Gold Catalysis

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

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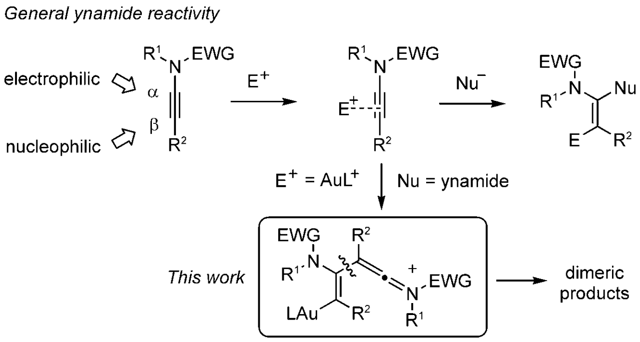
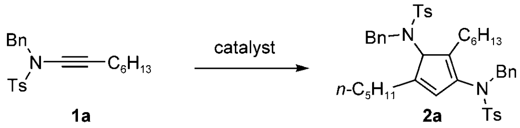
Ynamide derivatives are easily accessible and relatively stable compounds which have proved to be useful buildings blocks for the synthesis of a large variety of nitrogen-containing molecules.[1] Owing to the polarization of the triple bond, ynamides can be regioselectively activated by an electrophile 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, 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 products appear to be dependent on the electronic nature of the substituents located on the nitrogen atom and at the alkyne terminus.



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

During the course of our investigations on the gold-catalyzed 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 ^{1}H 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 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 $HNTf_2$ did not catalyse this transformation (Table 1, entry 3), while AgOTf was almost as inefficient (Table 1, entry 4).

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



Entry	Catalyst (mol %)	T [°C]	t [h]	Yield [%][b]
1	$[(Ph_3P)AuNTf_2]$ (2)	20	0.5	85
2	$[(Ph_3P)AuNTf_2]$ (2)	40	0.5	98
3	$HNTf_2$ (20)	40	2	0[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 ^{1}H NMR spectroscopy. Bn = benzyl, Tf = trifluoromethanesulfonyl, Ts = p-toluenesulfonyl.

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

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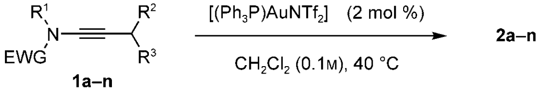
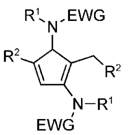
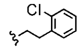
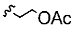
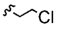
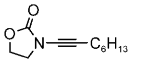
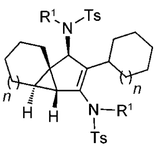
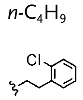
Table 2: Dimerization of alkyl-substituted ynamides.



Entry	Substrate					t [h]	Product		Yield [%][a]
	EWG	R^1	R^2	R^3					
1	Ts	Bn	n-C_5H_{11}	H	**1a**	0.5		**2a**	98
2	Ts	Bn	n-C_3H_7	H	**1b**	0.5		**2b**	90
3	Ts	n-C_4H_9	n-C_5H_{11}	H	**1c**	1		**2c**	91
4	Ts		n-C_5H_{11}	H	**1d**	2		**2d**	76
5	Ts	n-C_4H_9		H	**1e**	3		**2e**	73
6[b]	Ts	Bn		H	**1f**	0.5		**2f**[d]	83
7[b]	Ts	Bn		H	**1g**	0.5		**2g**	87
8	Mbs	Bn	n-C_5H_{11}	H	**1h**	0.5		**2h**	91
9	Nos	Bn	n-C_5H_{11}	H	**1i**	24		**2i**	0
10					**1j**	24		**2j**	0
11	Ts	Bn	-C_5H_{10}-[e]		**1k**	18		**2k** $n=1$	96
12	Ts	n-C_4H_9	-C_5H_{10}-[e]		**1l**	5		**2l** $n=1$	80
13[c]	Ts		-C_5H_{10}-[e]		**1m**	24		**2m** $n=1$	85
14[b]	Ts	Bn	-C_6H_{12}-[e]		**1n**	24		**2n** $n=2$	79

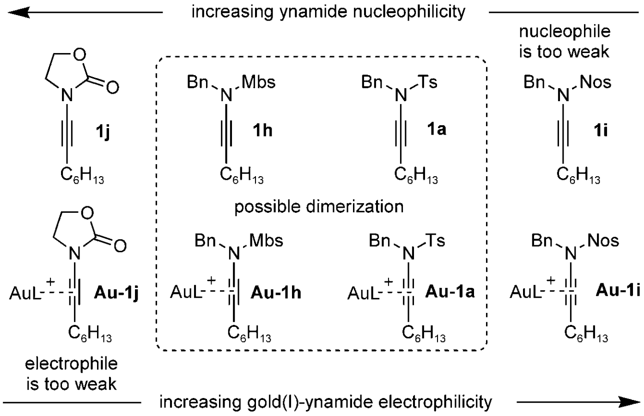
[a] Yield of the isolated product. [b] 5 mol% of catalyst was used. [c] 4 mol% of catalyst was used. [d] Unstable compound. [e] R^2—R^3 = cycloalkyl. Mbs = *para*-methoxybenzenesulfonyl, Nos = *para*-nitrobenzenesulfonyl, Phth = phthalimido.

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).

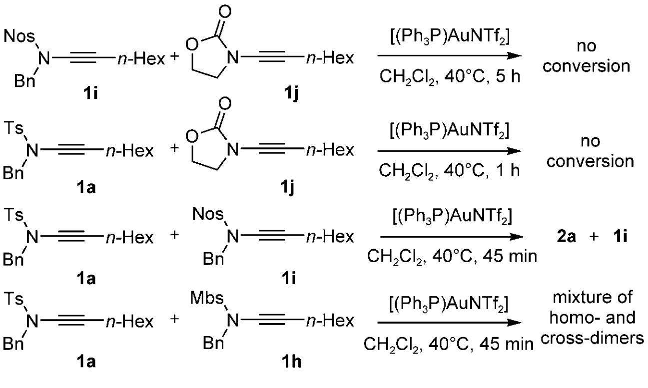
Ynamides containing a tosyl or a methoxybenzenesulfonyl group seem to favor the dimerization because the gold-complexed ynamide is electrophilic enough and the ynamide is nucleophilic enough for the reaction to proceed. The unsuccessful homodimerizations of substrates **1i** and **1j** (Table 2, entries 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 cross-dimerization 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 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]

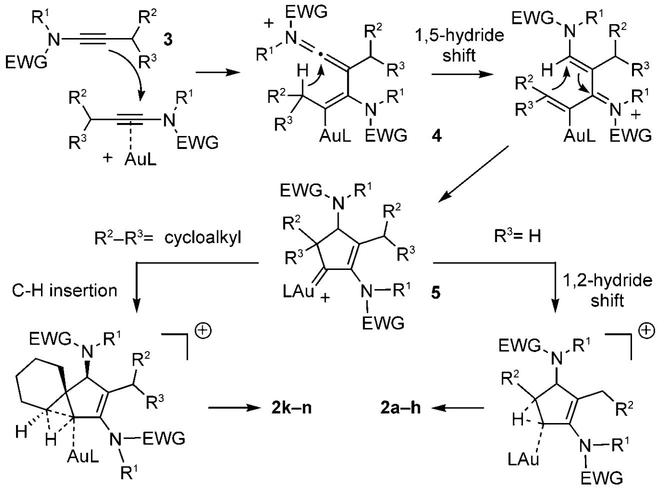


Scheme 2. Influence of the electronic properties of the ynamide.



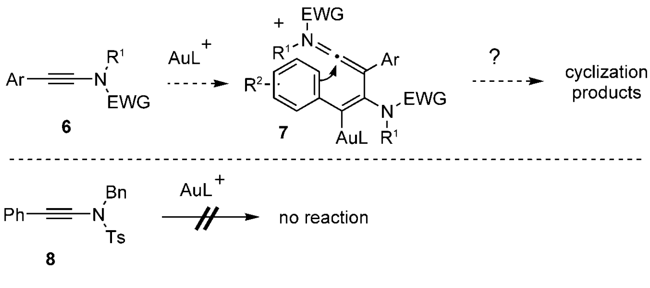
Scheme 3. Investigations into cross-dimerization.

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 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 cycloisomerization 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]



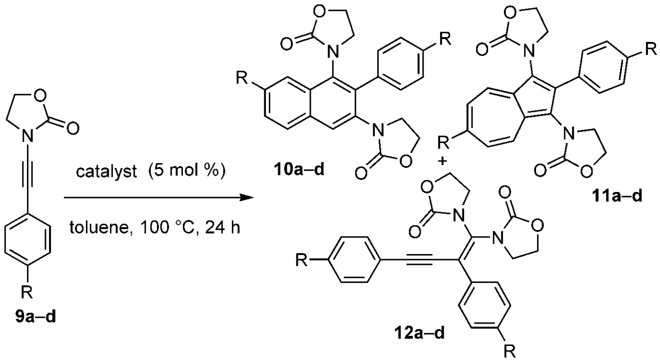
Scheme 4. Mechanistic proposal for dimerization of alkyl-substituted ynamides.

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 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 [(JohnPhos)AuSbF$_6$][15] (Table 3, entry 1).



Scheme 5. Proposed dimerization of aryl-substituted ynamides.

Table 3: Dimerization of aryl-substituted ynamides.

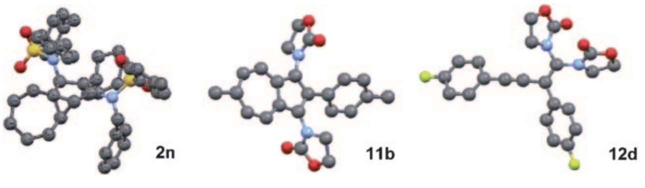


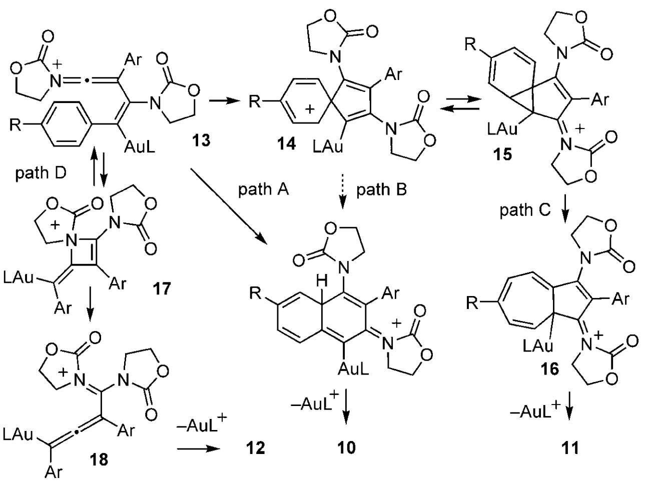
Entry	Substrate	Catalyst	Yield [%][a] Combined	10	11	12
1	**9a** (R=H)	[(JohnPhos)AuSbF$_6$]	75	55	9	11
2	**9a** (R=H)	[(IPr)AuSbF$_6$]	88	35	24	29
3	**9b** (R=Me)	[(JohnPhos)AuSbF$_6$]	82	26	39	17
4	**9c** (R=OMe)	[(JohnPhos)AuSbF$_6$]	57	9	32	16
5	**9d** (R=F)	[(JohnPhos)AuSbF$_6$]	76	12	28	36

[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)AuSbF$_6$] 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)AuSbF$_6$] 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





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 enyne **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 electronic properties of the ynamide, which acts both as 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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[4] For recent contributions from our research group, see: a) S. Kramer, J. L. H. Madsen, M. Rottländer, T. Skrydstrup, *Org. Lett.* **2010**, *12*, 2758; b) S. Kramer, K. Dooleweerdt, A. T. Lindhardt, M. Rottländer, T. Skrydstrup, *Org. Lett.* **2009**, *11*, 4208.

[5] The cyclopentadiene core structure of compound **2a** was confirmed by X-ray crystallographic analysis (see the Supporting Information). CCDC 811770 (**2a**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

[6] See the Supporting Information for details about the optimization of the catalytic system.

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[8] Attempts to cross-dimerize ynamide **9a** with **1a** were also unsuccessful.

[9] The structures of **2k–n** were assigned on the basis of ^{1}H NMR spectroscopic analysis, and confirmed by X-ray crystallographic analysis of **2n**. CCDC 811773 (**2n**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

[10] Gold-catalyzed alkyne–alkyne coupling is a rare process. For an example of intramolecular alkyne–alkyne couplings leading to enynes, see: a) Y. Odabachian, X. F. Le Goff, F. Gagosz, *Chem. Eur. J.* **2009**, *15*, 8966; for the cyclization of diaryldiynes, see: b) J.-J. Lian, P.-C. Chen, Y.-P. Lin, H.-C. Ting, R.-S. Liu, *J. Am. Chem. Soc.* **2006**, *128*, 11372; c) T. Shibata, R. Fujiwara, D. Takano, *Synlett* **2005**, 2062.

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[16] The structures of **11a–d** and **12a–d** were assigned on the basis of ^1H NMR spectroscopic analysis, and confirmed by X-ray crystallographic analysis of **11b** and **12d**. CCDC 811771 (**11b**) and 811772 (**12d**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

[17] Despite intensive investigation, we did not manage to find a catalytic system that resulted in the selective formation of one of the products.

[18] Lower combined yields were obtained when [(IPr)AuSbF$_6$] was used as a catalyst for the dimerization of ynamides **9b–d**.

[19] R. P. Hsung, C. A. Zificsak, L.-L. Wei, C. J. Douglas, H. Xiong, J. A. Mulder, *Org. Lett.* **1999**, *1*, 1237.