

Highly Diastereodivergent Synthesis of Tetrasubstituted Cyclohexanes Catalyzed by Modularly Designed Organocatalysts**

Nirmal K. Rana, Huicai Huang, and John C.-G. Zhao*

Abstract: A highly diastereodivergent synthesis of tetrasubstituted cyclohexanes has been achieved using modularly designed organocatalysts (MDOs) which are self-assembled *in situ* from amino acids and cinchona alkaloid derivatives. Diastereodivergence is realized through controlling the stereoselectivity of the individual steps of a tandem Michael/Michael reaction. Up to 8 of the 16 possible stereoisomers have been successfully obtained in high stereoselectivities using MDOs for the tandem reaction and an ensuing epimerization. The method was used in the enantioselective synthesis of the natural products (–)- α - and β -lycoranes.

With the advent of novel methods based on metal catalysis, biocatalysis, and organocatalysis, individual enantiomers of many organic compounds can now be routinely obtained in high enantiopurity.^[1] Nonetheless, despite the great progress made on asymmetric catalysis in the past decades, for compounds containing multiple stereogenic centers, it still remains a great challenge to freely access all the possible stereoisomers from the same starting materials with high stereocontrol. Previously, diastereodivergence has been achieved by changing the solvent,^[2] using different chiral catalysts,^[3] or adding additives.^[4] MacMillan and co-workers also developed cycle-specific organocatalysis to achieve diastereodivergence by employing two different chiral amine catalysts in a sequential reaction with separate iminium and enamine activation.^[5] Most recently, Carreira and co-workers demonstrated an elegant synthesis of all four stereoisomers of α -allyl aldehydes using dual catalysis which involves amine and iridium activations.^[6]

The tandem reaction is a highly efficient way for assembling complex molecules with multiple stereogenic centers from relatively simple starting materials.^[7] We envisioned that, if the stereochemistry of the individual steps of a tandem reaction could be separately controlled by different moieties of the catalyst, diastereodivergence would be achieved with diastereomeric catalysts. Theoretically, multiple diastereomers of a compound with more than two stereogenic centers can be accessed using this novel approach. Unfortunately, to

obtain conventional diastereomeric catalysts separate syntheses are required, and therefore are tedious and time consuming.

Recently there has been growing interest in applying self-assembled organocatalysts^[8,9] in asymmetric catalyses.^[10] Previously we demonstrated that modularly designed organocatalysts (MDOs),^[11] self-assembled from amino acids and cinchona alkaloid thiourea derivatives, are highly efficient catalysts for Michael, hetero-Diels–Alder, aldol, and Mannich reactions. Both the amino acid and the cinchona alkaloid thiourea modules of the MDO play an important role in the stereocontrol in these reactions.^[11] Since quinidine thiourea (QDT) and quinine thiourea (QNT) are pseudoenantiomeric (Figure 1), the MDOs self-assembled from QDT and QNT

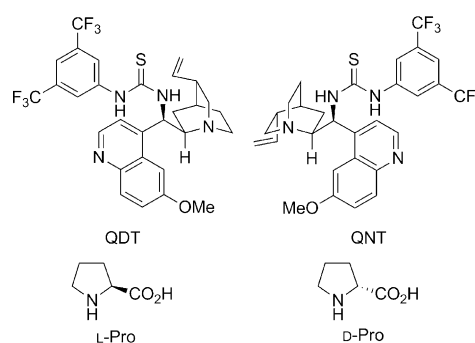


Figure 1. Structures of selected precatalyst modules.

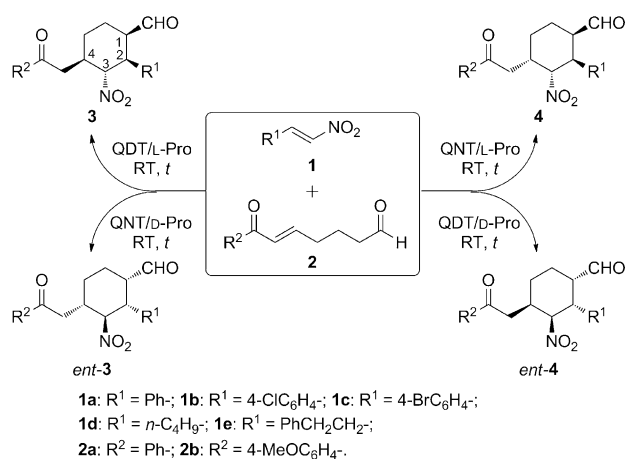
and a given enantiomer of proline (i.e., L-Pro or D-Pro, Figure 1) are pseudodiastereomeric. Thus, it is very convenient to obtain pseudodiastereomeric catalysts in this way. Ideally, if the individual steps of a tandem reaction are separately controlled by these two modules, then diastereodivergence should be achieved. Herein we report that up to 8 of the 16 possible stereoisomers of tetrasubstituted cyclohexanes^[12] may be synthesized from the same substrates in high diastereo- and enantioselectivities using MDOs self-assembled from both enantiomers of Pro and the cinchona alkaloid thiourea derivatives QDT and QNT (Figure 1), through a diastereodivergent tandem Michael/Michael reaction coupled with an epimerization.

To test our hypothesis, we designed a tandem Michael/Michael reaction between the nitroalkenes **1** and compounds **2** (Scheme 1). The substrates were so chosen that the first intermolecular Michael reaction would involve amine catalysis via an enamine intermediate^[13] and the second intramolecular Michael reaction would be catalyzed by the thiourea moiety through noncovalent catalysis.^[14] Using

[*] Dr. N. K. Rana, Dr. H. Huang, Prof. Dr. J. C.-G. Zhao
Department of Chemistry, University of Texas at San Antonio
One UTSA Circle, San Antonio, TX 78249-0698 (USA)
E-mail: cong.zhao@utsa.edu

[**] This work was financially supported by the Welch Foundation (Grant No. AX-1593) and partially by the NSF (Grant No. CHE 0909954). We thank Dr. Hadi Arman for the assistance with the X-ray crystallographic analysis of the reaction products.

Supporting information for this article is available on the WWW under <http://dx.doi.org/10.1002/anie.201404072>.



Scheme 1. MDO for the synthesis of four 1,2-*syn* diastereomers of tetrasubstituted cyclohexanes from common substrates.

trans-β-nitrostyrene (**1a**, R¹ = Ph) and the compound **2a** (R² = Ph) as the model substrates, we first screened the MDOs self-assembled from proline and cinchona alkaloid thioureas for their ability to achieve the desired diastereodivergence.^[15] Indeed, the MDO of QDT/L-Pro and its pseudodiastereomer QNT/L-Pro led to the formation of different diastereomers (Scheme 1).

Through careful screening (see Tables S1 and S2 in the Supporting Information),^[15] we eventually found that L-Pro and D-Pro are the best reaction-center modules^[11] and that QDT and QNT are the best stereocontrolling modules^[11] for this reaction. As summarized in Table 1 and Scheme 1, under the optimized reaction conditions, the MDO of QDT/L-Pro led to the formation the major *syn,anti,anti*-product **3a** in toluene at room temperature (Scheme 1, upper left), whereas the pseudodiastereomeric MDO of QNT/L-Pro led to the formation of the major *syn,anti,syn*-product **4a** (Scheme 1, upper right). The enantiomers of these two compounds (*ent*-**3a** and *ent*-**4a**) may be obtained by using the pseudoenantiomers of these two catalysts, QNT/D-Pro and QDT/D-Pro, respectively (Scheme 1, lower left and right). While all these MDOs lead to 1,2-*syn* compounds as the major products, they differ in the stereochemical outcome at C3/C4. In contrast, the *trans*-configuration of β-nitrostyrene is completely retained in these four products. The diastereoselectivities at C1/C2 (1,2-*syn*/1,2-*anti*) are around 80:20, where in the major products the diastereoselectivities at C3/C4 are no less than 92:8. Most importantly, all of the major diastereomeric products were obtained essentially as a pure enantiomer (≥ 99% *ee*) in good yields (Table 1, entries 1–4). Control experiments indicate that the present catalysis is not a cycle-specific process since both of the two MDO modules are important for the observed reactivity and stereoselectivities in each of the two individual Michael steps (see the control experiments in Scheme S3).^[15] Similar results were also obtained for 4-chloro- (R¹ = 4-ClC₆H₄; **1b**) and 4-bromo-substituted (R¹ = 4-BrC₆H₄; **1c**) *trans*-β-nitrostyrenes, except that slightly higher 1,2-*syn*/1,2-*anti* diastereoselectivities were obtained in these cases (entries 5–12). When an aliphatic *trans*-1-nitrohex-1-ene (R¹ = *n*-C₄H₉; **1d**) was used as the substrate, only the 1,2-*syn*-

Table 1: Synthesis of four 1,2-*syn* diastereomers of cyclohexanes using MDOs.^[a]

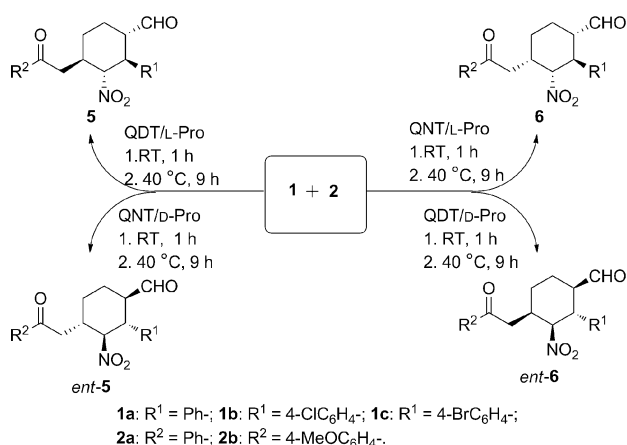
Entry	1	2	d.r. ^[b]		3 or 4	Yield [%] ^[c]	<i>ee</i> [%] ^[d]
			1,2- <i>syn</i> / <i>anti</i>	3/4			
1 ^[e]	1a	2a	80:20	96:4	3a	73	> 99
2 ^[f]	1a	2a	82:18	6:94	4a	72	> 99
3 ^[g]	1a	2a	82:18	92:8	<i>ent</i> - 3a	74	> 99
4 ^[h]	1a	2a	80:20	5:95	<i>ent</i> - 4a	72	> 99
5 ^[e]	1b	2a	84:16	94:6	3b	79	> 99
6 ^[f]	1b	2a	90:10	10:90	4b	83	> 99
7 ^[g]	1b	2a	87:13	93:7	<i>ent</i> - 3b	80	> 99
8 ^[h]	1b	2a	85:15	8:92	<i>ent</i> - 4b	80	> 99
9 ^[e]	1c	2a	86:14	93:7	3c	77	> 99
10 ^[f]	1c	2a	88:12	7:93	4c	80	> 99
11 ^[g]	1c	2a	88:12	92:8	<i>ent</i> - 3c	79	> 99
12 ^[h]	1c	2a	91:9	8:92	<i>ent</i> - 4c	82	> 99
13 ^[e,i]	1d	2a	> 99:1	95:5	3d	90	> 99
14 ^[f,i]	1d	2a	> 99:1	6:94	4d	92	> 99
15 ^[g,i]	1d	2a	> 99:1	94:6	<i>ent</i> - 3d	92	> 99
16 ^[h,i]	1d	2a	> 99:1	5:95	<i>ent</i> - 4d	91	> 99
17 ^[e,i]	1e	2a	> 99:1	91:9	3e	92	> 99
18 ^[f,i]	1e	2a	> 99:1	10:90	4e	90	> 99
19 ^[g,i]	1e	2a	> 99:1	92:8	<i>ent</i> - 3e	81	> 99
20 ^[h,i]	1e	2a	> 99:1	7:93	<i>ent</i> - 4e	92	> 99
21 ^[e]	1c	2b	85:15	95:5	3f	79	> 99
22 ^[f]	1c	2b	86:14	4:96	4f	79	> 99
23 ^[g]	1c	2b	85:15	94:6	<i>ent</i> - 3f	78	> 99
24 ^[h]	1c	2b	87:13	8:92	<i>ent</i> - 4f	81	> 99

[a] Unless otherwise indicated, all reactions were conducted with **1** (0.22 mmol), **2** (0.20 mmol), and 10 mol% (0.020 mmol) of each of the two precatalyst modules in toluene (1.0 mL) at RT for 1 h. [b] Determined by ¹H NMR analysis of the crude reaction mixture. [c] Combined yield of both diastereomers (**3** and **4**) after column chromatography. [d] Determined by HPLC analysis on the corresponding reduced alcohol using a chiral stationary phase. [e] With the catalyst QDT/L-Pro (**A**). [f] With the catalyst QNT/L-Pro (**B**). [g] With the catalyst QNT/D-Pro (**C**). [h] With the catalyst QDT/D-Pro (**D**). [i] The reaction time was 2 h.

diastereomers were formed (1,2-*syn*/1,2-*anti* > 99:1 in all cases), whereas the diastereoselectivities at C3/C4 and the *ee* values of these four diastereomers remain excellent (entries 13–16). Similar results were also obtained for the products of 2-phenylethyl-substituted nitroalkene **1e** (entries 17–20). As expected, when **1c** and **2b** (R² = 4-MeOC₆H₄) were used as the substrates, similar results to those listed in entries 1–12 were obtained (entries 21–24).

During the catalyst screening, we also noticed that the formyl-substituted C1 stereogenic center in **3a** and **4a** is prone to epimerization under the reaction conditions. Actually this is the competing process which leads to the lower 1,2-*syn* diastereoselectivities observed for the 2-aryl-substituted products (i.e., **3a–c**, **f** and **4a–c**, **f**) compared to those of the 2-alkyl-substituted ones (i.e., **3d–e** and **4d–e**). Although this property is undesirable for obtaining the 1,2-*syn*-diastereomers, we realized that it could be utilized to access the 1,2-*anti* diastereomers, which were formed only as minor products in the tandem reactions.^[16]

After some optimization, we found that, by conducting the reaction at room temperature first and then elevating the reaction temperature to 40 °C for 9 hours, all the 1,2-*syn*-diastereomers could be completely converted into the corresponding 1,2-*anti* diastereomers. As shown in Scheme 2



Scheme 2. MDO for the synthesis of four 1,2-*anti* diastereomers.

(upper left and right), in this way, the diastereomers **5** and **6** were readily obtained from the MDOs which lead to the formation of **3** and **4**, respectively. Similarly, their enantiomers could be obtained from the reactions that form *ent*-**3** and *ent*-**4**, respectively (Scheme 2, lower left and right). As the data in Table 2 show, pure 1,2-*anti* diastereomers (1,2-*anti*/1,2-*syn* > 99:1) were obtained in excellent yields, while the original diastereoselectivities at C3/C4 and the product *ee* values were not affected (entries 1–4). Similarly, the 2-aryl-substituted **3b**, **3c**, **4b**, **4c**, **3f**, and **4f** were by completely converted in situ into their corresponding 1,2-*anti* diastereomers (1,2-*anti*/*syn* > 99:1) using the respective MDOs under similar reaction conditions, without affecting the d.r. at C3/C4 and the product *ee* values (entries 5–16). In contrast, the 2-alkyl-substituted **3d**, **4d**, **3e**, and **4e** (Scheme 1) are much less

Table 2: Synthesis of the 1,2-*anti* diastereomers using MDOs.^[a]

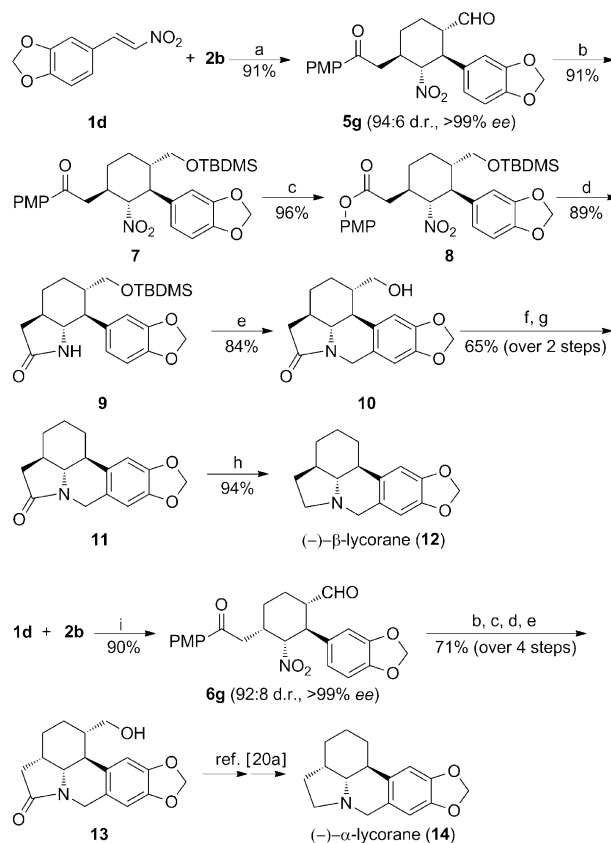
Entry	1	2	Cat. ^[b]	d.r. ^[c] 3,4- <i>anti</i> / <i>syn</i>	5 or 6	Yield [%] ^[d]	<i>ee</i> [%] ^[e]
1	1a	2a	A	96:4	5a	94	99
2	1a	2a	B	6:94	6a	93	99
3	1a	2a	C	92:8	<i>ent</i> -5a	93	99
4	1a	2a	D	5:95	<i>ent</i> -6a	93	99
5	1b	2a	A	94:6	5b	93	> 99
6	1b	2a	B	10:90	6b	91	> 99
7	1b	2a	C	93:7	<i>ent</i> -5b	94	> 99
8	1b	2a	D	8:92	<i>ent</i> -6b	92	> 99
9	1c	2a	A	93:7	5c	92	> 99
10	1c	2a	B	7:93	6c	94	> 99
11	1c	2a	C	92:8	<i>ent</i> -5c	93	> 99
12	1c	2a	D	8:92	<i>ent</i> -6c	94	> 99
13	1c	2b	A	95:5	5f	90	> 99
14	1c	2b	B	96:4	6f	91	> 99
15	1c	2b	C	6:94	<i>ent</i> -5f	92	> 99
16	1c	2b	D	8:92	<i>ent</i> -6f	92	> 99

[a] The reactions were first conducted at RT as described in Table 1 and then continued at 40 °C for 9 h. [b] Catalysts: **A**: QDT/L-Pro; **B**: QNT/L-Pro; **C**: QNT/d-Pro; **D**: QDT/d-Pro. [c] Determined by ¹H NMR analysis of the crude products; 1,2-*anti*/1,2-*syn* > 99:1 in all cases. [d] Combined yield of both diastereomers (**5** and **6**) after column chromatography. [e] Determined by HPLC analysis on the corresponding reduced alcohol using a chiral stationary phase.

prone to this epimerization process and the in situ epimerization with the MDOs is very slow even at elevated temperature. Instead, these compounds may be isolated from the tandem reactions using the MDOs (Table 1) and then epimerized using the pyrrolidine/acetic acid combination as the catalyst at 40 °C. When the reaction finally reaches equilibrium (5 h), a 1,2-*anti*/*syn* ratio around 80:20 may be achieved without affecting the original d.r. at C3/C4 and the product *ee* values (see Table S4).^[15]

The relative and absolute configurations of the cyclohexane derivatives obtained in this study were determined by NOE experiments (using compounds **3a**, *ent*-**4a**, **5a**) and X-ray crystallography of the compounds **3c**, the reduced *ent*-**5a**, and a tosylate derivative of the reduced *ent*-**6c** (see Figure S2–S4).^[15]

The lycorane-type alkaloids are natural products possessing many biological activities.^[17] Therefore, considerable effort has been made towards the total synthesis of these alkaloids. However, most of the syntheses yield racemic



Scheme 3. Enantioselective total synthesis of (–)-β-lycorane and formal total synthesis of (–)-α-lycorane. Reaction conditions: a) QDT/L-Pro (10 mol %), toluene, RT, 4 h, then 40 °C, 10 h; b) 1. NaBH₄, CH₂Cl₂/EtOH (5:1, v/v), –78 °C, 2.5 h; 2. TBDMSCl, DMAP, imidazole, DMF, RT, 18 h; c) mCPBA, NaHCO₃, CH₂Cl₂, RT, 48 h; d) NaBH₄, NiCl₂·6H₂O, MeOH, 0 °C to RT, 18 h; e) (CH₂O)_n, TFA, CH₂Cl₂, RT, 18 h; f) PCC, CH₂Cl₂, RT, 3 h; g) [Rh(PPh₃)₃Cl], benzonitrile, reflux, 18 h; h) LiAlH₄, THF, reflux, 18 h; i) QNT/L-Pro (10 mol %), toluene, RT, 4 h, then 40 °C, 10 h. DMAP = 4-(N,N-dimethylamino)pyridine, DMF = N,N-dimethylformamide, mCPBA = meta-chloroperoxybenzoic acid, PMP = para-methoxyphenyl, TBDMS = tert-butyldimethylsilyl, TFA = trifluoroacetic acid.

lycoranes.^[18] The asymmetric syntheses of β -lycorane^[19] and α -lycorane^[19b,20] are limited. To show the synthetic utility of this novel diastereodivergent catalysis, we applied our method to the facile enantioselective synthesis of (–)- β -lycorane (**12**) and a formal synthesis of (–)- α -lycorane (**14**) from the same substrates, **1d** and **2b**, and using QDT/L-Pro and QNT/L-Pro as the catalyst, respectively (Scheme 3). As shown in Scheme 3, both (–)- β -lycorane and the key precursor^[20a] to (–)- α -lycorane were obtained in good overall yields.

In summary, we have developed a conceptually different approach to achieve diastereodivergence through controlling stereochemistry of the individual steps of a tandem reaction using pseudodiastereomeric MDOs self-assembled from proline and cinchona alkaloid thioureas. Up to eight stereoisomers of tetrasubstituted cyclohexane derivatives may be readily obtained in high diastereoselectivities and excellent enantioselectivities using a MDOs for a tandem Michael/Michael addition and an ensuing epimerization. The method may be used in the enantioselective synthesis of natural products α - and β -lycoranes. Application of this method in the diastereodivergent synthesis of other functional molecules is currently underway.

Experimental Section

General procedure for the synthesis of 1,2-*syn* products **3** and **4**: The precatalyst module QDT (11.9 mg, 0.020 mmol, 10.0 mol %), L-Pro (2.3 mg, 0.020 mmol, 10.0 mol %), and dry toluene (1.0 mL) were added to a vial sequentially. The resulting mixture was stirred at room temperature for 15 min. (*E*)-7-Oxo-7-phenylhept-5-enal (**2a**, 40.5 mg, 0.20 mmol) was then added and the mixture was stirred for 5 min before the addition of the *trans*-nitroalkene **1** (0.22 mmol). The reaction mixture was stirred at RT for the time as specified in Table 1 (monitored by TLC). Upon the completion of the reaction, diastereomeric ratio was determined by ¹H NMR analysis of the crude reaction mixture. Then the mixture was purified by flash column chromatography (EtOAc/hexanes 1:1, v/v as the eluent) to obtain **3**. The enantiomeric excess was determined after converting the aldehyde into the corresponding alcohol.

General procedure for the synthesis of 1,2-*anti* products **5** and **6**: The reaction was set up exactly as described above for the 1,2-*syn* products, except that the reaction mixture was first stirred at RT for 1 h and then at 40 °C for 9 h. Diastereomeric ratio at this stage was determined by the ¹H NMR analysis of the crude reaction mixture. Then the mixture was purified by flash column chromatography (EtOAc/hexanes 1:1, v/v as the eluent) to obtain **5**. Enantiomeric excess was determined after converting the aldehyde into the corresponding alcohol.

Received: April 7, 2014

Published online: June 12, 2014

Keywords: carbocycles · cyclization · diastereoselectivity · organocatalysis · synthetic methods

[1] *Comprehensive Asymmetric Catalysis I–III, Suppl. I–II* (Eds.: E. N. Jacobsen, A. Pfaltz, H. Yamamoto), Springer, New York, 1999.

[2] M. Morgen, S. Bretzke, P. Li, D. Menche, *Org. Lett.* **2010**, *12*, 4494–4497.

- [3] a) B. Wang, F. Wu, Y. Wang, X. Liu, L. Deng, *J. Am. Chem. Soc.* **2007**, *129*, 768–769; b) X.-X. Yan, Q. Peng, Q. Li, K. Zhang, J. Yao, X.-L. Hou, Y.-D. Wu, *J. Am. Chem. Soc.* **2008**, *130*, 14362–14363; c) P.-O. Delaye, D. Didier, I. Marek, *Angew. Chem.* **2013**, *125*, 5441–5445; *Angew. Chem. Int. Ed.* **2013**, *52*, 5333–5337; d) X. Feng, Z. Zhou, R. Zhou, Q.-Q. Zhou, L. Dong, Y.-C. Chen, *J. Am. Chem. Soc.* **2012**, *134*, 19942–19947; e) Y. Chi, S. T. Scroggins, J. M. J. Fréchet, *J. Am. Chem. Soc.* **2008**, *130*, 6223–6323; f) Y. Wang, R.-G. Han, Y.-L. Zhao, S. Yang, P.-F. Xu, D. J. Dixon, *Angew. Chem.* **2009**, *121*, 10018–10022; *Angew. Chem. Int. Ed.* **2009**, *48*, 9834–9838.
- [4] a) E. L. McInturff, E. Yamaguchi, M. J. Krische, *J. Am. Chem. Soc.* **2012**, *134*, 20628–20631; b) X. Tian, C. Cassani, Y. Liu, A. Moran, A. Urakawa, P. Galzerano, E. Arceo, P. Melchiorre, *J. Am. Chem. Soc.* **2011**, *133*, 17934–17941; c) G. Ma, S. Lin, I. Ibrahim, G. Kubik, L. Liu, J. Sun, A. Córdova, *Adv. Synth. Catal.* **2012**, *354*, 2865–2872; d) Y. Chi, S. T. Scroggins, J. M. J. Fréchet, *J. Am. Chem. Soc.* **2008**, *130*, 6322–6323; e) T. Hameury, J. Guillemon, L. Van Hijfte, V. Bellosta, J. Cossy, *Org. Lett.* **2009**, *11*, 2397–2400.
- [5] a) Y. Huang, A. M. Walji, C. H. Larsen, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2005**, *127*, 15051–15053; b) B. Simmons, A. M. Walji, D. W. C. MacMillan, *Angew. Chem.* **2009**, *121*, 4413–4417; *Angew. Chem. Int. Ed.* **2009**, *48*, 4349–4353.
- [6] S. Krautwald, D. Sarlah, M. A. Schafröth, E. M. Carreira, *Science* **2013**, *340*, 1065–1068.
- [7] For reviews, see: a) L. F. Tietze, *Chem. Rev.* **1996**, *96*, 115–136; b) C. Grondal, M. Jeanty, D. Enders, *Nat. Chem.* **2010**, *2*, 167–178.
- [8] For some selected examples, see: a) M. L. Clarke, J. A. Fuentes, *Angew. Chem.* **2007**, *119*, 948–951; *Angew. Chem. Int. Ed.* **2007**, *46*, 930–933; b) D. Uraguchi, Y. Ueki, T. Ooi, *Science* **2009**, *326*, 120–123; c) N. El-Hamdouni, X. Companyó, R. Rios, A. Moyano, *Chem. Eur. J.* **2010**, *16*, 1142–1148; d) A.-B. Xia, D.-Q. Xu, S.-P. Luo, J.-R. Jiang, J. Tang, Y.-F. Wang, Z.-Y. Xu, *Chem. Eur. J.* **2010**, *16*, 801–804; e) T. C. Nugent, A. Sadiq, A. Bibi, T. Heine, L. L. Zeonjuk, N. Vankova, B. S. Bassil, *Chem. Eur. J.* **2012**, *18*, 4088–4098; f) J. A. Fuentes, T. Lebl, A. M. Z. Slawin, M. L. Clarke, *Chem. Sci.* **2011**, *2*, 1997–2005; g) G. Ma, A. Bartoszewicz, I. Ibrahim, A. Córdova, *Adv. Synth. Catal.* **2011**, *353*, 3114–3122; h) Y. Yao, J.-L. Li, Q.-Q. Zhou, L. Dong, Y.-C. Chen, *Chem. Eur. J.* **2013**, *19*, 9447–9451; i) B. D. Ramachary, R. Madhavachary, M. S. Prasad, *Org. Biomol. Chem.* **2012**, *10*, 5825–5829; j) B. D. Ramachary, R. Sakthidevi, K. S. Sruthi, *Chem. Eur. J.* **2012**, *18*, 8008–8012; k) G. Bartoli, M. Bosco, A. Carlone, F. Pesciaoli, L. Sambri, P. Melchiorre, *Org. Lett.* **2007**, *9*, 1403–1406; l) F. Pesciaoli, F. De Vincentiis, P. Galzerano, G. Bencivenni, G. Bartoli, A. Mazzanti, P. Melchiorre, *Angew. Chem.* **2008**, *120*, 8831–8834; *Angew. Chem. Int. Ed.* **2008**, *47*, 8703–8706.
- [9] For a review, see: J. Meeuwissen, J. N. H. Reek, *Nat. Chem.* **2010**, *2*, 615–621.
- [10] For general reviews on organocatalysis, see: a) *Asymmetric Organocatalysis, I–II* (Eds.: B. List, K. Maruoka), Thieme, Stuttgart, **2012**; b) *Asymmetric Organocatalysis* (Eds.: A. Berkessel, H. Gröger), Wiley-VCH, Weinheim, **2005**.
- [11] a) T. Mandal, C.-G. Zhao, *Angew. Chem.* **2008**, *120*, 7828–7831; *Angew. Chem. Int. Ed.* **2008**, *47*, 7714–7717; b) S. Muramulla, J.-A. Ma, J. C.-G. Zhao, *Adv. Synth. Catal.* **2013**, *355*, 1260–1264; c) S. Muramulla, C.-G. Zhao, *Tetrahedron Lett.* **2011**, *52*, 3905–3908; d) D. Sinha, S. Perera, J. C.-G. Zhao, *Chem. Eur. J.* **2013**, *19*, 6976–6979; e) D. Sinha, T. Mandal, S. Gogoi, J. J. Goldman, J. C.-G. Zhao, *Chin. J. Chem.* **2012**, *30*, 2624–2630; f) S. Perera, D. Sinha, N. K. Rana, V. Trieu-Do, J. C.-G. Zhao, *J. Org. Chem.* **2013**, *78*, 10947–10953.

- [12] Polyfunctional cyclohexanes are very useful building blocks in organic synthesis, see: D. Enders, M. R. M. Hüttl, C. Grondal, G. Raabe, *Nature* **2006**, *441*, 861–863.
- [13] For a review, see: S. Mukherjee, J. W. Yang, S. Hoffmann, B. List, *Chem. Rev.* **2007**, *107*, 5471–5569.
- [14] For reviews, see: a) S. J. Connon, *Chem. Commun.* **2008**, 2499–2510; b) A. G. Doyle, E. N. Jacobsen, *Chem. Rev.* **2007**, *107*, 5713–5743.
- [15] For details, please see the Supporting Information.
- [16] For examples of creating diastereodivergence in the products through epimerization, see: a) X. Dou, Y. Lu, *Chem. Eur. J.* **2012**, *18*, 8315–8319; b) M. Luparia, M. T. Oliveira, D. Audisio, F. Frebault, R. Goddard, N. Maulide, *Angew. Chem.* **2011**, *123*, 12840–12844; *Angew. Chem. Int. Ed.* **2011**, *50*, 12631–12635; c) K. L. Jensen, C. F. Weise, G. Dickmeiss, F. Morana, R. L. Davis, K. A. Jørgensen, *Chem. Eur. J.* **2012**, *18*, 11913–11918.
- [17] J. R. Lewis, *Nat. Prod. Rep.* **1994**, *11*, 329–332.
- [18] Some selected examples: a) K. Tomioka, T. Yasuhara, K. Nishimura, M. Yamashita, N. Fukuyama, K. I. Yamada, O. Muraoka, *Org. Lett.* **2003**, *5*, 1123–1126; b) S. Gao, Y. Q. Tu, Z. Song, A. Wang, X. Fan, Y. Jiang, *J. Org. Chem.* **2005**, *70*, 6523–6525; c) R. J. Huntley, R. L. Funk, *Tetrahedron Lett.* **2011**, *52*, 6671–6674.
- [19] a) L. Dong, Y.-J. Xu, W.-C. Yuan, X. Cui, L.-F. Cun, L.-Z. Gong, *Eur. J. Org. Chem.* **2006**, 4093–4105; b) B.-C. Hong, R. Y. Nimje, M.-F. Wu, A. A. Sadani, *Eur. J. Org. Chem.* **2008**, 1449–1457.
- [20] a) Y. Wang, Y.-C. Luo, H.-B. Zhang, P.-F. Xu, *Org. Biomol. Chem.* **2012**, *10*, 8211–8215; b) G. Li, J.-H. Xie, J. Hou, S.-F. Zhu, Q.-L. Zhou, *Adv. Synth. Catal.* **2013**, *355*, 1597–1604.