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O-Monoacyltartaric Acid/(Thio)urea Cooperative Organocatalysis for Enantioselective Conjugate Addition of Boronic Acid

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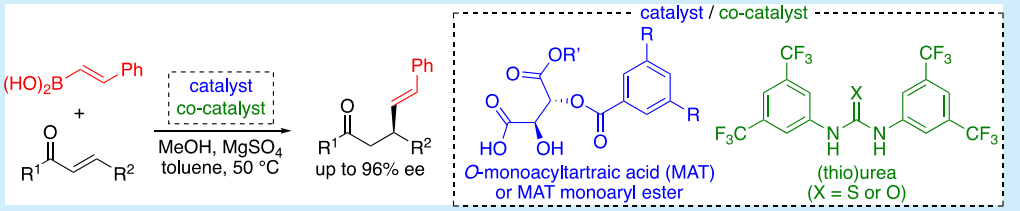

ABSTRACT: (Thio)urea cocatalyst accelerates *O*-monoacyltartaric acid (MAT)-catalyzed enantioselective conjugate addition of boronic acid to unsaturated ketone. Kinetic studies of this reaction revealed first-order dependence of each substrate and catalyst and second-order dependence of (thio)urea, leading to reduction of the catalyst loading and development of more active and enantioselective MAT monoaryl ester catalyst.

Organocatalysts offer several advantages such as designability, reusability, and low toxicity. Despite these benefits, their low catalytic activity is often a major limitation in their use.[1] Cooperative use of a hydrogen bond donor may greatly improve their catalytic activity.[2] Although the examples are still limited, combination of carboxylic acids and thioureas is one of the key strategies for cooperative Brønsted acid catalysis (Scheme 1).[3] For instance, Schreiner's thiourea **1a**[4,5] accelerates mandelic acid-catalyzed alcoholysis of styrene epoxides (Scheme 1a)[3a] and proline-catalyzed asymmetric aldol reactions (Scheme 1b).[3b−d,h] Combination of a chiral thiourea and benzoic acid catalyzes cyanosilylation of aldehydes (Scheme 1c).[3e] Thiourea/carboxylic acid-combined chiral catalysts effectively mediate asymmetric Povarov, Pictet−Spengler, and related reactions (Scheme 1d).[3f−o] Hydrogen bonding between thioureas and carboxylic acids (or their conjugate bases) enhances their acidities and creates an effective chiral environment. *O*-Monoacyltartaric acids (MAT) **2** (Scheme 1e) have been proven in our previous work as a class of asymmetric organocatalysts for 1,4-addition of boron compounds to α,β-unsaturated ketones.[6−8] Among the acyl groups tested, bulky benzoyl groups (R = *tert*-butyl or 1-adamantyl, R′ = H) gave optimal results. However, using 10 mol % of MAT catalyst is usually required to attain sufficient catalytic activity. Therefore, the use of thiourea **1a** and urea **1b** as cocatalysts was attempted, and kinetic studies were conducted to elucidate their effects. Here, we report MAT/(thio)urea cooperative catalysis leading to further improvement in catalytic activity and development of more active MAT monoaryl ester catalysts (R′ = aryl).

The reaction of chalcone (**3a**) and (*E*)-styrylboronic acid (**4a**) with 10 mol % of 3,5-di(1-adamantyl)benzoyl tartaric acid (**2a**)[6d] under previously optimized reaction conditions[6a] provided adduct **5aa** in a high yield with 88% ee (Table 1, entry 1). When the amount of catalyst **2a** was reduced from 10 to 3 mol %, the yield was decreased by half, and the enantioselectivity was also reduced (entry 2). Therefore, Schreiner's thiourea **1a** (9 mol %) was examined as cocatalyst and was found to recover both the yield and selectivity (entry 3). However, reproducibility was impeded: yields were sometimes in the 90% range and sometimes reduced to the 60% range. It was therefore rationalized that unknown amounts of water which may have been present in the boronic acid due to dehydrative formation of the corresponding boroxine might have suppressed the reaction progress. It has already been confirmed that appropriate amounts of methanol or water prevented uncatalyzed background reactions, but excess amounts suppressed even the desired catalytic reactions. To control the amount of water in the reaction medium, anhydrous $MgSO_4$, which was effective for conjugate addition of diborons,[6d] was used and assessed as a drying agent. Reproducible results were obtained (entry 4).

With the more-reproducible reaction conditions (MeOH and $MgSO_4$ additives), kinetic studies were conducted using 3,5-di(*tert*-butyl)benzoyltartaric acid (**2b**),[6a] which has been extensively studied in our work. The reaction of **3a** and **4a** (0.3 mmol each) in toluene was performed in the presence of 1,4-

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Org. Lett. XXXX, XXX, XXX−XXX

Scheme 1. Carboxylic Acid/(Thio)urea Cooperative Catalysis

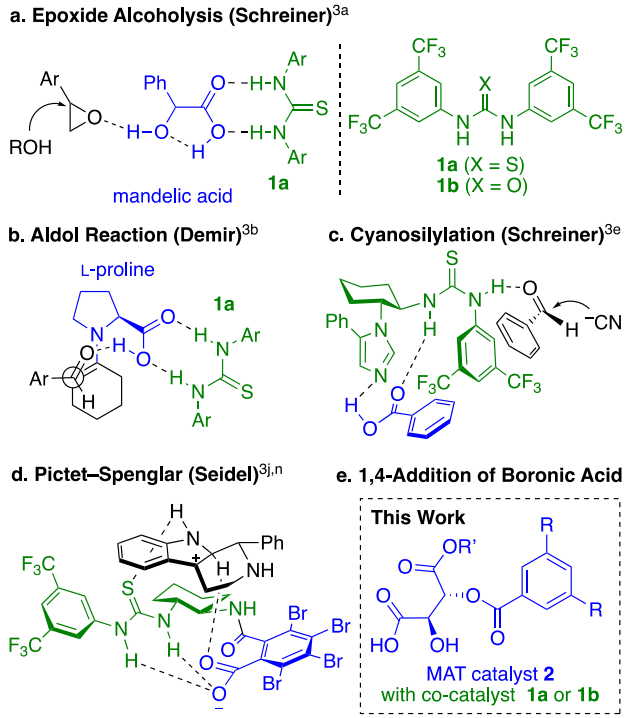
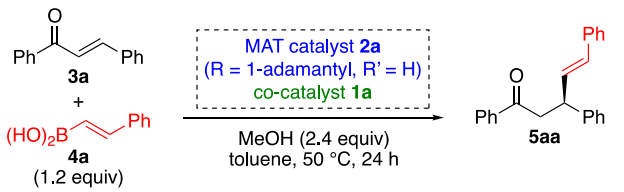


Table 1. Effect of Thiourea 1a on MAT-Catalyzed Conjugate Addition[a]



entry	2a (mol %)	1a (mol %)	yield (%)	ee (%)
1	10	0	98	88
2	3	0	46	85
3	3	9	92, 66, 62[c]	88, 85, 85[c]
4[b]	3	9	88, 91[d]	87, 87[d]

[a]Performed using MAT **2a**, chalcone (0.3 mmol), styrylboronic acid (0.36 mmol), and methanol (0.72 mmol) in toluene (1 mL) at 50 °C. [b]With anhydrous $MgSO_4$ (90 mg). [c]Results of three trials. [d]Results of two trials.

dimethoxybenzene as an internal standard and monitored by ^{1}H NMR analysis by taking aliquots of the reaction mixtures every hour until 5 h.[9] The presence of 1,4-dimethoxybenzene did not affect the reaction outcome. It turned out that the reaction rate followed first-order dependence of each substrate and catalyst concentration (Table 2 and eqs 1−3).[9,10]

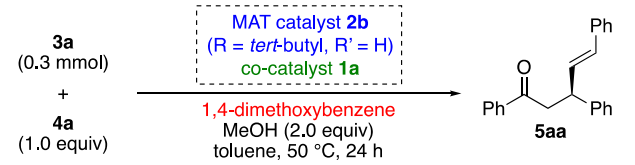
$$d[5aa]/dt = k'[3a][4a] = k'[3a]^2 \quad (1)$$

$$1/[3a] - 1/[3a]_0 = 2k't \quad (2)$$

$$k' = k[2b] \quad (3)$$

Next, the kinetic effect of thiourea **1a** and urea **1b** as the cocatalyst was investigated for the reaction using 3 mol % of MAT catalyst **2b** (Table 3). It was interesting that the rate

Table 2. Kinetic Study Using an Internal Standard[a]



entry	2b (mol %)	k' (M^{-1} h^{-1})	ee (%)
1	10	0.307	86
2	7	0.204	86
3	5	0.140	86
4	3	0.058	81

[a]Performed using MAT **2b**, chalcone (0.3 mmol), styrylboronic acid (0.3 mmol), 1,4-methoxybenzene (0.075 mmol), methanol (0.6 mmol), and $MgSO_4$ (90 mg) in toluene (1 mL) at 50 °C.

Table 3. Effect of Cocatalyst 1[a]

entry	cocatalyst	mol %	k' (M^{-1} h^{-1})	ee (%)
1		0	0.058	81
2	**1a**	3	0.072	85
3	**1a**	6	0.106	85
4	**1a**	9	0.188	84
5	**1b**	3	0.093	84
6	**1b**	6	0.143	83
7	**1b**	9	0.259	82

[a]With MAT **2b** (3 mol %), cocatalyst **1** (0, 3, 6, or 9 mol %), **3a** (0.3 mmol), **4a** (0.3 mmol), 1,4-dimethoxybenzene (0.075 mmol), methanol (0.6 mmol), and anhydrous $MgSO_4$ (90 mg) in toluene (1 mL) at 50 °C.

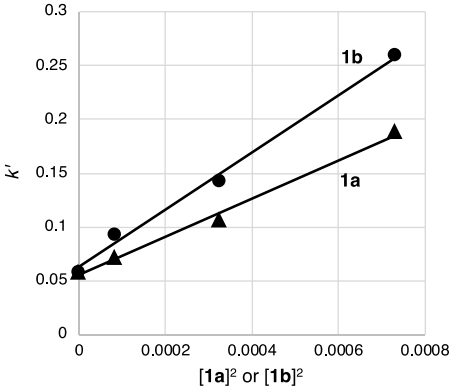


Figure 1. Plot of rate constant k' vs $[1]^2$.

constant k' exhibited a second-order dependence on the concentration of **1a** or **1b** (Figure 1). Urea **1b** was slightly more active than thiourea **1a**.[11,12] Close to no acceleration was observed with only **1a** or **1b** in the absence of catalyst **2b**. The enantioselectivity was also improved, although it tended to decrease as the amount of **1a** or **1b** increased. These results suggest that two molecules of **1a** or **1b** are associated in the rate-determining transition state.

Figure 2 shows a possible reaction mechanism. The MAT catalyst **2** reacts with boronic acid **4a** or the corresponding boroxine or methyl ester to generate dioxaborolanone **6a**, to which enone **3a** coordinates to form ternary complex **7aa**. Formation of **6a** was previously confirmed by ^{1}H NMR analysis.[6c] Because the reaction rate showed the first-order dependences on concentration of each substrate and catalyst as described above, generation of **7aa** is supposed to be

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Org. Lett. XXXX, XXX, XXX−XXX

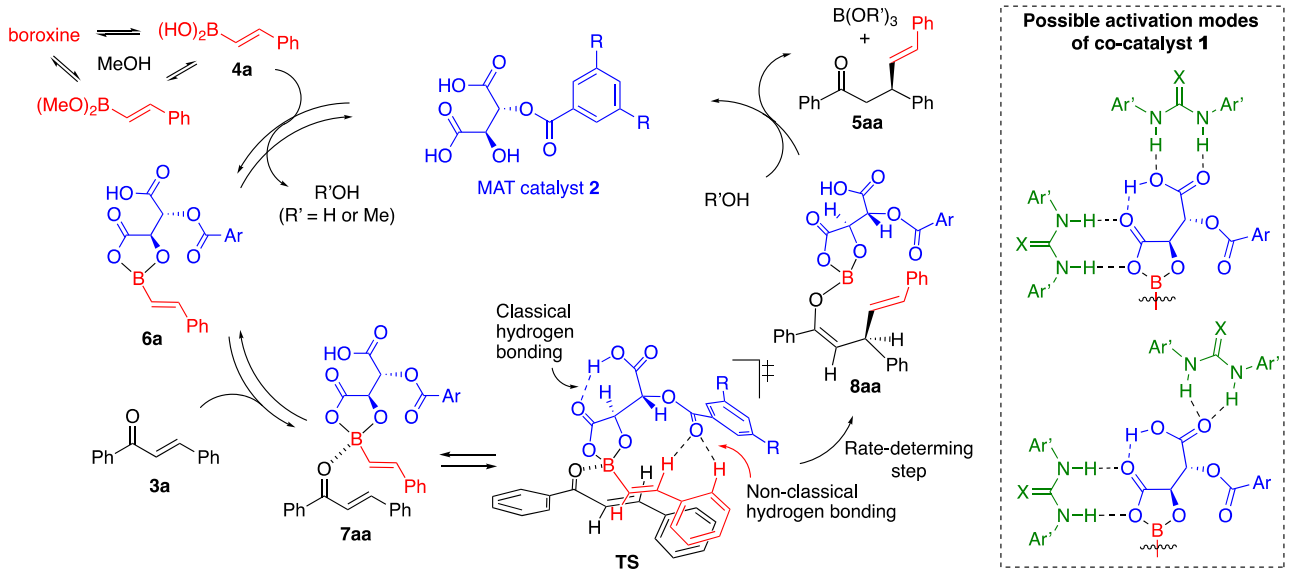
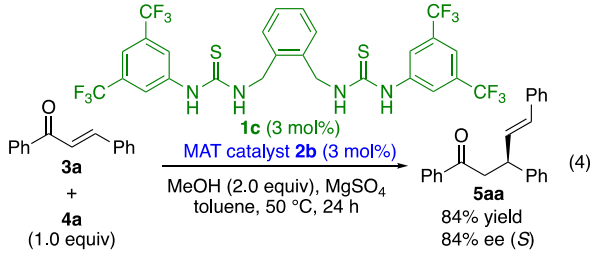


Figure 2. Assumed reaction mechanism.

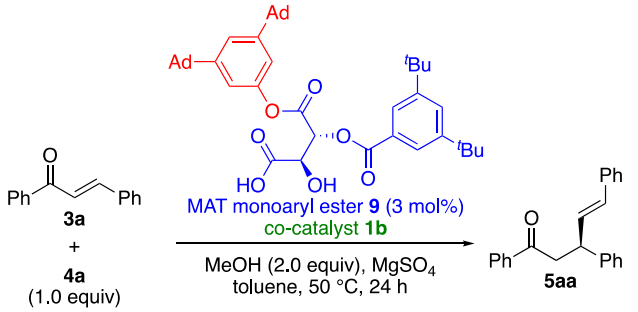
reversible.[13] The complex **7aa** next goes through the rate- and stereodetermining transition state **TS**, giving boron enolate **8aa**, which is immediately protonated by methanol or water to give product **5aa** along with regeneration of catalyst **2**. One might think that the boron byproduct $B(OR')_3$ is attached to MAT catalyst **2** and suppresses the catalyst turnover. This possibility was ruled out because the reaction proceeded at a similar rate in the presence of $B(OMe)_3$ (1.0 equiv) instead of methanol (2.4 equiv).[9] The computational studies[6c] on the most favored transition state **TS** have revealed that both the classical and nonclassical hydrogen bonding make **TS** the most stable, leading to product (*S*)-**5aa**. Considering the second-order dependence of thiourea **1a** or urea **1b**, two cocatalyst molecules could be associated in the rate-determining **TS**. It can be speculated that both the dioxaborolanone ring and the carboxy group are activated by hydrogen bond formation, as depicted in the dashed rectangle in Figure 2. The activation of the dioxaborolanone seems reasonable because the mandelic acid-catalyzed reaction was also accelerated by thiourea **1a**.[9]

It was thus envisaged that certain bis(thiourea)s should promote the reaction effectively. Screening several bis(thiourea)s revealed that 3 mol % of cocatalyst **1c**[14] was as effective as 6 mol % of thiourea **1a** (eq 4).



A question was raised as to how much catalytic activity would be expected if the carboxy group of the MAT **2b** bound to the cocatalyst was protected as an ester group. After screening of several MAT monoesters, 3,5-di(1-adamantyl)-phenyl ester **9**[15] was found to promote the reaction even more effectively than MAT **2b** (Table 4, entry 1 vs Table 2, entry 4). The reaction with catalyst **9** was also accelerated by urea **1b** (entries 1−3) and exhibited the first-order dependence of cocatalyst **1b** as expected.[9]

Table 4. Catalysis by MAT Monoaryl Ester 9[a]



entry	**1b** (mol %)	k' (M^{-1} h^{-1})	ee (%)
1	0	0.204	90
2	3	0.306	90
3	6	0.426	89

[a]Performed using catalyst **9** (3 mol %), cocatalyst **1b** (0, 3, or 6 mol %), **3a** (0.3 mmol), **4a** (0.3 mmol), methanol (0.6 mmol), and anhydrous $MgSO_4$ (90 mg) in toluene (1 mL) at 50 °C.

Finally, MAT monoester **9**/urea **1b** cooperative catalysis was applied to the reactions of other substrates (Table 5). The reaction of an electron-rich, heterocyclic boronic acid **4b** instead of (*E*)-styrylboronic acid (**4a**) proceeded smoothly to give good enantioselectivity (entry 2). The *o*-methoxy-substituted chalcone **3c** provided superior enantioselectivity, compared to *p*-methoxy- or *o*-bromo-substituted chalcone **3b** and **3d** (entries 3−5). This indicates that high enantioselectivity can be obtained when the enone has an electron-rich, sterically congested aromatic ring at the *β*-position. In fact, 1-naphthyl-substituted enone **3e** also provided high selectivity (entry 6). In the reaction of dienone **3f**, monostyrylated adduct **5fa**, which still has the enone function, was obtained with high selectivity (entry 7). In all cases, higher enantioselectivities were obtained with 3 mol % each of catalyst **9** and cocatalyst **1b** than when using 10 mol % of MAT **2b**.[16]

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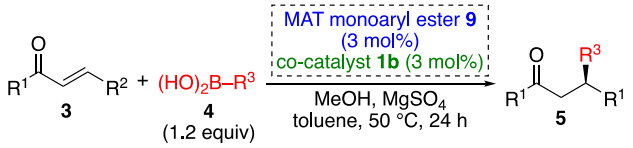
Org. Lett. XXXX, XXX, XXX−XXX

Table 5. Cooperative Catalysis for Conjugate Addition of Other Substrates.[a]



entry	3 (R^1, R^2)	4 (R^3)	5	yield (%)	ee (%)
1	**3a** (Ph, Ph)	**4a** [(*E*)-styryl]	**5aa**	97	90
2	**3a** (Ph, Ph)	**4b** (Ar[b])	**5ab**	89	83
3	**3b** (Ph, *p*-$MeOC_6H_4$)	**4a**	**5ba**	86	90
4[c]	**3c** (Ph, *o*-$MeOC_6H_4$)	**4a**	**5ca**	96	96
5	**3d** (Ph, *o*-BrC_6H_4)	**4a**	**5da**	91	88
6	**3e** (Ph, 1-naphthyl)	**4a**	**5ea**	93	94
7	**3f** ((*E*)-styryl, Ph)	**4a**[d]	**5fa**	81	92

[a]Performed using catalyst **9** (3 mol %), cocatalyst **1b** (3 mol %), **3** (0.3 mmol), **4** (0.36 mmol), methanol (0.72 mmol), and anhydrous $MgSO_4$ (90 mg) in toluene (1 mL) at 50 °C for 24 h. [b]Ar = 2-benzofuranyl. [c]Performed using **3c** (1.2 mmol) and **4a** (1.44 mmol). [d]With **4a** (1.0 equiv).

In summary, we demonstrated *O*-monoacyltartaric acid (MAT)/(thio)urea cooperative catalysis for enantioselective conjugate addition of boronic acids to enones. The kinetic studies have revealed second-order dependence of (thio)urea cocatalyst. This has led to reduction of the catalyst amount and development of more active MAT monoaryl ester catalysts. Computational studies on the cooperative catalysis and development of rationally designed, carboxylic acid-organocatalysts are ongoing.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.0c00981.

Experimental procedures, data of kinetic studies, ^1H and ^{13}C NMR spectra of new compounds, and HPLC chromatograms of optically active compounds (PDF)

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Notes

The authors declare no competing financial interest.

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(9) See Supporting Information.

(10) The first-order dependence of each substrate was also confirmed by monitoring the reactions between **3a** and **4a** in 1:2 or 2:1 ratio and by kinetic analysis using the initial velocity method for **4a**. See Supporting Information.

(11) For superiority of urea **1b** over thiourea **1a** in organocatalysis, see: (a) Maher, D. J.; Connon, S. J. Acceleration of the DABCO-promoted Baylis-Hillman Reaction using a Recoverable H-bonding Organocatalyst. *Tetrahedron Lett.* **2004**, *45*, 1301−1305. (b) Sun, L.; Wu, X.; Xiong, D.-C.; Ye, X.-S. Stereoselective Koenigs-Knorr Glycosylation Catalyzed by Urea. *Angew. Chem., Int. Ed.* **2016**, *55*, 8041−8044. (c) Maskeri, M. A.; O'Connor, M. J.; Jaworski, A. A.; Davies, A. V.; Scheidt, K. A. A Cooperative Hydrogen Bond Donor-Brønsted Acid System for the Enantioselective Synthesis of Tetrahydropyrans. *Angew. Chem., Int. Ed.* **2018**, *57*, 17225−17229.

(12) The superiority of urea **1b** over thiourea **1a** would be ascribed not to its acidity but to its planarity. The aromatic rings of thiourea **1a** are more twisted from the plane of the (thio)carbonyl group than those of urea **1b**. For the relationship with the chloride association constants, see: Ho, J.; Zwicker, V. E.; Yuen, K. K. Y.; Jolliffe, K. A. Quantum Chemical Prediction of Equilibrium Acidities of Ureas, Deltamides, Squaramides, and Croconamides. *J. Org. Chem.* **2017**, *82*, 10732−10736.

(13) A possible interpretation to support the reversibility is provided in Supporting Information.

(14) Jones, C. E. S.; Turega, S. M.; Clarke, M. L.; Philp, D. A Rationally Designed Cocatalyst for the Morita-Baylis-Hillman Reaction. *Tetrahedron Lett.* **2008**, *49*, 4666−4669.

(15) MAT monoester **9** was prepared by acetonide protection of MAT **2b** followed by condensation of the corresponding phenol with EDC·I. See Supporting Information.

(16) Based on the data in Table 5, the turnover numbers (TONs) and turnover frequencies (TOFs) were calculated to be 27−32.3 and 1.13−1.35 h^{-1}, respectively.

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