

Cite this: *Chem. Sci.*, 2020, 11, 5572

All publication charges for this article have been paid for by the Royal Society of Chemistry

A solvent-dependent chirality-switchable thia-Michael addition to α,β -unsaturated carboxylic acids using a chiral multifunctional thiourea catalyst†

Noboru Hayama,^{ab} Yusuke Kobayashi,^{id} a Eriko Sekimoto,^b Anna Miyazaki,^b Kiyofumi Inamoto,^b Tetsutaro Kimachi^b and Yoshiji Takemoto^{id} *^aReceived 25th March 2020
Accepted 14th May 2020

DOI: 10.1039/d0sc01729a

rsc.li/chemical-science

An asymmetric thia-Michael addition of arylthiols to α,β -unsaturated carboxylic acids using a thiourea catalyst that bears arylboronic acid and tertiary amine moieties is reported. Both enantiomers of the Michael adducts can be obtained in high enantioselectivity and good yield merely by changing the solvent. The origin of the chirality switch in the products was examined in each solvent *via* spectroscopic analyses.

Introduction

Due to the importance of organosulfur compounds in medicinal chemistry and biochemistry, their asymmetric synthesis has been studied extensively.¹ The catalytic asymmetric thia-Michael addition (TMA) to α,β -unsaturated carbonyl compounds (Fig. 1A) is of particular importance in this context on account of their ability to furnish versatile synthetic intermediates for a variety of biologically active compounds such as benzothiazepine derivatives.^{2,3} Various activated Michael acceptors have been successfully used for TMA,⁴ *e.g.* α,β -unsaturated oxazolidinones,⁵ imides,⁶ nitro alkenyl isoxazoles,⁷ thioamides,⁸ acylpyrazoles,⁹ carboxylic acid anhydrides,¹⁰ and enone diesters.¹¹ However, due to their low inherent electrophilicity, catalytic asymmetric TMA to unactivated Michael acceptors such as α,β -unsaturated esters,¹² amides, and carboxylic acids¹³ remains a challenge. In general, thia-Michael adducts need derivatization to produce biologically active compounds, *e.g.* a conversion of the carbonyl moiety to carboxylic acid *via* hydrolysis or oxidation.² Considering atom and step economy, direct catalytic TMA to α,β -unsaturated carboxylic acids would thus be highly desirable.

Herein, we report a direct asymmetric TMA to α,β -unsaturated carboxylic acids using a multifunctional organocatalyst, which comprises (1) thiourea as a hydrogen bond (HB) donor, (2) a chiral tertiary amine derived from (*R,R*)-cyclohexane diamine, and (3) aryl boronic acid moieties (Fig. 1B). Based on our previous work,¹⁴ in

a non-polar solvent and in the presence of two equivalents of carboxylic acid and molecular sieves (MS), we expect the catalyst to form ternary complex A, which promotes the addition of a nucleophile to the 'unusual' *s-trans*-form of the α,β -unsaturated carboxylate to generate the corresponding (*S*)-adduct.

Furthermore, we propose that a conformational change of the catalyst¹⁵ *via* further dehydration may be possible in an aprotic polar solvent, producing the 'usual' (*R*)-adduct¹⁶ *via* addition to the *s-cis*-form of the α,β -unsaturated carboxylate in complex B. As the acidity of boron influences the strength of N-B dative bonds,¹⁷ we altered the structure of the catalyst by modifying the aryl boronic acid moiety. Chirality-switch systems¹⁸ that use a catalyst from the same chiral source¹⁹ are rare, even though they offer great potential for the construction of chemical libraries for drug discovery.

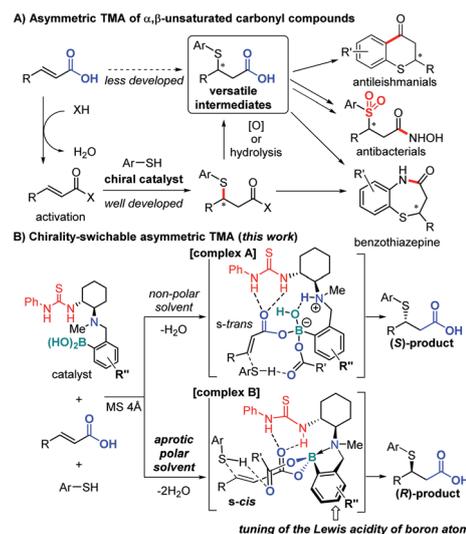


Fig. 1 Summary and working hypothesis of this work.

^aGraduate School of Pharmaceutical Sciences, Kyoto University, Yoshida, Sakyo-ku, Kyoto 606-8501, Japan. E-mail: takemoto@pharm.kyoto-u.ac.jp

^bSchool of Pharmacy and Pharmaceutical Sciences, Mukogawa Women's University, 11-68, 9-Bancho, Koshien, Nishinomiya, Hyogo 663-8179, Japan

† Electronic supplementary information (ESI) available: Experimental procedures, spectroscopic data, copies of ¹H and ¹³C NMR spectra, and HPLC chromatograms. See DOI: 10.1039/d0sc01729a

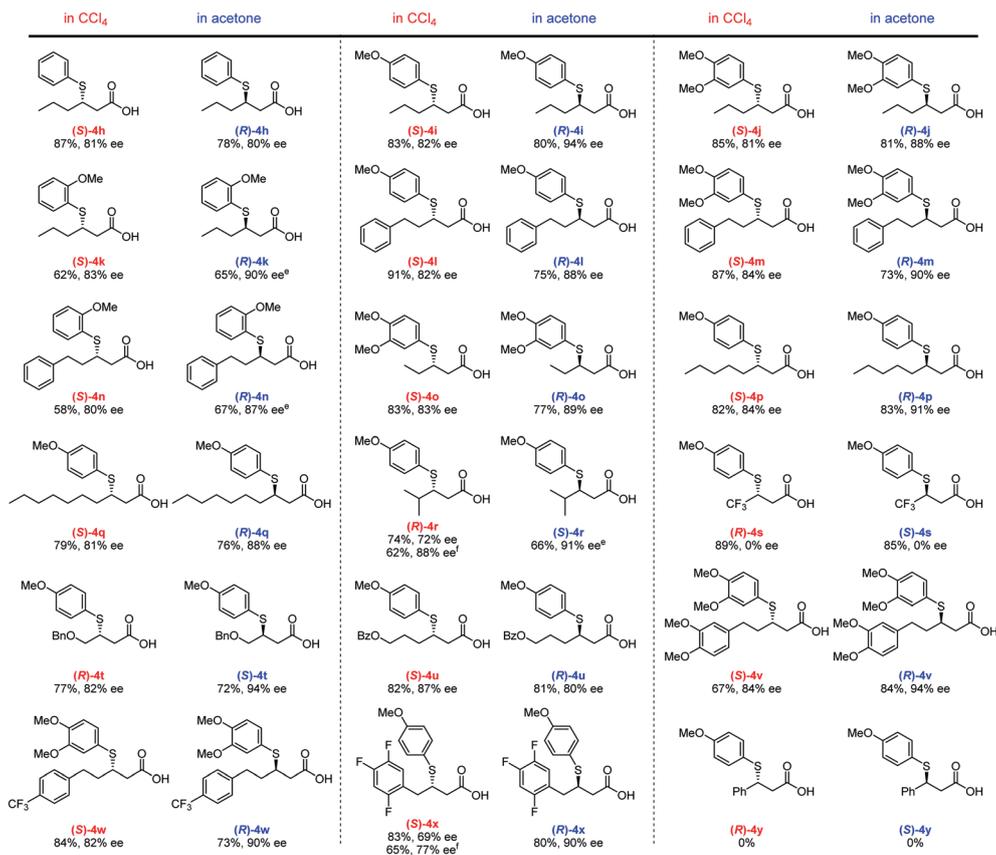


Fig. 3 Substrate scope with respect to α,β -unsaturated carboxylic acids^{a-d}. ^aUnless otherwise noted, the reaction was carried out using **3** (0.1 mmol), **2** (1.0 equiv.), **1a** (0.1 equiv.), and 4 Å MS (20 mg) in CCl₄ (50 μ L) at room temperature for 24 h. ^bThe reaction was carried out using **3** (0.1 mmol), **2** (1.0 equiv.), **1g** (0.1 equiv.), and 4 Å MS (100 mg) in acetone (1.0 mL) at room temperature for 24 h. ^cIsolated yield after treatment with TMSCHN₂. ^dee values were estimated using chiral HPLC analysis after treatment with TMSCHN₂. ^eThe reaction was performed for 48 h. ^fOne equivalent of benzoic acid was added.

Using the optimized conditions, we then investigated the substrate scope with respect to α,β -unsaturated carboxylic acids **3** (Fig. 3). Several different aliphatic α,β -unsaturated carboxylic acids furnish the corresponding adducts (**4h–4q**) in good yield with good to high ee values in both solvents. An efficient TMA was observed for the linear alkyl Michael acceptors producing ee values of 81–91% (**4o–4q**). Notably, a γ -branched α,β -unsaturated carboxylic acid generates adducts (**R**)-**4r** (88% ee) and (**S**)-**4r** (91% ee) in CCl₄ and acetone, respectively; however, the yield is somewhat decreased due to steric hindrance. Although enantioselectivity was not observed for adduct **4s** using highly reactive trifluoromethyl-substituted α,β -unsaturated carboxylic acids as Michael acceptors, our solvent-dependent chirality-switchable TMA successfully produces both enantiomers of **4t–x** in combination with substrates bearing ether, ester, and various aryl groups. One of the limitations of this method is the addition to cinnamic acid derivatives, which resulted in recovery of the starting materials. It is worth mentioning that, using benzoic acid as an additive, a slight increase in ee (*ca.* 10%) is observed, especially when bulky substrates are employed to obtain (**R**)-**4r** and (**S**)-**4x** in CCl₄.^{14c}

Mechanistic insight into the solvent-dependent chirality-switchable TMA was obtained using NMR spectroscopic analysis (Fig. 4) in CDCl₃ and CD₂Cl₂ as substitutes for CCl₄ (Fig. S1–S2†), as well as in acetone-*d*₆ (Fig. S3†).

In the presence of thiol **2a** (10 equiv.), carboxylic acid **3a** (10 equiv.), and 4 Å MS in CDCl₃, the ¹¹B NMR resonances for **1a** converge at 4 ppm after 1 h (Fig. 4a). This result indicates the formation of the tetrahedral boron complex **A** and is consistent with previous work on aza-Michael additions. The addition of a nucleophile to the *s-trans* form of α,β -unsaturated carboxylate **A** (Fig. 1B) is favored over the addition to the *s-cis* form, which is due to steric repulsion between the *s-cis* form and the aromatic ring of the catalyst.^{14c} Interestingly, in acetone-*d*₆, the peaks of **1a** gradually converge at 10 ppm in the presence of thiol **2a** (10 equiv.), carboxylic acid **3a** (10 equiv.), and 4 Å MS (Fig. 4b). We assume that the 10 ppm peak is derived from an N–B dative bond in *e.g.* complex **B**, as the N–B dative bond signals shift *ca.* 4–7 ppm downfield relative to the signals of tetrahedral borate complexes coordinated by water.¹⁵ An ESI-MS analysis of mixtures of **1a**, **2a**, and 4 Å MS in acetone further support the formation of an N–B dative bond (Fig. 4c). The exact mass peak of complex **B** (*m/z* calculated for C₂₉H₃₅BN₃O₄S [M – H][–]: 532.2447) was detected at 532.2440 with an error of no more



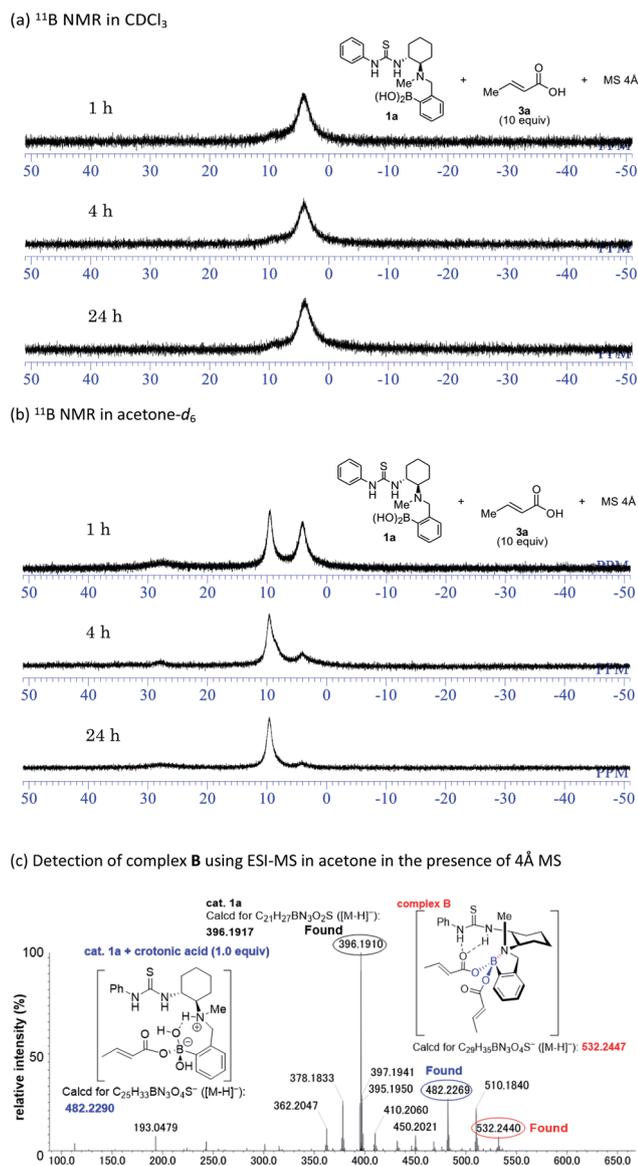
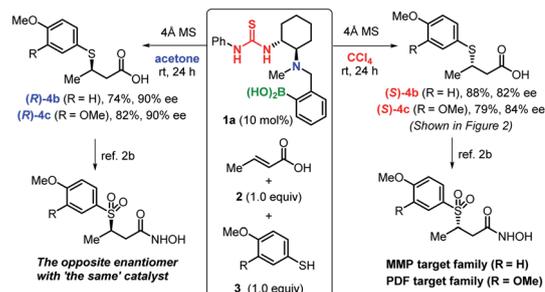


Fig. 4 Spectral data in support of the proposed mechanism.

than 5 ppm. It should be mentioned here that such a peak was not detected in CCl_4 or CHCl_3 (Fig. S4[†]). Complex B is allegedly generated by the dehydration of complex A or its dimer,^{14c} which is assisted by coordination of acetone to the boron atom. Preliminary computational studies suggest that nucleophilic addition to the *s-cis* form of complex B (Fig. 1B) is by 2.0 kcal mol⁻¹ more favorable than addition to the *s-trans* form (Fig. S6–S7[†]),²⁴ as the N–B chelation forces the carboxylate moiety away from the aromatic ring of the catalyst. The formation of an N–B bond is further supported by experimental results using catalyst **1g**; the methoxyl group at the *para*-position relative to the boron atom on the aromatic ring of **1g** facilitates dehydration *via* the mesomeric effect to form complex B, resulting in high enantioselectivity in acetone (Table 1).²⁵

Finally, using ‘the same’ catalyst, we demonstrate the efficient production of both enantiomers of biologically active



Scheme 1 An efficient approach to generate both target enantiomers of **4b,c** using catalyst **1a**.

compounds^{2b} (Scheme 1). For example, β -sulfonylhydroxamic acid derivatives show potent inhibitory activity towards peptide deformylase and matrix metalloproteases, whereby the activity of one enantiomer is by two orders of magnitude higher than that of the other.^{2b,c} The construction of a library of both enantiomers can be expected to aid clarifying the exact biological activity and to suppress adverse effects caused by these compounds. The chirality-switchable system based on catalyst **1a** allows the production of enantiomers **4b,c** from thiols **2** and α,β -unsaturated carboxylic acids **3** simply by changing the solvent from CCl_4 to acetone.

Conclusions

We have developed a solvent-dependent asymmetric thia-Michael addition (TMA) of thiols to α,β -unsaturated carboxylic acids, wherein both (*S*)- and (*R*)-adducts can be obtained in good yield and high enantioselectivity. Using ^{11}B NMR spectroscopy and ESI-MS analyses, we found that the coordination state of boron in the catalyst depends on the coordinating nature of the aprotic solvent. These findings can be expected to lead to the development of new organoboron catalysts and the construction of chemical libraries. Studies to extend the synthetic applications of this catalytic system are currently in progress in our laboratory.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

This work was supported by JSPS KAKENHI grant 16H06384.

Notes and references

- (a) J. Clayden and P. MacLellan, *Beilstein J. Org. Chem.*, 2011, 7, 582–595; (b) P. Chauhan, S. Mahajan and D. Enders, *Chem. Rev.*, 2014, 114, 8807–8864.
- (a) C. J. Burns, R. D. Groneberg, J. M. Salvino, G. McGeehan, S. M. Condon, R. Morris, M. Morrisette, R. Mathew, S. Darnbrough, K. Neuenschwander, A. Scotese, S. W. Djuric, J. Ullrich and R. Labaudiniere, *Angew. Chem., Int. Ed.*, 1998, 37, 2848–2850; (b) C. Apfel, D. W. Banner,



- D. Bur, M. Dietz, T. Hirata, C. Hubschwerlen, H. Locher, M. G. P. Page, W. Pirson, G. Rossé and J.-L. Specklin, *J. Med. Chem.*, 2000, **43**, 2324–2331; (c) J. M. Salvino, R. Mathew, T. Kiesow, R. Narensingh, H. J. Mason, A. Dodd, R. Groneberg, C. J. Burns, G. McGeehan, J. Kline, E. Orton, S.-Y. Tang, M. Morrisette and R. Labaudiniere, *Bioorg. Med. Chem. Lett.*, 2000, **10**, 1637–1640; (d) M. Sani, G. Candiani, F. Pecker, L. Malpezzi and M. Zanda, *Tetrahedron Lett.*, 2005, **46**, 2393–2396.
- 3 J. B. Bariwal, K. D. Upadhyay, A. T. Manvar, J. C. Trivedi, J. S. Singh, K. S. Jain and A. K. Shah, *Eur. J. Med. Chem.*, 2008, **43**, 2279–2290.
- 4 (a) D. Enders, K. Lüttgen and A. A. Narine, *Synthesis*, 2007, 959–980; (b) P. Wadhwa, A. Kharbanda and A. Sharma, *Asian J. Org. Chem.*, 2018, **7**, 634–661.
- 5 (a) S. Kanemasa, Y. Oderatoshi and E. Wada, *J. Am. Chem. Soc.*, 1999, **121**, 8675–8676; (b) S. Kobayashi, C. Ogawa, M. Kawamura and M. Sugiura, *Synlett*, 2001, 983–985; (c) K. Matsumoto, A. Watanabe, T. Uchida, K. Ogi and T. Katsuki, *Tetrahedron Lett.*, 2004, **45**, 2385–2388; (d) S. J. K. Sauerland, E. Kiljunen and A. M. P. Koskinen, *Tetrahedron Lett.*, 2006, **47**, 1291–1293; (e) S. Lauzon, H. Keipour, V. Gandon and T. Ollevier, *Org. Lett.*, 2017, **19**, 6324–6327.
- 6 B.-J. Li, L. Jiang, M. Liu, Y.-C. Chen, L. S. Ding and Y. Wu, *Synlett*, 2005, 603–606.
- 7 Q.-L. Pei, H.-W. Sun, Z.-J. Wu, X.-L. Du, X.-M. Zhang and W.-C. Yuan, *J. Org. Chem.*, 2011, **76**, 7849–7859.
- 8 T. Ogawa, N. Kumagai and M. Shibasaki, *Angew. Chem., Int. Ed.*, 2012, **51**, 8551–8554.
- 9 (a) X.-Q. Dong, X. Fang, H.-Y. Tao, X. Zhou and C.-J. Wang, *Adv. Synth. Catal.*, 2012, **354**, 1141–1147; (b) G. Wang, Y. Tang, Y. Zhang, X. Liu, L. Lin and X. Feng, *Chem.–Eur. J.*, 2017, **23**, 554–557; (c) S. Meninno, C. Volpe and A. Lattanzi, *Chem.–Eur. J.*, 2017, **23**, 4547–4550; (d) S. Meninno, S. Naddeo, L. Varricchio, A. Capobianco and A. Lattanzi, *Org. Chem. Front.*, 2018, **5**, 1967–1977.
- 10 (a) Y. Fukata, K. Asano and S. Matsubara, *J. Am. Chem. Soc.*, 2015, **137**, 5320–5323; (b) Y. Fukata, K. Yao, R. Miyaji, K. Asano and S. Matsubara, *J. Org. Chem.*, 2017, **82**, 12655–12668.
- 11 (a) R. Wang, J. Liu and J. Xu, *Adv. Synth. Catal.*, 2015, **357**, 159–167; (b) J. L. Fulton, M. A. Horwitz, E. L. Bruske and J. S. Johnson, *J. Org. Chem.*, 2018, **83**, 3385–3391.
- 12 (a) K. Nishimura, M. Ono, Y. Nagaoka and K. Tomioka, *J. Am. Chem. Soc.*, 1997, **119**, 12974–12975; (b) X.-Q. Dong, X. Fang and C.-J. Wang, *Org. Lett.*, 2011, **13**, 4426–4429; (c) X. Fang, J. Li and C.-J. Wang, *Org. Lett.*, 2013, **15**, 3448–3451; (d) P. Yuan, S. Meng, J. Chen and Y. Huang, *Synlett*, 2016, **27**, 1068–1072; (e) J. Yang, A. J. M. Farley and D. J. Dixon, *Chem. Sci.*, 2017, **8**, 606–610.
- 13 To the best of our knowledge, there is only one report of a catalytic asymmetric thia-Michael addition involving α,β -unsaturated carboxylic acids; for details, see: P. N. Kalaria, J. R. Avalani and D. K. Raval, *Tetrahedron: Asymmetry*, 2016, **27**, 947–953.
- 14 (a) N. Hayama, T. Azuma, Y. Kobayashi and Y. Takemoto, *Chem. Pharm. Bull.*, 2016, **64**, 704–717; (b) T. Azuma, A. Murata, Y. Kobayashi, T. Inokuma and Y. Takemoto, *Org. Lett.*, 2014, **16**, 4256–4259; (c) N. Hayama, R. Kuramoto, T. Földes, K. Nishibayashi, Y. Kobayashi, I. Pápai and Y. Takemoto, *J. Am. Chem. Soc.*, 2018, **140**, 12216–12225; (d) K. Michigami, H. Murakami, T. Nakamura, N. Hayama and Y. Takemoto, *Org. Biomol. Chem.*, 2019, **17**, 2331–2335.
- 15 (a) L. Zhu, S. H. Shabbir, M. Gray, V. M. Lynch, S. Sorey and E. V. Anslyn, *J. Am. Chem. Soc.*, 2006, **128**, 1222–1232; (b) B. E. Collins, S. Sorey, A. E. Hargrove, S. H. Shabbir, V. M. Lynch and E. V. Anslyn, *J. Org. Chem.*, 2009, **74**, 4055–4060; (c) I. Georgiou, G. Ilyashenko and A. Whiting, *Acc. Chem. Res.*, 2009, **42**, 756–768; (d) J. D. Larkin, J. S. Fossey, T. D. James, B. R. Brooks and C. W. Bock, *J. Phys. Chem. A*, 2010, **114**, 12531–12539; (e) A. Sakakura, T. Ohkubo, R. Yamashita, M. Akakura and K. Ishihara, *Org. Lett.*, 2011, **13**, 892–895; (f) X. Sun, B. M. Chapin, P. Metola, B. Collins, B. Wang, T. D. James and E. V. Anslyn, *Nat. Chem.*, 2019, **11**, 768–778.
- 16 (a) Y. Kobayashi, Y. Taniguchi, N. Hayama, T. Inokuma and Y. Takemoto, *Angew. Chem., Int. Ed.*, 2013, **52**, 11114–11118; (b) Y. Kobayashi, S. Li and Y. Takemoto, *Asian J. Org. Chem.*, 2014, **3**, 403–407.
- 17 B. G. Janesko, *J. Chem. Theory Comput.*, 2010, **6**, 1825–1833.
- 18 For reviews, see: (a) G. Romanazzi, L. Degennaro, P. Mastroianni and R. Luisi, *ACS Catal.*, 2017, **7**, 4100–4114. For examples of solvent-controlled chirality-switchable systems, see: ; (b) Y. Sohtome, S. Tanaka, K. Takada, T. Yamaguchi and K. Nagasawa, *Angew. Chem., Int. Ed.*, 2010, **49**, 9254–9257; (c) J. Flores-Ferrándiz and R. Chinchilla, *Tetrahedron: Asymmetry*, 2014, **25**, 1091–1094; (d) R. J. Chew, X.-R. Li, Y. Li, S. A. Pullarkat and P.-H. Leung, *Chem.–Eur. J.*, 2015, **21**, 4800–4804. For an example of solvent-controlled diastereoselectivity, see: (e) X. Tian, C. Cassani, Y. Liu, A. Moran, A. Urakawa, P. Galzerano, E. Arceo and P. Melchiorre, *J. Am. Chem. Soc.*, 2011, **133**, 17934–17941.
- 19 Y. Fukata, K. Asano and S. Matsubara, *J. Am. Chem. Soc.*, 2013, **135**, 12160–12163.
- 20 The absolute configuration of **4a** was determined by comparing the specific optical rotation to that of an authentic sample. For further details, see the ESI.†
- 21 Presumably, these moderate results were caused by the poor solubility **1h** in acetone.
- 22 Benzyl mercaptan (BnSH) did not produce the corresponding adduct in both solvents, presumably due to the insufficient acidity of S–H proton.
- 23 For example, the TMA of 4-trifluoromethylbenzenthioi with crotonic acid proceeded in *ca.* 50% yield in acetone (in the presence of MS without a catalyst).
- 24 Alternative pathways for the formation of the (*R*)-adduct, including the coordination of thiol to the boron atom, cannot be ruled out at this point.
- 25 In the presence of acetone, the reaction *via* complex **A** was unlikely to proceed. See the ESI† for the effect of acetone in CCl₄ (Scheme S3a†). The effect of pre-mixing of catalyst and **3a** in acetone was also described in Schemes S3b and c.†

