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Asymmetric Petasis Reactions Catalyzed by Chiral Biphenols

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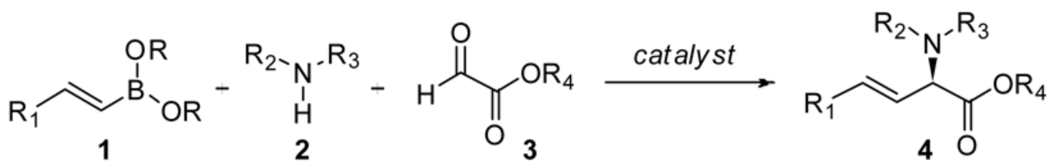
Asymmetric multicomponent reactions efficiently yield chiral compounds in a single process.[1] The Petasis reaction is the multicomponent condensation of boronic acids with amines and aldehydes.[2] Accessibility of the reagents and the mild reaction conditions make the method extremely practical. The use of glyoxylates in the reaction results in the construction of α-amino acids.[2b] If the reaction were rendered asymmetric, the process would be an attractive approach for the synthesis of chiral amino acids.[3] Asymmetric approaches have focused on the use of chiral substrates.[4] Chiral amines[4a,c,d] and chiral boronate esters[4b] have been used to access enantioenriched α-amino acids. More recently, a chiral organic catalyst promoted the asymmetric addition of boronates to activated quinolines.[5] Chiral biphenol-derived diols serve as proficient catalysts for asymmetric reactions involving boronates[6] and we postulated their utility could be expanded to include multicomponent condensation reactions. Herein we report the development of an asymmetric Petasis reaction between alkenyl boronates, secondary amines, glyoxylates, and chiral biphenol catalysts to afford chiral α-amino acids (eq 1).



(1)

We initiated our investigation with the reaction of (*E*)-styrylboronates with dibenzylamine and ethyl glyoxylate (Table 1). In the absence of any catalyst, the reaction of styrylboronic acid **6a** afforded the racemic α-amino ester **9** in 80% isolated yield at −15 °C (entry 1). In contrast, only trace amount of desired product was formed when (*E*)-diisopropyl styrylboronate **6b** was subjected to the reaction (entry 2). Addition of 20 mol% (*S*)-BINOL to the reaction mixture resulted in a significant rate enhancement and moderate enantioselectivity (er = 60:40, entry 3). Evaluating other chiral BINOL derivatives and solvents did not provide a significant improvement in yield or enantioselectivity with the (*S*)-3,3′-Br_2-BINOL catalyzed reaction in toluene affording the product in 65% isolated yield and 3:1 er as the best result (entry 4). Diminished yields and enantioselectivities were observed from the use of catalysts that possess large substituents at the 3,3′-positions (entries 5 & 6). Electron withdrawing substituents at these positions resulted in higher yields, but the enantioselectivity was still low (entry 7). Monosubstituted BINOL derivatives were also evaluated in the reaction (entries 8 – 10). Interestingly 3-CF_3SO_2-BINOL **5h** catalyzed reaction resulted in higher yield and enantioselectivity (72:28 er). Finally, the use of vaulted biaryl phenols (*S*)-VANOL and (*S*)-VAPOL[7] as catalysts afford the chiral α-amino ester in good yields (>77%) and good er's (>87:13, entries 11 & 12). We next evaluated the effect of the boronate alcohol ligands on the

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enantioselectivity of the reaction. Dimethyl boronate resulted in higher yields and improved enantioselectivity (entry 13). However, diethyl and dibutyl boronate gave higher enantioselectivities with diethyl styrylboronate affording **9** in highest er (95.5:4.5, entry 14). The reaction of **6a** in the presence of **5j** resulted in almost no enantioselectivity but high yields most likely due to a high rate of uncatalyzed reaction (entry 16).

The optimized reaction conditions for dibenzylamine and ethyl glyoxylate required 15 mol% (*S*)-VAPOL **5j**, diethyl boronate, and 3Å molecular sieves. Catalyst **5j** could be recovered from the reaction and reused without lost of activity or enantioselectivity. These conditions proved to be general for a variety of alkenyl boronates (Table 2). Electron rich and electron deficient styrenyl boronates afforded corresponding α-amino ester in good yields and high er's (entries 1 – 5). Heteroaromatic substituted alkenyl boronate **14f** was also a good substrate for the reaction (entry 6). Reactions using alkyl substituted boronates displayed slower reaction rates but the selectivities remained high (entries 7 – 9). Disubstituted vinyl boronates also proved equally effective in the reaction (entries 10 & 11). We next evaluated the scope of secondary amines using the general reaction conditions (Table 3). Secondary benzyl amines afforded the corresponding α-amino esters in good yield and enantioselectivities (entries 1 –6).

Good functional group tolerance was observed with more complex amines (entries 4 – 6). The less nucleophilic ethyl aniline (entry 7) resulted in slightly lower yield and selectivity. Diallylamine proved effective in the reaction (entry 8). Both enantiomers of allyl α-methyl-benzylamine were subjected to the (*S*)-**5j**-catalyzed reaction. The (*R*)-derived amine resulted in 9:1 dr with (*R*,*R*)-**17i** as major product (entry 9). With the (*S*)-amine the catalyst still appeared to control the selectivity (84:16 dr, entry 10). Diamines were also good coupling partners for the reaction. The reaction of diamine **18** with boronate **6d** and ethyl glyoxylate generated piperazinone **19** in good yield er (Scheme 1).[8]

Mechanistic studies using NMR and ESI-MS analysis of reaction mixtures at room temperature indicated single ligand exchange consistent with our previous observations.[6d] Monitoring the reaction by ^{11}B-NMR demonstrated conversion of a trivalent vinyl boronate to a tetravalent boronate species at 5.4 ppm consistent with previous observations.[9] Also congruous with observations made by Petasis,[2a] aminals **20** and **21** were found to be equally reactive in the reaction to afford **9** in comparable yield and er's whereas the use of (dibenzylamino) methanol **22** resulted in little product formation (Scheme 2). These observations highlight the possible intermediacy of an aminal and the importance of the glyoxylate ester functionality.

In summary, we have developed an enantioselective Petasis reaction catalyzed by chiral biphenols. Mechanistic studies are ongoing to facilitate expansion of the scope and utility.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgements

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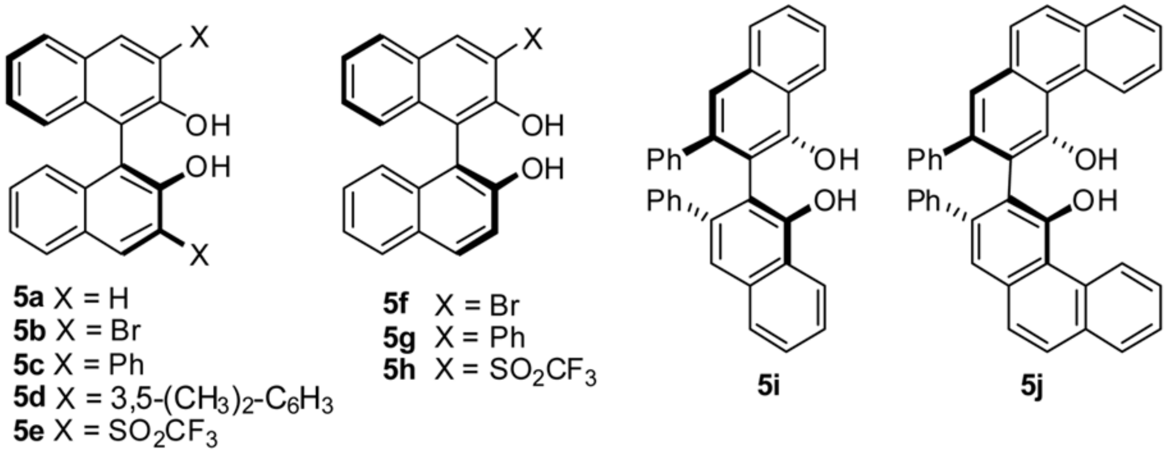
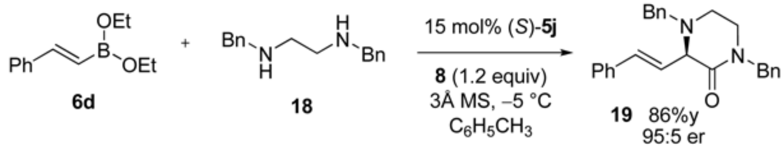
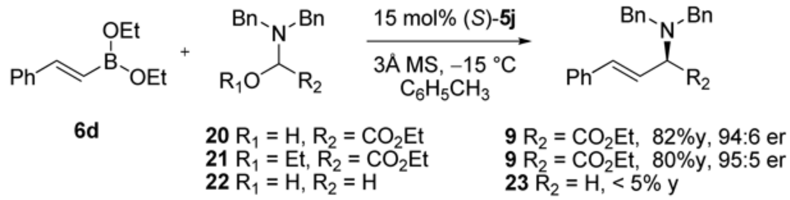


Figure 1.
Chiral Biphenols.


OEt
Ph
B
OEt
6d
+
Bn
N
H
H
N
Bn
18
15 mol% (S)-5j
8 (1.2 equiv)
3Å MS, –5 °C
$C_6H_5CH_3$
Bn
N
Ph
N
Bn
O
19 86%y
95:5 er

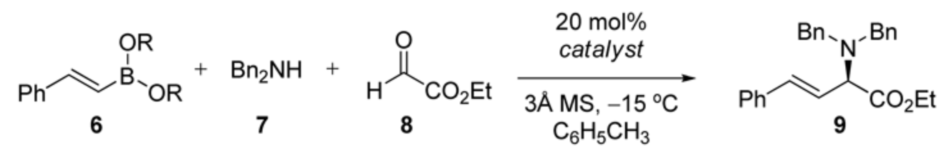
Scheme 1.


OEt
Ph
B
OEt
6d
+
Bn
N
Bn
R1O
R2
20 R1 = H, R2 = CO2Et
21 R1 = Et, R2 = CO2Et
22 R1 = H, R2 = H
15 mol% (S)-5j
3Å MS, –15 °C
C6H5CH3
Bn
N
Bn
Ph
R2
9 R2 = CO2Et, 82%y, 94:6 er
9 R2 = CO2Et, 80%y, 95:5 er
23 R2 = H, < 5% y

Scheme 2.

Table 1

Asymmetric Petasis Reaction Catalyzed by Chiral Diols[a]



entry	boronate	R	catalyst	% yield[b]	er[c]
1	**6a**	H	-	80	-
2	**6b**	*i*-Pr	-	<5	-
3	**6b**	*i*-Pr	**5a**	45	60:40
4	**6b**	*i*-Pr	**5b**	65	75:25
5	**6b**	*i*-Pr	**5c**	51	70:30
6	**6b**	*i*-Pr	**5d**	25	59:41
7	**6b**	*i*-Pr	**5e**	70	55:45
8	**6b**	*i*-Pr	**5f**	60	70:30
9	**6b**	*i*-Pr	**5g**	43	64:36
10	**6b**	*i*-Pr	**5h**	67	72:28
11	**6b**	*i*-Pr	**5i**	77	85:15
12	**6b**	*i*-Pr	**5j**	80	87:13
13	**6c**	CH_3	**5j**	90	90:10
14	**6d**	Et	**5j**	81	95.5:4.5
15	**6e**	*n*-Bu	**5j**	77	93:7
16	**6a**	H	**5j**	90	57:43

[a] Reactions were run with 0.15 mmol boronate, 0.10 mmol dibenzylamine, 0.10 mmol glyoxylate, 0.020 mmol catalyst, and 3Å molecular sieves in toluene (0.1 M) for 24 h under Ar, followed by flash chromatography on silica gel.

[b] Isolated yield.

[c] Enantiomeric ratios determined by chiral HPLC analysis.

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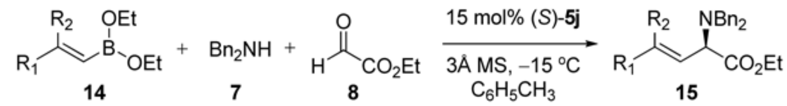
Table 2

Asymmetric Petasis Reaction with Dibenzylamine **7**[a]



entry	R_1	R_2	product	% yield[b]	er[c]
1	Ph	H	**15a**	81	95.5:4.5
2	*p*-CH_3O-C_6H_4	H	**15b**	84	96:4
3	*p*-Br-C_6H_4	H	**15c**	82	95:5
4	*m*-F-C_6H_4	H	**15d**	80	95:5
5	*m*-CF_3-C_6H_4	H	**15e**	82	95:5
6	3-C_4H_3S	H	**15f**	87	95:5
7[d]	C_6H_{11}	H	**15g**	76	97:3
8[d]	*n*-Bu	H	**15h**	73	95:5
9[d]	$BnOCH_2$	H	**15i**	74	95.5:4.5
10	Ph	CH_3	**15j**	78	95:5
11[d]	*n*-Bu	CH_3	**15k**	71	93:7

[a] Reactions were run with 0.25 mmol **14**, 0.25 mmol amine, 0.25 mmol glyoxylate, 0.0375 mmol (*S*)-**5j**, and 3Å molecular sieves in toluene for 36 h under Ar, followed by flash chromatography on silica gel.

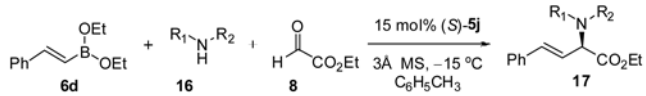
[b] Isolated yield.

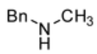
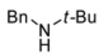
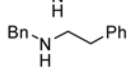
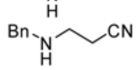
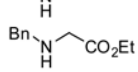
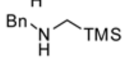
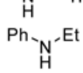
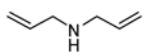
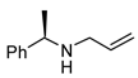
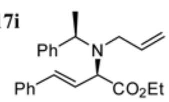
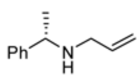
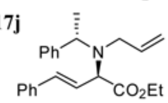
[c] Determined by chiral HPLC analysis.

[d] Reactions were run at 0 °C.

Table 3

Asymmetric Petasis Reaction with Boronate **6d**[a]



entry	amine	product	% yield[b]	er[c]
1		**17a**	81	95:5
2		**17b**	73	93:7
3		**17c**	82	97:3
4		**17d**	80	98.5:1.5
5		**17e**	94	95:5
6		**17f**	84	95.5:4.5
7		**17g**	74	89:11
8		**17h**	87	97:3
9		**17i** 	81	dr 90:10 (*R*,*R*:*R*,*S*)
10		**17j** 	89	dr 84:16 (*S*,*R*:*S*,*S*)

[a]Reactions were run with 0.25 mmol **6d**, 0.25 mmol amine, and 15 mol % catalyst and 3Å molecular sieves in toluene for 36 h under Ar, followed by flash chromatography on silica gel.

[b]Isolated yield.

[c]Determined by chiral HPLC analysis.