Asymmetric Synthesis

DOI: 10.1002/anie.201309719

Direct Catalytic Enantio- and Diastereoselective Mannich Reaction of Isocyanoacetates and Ketimines**

*Irene Ortín and Darren J. Dixon**

Abstract: *A catalytic asymmetric synthesis of imidazolines with a fully substituted β-carbon atom by a Mannich-type addition/cyclization reaction of isocyanoacetate pronucleophiles and N-diphenylphosphinoyl ketimines has been developed. When a combination of a cinchona-derived aminophosphine precatalyst and silver oxide was employed as a binary catalyst system, good reactivity, high diastereoselectivities (up to 99:1 d.r.), and excellent enantioselectivities (up to 99% ee) were obtained for a range of substrates.*

Stereochemically defined α,β-diaminoacids are important structural motifs that are contained within many bioactive natural compounds.[1] This abundance has stimulated the development of methods towards their stereoselective construction; a common approach is based on catalytic asymmetric Mannich-type reactions of derivatives[2,3] of or precursors[4] to α-amino acids. The vast majority of these methods have targeted structures that possess a tertiary stereocenter at the β-position through additions to aldimines.[2,3] Reports of catalytic asymmetric methods that afford derivatives possessing a fully substituted stereocenter at the β-position are rare.[5] However, in work relevant to this study, Matsunaga and Shibasaki employed ketimine electrophiles in Mannich reactions with isothiocyanoato esters to afford cyclic tetrasubstituted thiourea derivatives with high selectivities.[5a]

A complementary and practical route to α,β-diaminoacids proceeds via imidazoline heterocycles, which may be directly formed by catalytic asymmetric Mannich-type addition/cyclization reactions of isocyanoester pronucleophiles with imine electrophiles.[6,4p] The reactants are readily prepared on a large scale, and the imidazoline products, unlike cyclic thioureas, are readily converted into target α,β-diaminoacids through standard hydrolytic or reductive manipulation.[7] Furthermore, imidazolines form the structural core of many biologically active compounds,[8] and they are useful building blocks for the synthesis of cyclopalladated complexes, chiral catalysts, and chiral solvating agents.[9] Highly stereoselective syntheses using either metal-based or metal-free catalyst systems have been reported.[6] To date, however, only aldimines have been employed, and the analogous asymmetric transformation of the significantly less reactive ketimines[10] has not been reported despite its potential to provide a direct route to chiral imidazolines that possess vicinal stereogenic centers, including a fully substituted β-carbon atom.

Recently, our group reported the highly enantio- and diastereoselective synthesis of oxazolines[11] from isocyanoacetate pronucleophiles and aldehydes using a binary catalyst system that combines "soft" metal ions and cinchona-derived aminophosphine precatalysts **1**.[12] To promote reactivity and govern selectivity in a cooperative fashion with metal ion additives, these precatalysts possess Brønsted basic, Lewis basic, and hydrogen-bond-donor groups that are situated in close proximity around a chiral pocket that is created by the cinchona scaffold (Figure 1). We believed that a true test of the utility of this catalyst system was to attain new reactivity and stereocontrol in challenging reactions for which no precedent exists. The catalytic asymmetric Mannich-type addition/cyclization reaction of isocyanoester pronucleophiles **I** with ketimines **II** to afford imidazolines **III**, which possess a fully substituted stereocenter at the β-carbon atom (Scheme 1), indeed provided this opportunity, and herein we present our findings.

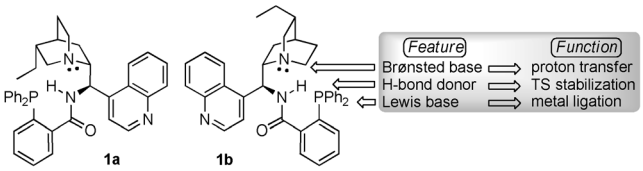
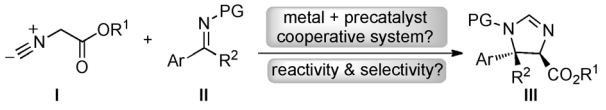


Figure 1. Structure, design, and features of multifunctional aminophosphine precatalysts **1a** and **1b**. TS = transition state.

Initial proof-of-concept studies were performed with readily prepared diphenylmethylisocyanoacetate (**2a**) as the pronucleophile and *N*-diphenylphosphinoyl (DPP)-protected and acetophenone-derived imine **3a**. Such imines are readily prepared from the parent ketone, and subsequent cleavage of the DPP group of imidazolines **4** was anticipated to be clean and efficient under mildly acidic conditions.[13]



Scheme 1. Proposed catalytic Mannich-type addition/cyclization reaction of isocyanoacetates and ketimines. PG = protecting group.

[*] Dr. I. Ortín, Prof. Dr. D. J. Dixon
Department of Chemistry, Chemistry Research Laboratory
University of Oxford
Mansfield Road, Oxford OX1 3TA (UK)
E-mail: darren.dixon@chem.ox.ac.uk

[**] We thank the EPSRC (Leadership Fellowship to D.J.D.) and the EC [IEF to I.O. (PIEF-GA-2010-275788)] for funding, Alison Hawkins and David Barber of the Department of Chemistry, University of Oxford, for X-ray analysis, and the Oxford Chemical Crystallography Service for the use of their instrumentation.

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/anie.201309719.

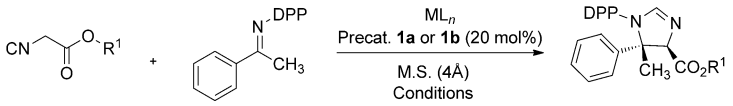
Initially, a catalyst system that consists of silver oxide (5 mol%) and cinchonine-derived aminophosphine **1a** (20 mol%) was examined in dichloromethane at room temperature. A 2:1 ratio of precatalyst to metal ion was chosen to suppress any competing background reactions. Pleasingly, the *trans*-configured imidazoline product, (4*S*,5*R*)-**4a**, was obtained with significant diastereo- and enantioselectivity (Table 1, entry 1; 71:29 d.r., 72% *ee*). A screen of metal salts confirmed silver (rather than gold or copper) to be the best match for precatalyst **1a** in this reaction (entries 1–3).

A solvent survey revealed ethyl acetate as the preferred choice in terms of both diastereo- and enantiocontrol (entries 1, 4, and 5). Lowering the temperature of the reaction to −20 °C was found to be beneficial for the enantioselectivity (entry 6; 89:11 d.r., 82% *ee*). The bulky *tert*-butylisocyanoacetate was also reactive and afforded the *trans* imidazoline (4*S*,5*R*)-**4b** as the major product in better yield and enantioselectivity (entry 7; 89%, 88:12 d.r., 89% *ee*). In contrast, use of methyl isocyanoacetate **2c** resulted in diminished enantioselectivity for the major *trans* diastereomer (4*S*,5*R*)-**4c** (entry 8; 94%, 91:9 d.r., 74% *ee*). Significantly, control experiments confirmed the importance of both the silver salt and the aminophosphine precatalyst: In the absence of the silver salt, there was no reaction (entry 9); without the precatalyst, enantiocontrol was (naturally) absent, the reaction was significantly slower, and the *cis* diastereomer was formed predominantly (entry 10; 18:82 d.r.). Employing pseudoenantiomeric **1b** instead of **1a** in conjunction with isocyanoacetates **2a** and **2b** afforded the enantiomeric products (4*R*,5*S*)-**4a** and (4*R*,5*S*)-**4b**, respectively, as expected, but pleasingly with enhanced enantioselectivities of 96% *ee* in both cases (entries 11 and 12).

With the optimized reaction conditions established, the scope of the reaction that is catalyzed by cinchonidine-derived aminophosphine precatalyst **1b** and Ag_2O was assessed by probing changes to both the aryl and alkyl groups of the ketimine in reactions with bulky isocyanoacetates **2a** and **2b** (Table 2). With *tert*-butylisocyanoacetate pronucleophile **2b** good to excellent diastereoselectivities and excellent enantioselectivities (93–99% *ee*) were observed for DPP-protected *para*-substituted aryl methyl ketimines with either electron-withdrawing or electron-donating groups (entries 2–6). Importantly, imine **3f**, which is derived from ethyl phenyl ketone, was also an excellent substrate and afforded *trans* imidazoline **4h** in high yield, good diastereoselectivity, and with an excellent *ee* of 97% (entry 7).

Using diphenylmethylisocyanoacetate pronucleophile **2a** a wide range of ketimines that are derived from aryl methyl ketones and bear various electron-donating or electron-withdrawing substituents in the *ortho*, *meta*, and *para* positions were suitable substrates. Enantioselectivities for the major *trans* diastereoisomer ranged from 94% *ee* with

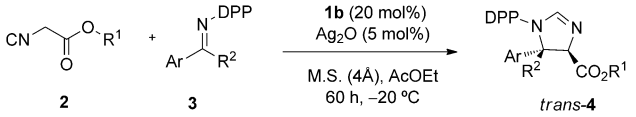
Table 1: Optimization studies.



Entry	Precat.	ML_n (mol%)	R^1	2	T [°C]	Solvent	Time [h]	4	Yield[a] [%]	d.r.[b]	ee[c]
1	**1a**	Ag_2O (5)	$CH(Ph)_2$	**2a**	RT	CH_2Cl_2	48	**4a**	70	71:29	72
2	**1a**	AuCl (10)	$CH(Ph)_2$	**2a**	RT	CH_2Cl_2	48	**4a**	20	14:86	2
3	**1a**	CuCl (10)	$CH(Ph)_2$	**2a**	RT	CH_2Cl_2	48	**4a**	23	43:57	2
4	**1a**	Ag_2O (5)	$CH(Ph)_2$	**2a**	RT	TBME	24	**4a**	44	37:63	70
5	**1a**	Ag_2O (5)	$CH(Ph)_2$	**2a**	RT	EtOAc	24	**4a**	68	83:17	78
6	**1a**	Ag_2O (5)	$CH(Ph)_2$	**2a**	−20	EtOAc	60	**4a**	78	89:11	82
7	**1a**	Ag_2O (5)	*t*Bu	**2b**	−20	EtOAc	60	**4b**	89	88:12	89
8	**1a**	Ag_2O (5)	CH_3	**2c**	−20	EtOAc	60	**4c**	94	91:9	74
9	**1a**	–	$CH(Ph)_2$	**2a**	−20	EtOAc	120	**4a**	0	–	–
10	–	Ag_2O (5)	$CH(Ph)_2$	**2a**	−20	EtOAc	120	**4a**	83	18:82	0
11	**1b**	Ag_2O (5)	$CH(Ph)_2$	**2a**	−20	EtOAc	60	**4a**	70	84:16	96
12	**1b**	Ag_2O (5)	*t*Bu	**2b**	−20	EtOAc	60	**4b**	92	99:1	96

[a] Combined yield of both diastereomers after flash column chromatography. [b] The diastereomeric ratio (d.r.) of the *trans*/*cis* diastereomers was determined by ^{1}H NMR analysis of the crude reaction mixture. [c] The enantiomeric excess (*ee*) of the major diastereomer was determined by HPLC analysis on a chiral stationary phase after DPP removal. M.S. = molecular sieves, TBME = *tert*-butyl methyl ether.

Table 2: Substrate scope.



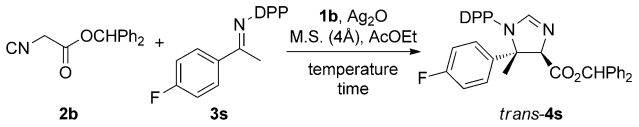
Entry	Ar	R^2	2	4	Yield[a] [%]	d.r.[b]	ee[c]
1	Ph	CH_3	**2a**	**4a**	70	84:16	96
2	Ph	CH_3	**2b**	**4b**	92	99:1	96
3	*p*-$NO_2C_6H_4$	CH_3	**2b**	**4d**	87	80:20	95
4	*p*-ClC_6H_4	CH_3	**2b**	**4e**	96	96:4	93
5	*p*-$CH_3C_6H_4$	CH_3	**2b**	**4f**	78	90:10	98
6	*p*-$CH_3OC_6H_4$	CH_3	**2b**	**4g**	87	75:25	99
7	Ph	Et	**2b**	**4h**	85	88:12	97
8	*p*-ClC_6H_4	CH_3	**2a**	**4i**	83	86:14	97
9	*p*-$CH_3C_6H_4$	CH_3	**2a**	**4j**	96	95:5	96
10	*p*-$CH_3OC_6H_4$	CH_3	**2a**	**4k**	96	73:27	98
11	Ph	Et	**2a**	**4l**	80	81:19	90
12	*m*-$CH_3OC_6H_4$	CH_3	**2a**	**4m**	82	74:26	96
13	*o*-$CH_3OC_6H_4$	CH_3	**2a**	**4n**	96	80:20	97
14	*p*-PhC_6H_4	CH_3	**2a**	**4o**	97	90:10	97
15	*p*-BrC_6H_4	CH_3	**2a**	**4p**	98	78:22	94
16	*o*-BrC_6H_4	CH_3	**2a**	**4q**	97	99:1	96
17	*o*-FC_6H_4	CH_3	**2a**	**4r**	95	84:16	96
18	*p*-FC_6H_4	CH_3	**2a**	**4s**	95	83:17	96
19	3,4-$(Cl)_2$-C_6H_3	CH_3	**2a**	**4t**	84	85:15	95

[a] Combined yield of both diastereomers after flash column chromatography. [b] The diastereomeric ratio (d.r.) of the *trans*/*cis* diastereomers was determined by ^{1}H NMR analysis of the crude reaction mixture. [c] The *ee* of the major diastereomer was determined by HPLC analysis on a chiral stationary phase after DPP removal.

para-bromophenyl methyl ketimine (entry 15) to 98% *ee* with DPP-protected *para*-methoxyphenyl methyl ketimine (entry 10). Pleasingly, DPP-protected phenyl ethyl ketimine gave the reaction product **4l** in a combined 80% yield for both diastereomers, and with 81:19 d.r. and 90% *ee* for the major *trans* diastereoisomer. In total, in the presence of a combination of **1b** and Ag_2O, thirteen substrates proved effective and could be converted into the corresponding *trans* diastereomers with excellent enantio- and good diastereoselectivities.

Although a precatalyst loading of 20 mol% was found to be convenient for assessing the substrate scope, the loading of precatalyst **1b** was reduced from 20 mol% to 10 mol%, 5 mol%, and 1 mol% at −20°C to demonstrate the practicability of this transformation (Table 3, entries 1–3). The observed diastereo- and enantioselectivities were comparable to those obtained with a precatalyst loading of 20 mol%; however, the reaction became prohibitively slow. To shorten the reaction time, the temperature was increased to 0°C.

Table 3: Variation of the catalyst loading.

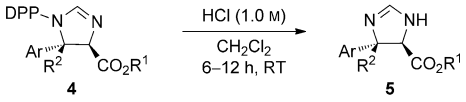


2b **3s** *trans*-**4s**

Entry	**1b** [mol%]	Ag_2O [mol%]	*T* [°C]	Time [h]	Yield[a] [%]	d.r.[b]	*ee*[c]
1	10	2.5	−20	60	87	94:6	96
2	5	1.25	−20	120	78	93:7	96
3	1	0.25	−20	160	77	92:8	95
4	10	2.5	0	24	89	89:11	95
5	5	1.25	0	60	87	86:14	93
6	1	0.25	0	60	58	87:13	94

[a] Combined yield of both diastereomers after flash column chromatography. [b] The diastereomeric ratio (d.r.) of the *trans*/*cis* diastereoisomers was determined by ^{1}H NMR analysis of the crude reaction mixture. [c] The *ee* of the major diastereomer was determined by HPLC analysis on a chiral stationary phase after deprotection.

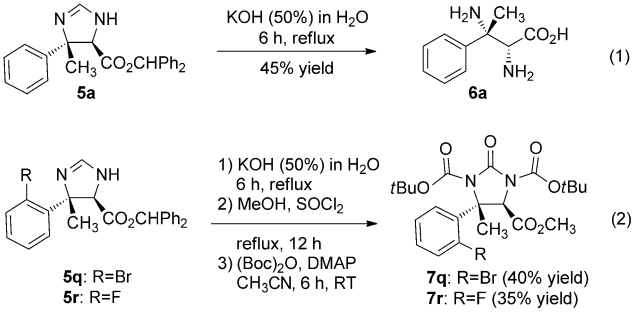
Table 4: Removal of the DPP protecting group.



4 **5**

Entry	**5**	R^2	Ar	R^1	Yield[a] [%]
1	**5a**	CH_3	Ph	$CH(Ph)_2$	90
2	**5b**	CH_3	Ph	*t*Bu	89
3	**5d**	CH_3	*p*-$NO_2C_6H_4$	*t*Bu	89
4	**5e**	CH_3	*p*-ClC_6H_4	*t*Bu	95
5	**5f**	CH_3	*p*-$CH_3C_6H_4$	*t*Bu	85
6	**5g**	CH_3	*p*-$CH_3OC_6H_4$	*t*Bu	63
7	**5h**	Et	Ph	*t*Bu	95
8	**5i**	CH_3	*p*-ClC_6H_4	$CH(Ph)_2$	60
9	**5j**	CH_3	*p*-$CH_3C_6H_4$	$CH(Ph)_2$	81
10	**5k**	CH_3	*p*-$CH_3OC_6H_4$	$CH(Ph)_2$	83
11	**5l**	Et	Ph	$CH(Ph)_2$	67
12	**5m**	CH_3	*m*-$CH_3OC_6H_4$	$CH(Ph)_2$	85
13	**5n**	CH_3	*o*-$CH_3OC_6H_4$	$CH(Ph)_2$	59
14	**5o**	CH_3	*p*-PhC_6H_4	$CH(Ph)_2$	90
15	**5p**	CH_3	*p*-BrC_6H_4	$CH(Ph)_2$	75
16	**5q**	CH_3	*o*-BrC_6H_4	$CH(Ph)_2$	70
17	**5r**	CH_3	*o*-FC_6H_4	$CH(Ph)_2$	61
18	**5s**	CH_3	*p*-FC_6H_4	$CH(Ph)_2$	87
19	**5t**	CH_3	3,4-$(Cl)_2$-C_6H_3	$CH(Ph)_2$	73

[a] Yield of isolated product after flash column chromatography.



Scheme 2. Chemical transformations of imidazolines.

Pleasingly, this was possible without significant detriment to either enantio- or diastereocontrol (entries 4–6).

Aside from the high yields and stereoselectivities, an advantage of our described method lies in the simple and efficient synthetic manipulation of the direct Mannich products into desirable building blocks and motifs. Protecting-group-free imidazolines were obtained by the efficient cleavage of the diphenylphosphinoyl group[13] using a 1.0 M solution of HCl in dichloromethane at room temperature (Table 4, entries 1–19). The deprotection could be carried out without compromising the diastereo- or enantiopurity. Importantly, the absolute configuration of the imidazolines was confirmed by single-crystal X-ray analysis of **5u**, a *N*-(4-bromophenylsulfonyl) derivative of **5p** (see the Supporting Information for details). Furthermore, treatment of imidazoline *trans*-**5a** with an aqueous solution of potassium hydroxide (50%) gave α,β-diaminoacid[7] **6a** without a deterioration of enantiopurity [Scheme 2, Eq. (1)]. Imidazolines *trans*-**5q** and *trans*-**5r** were transformed into the cyclic ureas **7q** and **7r** by alkaline hydrolysis, esterification, and treatment with an excess amount of Boc_2O and DMAP [Scheme 2, Eq. (2); Boc = *tert*-butoxycarbonyl, DMAP = 4-dimethylaminopyridine]. The relative and absolute stereochemical configuration of **7q** was established by single-crystal X-ray analysis (for details, see the Supporting Information).

In conclusion, we have developed an efficient and general, diastereo- and enantioselective method for the synthesis of highly functionalized imidazolines that possess a fully substituted stereocenter at the β-position through a Mannich-type addition/cyclization reaction of isocyanoacetate pronucleophiles and ketimines using a silver salt and cinchona-derived aminophosphine binary catalyst system. We have also demonstrated that chiral unprotected imidazolines and α,β-diaminoacids can be easily obtained from the protected imidazoline reaction products. Further studies into the asymmetric synthesis of imidazolines with two contiguous quaternary centers are underway, and the findings will be reported in due course.

Received: November 7, 2013
Published online: February 24, 2014

Keywords: asymmetric catalysis · cooperative catalysis · imidazolines · ketimines · Mannich reaction

[1] For reviews, see: a) A. Viso, R. Fernández de La Pradilla, A. García, A. Flores, *Chem. Rev.* **2005**, *105*, 3167 – 3196; b) A. Viso, R. F. De La Pradilla, M. Tortosa, A. García, A. Flores, *Chem. Rev.* **2011**, *111*, PR1 – PR42.

[2] For reviews, see: a) R. G. Arrayás, J. C. Carretero, *Chem. Soc. Rev.* **2009**, *38*, 1940 – 1948; b) B. Karimi, D. Enders, E. Jafari, *Synthesis* **2013**, *45*, 2769 – 2812, and references therein.

[3] a) L. Bernardi, A. S. Gothelf, R. G. Hazell, K. A. Jørgensen, *J. Org. Chem.* **2003**, *68*, 2583 – 2591; b) T. Ooi, M. Kameda, J.-I. Fujii, K. Maruoka, *Org. Lett.* **2004**, *6*, 2397 – 2399; c) A. Okada, T. Shibuguchi, T. Ohshima, H. Masu, K. Yamaguchi, M. Shibasaki, *Angew. Chem.* **2005**, *117*, 4640 – 4643; *Angew. Chem. Int. Ed.* **2005**, *44*, 4564 – 4567; d) N. S. Chowdari, M. Ahmad, K. Albertshofer, F. Tanaka, C. F. Barbas III, *Org. Lett.* **2006**, *8*, 2839 – 2842; e) S. Kobayashi, R. Yazaki, K. Seki, Y. Yamashita, *Angew. Chem.* **2008**, *120*, 5695 – 5697; *Angew. Chem. Int. Ed.* **2008**, *47*, 5613 – 5615; f) J. Hernández-Toribio, R. G. Arrayás, J. C. Carretero, *J. Am. Chem. Soc.* **2008**, *130*, 16150 – 16151; g) X.-X. Yan, Q. Peng, Q. Li, K. Zhang, J. Yao, X.-L. Hou, Y.-D. Wu, *J. Am. Chem. Soc.* **2008**, *130*, 14362 – 14363; h) D. Shang, Y. Liu, X. Zhou, X. Liu, X. Feng, *Chem. Eur. J.* **2009**, *15*, 3678 – 3681; i) H. Zhang, S. Syed, C. F. Barbas, *Org. Lett.* **2010**, *12*, 708 – 711; j) J. Hernández-Toribio, R. G. Arraý, J. C. Carretero, *Chem. Eur. J.* **2010**, *16*, 1153 – 1157; k) G. Liang, M.-C. Tong, H. Tao, C.-J. Wang, *Adv. Synth. Catal.* **2010**, *352*, 1851 – 1855; l) E. Hernando, R. G. Arrayás, J. C. Carretero, *Chem. Commun.* **2012**, *48*, 9622 – 9624.

[4] a) K. R. Knudsen, K. A. Jørgensen, *Org. Biomol. Chem.* **2005**, *3*, 1362 – 1364; b) G. A. Cutting, N. E. Stainforth, M. P. John, G. Kociok-Köhn, M. C. Willis, *J. Am. Chem. Soc.* **2007**, *129*, 10632 – 10633; c) Z. Chen, H. Morimoto, S. Matsunaga, M. Shibasaki, *J. Am. Chem. Soc.* **2008**, *130*, 2170 – 2171; d) A. Singh, J. N. Johnston, *J. Am. Chem. Soc.* **2008**, *130*, 5866 – 5867; e) B. Han, Q.-P. Liu, R. Li, X. Tian, X.-F. Xiong, J.-G. Deng, Y.-C. Chen, *Chem. Eur. J.* **2008**, *14*, 8094 – 8097; f) D. Uraguchi, K. Koshimoto, T. Ooi, *J. Am. Chem. Soc.* **2008**, *130*, 10878 – 10879; g) D. Uraguchi, Y. Ueki, T. Ooi, *J. Am. Chem. Soc.* **2008**, *130*, 14088 – 14089; h) A. Puglisi, L. Raimondi, M. Benaglia, M. Bonsignore, S. Rossi, *Tetrahedron Lett.* **2009**, *50*, 4340 – 4342; i) L. Li, M. Ganesh, D. Seidel, *J. Am. Chem. Soc.* **2009**, *131*, 11648 – 11649; j) D. Uraguchi, K. Koshimoto, C. Sanada, T. Ooi, *Tetrahedron: Asymmetry* **2010**, *21*, 1189 – 1190; k) X. Liu, L. Deng, X. Jiang, W. Yan, C. Liu, R. Wang, *Org. Lett.* **2010**, *12*, 876 – 879; l) X. Chen, S. Dong, Z. Qiao, Y. Zhu, M. Xie, L. Lin, X. Liu, X. Feng, *Chem. Eur. J.* **2011**, *17*, 2583 – 2586; m) A. D. Melhado, G. W. Amarante, Z. J. Wang, M. Luparia, F. D. Toste, *J. Am. Chem. Soc.* **2011**, *133*, 3517 – 3527; n) J. Jiang, H.-D. Xu, J.-B. Xi, B.-Y. Ren, F.-P. Lv, X. Guo, L.-Q. Jiang, Z.-Y. Zhang, W.-H. Hu, *J. Am. Chem. Soc.* **2011**, *133*, 8428 – 8431; o) S.-H. Shi, F.-P. Huang, P. Zhu, Z.-W. Dong, X.-P. Hui, *Org. Lett.* **2012**, *14*, 2010 – 2013; p) S. Nakamura, Y. Maeno, M. Ohara, A. Yamamura, Y. Funahashi, N. Shibata, *Org. Lett.* **2012**, *14*, 2960 – 2963; q) W.-Q. Zhang, L.-F. Cheng, J. Yu, L.-Z. Gong, *Angew. Chem.* **2012**, *124*, 4161 – 4164; *Angew. Chem. Int. Ed.* **2012**, *51*, 4085 – 4088.

[5] See, for example: a) G. Lu, T. Yoshino, H. Morimoto, S. Matsunaga, M. Shibasaki, *Angew. Chem.* **2011**, *123*, 4474 – 4477; *Angew. Chem. Int. Ed.* **2011**, *50*, 4382 – 4385; b) J. Jiang, X. Ma, S. Liu, Y. Qian, F. Lv, L. Qiu, X. Wu, W. Hu, *Chem. Commun.* **2013**, *49*, 4238 – 4240.

[6] a) X.-T. Zhou, Y.-R. Lin, L.-X. Dai, J. Sun, L.-J. Xia, M.-H. Tang, *J. Org. Chem.* **1999**, *64*, 1331 – 1334; b) J. Aydin, A. Rydén, K. J. Szabó, *Tetrahedron: Asymmetry* **2008**, *19*, 1867 – 1870; c) Z.-W. Zhang, G. Lu, M.-M. Chen, N. Lin, Y.-B. Li, T. Hayashi, A. S. C. Chan, *Tetrahedron: Asymmetry* **2010**, *21*, 1715 – 1721.

[7] For reports that describe the hydrolysis of the imidazoline ring to afford the α,β-diaminoacid, see: a) J. Sang-Hun, K. Harold, *Tetrahedron Lett.* **1984**, *25*, 399 – 402; b) R. Meyer, U. Schöllkopf, P. Bohme, *Liebigs Ann. Chem.* **1977**, 1183 – 1193.

[8] See, for example: a) C. Betschart, L. S. Hegedus, *J. Am. Chem. Soc.* **1992**, *114*, 5010 – 5017; b) F. Rondu, G. Le Bihan, X. Wang, A. Lamouri, E. Touboul, G. Dive, T. Bellahsene, B. Pfeiffer, P. Renard, B. Guardiola-Lamaitre, D. Manechez, L. Penicaud, A. Ktorza, J. J. Godfroid, *J. Med. Chem.* **1997**, *40*, 3793 – 3803; c) Y. Hsiao, L. S. Hegedus, *J. Org. Chem.* **1997**, *62*, 3586 – 3591.

[9] See, for example: a) J. Xu, Y. Guan, S. Yang, Y. Ng, G. Peh, C.-H. Tan, *Chem. Asian J.* **2006**, *1*, 724 – 729; b) H. Liu, D.-M. Du, *Adv. Synth. Catal.* **2010**, *352*, 1113 – 1118; c) H. Liu, D.-M. Du, *Adv. Synth. Catal.* **2009**, *351*, 489 – 519.

[10] For enantioselective addition reactions of other nucleophiles or pronucleophiles to ketimines, see: a) S. Saaby, K. Nakama, M. A. Lie, R. G. Hazell, K. A. Jørgensen, *Chem. Eur. J.* **2003**, *9*, 6145 – 6154; b) W. Zhuang, S. Saaby, K. A. Jørgensen, *Angew. Chem.* **2004**, *116*, 4576 – 4578; *Angew. Chem. Int. Ed.* **2004**, *43*, 4476 – 4478; c) Y. Suto, M. Kanai, M. Shibasaki, *J. Am. Chem. Soc.* **2007**, *129*, 500 – 501; d) C. Baudequin, A. Zamfir, S. B. Tsogoeva, *Chem. Commun.* **2008**, 4637 – 4639; e) Y. Du, L.-W. Xu, Y. Shimizu, K. Oisaki, M. Kanai, M. Shibasaki, *J. Am. Chem. Soc.* **2008**, *130*, 16146 – 16147; f) V. A. Sukach, N. M. Golovach, V. V. Pirozhenko, E. B. Rusanov, M. V. Vovk, *Tetrahedron: Asymmetry* **2008**, *19*, 761 – 764; g) B. Jiang, J. J. Dong, Y. G. Si, X. L. Zhao, Z. G. Huang, M. Xu, *Adv. Synth. Catal.* **2008**, *350*, 1360 – 1366; h) L. C. Wieland, E. M. Vieira, M. L. Snapper, A. H. Hoveyda, *J. Am. Chem. Soc.* **2009**, *131*, 570 – 576; i) N. Hara, R. Tamura, Y. Funahashi, S. Nakamura, *Org. Lett.* **2011**, *13*, 1662 – 1665; j) N. Hara, S. Nakamura, M. Sano, R. Tamura, Y. Funahashi, N. Shibata, *Chem. Eur. J.* **2012**, *18*, 9276 – 9280; k) W. Yan, D. Wang, J. Feng, P. Li, D. Zhao, R. Wang, *Org. Lett.* **2012**, *14*, 2512 – 2515; l) T. Kano, S. Song, Y. Kubota, K. Maruoka, *Angew. Chem.* **2012**, *124*, 1217 – 1220; *Angew. Chem. Int. Ed.* **2012**, *51*, 1191 – 1194; m) M. Hayashi, M. Sano, Y. Funahashi, S. Nakamura, *Angew. Chem.* **2013**, *125*, 5667 – 5670; *Angew. Chem. Int. Ed.* **2013**, *52*, 5557 – 5560.

[11] F. Sladojevich, A. Trabocchi, A. Guarna, D. J. Dixon, *J. Am. Chem. Soc.* **2011**, *133*, 1710 – 1713.

[12] For a review, see: a) L. Stegbauer, F. Sladojevich, D. J. Dixon, *Chem. Sci.* **2012**, *3*, 942 – 958; for relevant previous work from our group on the use of metal salts, see: b) M. Li, S. Datta, D. M. Barber, D. J. Dixon, *Org. Lett.* **2012**, *14*, 6350 – 6353; c) T. Yang, A. Ferrali, F. Sladojevich, L. Campbell, D. J. Dixon, *J. Am. Chem. Soc.* **2009**, *131*, 9140 – 9141; d) D. M. Barber, H. J. Sanganee, D. J. Dixon, *Org. Lett.* **2012**, *14*, 5290 – 5293.

[13] For selected examples of the removal of the diphenylphosphinoyl protecting group, see: a) S. Coulton, G. A. Moore, R. Ramage, *Tetrahedron Lett.* **1976**, *17*, 4005 – 4008; b) A. Zwierzak, I. Podstawezyńska, *Angew. Chem.* **1977**, *89*, 737 – 738; *Angew. Chem. Int. Ed. Engl.* **1977**, *16*, 702 – 704.

