Multicomponent Reactions

DOI: 10.1002/anie.201103271

Catalytic Diastereoselective Petasis Reactions**

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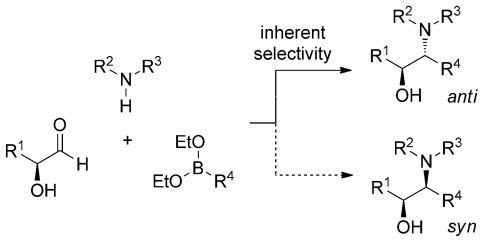
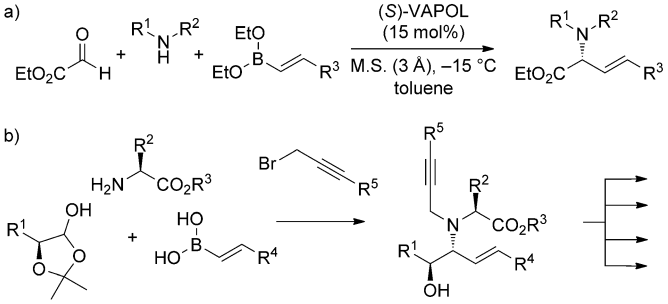
The Petasis boronic acid Mannich reaction is a versatile multicomponent reaction of boronic acids, amines, and aldehydes that generates highly functionalized α-amino acids and β-amino alcohols.[1] When enantiopure α-hydroxy aldehyde derivatives are used as the carbonyl component in the reaction, enantiopure β-amino alcohols are produced with exclusively *anti* diastereoselectivity.[2] This motif has proven useful in the synthesis of stereodefined, biologically active molecules including sialic acids,[3] iminocyclitols,[4] and pyrrolizidine alkaloids.[5] The characteristic of the diastereoselective boronic acid Mannich reaction that makes it valuable, namely its predictable sense of *anti* diastereoselectivity, is also its limitation because *syn* β-amino alcohols are unattainable under these conditions [Eq. (1)].[6] Previous attempts to



(1)

obtain *syn* β-amino alcohols through the Petasis reaction have been unsuccessful and underscore the difficulty in overriding the intrinsic selectivity of the reaction.[7] Herein, we report the first diastereoselective Petasis reaction catalyzed by chiral biphenols that enables the synthesis of *anti* and *syn* β-amino alcohols in pure form.

This collaborative project was undertaken with the goal of developing a catalyst-controlled diastereoselective Petasis reaction. We recently developed the first enantioselective Petasis reaction between alkenyl boronates, secondary amines, and ethyl glyoxylates catalyzed by chiral biphenols (Scheme 1 a) and anticipated this type of ligand-exchange



Scheme 1. a) Catalytic enantioselective Petasis reaction and b) a DOS library synthesis utilizing the diastereoselective Petasis reaction. M.S. = molecular sieves.

catalysis would be applicable to the diastereoselective variant.[8,9] An immediate application of this methodology is a synthetic route to the full matrix of stereoisomeric products of a pathway conceived for use in small-molecule screening (Scheme 1 b).[10] This type of library development continues to represent a substantial challenge given current limitations in synthetic methodology. The synthesis of compounds having stereogenic carbon centers in diversity-oriented synthesis (DOS) appears to be useful based on one study showing a correlation between compounds with intermediate stereochemical complexity and improved binding selectivity.[11] In addition, stereochemistry-based structure–activity relationships (SSAR) can provide important clues that facilitate optimization and modification studies following the discovery of a small-molecule lead.[12]

Initial development of the *syn*-selective Petasis reaction focused on (*S*)-5-benzyl-2,2-dimethyl-1,3-dioxolan-4-ol **5a**, L-phenylalanine methyl ester **6a**, and (*E*)-diethyl styrylboronate **7a**—a modified reaction from our previous library synthesis.[10] The uncatalyzed reaction of these components produced exclusively the *anti* β-amino alcohol **8** (Table 1, entry 1). Catalysts (*S*)-VAPOL **1**, (*S*)-H_8-BINOLs **2a** and **2b**, (*S*)-BINOLs **3a** and **3b** were tested in the reaction, and although *syn* β-amino alcohol **8** was observed in the product mixture, these catalysts primarily gave the *anti* diastereomer (Table 1, entries 2–6). A breakthrough occurred with catalyst (*S*)-3,3′-Br_2-BINOL **4**, which produced the *syn* diastereomer **8** as the major product in 4:1 d.r. (Table 1, entry 7). Attempts to optimize the diastereoselectivity through solvent effects (Table 1, entries 9–11) and boronate ligation were unsuccessful (Table 1, entries 12 and 13); however, an increase in *syn* selectivity to 5.5:1 d.r. was found with the addition of molecular sieves (4 Å; Table 1, entry 8). In addition, the two diastereomers were separable on normal-phase chromatography allowing for isolation of the *syn* product in 54% yield.

This result shows for the first time that it is possible to overcome the inherent selectivity of the diastereomeric

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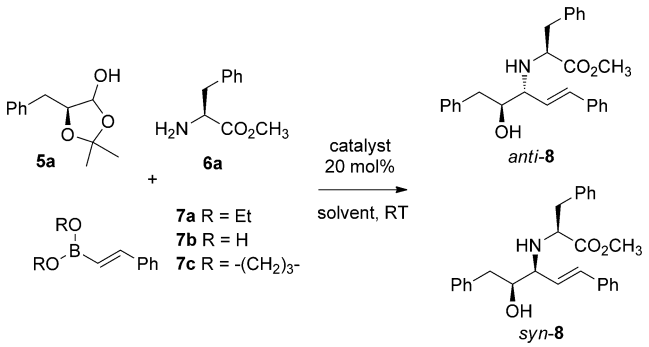
[**] This research was supported by the NIH (R01 GM078240, S.E.S. and P.N.M.). The NIGMS-sponsored Center of Excellence in Chemical Methodology and Library Development (P50-GM069721, S.L.S and G.M.) enabled this research.

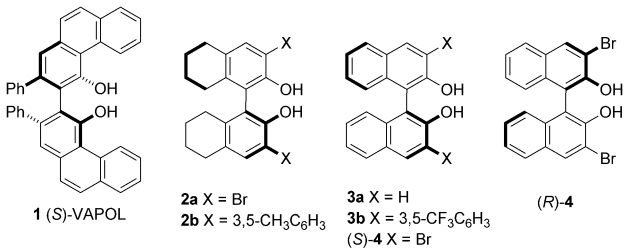
Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/anie.201103271.

Table 1: Diastereoselective Petasis reaction.[a]



Entry	Catalyst	Boronate	Solvent	Yield [%][b]	d.r. *syn*/*anti*[c]
1	–	**7a**	$PhCF_3$	24	*anti* only
2	**1**	**7a**	$PhCF_3$	69	1:10
3	**2a**	**7a**	$PhCF_3$	73	1:6
4	**2b**	**7a**	$PhCF_3$	66	1:8
5	**3a**	**7a**	$PhCF_3$	41	1:4
6	**3b**	**7a**	$PhCF_3$	81	2:3
7	(*S*)-**4**	**7a**	$PhCF_3$	70	4:1
8	(*S*)-**4**	**7a**	$PhCF_3$	68 (54)	5.5:1[d]
9	(*S*)-**4**	**7a**	toluene	67	1:1
10	(*S*)-**4**	**7a**	CH_2Cl_2	57	1:3
11	(*S*)-**4**	**7a**	THF	<5	n.d.
12	(*S*)-**4**	**7b**	$PhCF_3$	48	1:1.5
13	(*S*)-**4**	**7c**	$PhCF_3$	<5	n.d.
14	(*R*)-**4**	**7a**	$PhCF_3$	86	*anti* only
15	*rac*-**4**	**7a**	$PhCF_3$	84	1:9

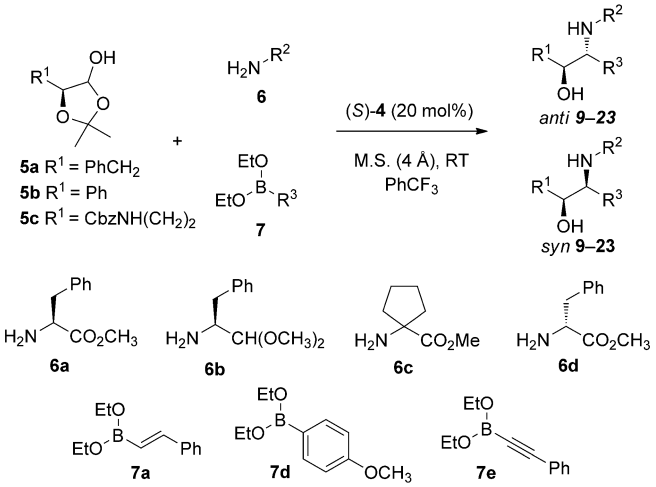
[a] Reactions were run with 0.4 mmol of boronate, 0.2 mmol of lactol, 0.2 mmol of amine, and 20 mol% of catalyst in organic solvent (0.2 M) for 24 h under Ar, and subsequently purified by flash chromatography on silica gel. [b] Yield of diastereomeric mixture upon isolation. Yield in parenthesis is the yield of the isolated *syn* diastereomer (>20:1 d.r.). [c] Determined by ^{1}H NMR spectroscopy. [d] Run with molecular sieves (4 Å). n.d = not determined.



Petasis reaction and obtain *syn* β-amino alcohols in their pure form. The ability of the catalyst to control the diastereoselectivity from >99:1 d.r. (*anti* as major product) to 5.5:1 d.r. (*syn* as major product) represents remarkable kinetic control of the reaction. Interestingly, the enantiomers of the catalysts form a matched and a mismatched relationship with other components of the reaction. When enantiomeric catalyst (*R*)-**4** was used in the reaction the *anti* product was formed exclusively in 86% yield (Table 1, entry 14), while the racemic catalyst (±)-**4** gave the *anti* product in 9:1 d.r. (Table 1, entry 15). Therefore, the *S*-configured catalysts give mismatched selectivity and form the *syn* product, while the *R*-configured catalysts are matched and reinforce the *anti* pathway.

With optimized conditions in hand, we explored the scope of the *syn*-selective reaction. In all cases, the uncatalyzed reaction gave only the *anti* β-amino alcohol. Alkene addition with boronate **7a** formed primarily the *syn* diastereomer with lactol **5b** and L-phenylalanine-derived amines **6a** and **6b** (Table 2, entries 1 and 2). The Cbz-protected amino lactol **5c** was also successful, thus indicating high functional group tolerance in the reaction (Table 2, entries 3 and 4). Isolation of the pure *syn* β-amino alcohols **9**–**12** was possible in these reactions in yields up to 80%. Aryl addition was also possible in the reaction using 4-methoxyphenylboronate **7d**, which afforded the *syn* product with amino ester **6a** (Table 2, entries 5–7). However, the use of amino acetal **6b** in the aryl addition reaction led to poor diastereoselectivity and the products were inseparable by chromatography on silica gel (Table 2, entries 8–10). Alkynylboronate **7e** in combination with lactol **5a** and amine **6a** afforded the *syn* product in

Table 2: Diastereoselective Petasis reaction[a]



Entry	Lactol	Amine	Boronate	Product	Yield [%][b]	d.r. *syn*/*anti*[c]
1	**5b**	**6a**	**7a**	**9**	95 (80)	5.5:1
2	**5b**	**6b**	**7a**	**10**	96 (84)	7:1
3	**5c**	**6a**	**7a**	**11**	84 (56)	2:1
4	**5c**	**6b**	**7a**	**12**	77 (45)	1.5:1
5	**5a**	**6a**	**7d**	**13**	62 (n.d.)	5:1
6	**5b**	**6a**	**7d**	**14**	75 (n.d.)	4:1
7	**5c**	**6a**	**7d**	**15**	73 (n.d.)	2:1
8	**5a**	**6b**	**7d**	**16**	65 (n.d.)	1:1
9	**5b**	**6b**	**7d**	**17**	70 (n.d.)	1:10
10	**5c**	**6b**	**7d**	**18**	71 (n.d.)	1:4
11	**5a**	**6a**	**7e**	**19**	77 (62)	5:1
12	**5a**	**6c**	**7a**	**20**	70 (45)	2:1
13	**5b**	**6c**	**7a**	**21**	71 (40)	1.5:1
14	**5c**	**6c**	**7a**	**22**	69 (33)	1:1
15	**5a**	**6d**	**7a**	**23**	61 (n.d.)	1:3

[a] Reactions were run with 0.2 mmol of boronate, 0.1 mmol of lactol, 0.1 mmol of amine, 20 mol% of catalyst, and M.S. (4 Å) in $PhCF_3$ (0.2 M) for 16–60 h under Ar, and subsequently purified by flash chromatography on silica gel. [b] Yield of the diastereomeric mixture upon isolation. Yield in parenthesis is the yield of the isolated *syn* diastereomer (>20:1 d.r.). [c] Determined by ^{1}H NMR spectroscopy. The *anti* products were synthesized using the matched catalyst (*R*)-**4** and the same reaction conditions. Cbz = benzyloxycarbonyl.

5:1 d.r. with 62% yield of the pure *syn* diastereomer (Table 2, entry 11).

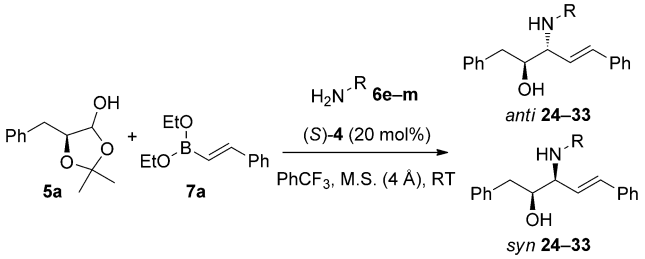
Next, the achiral amino ester **6c** and D-amino ester **6d** were tested under the catalyzed conditions. The reaction of amine **6c**, alkenylboronate **7a**, and lactol **5a** gave the *syn* diastereomer with 2:1 d.r. in 70% yield (Table 2, entry 12). Changing the aldehyde component afforded the *syn* product in 1.5:1 d.r. with lactol **6b** and 1:1 d.r. with lactol **6c** (Table 2, entries 13 and 14). The reaction with D-phenylalanine methyl ester **6d**, boronate **7a**, lactol **5a**, and (*S*)-**4** formed primarily the *anti* product **23** in 3:1 d.r. (Table 2, entry 15). Attempts to optimize the reaction through the use of other biphenol catalysts failed to generate better diastereoselectivity.[13] These results dramatically demonstrate the influence of the amine stereogenic center as a third element of diastereocontrol. It becomes apparent that the D-amine is a matched pair with (*S*)-lactol and reinforces the *anti* selectivity of the reaction, while the L-amine has matched selectivity with the *S*-configured catalyst to form the *syn* product.

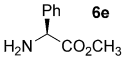
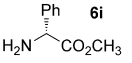
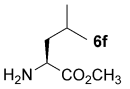
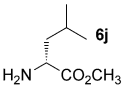
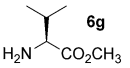
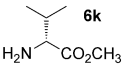
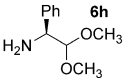
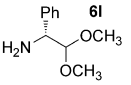
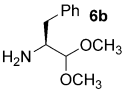
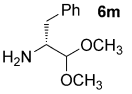
Owing to the significance of the amino acid configuration on product diastereoselectivity, we compared the catalyzed reaction of boronate **7a** and lactol **5a** with the various D- and L-amino acid derivatives. Whereas the L-phenylglycine amino ester **6e** gave the *syn* product in 2:1 d.r., the D enantiomer **6i** produced the *anti* product in 20:1 d.r. (Table 3, entries 1 and 6). Similar results appeared in the reaction with enantiomers of leucine-derived **6f** and **6j** and valine-derived amino esters **6g** and **6k** (Table 3, entries 2, 7, 3 and 8, respectively), in which the L-amine provides the *syn* product and the D-amine provides *anti* product. The size of the substituents also affects the selectivity of the reaction, with smaller groups affording higher quantities of *syn* product. Interestingly, the D-phenylalanine dimethyl acetal **6m** gave the *syn* product in 4:1 d.r. under the catalyzed conditions and was isolated as the pure *syn* diastereomer in 38% yield (Table 3, entry 10). Therefore, phenylalanine dimethyl acetals **6b** and **6m** are able to form the full matrix of stereoisomeric products in the library.

As an extension of this methodology, glycolaldehyde dimer **34** was used in the reaction to synthesize primary β-amino alcohols. The uncatalyzed reaction of amine **6e**, boronate **7a**, and glycolaldehyde **34** produced a 4:1 mixture of the (*S*,*S*)-amino alcohol **35** and (*S*,*R*)-amino alcohol **36** (Scheme 2). Use of 20 mol% of (*S*)-**4** gave > 20:1 d.r. of (*S*,*S*)-amino alcohol **35**. This result indicates that both the catalyst and amine direct the boronate addition to the form of the *S*-stereogenic center of the amino alcohol. The *R*-configured catalyst (*R*)-**4** produced the opposite diastereomers **36** in 10:1 d.r. and easily overcomes the inherent selectivity of the amine component. These results are further evidence of the matched selectivity of catalyst (*S*)-**4** with L-amino acids and catalyst (*R*)-**4** with D-amino acids.

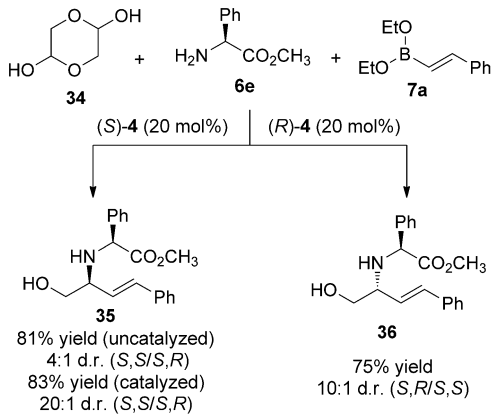
Next, we undertook a preliminary mechanistic investigation of the catalyzed reaction. The stereochemical model for

Table 3: Diastereoselective Petasis reaction with L- and D-amines.[a]



Entry	L-Amine	Yield [%][b]	d.r. *syn*/*anti*[c]	Entry	D-Amine	Yield [%][b]	d.r. *syn*/*anti*[c]
1	 **6e**	55 (n.d.)	2:1	6	 **6i**	57 (n.d.)	1:20
2	 **6f**	80 (56)	7.5:1	7	 **6j**	71 (n.d.)	1:2
3	 **6g**	65 (n.d.)	2.5:1	8	 **6k**	68 (n.d.)	1:6
4	 **6h**	72 (48)	2:1	9	 **6l**	74 (n.d.)	1:10
5	 **6b**	94 (80)	6:1	10	 **6m**	83 (38)	4:1

[a] Reactions were run with 0.2 mmol of boronate, 0.1 mmol of lactol, 0.1 mmol of amine, 20 mol% of catalyst, and M.S. (4 Å) in $PhCF_3$ (0.2 M) for 16–60 h under Ar, and subsequently purified by flash chromatography on silica gel. [b] Yield of diastereomeric mixture upon isolation. Yield in parenthesis is the yield of only the isolated *syn* diastereomer. [c] Determined by ^1H NMR spectroscopy. The *anti* products were synthesized using the matched catalyst (*R*)-**4** and the same reaction conditions.



Scheme 2. Catalytic Petasis reaction using glycolaldehyde.

the *anti* diastereoselective Petasis reaction involves an α-hydroxy-directed boronate addition to the imine, and proceeds through a Felkin–Anh-type transition state.[14] Unsurprisingly, the use of 3-phenylpropanal and (*S*)-2-methoxy-3-phenylpropanal in the catalyzed reaction gave only trace amounts of product (< 1% yield). This outcome indicates that the boronate coordination to the α-hydroxy group remains

critical for reactivity and explains the immense stereochemical influence of the lactol. The boronate also appears to undergo a single-ligand exchange with the catalyst as evidenced by ^{1}H NMR and ESI-MS analysis.[13] Therefore, it appears the boronate undergoes both ligand exchange with the catalyst and coordination with the α-hydroxy aldehyde during the course of the reaction. This type of activation is in line with the current mechanistic model of the diastereoselective Petasis reaction, as well as previous models for catalytic activation of boronates with chiral diols.[8,9]

Because this reaction relies on three stereocontrolling elements, it can be classified as a catalytic triple-diastereoselective reaction. Although catalytic reactions involving double diastereoselectivity are well studied, catalyzed reactions involving three elements of diastereocontrol are rare. To this end, the research groups of Masamune and Kishi have pioneered and produced elegant studies in this area.[15] However, because these initial reports have not investigated all enantiomers of the three stereocontrolling elements, this is the first report for which all enantiomers of the components have been examined. What we learned from this reaction can be simplified into a few generalized rules. 1) The uncatalyzed reaction maintains exclusively *anti* diastereoselectivity regardless of the amine, lactol, or boronate components. 2) Although the amine is unable to overcome the diastereocontrol of the lactol, the structure and configuration of the amine play a large role in the diastereoselectivity of the catalyzed reaction. 3) The matched combination of an L-amine and *S*-configured catalyst usually produces predominantly the *syn* diastereomers. 4) In general, the matched combination of D-amine and (*S*)-lactol using the catalyst-promoted conditions leads to the *anti* β-amino alcohol with the exception of amino acetal **6m**, a characteristic of this particular reaction we are continuing to explore.

In conclusion, we have reported the first diastereoselective Petasis reaction of boronates, α-hydroxy aldehydes, and amines to produce *syn* β-amino alcohols. In many cases the *syn* product can be obtained in isomerically pure form for further elaboration. Furthermore, the full matrix of stereoisomers for use in library synthesis was achieved using phenylalanine methyl acetal, and we believe other amines will be successful at this task. Although these preliminary results indicate that a number of challenges have yet to be met, this study represents a substantial improvement in the utility and scope of the reaction. Our current efforts are focused on the improvement of this catalyst system and further investigations are ongoing to understand the mechanism and activity of this reaction.

Received: May 12, 2011
Published online: July 12, 2011

Keywords: asymmetric catalysis · boronic acids · multicomponent reactions · organocatalysis · Petasis reaction

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