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Synthesis of Optically Active *N*-Aryl Amino Acid Derivatives through the Asymmetric Petasis Reaction Catalyzed by a Novel Hydroxy–Thiourea Catalyst

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Optically active nonproteinogenic amino acid derivatives have received considerable interest due to their biological activities and ability to serve as chiral building blocks in asymmetric synthesis. *N*-Aryl-substituted amino acid derivatives can act as a fibrinogen receptor antagonist,[1] hepatitis C virus replication inhibitor,[2] glycine antagonist[3] or an angiotensin receptor antagonist[4] as shown in Figure 1. In addition, it is known that some compounds of this class are protein kinase C (PKC) activators,[5] *N*-methyl-D-aspartate (NMDA) receptor antagonists,[6] and angiotensin converting enzyme (ACE) inhibitors.[7] Others have been shown to have anti-ulcer[8] and cyclosporine receptor-binding activity.[9] Notably, some consist of more than one amino acid moiety. However, despite the great importance of these structures, existing methods for their preparation rely heavily on the copper-catalyzed Ullmann-type N-arylation of amino acids.[10] For the synthesis of optically active derivatives, it is necessary to prepare the optically active parent α-amino acids. In addition, suitable aryl donors are limited to relatively electron-deficient and sparsely substituted aromatic compounds. On the other hand, several groups have reported catalytic asymmetric approaches for the synthesis of *N*-aryl amino acid units by using the 1,2-addition of *N*-aryl-α-iminoesters with several nucleophiles.[11] We considered that if a similar process was applied to *N*-aryl-α-imino amides instead of esters, it could be a direct and more useful method for the synthesis of peptides that contain *N*-aryl amino acid moieties. Recently, Li et al. reported the racemic 1,2-addition of *N*-aryl-α-imino amides and organoboronic acids.[12] However, to the best of our knowledge, an asymmetric version of this reaction has not yet been reported.

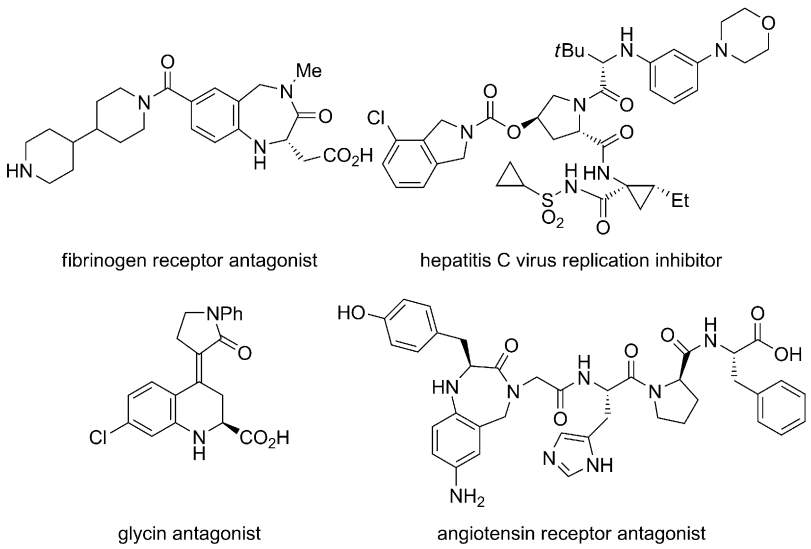

Figure 1. Examples of *N*-aryl amino acid derivatives.

The Petasis reaction is a powerful method for the synthesis of α-amino acid derivatives.[13] However, to date, there have been only two reports on asymmetric catalytic Petasis reactions.[14,15] We reported the Petasis reaction of quinolinium and vinyl boronic acids using a thiourea catalyst that contains an amino alcohol moiety.[14,16,17] The Schaus research group reported the three-component asymmetric organocatalytic Petasis reaction of ethyl glyoxylate, an aliphat-

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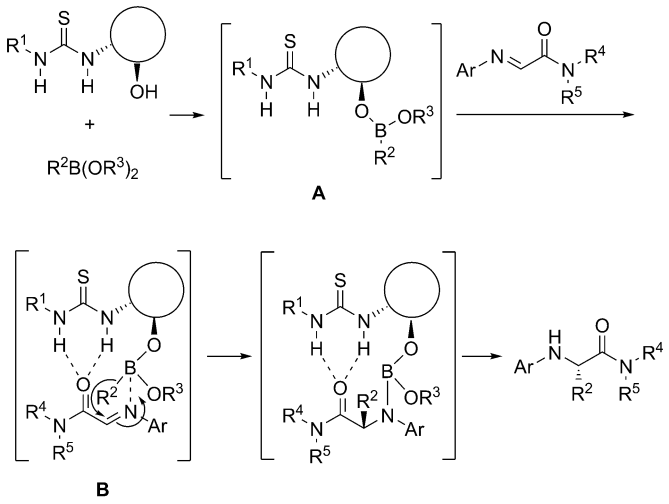
ic secondary amine, and vinylboronates.[15] In these reports, highly reactive iminium species were used as substrates. In the current project we planned to use *N*-aryl-α-imino amides as substrates and considered another methodology to achieve the asymmetric Petasis reaction. Our hypothesis is outlined in Scheme 1. When the thiourea and organobor-



Scheme 1. Our mechanistic proposal.

onic acid are combined, the chiral boronic acid–thiourea species **A** is formed. We considered that species **A** is a suitable component for the Petasis reaction with *N*-aryl-α-imino amides. It is predicted that the Lewis acidic boron atom of **A** would coordinate to the nitrogen atom of the imino group and the thiourea moiety would form hydrogen bonds with the amide carbonyl group. The resulting intermediate **B** would allow for the quasi-intramolecular attack of the R^2 substituent from the boron atom to the imino group owing to double activation. Herein, we report the first asymmetric 1,2-addition of *N*-aryl-α-imino amides using the thiourea catalyst we developed for the synthesis of *N*-aryl amino acid derivatives (Figure 2).

Initially, the asymmetric Petasis reaction of imino amide **4a**, which was readily prepared from **2a**[18] and **3a**, with *trans*-2-phenylvinylboronic acid diisopropyl ester **5a** was examined in the presence of 10 mol% of different catalysts **1** (Table 1). When amino alcohol-type thiourea **1a**, which we had previously reported as the best catalyst for the Petasis reaction of quinolines and vinylboronic acids,[14] was used, the desired adduct **6a** was obtained in poor yield and almost racemic form (Table 1, entry 1). Similarly, iminophenol-type catalyst **1b**[19] also did not give a good result (Table 1, entry 2). We anticipated that the basic amino or imino groups in catalysts **1a** and **1b** might prevent the boronates from coordinating to the nitrogen atom of **4a**. Therefore, we screened other hydroxy-type thioureas that did not contain basic sites. In the case of **1c**, while the enantiomeric excess was improved compared to those of **1a** and **1b**, the chemical yield remained low (Table 1, entry 3). Next, we tested the

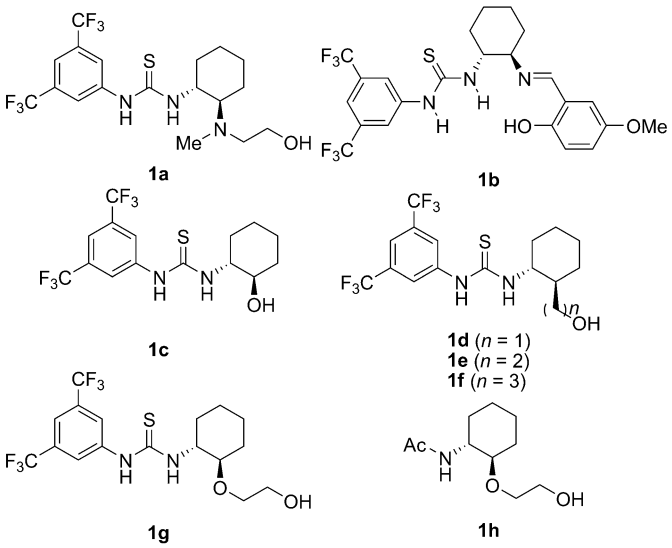
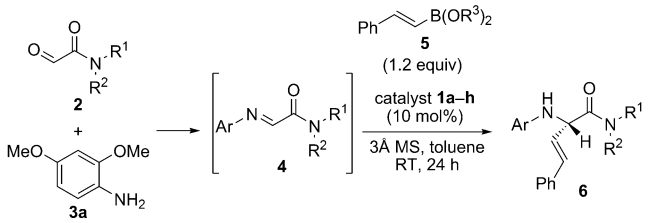


Figure 2. Organocatalysts examined in this study.

Table 1. Optimization of the reaction conditions.[a]



Entry	R^1	R^2	R^3	**1**	Yield [%][b]	*ee* [%][c]
1	Me	Me (**2a**)	*i*Pr (**5a**)	**1a**	21 (**6a**)	1
2	Me	Me (**2a**)	*i*Pr (**5a**)	**1b**	22 (**6a**)	30
3	Me	Me (**2a**)	*i*Pr (**5a**)	**1c**	18 (**6a**)	50
4	Me	Me (**2a**)	*i*Pr (**5a**)	**1d**	27 (**6a**)	12
5	Me	Me (**2a**)	*i*Pr (**5a**)	**1e**	29 (**6a**)	0
6	Me	Me (**2a**)	*i*Pr (**5a**)	**1f**	51 (**6a**)	46
7	Me	Me (**2a**)	*i*Pr (**5a**)	**1g**	47 (**6a**)	74
8	Me	Me (**2a**)	*i*Pr (**5a**)	**1h**	27 (**6a**)	1
9	Ph	Me (**2b**)	*i*Pr (**5a**)	**1g**	75 (**6b**)	86
10	Ph	Et (**2c**)	*i*Pr (**5a**)	**1g**	74 (**6c**)	90
11	Ph	Et (**2c**)	H (**5b**)	**1g**	72 (**6c**)	77
12	Ph	Et (**2c**)	Me (**5c**)	**1g**	69 (**6c**)	88
13	Ph	Et (**2c**)	Et (**5d**)	**1g**	70 (**6c**)	88
14[d]	Ph	Et (**2c**)	*i*Pr (**5a**)	**1g**	71 (**6c**)	62
15[e]	Ph	Et (**2c**)	*i*Pr (**5a**)	**1g**	8 (**6c**)	59
16[f]	Ph	Et (**2c**)	*i*Pr (**5a**)	**1g**	74 (**6c**)	92

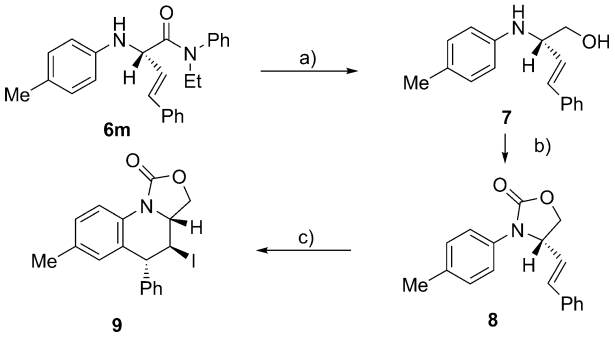
[a] Unless otherwise noted, the reactions were conducted with **2** (1.0 equiv), **3a** (1.0 equiv), **5** (1.2 equiv), **1** (10 mol%), and 3 Å MS (100 mg/1 mmol of **2**) in toluene at room temperature for 24 h. [b] Yield of isolated product for the two-step process based on **2**. [c] Determined by chiral HPLC analysis. [d] CH_2Cl_2 was used as the solvent. [e] Tetrahydrofuran (THF) was used as the solvent. [f] Cyclohexane was used as the solvent.

homologated thioureas **1d–f**. Although the enantioselectivities decreased with **1d** and **1e**, the chemical yields improved slightly by using catalysts with a linker between the chiral scaffolds and the hydroxy group. A pronounced increase in yield was observed with the three-carbon linker of thiourea **1f** (Table 1, entries 4–6). We assumed that the introduction

of another weak Lewis basic site into the carbon linker of the catalyst should result in the effective formation of a complex between the organoboronic acid and the catalyst. When we employed thiourea **1g**, which contained an ether moiety, we observed an improved result (Table 1, entry 7). Based on the results of the reaction catalyzed by the corresponding amide **1h**, it became clear that the thiourea moiety was necessary for the catalytic activity (Table 1, entry 8). Both the yield and enantioselectivity were further improved when we used the *N*-phenyl-*N*-methyl amide **4b**, and *N*-phenyl-*N*-ethyl amide **4c** was found to be the optimal substrate (Table 1, entries 9 and 10). With regard to the substituents of the boronic acid ester moieties, boronic acid **5b** gave a diminished enantioselectivity and other aliphatic boronates such as **5c** and **5d** gave results similar to those with **5a** (Table 1, entries 11–13). Next, we screened several solvents and found that less-polar solvents were desirable in this reaction, similar to that of other thiourea-catalyzed asymmetric reactions (Table 1, entries 14–16). The best result was obtained when we used cyclohexane as the solvent.[20]

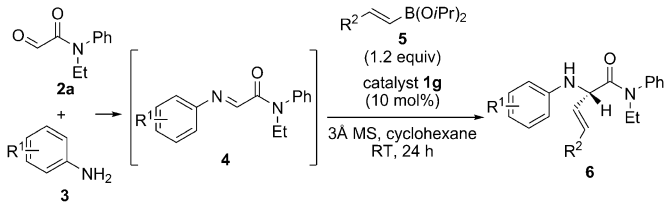
Next, we explored the scope of this reaction. The results are shown in Table 2. As expected, electron-rich vinyl boronates such as **5e** and **5f** gave good results with excellent enantiomeric excess (Table 2, entries 1 and 2). In addition, electron-poor **5g** could also be used and the enantioselectivity remained high (Table 2, entry 3). The position of the substituents in the aromatic ring did not influence the results (Table 2, entries 4 and 5). Heteroaromatic boronic acid ester **5j** gave the corresponding adduct **6i** in high stereoselectivity (Table 2, entry 6). In the case of the aliphatic vinyl boronic acid ester **5k**, although the reactivity was somewhat low, the enantioselectivity was maintained at a high level (Table 2, entry 7). With regard to the aromatic rings at the imine nitrogen atom, electron-rich substrates were preferred, in contrast to copper-catalyzed N-arylation reactions[10] (Table 2, entries 8–12). In addition, derivatives that contained hydroxymethyl or amino groups were also accessible (Table 2, entries 13 and 14).

We then investigated the interconversion of the obtained *N*-aryl amino acid derivatives into pharmacologically important heterocyclic structures, as shown in Scheme 2. The amide moiety of **6m** could be reduced into amino alcohol **7** by using $LiBHEt_3$,[21] and subsequently converted into the corresponding oxazolidinone **8**. When **8** was treated with benzyltrimethylammonium dichloroiodate ($BTMA{\cdot}ICl_2$) and $ZnCl_2$,[22] an intramolecular iodoarylation occurred to give the tricyclic dihydroquinoline derivative **9**, which could be a valuable pharmacophore, as a single diastereoisomer.[23] The diastereoselectivity of this reaction could be explained as follows. When the olefin moiety of **8** reacts with $BTMA{\cdot}ICl_2$, two possible diastereomers of the iodinium intermediates are produced. However, this step would be reversible and in only one of the diastereomers the phenyl ring is in the proper position to attack the iodonium, thereby producing the single diastereomer **9** under kinetic control.



Scheme 2. Synthesis of heterocycle **9**. Reaction conditions: a) $LiBHEt_3$, THF, −78 °C to RT, 30 min (71 %); b) 1,1-carbonyldiimidazole, toluene, 80 °C, 3 h (91 %); c) $BTMA{\cdot}ICl_2$, $ZnCl_2$, AcOH, RT, 1 h (65 %).

Table 2. Scope of boronates and anilines.[a]

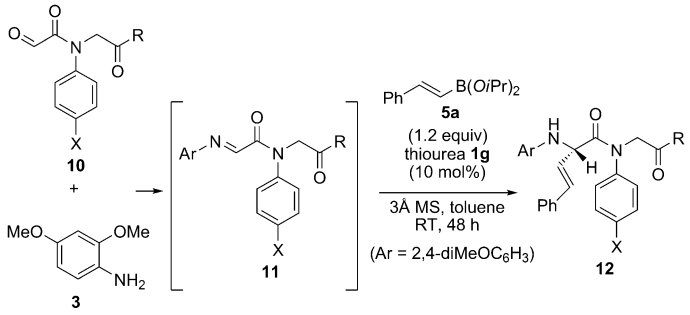


Entry	R^1	R^2	Yield [%][b]	*ee* [%][c]
1	2,4-$(MeO)_2$ (**4c**)	4-$MeOC_6H_4$(**5e**)	77 (**6d**)	87
2	2,4-$(MeO)_2$ (**4c**)	4-MeC_6H_4(**5f**)	76 (**6e**)	90
3	2,4-$(MeO)_2$ (**4c**)	4-ClC_6H_4(**5g**)	65 (**6f**)	90
4	2,4-$(MeO)_2$ (**4c**)	3-$MeOC_6H_4$(**5h**)	69 (**6g**)	89
5	2,4-$(MeO)_2$ (**4c**)	2-MeC_6H_4(**5i**)	86 (**6h**)	93
6	2,4-$(MeO)_2$ (**4c**)	3-thienyl(**5j**)	77 (**6i**)	89
7	2,4-$(MeO)_2$ (**4c**)	Cy(**5k**)	53 (**6j**)	80
8[d]	4-MeO (**4d**)	Ph (**5a**)	62 (**6k**)	82
9[d]	2-MeO (**4e**)	Ph (**5a**)	77 (**6l**)	86
10[d]	4-Me (**4f**)	Ph (**5a**)	78 (**6m**)	87
11[d]	H (**4g**)	Ph (**5a**)	58 (**6n**)	84
12[d]	2,3-Me_2 (**4h**)	Ph (**5a**)	56 (**6o**)	90
13[e]	2-$TBSOCH_2$ (**4i**)	Ph (**5a**)	63 (**6p**)	82
14[e]	3-NHBoc (**4j**)	Ph (**5a**)	54 (**6q**)	90

[a] Unless otherwise noted, the reactions were conducted with **2a** (1.0 equiv), **3** (1.0 equiv), **1g** (10 mol %), **5** (1.2 equiv), and 3 Å MS (100 mg/1 mmol of **2**) in cyclohexane at room temperature. [b] Yield of isolated product for the two-step process based on **2**. [c] Determined by chiral HPLC analysis. [d] Petasis reaction was performed for 48 h. [e] Petasis reaction was performed for 72 h. TBS = *tert*-butyldimethylsilyl; Boc = *tert*-butoxycarbonyl.

Next, we applied this reaction to the modification of peptide compounds (Table 3).[24] The reaction of **11a** with **5a** proceeded to give the Gly-(styryl glycine) compound **12a** in 82 % enantiomeric excess. Substrate **11b** containing a 4-bromophenyl group on the amide nitrogen atom could also be converted into the corresponding adduct **12b**, which can be used for further elaboration of the chemical structure by manipulation of the bromine atom (Table 3, entry 2). Next, we examined the synthesis of tripeptides. When we used **11c**, we obtained the desired tripeptide **12c** in good diastereoselectivity (Table 3, entry 3). The use of the enantiomeric

Table 3. Application in the peptide modification.[a]



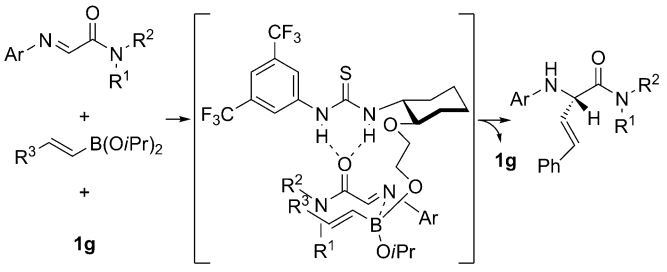
Entry	R	X	Yield [%][b]	*ee* [%][c]	d.r.[d]
1	-OMe	OMe (**10a**)	67 (**12a**)	82	–
2	-OMe	Br (**10b**)	71 (**12b**)	92	–
3	-(L)-Ala-OMe	OMe (**10c**)	58 (**12c**)	–	85:15
4	-(D)-Ala-OMe	OMe (*ent*-**10c**)	57 (**12d**)	–	89:11
5	-(L)-Phe-OMe	OMe (**10d**)	60 (**12e**)	–	88:12

[a] The reactions were conducted with **10** (1.0 equiv), **3** (1.0 equiv), **5a** (1.2 equiv), **1g** (10 mol%), and 3 Å MS (100 mg/1 mmol of **10**) in toluene at room temperature. [b] Yield of isolated product for the two-step process based on **10**. [c] Determined by chiral HPLC analysis. [d] Determined by ^{1}H NMR analysis.

substrate *ent*-**11c** gave the other diastereoisomer of **12c** as a major product (Table 3, entry 4). Therefore, the stereoselectivity of this process is controlled by the catalyst. In addition, **11d**, which contains a more bulky amino acid unit than that of **11c**, could be converted to the corresponding tripeptide **12e** (Table 3, entry 5).

Finally, we have performed spectroscopic experiments to obtain insight into the reaction mechanism.[25] When a 10:1 mixture of **5d** and **1g** was analyzed in toluene by ESI-MS,[26] the mass of the 1:1 complex of **5d** and **1g** was observed. In addition, ^{1}H NMR studies revealed that the boronate **5d** immediately exchanged an ethoxy group for the hydroxy thiourea at room temperature, thus liberating ethanol. An equilibrium between **1g**, **5d**, and the complex was quickly reached (< 5 min), and the composition of the mixture did not change over time. Similar results were seen with **1g** and **1f**. Therefore, we conclude that the ether moiety of **1g** does not serve to accelerate the formation of the thiourea–boronate complex.

One possible reaction intermediate is shown in Scheme 3. As shown in our proposal (Scheme 1), the boron atom coordinates to the nitrogen atom of the imine moiety, and the thiourea moiety forms a hydrogen bond with the amide carbonyl oxygen. We assume that the higher enantioselectivity of **1g** is a result of the additional dipole moment introduced by the oxygen in the alcohol chain. The dipole moments of the carbon–oxygen bonds in the $ROCH_2CH_2OH$ subunit might align themselves so that the overall dipole moment is minimized. This limits the number of possible conformations of the transition state as compared to, for example, catalyst **1f**. Further studies are currently underway to clarify the precise mechanism of this reaction.



Scheme 3. Possible reaction pathway.

In summary, we have developed a bifunctional hydroxy thiourea-catalyzed asymmetric Petasis reaction of *N*-aryl-α-imino amides and vinyl boronates. This process can be used not only for the asymmetric synthesis of unnatural amino acid derivatives but also for the stereoselective synthesis of modified dipeptides and tripeptides. Further studies are currently underway to reveal the reaction mechanism.

Experimental Section

A mixture of *N*-ethyl-*N*-phenyl glyoxylamide **2c** (84.1 mg, 0.475 mmol), 2,4-dimethoxyaniline **3a** (72.7 mg, 0.475 mmol), and Na_2SO_4 (67.5 mg, 0.475 mmol) in toluene (2.0 mL) was stirred at room temperature for 1 h. After that, the mixture was filtered and the filtrate was evaporated in vacuo to afford the imine **4c**, which was used without further purification. A mixture of **4c**, **5a** (132 mg, 0.570 mmol), 3 Å molecular sieves (47.5 mg), and thiourea catalyst **1g** (20.4 mg, 0.0475 mmol) in cyclohexane (9.5 mL) was stirred under an argon atmosphere at room temperature. After 24 h, the reaction mixture was directly purified by silica-gel column chromatography (eluent hexane/EtOAc 2:1) to obtain the desired product **4c** (146 mg, 74% over 2 steps, 92% *ee*).

Acknowledgements

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Keywords: amino acids · asymmetric synthesis · organocatalysis · Petasis reaction · thiourea

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