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Asymmetric Michael Additions of α-Nitrocyclohexanone to Aryl Nitroalkenes Catalyzed by Natural Amino Acid-Derived Bifunctional Thioureas

Manuel Jörres, Ingo Schiffers, Iuliana Atodiresei, and Carsten Bolm*

Institute of Organic Chemistry, RWTH Aachen University, Landoltweg1, D-52074 Aachen, Germany

carsten.bolm@oc.rwth-aachen.de

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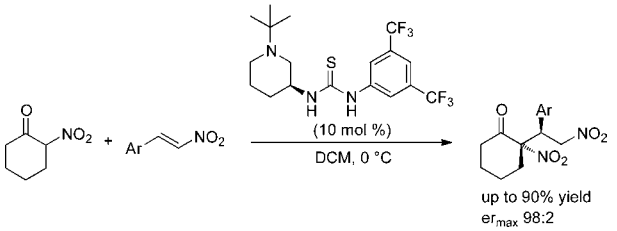
ABSTRACT



A series of new thiourea catalysts prepared from natural amino acids have been applied in organocatalytic asymmetric Michael additions of α-nitrocyclohexanone to nitroalkenes. The resulting addition products are formed with excellent enantioselectivities (up to an er of 98:2) in good yields (up to 90%).

Organocatalysis has become a well-respected methodology in asymmetric organic synthesis.[1,2] Besides activation via enamines or imminium ions, hydrogen bonding plays a major role.[3] Catalysts combining both a hydrogen donor and a hydrogen acceptor are of particular interest because they allow a simultaneous activation of two reactants.[4] Excellent examples include the thioureas by Takemoto[5] and Jacobsen,[6] in which the H-binding cores are combined with (di)amino-based H-acceptors.[7]

Initially, our work was focused on the use of bifunctional thioureas in the enantioselective desymmetrization of *meso*-anhydrides.[8] Further interest in this catalyst type

(1) For recent books, see: (a) *Enantioselective Organocatalysis*; Dalko, P. I., Ed.; Wiley-VCH: Weinheim, 2007. (b) *Organocatalysis*; Reetz, M. T., List, B., Jaroch, S., Weinmann, H., Eds.; Springer: Berlin, 2008.

(2) For selected recent reviews on organocatalysis, see: (a) Mukherjee, S.; Yang, J. W.; Hoffmann, S.; List, B. *Chem. Rev.* **2007**, *107*, 5471. (b) Enders, D.; Grondal, C.; Hüttl, M. R. M. *Angew. Chem., Int. Ed.* **2007**, *46*, 1570. (c) MacMillan, D. W. C. *Nature* **2008**, *455*, 304. (d) Dondoni, A.; Massi, A. *Angew. Chem., Int. Ed.* **2008**, *47*, 4638. (e) Melchiorre, P.; Marigo, M.; Carlone, A.; Bartoli, G. *Angew. Chem., Int. Ed.* **2008**, *47*, 6138. (f) Yu, X.; Wang, W. *Chem. Asian J.* **2008**, *3*, 516. (g) Bertelsen, S.; Jørgensen, K. A. *Chem. Soc. Rev.* **2009**, *38*, 2178. (h) Pihko, P. M.; Majander, I.; Erkkilä, A. *Top. Curr. Chem.* **2010**, *291*, 29.

(3) For reviews on hydrogen-bonding catalysis, see: (a) Schreiner, P. R.; Wittkopp, A. *Org. Lett.* **2002**, *4*, 217. (b) Schreiner, P. R. *Chem. Soc. Rev.* **2003**, *32*, 289. (c) Pihko, P. M. *Angew. Chem., Int. Ed.* **2004**, *43*, 2062. (d) Doyle, A. G.; Jacobsen, E. N. *Chem. Rev.* **2007**, *107*, 5713. (e) Zhang, Z.; Schreiner, P. R. *Chem. Soc. Rev.* **2009**, *38*, 1187.

(4) For reviews on bifunctional hydrogen-bonding catalysis, see: (a) Takemoto, Y. *Org. Biomol. Chem.* **2005**, *3*, 4299. (b) Taylor, M. S.; Jacobsen, E. N. *Angew. Chem., Int. Ed.* **2006**, *45*, 1520. (c) Connon, S. J. *Chem. Commun.* **2008**, 2499. (d) Connon, S. J. *Synlett* **2009**, 354. (e) Lu, L.-Q.; An, X.-L.; Chen, J.-R.; Xiao, W.-J. *Synlett* **2012**, *23*, 490.

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(7) For other examples, see: (a) Vakulya, B.; Varga, S.; Csámpai, A.; Soós, T. *Org. Lett.* **2005**, *7*, 1967. (b) McCooey, S. H.; Connon, S. J. *Angew. Chem., Int. Ed.* **2005**, *44*, 6367. (c) Andrés, J. M.; Manzano, R.; Pedrosa, R. *Chem.—Eur. J.* **2008**, *14*, 5116. (d) Ma, Z.-W.; Liu, Y.-X.; Huo, L.-J.; Gao, X.; Tao, J.-C. *Tetrahedron: Asymmetry* **2012**, *23*, 443.

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(10) For other recent examples of thiourea-catalyzed Michael addition reactions, see: (a) Cao, Y.; Jiang, X.; Liu, L.; Shen, F.; Zhang, F.; Wang, R. *Angew. Chem., Int. Ed.* **2011**, *50*, 9124. (b) Dong, X.-Q.; Fang, X.; Wang, C.-J. *Org. Lett.* **2011**, *13*, 4426. (c) Ramireddy, N.; Abbaraju, S.; Zhao, C.-G. *Tetrahedron Lett.* **2011**, *52*, 6792. (d) Rana, N. K.; Singh, V. K. *Org. Lett.* **2011**, *13*, 6520. (e) Bai, J.-F.; Wang, L.-L.; Peng, L.; Guo, Y.-L.; Jia, L.-N.; Tian, F.; He, G.-Y.; Xu, X.-Y.; Wang, L.-X. *J. Org. Chem.* **2012**, *77*, 2947. (f) Urbanietz, G.; Cassens-Sasse, E.; Keeß, S.; Raabe, G.; Enders, D. *Adv. Synth. Catal.* **2012**, *354*, 1481. (g) Parra, A.; Uria, U.; Besselièvre, F.; Merino, E.; Rueping, M. *Org. Lett.* **2010**, *12*, 5680. (h) Raimondi, W.; Basl, O.; Constantieux, T.; Bonne, D.; Rodriguez, J. *Adv. Synth. Catal.* **2012**, *354*, 563. (i) Li, X.; Zhang, Y.-Y.; Xue, X.-S.; Jin, J.-L.; Tan, B.-X.; Liu, C.; Dong, N.; Cheng, J.-P. *Eur. J. Org. Chem.* **2012**, 1774.

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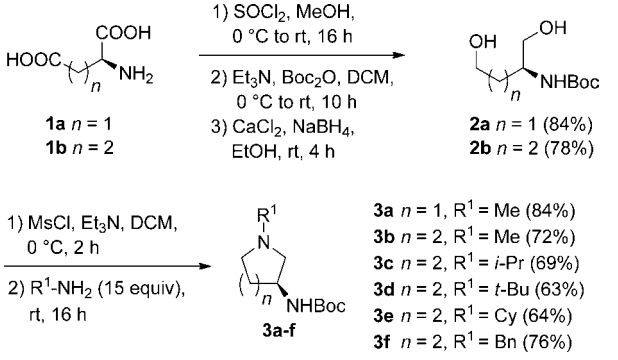
led us to study Michael addition reactions,[9,10] which are among the most efficient methods for C−C and C−X bond formations.[11] If α-substituted cyclic ketones are applied in such reactions, products with a quaternary stereogenic center are formed.[12,13] Additions to nitroalkenes provide synthetically attractive intermediates with an easy-to-convert flexible functional group.[11,14] Here, we report the syntheses of new bifunctional thioureas starting from natural amino acid-derived *N*-substituted 3-amino piperidines and a 5-membered analogue, and we demonstrate their excellent organocatalytic potential in asymmetric Michael addition of α-nitrocyclohexanone to nitroalkenes.[15,16]

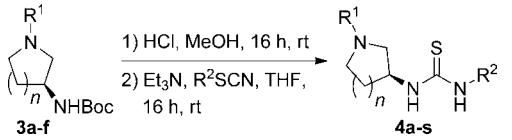
The preparation of enantiomerically pure 3-amino-substituted cyclic amines from α-amino acids was first reported by Moon and Lee.[17,18] Following their procedure with slight modifications, *N*-Boc-protected diamines **3a**−**f** were accessible in good yields (Scheme 1). Accordingly, starting from L-aspartic acid (**1a**) and L-glutamic acid (**1b**) the syntheses of pyrrolidine **3a** and piperidines **3b**−**f** proceeded via amino diols **2a** and **2b**, respectively. Dimesylations of the latter followed by cyclizations of the doubly activated substrates upon treatment with primary amines gave access to **3a**−**f** in overall yields of up to 71% (over five steps).

Scheme 1. Syntheses of *N*-Boc-Protected 3-Amino Cyclic Amines from Natural Amino Acids



The *N*-Boc group cleavages of diamines **3a**−**f** were effected with hydrochloric acid, which afforded the corresponding HCl salts. Subsequent treatments of those with triethylamine and additions of the respective thioisocyanates to the liberated diamines led to thioureas **4a**−**s** in good to excellent yields (66−99%; Table 1).

Table 1. Syntheses of Thioureas from *N*-Boc-Protected Cyclic Diamines



entry	diamine	R^1	R^2	product	yield[a] (%)
1	**3a** (n = 1)	Me	3,5-$(CF_3)_2C_6H_3$	**4a**	86
2	**3b** (n = 2)	Me	3,5-$(CF_3)_2C_6H_3$	**4b**	81
3	**3c** (n = 2)	*i*-Pr	3,5-$(CF_3)_2C_6H_3$	**4c**	66
4	**3d** (n = 2)	*t*-Bu	3,5-$(CF_3)_2C_6H_3$	**4d**	82
5	**3e** (n = 2)	Cy	3,5-$(CF_3)_2C_6H_3$	**4e**	92
6	**3f** (n = 2)	Bn	3,5-$(CF_3)_2C_6H_3$	**4f**	94
7	**3b** (n = 2)	Me	C_6H_5	**4g**	89
8	**3b** (n = 2)	Me	*p*-$(CH_3)C_6H_4$	**4h**	67
9	**3b** (n = 2)	Me	*p*-$(CF_3)C_6H_4$	**4i**	98
10	**3b** (n = 2)	Me	*p*-$(NO_2)C_6H_4$	**4j**	99
11	**3b** (n = 2)	Me	*p*-ClC_6H_4	**4k**	95
12	**3b** (n = 2)	Me	3,5-$Cl_2C_6H_3$	**4l**	70
13	**3b** (n = 2)	Me	*p*-FC_6H_4	**4m**	96
14	**3b** (n = 2)	Me	2-naphthyl	**4n**	97
15	**3b** (n = 2)	Me	2,6-$(CH_3)_2C_6H_3$	**4o**	79
16	**3b** (n = 2)	Me	Bn	**4p**	96
17	**3b** (n = 2)	Me	*i*-Bu	**4q**	94
18	**3b** (n = 2)	Me	CH_2Cy	**4r**	99
19	**3d** (n = 2)	*t*-Bu	Bn	**4s**	97

[a] After column chromatography.

With the goal of evaluating the organocatalytic potential of the newly prepared thioureas, they were tested in Michael addition reactions of α-nitrocyclohexanone (**5**) to 2-fluoro-β-nitrostyrene (**6a**) (Table 2). The transformation was expected to reveal eventual catalytic activities of **4a**−**s** and to be a good indicator for the intrinsic stereoselectivity during the C−C bond formation affording dinitrocyclohexanone **7a** having two stereogenic centers with one being quaternary.

First, thiourea **4a** derived from *N*-methylpyrrolidine **3a** and 3,5-bis(trifluoromethyl)phenyl thioisocyanate was

(11) For reviews with a focus on Michael-type additions to nitroalkenes, see: (a) Berner, O. M.; Tedeschi, L.; Enders, D. *Eur. J. Org. Chem.* **2002**, 1877. (b) Tsogoeva, S. B. *Eur. J. Org. Chem.* **2007**, 1701. (c) Almasi, D.; Alonso, D. A.; Najera, C. *Tetrahedron: Asymmetry* **2007**, *18*, 299. (d) Vicario, J. L.; Badia, D.; Carrillo, L. *Synthesis* **2007**, 2065. (e) Sulzer-Mosse, S.; Alexakis, A. *Chem. Commun.* **2007**, 3123.

(12) For the formation of quaternary centers in organic synthesis, see: (a) *Quaternary Stereocenters: Challenges and Solutions for Organic Synthesis*; Christoffers, J., Baro, A., Eds.; Wiley-VCH: Weinheim, 2005. (b) Christoffers, J.; Baro, A. *Adv. Synth. Catal.* **2005**, *347*, 1473. (c) Cozzi, P. G.; Hilgraf, R.; Zimmermann, N. *Eur. J. Org. Chem.* **2007**, 5969. (d) Bella, M.; Gasperi, T. *Synthesis* **2009**, 1583.

(13) For selected recent examples of Michael additions to α-substituted cyclic ketones, see: (a) Zhang, Z.-H.; Dong, X.-Q.; Chen, D.; Wang, C.-J. *Chem.—Eur. J.* **2008**, *14*, 8780. (b) Luo, J.; Xu, L.-W.; Hay, R. A. S.; Lu, Y. *Org. Lett.* **2009**, *11*, 437. (c) Manzano, R.; Andrés, J. M.; Muruzábal, M. D.; Pedrosa, R. *Adv. Synth. Catal.* **2010**, *352*, 3364. (d) Dong, X.-Q.; Teng, H.-L.; Tong, M.-C.; Huang, H.; Taoa, H.-Y.; Wang, C.-J. *Chem. Commun.* **2010**, *46*, 6840. (e) Hong, B.-C.; Kotame, P.; Lee, G.-H. *Org. Lett.* **2011**, *13*, 5758.

(14) (a) Ono, N. *The Nitro Group in Organic Synthesis*; Wiley-VCH: New York, 2001. (b) Ballini, R.; Petrini, M. *Tetrahedron* **2004**, *60*, 1017.

(15) For a review on conjugate additons of nitroalkanes to electron-poor alkenes, see: Ballini, R.; Bosica, G.; Fiorini, D.; Palmieri, A.; Petrini, M. *Chem. Rev.* **2005**, *105*, 933.

(16) In an early example of an organocatalytic asymmetric Michael addition of 2-nitrocycloalkanones to methyl vinyl ketone, see: Latvala, A.; Stanchev, S.; Linden, A.; Hesse, M. *Tetrahedron: Asymmetry* **1993**, *4*, 173.

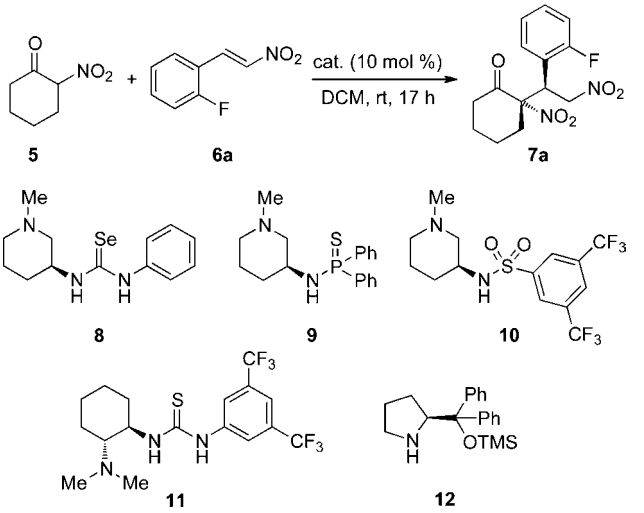
(17) Moon, S.-H.; Lee, S. *Synth. Commun.* **1998**, *28*, 3919.

(18) For recent publications on 3-amino-substituted cyclic amines, see: (a) Camps, P.; Galdeano, C.; Muñoz-Torrero, D.; Rull, J.; Calvet, T.; Font-Bardia, M. *Tetrahedron: Asymmetry* **2011**, *22*, 745. (b) Cochi, A.; Pardo, D. G.; Cossy, J. *Eur. J. Org. Chem.* **2012**, 2023. (c) Sakurai, R.; Sakai, K.; Kodama, K.; Yamaura, M. *Tetrahedron: Asymmetry* **2012**, *23*, 221.

applied. To our delight, the reaction proceeded at room temperature and was complete after 17 h (Table 2, entry 1). Product **7a** was isolated in 78% yield, and its dr and er were 94:6 and 85:15, respectively. No reaction occurred in the absence of the catalyst. Both yield and stereoselectivity were improved in catalyses with pyrrolidine-based thioureas. For example, the direct analogue to **4a**, thiourea **4b**, gave **7a** in 90% yield (Table 2, entry 2). While the dr was identical (94:6), the er raised to 94:6. Increasing the steric bulk of the substituent at the endocyclic nitrogen of the catalyst led to further improvements (Table 2, entries 3–6). Hence, the best result (with respect to yield and er) was achieved with thiourea **4d** having an *N*-*tert*-butyl substituent. With 10 mol % of that catalyst, **7a** was obtained in 91% yield with dr and er values of 90:10 and 97:3, respectively (Table 2, entry 4).[19] Attempts to further optimize the catalyst structure by modifying the thiourea aryl fragment remained unsuccessful.[20] As shown in a series of *N*-methyl-substituted piperidine-based thioureas (Table 2, entries 7–15), the yields in the formation of **7a** varied and the diastereselectivities were high. However, the enantioselectivity did not improve. Interestingly, an exchange of the thiourea aryl by a benzyl group did lead to the desired increase in stereoselectivity, and, with **4p**, product **7a** was obtained in 91% yield having a dr of 94:6 and an er of 96:4 (Table 2, entry 16). With respect to the yield (90%) and er (97:3), almost the same values were observed in a catalysis with thiourea **4s** which combined the *N*-*tert*-butyl-substituted piperidine core with the benzyl substituent (Table 2, entry 19). To our surprise, the dr (82:18) was remarkably low here.

With the goal to compare the aformentioned results with those obtainable with related and established catalyst structures, compounds **8**–**12** became part of the screening process (Table 2, entries 20–24). Those included selenourea **8**,[21] thiophosphinamide **9**,[22] and sulfonamide **10**, which all contained the *N*-methyl-substituted piperidine core. Furthermore, Takemoto's thiourea **11**[5] and the Jørgensen/Hayashi catalyst **12**[23] were tested. None of these compounds, however, proved superior over the newly reported thioureas **4**, and, with the exception of selenourea **8** which gave **7a** in 64% yield with a dr of 92:8 and an er of 87:13 (Table 2, entry 20), all stereoselectivities were low to moderate.

Table 2. Catalyst Screening[a]



entry	cat.	yield of **7a**[b] (%)	dr (*anti*:*syn*)[c]	er[c]
1	**4a**	78	94:6	85:15
2	**4b**	90	94:6	94:6
3	**4c**	76	90:10	96:4
4	**4d**	91	90:10	97:3
5	**4e**	72	90:10	96:4
6	**4f**	79	94:6	94:6
7	**4g**	56	88:12	88:12
8	**4h**	33	92:8	88:12
9	**4i**	65	93:7	91:9
10	**4j**	25	95:5	89:11
11	**4k**	84	93:7	91:9
12	**4l**	79	91:9	92:8
13	**4m**	82	93:7	92:8
14	**4n**	82	89:11	89:11
15	**4o**	84	95:5	87:13
16	**4p**	91	94:6	96:4
17	**4q**	58	93:7	92:8
18	**4r**	74	92:8	92:8
19	**4s**	90	82:18	97:3
20	**8**[d]	64	92:8	87:13
21	**9**[d]	23	66:34	50:50
22	**10**[d]	17	87:13	40:60
23	**11**	89	94:6	22:78
24	**12**	31	92:8	56:44

[a] Use of 0.3 mmol of **5** and 0.2 mmol of **6a** in 1 mL of solvent. [b] After column chromatography. [c] Determined by HPLC of the crude product using a chiral stationary phase. [d] For synthetic details, see the Supporting Information.

On the basis of the results of the catalyst screening summarized in Table 2, thiourea **4d** was chosen for the subsequent studies.

Next, the substrate scope with respect to the nitroalkenes was studied. In general, the reaction conditions were kept unchanged, except for the temperature which was lowered from ambient temperature to 0 °C and the substrate ratio which now involved a 1.5 fold excess of the nitroalkene. To our delight, all compounds, including 2-furyl-substituted

(19) Use of *ent*-**4d** gave **7a** with a dr of 95:5 and an er of 3:97 in 81% yield. Why in this case the yield and the dr differed from the result with **4d** remain uninvestigated.

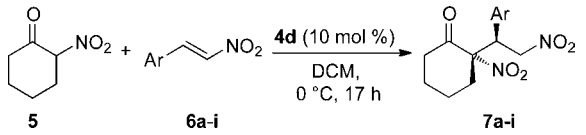
(20) For effects of electronic variations of thiourea moieties, see: (a) Li, X.; Deng, H.; Zhang, B.; Li, J.; Zhang, L.; Luo, S.; Cheng, J.-P. *Chem.—Eur. J.* **2010**, *16*, 450. (b) Jakab, G.; Tancon, C.; Zhang, Z.; Lippert, K. M.; Schreiner, P. R. *Org. Lett.* **2012**, *14*, 1724.

(21) To the best of our knowledge, this is the first reported use of a selenourea in an asymmetric organocatalysis. Unfortunately, compound **8** appeared to decompose under the applied reaction conditions. The synthesis of **8** involved the addition of **3b** to phenyl isoselenocyanate. For preparative aspects of isoselenocyanates, see: Barton, D. H. R.; Parekh, S. I.; Tajbakhsh, M.; Theodorakis, E. A.; Tse, C.-L. *Tetrahedron* **1994**, *50*, 639.

(22) For recent examples of (thio)phosphorodiamide-catalyzed Michael additions to nitroolefins, see: Wu, R.; Chang, X.; Lu, A.; Wang, Y.; Wu, G.; Song, H.; Zhou, Z.; Tang, C. *Chem. Commun.* **2011**, *47*, 5034.

(23) (a) Marigo, M.; Wabnitz, T. C.; Fielenbach, D.; Jørgensen, K. A. *Angew. Chem., Int. Ed.* **2005**, *44*, 794. (b) Hayashi, Y.; Gotoh, H.; Hayashi, T.; Shoji, M. *Angew. Chem., Int. Ed.* **2005**, *44*, 4212.

Table 3. Substrate Scope[a]



5 6a-i 7a-i

entry	nitroalkene	Ar	product	yield[b] (%)	dr[c]	er[c]
1	**6a**	*o*-FC_6H_4	**7a**	90	91:9	98:2[d]
2	**6b**	C_6H_5	**7b**	77	99:1	97:3
3	**6c**	*o*-ClC_6H_4	**7c**	58	89:11	97:3[d]
4	**6d**	*p*-FC_6H_4	**7d**	75	93:7	97:3
4	**6e**	*p*-ClC_6H_4	**7e**	73	91:9	97:3
6	**6f**	*p*-BrC_6H_4	**7f**	82	88:12	97:3
7	**6g**	*p*-$MeOC_6H_4$	**7g**	88	97:3	98:2
8	**6h**	*p*-MeC_6H_4	**7h**	78	93:7	98:2
9	**6i**	2-furyl	**7i**	73	97:3	96:4

[a] Use of **5** (0.4 mmol), **6** (0.6 mmol), and thiourea **4d** (0.04 mmol) in DCM (2 mL) at 0 °C. [b] After column chromatography. [c] Determined by HPLC of the crude product on a chiral stationary phase; dr values refer to *anti*:*syn* ratios. [d] The er of the product could be improved to >99.5:0.5 (as single diastereomer) by recrystallization from Et_2O.

nitroalkene **6i**, reacted well, and the corresponding addition products **7a**–**i** were obtained in yields ranging between 58% and 90% (Table 3). Although the catalysis with *o*-fluoro-substituted nitroalkene **6a** provided 90% of **7a** (Table 3, entry 1), the low yield (58%) in the conversion of the nitroalkene **6c** with the *o*-chloro substituent (Table 3, entry 3) appeared to indicate that steric reasons played an important role in the catalysis of the C–C bond-forming process. For the yields of the addition products, neither electron-withdrawing nor electron-donating substituents on the aryl of the nitroalkenes seemed to matter to a large extent. The diastereoselectivities were generally high, leading to dr values of about 90:10. All enantioselectivities were above an er of 96:4. Also in that respect, *o*-fluoro-substituted product **7a** gave the best result (er of 98:2), which was identical to the corresponding data for products **7g** and **7h** (Table 3, entries 1, 7, and 8). It was also confirmed that the reaction could be performed on an enlarged scale. Thus, starting from 3.6 mmol of 2-fluoro-β-nitrostyrene (**6a**), 0.927 g (83%) of product **7a** with an er of 98:2 was obtained. Apparently, the up-scaling was unproblematic.

Finally, the relative and absolute configuration of Michael adduct **7c** was determined to be *S*,*S* by X-ray crystallographic analysis (Figure 1).[24]

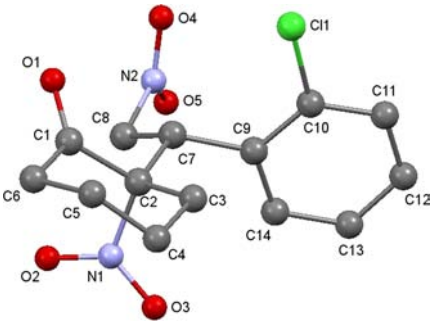


Figure 1. X-ray crystal structure of **7c**.

In summary, we prepared new bifunctional thioureas using *N*-alkylated 3-amino-substituted pyrrolidines and piperidines derived from L-aspartic and L-glutamic acid, respectively. Their applications in organocatalytic asymmetric Michael additions of α-nitrocyclohexanone (**5**) to aryl nitroalkenes **6a**–**i** provided products with excellent stereoselectivities in high yields.

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Supporting Information Available. Experimental procedures, full characterization of new products, copies of NMR spectra, er determinations, and X-ray crystal data for **7c** (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

(24) CCDC (**7c**) 897030 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/datarequest/cif.

The authors declare no competing financial interest.