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Binap-gold(I) trifluoroacetate as a bifunctional catalyst for the synthesis of chiral prolines through 1,3-dipolar cycloaddition of azomethine ylides

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Dedicated to Professor Henri Kagan on the occasion of his 80th birthday

ABSTRACT

Highly enantioselective 1,3-dipolar cycloadditions of amino acid-derived azomethine ylides with alkenes have been performed, for the first time, under gold-catalysis using (S_a)- or (R_a)-Binap-gold(I) trifluoroacetate complexes, with the cationic Binap-gold acting as a Lewis acid and the counteranion as a base. Maleimides and *trans*-1,2-bis(phenylsulfonyl)ethylene were reacted with imino esters at room temperature in the absence of a base to afford, in very good yields, the corresponding polysubstituted prolines with total *endo*-diastereoselection and higher enantioselectivities than the Binap-silver trifluoroacetate complex.

1. Introduction

Coinage metals attract particular interest from synthetic organic chemists, because those metals become useful catalysts for synthesizing the core of many important drugs containing heterocyclic structures.[1] The main features of these metal complexes are good chemoselectivity, good functional group compatibility, and stability, traits that are crucial for application in complex molecular environments. One of the most representative examples concerns the synthesis of enantiomerically enriched prolines[2] through the catalytic enantioselective 1,3-dipolar cycloaddition[3] (1,3-DC) between azomethine ylide and alkenes. In fact, silver- and copper-catalyzed 1,3-DC are very well known and constitute as the most reliable and inexpensive enantioselective methodology to build up to four stereogenic centers of the resulting proline derivatives, in only one reaction step. In addition, they exhibit more versatility and a wider scope than the analogous enantioselective organocatalyzed 1,3-dipolar cycloadditions.[3a]

Chiral gold complexes have been employed in the enantioselective activation of allenes, and in the nucleophilic additions onto alkynes and alkenes.[4] Toste et al. reported a very efficient enantioselective cycloaddition of münchnones and electron-deficient alkenes employing (S_a)-Cy-SEGPHOS(AuOBz)$_2$ as a catalyst. This transformation, followed by an ester/amide formation, furnished pyrrolines in very high enantioselectivity.[5] However, chiral gold complexes have not been employed as catalysts for the 1,3-DC of amino acids-derived iminoesters.

The first attempt for the enantioselective 1,3-DC of azomethine ylides with dimethyl maleate was described in 2002 using 3 mol % of (S_a)-Binap and AgOAc and Et_3N as base with very poor results.[6] Our research group found that (S_a)- or (R_a)-Binap-$AgClO_4$ complexes were excellent recoverable catalysts for the 1,3-DC of azomethine ylides and maleimides furnishing excellent enantioselections[7] Recently, we also reported an improvement of this reaction using $AgSbF_6$ instead of silver perchlorate.[8] In general, these last two mediated (S_a)-Binap-Ag(I) cycloadditions are very sensitive to the presence of a bulky substituent in the dipole and in the maleimide and to the organic base used as a co-catalyst. In order to overcome it, we envisaged that the existence of a larger cationic center such as gold(I) in the presence of a basic counteranion would be interesting to test in this catalytic enantioselective 1,3-DC. Herein, we survey the efficiency of (R_a)- and (S_a)-Binap-gold(I) trifluoroacetate in the intermolecular 1,3-DC employing iminoesters and electrophilic alkenes.

2. Results and discussion

Chiral (R_a)- and (S_a)-Binap-AuCl complexes were prepared by mixing (Me_2S)AuCl and the corresponding amount of the chiral diphosphane ligand. These complexes were treated with different silver salts derived from carboxylic acids for 1 h in toluene. The resulting suspension was filtered through a celite plug and the solution was evaporated to yield the title complexes. These cationic complexes were immediately employed in the catalytic enantioselective 1,3-DC of imino ester **1a** and *N*-methylmaleimide (NMM) in toluene at rt (Scheme 1 and Table 1). When this cycloaddition was performed in the presence of 10 mol % of diisopropylethylamine (DIPEA) and 10 mol % of complex (S_a)-Binap-AuCl, product *endo*-**2aa** was obtained with high conversion but in racemic form (Table 1, entry 1). In the case of the gold(I) acetate complex, product *endo*-**2aa** was obtained with high conversion and 60% ee in the presence of DIPEA and in 70% ee in the absence of base (Table 1, entries 2 and 3). Better results were achieved when using the

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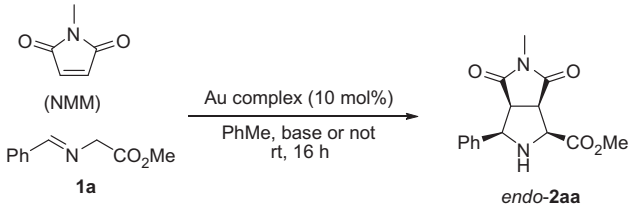
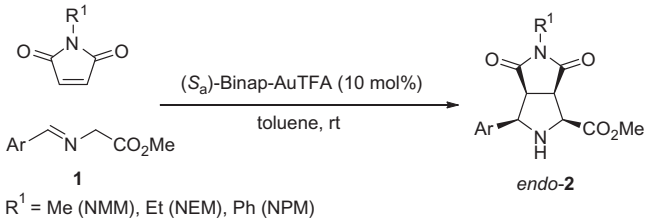


Scheme 1.



Scheme 2.

Table 1
Catalyst studies for 1,3-DC between iminoester **1a** and NMM

Entry	Gold(I) catalyst (10 mol %)	Base (10 mol %)	Conv.[a,b] (%)	ee[c] (%)
1	(S_a)-Binap-AuCl	DIPEA	>95	rac.
2	(S_a)-Binap-AuCl/AgOAc	DIPEA	>95	62
3	(S_a)-Binap-AuCl/AgOAc	—	>95	70
4	(S_a)-Binap-AuCl/AgOBz	DIPEA	>95	74
5	(S_a)-Binap-AuCl/AgOBz	—	>95	94[d]
6	(S_a)-Binap-AuCl/AgTFA	DIPEA	>95	74
7	(S_a)-Binap-AuCl/AgTFA	—	90	99
8	(R_a)-Binap-AuCl/AgTFA	—	>95	*ent*-99
9	(S_a)-Binap-AgTFA	—	>95	99
10	(S_a)-Binap-$(AuCl)_2$/$(AgTFA)_2$	—	>95	rac.
11	(S_a)-Binap-AuCl/AgTFA[e]	—	90	60

[a] Determined by ^{1}H NMR of the crude sample.
[b] The observed *endo*:*exo* ratio was always >98:2 (^{1}H NMR).
[c] Determined by chiral HPLC analysis (Daicel, Chiralpak AS).
[d] Notable amounts of unidentified side products were observed (^{1}H NMR).
[e] The reaction was performed with 5 mol % of catalyst.

benzoate anion to afford *endo*-**2aa** in 74% and 94% ees (Table 1, entries 4 and 5). Although product *endo*-**2aa** was obtained in higher 94% ee in the absence of DIPEA, it was contaminated with secondary by-products (Table 1, entry 5). When gold(I) trifluoroacetate complexes were used as catalysts, 74% ee was obtained in the presence of DIPEA (Table 1, entry 6), whereas without base, 99% ee was obtained (Table 1, entries 7 and 8). A similar result was obtained when the reaction was performed with the chiral complex (S_a)-Binap-AgTFA in the absence of base (Table 1, entry 9). On the other hand, the (S_a)-Binap-$(AuCl)_2$/$(AgTFA)_2$ complex proved to be ineffective catalysts because *endo*-**2aa** was obtained as a racemate (Table 1, entry 10). Attempts to decrease the (S_a)-Binap-AuTFA loading to 5 mol % gave lower enantioslectivity (Table 1, entry 11).

The scope of this enantioselective 1,3-DC was studied using different iminoesters and maleimides under the best reaction conditions (Scheme 2 and Table 2). Products **2** were obtained as *endo*-diastereomers (>98:2, determined by ^{1}H NMR spectroscopy). In the first examples performed with *N*-ethyl and *N*-phenylmaleimide the absence of base gave products **2ab** and **2ac** with higher enantioselectivity (Table 2, compare entries 1 with 2 and 3 with 4). The result obtained when NPM was employed as a dipolarophile is particularly noteworthy. When (S_a)-Binap-AgTFA was used as catalyst racemic product **2ac** was obtained. For the 1,3-DC of other arylideneaminoesters **1b**, **c**, **d**, and **e** with NMM, products **2ba**, **2ca**, **2da**, and **2ea** were obtained in high yields and enantioselectivities (Table 2, entries 5–8). When the catalyst loading employed was reduced to 5 mol % these 1,3-DC needed longer periods to complete, yielding *endo*-cycloadducts **2** with lower enantioselection.

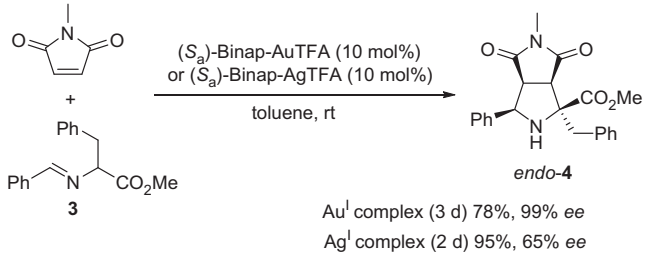
The insertion of a substituent at the α-position of the 1,3-dipole precursor was next evaluated. Thus, when methyl benzylideneiminophenylalaninate **3** was allowed to react with NMM under the standard reaction conditions, the reaction performed with the gold(I) complex needed 24 h more than the corresponding reaction using the analogous silver(I) complex for achieving almost

Table 2
Gold-catalyzed 1,3-DC between iminoglycinates **1** and maleimides

Entry	**1**	Ar	R^1	Base	Time (h)	**2**	Yield[a,b] (%)	ee[c] (%)
1	**1a**	Ph	Et	DIPEA	16	**2ab**	Quant.	70
2	**1a**	Ph	Et	—	48	**2ab**	Quant.	99
3	**1a**	Ph	Ph	DIPEA	16	**2ac**	90	64
4	**1a**	Ph	Ph	—	48	**2ac**	92	80
5	**1b**	2-MeC_6H_4	Me	—	48	**2ba**	86	88
6	**1c**	2-ClC_6H_4	Me	—	48	**2ca**	88	99
7	**1d**	4-(MeO)C_6H_4	Me	—	48	**2da**	95	>99
8	**1e**	2-Naphthyl	Me	—	48	**2ea**	94	91

[a] Isolated yields after flash chromatography (silica gel).
[b] The observed *endo*:*exo* ratio was >98:2 (^{1}H NMR).
[c] Determined by chiral HPLC analysis.

total conversions (Scheme 3). The enantioselection showed by (S_a)-Binap-AuTFA complex (99% ee) was higher than in the case of using (S_a)-BinapAgTFA (65% ee) as a catalyst.

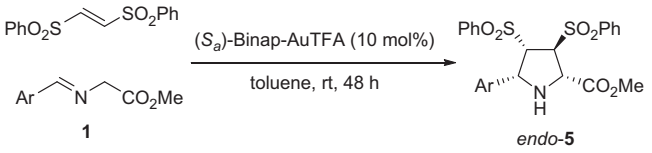


Scheme 3.

According to our experience with the results obtained from the application of chiral Binap-silver(I) complexes in the enantioselective 1,3-DC of azomethine ylide and electrophilic alkenes,[7,8] we also tested the efficiency of the Binap-gold(I) trifluoroacetate complexes in the enantioselective cycloaddition of azomethine ylides and *trans*-1,2-bis(phenylsulfonyl)ethylene, a synthetic equivalent of acetylene (Scheme 4 and Table 3). The reaction performed with 10 mol % of the gold(I) catalyst afforded cycloadducts **5** in similar or higher enantioselectivities in the absence of DIPEA. In the case of product **5a**, a lower enantiomeric excess was obtained when (S_a)-Binap-AgTFA was used as catalyst (Table 3, compare entries 1 and 3). Compounds *endo*-**5f** and **5g** were obtained in better enantiomeric excesses in the absence of base (Table 3, entries 4–7).

The absolute configuration of the *endo*-cycloadducts was assigned according to the chiral HPLC retention times and by comparison of the physical properties of the isolated samples with the properties published in the literature for the analogous compounds.

The full characterization of the dimeric species [(rac)-Binap-AuTFA]$_2$ was published by Puddephatt et al.[9] when they mixed equimolar amounts of the ligand and gold(I) salt. In our case, all



Scheme 4.

Table 3
Gold-catalyzed 1,3-DC between iminoglycinates **1** and *trans*-1,2-bis(phenylsulfonyl)ethylene

Entry	1	Ar	Base (10 mol %)	5	Yield[a,b] (%)	ee[c] (%)
1	**1a**	Ph	DIPEA	**5a**	80	86
2	**1a**	Ph	—	**5a**	74	99
3[d]	**1a**	Ph	—	**5a**	76	96
4	**1f**	4-MeC_6H_4	DIPEA	**5f**	81	88
5	**1f**	4-MeC_6H_4	—	**5f**	67	99
6	**1g**	3-Pyridyl	DIPEA	**5g**	73	96
7	**1g**	3-Pyridyl	—	**5g**	73	96

[a] Isolated yields after flash chromatography (silica gel).
[b] The observed *endo*:*exo* ratio was always >98:2 (^{1}H NMR).
[c] Determined by chiral HPLC analysis.
[d] Reaction performed with (S_a)-Binap-AgTFA.

the data obtained were in accordance with those published. Thus, the ^{31}P NMR analysis of [(S_a)-Binap-AuTFA]$_2$ in $CDCl_3$ showed a singlet at 41.1 ppm, whereas the (S_a)-Binap-AuCl complex gave a singlet at 23.3 ppm; in the case of ESI-MS experiments, peaks at 819, 819.2 and 819.6 were observed on elution with a mixture of acetonitrile and water, demonstrating the existence of such a dimeric complex. Further experimental and theoretical studies on the structure of the dimeric 1:1 Binap-gold complexes and the 1,3-dipole are currently underway.

3. Conclusion

In conclusion, it has been demonstrated that cationic gold complexes efficiently catalyze 1,3-DC of azomethine ylides and dipolarophiles. Chiral (R_a)- and (S_a)-Binap-AuTFA complexes work as bifunctional catalysts.[10] The trifluoroacetate acts as Brønsted base forming the imino ester enolate, which is coordinated with the Lewis acid, the Binap-gold cation. In general, the (S_a)-Binap-gold(I) trifluoroacetate complex induces higher enantioselections, even with sterically hindered substrates such as, NPM, *trans*-1,2-bis(phenylsulfonyl)ethylene, and α-substituted iminoesters, than the (S_a)-Binap-silver(I) trifluoroacetate complex.[11]

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11. General procedure for the catalytic enantioselective 1,3-DC using (R_a)- or (S_a)-BinapAuTFA complexes: To a solution of the in situ prepared chiral gold complex (0.05 mmol, 46 mg) in toluene (2 mL) was added at room temperature a solution of the iminoester (0.5 mmol) and dipolarophile (0.5 mmol) in toluene (2 mL). In some cases DIPEA (0.05 mmol, 14 μL) was added (see Tables) and the mixture was stirred at room temperature for 16–48 h (see Tables) The reaction was filtered off and the organic filtrate was directly evaporated and the residue was purified by recrystallization or by flash chromatography yielding pure *endo*-cycloadducts **2**, **4**, or **5**.