 (e.g. R = Me, OMe). Enyne 12 might be formed by the alternative nucleophilic addition of the pendant oxazolidinone moiety to keteniminium 13 (path D). The resulting four-membered cyclic species 17 might then rearrange to produce an allenyliminum intermediate 18,^[19] which would finally produce 12 by the elimination of the cationic gold fragment. The formation of envne 12 corresponds to a formal stereoselective insertion of the alkyne functionality into the C-N bond of the ynamide. This process should be more favored when the nucleophilicity of the aryl group is lowered (e.g. R = F).

In conclusion, we have discovered a range of new reactions that involve ynamides, thus showing that these compounds can be dimerized in the presence of a catalytic amount of an electrophilic gold(I) complex. The efficiency of the transformation was directly dependent on the electrophile and the nucleophile in the catalytic process. Depending on the substitution pattern of the ynamide, the common keteniminium intermediate can form various dimeric compounds by either a 1,5-hydride shift, an arylation, or a 1,3-oxazolidinone shift. Further studies on this new process are in progress and will be reported in due course.

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Communications

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