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A New Family of Cinchona-Derived Amino Phosphine Precatalysts: Application to the Highly Enantio- and Diastereoselective Silver-Catalyzed Isocyanoacetate Aldol Reaction

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Supporting Information

ABSTRACT: A new class of readily accessible chiral amino-phosphine precatalysts derived from 9-amino(9-deoxy) epicinchona alkaloids has been developed. In combination with Ag(I) salts, these amino-phosphines performed as effective cooperative Brønsted base/Lewis acid catalysts in the asymmetric aldol reaction of isocyanoacetate nucleophiles. Under optimal conditions, high diastereoselectivities (up to 98%) and enantioselectivities (up to 98%) were obtained.

Cooperative catalysis using multifunctional organic scaffolds in combination with transition metal ions is emerging as a powerful tool in asymmetric synthesis and has allowed the development of unprecedented transformations in terms of reactivity and stereocontrol.[1] The design and synthesis of new, readily accessible catalytic systems plays a pivotal role in this field of research, allowing the discovery of useful synthetic pathways, rapid optimization of the ligand canopy, and a better understanding of the mechanism and origins of stereocontrol. To this end, we recently reported the cooperative combination of Cu(I)OTf and bifunctional, 9-amino(9-deoxy) epicinchona-derived urea precatalysts as an efficient and effective catalytic system for the enantioselective Conia-ene reaction of β-keto esters.[2]

To further advance our work in this field, we wanted to access differently functionalized precatalysts based on the privileged and easy-to-prepare 9-amino(9-deoxy) epicinchona scaffold. Specifically, we reasoned that the functionalization of the amino group of 9-amino(9-deoxy) epicinchona alkaloids with appropriately spaced diaryl phosphine ligands could provide a new class of chiral amino-phosphines, with the potential to perform as effective asymmetric precatalysts when used in combination with transition metal ions. We envisaged that the differential in hard/soft character of the two Lewis bases (Scheme 1) would allow a selective binding of the phosphine to an appropriate (soft) metal ion, leaving the amine partially free from complexation and therefore able to act as an organic base in the reaction of interest. As well as enhancing rates, this cooperativity between the phosphine-ligated metal ion and the (Lewis/Brønsted) basic nitrogen could also lead to high levels of stereocontrol through organized multipoint binding of the reacting components in the transition structure. Herein we wish to report our preliminary findings.

A small library of precatalysts **1**−**4** was readily formed by reacting a selection of 9-amino(9-deoxy) epicinchona alkaloids with commercially available aryl diphenylphosphino acids. As a first application of this new family of precatalysts, we selected the aldol reaction of isocyanoacetates with aldehydes.[3] We hypothesized that the acidity of the α-C−H of isocyanoacetates could be enhanced after complexation with a suitably "soft" transition metal ion (complex). This would allow deprotonation by the bridgehead nitrogen, affording the bound and activated nucleophilic component poised for reaction with Lewis acid activated aldehydes (Scheme 2). The reaction between *tert*-butyl isocyanoacetate **5a** and benzaldehyde **6a** was chosen to probe reactivity and stereocontrol.

From a screen of metal ion complexes, it was soon realized that silver salts[4] provided the best reactivity, by catalyzing smooth conversion to oxazoline product **7a** in the presence of all the precatalysts (Table 1). Silver oxide was the most effective in terms of reactivity and stereocontrol, allowing the reaction to be performed at lower temperatures. The use of AcOEt and ethereal solvents such as MTBE was also beneficial in terms of enantio- and diastereoselectivity. Further adjustment of the *tert*-butyl isocyanoacetate concentration to 0.3 M and addition of powdered 4 Å MS allowed an enantiomeric excess of 96% to be reached for the major diastereoisomer in a highly diastereoselective reaction (entry 10). Finally, control experiments (entries 12 and 13) proved that the presence of both the amino-phosphine **2** and Ag_2O was required to achieve optimal reactivity. A reaction in the absence of amino-phosphine **2** required 5 days at −20 °C to reach completion, while a reaction in the presence of the ligand **2** but without silver additive gave only traces of product after 5 days at −20 °C. The scope of the reaction with respect to the aldehyde was then probed (Table 2).

A variety of aromatic aldehydes (entries 1−5, Table 2) proved effective, giving rise to excellent enantio- and diastereoselectivities for the trans diastereomers. Aliphatic aldehydes were also effective substrates (entries 6−8, Table 2), with the best enantioselectivities provided by hindered aldehydes such as pivaldehyde, while other substrates gave rise to lower levels of enantiocontrol.[5] The substitution of amino-phosphine **2** with the pseudoenantiomeric **3** afforded oxazoline (4*R*,5*S*)-**7a** with comparable yield and enantiocontrol (92%, entry 2, Table 2). The use of methyl isocyanoacetate **5b** was also possible, resulting in good levels of reactivity but a slightly decreased diastereo- and enantioselectivity (entry 9, Table 2, 14:1 dr, 81% ee) when compared to *tert*-butyl isocyanoacetate. Pleasingly, the new catalytic system was also effective with α-substituted

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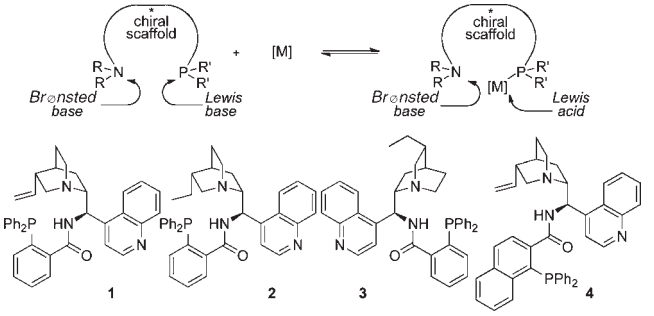
Scheme 1. Cooperative Catalysis Concept from Aminophosphines and Metal Ions and a Library of Cinchona-Derived Precatalysts



Scheme 2. Postulated Catalyst Activation Mode

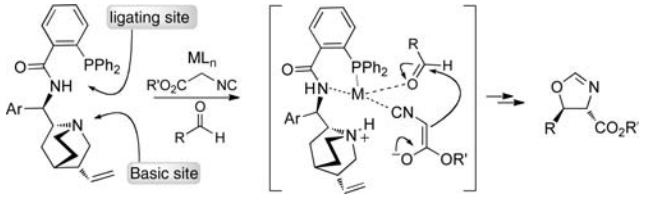
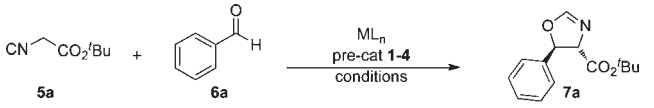


Table 1. Optimization of Reaction Conditions

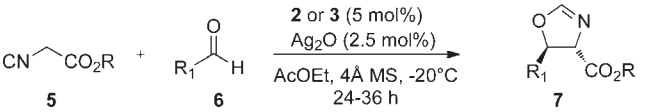


entry	precat	ML_n	T (°C)	solvent	time (h)	conv[a] (%)	dr[a]	ee[b] (%)
1	**2**	AgOAc	25	CH_2Cl_2	18	100	5:1	62
2	**2**	CuCl	25	CH_2Cl_2	48	30	4:1	0
3	**2**	Ag_2CO_3	25	CH_2Cl_2	4	100	5:1	64
4	**2**	Ag_2O	25	CH_2Cl_2	3	100	6:1	71
5	**2**	$Au(PPh_3)Cl$	25	CH_2Cl_2	48	100	2:1	44
6	**2**	Ag_2O	−20	MTBE	24	100	19:1	90
7	**4**	Ag_2O	−20	MTBE	36	100	13:1	76
8	**1**	Ag_2O	−20	MTBE	24	100	11:1	76
9	**2**	Ag_2O	−20	AcOEt	24	100	13:1	94
10[c]	**2**	*Ag_2O*	*−20*	*AcOEt*	*24*	*100*	*21:1*	*96*
11[c]	**3**	Ag_2O	−20	AcOEt	24	100	21:1	91[d]
12	—	Ag_2O	−20	AcOEt	120	100	—	0
13	**2**	—	−20	AcOEt	24	traces	—	—

[a] Determined by ^{1}H NMR analysis of the crude reaction mixture. [b] Determined by chiral HPLC analysis after conversion to the corresponding *N*-benzoylated amino-ester. [c] Isocyanoacetate concentration 0.3 M and 4 Å MS added. [d] Opposite enantiomer obtained.

isocyanoacetates **8a** and **8b**.[6] When α-substituted isocyanoacetates **8** were reacted with aldehydes, the corresponding oxazolines were obtained in high enantioselectivities (up to 98%) and good diastereoselectivities (up to 18:1), allowing the simultaneous

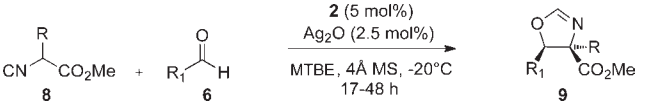
Table 2. Scope of the Glycine-Derived Isocyanoacetate Aldol Reaction



entry	R	5	R_1	6	7	yield (%)[a]	dr[b]	ee (%)[c]
1	^{t}Bu	**a**	Ph	**a**	(4*S*,5*R*)-**7a**	72[d]	21:1	96
2	^{t}Bu	**a**	Ph	**a**	(4*R*,5*S*)-**7a**	76[d]	21:1	92[e]
3	^{t}Bu	**a**	3-Br-C_6H_4	**b**	(4*S*,5*R*)-**7b**	69	10:1	92
4	^{t}Bu	**a**	4-F-C_6H_4	**c**	(4*S*,5*R*)-**7c**	77	15:1	92
5	^{t}Bu	**a**	4-OMe-C_6H_4	**d**	(4*S*,5*R*)-**7d**	60	13:1	89
6[f]	^{t}Bu	**a**	$C(Me)_2$-CO_2Me	**e**	(4*S*,5*R*)-**7e**	89	16:1	81
7	^{t}Bu	**a**	^{t}Bu	**f**	(4*S*,5*R*)-**7f**	81[g]	99:1	91
8[f]	^{t}Bu	**a**	^{i}Pr	**g**	(4*S*,5*R*)-**7g**	85[g]	48:1	61
9	Me	**b**	Ph	**a**	(4*S*,5*R*)-**7h**	73	14:1	81
10	^{t}Bu	**a**	Me	**o**	—	—	—	—

[a] Isolated yield of major diastereomer. [b] Determined by ^{1}H NMR analysis. [c] ee of the major diastereomer determined by chiral HPLC. [d] Isolated yield after conversion to the corresponding *N*-benzoylated amino-ester. [e] Opposite enantiomer obtained using pseudoenantiomeric catalyst **3**. [f] Reaction run at 0 °C. [g] Isolated yield of the major diastereoisomer after conversion to the corresponding formamide.

Table 3. Scope of the Aldol Reaction with α-Substituted Isocyanoacetates



entry	R	8	R_1	6	9	dr[a]	yield (%)[b]	ee (%)[c]
1	Ph	**8a**	3-Br-C_6H_4	**b**	(4*R*,5*R*)-**9a**	10:1	90	97
2	Ph	**8a**	4-F-C_6H_4	**c**	(4*R*,5*R*)-**9b**	11:1	78	94
3[d]	Ph	**8a**	3-F-C_6H_4	**h**	(4*R*,5*R*)-**9c**	15:1	93	97
4	Ph	**8a**	4-Br-C_6H_4	**i**	(4*R*,5*R*)-**9d**	18:1	85	98
5	Ph	**8a**	3-MeO-C_6H_4	**l**	(4*R*,5*R*)-**9e**	12:1	50	93
6	Ph	**8a**	4-Cl-C_6H_4	**m**	(4*R*,5*R*)-**9f**	11:1	56	96
7	Ph	**8a**	4-CO_2Me-C_6H_4	**n**	(4*R*,5*R*)-**9g**	8:1	57	93
8	Bn	**8b**	4-Br-C_6H_4	**i**	(4*R*,5*R*)-**9h**	4:1	72	71

[a] Determined by ^{1}H NMR analysis. [b] Isolated yield of major diastereomer. [c] ee of the major diastereomer determined by chiral HPLC. [d] Relative stereochemistry determined by single crystal X-ray analysis.

creation of two adjacent stereocenters, one of them being fully substituted (Table 3). Notably, in all cases reported in Tables 2 and 3, complete conversion of the isocyanoacetates to products was observed, and all yields in Tables 2 and 3 refer to isolated pure major diastereomer.[7] Interestingly, when α-substituted isocyanoacetates **8a** and **8b** were used, the opposite facial selectivity in the nucleophilic component was observed (in comparison to Table 2). However, facial selectivity on the aldehyde remained the same. Although the reason for the reversal in the observed selectivity is

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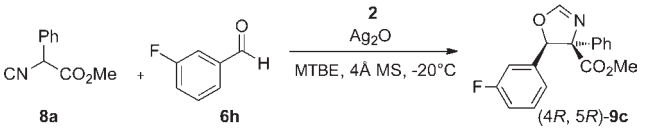
Table 4. Aldol Reaction at Low Catalyst Loadings



entry	2 (mol %)	Ag_2O (mol %)	time (h)	conv (%)[a]	yield (%)[b]	dr[a]	ee (%)[c]
1	2	1	24	100	44	1:1	48
2	2	0.5	24	100	90	14:1	94

[a] Determined by ^{1}H NMR analysis. [b] Isolated yield of major diastereomer. [c] ee of the major diastereomer determined by chiral HPLC.

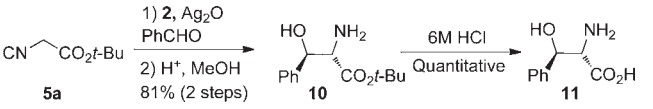
not apparent, this suggests that the mode of action of our catalytic system differs from the seminal findings of Ito and Togni.[4a,4b] One possible rationale for this observation could be that the diastereomers are interconverting under the reaction conditions. However, when an enantioenriched sample of (4*R*,5*R*)-**9c** was treated with amino-phosphine **2** and Ag_2O under the optimized conditions, no epimerization or racemization was observed. When the minor diastereomer obtained during the formation of (4*R*,5*R*)-**9c** was treated in the same manner, no epimerization was observed.

We then turned our attention to the possibility of lowering the catalyst loading. When oxazoline (4*R*,5*R*)-**9c** was prepared using 2 mol % of precatalyst **2** and 1 mol % of Ag_2O, the reaction occurred smoothly, but the product was obtained in 48% enantiomeric excess (entry 1, Table 4). In order to restore high levels of enantioselectivity, the loading of Ag_2O had to be further lowered to 0.5 mol %, keeping the precatalyst loading at 2 mol % (entry 2, Table 4). We postulate that at low catalyst loadings, isocyanoacetate **8a** competes with precatalyst **2** in the Ag^+ complexation and a non-asymmetric pathway is occurring. In order to minimize the background and restore high levels of enantioselectivity, the ratio of **2**:Ag_2O had to be changed from 2:1 to 4:1.

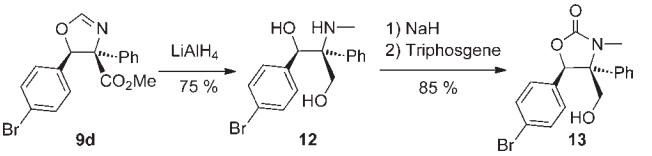
To highlight the utility of the isocyanoacetate aldol reaction products in synthesis, we explored their conversion to the corresponding amino acid derivatives. For example, a mild methanolysis allowed the conversion of oxazoline (4*R*,5*S*)-**7a** directly to the corresponding *tert*-butyl ester **10**, proving the utility of our method for the direct preparation of protected *β*-hydroxy-α-amino acid *tert*-butyl esters (Scheme 3). Hydrolysis of **10** gave the parent amino acid in quantitative yield; this enabled assignment of the absolute stereochemistry by comparison of its specific rotation with those reported in the literature.[4a,8] Reduction of **9d** with $LiAlH_4$ furnished amino alcohol **12**, which was further derivatized to oxazolidinone **13** (Scheme 4) in order to assign absolute stereochemistry of **9a**−**h** by single-crystal X-ray analysis.

In summary, we have developed a new class of chiral amino-phosphine precatalysts that, in combination with an appropriate transition metal ion, can perform as effective cooperative Brønsted base/Lewis acid catalysts. This concept has been successfully applied to the highly enantio- and diastereoselective aldol reaction of isocyanoacetate nucleophiles in the presence of Ag(I) salts. The protocol proved to be operationally simple and could be performed by mixing together the ligand and Ag_2O, without the need to preform the active catalytic species. The catalytic system proved particularly effective in inducing high levels of stereocontrol with aromatic and branched aliphatic aldehydes, while linear aliphatic aldehydes furnished the desired products with lower

Scheme 3. Hydrolysis of Oxazolines



Scheme 4. Reductive Manipulation of Oxazoline 9d



enantioselectivities. The possibility of lowering the catalyst loading has been investigated, and good levels of reactivity and stereocontrol can be obtained with a combination of 2 mol % of ligand **2** and 0.5 mol % of Ag_2O. Work to probe the origin of stereocontrol and to uncover further catalytic applications of ligands **1**−**4** is under investigation in our laboratories and will be reported in due course.

■ ASSOCIATED CONTENT

Supporting Information. Experimental procedures and spectral data for compounds **1**−**4**, **7a**−**h**, **9a**−**h**, **11**−**13** and CIF files for compounds **9c** and **13**. This material is available free of charge via the Internet at http://pubs.acs.org.

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