Asymmetric Catalysis

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Catalytic Enantioselective 1,3-Dipolar Cycloaddition Reactions of Azomethine Ylides and Alkenes by Using Phosphoramidite–Silver(I) Complexes**

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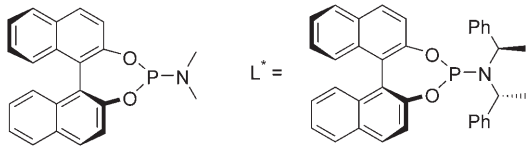
Dedicated to Professor Miguel Yus on the occasion of his 60th birthday

Proline derivatives are very important molecules in many scientific areas. The demand of these particular structures with a determined absolute configuration motivates the development of new asymmetric synthetic routes to obtain them with high optical purities.[1] The best approach to generate enantiomerically enriched polysubstituted prolines or pyrrolidine derivatives is the 1,3-dipolar cycloaddition (1,3-DC) between electrophilic alkenes and stabilized or nonstabilized dipoles, respectively. This strategy allows the creation of up to four stereogenic centers in only one step[2] with high regioselectivity and *endo*/*exo*-diastereoselectivities.[1] The first enantioselective 1,3-DC of stabilized azomethine ylides, pioneered by Allway and Grigg,[3] derived from iminoglycinates were shown to be highly efficient in 2002 by using a substoichiometric amount of a chiral Ag^I complex as the catalyst.[4] Since then, many chiral metal complexes that are able to generate metallodipoles have shown efficient catalytic activity for the reaction,[5–9] and recently, organocatalysts have been used.[10] These metal complexes constitute of a bidentate chiral ligand coordinated to metal cations, for example, chiral bisphosphanes with Ag^I[4,5a] or Cu^{II},[7] chiral nitrogenated phosphanes with Ag^I[5b,d,e,f,g,6g] or Cu^I,[6b,e] and sulfur-containing phosphanes with Ag^I[5c] or Cu^I.[6a,c,d,f,h] Bisimines with Zn^{II}[8b] and Ni^{II}[9] salts, as well as chiral amino alcohols complexes with Zn^{II}[8a] have demonstrated a less extensive reaction scope compared to the above-mentioned catalysts. The double coordination of the chiral ligand to the metal generates rigid and compact chiral environments, thus allowing high enantioselectivity, especially with less sterically hindered 1,3-dipoles derived from iminoglycinates. However, very poor results have been obtained with iminoesters obtained from α-substituted α amino acids.

Recently, substituted prolines derived from leucine iminoesters have become important molecules because of their extraordinary activity against the hepatitis C virus.[5a,11] We envisaged that a monodentate chiral ligand, such as phosphoramidite, coordinated to a silver cation would be less sterically demanding than the bidentate chiral ligand complexes, allowing more successful enantioselectivity of the α-branched 1,3-dipoles in the 1,3-DC reaction. Phosphoramidites **1** and **2**[12] have been extensively used in asymmetric hydrogenations,[1,13] as well as other metal-mediated transformations, such as allylations, Michael-type additions, and carbonyl addition reactions.[13b] However, to the best of our knowledge, coordination between a phosphoramidite ligand and a silver cation has not been reported. Herein we report a complex of either chiral phosphoramidite **1** or **2** and Ag^I salts that efficiently catalyze the enantioselective 1,3-DC of azomethine ylides derived from glycine with α-substituted amino acids having electron-deficient alkenes.



Monophos (**1**) (S_a,*R*,*R*)-**2**

L^* • $AgClO_4$ (**3**)
L^*_2 • $AgClO_4$ (**4**)

Initially, a 5 mol% of a 1:1 mixture of monophos **1** or phosphoramidite **2** and different Ag^I salts with Et_3N as the base (5 mol%), were used in the 1,3-DC of methyl benzylideneiminoglycinate (**5aa**) and *tert*-butyl acrylate at room temperature in toluene (Table 1). Monophos **1** and $AgClO_4$ furnished exclusively *endo*-**6aa** with an e.r. value of 76:24, whereas ligand **2** and $AgClO_4$ gave the best e.r. value and purity of the cycloadduct (Table 1, entries 1 and 2). When a 2:1 mixture of **2**:$AgClO_4$ was used as the catalyst, a lower e.r. value was obtained (Table 1, entry 3). The use of AgOAc or AgOTf in a 1:1 ratio relative to ligand **2**, gave e.r. values similar to those with $AgClO_4$, but the triflate did not afford reproducible results and the reaction run with the acetate furnished a complex mixture of crude proline derivatives

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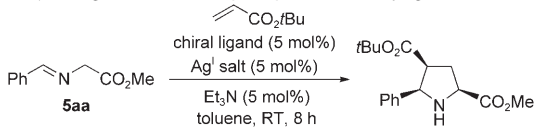
Table 1: Enantioselective 1,3-DC of iminoglycinate **5** and *tert*-butyl acrylate by using several chiral phosphoramidites/Ag^I salts.



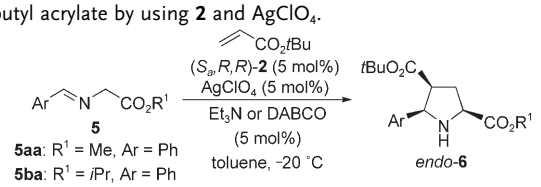
Entry	Ag^I salt	Ligand	Conv. [%]	e.r.[a]
1	$AgClO_4$	**1**	98	76:24
2	$AgClO_4$	**2**	98	85:15
3	$AgClO_4$	**2**[b]	95	74:26
4	AgOAc	**2**	98	80:20
5	AgOTf	**2**	98	84:16
6	AgF	**2**	90	76:24
7	$AgBF_4$	**2**	95	60:40
8	$AgClO_4$	**2**[c]	98	90:10

[a] Determined by chiral HPLC analysis (Daicel, Chiralpak AS), more than 98:2 *endo/exo* ratio (^{1}H NMR). [b] 10 mol% of the ligand was added. [c] Reaction performed at −20°C.

(Table 1, entries 4 and 5). In the case of the AgF and $AgBF_4$ salts, there was no improvement over those achieved by using $AgClO_4$ (Table 1, entries 6 and 7). Other solvents, such as THF, dichloromethane, diethyl ether, acetonitrile, and methanol gave both lower conversions and e.r. values. The influence of the temperature was analyzed within the range from 0 to −60°C, and the best enantioselectivity was obtained at −20°C (Table 1, entry 8).

Next, other crucial reaction parameters, such as the ester substituent, the amine (base), the matched and mismatched ligands, and the catalyst loading, were analyzed (Table 2). The 1,3-DC of methyl benzylideneiminoglycinate (**5aa**) with *tert*-butyl acrylate by using 5 mol% of a 1:1 mixture of phosphoramidite **2**:$AgClO_4$ gave *endo*-**6aa** with a higher e.r. value with

Table 2: Optimized enantioselective 1,3-DC of iminoglycinates **5** and *tert*-butyl acrylate by using **2** and $AgClO_4$.



Entry	**5**	Base	*endo*-**6**[a] e.r.[b]	Product	Yield [%][c]	e.r.[d]
1	**5aa**	Et_3N	90:10	**6aa**	80	90:10
2	**5aa**	DABCO	94:6	**6aa**	80	94:6
3	**5ba**	Et_3N	>99:1	**6ba**	83	>99:1
4	**5ba**	DABCO	>99:1	**6ba**	81	>99:1
5	**5ba**	Et_3N[e]	<1:99	*ent*-**6ba**	81	<1:99
6	**5ba**	Et_3N[f]	28:72	*ent*-**6ba**	80	28:72
7	**5ba**	Et_3N[g]	98:2	**6ba**	67	98:2

[a] Reaction run overnight at −20°C with conversions of greater than 98% as determined by ^{1}H NMR spectroscopy. [b] The e.r. values of the crude material were determined by chiral HPLC analysis (Daicel, Chiralpak AS), >98:2 *endo/exo* ratio (^{1}H NMR). [c] Yield of product isolated after recrystallization or flash chromatography. [d] The e.r. values were determined after purification. [e] Reaction carried out with the (R_a,*S*,*S*)-**2**. [f] Reaction carried out with (R_a,*R*,*R*)-**2**. [g] Reaction performed with a 3 mol% of catalyst (S_a,*R*,*R*)-**2**.

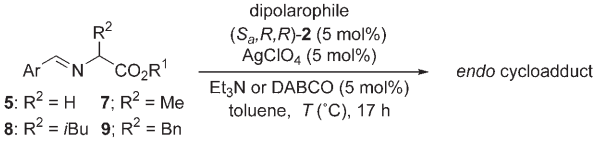
1,4-diazabicyclo[2.2.2]octane (DABCO) compared to using Et_3N (Table 2, entries 1 and 2). However, other bases, such as pyridine, imidazole, Hünig's base, 1,8-diazabicyclo[5.4.0]-undec-7-ene (DBU), or KOH afforded lower conversions and enantioselectivities. Isopropyl ester derivative **5ba** gave higher enantioselectivity than the analogous methyl ester in the presence of either base (Table 2, entries 3 and 4). Enantiomerically pure *endo*-**6ba** was obtained in good yield with excellent an e.r. value by employing the corresponding chiral (R_a,*S*,*S*)-**2** (Table 2, entry 5). Nevertheless, the reaction performed with the mismatched silver complex, (R_a,*R*,*R*)-**2**, furnished a lower enantioselectivity than that obtained with the (S_a,*R*,*R*)-**2** ligand (Table 2, entry 6). By using a lower catalyst loading (3 mol%), a lower conversion and slightly lower enantioselectivity was detected (Table 2, entry 7).

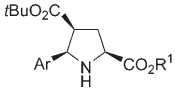
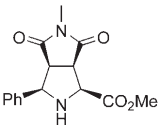
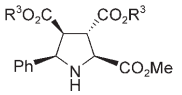
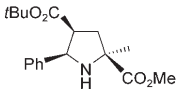
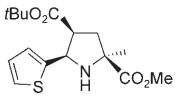
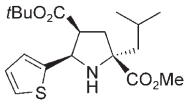
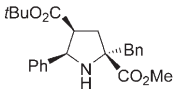
The scope of this 1,3-DC reaction with different α amino acid derived iminoesters (**5**–**9**) and dipolarophiles is shown in Table 3. The results obtained from using modified aryl moieties suggested that new stereoelectronic effects appeared, which could be tuned by carefully selecting the ester group (R^1 = Me, *i*Pr) and the amine (DABCO or Et_3N). Thus, *o*-substituted aryl imines preferentially reacted with methyl ester **5ab** or **5ac** (R^1 = Me) and DABCO as the base (Table 3, entries 1 and 2). In contrast, *p*-substituted iminoglycinate **5bd** reacted preferentially with isopropyl esters and Et_3N as the base. (Table 3, entry 4). Other dipolarophiles such as *N*-methylmaleimide (NMM) and isopropyl or isobutyl fumarates afforded products **10** and **11**, respectively, with good yields and e.r. values when methyl benzylideneiminoglycinate (**5aa**) was employed as 1,3-dipole precursor (Table 3, entries 5–7). The behavior of NMM as a dipolarophile was different to other assayed electrophilic alkenes. The reaction was stopped after 6 hours at room temperature, leading to *endo*-**10** with excellent enantioselectivity (Table 3, entry 5).

As predicted, alanine, leucine, and phenylalanine derived iminoesters **7**–**9** gave products **12**–**15** in good yields with very high e.r. values. The reactions with alanine metallodipoles were run for 17 hours at −20°C by using 1.1 equivalents of the dipolarophile (Table 3, entries 8 and 9). However, the more substituted imines derived from leucine (**8**) and phenylalanine (**9**) required 3 equivalents of *tert*-butyl acrylate, providing *endo*-**14**[14] and *endo*-**15** in 80 and 77% yields, respectively, after 2–3 days at −20°C (Table 3, entries 10 and 11). In all examples shown in Table 3, the *endo* adduct was obtained as the major stereoisomer with a d.r. value of more than 98:2 (^{1}H NMR). All of the e.r. values were determined by chiral HPLC analysis, and the absolute configuration was determined by comparison of the optical rotations between the newly generated products and the reported values for the known compounds.[4,5a,6d]

The new 1:1 and 2:1 complexes, **3** and **4**, respectively, were characterized by X-ray crystallographic diffraction analysis of monocrystals to obtain very interesting data on the solid state of the complexes. Complex **3** formed cross-linked sheets,[15] the formation of these polymeric assemblies being typical of Ag complexes, independent of the mono- or bidentate character of the corresponding ligand.[16] The structure of the active catalytic species can be attributed to complex **4**.[17]

Table 3: Scope of the enantioselective 1,3-DC of iminoglycinates **5**–**9** with dipolarophiles catalyzed by **2** and $AgClO_4$.



Entry	R^1, Ar	Base	Dipolarophile	T [°C]	e.r.[a]	*endo* Cycloadduct Structure	Product	Yield [%][b]	e.r.[c]
1	Me, 2-MeC_6H_4 (**5ab**)	DABCO	*tert*-butyl acrylate	−20	99:1		**6ab**	83	99:1
2	Me, 2-ClC_6H_4 (**5ac**)	DABCO	*tert*-butyl acrylate	−20	>99:1		**6ac**	90	>99:1
3	*i*Pr, Ph (**5ba**)	DABCO	*tert*-butyl acrylate	0	>99:1		**6ba**	81	>99:1
4	*i*Pr, 4-$MeOC_6H_4$ (**5bd**)	Et_3N	*tert*-butyl acrylate	−20	99:1		**6bd**	79	99:1
5	Me, Ph (**5aa**)	DABCO	NMM[d]	25	>99:1		**10**	80	>99:1
6	Me, Ph (**5aa**)	Et_3N	diisopropyl fumarate	−20	91:9		**11a**	81	91:9
7	Me, Ph (**5aa**)	DABCO	diisobutyl fumarate	0	91:9		**11b**	79	91:9
8	Me, Ph (**7aa**)	Et_3N	*tert*-butyl acrylate	−20	96:4		**12**	78	97:3
9	Me, 2-thienyl (**7ae**)	Et_3N	*tert*-butyl acrylate	−20	96:4		**13**	77	96:4
10	Me, 2-thienyl (**8ae**)	Et_3N	*tert*-butyl acrylate[e]	−20	92:8		**14**	70	91:9
11	Me, Ph (**9aa**)	Et_3N	*tert*-Butyl acrylate[e]	−20	99:1		**15**	77	99:1

[a] The e.r. values of the crude material were determined by chiral HPLC analysis (Daicel, Chiralpak AS), >98:2 *endo*/*exo* ratio. [b] Yield of isolated product after recrystallization or flash chromatography. All new compounds gave satisfactory spectroscopic and spectrometric data. [c] The e.r. values determined after purification. [d] 6 h reaction time. [e] 3 equiv were added and the reaction took 2 days to go to completion.

The X-ray crystallographic diffraction analysis obtained for this solid aggregate support this hypothesis. The second equivalent of phosphoramidite **2** is interrupted the Ag–π interactions as a consequence of the strong phosphorous affinity exhibited by the silver cation (see the Supporting Information).

In the light of the results described, it can be concluded that novel monodentate phosphoramidite–silver complex **3** is a very efficient chiral catalyst for a wide range of 1,3-dipolar cycloaddition reactions between azomethine ylides and dipolarophiles. This type of monodentate complex provides new opportunities in this and other reactions because of the ability to run cycloadditions involving sterically hindered components, the fine-tuning of which can be achieved by modification of the temperature, base, and ester substituent.

Experimental Section

A solution of $AgClO_4$ (10.4 mg, 0.05 mmol) and chiral ligand **2** (27 mg, 0.05 mmol) in toluene (1 mL) was stirred at RT for 1 h. The reaction mixture was then cooled to the corresponding temperature and the iminoester (1 mmol), dipolarophile (1 mmol), and the base (5 mol%) were added sequentially. After the reaction was judged to be complete, the solvent was evaporated and the crude reaction mixture was filtered and analyzed by chiral HPLC analysis. The pure cycloadduct was obtained after recrystallization or by flash chromatography.

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Keywords: azomethine ylides · chirality · cycloaddition · phosphoramidites · silver

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[14] This compound belongs to a family of inhibitors of the replication of hepatitis C virus (see reference [5a]). The results concerning the synthesis of this kind of molecules with this important activity are currently evaluated for a patent application.
[15] CCDC 681931 [unit cell parameters: a 10.806(4) b 15.391(6) c 11.566(4) beta 102.882(8), space group P21)] and 681932 [a 10.806(4) b 15.391(6) c 11.566(4) beta 102.882(8), space group P21] 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.
[16] a) D. L. Reger, R. F. Semeniuc, J. D. Elgin, V. Rassolov, M. D. Smith, *Cryst. Growth Des.* **2006**, *6*, 2758 – 2768; b) M.-C. Brandys, R. J. Puddephatt, *J. Am. Chem. Soc.* **2002**, *124*, 3946 – 3950; c) M. Munakata, M. Wen, Y. Suenaga, T. Kuroda-Sowa, M. Maekawa, M. Anahata, *Polyhedron* **2001**, *20*, 2037 – 2043; d) O. Mamula, A. von Zelewsky, T. Bark, G. Bernardinelli, *Angew. Chem.* **1999**, *111*, 3129 – 3133; *Angew. Chem. Int. Ed.* **1999**, *38*, 2945 – 2948.
[17] CCDC 681933 [unit cell parameters: a 10.3809(2) c 56.6864(16), space group P41212] 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.

