Asymmetric Synthesis

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Organocatalytic Asymmetric Conjugate Addition of 1,3-Dicarbonyl Compounds to Maleimides**

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Dedicated to Professor Achille Umani-Ronchi on the occasion of his 70th birthday

The enantioselective construction of quaternary stereogenic centers bonded to four carbon atoms by efficient asymmetric methods is a great synthetic challenge, as the creation of such complex fragments is complicated by steric factors.[1] Currently, despite the substantial progress that has been made in the last few years, only a few catalytic asymmetric C–C bond-forming strategies have proven to be useful for forming quaternary carbon centers.[2] Among them, the catalytic conjugate addition[3] of compounds with a prochiral trisubstituted nucleophilic carbon atom to β-substituted Michael acceptors constitutes an effective approach for the asymmetric construction of highly functionalized products with adjacent quaternary and tertiary carbon centers. The stereocontrolled, one-step synthesis of such important congested motifs from simple precursors is a formidable synthetic challenge, as the catalyst must provide high levels of stereoselectivity in a sterically demanding C–C bond-forming process.[4] To date, the acceptors employed in this powerful type of strategy have been enones,[5] nitroalkenes,[6] and unsaturated imides.[7] Expansion of the scope of such an efficient strategy to other classes of Michael acceptors is a useful and challenging objective.

Herein, we report the development of the first asymmetric direct conjugate addition of 1,3-dicarbonyl compounds to

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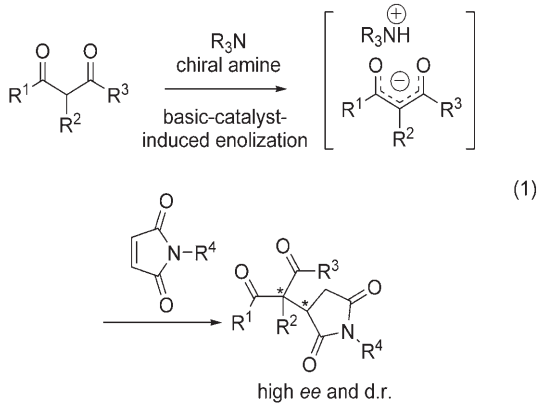
maleimides promoted by natural cinchona alkaloids as chiral-base catalysts.[8] The reaction affords highly functionalized products with two adjacent stereogenic carbon atoms, one of which is quaternary with only carbon-centered substituents [Eq. (1)]. This organocatalytic[9] approach affords high levels

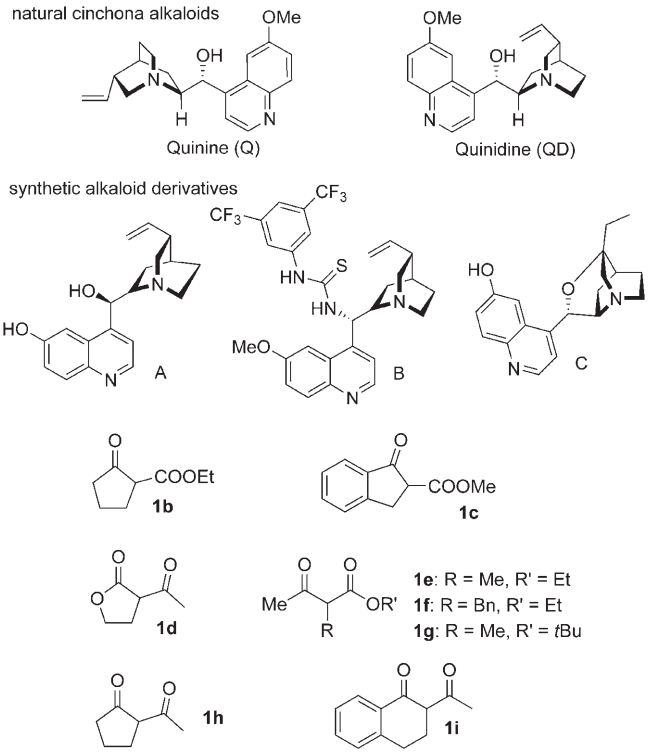


(1)

of both enantio- (up to 98% *ee*) and diastereoselectivity (d.r. = up to > 98:2) with both cyclic and acyclic β-ketoesters and with cyclic β-diketones. Furthermore, the strategy is based on an operationally simple procedure in which unmodified cheap and commercially available starting materials and catalysts are used.

The asymmetric conjugate addition of carbon-centered nucleophiles to maleimides should provide a practical route to synthetically and biologically important chiral α-substituted succinimides.[10] Therefore, it is surprising that, to our knowledge, just one effective asymmetric strategy has been described to date.[11] The feasibility of our organocatalytic asymmetric approach was first tested by mixing methyl-2-oxo-1-indanecarboxylate (**1a**) and maleimide (**2a**) in dichloromethane (0.5 M) in the presence of a catalytic amount of a cinchona alkaloid derivative (10 mol%); representative results of the extensive screen of reaction conditions using the alkaloids shown in Scheme 1 are listed in Table 1. The natural cinchona alkaloid quinine (Q) proved to be the most promising catalyst and afforded the 1,4-adduct with relatively good diastereo- and enantioselectivity (Table 1, entry 2). The synthetic cinchona alkaloid derivatives A and B, which are broadly effective bifunctional organocatalysts for several asymmetric C–C bond-forming reactions,[12] gave poor results (Table 1, entries 3 and 4). The rigid phenolic quinidine derivative β-isocupreidine (C; Scheme 1)[13] promoted the conjugate addition with satisfactory selectivity (Table 1, entry 5), but the results obtained when the reaction was performed at −20 °C indicated a significant difference between Q and C in terms of catalytic activity (Table 1, entries 6/7 and 8/9).

Next, we identified the nature of the substituent on the N atom of the maleimide as a critical parameter for the stereochemical outcome of the process (Table 1, entries 8, 10, and 11). The presence of a benzyl substituent had a dramatic impact on the enantioselectivity and, more importantly, on the diastereoselectivity: When the quinine-catalyzed reaction



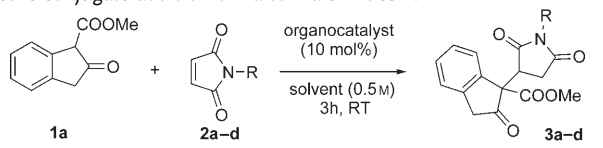
Scheme 1. Alkaloid catalysts and 1,3-dicarbonyl compounds **1b–1i** used in this study.

was performed at −20 °C in CH_2Cl_2, the product was isolated after 24 h in quantitative yield, with considerable preference shown for one of the two possible diastereomers (d.r. = 94:6) and with high enantioselectivity (92% *ee*; Table 1, entry 11). Importantly, the use of "pseudoenantiomeric" quinidine (QD) allowed access to the opposite enantiomer of the 1,4-adduct with similar selectivity (Table 1, entry 12). Further optimization of the reaction conditions revealed that apolar solvents favored optimal stereoselectivity (Table 1, entries 11–14); CH_2Cl_2 was selected as the solvent of choice for its ability to increase reactivity. The use of hydrogen-bond-accepting solvents led to a drastic decrease in stereoselectivity (Table 1, entries 15 and 16).

The result obtained by using benzoylquinine (BQ) as the catalyst (Table 1, entry 17) clearly demonstrated that the presence of the free hydroxy group on Q is essential for high levels of reactivity and selectivity. This experimental evidence, together with preliminary kinetic studies, which established a first-order rate dependence on the catalyst, nucleophile, and electrophile for the conjugate addition (see the Supporting Information for details), is consistent with an acid–base bifunctional mode of catalysis by quinine. Importantly, although the double-activation ability of natural cinchona alkaloids was established 25 years ago by the seminal studies of Hiemstra and Wynberg,[14] there have been no previous reports of a very stereoselective (> 90% *ee*) conjugate addition reaction catalyzed by these compounds.[15]

We then examined the generality of this new organocatalytic asymmetric strategy under the optimized reaction conditions. Experiments that probe the range of possible 1,3-

Table 1: Screening of reaction conditions for the organocatalytic asymmetric conjugate addition of **1a** to maleimides **2**.[a]



1a **2a–d** **3a–d**

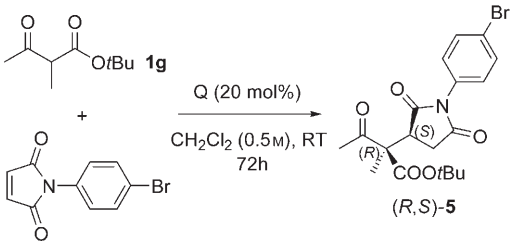
Entry	Catalyst	R	Solvent	Conversion [%][b]	3	d.r.[b]	*ee* [%][c]
1	–	H (**2a**)	CH_2Cl_2	0	**a**	–	–
2	Q	H (**2a**)	CH_2Cl_2	>95	**a**	74:26	69/28
3	A	H (**2a**)	CH_2Cl_2	30	**a**	77:23	14/17
4	B	H (**2a**)	CH_2Cl_2	65	**a**	75:25	33/34[d]
5	C	H (**2a**)	CH_2Cl_2	75	**a**	65:35	62/45
6[e]	Q	H (**2a**)	CH_2Cl_2	75	**a**	82:18	81/70
7[e]	C	H (**2a**)	CH_2Cl_2	25	**a**	75:25	74/–
8[e]	Q	Ph (**2b**)	CH_2Cl_2	>95	**b**	87:13	63/40
9[e]	C	Ph (**2b**)	CH_2Cl_2	13	**b**	70:30	–/–
10[e]	Q	*t*Bu(**2c**)	CH_2Cl_2	15	**c**	95:5	–/–
11[e]	Q	Bn (**2d**)	CH_2Cl_2	>95 (97)[f]	**d**	94:6	92/5
12[e]	QD	Bn (**2d**)	CH_2Cl_2	>95 (95)[f]	**d**	94:6	87/4[d]
13[e]	Q	Bn (**2d**)	toluene	80	**d**	95:5	92/6
14[e]	Q	Bn (**2d**)	THF	56	**d**	95:5	90/5
15[g]	Q	Bn (**2d**)	CH_3CN	>95	**d**	85:15	66/0
16[g]	Q	Bn (**2d**)	MeOH	>95	**d**	44:56	24/0
17	BQ	Bn (**2d**)	CH_2Cl_2	45	**d**	81:19	5/12

[a] The formulae of the catalysts can be found in Scheme 1. Experimental conditions (0.2-mmol scale): The reactions were carried out open to the air in undistilled solvent with a 1:1.2 ratio of **1a** to **2**. [b] Conversion and d.r. were determined by ^{1}H NMR spectroscopic analysis of the crude-product mixture. [c] Determined by HPLC analysis on commercially available chiral stationary phases; values for both diastereomers are given. [d] The opposite enantiomer was obtained. [e] Reaction time: 24 h, reaction temperature: −20 °C. [f] Number in parenthesis indicates the yield of the isolated product **3d**. [g] Reaction time: 16 h, reaction temperature: −20 °C.

dicarbonyl substrates are summarized in Table 2. Both enantiomers of the 1,4-adducts were synthesized efficiently with high selectivity by appropriate selection of the catalyst (Q or QD). The cyclic β-ketoesters **1b–d** were all converted into the corresponding 1,4-adducts in good yields and with very high levels of both diastereo- and enantioselectivity (Table 2, entries 1–6). The protocol also proved to be effective for acyclic β-ketoesters; the expected products were formed with high selectivity, although decreased reactivity was observed (Table 2, entries 7 and 8). Interestingly, we found that the size of the ester group had a significant effect on the stereoselectivity: the reaction of the acyclic *tert*-butyl ketoester **1g** occurred in a highly enantio- and diasteroselective fashion even at room temperature (92 % *ee*, d.r. = 92:8; Table 2, entry 9).[16] Outstanding results were obtained with β-diketones (Table 2, entries 10–13), a particularly challenging class of substrates, for which, to our knowledge, just two examples of effective asymmetric organocatalytic conjugate addition have been reported.[17]

As the conjugate addition products **4** are generally solid substances, it is possible to obtain a single stereoisomer in essentially enantiomerically pure form after a single crystallization, as demonstrated for adducts **4c** and **4d** (Table 2, entries 4 and 6).

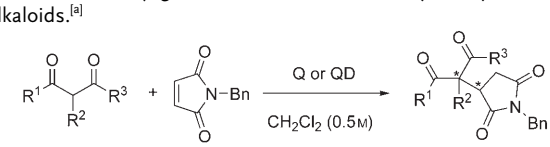
The absolute configuration of compound **5**, generated by the quinine-catalyzed addition of **1g** to *N*-(4-bromophenyl)-maleimide [Eq. (2)], was assigned by X-ray crystallographic



analysis.[18] The relative configuration of **4d** was determined unequivocally by X-ray crystallographic analysis,[18] whereas the relative configurations of **4b** and **4h** were assigned by NMR spectroscopic analysis with extensive NOE interaction studies (see the Supporting Information for details).

The synthetic utility of our organocatalytic approach was evaluated by a gram-scale experiment (10 mmol), which gave

Table 2: Highly stereoselective conjugate addition of 1,3-dicarbonyl compounds **1** to **2d** catalyzed by natural cinchona alkaloids.[a]

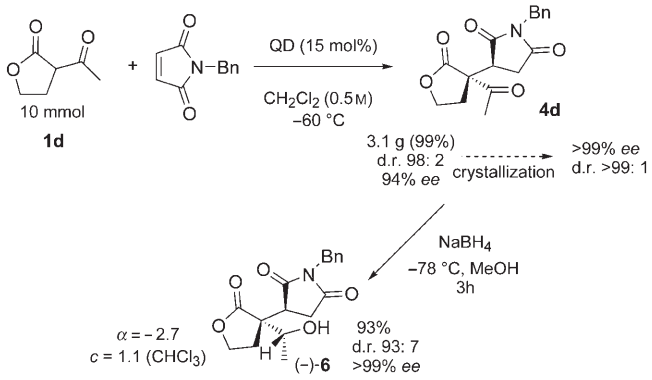


1b–i **2d** **4b–i**

Entry	1/4	Cat.	(mol %)[b]	*T* [°C]	*t* [h]	Yield [%][c]	d.r.[d]	*ee* [%][e]
1	**b**	Q	(10)	−30	24	99	84:16	94
2	**b**	QD	(10)	−60	40	99	87:13	98
3	**c**	Q	(10)	−60	38	98	91:9	94
4	**c**	QD	(10)	−60	38	99	90:10	95 (>99[f])
5	**d**	Q	(15)	−60	40	99	>98:2	89
6	**d**	QD	(15)	−60	40	91	>98:2	93 (>99[f])
7	**e**	QD	(20)	−15	50	52 (55)	93:7	85
8	**f**	QD	(20)	−15	88	63 (65)	77:23	85
9	**g**	Q	(20)	RT	72	75 (78)	92:8	92
10	**h**	Q	(15)	−30	24	72 (80)	92:8	82
11	**h**	QD	(15)	−60	40	99	92:8	91
12	**i**	Q	(20)	−15	48	55 (58)	95:5	82
13	**i**	QD (20)	−30	66	72 (75)	95:5	84	

[a] The formulae of **1b–1i** can be found in Scheme 1. Experimental conditions (0.2-mmol scale): The reactions were carried out open to the air in undistilled dichloromethane with a 1:1.2 ratio of **1** to **2d**. [b] The catalysts Q and QD gave opposite enantiomers of the product diastereomer. [c] Yield of the isolated products **4**. Numbers in parenthesis indicates reaction conversion, as determined by ^{1}H NMR spectroscopic analysis. [d] Determined by ^{1}H NMR spectroscopic analysis of the crude-product mixture. [e] Determined by HPLC analysis on commercially available chiral stationary phases; values for the major diastereomer are given. For the *ee* values of minor diastereomers, see the Supporting Information. [f] After a single crystallization.

4d in quantitative yield (Scheme 2). A single crystallization from an EtOH/Et_2O mixture afforded the optically pure product. Subsequent highly stereo- and chemoselective reduction of the keto group allowed access to compound (−)-**6**, which has three consecutive stereogenic centers of defined absolute configuration.[19]



Scheme 2. Stereo- and chemoselective synthesis and reduction of **4d**.

In summary, we have developed an operationally simple protocol that employs unmodified and commercially available materials and catalysts for the first asymmetric organocatalytic conjugate addition of 1,3-dicarbonyl compounds to maleimides. The enantioselectivity of the reaction is the highest reported to date for this class of Michael acceptors. Natural cinchona alkaloids proved to be highly efficient catalysts. They promoted the one-step construction of functionalized products with two adjacent stereogenic carbon atoms with very high diastereo- and enantioselectivity. Investigations are currently underway toward a mechanistic understanding of the process and fully defining its utility as a synthetic tool in asymmetric synthesis.

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[1] For reviews on the asymmetric construction of quaternary carbon centers, see: a) C. J. Douglas, L. E. Overman, *Proc. Natl. Acad. Sci. USA* **2004**, *101*, 5363, and references therein; b) J. Christoffers, A. Baro, *Angew. Chem.* **2003**, *115*, 1726; *Angew. Chem. Int. Ed.* **2003**, *42*, 1688; c) E. J. Corey, A. Guzman-Perez, *Angew. Chem.* **1998**, *110*, 402; *Angew. Chem. Int. Ed.* **1998**, *37*, 388.

[2] For some leading examples that rely on different strategies, see: a) F. Wu, H. Li, R. Hong, L. Deng, *Angew. Chem.* **2006**, *118*, 961; *Angew. Chem. Int. Ed.* **2006**, *45*, 947; b) B. K. Corkey, F. D. Toste, *J. Am. Chem. Soc.* **2005**, *127*, 17168; c) P. Mauleòn, J. C. Carretero, *Chem. Commun.* **2005**, 4961; d) M. D. Augustin, L. Palais, A. Alexakis, *Angew. Chem.* **2005**, *117*, 1400; *Angew. Chem. Int. Ed.* **2005**, *44*, 1376; e) A. W. Hird, A. H. Hoveyda, *J. Am. Chem. Soc.* **2005**, *127*, 14988.

[3] For recent reviews on catalytic asymmetric conjugate additions, see: a) T. Hayashi, K. Yamasaki, *Chem. Rev.* **2003**, *103*, 2829; b) N. Krause, A. Hoffmann-Röder, *Synthesis* **2001**, 171.

[4] For the catalytic asymmetric construction of adjacent tertiary and quaternary centers, see: a) T. B. Poulsen, C. Alemparte, S. Saaby, M. Bella, K. A. Jørgensen, *Angew. Chem.* **2005**, *117*, 2956; *Angew. Chem. Int. Ed.* **2005**, *44*, 2896; b) J. F. Austin, S.-G. Kim, C. J. Sinz, W.-J. Xiao, D. W. C. MacMillan, *Proc. Natl. Acad. Sci. USA* **2004**, *101*, 5482.

[5] a) M. S. Taylor, D. N. Zalatan, A. M. Lerchner, E. N. Jacobsen, *J. Am. Chem. Soc.* **2005**, *127*, 1313; b) Y. Hamashima, D. Hotta, M. Sodeoka, *J. Am. Chem. Soc.* **2002**, *124*, 11240; see also reference [2a].

[6] H. Li, Y. Wang, L. Tang, F. Wu, X. Liu, C. Guo, B. M. Foxman, L. Deng, *Angew. Chem.* **2005**, *117*, 107; *Angew. Chem. Int. Ed.* **2005**, *44*, 105.

[7] M. S. Taylor, E. N. Jacobsen, *J. Am. Chem. Soc.* **2003**, *125*, 11204.

[8] For recent examples of the use of cinchona alkaloid derivatives as efficient chiral-base catalysts, see: a) S. Sobhani, D. Fielenbach, M. Marigo, T. C. Wabnitz, K. A. Jørgensen, *Chem. Eur. J.* **2005**, *11*, 5689; b) G. Bartoli, M. Bosco, A. Carlone, M. Locatelli, P. Melchiorre, L. Sambri, *Angew. Chem.* **2005**, *117*, 6375; *Angew. Chem. Int. Ed.* **2005**, *44*, 6219; for a recent review, see: c) S.-K. Tian, Y. Chen, J. Hang, L. Tang, P. McDaid, L. Deng, *Acc. Chem. Res.* **2004**, *37*, 621.

[9] For general reviews on organocatalysis, see: a) *Asymmetric Organocatalysis* (Eds.: A. Berkessel, H. Gröger), Wiley-VCH, Weinheim, **2004**; b) *Acc. Chem. Res.* **2004**, *37*(8), special issue (Eds.: K. N. Houk, B. List); c) P. I. Dalko, L. Moisan, *Angew. Chem.* **2004**, *116*, 5248; *Angew. Chem. Int. Ed.* **2004**, *43*, 5138.

[10] For some biological studies on enantioenriched α-substituted succinimides, see: a) S. Ahmed, *Drug Des. Discovery* **1996**, *14*, 77; b) M. L. Curtin, R. B. Garland, H. R. Heyman, R. R. Frey, M. R. Michaelides, J. Li, L. J. Pease, K. B. Glaser, P. A. Marcotte, S. K. Davidsen, *Bioorg. Med. Chem. Lett.* **2002**, *12*, 2919; for the synthetic derivatization of this useful scaffold to afford functionalized open-chain derivatives and substituted pyrrolidines, see: c) A. R. Katritzky, J. Yao, M. Qi, Y. Chou, D. J. Sikora, S. Davis, *Heterocycles* **1998**, *48*, 2677; d) R. Ballini, G. Bosica, G. Cioci, D. Fiorini, M. Petrini, *Tetrahedron* **2003**, *59*, 3603.

[11] a) R. Shintani, W.-L. Duan, T. Nagano, A. Okada, T. Hayashi, *Angew. Chem.* **2005**, *117*, 4687; *Angew. Chem. Int. Ed.* **2005**, *44*, 4611; b) R. Shintani, K. Ueyama, I. Yamada, T. Hayashi, *Org. Lett.* **2004**, *6*, 3425. After our manuscript had been submitted, the use of the same strategy for asymmetric addition to substituted maleimides to afford quaternary stereocenters was reported: c) R. Shintani, W.-L. Duan, T. Hayashi, *J. Am. Chem. Soc.* **2006**, *128*, 5628.

[12] For selected examples, see: a) B. Vakulya, Sz. Varga, A. Csámpai, T. Soos, *Org. Lett.* **2005**, *7*, 1967; b) S. H. McCooey, S. J. Connon, *Angew. Chem.* **2005**, *117*, 6525; *Angew. Chem. Int. Ed.* **2005**, *44*, 6367; c) Y. Wang, X. Liu, L. Deng, *J. Am. Chem. Soc.* **2006**, *128*, 3928.

[13] a) Y. Iwabuchi, M. Nakatani, N. Yokoyama, S. Hatakeyama, *J. Am. Chem. Soc.* **1999**, *121*, 10219; b) S. Kawahara, A. Nakano, T. Esumi, Y. Iwabuchi, S. Hatakeyama, *Org. Lett.* **2003**, *5*, 3103.

[14] a) H. Hiemstra, H. Wynberg, *J. Am. Chem. Soc.* **1981**, *103*, 417; b) H. Wynberg, *Top. Stereochem.* **1986**, *16*, 87.

[15] For quinine-catalyzed conjugate additions of carbon-centered nucleophiles with low selectivity, see: a) H. Wynberg, R. Helder, *Tetrahedron Lett.* **1975**, *16*, 4057; b) G. Szöllösi, M. Bartók, *Chirality* **2001**, *13*, 614; for a review, see: c) K. Kacprzak, J. Gawroñsky, *Synthesis* **2001**, 961; during our studies, two highly selective reactions catalyzed by natural cinchona alkaloids were reported: d) B. Török, M. Abid, G. London, J. Esquibel, M. Török, S. C. Mhadgut, P. Yan, G. K. S. Prakash, *Angew. Chem.* **2005**, *117*, 3146; *Angew. Chem. Int. Ed.* **2005**, *44*, 3086; e) S. Lou,

B. M. Taoka, A. Ting, S. E. Schaus, *J. Am. Chem. Soc.* **2005**, *127*, 11256.
[16] For similar effects of the size of the ester group on the selectivity of organocatalytic asymmetric transformations, see references [2a] and [8a].
[17] M. Bella, K. A. Jørgensen, *J. Am. Chem. Soc.* **2004**, *126*, 5672; see also reference [6].
[18] Compound **5**, obtained in 65% yield, 85% *ee*, and d.r. = 96:4, was crystallized slowly from a mixture of hexane/Et_2O to give fine colorless needles of a single diastereomer with the configuration shown in Equation (2). The same crystal used for X-ray crystallography was analyzed by chiral HPLC, which confirmed the presence of the major enantiomer. CCDC-296418 (**5**) and -605040 (**4d**) contain 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/data_request/cif.
[19] The relative configuration of **6** was assigned by using NMR spectroscopic analysis with extensive NOE interaction studies; see the Supporting Information for details.

