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ARTICLE

A Solvent-dependent Chirality-switchable Thia-Michael Addition to α,β-Unsaturated Carboxylic Acids using a Chiral Multifunctional Thiourea Catalyst

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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 (Figure 1A) is of particular importance in this context on account of its 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 acids[13] 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 (Figure 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.

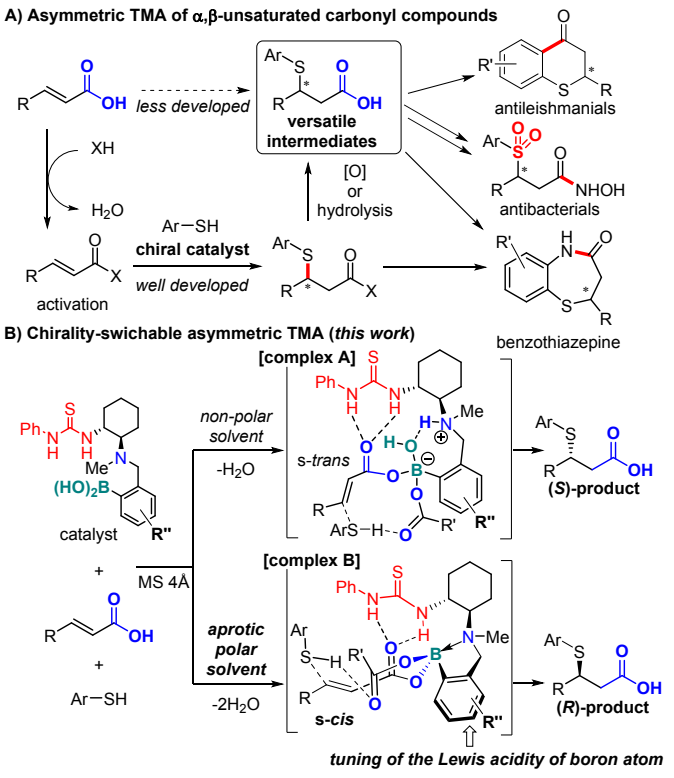

Figure 1. Summary and working hypothesis of this work.

Furthermore, we propose that a conformational change of the catalyst[15] via further dehydration may be possible in an aprotic polar solvent, producing the 'usual' (*R*)-adduct[16] 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

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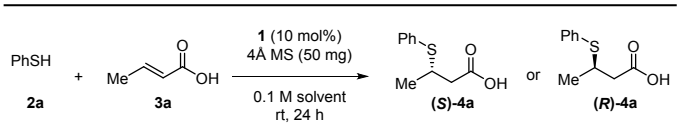
† Electronic Supplementary Information (ESI) available: Experimental procedures, spectroscopic data, copies of ^{1}H and ^{13}C NMR spectra, and HPLC chromatograms. See DOI: 10.1039/x0xx00000x

bonds,[17] we altered the structure of the catalyst by modifying the aryl boronic acid moiety. Chirality-switch systems[18] that use a catalyst from the same chiral source[19] are rare, even though they offer great potential for the construction of chemical libraries for drug discovery.

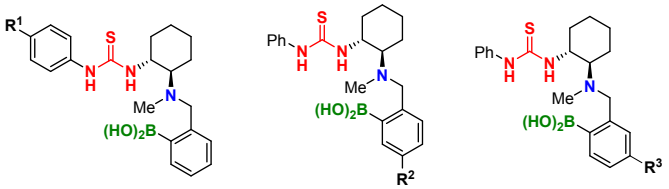
Results and discussion

Initially, we explored the TMA of thiophenol **2a** to crotonic acid **3a** using 10 mol% of catalyst **1a** and 4Å MS in CCl_4 (Table 1).

Table 1. Solvent and catalyst screening[a]



Entry	solvent	catalyst	yield[b] (%)	ee[c] (%)
1	CCl_4	**1a**	90	41 (*S*)
2	CH_2Cl_2	**1a**	21	22 (*S*)
3	*n*-hexane	**1a**	28	48 (*S*)
4	CH_3CN	**1a**	36	39 (*R*)
5	acetone	**1a**	68	82 (*R*)
6	MeOH	**1a**	0	-
7[d]	CCl_4	**1a**	0	-
8[d]	acetone	**1a**	11	15 (*R*)
9[e]	CCl_4	**1a**	91	81 (*S*)
10	acetone	**1b**	35	33 (*R*)
11	acetone	**1c**	67	78 (*R*)
12	acetone	**1d**	57	81 (*R*)
13	acetone	**1e**	61	68 (*R*)
14	acetone	**1f**	35	45 (*R*)
15	acetone	**1g**	60	92 (*R*)
16	acetone	**1h**	53	45 (*R*)
17[f]	acetone	**1g**	80	92 (*R*)
18[e]	CCl_4	**1g**	78	75 (*S*)



1a (R^1 = H)
1b (R^1 = NO_2)
1c (R^1 = OMe)

1d (R^2 = CF_3)
1e (R^2 = OMe)

1f (R^3 = CF_3)
1g (R^3 = OMe)
1h (R^3 = NMe_2)

[a] Unless otherwise noted, the reactions were carried out using **3a** (0.1 mmol), **2a** (1.0 equiv), **1a** (0.1 equiv), and 4Å MS (50 mg) in the specified solvent (1.0 mL) at room temperature for 24 h. [b] Isolated yield after treatment with $TMSCHN_2$. [c] Estimated using chiral HPLC after treatment with $TMSCHN_2$. The absolute configuration is indicated in parentheses. [d]Without 4Å MS. [e] CCl_4 (50 µL) and 4Å MS (20 mg). [f] 4Å MS (100 mg).

This reaction furnished Michael adduct (*S*)-**4a**, which exhibits the same chirality as that of the aza-Michael addition (Table 1, entry 1).[14a] In the presence of non-polar solvents such as CCl_4, CH_2Cl_2, and *n*-hexane, the major isomer of the Michael adduct is (*S*)-**4a**[20] (Table 1, entries 1-3). In contrast, in the presence of aprotic polar solvents such as acetonitrile and acetone, the major product is (*R*)-**4a** (Table 1, entries 4 and 5). The reaction did not proceed in MeOH, presumably due to its coordination to the boron atom of the catalyst (Table 1, entry 6). Notably, the catalytic activity of **1a** is significantly reduced in the absence of MS; this result suggests that the formation of a boron complex via dehydration is essential for the successful TMA in both polar and non-polar solvents (Table 1, entries 7 and 8). The (*S*)-selectivity (81% ee) is significantly improved at higher concentrations in CCl_4 (Table 1, entry 1 vs 9). This is presumably due to the rapid formation of complex **A** (^{11}B NMR: 4 ppm; Figure S6), which supresses the undesired formation of the (*R*)-adduct (for further details, see the ESI). Subsequently, we investigated the effect of substituents (R^1, R^2, R^3) on the catalyst in order to improve the yield and (*R*)-selectivity in acetone. Thioureas **1b-c** with different R^1 substituents (OMe, NO_2) neither improve the yield nor the enantioselectivity (Table 1, entries 10 and 11). Then, we examined the electronic effect of the boronic acid moiety by introducing electron-withdrawing and donating groups (R^2, R^3) into the aromatic ring of the arylboronic acid moieties. We found that catalysts **1d** and **1e**, which contain substituents at the *meta*-position relative to the boron atom (R^2), only have a marginal effect on the results (Table 1, entries 12 and 13). However, when substituents are at the *para*-position relative to the boron atom (R^3), a significant improvement of the reactivity and enantioselectivity was observed (Table 1, entries 14-16).This is demonstrated by the excellent results from catalyst **1g**, which bears a methoxy group.[21] In addition, increasing the amount of MS provides the (*R*)-adduct in 80% yield with 92% ee (Table 1, entry 17).

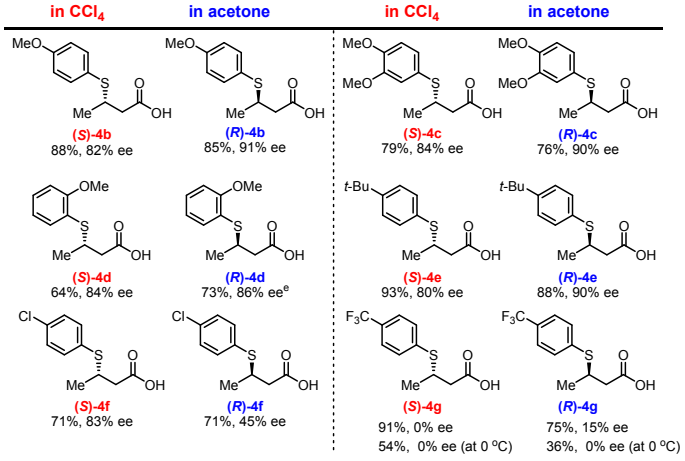


Figure 2. Substrate scope with respect to thiols [a-d]

[a] The reaction was carried out using **3a** (0.1 mmol), **2a** (1.0 equiv), **1a** (0.1 equiv), and 4Å MS (20 mg) in CCl_4 (50 µL) at room temperature for 24 h. [b] The reaction was carried out using **3a** (0.1 mmol), **2a** (1.0 equiv), **1g** (0.1 equiv), and 4Å MS (100 mg) in acetone (1.0 mL) at room temperature for 24 h. [c] Isolated yield after treatment with $TMSCHN_2$. [d] Ee values were estimated using chiral HPLC analysis after treatment with $TMSCHN_2$. [e] The reaction was performed for 48 h.

With the optimized conditions in hand, we investigated the electronic and steric effects of thiols[22] on the asymmetric TMA in two different solvents (Figure 2). In both solvents, electron-rich aryl thiols generally produce the corresponding adducts (**4b**-**4d**) in good yield (64-88%) with high enantioselectivity (80-91% ee). However, a slight decrease in reaction rate was observed for *ortho*-substituted thiols (**4d**). Similarly, *tert*-butyl-

substituted benzenethiol produced both enantiomers of **4e** with high yield and enantioselectivity. In contrast, the use of thiols with electron-withdrawing substituents, such as chlorine (Cl) and trifluoromethyl (CF_3) groups on the aromatic ring, dramatically decreases the enantioselectivity of the adducts **4f** and **4g**, which was partially ascribed to background reactions.[23] The enantioselectivity of **4g** was not improved even at lower temperature, and the chemical yield of **4g** significantly dropped presumably due to the decreased solubility of the substrates.

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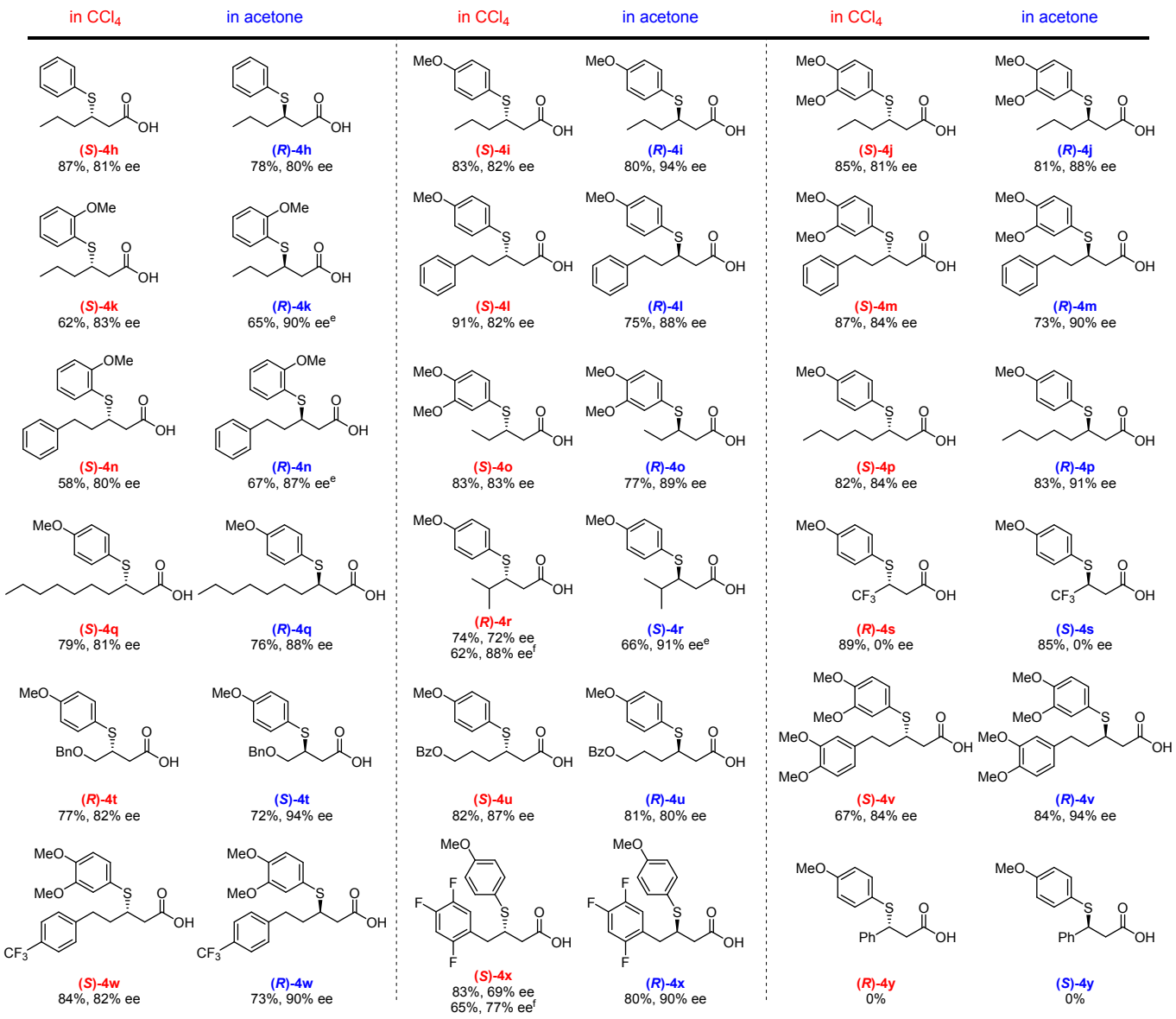


Figure 3. Substrate scope with respect to α,β-unsaturated carboxylic acids [a-d]

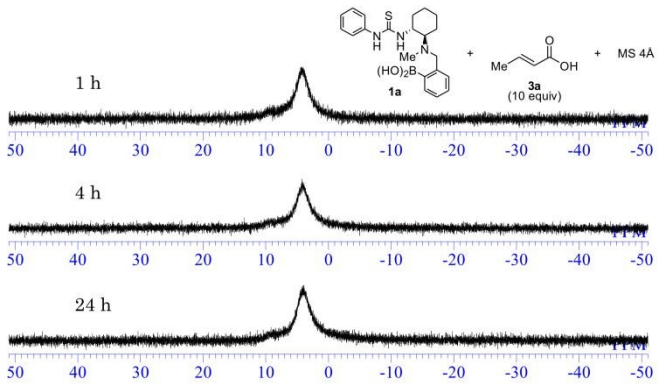
[a] Unless otherwise noted, the reaction was carried out using **3** (0.1 mmol), **2** (1.0 equiv), **1a** (0.1 equiv), and 4Å MS (20 mg) in CCl_4 (50 μL) at room temperature for 24 h. [b] The reaction was carried out using **3** (0.1 mmol), **2** (1.0 equiv), **1g** (0.1 equiv), and 4Å MS (100 mg) in acetone (1.0 mL) at room temperature for 24 h. [c] Isolated yield after treatment with $TMSCHN_2$. [d] ee Values were estimated using chiral HPLC analysis after treatment with $TMSCHN_2$. [e] The reaction was performed for 48 h. [f] One 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** (Figure 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 CCl_4 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

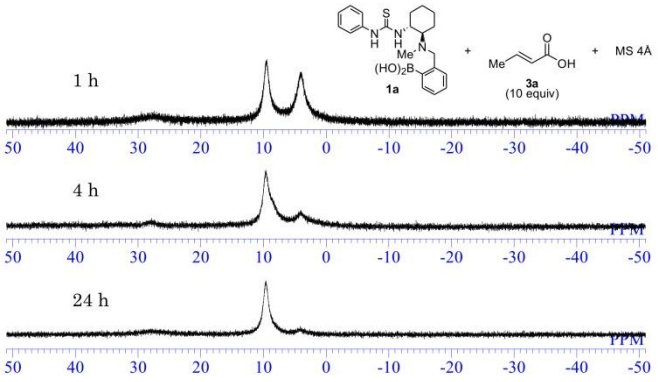
the limitations of this method is the addition to cinnamic acid derivatives, which resulted in recovery of the starting materials. It is worth mentioning that, using benzoic acid as an additive, a slight increase in ee (ca. 10%) is observed, especially when bulky substrates are employed to obtain (*R*)-**4r** and (*S*)-**4x** in CCl_4. A similar effect was observed in the asymmetric aza-Michael addition to α,β-unsaturated carboxylic acids in CCl_4.[14c]

Mechanistic insight into the solvent-dependent chirality-switchable TMA was obtained using NMR spectroscopic analysis (Figure 4) in $CDCl_3$ and CD_2Cl_2 as substitutes for CCl_4 (Figure S1-S2), as well as in acetone-d_6 (Figure S3).

(a) ^{11}B NMR in $CDCl_3$



(b) ^{11}B NMR in acetone-d_6



(c) Detection of complex **B** using ESI-MS in acetone in the presence of 4Å MS

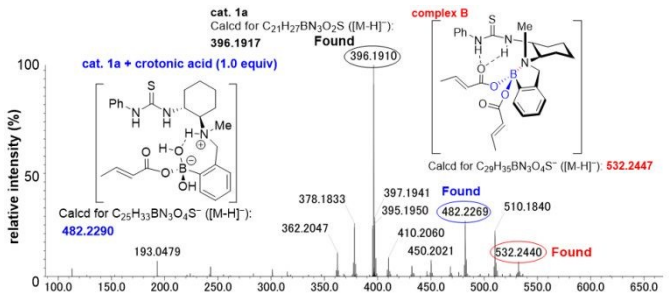
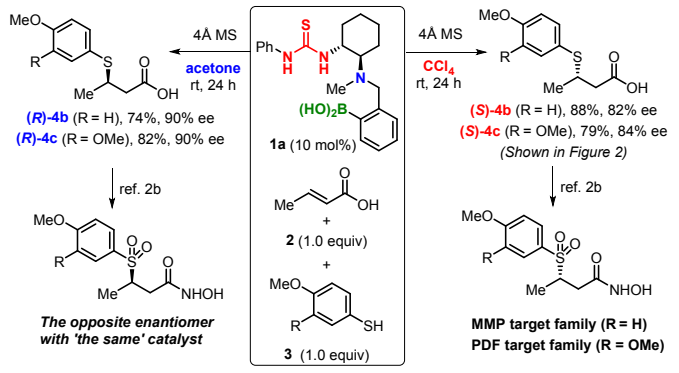


Figure 4. Spectral data in support of the proposed mechanism.

In the presence of thiol **2a** (10 equiv), carboxylic acid **3a** (10 equiv), and 4Å MS in $CDCl_3$, the ^{11}B NMR resonances for **1a** converge at 4 ppm after 1 h (Figure 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** (Figure 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 4Å MS (Figure 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 4Å MS in acetone further support the formation of an N-B dative bond (Figure 4c). The exact mass peak of complex **B** (*m/z* calculated for $C_{29}H_{35}BN_3O_4S$ $[M-H]^-$: 532.2447) was detected at 532.2440 with an error of no more than 5 ppm. It should be mentioned here that such a peak was not detected in CCl_4 or $CHCl_3$ (Figure 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** (Figure 1B) is by 2.0 kcal/mol more favorable than addition to the s-*trans* form (Figure 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 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.



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

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

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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 of **1h** in acetone.

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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-trifluoromethylbenzenthiol 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 Supplementary Information for the effect of acetone in CCl_4 (Scheme S3a). The effect of pre-mixing of catalyst and **3a** in acetone was also described in Scheme S3b,c.