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Catalytic Asymmetric 1,3-Dipolar Cycloaddition of α-Iminonitriles

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Dedicated to Professor Josep M. Ribó on the occasion of his 70th birthday

The 1,3-dipolar cycloaddition of azomethine ylides with alkenes is one of the most powerful and convergent methods for the stereoselective synthesis of pyrrolidines,[1] a heterocyclic moiety widely present in the structure of natural products, pharmaceuticals[2] and chiral ligands.[3] Improving the overall chemical and stereochemical efficiency of this reaction, pioneered by Grigg with stoichiometric metal chiral complexes,[4] a great effort has been devoted in recent years in the development of catalytic asymmetric protocols. In this field a wide variety of outstanding chiral complex catalysts have been reported,[5] mainly Ag^{I},[5f,g,j,m,q–s] Cu^{I}[5e,h,i,k,l,o,t–w] and Cu^{II}[5d] catalysts, but also Zn^{II},[5x] Ni^{II}[5n] and Ca^{II}[5p] complexes. In addition, several organocatalytic asymmetric methods have been also developed in the last few years.[6] Concerning the scope of the catalytic asymmetric 1,3-dipolar cycloaddition of azomethine ylides, although there is an ample tolerance with regard to the nature of the dipolarophile (i.e., α,β-unsaturated esters, maleimides, α,β-unsaturated nitriles, enones, enals, nitroalkenes, vinyl sulfones and fullerene), the structural variety at the azomethine dipole is much more limited. By far most catalytic asymmetric versions reported to date are based on the use of α-iminocarbonyl substrates, specifically α-iminoesters. The great effectiveness of α-iminoesters as dipole precursors relies on the enhanced acidity of the α-position and the formation of a robust five-membered, N,O-bidentate-metalated, azomethine ylide, which facilitates the asymmetric induction from the chiral ligand. The inherent limitation of this strategy is the restricted structural versatility with regard to the substitution at C2, always providing pyrrolidines with a C2 carboxylate ester substitution.

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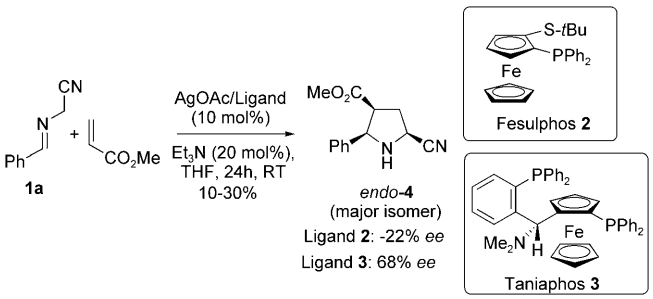
To access other types of substituted pyrrolidines, α-iminonitrile precursors are very appealing, since in the resulting 2-cyanopyrrolidines[7] the cyano group could further act as leaving group allowing its formal substitution by hydrogen or by a carbon nucleophile,[8] and thus leading to a wider variety of substituted pyrrolidines. Two decades ago Kanemasa, Tsuge et al. reported the non-enantioselective thermal[9] and LDA-promoted (LDA = lithium diisopropylamide)[10] cycloaddition of alkyl-substituted α-iminonitriles with electron-deficient dipolarophiles, but the catalytic asymmetric version of this process remained to be developed. We describe herein the first catalytic asymmetric procedure for the 1,3-dipolar cycloaddition of α-iminonitriles, as well as some synthetic applications and a DFT theoretical study on the presumed nature of the metalated 1,3-dipole.

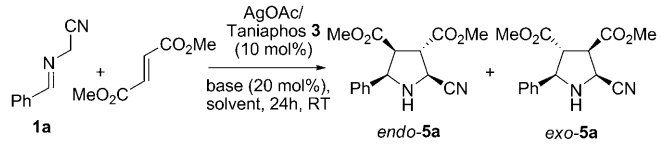
To evaluate the viability of α-iminonitriles as dipole precursors in catalytic asymmetric 1,3-dipolar cycloadditions, we first studied the reaction of *N*-benzylidenaminoacetonitrile (**1**) with methyl acrylate in the presence of ligand Fesulphos (**2**, 10 mol%). This ligand had proved to be very efficient in the 1,3-dipolar cycloadditions of α-iminoesters with a wide variety of dipolarophiles (acrylates, maleates, fumarates, maleimides,[5t] enones,[5i] bissulfonylethylenes[5h] and fullerene[5d]), providing the pyrrolidines usually with high control of the *endo*/*exo* selectivity and enantioselectivity. However, a very poor reactivity and stereoselectivity was obtained in the reaction of methyl acrylate with α-iminonitrile **1a** in the presence of a variety of copper and silver salts[11] (11% yield and 22% *ee* for the major adduct[12] as the best results, Scheme 1). In an attempt to find a more efficient catalyst system for this reaction we next tested a variety of ligands,[13] albeit with moderate success. A promising enantioselectivity was found with AgOAc/Taniaphos (**3**) as catalyst system (30% yield, 68% *ee* for *endo*-**4**).

To improve the efficiency of the process we next applied this catalyst system to a more reactive dipolarophile, such as dimethyl fumarate (Table 1). Interestingly, unlike the previously reported thermal or LDA-mediated reactions, which give rise to C2/C5 *cis*/*trans* mixtures of isomers,[9,10] this catalytic asymmetric reaction provided exclusively the C2/C5



Scheme 1. Ag-catalysed 1,3-dipolar cycloaddition of α-iminonitrile **1a** and methyl acrylate with Fesulphos and Taniaphos ligands.

Table 1. Optimisation of the reaction conditions.



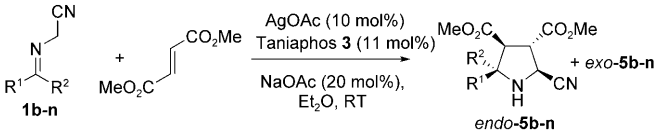
	Solvent	Base	*endo*/*exo*[a]	Yield [%][b]	*ee* [%][c]
1	THF	Et_3N	88/12	53	79
2	toluene	Et_3N	88/12	46	81
3	CH_2Cl_2	Et_3N	88/12	44	73
4	Et_2O	Et_3N	89/11	61	78
5[d]	Et_2O	Et_3N	89/11	43	78
6	Et_2O	DIPEA	86/14	76	79
7	Et_2O	K_2CO_3	87/13	82	79
8	Et_2O	NaOAc	85/15	81	81
9[e]	Et_2O	NaOAc	85/15	57	78

[a] By ^{1}H NMR spectroscopy from the crude reaction mixture [b] In pure *endo*-**5a** after column chromatography. [c] For *endo*-**5a**; determined by HPLC, see Supporting Information for details. [d] Reaction run at 0 °C. [e] 5 mol % of catalyst system.

cis-substituted pyrrolidines, mainly as the *endo* isomer (*endo*-**5a**). After surveying different solvents and bases (entries 1–8), the best results in terms of reactivity and enantioselectivity were obtained in Et_2O using 20 mol % of NaOAc as base (81 % isolated yield and 81 % *ee* for *endo*-**5a**; entry 8). A reduction in the catalyst loading to 5 mol % resulted in a similar enantioselectivity, albeit with a significant drop in the reactivity (entry 9).

With these optimal reaction conditions in hand, Table 2 shows the scope of this cycloaddition with regard to the substitution at the α-iminonitrile. As in the case of the model reaction, all cycloadditions provided the *endo* adduct (*endo* **5b**–**n**) as the major isomer (*endo*/*exo* ratio ranging from 75:25 to 93:7), which was readily isolated by standard chromatographic purification. In the case of the α-iminonitriles derived from homoaromatic aldehydes, the enantioselectivity was rather similar (entries 1–5; 71–77 % *ee*), albeit electron-deficient aryl iminonitriles provided the corresponding pyrrolidines with higher yields than electron-rich substrates (compare entries 1/2 with 3/4). Heteroaryl α-iminonitriles also proved to be suitable substrates, undergoing the cycloaddition with high *endo*/*exo* selectivities and enantioselectivities (entries 6–9). Particularly noticeable was the excellent control achieved in the case of the 2-thienyl derivative (entry 6, 92 % yield and 98 % *ee*). The cycloaddition also tolerates an alkenyl substitution at the imine moiety, although the enantioselectivity was moderate (entry 10, 68 % *ee*). Unfortunately, no cycloaddition was observed in the case of alkyl-substituted iminonitriles (entry 11). Finally, we also studied the cycloaddition of α-iminonitriles derived from ketimines, which are interesting substrates, since they generate a quaternary centre at C5 (entries 12 and 13). These imines are sterically more demanding and, as it was expected, they showed a lower reactivity (reaction time of 96 h instead of 2–24 h for the aldimine substrates), but pleasingly they reacted in a highly *endo*/*exo* selective and enantioselective manner (85–87 % *ee*).

Table 2. AgOAc/Taniaphos-catalysed 1,3-dipolar cycloaddition of α-iminonitriles **1b–n** with dimethyl fumarate.

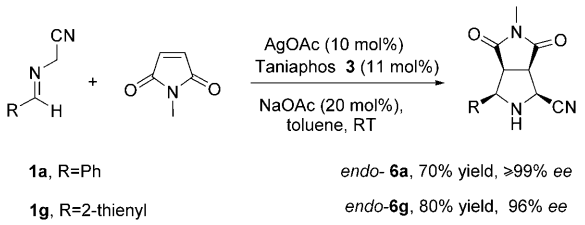


	R^1	R^2	*t* [h]	Product	*endo*/*exo*[a]	Yield [%][b]	*ee* [%][c]
1	*m*-FC_6H_4	H	6	**5b**	75/25	74	71
2	*p*-BrC_6H_4	H	5	**5c**	80/20	61	77(≥99)[d]
3	*p*-$MeOC_6H_4$	H	24	**5d**	87/13	35	79
4	*o*-$MeOC_6H_4$	H	24	**5e**	80/20	44	72
5	*o*-MeC_6H_4	H	24	**5f**	79/21	45	74
6	2-thienyl	H	6	**5g**	93/7	92	98(≥99)[d]
7	2-pyridyl	H	25	**5h**	85/15	81	76
8	2-furyl	H	3	**5i**	93/7	74	89(≥99)[d]
9	*N*-Boc-2-pyrryl	H	24	**5j**	91/9	87	84
10	CH=CH-Ph	H	2	**5k**	80/20	64	68(96)[d]
11	Cy	H	24	**5l**	–	–	–
12	Ph	Ph	96	**5m**	92/8	64	87
13	*p*-FC_6H_4	*p*-FC_6H_4	96	**5n**	91/9	59	85

[a] By ^{1}H NMR spectroscopy from the crude reaction mixture [b] In pure adducts *endo*-**5b**–**n** after column chromatography. [c] By HPLC for *endo* **5b**–**n**; see Supporting Information for details. [d] *ee* after recrystallisation.

From a practical point of view, it is interesting to note that the enantiopurity of the major adduct *endo*-**5** can be enhanced to 96–≥99 % *ee* by simple recrystallisation with *i*PrOH (entries 2, 6, 8 and 10; 45–73 % recrystallisation yields). In addition, the stereochemical and configurational assignment of (+)-*endo*-**5c** was unequivocally established by X-ray diffraction of a recrystallised sample of *endo*-**5c** > 99 % *ee*.[14]

To extend this asymmetric protocol to other dipolarophiles, we next investigated the 1,3-dipolar cycloaddition of α-iminonitriles with *N*-methylmalemide (Scheme 2). The reaction of **1a** or **1g**, under similar reaction conditions to those used with dimethyl fumarate, but using toluene as solvent, afforded the bicyclic pyrrolidine *endo*-**6a** or *endo*-**6g** as major isomers[15] in good yields and excellent enantiocontrol (> 99 and 96 % *ee*, respectively).



Scheme 2. Catalytic asymmetric 1,3-dipolar cycloaddition of α-iminonitriles **1a**,**g** with *N*-methylmaleimide.

The high selectivity for the formation of C2/C5 *cis*-substituted pyrrolidines in all the reactions with α-iminonitriles suggests the participation of *syn*-metalated 1,3-dipole complexes. However, unlike the well-established *syn* arrangement in the five-membered, N,O-bidentate-metalated, azomethine ylides derived from α-iminoesters, the structure of the metal-complex ylides derived from α-iminonitriles is unclear.[10] To shed some light on this point, a theoretical study at the DFT (B3LYP)[16] level by using the Gaussian 03 program[17,18] was carried out. Fesulphos–Ag^{I} complexes with the azomethine ylide derived from *N*-benzylidenaminoacetonitrile **1a** were used as models.[19] Their molecular structures are shown in Figure 1.

Complexes **I** and **II** show a *syn* arrangement of the dipole moiety with very similar bond lengths around Ag atom. The P–Ag, S–Ag and N_i–Ag (N_i = imine N atom) distances as well as the lower stability of complex **II**, mainly due to steric effects, are also comparable with those found in the case of iminoesters complexes.[5t] The distance between the metal atom and the nitrile group is significantly longer, which implies a smaller interaction. However, the *syn* orientation of this group has a very important stabilizing effect (compare the stability of complexes **I** and **II** with that of **III**).[20] The NBO analysis[21] of complex **I** show a two-electron donation from the lone pair at N_n (N_n = nitrile N atom) along with the π-C1=N_n and the π-C1=C2 to the empty 5s AO of Ag^{I}. These combined orbital interactions result in total second-order perturbation energy of about −4.0 kcal mol^{-1}. Besides, there are two hydrogen bonds that contribute to the stabilisation of complex **I**. One of them is formed between N_n and the closest H atom of one of the phenyl groups of the PPh_2 subunit (d(N_n–H) = 2.40 Å). The second is formed between N_n and the closest H atom of the nearby cyclopentadienyl ring of ferrocene moiety (d(N_n–H) = 2.37 Å). The total second-order perturbation energy associated with these stabilizing interactions is about −5.0 kcal mol^{-1}.

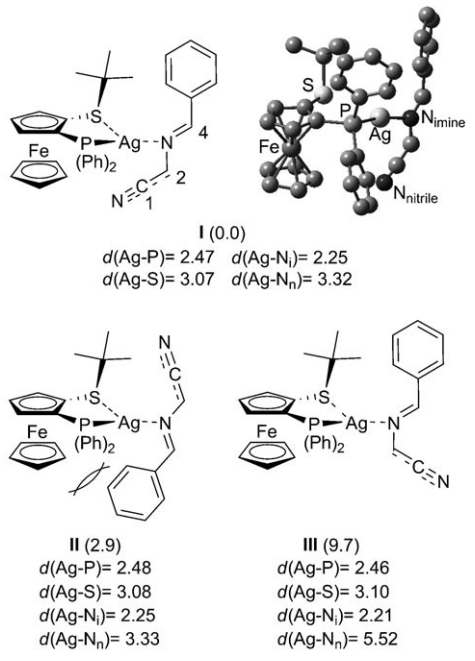


Figure 1. Molecular structure, representative distances [Å] and relative energies [kcal mol^{-1}, ZPE correction included] of complexes **I**, **II** and **III**. Spatial representation of the most stable complex **I**, in which hydrogen atoms have been omitted for clarity, is also included. N_i and N_n refer to nitrogen atoms of the imine and nitrile group, respectively.

The next step in our study was to understand the origin of the good enantioselectivity found with Taniaphos. First, to determine the coordination mode of Taniaphos (**3**) with silver(I), we isolated and studied by X-ray diffraction the complex [AgOAc(**3**)], prepared by treatment of Taniaphos **3** with AgOAc in THF and further recrystallisation in CH_2Cl_2/hexane[22] (Figure 2). This complex shows a P,P-bidentate coordination to silver, similar to that found in Pt^{II}–Taniaphos complexes.[23] The eight-membered metallacycle adopts a relatively rigid boat-like conformation, minimizing the steric interactions and likely stabilised by π-stacking interactions between the aromatic rings bonded to both phosphorous atoms; the distance between the silver and iron atoms is 4.41 Å. Taking the structure of complex [AgOAc(**3**)] as starting point, the acetate anion was substituted by the model azomethine ylide with a coordination mode similar to that found in the previously studied most stable complex with Fesulphos (complex **I**). The resulting structure was fully optimised giving rise to complex **IV** (Figure 2) in which the conformation of the ligand remains almost unaltered (for example, d(Ag···Fe) = 4.65 Å) with respect to the X-ray structure. A slight elongation of the P–Ag distances was observed. Interestingly, the well-defined steric environment in complex **IV** and the fact that the orientation of the azomethine ylide moiety is different than in the starting complex **I** (dihedral angle C_1-C_2-N_i-Ag increases from −8.8 to −13.6°) gives rise to a better steric differentiation of its faces. Thus, in complex **IV** the approach of the dipolarophile to the (2*Re*,4*Si*)-face of the azomethine would be hindered by a combination of two effects: 1) the unsubstituted cyclopentadinyl ring of the ferrocene unit blocks the approach of the dipolarophile to C2 (smaller distance Cp–C2 = 3.11 Å) and 2) one of the phenyl groups on P2 blocks the approach to C4 (smaller distance Ph–C4 = 2.76 Å). Consequently, the selective approach of the dipolarophile to the less hindered (2*Si*,4*Re*)-face of the azomethine in complex **IV** could ex-

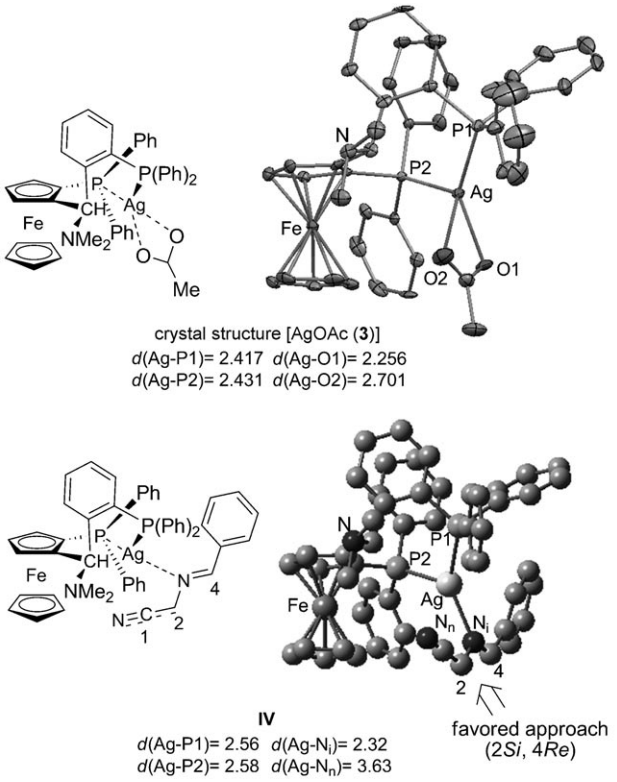
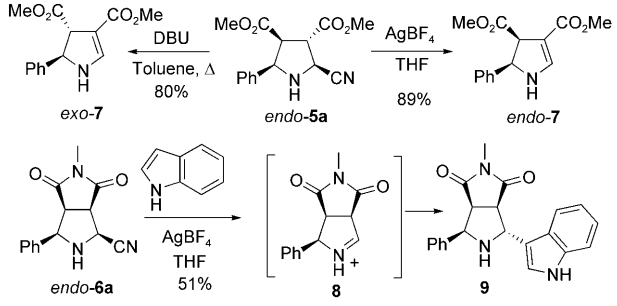


Figure 2. Molecular structure and representative distances [Å] around the metal of crystal complex [AgOAc(**3**)], studied by X-ray diffraction, and theoretically studied α-iminonitrile complex **IV**. Spatial representation is also included. Hydrogen atoms have been omitted for clarity. N_i and N_n refer to nitrogen atoms of the imine and nitrile, group respectively.

plain the good enantioselectivity of the cycloaddition in favour of the pyrrolidines with 2*S*,5*R* configuration[24]

From a synthetic point of view, an interesting aspect of using α-iminonitriles as 1,3-dipoles, compared with α-iminoesters, is that in the resulting 2-cyanopyrrolidines the cyano group can further behave as a leaving group, owing to the facile formation of an iminium intermediate that can evolve by conversion into the enamine tautomer or be trapped by an added nucleophile.[8] This is apparent from the transformations depicted in Scheme 3. As previously reported by Tsuge,[10] the treatment of pyrrolidine *endo*-**5a** with a catalytic amount of DBU in toluene at reflux afforded the



Scheme 3. Synthetic transformations of 2-cyanopyrrolidines.

2-pyrroline *exo*-**7** with *trans* configuration at C4–C5, owing to the epimerisation at C4 under the basic reaction conditions. On the other hand, under milder reaction conditions, the treatment of pyrrolidine *endo*-**5a** with $AgBF_4$ in CH_2Cl_2 at room temperature selectively afforded the pyrroline *endo*-**7**[25] without epimerisation at C4 (89% yield). Interestingly, the reaction of pyrrolidine *endo*-**6a** with $AgBF_4$ in the presence of indole led, with complete stereoselectivity, to the C2–C5 *trans*-2-indolylpyrrolidine[26] **9** (51% yield), likely by reaction of indole to the least hindered face of the electrophilic iminium intermediate **8**.

In conclusion, an efficient protocol for the catalytic asymmetric 1,3-dipolar cycloaddition of α-iminonitriles has been developed. This process relies on the use of AgOAc/Taniaphos as catalyst system, providing 2-cyanopyrrolidines with good diastereo and enantioselectivity (68–≥99% *ee*) in the reaction with activates dipolarophiles, such as fumarates and maleimides. A combination of X-ray and theoretical DFT studies has been used to study the plausible coordination mode of the α-iminonitrile to the Ag/Taniaphos chiral complex. The further elimination or substitution of the cyano group on the 2-cyanopyrrolidine adducts highlights the versatility of this protocol for the enantioselective synthesis of substituted pyrrolidines.

Experimental Section

Typical procedure for the asymmetric 1,3-dipolar cycloaddition of α-iminonitriles: A solution of **1a** (25 mg, 0.17 mmol) in Et_2O (1.2 mL), and dimethyl fumarate (39 mg, 0.26 mmol) were successively added to a mixture of **3** (13.1 mg, 0.019 mmol), AgOAc (2.9 mg, 0.017 mmol) and NaOAc (2.8 mg, 0.035 mmol) in Et_2O (0.5 mL), under nitrogen atmosphere. After stirring for 24 h at room temperature, the mixture was filtered through a plug of Celite with the aid of CH_2Cl_2 (2 mL), and the solvent was removed under reduced pressure. The residue was purified by silica gel flash chromatography (hexane/EtOAc 3:1) to afford the adduct *endo*-**5a** (34 mg, 81%, white solid). M.p. = 85–87 °C; $[\alpha]_D^{20} = +29.5$ (c = 0.20, CH_2Cl_2), 81% *ee*.

Acknowledgements

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Keywords: asymmetric catalysis · azomethine ylides · cycloaddition · iminonitriles · pyrrolidines

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[25] Racemic *endo*- and *exo*-**7** have been previously described, see references [9a] and [10a], respectively.

[26] See the Supporting Information for the stereochemical assignment of **9**.

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