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Catalytic enantio- and diastereoselective Mannich reaction of α -substituted isocyanoacetates and ketimines†

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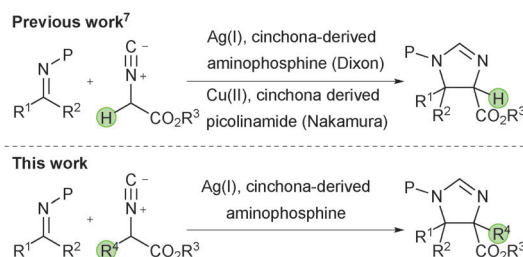
The highly diastereo- and enantioselective Mannich addition/cyclisation reaction of α -substituted isocyanoacetate ester pronucleophiles and (hetero)aryl and alkyl methyl ketone-derived ketimines using a silver acetate and a cinchona-derived amino phosphine binary catalyst system is reported.

The Mannich reaction is a powerful tool for the creation of carbon–carbon bonds¹ and since its discovery in the early 20th century great progress in the development of catalytic enantioselective variants has been made.² To date, the majority of studies have employed aldimines for the enantioselective preparation of amine derivatives possessing tertiary stereogenic centres.^{3,4} However recent efforts have focussed on the development of new catalytic Mannich reactions with ketimines for the stereoselective production of amine derivatives possessing tetrasubstituted stereogenic centres;⁵ the construction of which remains an important challenge in the field.⁶ To this end, our group recently developed a catalytic enantioselective Mannich reaction of isocyanoacetate esters and ketimines to generate trisubstituted chiral imidazolines possessing vicinal quaternary and tertiary stereogenic carbon atoms.⁷ Under the control of a binary catalyst system comprising silver oxide and a cinchona alkaloid-derived amino phosphine, impressive reactivity and high enantio- and diastereocontrol were achieved.⁸ As well as being important building blocks for the synthesis of α,β -diamino acids,⁹ substituted imidazolines, such as those produced by this chemistry, can be identified as the core of biologically active compounds.¹⁰

We recognised that the catalytic enantioselective Mannich reaction of α -substituted isocyanoacetate pronucleophiles with ketimines could provide a synthetically powerful approach for the enantioselective synthesis of imidazolines possessing two

vicinal tetrasubstituted stereocentres.¹¹ To this end, and in a further development of our ongoing research program, we wish to report our efforts leading to a catalytic enantioselective ketimine Mannich reaction of α -substituted isocyanoacetate esters affording chiral imidazolines with two contiguous fully substituted carbon stereocentres, promoted by a catalytic system made from a cinchona-derived amino phosphine ligand and a silver(i) salt (Scheme 1).

Initially we selected acetophenone-derived *N*-diphenylphosphinoyl ketimine **3a** as our model electrophile and investigated a range of 2-isocyanoopropanoate ester pronucleophiles **2** using our previously optimised^{7a} catalyst system comprising quinine-derived amino phosphine **1a** (20 mol%) and Ag₂O (5 mol%) in ethyl acetate at $-20\text{ }^{\circ}\text{C}$ (Table 1). Methyl 2-isocyanoopropanoate **2a** was first investigated as the pronucleophile. Very pleasingly after 60 hours, *N*-DPP protected *trans*-imidazoline **4a** was afforded as a single diastereomer. To allow full characterisation and determination of enantiomeric excess (ee) *via* HPLC analysis, DPP group removal using 1 M HCl was found to be necessary and imidazoline **5a** was afforded in 59% yield over the two steps, in 89% ee (entry 1). With reasonable reactivity and stereoselectivity identified, the performance of more bulky 2-isocyanoopropanoate esters – specifically iso-propyl (**2b**), *tert*-butyl (**2c**), benzyl (**2d**) and benzhydryl (**2e**) 2-isocyanoopropanoates – was studied (entries 2–5). With *tert*-butyl ester **2c** the high enantioselectivity (89% ee) was maintained and the reaction yield was slightly improved to 63% (entry 3),



Scheme 1 Enantioselective construction of chiral imidazolines with two contiguous tetrasubstituted stereocentres.

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Table 1 Optimisation studies^a

Entry	1 (mol%)	[Ag]	R ¹	2	5	t (h)	Yield ^b	ee ^c
1	1a (20)	Ag ₂ O	Me	2a	5a	60	59	89
2	1a (20)	Ag ₂ O	ⁱ Pr	2b	5b	60	77	79
3	1a (20)	Ag ₂ O	^t Bu	2c	5c	60	63	89
4	1a (20)	Ag ₂ O	Bn	2d	5d	60	77	83
5	1a (20)	Ag ₂ O	CHPh ₂	2e	5e	60	62	84
6	1a (10)	Ag ₂ O	^t Bu	2c	5c	60	85	89
7	1a (10)	Ag ₂ CO ₃	^t Bu	2c	5c	70	75	90
8	1a (10)	AgOAc	^t Bu	2c	5c	48	90	89
9	1b (10)	AgOAc	^t Bu	2c	5c	48	81	80 ^d
10	1c (10)	AgOAc	^t Bu	2c	5c	48	89	86
11 ^e	1a (10)	AgOAc	^t Bu	2c	5c	48	82	88
12 ^f	1a (10)	AgOAc	^t Bu	2c	5c	120	0	n/a
13	—	AgOAc	^t Bu	2c	5c	72	64	0
14	1a (10)	—	^t Bu	2c	5c	120	0	n/a
15	1a (2.5)	AgOAc	^t Bu	2c	5c	72	89	90
16 ^g	1a (10)	AgOAc	^t Bu	2c	5c	48	75	90

^a Performed under N₂ with 1 equiv. of 2, 1.1 equiv. of 3a, 1:Ag(I) in 2:1 ratio, 4 Å MS in AcOEt (0.09 M) at −20 °C. ^b Yield over two steps for isolated product 5 (single diastereomer) after flash column chromatography (FCC). ^c Enantiomeric excess (ee) of compound 5 determined by HPLC analysis on a chiral stationary phase. ^d Enantiomeric (4*R*,5*S*)-5c obtained. ^e At 0 °C. ^f At −30 °C. ^g With 10 mol% AgOAc and 10 mol% 1a.

therefore subsequent optimisation in terms of catalyst loading, reactivity and enantiocontrol was done using this pronucleophile. The loading with respect to amino phosphine 1 was lowered to 10 mol% and that of the Ag(I) ions to 5 mol% and the effect of the silver salt was investigated. Interestingly, when the reaction was run using Ag₂O in the presence of 1a the yield increased to 85% and enantioselectivity was maintained at 89% ee (entry 6). With silver carbonate a marginal increase in enantioselectivity (to 90% ee) was seen but the yield was lower (75%, entry 7). With silver acetate a marginal increase in enantioselectivity (to 90% ee) was seen but the yield was lower (75%, entry 7). With both Ag₂O and Ag₂CO₃ the formation of a translucent precipitate was observed. Efforts to form a more soluble complex were made by changing the silver source to AgOAc,¹² which pleasingly gave imidazoline 5c in high ee (89%) with an increased yield (90%) within a shorter reaction time (48 hours, entry 8). Quinidine-derived ligand 1b and cinchonidine-derived amino phosphine 1c with silver acetate afforded 5c in slightly lower enantioselectivity (entries 9 and 10, 80% and 86% ee respectively). Increasing the reaction temperature to 0 °C had a negligible effect on both ee and yield, whereas decreasing it to −30 °C completely suppressed reactivity (entries 11 and 12). Control experiments, first omitting 1a and secondly AgOAc, confirmed that the silver salt was critical for reactivity, whilst the amino phosphine was essential for stereocontrol and important for a high yield (entries 13 and 14).

It was possible to further reduce the ligand:AgOAc loading to 2.5:1.25 mol% with no effect on the ee or yield albeit with slightly increased reaction time (entry 15). A 1:1 ratio of ligand:AgOAc resulted in slightly lower yield (entry 16). For convenience in weighing out the small amounts of silver acetate, the scope of the reaction was assessed at 10:5 mol% ligand:AgOAc ratio at −20 °C.

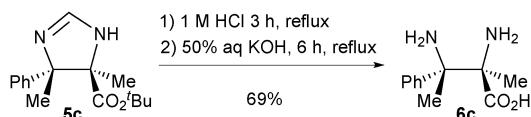
A range of ketimines derived from aromatic and hetero-aromatic methyl ketones^{1,3} (3a–3j) were subjected to the reaction conditions (Table 2). Electron-withdrawing and electron-donating groups in the 4-position of the aromatic ring were well tolerated, giving 5f–5j in good yield (71–89%) and enantiomeric excess (88–90% ee, entries 2–6). *Meta*- and *ortho*-substituted aromatic ketimines afforded the imidazolines 5k and 5l with lower yield (65% and 63% respectively) and good ee (87% and 95% respectively, entries 7 and 8). Heteroaromatic *N*-DPP ketimines derived from methyl 3-pyridyl ketone and methyl 2-furyl ketone gave products 5m and 5n in high yield and ee (entries 9 and 10). Aliphatic ketimine 3k derived from 4-phenyl-2-butanone could be converted to imidazoline 5o with moderate yield (48%) and good enantioselectivity (87% ee, entry 11). Next, *tert*-butyl 2-isocyanobutanoate 2f was assessed on a range of ketimines to afford exclusively the *trans* imidazolines 5p–5s with an ethyl

Table 2 Reaction scope^a

Entry	R ³	3	R ¹	R ²	2	5	Yield ^b	ee
1	Ph	3a	Me	^t Bu	2c	5c	90	89
2	4-MeC ₆ H ₄	3b	Me	^t Bu	2c	5f	71	89
3	4-PhC ₆ H ₄	3c	Me	^t Bu	2c	5g	87	88
4	4-FC ₆ H ₄	3d	Me	^t Bu	2c	5h	89	90
5	4-ClC ₆ H ₄	3e	Me	^t Bu	2c	5i	80	89
6	4-MeOC ₆ H ₄	3f	Me	^t Bu	2c	5j	80	90
7	3-ClC ₆ H ₄	3g	Me	^t Bu	2c	5k	65	87
8	2-FC ₆ H ₄	3h	Me	^t Bu	2c	5l	63	95
9	3-Pyridyl	3i	Me	^t Bu	2c	5m	80	87
10	2-Furyl	3j	Me	^t Bu	2c	5n	83	91
11	PhCH ₂ CH ₂	3k	Me	^t Bu	2c	5o	48 ^c	87
12	Ph	3a	Et	^t Bu	2f	5p	62	90
13	4-ClC ₆ H ₄	3e	Et	^t Bu	2f	5q	81	89
14	4-MeOC ₆ H ₄	3f	Et	^t Bu	2f	5r	79	92
15	2-Furyl	3j	Et	^t Bu	2f	5s	84	93
16	Ph	3a	ⁿ Bu	^t Bu	2g	5t	85	91
17	4-FC ₆ H ₄	3d	ⁿ Bu	^t Bu	2g	5u	83	90
18	4-ClC ₆ H ₄	3e	ⁿ Bu	^t Bu	2g	5v	80	88
19	2-Furyl	3j	ⁿ Bu	^t Bu	2g	5w	83	93
20	4-MeC ₆ H ₄	3b	Me	Me	2a	5y	28	87

^a Performed under N₂ with 1 equiv. of 2, 1.1 equiv. of 3, 0.1 equiv. of 1a, 0.05 equiv. of AgOAc, 4 Å MS in AcOEt (0.09 M) at −20 °C for 48 h. Imidazolines 4 were obtained with dr > 98:2 (determined by ¹H-NMR analysis of the crude reaction mixture) unless otherwise stated. ^b Yield over two steps for isolated product 5 (single diastereomer) after FCC. ^c *N*-DPP imidazoline 4o was obtained with a 5:1 dr in favour of the *trans* isomer, as determined by ¹H-NMR analysis of the crude reaction mixture.





Scheme 2 Application to the synthesis of fully substituted α,β -diamino acids.

substituent in the α -position in similarly high ee and yield (entries 12–15). The *tert*-butyl 2-isocyanohexanoate **2g** also performed well in the reaction to give products **5t–5w** in excellent yield and ee (entries 16–19).¹⁴ NOe NMR experiments established the relative *trans* stereochemical configuration of products **5f**, **5o**, **5q** and **5v**. Absolute configuration was determined by comparison of the specific rotation of imidazoline **5y** with that reported in the literature.^{5c}

As a demonstration of the synthetic utility of this newly established method, product **5c** was hydrolysed to afford α,β -diamino acid **6c** (Scheme 2). Such compounds are difficult to access in enantioenriched form by other methods.⁹

To gain insight into the importance of the various functional groups possessed by amino phosphines **1**, a series of control experiments using modified ligand structures (**1d–1g**) were performed (Table 3). Diastereomeric ligand **1d** gave imidazoline **5c** with a large decrease in enantioselectivity (entry 2). Ligand **1e**, lacking the phosphine moiety, was significantly worse: product **5c** was obtained in low yield with poor enantioselectivity (entry 3). Ligand **1f** with an ester linker gave imidazoline **5c** in slightly decreased yield and enantioselectivity (entry 4). Finally ligand **1g** with a *N*-methyl group on the amide promoted the reaction with a similar yield to **1a** but much lower levels of enantioselectivity (entry 5).

In order to better understand the results from the catalyst modification studies and to determine how ligand **1a** binds to AgOAc, a crystal of complex **1a**-AgOAc was grown (Fig. 1).¹⁵ Single crystal X-ray diffraction determined that in the solid

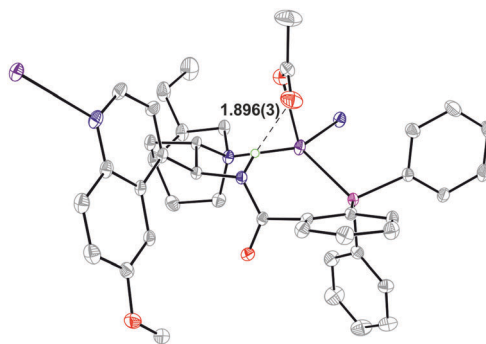


Fig. 1 Structure of **1a**-AgOAc from single crystal X-ray diffraction studies showing the intramolecular H-bond ($\text{H}\cdots\text{O} = 1.896(3)$ Å; $\text{N}\cdots\text{O} = 2.752(4)$ Å). Displacement ellipsoids drawn at 30% probability; solvent and selected hydrogen atoms omitted for clarity.

state **1a** acts as a *P,N*-bidentate ligand, binding silver through both the phosphine and the quinuclidine N atom to create a 9-membered macrocycle. The other groups coordinating to silver are the acetate and a quinoline unit belonging to a symmetry related molecule of **1a** leading to the formation of polymeric chains in the solid state. The four-coordinate silver adopts a distorted tetrahedral geometry. An intramolecular hydrogen bond between the acetate group on silver and the transannular amide N–H at 1.896(3) Å is present with a $\text{N}\cdots\text{O}$ distance of 2.752(4) Å. The π system of the amide group is oriented towards the silver with a distance of 2.9571(18) Å between the amide nitrogen and the silver centre suggesting a possible interaction. Such an interaction would transfer charge resulting in acidification of the amide NH thus enhancing its H-bond donor ability.

³¹P and ¹H NMR studies of a 1 : 1 ratio of amino phosphine **1a** and AgOAc at –20 °C were also performed (see ESI† for full NMR studies). The ³¹P NMR experiments showed a quantitative binding of silver(I) in solution and ¹H NMR analysis of the same mixture revealed a large downfield shift (approximately 3.4 ppm relative to that of the free ligand) of the amide N–H consistent with presence of the same H-bonding interaction. Additionally, the protons adjacent to the quinuclidine nitrogen were also shifted downfield, consistent with coordination of the quinuclidine nitrogen to silver. In the solution phase there is no strong evidence that the quinoline N atom binds the Ag centre; the change of chemical shift for the proton adjacent to the quinoline nitrogen is only 0.07 ppm. When methyl isocyanacetate is added to the solution of **1a** and AgOAc, the CH₂ group appears as a characteristic ABq system, providing evidence for complexation of the isonitrile to silver.

Building on the results of experiments using modified ligand structures (Table 3) and the structural data obtained from both the X-ray and NMR studies we propose a transition structure that rationalises the enantio- and diastereoselectivity observed in this Mannich reaction (Fig. 2). The N atom of the (*E*)-configured ketimine is postulated to make a key hydrogen bond to the amide N–H, which both orientates the electrophile and activates it towards nucleophilic addition. The aromatic ring of the H-bonded ketimine is oriented away from the quinuclidine and quinoline units on steric grounds and C–H/ π -interactions¹⁶

Table 3 Variation on ligand structure

Entry	1	Yield ^a	ee
1	1a	90	89
2	1d	89	20
3	1e	23	5
4	1f	75	72
5	1g	86	27

^a Yield over two steps for product **5c** (single diastereomer) after FCC.



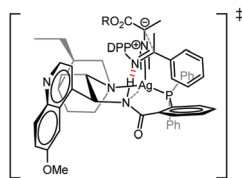


Fig. 2 Proposed transition structure.

between it and the aromatic ring of the carboxamide could provide additional binding/organisation, possibly accounting for the high enantiofacial selectivity observed using this catalyst.^{7a,8} The ester group of the isocyanacetate is oriented away from the aromatic group on the ketimine on steric grounds. Subsequent to the enantio- and diastereodetermining C–C bond forming step, ring closure and protonolysis would yield the *N*-DPP protected imidazoline with the observed stereochemical configuration. Satisfyingly, this transition state model, with its multipoint binding interactions, would also rationalise the stereochemical outcomes of the previously reported reactions with aldehydes^{8a} and ketones.^{8b}

In conclusion, we have developed a diastereo- and enantioselective Mannich reaction/cyclisation of α -substituted isocyanacetates and ketimines catalysed by silver acetate and a cinchona-derived amino phosphine. The reaction scope is broad and includes substituted aryl, heteroaryl and alkyl methyl ketimines as well as isocyanacetates with linear alkyl chains in the α -position. Hydrolysis of the product imidazolines provides access to fully substituted α,β -diamino acids. Information arising from X-ray and NMR studies, as well as control studies on the ligand, have allowed a detailed transition state model to be postulated.

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