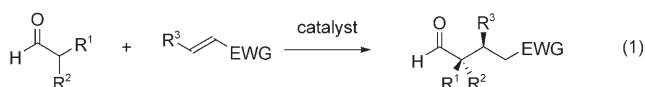


DOI: 10.1002/ange.200602221

A Chiral Primary Amine Thiourea Catalyst for the Highly Enantioselective Direct Conjugate Addition of α,α -Disubstituted Aldehydes to Nitroalkenes**

Mathieu P. Lalonde, Yonggang Chen, and
Eric N. Jacobsen*

The remarkable advances in the application of secondary amines as enantioselective catalysts are tied to the accessibility of divergent carbonyl activation pathways, either via nucleophilic enamines or electrophilic iminium ions, and to the highly effective stereoinduction that is achievable in reactions of such covalent intermediates.^[1] By comparison, little progress has been made in the development of small-molecule chiral primary amine catalysts,^[2] a fact that is attributable, at least in part, to unfavorable imine–secondary enamine equilibria.^[3] Nevertheless, primary amine catalysis is effectively exploited by enzymes such as type I aldolases, decarboxylases, and dehydratases, each of which contain catalytically active lysine residues.^[4] We became interested in the possible use of chiral primary amine thiourea derivatives in enamine catalysis motivated partly by their straightforward accessibility from chiral 1,2-diamines and partly by recent successes in the application of related tertiary amine thiourea frameworks as bifunctional catalysts in a wide variety of enantioselective catalytic reactions.^[5–7] In this vein, Tsogoeva and Wei, as well as our own group, reported recently the successful application of primary amine thiourea catalysts to the addition of ketones to nitroalkenes.^[8] The proven ability of secondary enamines to participate in conjugate addition reactions between sterically demanding partners^[9] prompted us to examine the primary amine thiourea catalyzed addition of racemic α,α -disubstituted aldehydes to β -substituted Michael acceptors [Eq. (1); EWG = electron-withdrawing



[*] M. P. Lalonde, Dr. Y. Chen, Prof. Dr. E. N. Jacobsen
Department of Chemistry and Chemical Biology
Harvard University
Cambridge, MA 02138 (USA)
Fax: (+1) 617-496-1880
E-mail: jacobson@chemistry.harvard.edu

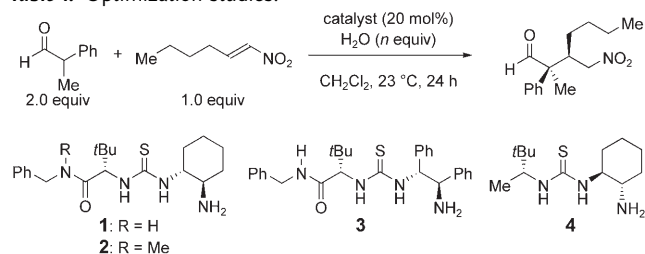
[**] This work was supported by the NIH (GM-43214 and P50 GM069721). M.P.L. gratefully acknowledges the NSERC and La Fondation Baxter et Alma Ricard for graduate scholarships. Dr. Richard Staples is acknowledged for the determination of the crystal structure of **22**.

Supporting information for this article is available on the WWW under <http://www.angewandte.org> or from the author.

group] as a possible attractive solution to the challenging problem of generating chiral building blocks with contiguous quaternary and tertiary stereogenic centers.^[10] We describe here the identification of primary amine thiourea derivatives as effective and general catalysts for the enantio- and diastereoselective conjugate addition of α,α -disubstituted aldehydes to nitroalkenes.

Despite extensive studies on secondary amine catalyzed conjugate additions of carbonyl compounds to nitroalkenes,^[11,12] only two reports by Barbas and co-workers have addressed α,α -disubstituted aldehydes as potential nucleophilic partners.^[13] We selected the challenging combination of 1-nitrohex-1-ene, a β -alkyl-substituted nitroalkene, and 2-phenylpropionaldehyde as model substrates for initial optimization studies,^[14] with the hope that broad reaction scope would ensue. Among the primary amine thiourea catalysts examined, derivatives **1** and **3** were found to induce particularly high diastereo- and enantioselectivities (Table 1,

Table 1: Optimization studies.



Entry	Catalyst	H ₂ O [equiv]	Yield [%] ^[a]	d.r. (syn/anti) ^[a]	ee [%] ^[b]
1	1	0	34	> 10:1	96
2	3	0	93	> 10:1	99
3	1	2.0	56	> 10:1	96
4	1	5.0	64	> 10:1	96
5	1	10	54	> 10:1	96
6	2	5.0	31	> 10:1	96
7	4	5.0	< 5	–	–
8	3	5.0	100	> 10:1	99

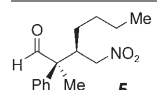
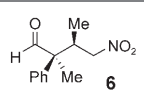
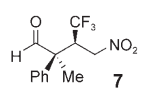
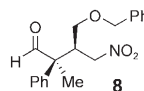
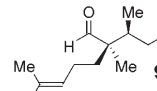
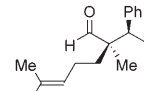
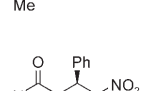
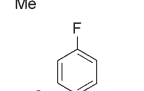
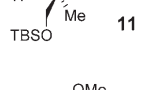
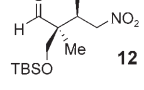
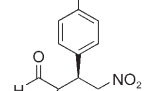
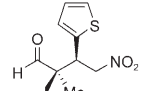
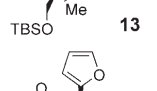
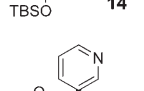
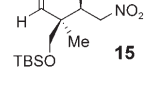
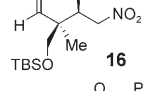
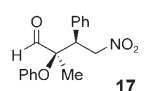
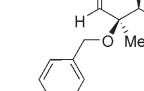
[a] Product yields determined by ¹H NMR spectroscopic analysis of the crude reaction mixture using trimethoxybenzene as an internal standard.
[b] Determined by chiral HPLC analysis compared with authentic racemic material.

entries 1 and 2). The best results were obtained using only a twofold excess of aldehyde relative to nitroalkene.^[15,16] Diaminocyclohexane-derived catalyst **1** proved more broadly applicable and was selected for further optimization as catalyst **3**, derived from diphenylethylene diamine, was found subsequently to afford optimal results only in reactions involving 2-phenylpropionaldehyde.^[17] Variation of standard reaction parameters (solvent, temperature, reagent ratios, concentration, catalyst loading) failed to improve the product yield, however, inclusion of controlled amounts of water led to significant improvements (Table 1, entry 1 vs 3–5, 2 vs 8).^[18] Catalysts bearing a secondary amide (**1** and **3**) afforded higher levels of substrate conversion and product yields than their tertiary amide counterparts (e.g. **2**), while derivatives lacking an amide, as in **4**, were virtually inactive (Table 1, entry 7).

A wide range of α,α -disubstituted aldehyde/nitroalkene combinations were surveyed to determine the scope and limitations of the methodology. Excellent enantioselectivity and useful levels of diastereoselectivity were obtained with a variety of substrates by using catalyst **1** (Table 2). The highest

levels of diastereoselectivity ($> 10:1$ d.r.) were observed for aldehydes bearing phenyl or etheral ($R^1 = \text{OPh}$ and $p\text{-MeOC}_6\text{H}_4\text{CH}_2\text{O}$) α -substituents. At the other extreme, only modest diastereoselectivities (2.1–4.7:1 d.r.) were obtained for adducts **9**, **10**, and **19–22**, results that were deemed

Table 2: Asymmetric addition of α,α -disubstituted aldehydes to nitroalkenes catalyzed by **1**.^[26]

$\begin{array}{c} \text{O} \\ \parallel \\ \text{H}-\text{C}-\text{R}^1 \\ \\ \text{Me} \\ \text{2.0 equiv} \end{array} + \begin{array}{c} \text{R}^2-\text{CH}=\text{CH}-\text{NO}_2 \\ \text{1.0 equiv} \end{array} \xrightarrow[\text{CH}_2\text{Cl}_2, 24 \text{ h, } 23^\circ\text{C; } 1\text{M HCl workup}]{\begin{array}{c} \textbf{1} \text{ (20 mol\%)} \\ \text{H}_2\text{O (5.0 equiv)} \end{array}} \begin{array}{c} \text{O} \\ \parallel \\ \text{H}-\text{C}-\text{R}^1 \\ \quad \\ \text{Me} \quad \text{R}^2 \\ \text{CH}_2\text{NO}_2 \end{array}$							
Product	Yield [%]	d.r. (<i>syn/anti</i>)	<i>ee</i> [%]	Product	Yield [%]	d.r. (<i>syn/anti</i>)	<i>ee</i> [%]
	54	28:1	96 (<i>syn</i>)		91	23:1	99 (<i>syn</i>)
	34	$> 50:1$	97 (<i>syn</i>)		87	$> 50:1$	99 (<i>syn</i>)
	61	3.3:1	99 (<i>syn</i>) 99 (<i>anti</i>)		82	3.9:1	99 (<i>syn</i>) 99 (<i>anti</i>)
	87	6.3:1	99 (<i>syn</i>) 98 (<i>anti</i>)		86	6.6:1	99 (<i>syn</i>) 94 (<i>anti</i>)
	85	7.1:1	99 (<i>syn</i>) 95 (<i>anti</i>)		85	6.6:1	99 (<i>syn</i>) 97 (<i>anti</i>)
	79	5.4:1	99 (<i>syn</i>) 95 (<i>anti</i>)		94	5.6:1	99 (<i>syn</i>) 96 (<i>anti</i>)
	78	10.4:1	94 (<i>syn</i>) 92 (<i>anti</i>)		78	13:1	96 (<i>syn</i>)
	98	2.1:1	99 (<i>syn</i>) 97 (<i>anti</i>)		82	3.1:1	99 (<i>syn</i>) 99 (<i>anti</i>)
	63	4.7:1	98 (<i>syn</i>) 92 (<i>anti</i>)		81	3.8:1	99 (<i>syn</i>) 99 (<i>anti</i>)

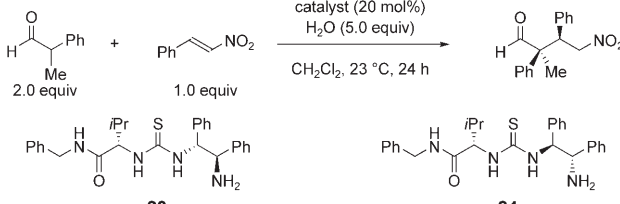
TBS = *tert*-butyldimethylsilyl.

satisfactory nonetheless given the minimal degree of steric differentiation between the aldehyde α -substituents. A variety of β -aryl-, β -heteroaryl-, and β -alkyl-substituted nitroalkenes underwent conjugate addition in good yields regardless of their electronic properties. The highly electrophilic 3,3,3-trifluoro-1-nitroprop-1-ene afforded adduct **7** in high *ee* and d.r. but only modest yield, a result ascribable to its susceptibility to effect alkylation of the primary amine group of **1**.^[19,20]

As noted above, diphenylethylene diamine derivative **3** proved a more effective catalyst than **1** in conjugate additions involving 2-phenylpropionaldehyde as the nucleophilic partner. The effect was especially pronounced in additions to *trans*- β -nitrostyrene, which proceeded in substantially higher enantioselectivity and diastereoselectivity with catalyst **3** compared to **1** (Table 3, entries 1–2). Further modifications to the catalyst structure led to the observation that valine-derived catalyst **23** afforded almost identical results to *tert*-leucine-derived **3**, a significant outcome given the substantially lower cost of the precursor amino acid and also because this equivalence has not been observed in any other *tert*-leucine-derived thiourea-catalyzed reactions. The significantly diminished yield and *ee* values obtained with mismatched catalyst **24** point to the cooperative role of the stereochemistry of both the amino acid and the diamine in simultaneously defining conjugate addition selectivity and catalyst activity.

A catalytic cycle consistent with our experimental observations is depicted in Scheme 1. Tautomerization of imine **A**, resulting from the condensation of aldehyde and catalyst **1**, leads to the formation of an *E* or *Z* enamine. Preferred reaction via the thermodynamically favorable *E* enamine **B** is proposed to account for the observed diastereoselectivities.^[21] Binding of the nitroalkene through only one oxygen atom allows the enamine to attain sufficiently close proximity for carbon–carbon bond formation to occur (intermediate **C**).^[22] Proton transfer (**D** to **E**) followed by imine hydrolysis yields the product and regenerates the catalyst. Zwitterionic species analogous to **D** have been invoked in numerous studies concerning the mechanism of conjugate addition of enamines to nitroalkenes.^[23] These intermediates may undergo hydrolysis to the nitroaldehyde product or collapse to 1,2-oxazine-*N*-oxide and cyclobutane intermediates **F** and **G**, respectively. Although 1,2-oxazine-*N*-oxides such as **F** undergo hydrolysis readily in the presence of atmospheric moisture,^[23] hydrolysis of cyclobutanes

Table 3: Diphenylethylene diamine derived catalysts in the addition of 2-phenylpropionaldehyde to *trans*- β -nitrostyrene.

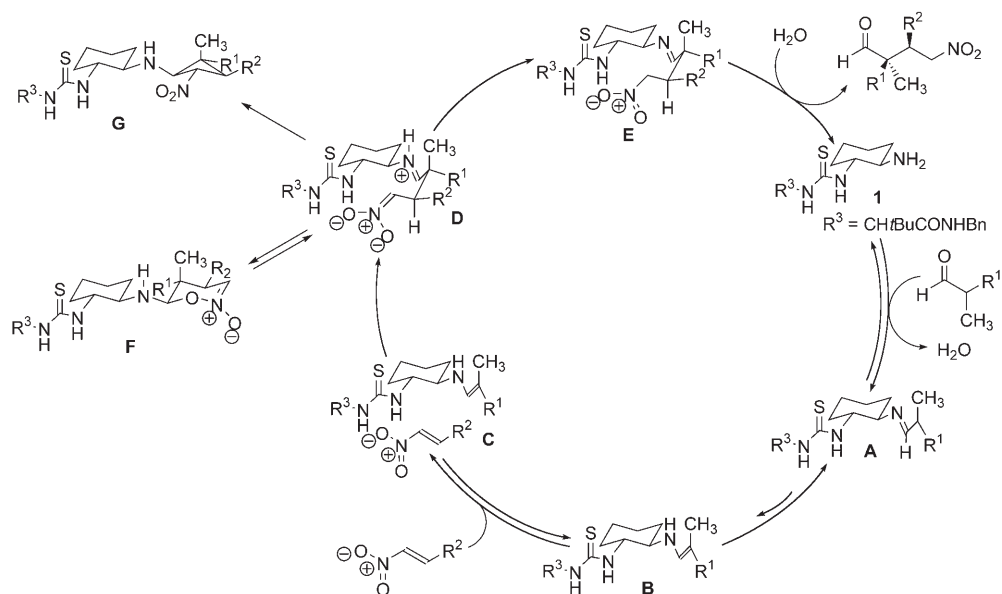


Entry	Catalyst	Yield [%] ^[a]	d.r. (syn/anti) ^[a]	<i>ee</i> [%] (syn/anti) ^[b]
1	1	100	1.2:1	67:3
2	3	86	8.6:1	97:24
3	23	84	11.9:1	97:32
4	24	35	6.9:1	71:40 ^[c]

[a] Product yields were determined by ¹H NMR spectroscopic analysis of the crude reaction mixture using trimethoxybenzene as an internal standard. [b] Determined by chiral HPLC analysis compared with authentic racemic material. [c] Products are of opposite absolute configuration to those in entries 1–3.

analogous to **G** requires strong aqueous acid.^[23i,l] The beneficial role of water may lie in increasing turnover by eliminating a potential catalyst sink (formation of **F**) and accelerating imine (**E**) hydrolysis. However, cyclobutane **G** is unlikely to undergo hydrolysis under the catalytic conditions, and its irreversible formation may be responsible for catalyst deactivation.^[24]

We have shown that chiral primary amine thiourea catalysts are highly effective in the addition of α,α -disubstituted aldehydes to nitroalkenes, generating synthetically versatile nitroaldehyde adducts. Simultaneous activation of both nucleophile and electrophile through a combination of effects typically associated with enzymes (approximation,



Scheme 1. Proposed mechanism for the asymmetric addition of α,α -disubstituted aldehydes to nitroalkenes catalyzed by **1**. Bn = benzyl.

hydrogen bonding, and covalent nucleophilic catalysis) allows this challenging transformation to take place under mild reaction conditions and with broad substrate scope. Interestingly, and in contrast to many enzymes, these bifunctional catalysts function by sequestering substrates from hydrophobic organic solvents into hydrophilic active sites. This study adds to a growing body of evidence suggesting that dual-activation catalysis with simple bifunctional organic frameworks holds substantial promise for asymmetric synthesis.^[25] Our current efforts are focused on further development of conjugate addition reactions promoted by thiourea amine derivatives, as well as on the design of new bifunctional frameworks for use in asymmetric catalysis.

Experimental Section

(2*S*,3*R*)-2,3-Dimethyl-4-nitro-2-phenylbutanal (**6**): Under a positive pressure of nitrogen at room temperature, thiourea catalyst **1** (75.3 mg, 0.20 mmol, 20 mol%) was loaded into an oven-dried 25-mL round-bottomed flask equipped with a magnetic stir bar, rubber septum, and nitrogen inlet. The catalyst was dissolved in dichloromethane (6.7 mL). Water (90.1 μ L, 5.0 mmol, 5.0 equiv) and 2-phenylpropionaldehyde (265.4 μ L, 2.0 mmol, 2.0 equiv) were subsequently added by syringe. The resulting clear colorless solution was stirred for approximately 2 min. Addition of 1-nitropropene (87.1 mg, 1.0 mmol, 1.0 equiv) by syringe produced a light yellow solution. The rubber septum was quickly replaced with a yellow polyethylene stopper (to avoid absorption of dichloromethane by the septum), and the reaction mixture was stirred for 24 h at room temperature. Aqueous hydrochloric acid solution (1*M*, 7 mL) was added to the reaction flask, and the resulting biphasic mixture was stirred vigorously for 5 min at room temperature. The biphasic mixture was transferred to a separating funnel, and additional portions of dichloromethane (30 mL) and 1*M* HCl (30 mL) were added. The phases were separated, and the aqueous layer was washed with dichloromethane (30 mL). The organic layers were combined and washed with saturated aqueous sodium bicarbonate solution (30 mL), saturated aqueous sodium chloride solution (30 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The resulting yellow residue was purified by chromatography on silica (8% diethyl ether/hexanes), providing the title compound as a colorless/light yellow liquid in 91% yield (201.1 mg) in 23:1 diastereomeric ratio and with 99% *ee* (major diastereomer) as determined by HPLC (Chiralpak AD-H, 2.0% propan-2-ol/hexanes, 1.0 mL min⁻¹, 230 nm; *t*_r(minor enantiomer, minor diastereomer) = 11.83 min, *t*_r(major enantiomer, minor diastereomer) = 12.87 min, *t*_r(minor enantiomer, major diastereomer) = 13.82 min, *t*_r(major enantiomer, major diastereomer) = 15.48 min). [α]_D²⁵ = +88.6° (*c* = 0.0200 g/2.0 mL, chloroform); ¹H NMR (400 MHz, CDCl₃): δ = 9.47 (1H, s), 7.42 (2H, t, *J* = 7.3 Hz), 7.34 (1H, t, *J* = 7.3 Hz), 7.24 (2H, d, *J* = 7.3 Hz), 4.57 (1H, dd, *J* = 3.3, 12.0 Hz), 4.19 (1H, dd, *J* = 10.6, 12.0 Hz), 3.17 (1H, m), 1.48 (3H, s), 0.81 ppm (3H, d, *J* = 7.0 Hz); ¹³C NMR (100 MHz, CDCl₃): δ = 200.6, 137.4, 129.4, 128.2, 127.4, 78.8, 55.9, 37.1, 14.6, 13.2 ppm; IR (neat): $\tilde{\nu}$ = 3060 (w), 2981 (m), 2819 (w), 2719 (w), 1722 (s), 1533 (s), 1496 (m), 1446 (m), 1377 (s), 763 (m), 702 (m); HRMS (ESI): calcd for [C₁₂H₁₅NO₃+NH₄]⁺: 239.1396; found: 239.1402.

Received: June 2, 2006

Published online: August 28, 2006

Keywords: amines · asymmetric catalysis · conjugate addition · organocatalysis

- [1] For a timely review, see: B. List, *Chem. Commun.* **2006**, 819–824.
- [2] a) S. Pizzarello, A. L. Weber, *Science* **2004**, *303*, 1151; b) F. Tanaka, R. Thayumanavan, N. Mase, C. F. Barbas III, *Tetrahedron Lett.* **2004**, *45*, 325–328; c) A. Córdova, I. Ibrahim, J. Casas, H. Sundén, M. Engqvist, E. Reyes, *Chem. Eur. J.* **2005**, *11*, 4772–4784; d) M. Amedjkouh, *Tetrahedron: Asymmetry* **2005**, *16*, 1411–1414; e) A. Córdova, W. Zou, I. Ibrahim, E. Reyes, M. Engqvist, W.-W. Liao, *Chem. Commun.* **2005**, 3586–3588; f) W. Zou, I. Ibrahim, P. Dziedzic, H. Sundén, A. Córdova, *Chem. Commun.* **2005**, 4946–4948; g) I. Ibrahim, W. Zou, M. Engqvist, Y. Xu, A. Córdova, *Chem. Eur. J.* **2005**, *11*, 7024–7029; h) A. Bassan, W. Zou, E. Reyes, F. Himo, A. Córdova, *Angew. Chem.* **2005**, *117*, 7190–7194; *Angew. Chem. Int. Ed.* **2005**, *44*, 7028–7032; i) Y. Xu, A. Córdova, *Chem. Commun.* **2006**, 460–462; j) Y. Xu, W. Zou, H. Sundén, I. Ibrahim, A. Córdova, *Adv. Synth. Catal.* **2006**, *348*, 418–424.
- [3] a) E. D. Bergmann, E. Zimkin, S. Pinchas, *Rec. Trav. Chim.* **1952**, *71*, 168–191; b) E. D. Bergmann, Y. Hirshberg, E. Zimkin, S. Pinchas, *Rec. Trav. Chim.* **1952**, *71*, 192–199; c) E. D. Bergmann, E. Meeron, Y. Hirshberg, S. Pinchas, *Rec. Trav. Chim.* **1952**, *71*, 200–212; d) B. Witkop, *J. Am. Chem. Soc.* **1956**, *78*, 2873–2882; e) M. Pfau, C. Ribière, *J. Chem. Soc. D* **1970**, 66–67; f) R. A. Clark, D. C. Parker, *J. Am. Chem. Soc.* **1971**, *93*, 7257–7261; g) B. De Jeso, J.-C. Pommier, *J. Chem. Soc. Chem. Commun.* **1977**, 565–566; h) B. De Jeso, J.-C. Pommier, *J. Organomet. Chem.* **1977**, *137*, 23–29; i) R. Knorr, A. Weiss, P. Löw, E. Rappé, *Chem. Ber.* **1980**, *113*, 2462–2489; j) D. R. Boyd, W. B. Jennings, L. C. Waring, *J. Org. Chem.* **1986**, *51*, 992–995; k) B. Capon, Z.-P. Wu, *J. Org. Chem.* **1990**, *55*, 2317–2324.
- [4] D. J. Hupe in *New Comprehensive Biochemistry*, Vol. 6 (Ed.: M. I. Page), Elsevier, Amsterdam, **1984**, pp. 271–301.
- [5] a) T. Okino, Y. Hoashi, Y. Takemoto, *J. Am. Chem. Soc.* **2003**, *125*, 12672–12673; b) T. Okino, S. Nakamura, T. Furukawa, Y. Takemoto, *Org. Lett.* **2004**, *6*, 625–627; c) Y. Hoashi, T. Yabuta, Y. Takemoto, *Tetrahedron Lett.* **2004**, *45*, 9185–9188; d) T. Okino, Y. Hoashi, T. Furukawa, X. Xu, Y. Takemoto, *J. Am. Chem. Soc.* **2005**, *127*, 119–125; e) A. Berkessel, F. Cleemann, S. Mukherjee, T. N. Müller, J. Lex, *Angew. Chem.* **2005**, *117*, 817–821; *Angew. Chem. Int. Ed.* **2005**, *44*, 807–811; f) Y. Hoashi, T. Okino, Y. Takemoto, *Angew. Chem.* **2005**, *117*, 4100–4103; *Angew. Chem. Int. Ed.* **2005**, *44*, 4032–4035; g) A. Berkessel, F. Cleemann, S. Mukherjee, *Angew. Chem.* **2005**, *117*, 7632–7635; *Angew. Chem. Int. Ed.* **2005**, *44*, 7466–7469; h) A. Berkessel, S. Mukherjee, F. Cleemann, T. N. Müller, J. Lex, *Chem. Commun.* **2005**, 1898–1900; i) A. P. Dove, R. C. Pratt, B. G. G. Lohmeijer, R. M. Waymouth, J. L. Hedrick, *J. Am. Chem. Soc.* **2005**, *127*, 13798–13799; j) B. Vakulya, S. Varga, A. Csámpal, T. Soós, *Org. Lett.* **2005**, *7*, 1967–1969; k) B.-J. Li, L. Jiang, M. Liu, Y.-C. Chen, L.-S. Ding, Y. Wu, *Synlett* **2005**, 603–606; l) S. H. McCooey, S. J. Connon, *Angew. Chem.* **2005**, *117*, 6525–6528; *Angew. Chem. Int. Ed.* **2005**, *44*, 6367–6370; m) J. Ye, D. J. Dixon, P. S. Hynes, *Chem. Commun.* **2005**, 4481–4483; n) D. E. Fuerst, E. N. Jacobsen, *J. Am. Chem. Soc.* **2005**, *127*, 8964–8965; o) J. Wang, H. Li, X. Yu, L. Zu, W. Wang, *Org. Lett.* **2005**, *7*, 4293–4296; p) J. Wang, H. Li, W. Duan, L. Zu, W. Wang, *Org. Lett.* **2005**, *7*, 4713–4716; q) X. Xu, T. Furukawa, T. Okino, H. Miyabe, Y. Takemoto, *Chem. Eur. J.* **2006**, *12*, 466–476.
- [6] For reviews concerning asymmetric catalysis by chiral thioureas (including tertiary amine thiourea derivatives), see: a) S. J. Connon, *Chem. Eur. J.* **2006**, *12*, 5418–5427; b) M. S. Taylor, E. N. Jacobsen, *Angew. Chem.* **2006**, *118*, 1550–1573; *Angew. Chem. Int. Ed.* **2006**, *45*, 1520–1543; c) P. R. Schreiner, *Chem. Soc. Rev.* **2003**, *32*, 289–296; d) Y. Takemoto, *Org. Biomol. Chem.* **2005**, *3*, 4299–4306.

- [7] Although thorough mechanistic investigations have as yet not been reported, tertiary amine thiourea catalysts are generally proposed to function by cooperative general acid/general base mechanisms reminiscent of more complex enzymatic systems, wherein reactivity and selectivity are imparted through binding, activation, and proper positioning of distinct substrates. For a discussion of the aforementioned concepts in enzyme catalysis, see: a) T. C. Bruice in *Enzymes*, Vol. 2, 3rd ed. (Ed.: P. D. Boyer), Academic Press, New York, **1970**, pp. 217–279; b) R. A. Copeland, *Enzymes: A Practical Introduction to Structure, Mechanism, and Data Analysis*, 2nd ed., Wiley, New York, **2000**, pp. 146–187.
- [8] a) S. B. Tsogoeva, S. Wei, *Chem. Commun.* **2006**, 1451–1453; b) H. Huang, E. N. Jacobsen, *J. Am. Chem. Soc.* **2006**, 128, 7170–7171.
- [9] J. d'Angelo, D. Desmaële, F. Dumas, A. Guingant, *Tetrahedron: Asymmetry* **1992**, 3, 459–505, and references therein.
- [10] For alternative asymmetric catalytic approaches to the preparation of compounds with contiguous quaternary and tertiary stereogenic centers, see: a) Y. Hamashima, D. Hota, M. Sodeoka, *J. Am. Chem. Soc.* **2002**, 124, 11240–11241; b) M. S. Taylor, E. N. Jacobsen, *J. Am. Chem. Soc.* **2003**, 125, 11204–11205; c) M. S. Taylor, D. N. Zalatan, A. M. Lerchner, E. N. Jacobsen, *J. Am. Chem. Soc.* **2005**, 127, 1313–1317; d) H. Li, Y. Wang, L. Tang, F. Wu, X. Liu, C. Guo, B. M. Foxman, L. Deng, *Angew. Chem.* **2005**, 117, 107–110; *Angew. Chem. Int. Ed.* **2005**, 44, 105–108; e) F. Wu, H. Li, L. Deng, *Angew. Chem.* **2006**, 118, 961–964; *Angew. Chem. Int. Ed.* **2006**, 45, 947–950.
- [11] For secondary amine catalyzed additions of unbranched aldehydes to nitroalkenes, see: a) J. M. Betancort, C. F. Barbas III, *Org. Lett.* **2001**, 3, 3737–3740; b) A. Alexakis, O. Andrey, *Org. Lett.* **2002**, 4, 3611–3614; c) O. Andrey, A. Alexakis, A. Tomassini, G. Bernardinelli, *Adv. Synth. Catal.* **2004**, 346, 1147–1168; d) P. Kotrusz, S. Toma, H.-G. Schmalz, A. Adler, *Eur. J. Org. Chem.* **2004**, 1577–1583; e) W. Wang, J. Wang, H. Li, *Angew. Chem.* **2005**, 117, 1393–1395; *Angew. Chem. Int. Ed.* **2005**, 44, 1369–1371; f) Y. Hayashi, H. Gotoh, T. Hayashi, M. Shoji, *Angew. Chem.* **2005**, 117, 4284–4287; *Angew. Chem. Int. Ed.* **2005**, 44, 4212–4215.
- [12] For a review of asymmetric conjugate additions to nitroalkenes, see: O. M. Berner, L. Tedeschi, D. Enders, *Eur. J. Org. Chem.* **2002**, 1877–1894.
- [13] a) N. Mase, R. Thayumanavan, F. Tanaka, C. F. Barbas III, *Org. Lett.* **2004**, 6, 2527–2530; b) N. Mase, K. Watanabe, H. Yoda, K. Tanabe, F. Tanaka, C. F. Barbas III, *J. Am. Chem. Soc.* **2006**, 128, 4966–4967.
- [14] Secondary enamines conjugated to aromatic systems are known to display low reactivity (see Ref. [9]). Relative to nitrostyrene derivatives, inferior product yields have been reported in additions of aldehydes to β -alkyl-substituted nitroalkenes (see Refs. [11a, c–e]).
- [15] Direct Michael additions to nitroalkenes promoted by secondary amine catalysts typically require large (e.g. tenfold) excess of aldehyde due to competing aldol pathways (see Ref. [11]).
- [16] 2-Phenylpropionaldehyde was recovered in 2.5% *ee*, thus indicating that a simple kinetic resolution mechanism is not operative.
- [17] The addition of 2-methylvaleraldehyde to *trans*- β -nitrostyrene catalyzed by 20 mol% **3** proceeded with less than 10% conversion.
- [18] The benefit of added water has been observed in other primary amine catalyzed transformations (see references [2c–j, 8a]).
- [19] For the conjugate addition of α -amino acid esters to *trans*-3,3,3-trifluoro-1-nitropropene, see: M. Molteni, A. Volonterio, M. Zanda, *Org. Lett.* **2003**, 5, 3887–3890.
- [20] The addition of amines to nitroalkenes has been extensively studied with very few stable adducts isolated. Anilines and electron-deficient nitroalkenes lead to relatively stable adducts. For representative studies, see: a) D. E. Worrall, *J. Am. Chem. Soc.* **1927**, 49, 1598–1605; b) R. L. Heath, J. D. Rose, *J. Chem. Soc.* **1947**, 1486–1489; c) F. Brower, H. Burkett, *J. Am. Chem. Soc.* **1953**, 75, 1082–1084; d) J. C. Sowden, A. Kirkland, K. O. Lloyd, *J. Org. Chem.* **1963**, 28, 3516–3518; e) É. S. Lipina, Z. F. Pavlova, T. Y. Paperno, V. V. Perekalin, L. V. Prikhod'ko, *Zh. Org. Khim.* **1970**, 6, 1123–1129.
- [21] Diastereomers are assumed to arise from competitive reaction of *E* and *Z* enamines rather than poor nitroalkene facial selectivity. Consistent with this notion, catalyst **1** promotes the reaction of nitrostyrene with isobutyraldehyde in 99% *ee* (see Supporting Information for details).
- [22] For a relevant analysis, see: D. A. Yalalov, S. B. Tsogoeva, S. Schmatz, *Adv. Synth. Catal.* **2006**, 348, 826–832.
- [23] a) K. C. Brannock, A. Bell, R. D. Burpitt, C. A. Kelly, *J. Org. Chem.* **1964**, 29, 801–812; b) M. E. Kuehne, L. Foley, *J. Org. Chem.* **1965**, 30, 4280–4284; c) A. Risaliti, S. Fatutta, M. Forchiassin, E. Valentin, *Tetrahedron Lett.* **1966**, 7, 1821–1825; d) A. Risaliti, M. Forchiassin, E. Valentin, *Tetrahedron Lett.* **1966**, 7, 6331–6335; e) A. T. Nielsen, T. G. Archibald, *Tetrahedron* **1970**, 26, 3475–3485; f) D. Seebach, J. Golinski, *Helv. Chim. Acta* **1981**, 64, 1413–1423; g) S. J. Blarer, W. B. Schweizer, D. Seebach, *Helv. Chim. Acta* **1982**, 65, 1637–1654; h) S. J. Blarer, D. Seebach, *Chem. Ber.* **1983**, 116, 3086–3096; i) D. Seebach, A. K. Beck, J. Golinski, J. N. Hay, T. Laube, *Helv. Chim. Acta* **1985**, 68, 162–172; j) F. Felluga, P. Nitti, G. Pitacco, E. Valentin, *Tetrahedron* **1989**, 45, 2099–2108; k) F. Felluga, P. Nitti, G. Pitacco, E. Valentin, *Tetrahedron* **1989**, 45, 5667–5678; l) F. Felluga, P. Nitti, G. Pitacco, E. Valentin, *J. Chem. Soc. Perkin Trans. 1* **1992**, 2331–2335.
- [24] See Supporting Information for experimental evidence for the formation of **G**.
- [25] For a discussion of dual activation within the context of asymmetric catalysis by chiral hydrogen-bond donors, see Ref. [6b].
- [26] Yields are of isolated products after column chromatography. Diastereomeric ratios and enantiomeric excesses were determined by SFC or HPLC analysis compared with authentic racemic material. The absolute configuration of **22** was determined by X-ray crystallography, whereas those of **6–21** were inferred.