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Recoverable (*R*)- and (*S*)-Binap–Ag(I) Complexes for the Enantioselective 1,3-Dipolar Cycloaddition Reaction of Azomethine Ylides§

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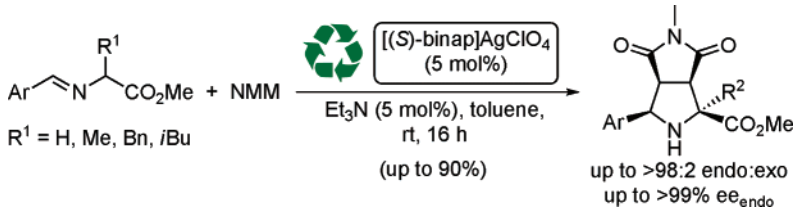
ABSTRACT



The first enantioselective 1,3-dipolar cycloaddition reaction of amino acid derived azomethine ylides and maleimides catalyzed by very stable and recyclable chiral (*R*)- or (*S*)-binap–$AgClO_4$ complexes is described. The reactions are performed at room temperature, in good yields, with high endo diastereoselectivity and enantioselectivity, the complex being recovered by simple filtration.

The development of recyclable and reusable catalysts has became a key issue in the field of asymmetric catalysis. Lots of work has gone into the achievement of recovery methods for metal complexes focused on waste minimization, regeneration, and recycling.[1,2] Traditionally, the employment of a solid support, which contains the ligand, is a very useful practice, but a lower catalytic activity and, in many occasions, the leaching of the ligand and the metal are two important drawbacks.

Particularly, the characterization, the recovery, and the recycling of the catalysts in the catalytic enantioselective 1,3-dipolar cycloaddition reaction (1,3-DCR) are still an important challenge. The asymmetric 1,3-DCR of azomethine ylides,[3] generated from the corresponding imino ester and alkenes, is one of the most fascinating transformations because the configuration of the four new stereogenic centers of the finally obtained proline[4,5] can be absolutely established in only one step with total atom economy. Very recent catalyzed enantioselective 1,3-DCRs[6−20] show that, in general, chiral silver and copper complexes are adequate catalysts

§ Dedicated to Professors Juan Forniés and José Gimeno on the occasion of their 60th birthdays.

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for the synthesis of endo and exo adducts, respectively. Bidentate ligands, such as bisphosphanes,[6,9] nitrogenated phosphanes,[7,10,11,15,17,19,20] and sulfur-containing phosphanes[14] have shown very high enantioselectivity levels.

Several stable silver triflate complexes **1**−**3** with (*R*)-binap as a ligand have been isolated and characterized by X-ray diffraction analysis by Yamamoto's group.[21] They play an important role as catalysts in the regio- and enantioselective *O*- and *N*-nitroso aldol synthesis of tin enolates (Figure 1).

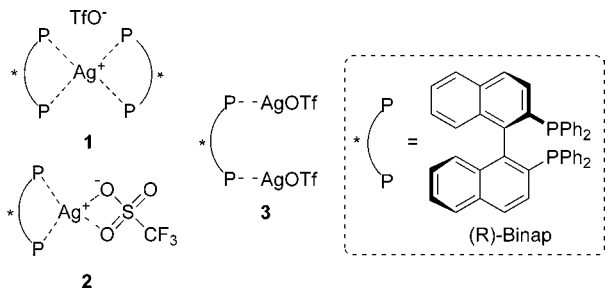
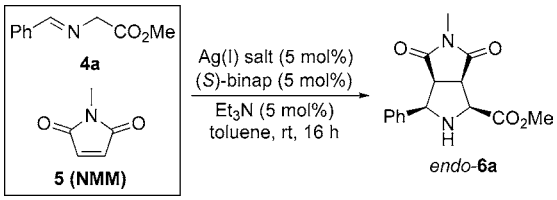


Figure 1. [(*R*)-Binap]AgOTf complexes.

In this communication, we describe a highly diastereo- and enantioselective 1,3-DCR between 1,3-dipoles generated from imino esters derived from α-amino acids and *N*-methylmaleimide (NMM) by using binap[22]−$AgClO_4$ complexes as recoverable and reusable catalysts.

Although the combination (*S*)-binap−AgOAc has shown low ee in 1,3-DCRs using dipoles derived from imino esters and dimethyl maleate (up to 13% ee)[6] or phenyl vinyl sulfone (up to 26% ee)[17,20] as dipolarophiles, our findings in a similar reaction but employing NMM as the dipolarophile were very promising. Initially, 1:1 (*S*)-binap−silver salt complexes, such as AgOAc, AgOTf, AgF, $AgClO_4$, and $AgClO_4 \cdot H_2O$, were essayed in the standard reaction of methyl benzyli-

Scheme 1. Optimization of the Enantioselective Synthesis of Product *endo*-**6a**



deneiminoglycinate **4a** and NMM **5** at room temperature, using toluene as solvent and a substoichiometric amount (5 mol %) of triethylamine as base in the absence of light (Scheme 1 and Table 1). The amounts of chiral ligand and silver salt employed were 5 mol % each and were mixed in toluene and stirred for 1 h before adding the reagents. The corresponding adduct *endo*-**6a**[23] was mainly obtained in all cases in good yields, and high enantioselectivity (Table 1, entries 1−6) and any exo product were detected by ^{1}H NMR experiments (indicated as endo/exo > 98:2). The reaction became slower (1.5 days) if 3 mol % of catalyst was employed, achieving similar yields and stereoselectivities (Table 1, entry 5). However, disappointing conversions, yields, and diastereo- and enantioselections appeared when using catalyst loadings lower than 3 mol %. The highest diastereo- and enantioselectivities were observed when we employed a 1:1 (*S*)-binap−$AgClO_4$ ratio instead of a 2:1 (*S*)-binap−$AgClO_4$ mixture (Table 1, compare entries 4 and 7). In addition, a 1:2 (*S*)-binap−$AgClO_4$ mixture afforded good yields and conversions but very low enantioselection (Table 1, entry 8). Other solvents such as THF or dichloromethane gave lower enantioselectivities of product **6a**. A similar effect was observed when the reaction was run at 0 °C, the reaction

Table 1. Evaluation of Silver Salts and Binap Complexes in the Enantioselective Synthesis of Cycloadduct **6a**

	(*S*)-binap: AgX	AgX	product **6a**[a] yield (%)[b]	endo/exo[c]	ee_{endo} (%)[d]
1	1:1	AgOAc	89	>98:2	99
2	1:1	AgOTf	88	90:10	99
3	1:1	AgF	81	90:10	98
4	1:1	$AgClO_4$	90	>98:2	>99
5	1:1	$AgClO_4$[e]	90	>98:2	>99
6	1:1	$AgClO_4 \cdot H_2O$	89	>98:2	99
7	2:1	$AgClO_4$	90	90:10	98
8	1:2	$AgClO_4$	91	90:10	<50

[a] The conversions were higher than 95% (determined by ^{1}H NMR spectroscopy). [b] Isolated yield after recrystallization. [c] Determined by ^{1}H NMR spectroscopy of the crude product. [d] Determined by chiral HPLC (Daicel Chiralpak AS) of the crude product. [e] Reaction performed with a 3 mol % loading of catalyst (*S*)-**7** after more than 1.5 days of the reaction time.

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(23) The term endo obeys to the approach of the dipolarophile with its electron-withdrawing group oriented to the metal center, independently of whether the reaction is concerted at the transition state.

becoming extremely slow. Any difference was detected by employing diisopropylethylamine or DBU as base instead of triethylamine.

Although the [(*S*)-binap]−AgOAc and [(*S*)-binap]−$AgClO_4$ salts gave similar results (Table 1, entries 1 and 4), the last one was rather insoluble in toluene and it could be separated almost quantitatively from the reaction mixture by filtration. The (*R*)- and (*S*)-binap−$AgClO_4$ complexes **7** were very stable, and any apparent decomposition occurred upon light exposure. These complexes **7** (Figure 2) were prepared

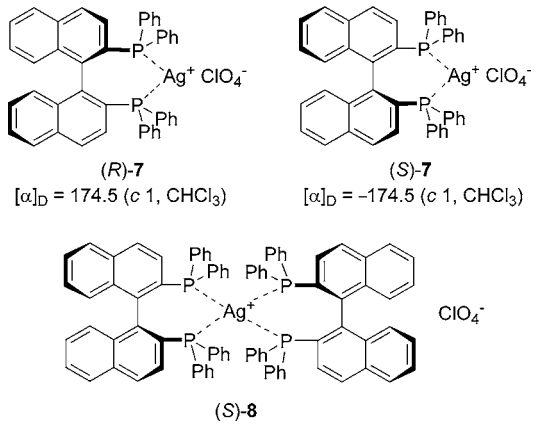


Figure 2. Structures of complexes (*R*)-**7**, (*S*)-**7**, and (*S*)-**8**.

and isolated upon reaction of (*R*)- or (*S*)-binap and $AgClO_4$ at room temperature, in toluene for 1 h. The 1:1 complex (*S*)-**7** was obtained in quantitative yield [$[\alpha]_D = -174.5$ (*c* 1, $CHCl_3$)] and was further characterized by ESI-MS experiments showing a $M^+ + 1$ signal at 731 and a tiny one at 1353. The same MS experiments revealed a peak at 1353 and a very small one at 731 for the complex (*S*)-**8** (Figure 2), generated by mixing a 2:1 ligand−silver salt ratio. However, these type of binap−$AgClO_4$ complexes **7** and **8** could not be differentiated by ^{31}P NMR spectroscopy.[24] Unfortunately, we could not obtain appropriate crystals for their characterization by X-ray diffraction analysis.

When the process was judged complete, the separation of the catalytic complex [(*S*)-binap]$AgClO_4$ from the reaction mixture was done by simple filtration (95−90% yield).[25] A series of cycles were run employing the same recovered catalyst [(*S*)-binap]$AgClO_4$ (*S*)-**7** used without any further purification (Scheme 1 and Table 2). The reaction shown in Scheme 1 was performed on a 1 mmol scale with 10 mol % of catalyst to facilitate its manipulation and successive reutilization. During the fourth cycles, the diastereo- and enantioselectivities remained unaltered achieving compound *endo*-**6a** in 89−91% yield and more than 99% ee (Table 2, cycles 1−4). The fifth cycle also afforded the titled product

(24) ^{31}P NMR ($CDCl_3$) of (*S*)-**7** (10% aqueous polyphosphoric acid as internal reference) δ (ppm): 15.26 (d, $J_{P-Ag(109)} = 259$ Hz) and 15.35 (d, $J_{P-Ag(107)} = 225$ Hz).

(25) Filters for HPLC samples (0.45 μm pore size) were employed (for other details, see Supporting Information).

Table 2. Recycling Experiments of the [(*S*)-Binap]$AgClO_4$ (*S*)-**7** Complex

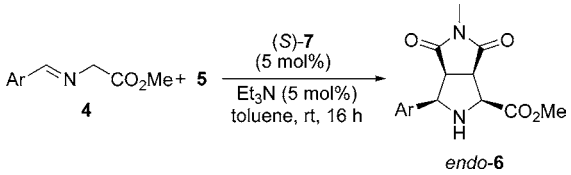
cycle	reaction (mmol)	(*S*)-**7** (mmol)[a]	recovered catalyst (%)	yield (%)[b]	ee_{endo} (%)[c]
1	0.6	0.060	95	91	>99
2	0.6	0.057[d]	93	89	>99
3	0.6	0.053[d]	92	91	>99
4	0.5	0.047[d]	90	90	99
5	0.4	0.042[d]	90	88	98

[a] Recovered after filtration of the crude reaction suspension and washed several times with toluene. [b] Isolated yield of compound *endo*-**6a** after recrystallization. The conversions were >99% and the endo/exo ratio was >98:2 in all of the essayed cycles. [c] Determined by chiral HPLC (Daicel Chiralpak AS). [d] Amount recovered from the previous cycle.

in high yield, but the ee decreased slightly to 98% (Table 2, cycle 5).

The scope of the reaction using different methyl glycinates was surveyed (Scheme 2 and Table 3). The methyl imino

Scheme 2. Enantioselective Synthesis of Products *endo*-**6**



esters **4**, derived from nonsubstituted aromatic aldehydes, such as benzaldehyde and 2-naphthalenecarboxaldehyde, were the best substrates due to the high enantioselections

Table 3. Enantioselective 1,3-DCRs of Iminoglycinates **4** and NMM (**5**) Catalyzed by the (*S*)-**7** Complex

		product *endo*-**6**			
	Ar	no.	yield (%)[a]	endo/exo[b]	ee_{endo} (%)[c]
1	Ph	**6a**	90	>98:2	>99 (>99)[d]
2	Ph	**6a**[e]	90	>98:2	>99 (>99)[d]
3	2-naphthyl	**6b**	89	>98:2	99 (>99)[d]
4	2-Cl-C_6H_4	**6c**	82[f]	>98:2	82 (85)
5	4-Me-C_6H_4	**6d**	88	>98:2	86 (88)[d]
6	4-Me-C_6H_4	**6d**	88[g]	>98:2	99 (>99)[d]
7	4-MeO-C_6H_4	**6e**	85	>98:2	80 (99)[h]
8	4-Cl-C_6H_4	**6f**	87	>98:2	64 (65)
9	4-Cl-C_6H_4	**6f**	87[g]	>98:2	98 (99)
10	2-thienyl	**6g**	87	>98:2	90 (92)[i]

[a] Isolated yield after recrystallization of the endo products. [b] Determined by ^1H NMR spectroscopy of the crude product. [c] For crude endo diastereomers, determined by chiral HPLC (Daicel Chiralcel OD−H). In parentheses is the ee of the purified compounds. [d] Determined by chiral HPLC (Daicel Chiralpak AS). [e] The enantiomer (2*R*,3*S*,4*S*,5*S*)-**6a** was obtained by using the [(*R*)-binap]$AgClO_4$ complex [(*R*)-**7**)] as the catalyst. [f] After column chromatography. [g] Reaction run with DBU (5 mol %) at 0 °C. [h] Second recrystallization (45% yield). [i] Determined by chiral HPLC (Daicel Chiralpak AD).

achieved for products **6a** and **6b**, respectively (Table 3, entries 1−3). When using the catalytic complex (*S*)-binap−$AgClO_4$ (*S*)-**7**, the absolute configuration of the resulting compounds *endo*-**6** was (2*R*,3*S*,4*S*,5*S*), established according to the published data for known compound **6a**.[18] In the example performed using the (*R*)-binap−$AgClO_4$ complex (*R*)-**7**, the corresponding enantiomer (2*S*,3*R*,4*R*,5*R*)-**6a** was obtained (Table 3, entry 2). Iminoglycinates derived from aromatic aldehydes bearing electron-donating or electron-withdrawing groups furnished, in general, lower enantioselections; for instance, products **6d** and **6f** were obtained in 86 and 64% ee, respectively, using triethylamine as base (Table 3, entries 5 and 8). Enantioselections were increased to 99 and 98% ee for compounds **6d** and **6f**, respectively, by working at 0 °C or −20 °C using DBU (5 mol %) instead of triethylamine as base (Table 3, entries 6 and 9). The employment of (*S*)-**8** afforded larger amounts of the exo adduct and 98% ee for the endo diastereoisomer, as shown above (Table 1, entry 7). When the substrate **4e** (Ar = 4-MeO-C_6H_4) was allowed to react with NMM in the presence of the (*S*)-**8** complex, at room temperature, a 40% ee was obtained vs the 85% ee obtained in the (*S*)-**7** complex-mediated reaction (Table 3, entry 7). Heteroaromatic iminoglycinate bearing a 2-thienyl group gave product **6g** with 92% ee after recrystallizaton (Table 3, entry 10). This compound and product **11** (see below, Figure 3) are particularly

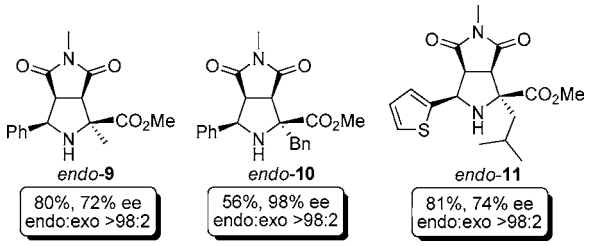


Figure 3. Products derived from the reaction of 1,3-dipoles derived from α-substituted α-amino acids and NMM.

important because they belong to a family of chiral polysubstituted pyrrolidines considered as very promising potential drugs for the treatment of hepatitis C.[26] In addition, the recovery of the complex (*S*)-**7** was accomplished in several examples (Table 3, entries 1, 3, 7, 9, and 10) in 88−93% yield by simple filtration.

When α-substituted benzaldimino esters, derived from (*S*)-alanine, (*S*)-phenylalanine, and (*S*)-leucine, were allowed to react with NMM (**5**), the corresponding endo adducts **9**−**11** were diastereoselectively obtained (>98:2 endo/exo ratio, Figure 3). Surprisingly, for the example of the phenylalanine surrogate *endo*-**10**, its enantiomeric excess was 64% for the crude product and rose to 98% after recrystallization.

The absolute configuration of these pyrrolidines incorporating a quaternary carbon at the 2-position was determined by X-ray diffraction analysis of structure **9** (see Supporting Information).[27] The structure confirmed the absolute configuration of (2*R*,3*S*,4*S*,5*S*), assumed by comparison with the known compound **6a**.

As a summary, this is the first catalyzed enantioselective 1,3-DCR between an azomethine ylide, generated from imino esters, and NMM where the catalytic complex Ag(binap)-ClO_4 can be recovered in very high yield (>90%) and with good reusability without any additional purification. Complex [(*S*)-binap]$AgClO_4$ (*S*)-**7** is stable to light exposure and afforded the corresponding polysubstituted pyrrolidines with (2*R*,3*S*,4*S*,5*S*) configuration, whereas the opposite one was readily available by using complex (*R*)-**7**. These are so far the highest enantioselections achieved for this type of 1,3-dipolar cycloaddition reaction in a chiral Ag(I) complex catalyzed 1,3-dipolar cycloaddition.

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Supporting Information Available: Experimental procedure, characterization, chiral HPLC conditions, spectra, and X-ray crystallographic details. This material is available free of charge via the Internet at http://pubs.acs.org.

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(27) The deposition number for compound *endo*-**11** is CCDC 644414. Crystallographic data for *endo*-**11**: $C_{16}H_{18}N_2O_4$, M_w = 302.18, monoclinic, space group I_a, a = 11.2478(12), b = 10.2523(11), c = 13.0845(12) Å; α = 90.000, β = 96.836(2), γ = 90.000°, V = 1498(2) Å^3, ρ_{calcd} = 1.340 g/cm^3, GOF = 1.016 ($I > 2.0\sigma(I)$). These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.