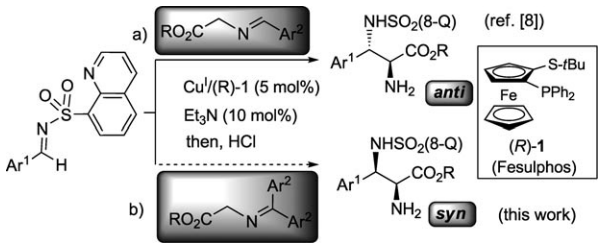
DOI: 10.1002/chem.200902258

Substrate-Controlled Diastereoselectivity Switch in Catalytic Asymmetric Direct Mannich Reaction of Glycine Derivatives with Imines: From *anti*- to *syn*-α,β-Diamino Acids

Jorge Hernández-Toribio, Ramón Gómez Arrayás,* and Juan Carlos Carretero*[a]

The construction of multiple stereocenters in flexible acyclic molecules in a single operation with complete diastereo- and enantiocontrol constitutes a central challenge within the field of asymmetric catalysis. Driven by their biological significance and synthetic value, the synthesis of optically active α,β-diamino acids[1] via catalytic asymmetric direct Mannich reaction[2] between a prochiral nitrogen pronucleophile and an imine represents a touchstone in meeting this challenge and has recently emerged as an active research area.[3] Two complementary approaches are receiving great attention: the direct Mannich reaction of glycine ester Schiff bases (and related species) with imines[4] and the direct aza-Henry reaction either between nitro compounds and α-imino esters,[5] or between α-nitro acetates and imines.[6,7] Despite the development of very efficient organometallic-based and metal-free catalytic procedures, which show high asymmetric induction and *syn*- or *anti*-diastereocontrol, the development of diastereoselective switchable methods providing access to either *syn*- or *anti*-configured α,β-diamino acids remains elusive. Just one catalyst system has been shown to enable tuning of diastereoselectivity, leading to either *anti*- or *syn*-configured α,β-diamino acid esters in good yields and high diastereo- and enantioselectivities.[4i] In such an example, a dramatic *anti*/*syn* diastereoselectivity switch was achieved in the Mannich reaction of glycine derivatives with imines by modifying the electronic properties of the chiral phosphine ligand. As a useful complementary method, herein we describe that the *syn*- or *anti*-diastereoselectivity of the Mannich products can be efficiently switched by tuning the steric and electronic properties of the pronucleophile component (i.e., the glycinate imine) while maintaining the same catalyst system.

Recently, we reported a route to *anti*-α,β-diamino acid derivatives based on the Cu^{I}–Fesulphos-catalyzed reaction of glycine ester aldimine pronucleophiles with the readily available *N*-(8-quinolyl)sulfonyl aldimines[8] (Scheme 1a). We envisioned that the use of ketimine-derived glycine pronucleophiles, instead of aldimine derivatives, could result in new critical steric interactions in the transition state that could potentially lead to a reversal in the sense of facial selectivity of the imine approach to the ester enolate, thus providing access to products with the opposite *syn*-configuration (Scheme 1b).



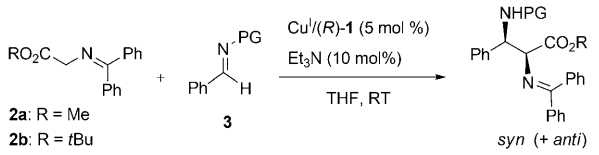
Scheme 1. Envisioned diastereoselectivity switch in the Mannich route to α,β-diamino acid derivatives.

Our working hypothesis was validated in the reaction of the glycine methyl ester benzophenone Schiff base **2a** with differently *N*-protected aldimines **3a–g** under the optimized Fesulphos–Cu^{I} catalyst system,[8,9] in all cases the *syn*-configured adduct being predominant in the reaction mixture (Table 1). However, very low *syn*-diastereocontrol was achieved with most of the protecting groups examined, except for the encouraging values provided by the Boc (substrate **3a**, entry 1) and *N*-(8-quinolyl)sulfonyl[10] (substrate **3f**, entry 6) groups. The nitrogen of the 8-quinolyl moiety seems to play an important role for high diastereocontrol since the

[a] J. Hernández-Toribio, Dr. R. Gómez Arrayás, Prof. Dr. J. C. Carretero
Departamento de Química Orgánica
Universidad Autónoma de Madrid (UAM)
Facultad de Ciencias, Cantoblanco, Cantoblanco
28049 Madrid (Spain)
Fax: (+34) 91-497-3966
E-mail: ramon.gomez@uam.es
juancarlos.carretero@uam.es

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/chem.200902258.

Table 1. Reaction of benzophenone-derived glycine derivatives **2a** and **2b** with aldimines **3**.



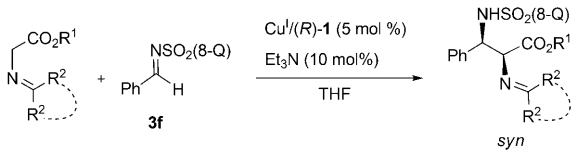
Entry	R	PG (imine)	Product	*syn*/*anti*[a]	Yield [%][b]	*ee* [%][c]	
						syn	*anti*
1	Me	Boc (**3a**)	**4**	73:27	93	96	98
2	Me	Ts (**3b**)	**5**	55:45	85	95	94
3	Me	(2-thienyl)SO_2 (**3c**)	**6**	58:42	78	–[d]	–[d]
4	Me	(2-pyridyl)SO_2 (**3d**)	**7**	68:32	78	97	88
5	Me	*o*-nosyl (**3e**)	**8**	60:40	94	–[d]	–[d]
6	Me	(8-quinolyl)SO_2 (**3f**)	**9**	77:23	79	97	96
7	Me	(1-naphthyl)SO_2 (**3g**)	**10**	52:48	94	–[d]	–[d]
8	*t*Bu	Boc (**3a**)	**11**	55:45	86	93	99
9	*t*Bu	(8-quinolyl)SO_2 (**3f**)	**12**	84:16	83	97	–[d]
10[e]	*t*Bu	(8-quinolyl)SO_2 (**3f**)	**12**	88:12	80	97	–[d]

[a] Determined by ^{1}H NMR from the crude reaction mixture. [b] In pure product (mixtures *syn*+*anti*) after chromatography. [c] Determined by chiral HPLC. [d] Not determined. [e] Reaction performed at −20 °C.

sterically similar 1-naphthylsulfonyl imine (**3g**) afforded a 55:45 mixture of *syn*/*anti* diastereomers under identical conditions (entry 7). The more encumbered *tert*-butyl ester derivative **2b** (R = *t*Bu) led to a drop in diastereoselectivity in the case of the *N*-Boc imine **3a** (entry 8), whereas it produced a positive impact in the case of the *N*-(8-quinolyl)sulfonyl imine (**3f**) (*syn*/*anti* 84:16, entry 9). The diastereomeric ratio was further increased to *syn*/*anti* 88:12 by performing the reaction at −20 °C, while maintaining high reactivity (80 % yield) and excellent enantiocontrol (97 % *ee* for the *syn* product, entry 10).

The electronic and steric nature of the glycinate component was tuned for further optimization (Table 2). Noteworthy despite the widespread use of glycinate imines in the synthesis of α-amino acid derivatives,[11] benzophenone imines are generally the substrates of choice and little work has been conducted on altering the steric or electronic properties of the imine moiety of these pronucleophiles.[12] The fluorenone imine **13**, which was reported to be much more reactive than the corresponding benzophenone imine in Mannich reactions,[12b] led to complete reaction with **3f** in only 30 min at room temperature, although with virtually no diastereocontrol (entry 1). The diastereoselectivity was not improved to a practical level by lowering the reaction temperature to −78 °C, whereas the asymmetric induction remained very high (> 90 % *ee* for both *anti* and *syn* adducts, entry 2). The electron-rich 4,4′-dimethoxybenzophenone derivative **2c** displayed decreased reactivity (55 % conversion after 8 h at room temperature) but slightly higher diastereocontrol (entry 3) than the parent substrate **2b**. In contrast, electron-withdrawing substituents at the *para*-position of the phenyl rings of the benzophenone unit led to a marked beneficial effect on both reactivity and diastereocontrol, without altering the outstanding level of enantioselectivity. For instance, the 4,4′-dichlorobenzophenone (**2d**) afforded the corresponding diamino ester derivative in excellent yield (91 %), *syn* selectivity (*syn*/*anti* 93:7) and enantiocontrol (99 % *ee* for both the *syn* and *anti* adducts) after 2 h at room temperature (entry 4). Moreover, the diastereoselectivity value was increased to *syn*/*anti* 97:3 at −20 °C, keeping the level of reactivity and enantioselectivity (entry 5). Further temperature decrease did not improve the values of diastereo- and enantiocontrol (entry 6). The more electrophilic 4,4′-difluorobenzophenone glycinate (**2e**) showed slightly lower performance (entry 7). The somewhat better behaviour of the sterically encumbered *tert*-butyl ester over the corresponding methyl ester was confirmed in the latter two substrates (entries 8 and 9).

Table 2. Fine tuning of the electronic and steric properties of the glycinate ketimine.

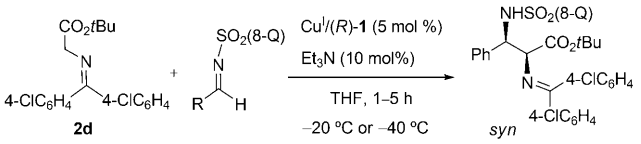


Entry	R^1	R^2 (Substrate)	*T* [°C]/*t* [h]	Product	*syn*/*anti*[a]	Yield [%][b]	*ee* [%][c]	
							syn	*anti*
1	*t*Bu	fluorene[d] (**13**)	25/0.5	**14**	55:45	76	–[e]	–[e]
2	*t*Bu	fluorene[d] (**13**)	−78/4	**14**	70:30	71	94	92
3	*t*Bu	4-$OMeC_6H_4$ (**2c**)	25/8	**15**	88:12	55[f]	–[e]	–[e]
4	*t*Bu	4-ClC_6H_4 (**2d**)	25/2	**16**	93:7	91	98	99
5	*t*Bu	4-ClC_6H_4 (**2d**)	−20/3	**16**	97:3	88	99	99
6	*t*Bu	4-ClC_6H_4 (**2d**)	−40/6	**16**	97:3	77	99	99
7	*t*Bu	4-FC_6H_4 (**2e**)	−20/3	**17**	94:6	71	98	99
8	Me	4-ClC_6H_4 (**2f**)	−40/5	**18**	95:5	74	99	99
9	Me	4-FC_6H_4 (**2g**)	−20/2	**19**	90:10	73	98	99

[a] Determined by ^{1}H NMR from the crude reaction mixture. [b] In pure product (mixtures *syn*+*anti*) after chromatography. [c] Determined by chiral HPLC. [d] Fluorenone imine. [e] Not determined. [f] Conversion yield.

The scope of this *syn*-diastereoselective synthesis of α,β-diamino ester derivatives was evaluated with a wide range of non-enolizable imines, including aryl, heteroaryl and α,β-unsaturated substrates (Table 3). Aliphatic imines could not be explored since we have not succeeded so far in the isolation of this more labile type of *N*-(het-

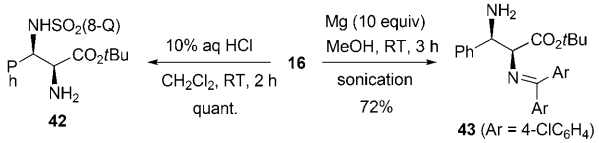
Table 3. Scope of the direct Mannich approach to *syn*-α,β-diamino acid derivatives.



Entry	R	Imine	T [°C]	Product	*syn*/*anti*[a]	Yield [%][b]	*ee* [%][c]
1	4-ClC_6H_4	**20**	–20	**31**	95:5	85	99
2	4-$(CF_3)C_6H_4$	**21**	–40	**32**	99:1	81	99
3	4-$OMeC_6H_4$	**22**	–20	**33**	89:11	84	98
4	2-naphthyl	**23**	–20	**34**	94:6	80	98
5	1-naphthyl	**24**	–40	**35**	95:5	82	99
6	2-MeC_6H_4	**25**	–40	**36**	97:3	82	99
7	2-furyl	**26**	–20	**37**	90:10	80	99
8	2-thienyl	**27**	–40	**38**	90:10	83	99
9	3-pyridyl	**28**	–20	**39**	99:1	80	99
10	PhCH=CH-	**29**	–20	**40**	97:3	78	98
11	(2-furyl)CH=CH-	**30**	–20	**41**	95:5	76	98

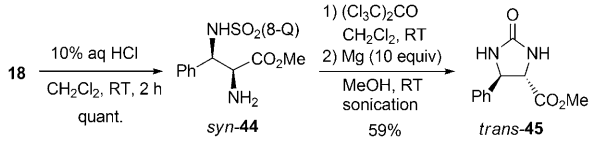
[a] Determined by ^{1}H NMR from the reaction mixture. [b] In pure product (mixtures *syn*+*anti*) after chromatography. [c] Determined by chiral HPLC.

eroaryl)sulfonyl imines. The homogeneously high values of reactivity (76–85% yield), diastereoselectivity (*syn*/*anti* 89:11–99:1) and, especially, enantiocontrol (98–99% *ee*) achieved in the 12 cases studied highlight the high degree of fidelity of the Fesulphos–Cu^I catalyst system. In addition to sterically and electronically varied aromatic imines (entries 1–6), heteroaryl imines are also excellent substrates for this reaction (entries 7–9), including the 3-pyridinecarboxaldehyde-derived substrate **28** (80% yield, *syn*/*anti* 99:1, 99% *ee*, entry 9). It is also noteworthy the comparable excellent performance, in terms of reactivity as well as diastereo- and enantiocontrol, displayed by α,β-unsaturated imines such as those from cinnamaldehyde (substrate **29**, entry 10) and 3-(2-furyl)-2-propenal (substrate **30**, entry 11). The resulting γ,δ-unsaturated-α,β-diamino acid products (**40** and **41**, respectively) offer interesting possibilities for further functionalization and serve as an alternative method to the use of aliphatic imines (upon hydrogenation). In spite of this interest, few catalyst systems have been reported for the direct Mannich reaction of glycinate derivatives with α,β-unsaturated imines (only from cinnamaldehyde).[4c,f,k]



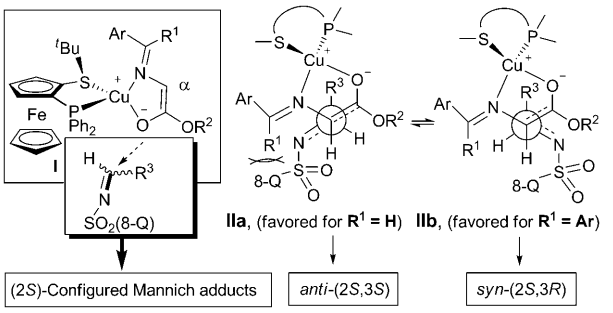
Scheme 2. Orthogonal deprotection of diamino acid derivative **16**.

Taking advantage of the orthogonal protection of the α,β-diaminoester adducts, Scheme 2 illustrates the selective deprotection of either of the two amino protecting groups of product **16** in good yield under mild reaction conditions. The imino function of **16** was removed quantitatively via smooth acid hydrolysis (10% aq HCl, CH_2Cl_2, RT, product **42**), whereas cleavage of the 8-quinolylsulfonyl group was easily achieved with excess of Mg turnings in MeOH (product **43**, 72% yield), this latter step being strongly accelerated under sonication. Scheme 3 shows the sequential double amino deprotection of **18** and its transformation into the known optically active urea *trans*-**45**,[13] which served to confirm the (2*S*,3*R*) configuration of the *syn*-Mannich adducts. The optically active amino ester *syn*-**44** was obtained from **18** upon acid hydrolysis. The transformation of **44** into the enantiopure urea *trans*-**45**,[13] was achieved in good yield by treatment with triphosgene (CH_2Cl_2, 0 °C to RT, 2 h) and subsequent *N*-sulfonyl deprotection (Mg, MeOH, RT, 3 h).



Scheme 3. Sequential double amino deprotection of **18** and transformation into a cyclic urea derivative.

The participation of the (*Z*)-enolate **I** as the active nucleophile in the direct Mannich reaction (Scheme 4) was assumed on the basis of previous experimental evidences and



Scheme 4. Working stereochemical models.

computational studies on the participation of the chiral Fesulphos–copper(I) enolate of glycine Schiff bases in azomethine ylide 1,3-dipolar cycloaddition reactions.[14] The tetracoordinated complex **I**, showing a highly distorted tetrahedral structure around the copper atom, was found to be the most stable geometry in the coordination of the metal atom with the P,S ligand Fesulphos and the azomethine species. In

this complex the high steric congestion imposed by the *tert*-butyl group linked to the sulfur atom in close proximity to the copper center hinders the approach of the *N*-(8-quinolyl)sulfonyl imine from the *Re* C-α enolate face of the azomethine. Thus, the approach of **I** from the more accessible *Si* C-α enolate face to the *N*-sulfonyl imine could explain the high stereoselectivity attained in the formation of the α,β-diamino esters with (2*S*) configuration in both the *syn*- and *anti*-configured α,β-diamino acid derivatives. As a working hypothesis, the diastereoselectivity switch from *anti* (when using aldimine-derived glycinate esters as pronucleophiles) to *syn* (in the case of ketimine-derived glycinates) could be explained invoking steric interactions during the approach of the imine to the enolate **I** (intermediates **II**). For instance, the reaction with aldimine pronucleophiles ($R^1 = H$) is assumed to proceed more favourably via the intermediate **IIa**, which accounts for the observed *anti*-(2*S*,3*S*) configuration in the Mannich adducts. The *Re* face approach of the *N*-sulfonyl aldimine minimizes the steric repulsion between its bulky *N*-sulfonyl substituent and the glycinate imine group ($R^1 = H$, Scheme 3). In contrast, the presence of a bulky *N*-diarylmethylene group ($R^1 = Ar$) in the ketimine pronucleophile would disfavor **IIa** because of its severe steric repulsion with the *N*-(8-quinolyl)sulfonyl group, thus forcing the imine to approach from its *Si* face via the intermediate **IIb** that would account for the formation of the *syn*-(2*S*,3*R*)-adducts.

In summary, a diastereoselectivity switch from *anti*- to *syn*- has been devised in the catalytic asymmetric direct Mannich reaction of glycine derivatives with *N*-(8-quinolyl)-sulfonyl imines by tuning the steric and electronic properties of the glycine imine. α,β-Diamino acids of *syn*-configuration are produced with glycinate esters derived from electron-deficient benzophenone-type ketimines, in contrast to aldimine-derived pronucleophiles that lead to *anti*-configured products. The Fesulphos–Cu^I catalyst is crucial for achieving high asymmetric induction. The selective orthogonal *N*-deprotection of the resulting α,β-diamino ester adducts can be effected under mild conditions in good yields.

Experimental Section

Representative procedure for the synthesis of *syn*-α,β-diamino acid derivatives: Reaction of *tert*-butylglycinate 4,4′-dicholorobenzophenone Schiff base (**2d**) with *N*-benzylidene-*N*-[(8-quinolyl)sulfonyl]imine (**3f**) to afford (2*S*,3*R*)-*tert*-butyl 2-[(bis(4-chlorophenyl)methylene)amino]-3-phenyl-3-[(8-quinolyl)-sulfonylamino]propanoate (**16**): To a solution of Fesulphos ligand (*R*)-**1** (1.9 mg, 0.005 mmol) and $Cu(CH_3CN)_4PF_6$ (2.3 mg, 0.005 mmol), in THF (0.5 mL) at −20 °C, were successively added a solution of **2d** (36.4 mg, 0.1 mmol) in THF (1.0 mL), Et_3N (1.4 μL, 0.01 mmol) and a solution of **3f** (32.6 mg, 0.11 mmol) in THF (1.0 mL). The mixture was stirred at −20 °C for 3 h before it was filtered through Celite and the filtrate concentrated to dryness. The residue was analyzed by ^1H NMR to determine the diastereomeric ratio and then purified by flash chromatography (*n*-hexane/EtOAc 3:1) to afford **16** as a white solid (58.1 mg, 88 %, *syn*/*anti* 97:3). M.p. 98–99 °C. See Supporting Information for spectroscopic data.

Acknowledgements

This work was supported by the Ministerio de Ciencia e Innovación (MICINN, project CTQ2006-01121). J.H.T. thanks the MICINN for a predoctoral fellowship.

Keywords: copper catalysis · diastereoselectivity · glycine · Mannich reaction

[1] For a comprehensive review on synthetic approaches and biological significance of α,β-diamino acids, see: A. Viso, R. Fernández de La Pradilla, A. García, A. Flores, *Chem. Rev.* **2005**, *105*, 3167.

[2] For recent reviews on catalytic asymmetric Mannich reaction: a) A. Ting, S. E. Schaus, *Eur. J. Org. Chem.* **2007**, 5797; b) J. M. M. Verkade, L. J. C. vanHemert, P. J. L. M. Quaedflieg, F. P. J. T. Rutjes, *Chem. Soc. Rev.* **2008**, *37*, 29.

[3] For a recent review on the synthesis of α,β-amino acids via catalytic asymmetric direct Mannich reaction, see: R. Gómez Arrayás, J. C. Carretero, *Chem. Soc. Rev.* **2009**, *38*, 1940.

[4] a) L. Bernardi, A. S. Gothelf, R. G. Hazell, K. A. Jørgensen, *J. Org. Chem.* **2003**, *68*, 2583; b) T. Ooi, M. Kameda, J.-i. Fujii, K. Maruoka, *Org. Lett.* **2004**, *6*, 2397; c) A. Okada, T. Shibuguchi, T. Ohshima, H. Masu, K. Yamaguchi, M. Shibasaki, *Angew. Chem.* **2005**, *117*, 4640; *Angew. Chem. Int. Ed.* **2005**, *44*, 4564; d) M. M. Salter, J. Kobayashi, Y. Shimizu, S. Kobayashi, *Org. Lett.* **2006**, *8*, 3533; e) T. Shibuguchi, H. Mihara, A. Kuramochi, T. Ohshima, M. Shibasaki, *Chem. Asian J.* **2007**, *2*, 794; f) G. A. Cutting, N. E. Stainforth, M. P. John, G. Kociok-Köhn, M. C. Willis, *J. Am. Chem. Soc.* **2007**, *129*, 10632; g) D. Uraguchi, Y. Ueki, T. Ooi, *J. Am. Chem. Soc.* **2008**, *130*, 14088; h) S. Kobayashi, R. Yazaki, K. Seki, Y. Yamashita, *Angew. Chem.* **2008**, *120*, 5695; *Angew. Chem. Int. Ed.* **2008**, *47*, 5613; i) X.-X. Yan, Q. Peng, Q. Li, K. Zhang, J. Yao, X.-L. Hou, Y.-D. Wu, *J. Am. Chem. Soc.* **2008**, *130*, 14362; j) D. Shang, Y. Liu, X. Zhou, X. Liu, X. Feng, *Chem. Eur. J.* **2009**, *15*, 3678; k) L. Li, M. Ganesh, D. Seidel, *J. Am. Chem. Soc.* **2009**, *131*, 11648.

[5] a) K. Juhl, N. Gathergood, K. A. Jørgensen, *Angew. Chem.* **2001**, *113*, 3083; *Angew. Chem. Int. Ed.* **2001**, *40*, 2995; b) M. Rueping, A. P. Antonchick, *Org. Lett.* **2008**, *10*, 1731.

[6] a) A. Singh, R. A. Yoder, B. Shen, J. N. Johnston, *J. Am. Chem. Soc.* **2007**, *129*, 3466; b) Z. Chen, H. Morimoto, S. Matsunaga, M. Shibasaki, *J. Am. Chem. Soc.* **2008**, *130*, 2170; c) D. Uraguchi, K. Koshimoto, T. Ooi, *J. Am. Chem. Soc.* **2008**, *130*, 10878; d) A. Singh, J. N. Johnston, *J. Am. Chem. Soc.* **2008**, *130*, 5866; 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.

[7] For the aza-Henry reaction between α-nitro acetates and α-imino esters, see: K. R. Knudsen, K. A. Jørgensen, *Org. Biomol. Chem.* **2005**, *3*, 1362.

[8] J. Hernández-Toribio, R. Gómez Arrayás, J. C. Carretero, *J. Am. Chem. Soc.* **2008**, *130*, 16150.

[9] For other recent applications of commercially available Fesulphos ligand in asymmetric catalysis, see: a) O. García Mancheño, R. Gómez Arrayás, J. Adrio, J. C. Carretero, *J. Org. Chem.* **2007**, *72*, 7832; b) A. Salvador González, M. Rogríguez Rivero, R. Gómez Arrayás, J. C. Carretero, *Org. Lett.* **2008**, *10*, 4335; c) A. López-Perez, J. Adrio, J. C. Carretero, *J. Am. Chem. Soc.* **2008**, *130*, 10084; d) S. Filipone, E. E. Maroto, A. Martín-Domenech, M. Suarez, N. Martín, *Nat. Chem.* **2009**, *1*, 578.

[10] For previous applications of *N*-(8-quinolyl)sulfonyl imines in asymmetric catalysis: a) J. Esquivias, R. Gómez Arrayás, J. C. Carretero, *J. Am. Chem. Soc.* **2007**, *129*, 1480; b) S. Nakamura, H. Nakashima, H. Sugimoto, H. Sano, M. Hattori, N. Shibata, T. Toru, *Chem. Eur. J.* **2008**, *14*, 2145. For recent applications of other heteroarylsulfonyl imines: c) H. Morimoto, G. Lu, N. Aoyama, S. Matsunaga, M. Shibasaki, *J. Am. Chem. Soc.* **2007**, *129*, 9588; d) S. Nakamura, H. Naka-

shima, A. Yamamura, N. Shibata, T. Toru, *Adv. Synth. Catal.* **2008**, *350*, 1209.
[11] For a recent review: T. Ooi, K. Maruoka, *Angew. Chem.* **2007**, *119*, 4300; *Angew. Chem. Int. Ed.* **2007**, *46*, 4222.
[12] Pioneering work by Kobayashi's group has revealed that the nature of the imine pronucleophile can significantly influence its reactivity and stereoselectivity in the Mannich-type reaction: a) S. Kobayashi, T. Tsubogo, S. Saito, Y. Yamashita, *Org. Lett.* **2008**, *10*, 807; b) S. Kobayashi, R. Yazaki, K. Seki, Y. Yamashita, *Angew. Chem.* **2008**, *120*, 5695; *Angew. Chem. Int. Ed.* **2008**, *47*, 5613. See also reference [4d].
[13] S. H. Lee, J. Yoon, S. H. Chung, Y. S. Lee, *Tetrahedron* **2001**, *57*, 2139.
[14] S. Cabrera, R. Gómez Arrayás, B. Martín-Matute, F. Cossío, J. C. Carretero, *Tetrahedron* **2007**, *63*, 6587.

Received: August 14, 2009
Published online: December 18, 2009

