Gold Catalysis

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Anion-Induced Enantioselective Cyclization of Diynamides to Pyrrolidines Catalyzed by Cationic Gold Complexes**

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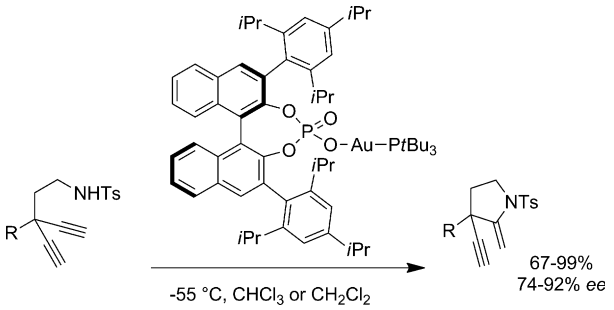
Dedicated to Professor Konstantin-Alexander Hossmann on the occasion of his 75th birthday

In the area of homogeneous catalysis few metals have received as much attention as gold in recent years, resulting in the discovery of a plethora of mechanistically diverse reactions.[1] The ability of gold complexes to activate C–C multiple bonds towards the attack of various nucleophiles under mild conditions makes this catalyst class highly valuable for the formation of unusual and complex structural motifs.[2–4] Enantioselective methods employing optically active gold catalysts are more limited in number.[5] Reliable methods using chiral phosphine or carbene ligands have been developed in particular for the transformation of allenes and enynes.[6] In contrast, only few examples of the enantioselective heterofunctionalization of simple alkynes have been reported.[7,8] Terminal alkynes in particular have proven to be very difficult substrates. This can be explained by the linear coordination geometry in gold(I)–alkyne complexes which results in a large distance between the chiral ligand and the incoming nucleophile. Based on the development of chiral Brønsted acids by Akiyama et al., Toste and co-workers reported the application of chiral counteranions in gold catalysis, thereby greatly extending the possibilities for stereocontrol, as exemplified by the functionalization of allenes.[9,10]

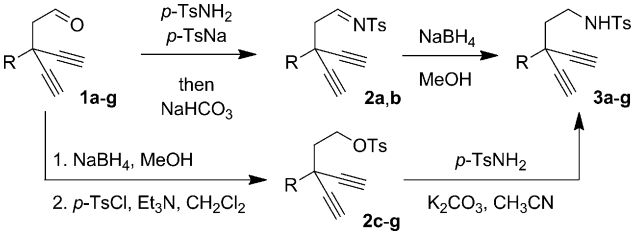
Recently, we have developed a new methodology for the gold-catalyzed cyclization of 1,4-diynes.[7a,11] We have demonstrated that diynols and diynamides can be effectively cyclized by cationic gold complexes to give the corresponding unsaturated heterocycles. However, in the screening of optically active phosphine and carbene ligands, products with enantioselectivities of only up to 60% *ee* were obtained.[7a,11] Herein we disclose the efficient enantioselective cycloisomerization of diynamides which is the first example of a highly stereoselective desymmetrization of terminal alkynes by gold catalysts with chiral counteranions (Scheme 1). The



Scheme 1. Enantioselective desymmetrization of 1,4-diynamides.

methylene pyrrolidine products incorporate an all-carbon-substituted quaternary stereocenter. Such scaffolds are found in many natural products, such as alkaloids, but are very challenging to prepare in enantiomerically pure form.[12,13]

The diynamide substrates **3a–g** were prepared from the corresponding diynals **1a–g** by formation of *p*-tosyl imines **2a**,**b** and subsequent reduction with $NaBH_4$ or by the S_N2 displacement of *p*-toluene sulfonates **2c–g** with *p*-toluene sulfonamide (Scheme 2).[11a,14]



Scheme 2. Preparation of 1,4-diynamides.

With the substrates in hand we first investigated suitable conditions for their gold-catalyzed cycloisomerization. It was found that cationic gold complexes could efficiently catalyze the formation of the methylene pyrrolidines (Table 1).[15] When catalysts incorporating various chiral phosphines were used, the products were isolated in yields up to 93% but very low enantioselectivities were observed (Table 1, entry 4).

Given these discouraging results with chiral ligands we investigated cationic gold complexes with optically active counteranions derived from binol hydrogen phosphate.[17] We could show that such catalysts are indeed active for the intended cycloisomerization (Table 2). Closely related gold

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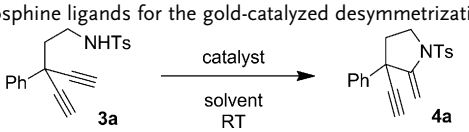
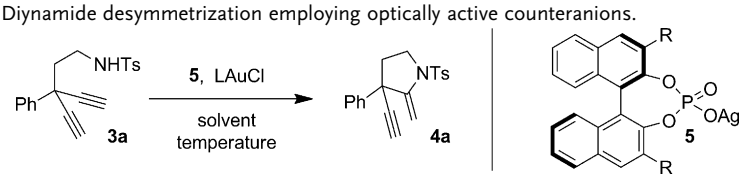
Table 1: Screening of phosphine ligands for the gold-catalyzed desymmetrization of diynamides.



Entry	Catalyst[16]	mol%	Solvent	*t* [h]	Yield [%]	*ee* [%][a]
1	$[(Ph_3P)AuCl]/AgBF_4$	4	THF	1	92	–
2	$[(DTBM\text{-}OMe\text{-}biphep)AuCl]/AgBF_4$	4	CH_2Cl_2	1	84	<3
3	$[(Tol\text{-}binap)(AuOPNB)_2]$	5	THF	3	7	n.d.[b]
4	$[(Tol\text{-}binap)(AuCl)_2]/AgBF_4$	8	THF CH_2Cl_2	18	93	9
5	$[(DTBM\text{-}segphos)(AuOPNB)_2]$	1	THF	3	11	<3
6	$[(DTBM\text{-}segphos)(AuCl)_2]/AgBF_4$	8	THF CH_2Cl_2	18	66	9

[a] Determined by HPLC on a chiral stationary phase. [b] Not determined.

Table 2: Diynamide desymmetrization employing optically active counteranions.



Entry	L	R (anion)	mol%	Solvent	*T* [°C]	*t* [h]	Yield [%]	*ee* [%]
1	Ph_3P	$SiPh_3$	4	CH_2Cl_2	RT	20	67	14
2	Ph_3P	$3,5\text{-}(CF_3)_2C_6H_3$	4	CH_2Cl_2	RT	1	87	30
3	Ph_3P	9-anthracenyl	4	CH_2Cl_2	RT	2	71	6
4	Ph_3P	9-phenanthryl	4	CH_2Cl_2	RT	2	23	16
5	Ph_3P	$2,4,6\text{-}iPr_3C_6H_2$	4	CH_2Cl_2	RT	2	87	56
6	Ph_3P	$2,4,6\text{-}iPr_3C_6H_2$	4	THF	RT	1	12	<3
7	Ph_3P	$2,4,6\text{-}iPr_3C_6H_2$	4	toluene	RT	24	20	42
8	Cy_3P	$2,4,6\text{-}iPr_3C_6H_2$	4	CH_2Cl_2	RT	2	<5	57
9	tBu_3P	$2,4,6\text{-}iPr_3C_6H_2$	4	CH_2Cl_2	RT	4	93	73
10	dppm	$2,4,6\text{-}iPr_3C_6H_2$	5	CH_2Cl_2	−55	4	27	<3
11	Ph_3P	$2,4,6\text{-}iPr_3C_6H_2$	4	CH_2Cl_2	−35	24	72	84
12	tBu_3P	$2,4,6\text{-}iPr_3C_6H_2$	4	CH_2Cl_2	−35	24	73	86
13	tBu_3P	$2,4,6\text{-}iPr_3C_6H_2$	5	CH_2Cl_2	−55	48	89	89
14	tBu_3P	$2,4,6\text{-}iPr_3C_6H_2$	5	CH_2Cl_2/ *n*-pentane	−55	24	53	82
15	tBu_3P	$2,4,6\text{-}iPr_3C_6H_2$	5	$CHCl_3$	−55	22	>99	92
16	tBu_3P	$2,4,6\text{-}iPr_3C_6H_2$	2	$CHCl_3$	−55	92	67	89
17	tBu_3P	$2,4,6\text{-}iPr_3C_6H_2$	5	$CHCl_3$/ CCl_4	−55	66	73	89

phosphate complexes ($L = PPh_3$, $R = SiPh_3$) were reported by Echavarren and co-workers to react with 1,6-enynes to form stable gold acetylides which did not undergo cycloisomerization.[18] Potentially, also in our case of diynamides **3**, gold acetylides may be formed, but reversible protonation by the *p*-tosylamide moiety might be responsible for restoring the observed catalytic activity.

In these studies we found that the substituent at the 3,3′-position of **5** plays a crucial role with respect to the enantioselectivity of the reaction (Table 2, entries 1–5). In particular silver 3,3′-(triisopropylphenyl)binol phosphate (TriPAg) gave promising results (56% *ee* at room temperature). Also the size of the phosphine ligand L has a significant influence on the stereoselectivity (Table 2, entries 8–11). The use of the electron-rich, sterically demanding tri-*tert*-butylphosphine ligand provided a fast and selective catalyst. The reaction was most selective at low temperatures in nonpolar solvents. This is in line with the assumption that a contact ion pair is formed by the cationic gold–alkyne complex and the anionic chiral phosphate.[19] Chlorinated solvents such as CH_2Cl_2 and $CHCl_3$ gave the best results (>99% yield, 92% *ee*; Table 2, entry 15). The enantiopurity of the product could be further increased to 96% *ee* by simple recrystallization from *n*-hexane. It was observed that selectivities varied significantly when the cationic gold catalyst was prepared in situ from the gold chloride complex and TriPAg. Reproducible results were obtained, however, when the gold phosphate was prepared in pure form beforehand.

Using the optimized conditions, the method was evaluated with respect to the substrate scope. Diynes bearing aromatic and aliphatic substituents were suitable substrates and the products were isolated in 67–99% yield (Table 3). Surprisingly, diynes bearing alkyl groups undergo the cycloisomerization much more slowly than the corresponding aromatic counterparts and require a higher catalyst loading (15 mol%). In these cases the best selectivities were consistently obtained using CH_2Cl_2 instead of $CHCl_3$.

In summary, we have developed a desymmetrization reaction of 1,4-diynamides facilitated by gold catalysis. Methylene pyrrolidines are formed in a cycloisomerization process using cationic gold catalysts with optically active and commercially available binol phosphates as counteranions. The best results were obtained in chlorinated solvents at low temperatures. The products are highly valuable chiral building blocks for organic synthesis because they incorporate an all-carbon-substituted quaternary stereocenter and are difficult to prepare in enantiomerically pure form by other methods. Currently, an application of this new methodology for the construction of more complex structures, such as alkaloids, is being investigated and will be reported in due course.

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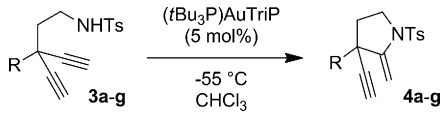
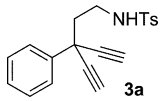
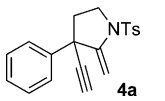
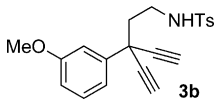
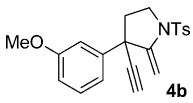
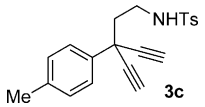
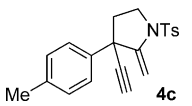
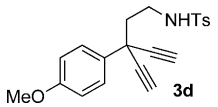
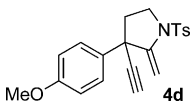
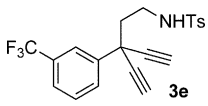
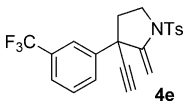
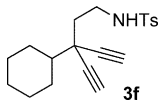
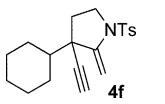
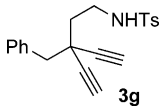
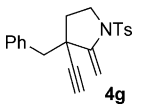
Keywords: alkynes · asymmetric catalysis · gold · nitrogen heterocycles · pyrrolidines

Table 3: Gold-catalyzed enantioselective synthesis of methylene pyrrolidines.[a]



Entry	Substrate	Product	Time	Yield [%][b]	*ee* [%][c]
1	 **3a**	 **4a**	22 h	>99	92
2	 **3b**	 **4b**	24 h	94	77
3	 **3c**	 **4c**	21 h	>99	86
4	 **3d**	 **4d**	21 h	93	82
5	 **3e**	 **4e**	24 h	87	81
6[d]	 **3f**	 **4f**	7 d	47	77
7[d,e]			7 d	67	82
8[d]	 **3g**	 **4g**	7 d	53	64
9[d,e]			7 d	80	74

[a] Reaction conditions: catalyst (5 mol%), −55 °C, chloroform (except for entries 7 and 9), 0.1 M. [b] Yield of isolated product. [c] Determined by HPLC on a chiral stationary phase. [d] 15 mol% of catalyst was employed. [e] CH_2Cl_2 was employed instead of $CHCl_3$.

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