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Diastereoselective Petasis-Borono-Mannich Crotylation Reactions of Chiral α-Heteroatom (F, OBz, OH) Aldehydes: Rapid Access to Valuable Mono and Bicyclic Heterocyclic Scaffolds

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The crotylation reactions of chiral α-F, α-OBz and α-OH aldehydes under Petasis-borono-Mannich conditions using (*E*)- or (*Z*)-crotylboronates and primary amines resulted in γ-addition products in high dr and high er. α-F and α-OBz aldehydes gave 1,2-*anti*-2,3-*syn* and 1,2-*anti*-2,3-*anti*, products, respectively while an α-OH aldehyde gave 1,2-*syn*-2,3-*syn* products. The stereochemical outcomes of reactions of the former aldehydes can be explained using a six-membered ring transition state (TS) model in which a Cornforth-like conformation around the imine intermediate is favoured resulting in 1,2-*anti* products. The 2,3-stereochemical outcome is dependent upon the geometry of the crotylboronate. These TS models were also supported by DFT calculations. The stereochemical outcomes of reactions employing an α-OH aldehyde can be rationalised as occurring via an open-TS involving H-bonding in the imine intermediate between the α-OH group and the imine N atom. Representative products were converted to highly functionalized 1,2,3,6-tetrahydropyridines and 3*H*-oxazolo[3,4-*a*]pyridine-3-ones which will be valuable scaffolds in synthesis.

Introduction

Modern organic chemistry seeks the rapid synthesis of chiral molecular architectures for diverse ends such as the synthesis of chiral ligands and catalysts,[1] tools for natural product synthesis and structure elucidation[2] and drug development.[3] One such method for the synthesis of chiral heteroatom substituted molecules is the Petasis-borono-Mannich (PBM) reaction,[4] a one-pot three-component coupling of typically a racemic or enantioenriched α-hydroxy- or an α-*N*-tosylamino-aldehyde, a primary or secondary amine and an aryl,[5] vinyl,[5a,6] allenyl[7] or alkynyl[8] boronic acid, ester or trifluoroborate (Scheme 1a).[9] The reaction classically exhibits strong *anti*-diastereoselectivity towards the respective 1,2-amino alcohol or 1,2-diamino products (Scheme 1a).[5a,7a,c,10] In contrast, recently investigated PBM reactions using allylboronates, ammonia as the amine component, and two chiral α-heteroatom (X=OH or OTBS) substituted aldehydes gave *syn*-1,2-amino alcohol products (Scheme 1b).[11] Simple, achiral aldehydes also reacted efficiently under similar reaction conditions to give homoallylic primary amines. The differences in stereochemical outcomes [*anti* (Scheme 1a) versus *syn* (Scheme 1b)] are consistent with different modes of reactivity of the aforementioned boron reagents and allyl boronate. The former group of boron reagents require an α-hydroxy substituent on the imine intermediate formed in situ to activate the boronate ($R^4B(OR)_2$) by complexation, leading to intramolecular delivery of the R^4 group to the imine via a conformation that minimizes 1,3-allylic strain.[7a,9,12] While the more reactive allylic boronates do not require such activation and usually react with imines through their γ-carbon.[13] Our most recent work has found *anti*-selective PBM allylation reactions using chiral α-fluoro-[14] and α-benzoyloxyaldehydes,[15] and *syn*-selective PBM allylation reactions using racemic glycolaldehydes (Scheme 1c).[15]

The use of the PBM reaction in crotylation reactions has been limited to achiral aldehydes (Scheme 2a).[11,16] The development of such reactions to include chiral α-heteroatom[17] (X=F, OBz or OH) aldehydes would expand the scope of the PBM reaction providing products having three contiguous stereogenic centres. Herein we report the results of our study of the crotylation reactions of chiral α-heteroatom aldehydes with the focus on the crotylation reactions of chiral α-fluoroaldehydes[18] due to the importance of fluorine as a substituent in drug,[19] chiral ligand and organocatalyst development.[20] Furthermore, we demonstrate the utility of these products in the synthesis of valuable, highly substituted 1,2,3,6-tetrahydropyridine[21] and 3*H*-oxazolo[3,4-*a*]pyridin-3-one scaffolds[22] (Scheme 2b).

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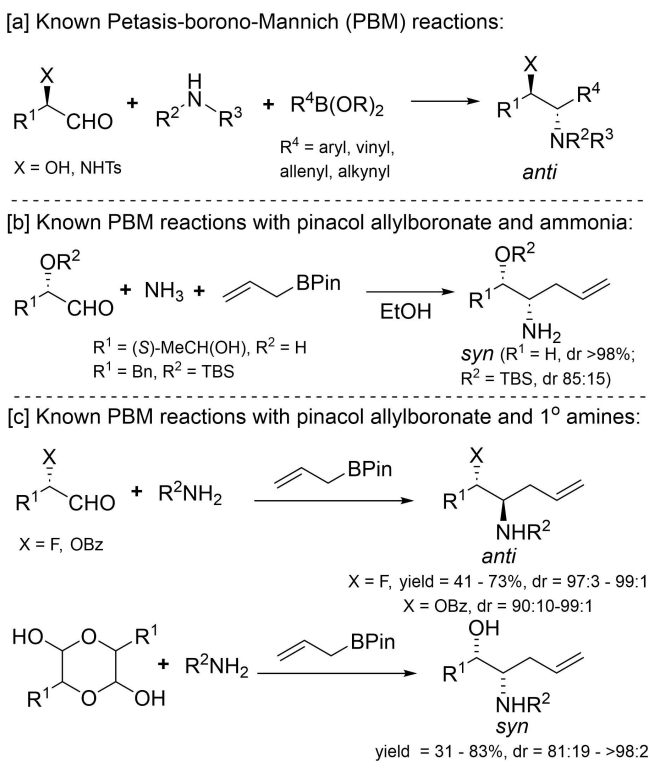
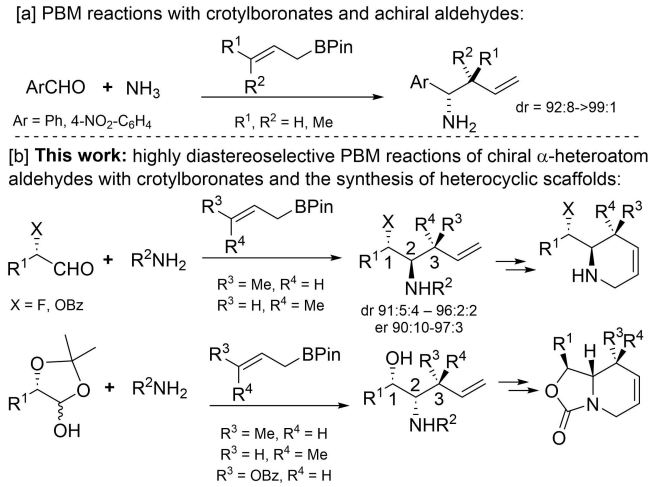


Scheme 1. [a] Classical Petasis-borono-Mannich (PBM) reaction giving 1,2-*anti*- products. [b] PBM reactions of allylboronates and NH_3 resulting in 1,2-*syn* amino alcohols. [c] Allylative PBM reactions of chiral α-heteroatom aldehydes giving *anti*-products, while those with glycolaldehydes gave *syn*-products.



Scheme 2. Crotylation PBM reactions. [a] Previous examples have been limited to benzaldehydes. [b] This work using chiral α-heteroatom aldehydes and the subsequent synthesis of valuable heterocyclic scaffolds.

Results and Discussion

Reactions with chiral α-fluoroaldehydes

The results of our crotylation reactions of chiral (*S*)-α-fluoroaldehydes (*S*)-**A-1** are summarised in Table 1. A similar procedure to that previously used in our PBM allylation reactions was initially applied for these crotylation reactions. This involved reacting chiral α-fluoroaldehydes (*S*)-**A-1** prepared via organocatalysis[23] with primary amines and pinacol (*E*)- or (*Z*)-crotylboronates in a methanol/pentane mixture.[14] Research into the isolation of α-fluoroaldehydes had been hampered by the high volatility of these compounds; in this study we discovered that the initially formed α-fluoroimine intermediate **B** was a solid and could be isolated by concentration *in vacuo*. In the case of the α-fluoroimine **B** (R^1=R^2=Bn), for example, its synthesis was readily evident by ^{1}H NMR spectroscopic analysis ([$CDCl_3$] δ 7.82 (ddt, *J* = 7.4, 4.2, 1.5 Hz, 1H); 5.26 (dt, *J* = 8.4, 4.3 Hz, 0.5H) and 5.17–5.11 (m, 0.5H), C*H*F; 4.71–4.58 (m, 2H), 3.26–3.02 (m, 2H)). Once isolated, the crude α-fluoroimine **B** was dissolved in methanol then treated with pinacol (*E*)- or (*Z*)-crotylboronate (r.t., 20 h). In the case of the PBM crotylation reactions of (2*S*)-fluoro-3-phenylpropanal with benzylamine these reactions could be conveniently monitored by ^{1}H NMR spectroscopy in CD_3OD solution, which revealed full consumption of the α-fluoroimine **B** (R^1=R^2=Bn), in 20 h for both isomers of the crotylboronate. The yields in Table 1 are overall yields for the three synthetic steps from the starting aldehyde (R^1CH_2CHO) and are based on the limiting reagent *N*-fluorobenzenesulfonimide (NFSI; F–N-($SO_2Ph)_2$). The reactions of α-fluoroaldehydes with (*E*)-crotylboronate gave the 1,2-*anti*-2,3-*syn* products **1a**–**1i** diastereoselectively with the corresponding 1,2-*anti*-2,3-*anti* products **2** being formed as the minor diastereomers (dr (**1**:**2**) 91:7 to 96:4) whereas reactions with (*Z*)-crotylboronate gave the 1,2-*anti*-2,3-*anti* products **2a**–**2f** diastereoselectively with the 1,2-*anti*-2,3-*syn* products **1** being the minor diastereomers (dr (**2**:**1**) 96:2 to 95:3). In each case a small amount (up to 5%) of a third diastereomer (labelled **x** and **x**′ in Table 1 and Figure 1) was also detected by ^{19}F NMR spectroscopy.

The ^{19}F NMR chemical shift similarity of **1a** (^{19}F NMR [377 MHz, $CDCl_3$] δ −184.72, −185.36 [major], −197.72) and **2a** (^{19}F NMR [377 MHz, $CDCl_3$] δ −184.72 [major], −185.37, −190.83) to the allylated analogue **3** (^{19}F NMR [377 MHz, $CDCl_3$] δ −188.72 [major, *anti*], −192.43 [minor, *syn*]) indicated that **1a** and **2a** had the 1,2-*anti* configuration (Figure 1), and by inference compounds **1** and **2** (Table 1). The minor third

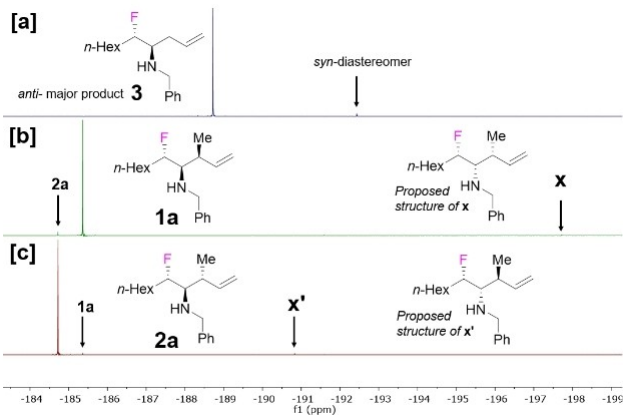
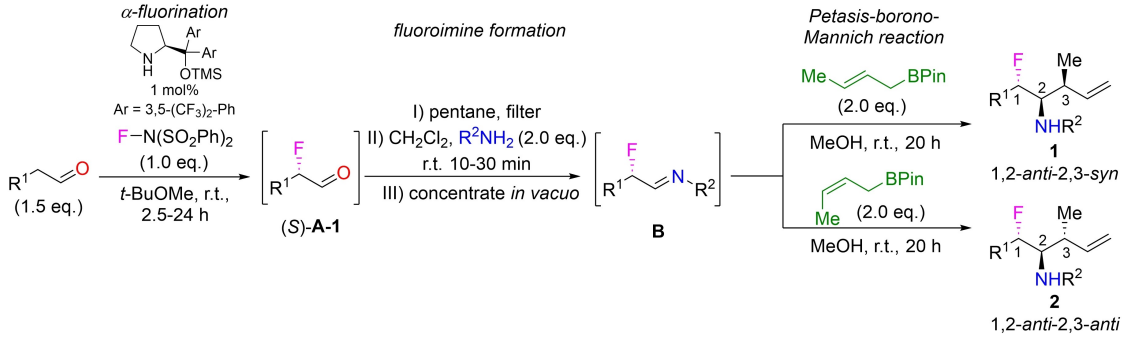
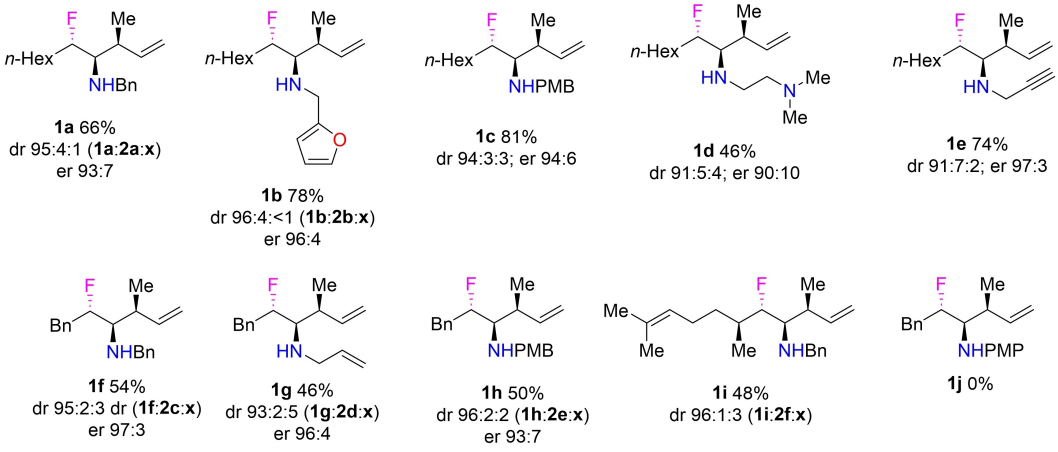


Figure 1. ^{19}F NMR spectra (377 MHz, $CDCl_3$) of [a] *anti*-allyl-β-fluoroamine **3** (dr = 97:3). [b] Crotylated product **1a** and [c] crotylated product **2a**, an epimer of **1a**.

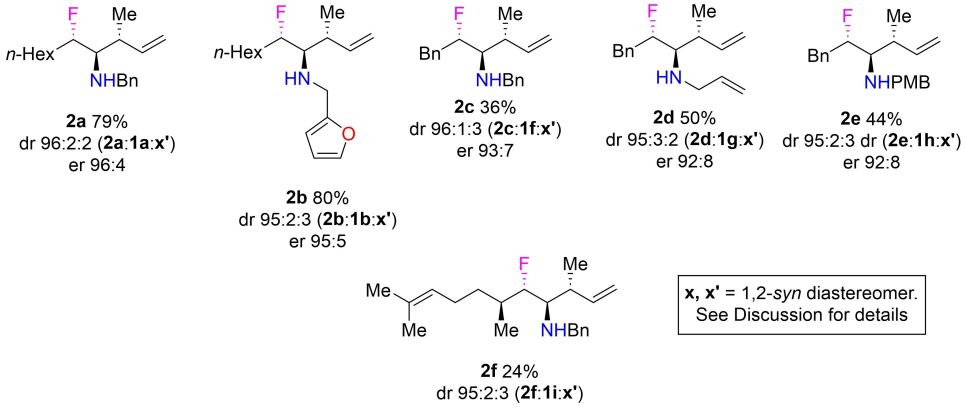
Table 1. Petasis-borono-Mannich crotylation reactions of chiral α-fluoroaldehydes.[a]



Examples from pinacol (*E*)-crotylboronate:



Examples from pinacol (*Z*)-crotylboronate:



[a] Reactions were performed using 0.45 mmol of the starting aldehyde and 0.30 mmol of NFSI as the limiting reagent.

observed diastereomer **x** and **x**′ we propose to be the 1,2-*syn*-fluoroamine compounds, based on the consistently more shielded ^{19}F NMR chemical shifts which are comparable to the 1,2-*syn*-minor diastereomers of the analogous allylated compound **3**. Nevertheless, unequivocal identification of the absolute configurations of **x**/**x**′ would only be possible by their independent total synthesis.

A total of 16 examples were synthesised with yields and drs being comparable to those of the analogous allylation reactions (Scheme 1c, X=F), where the limiting factor was the efficiency of the initial α-fluorination reaction.[14] The drs of **1** and **2**, formed as major diastereomers from (*E*)- and (*Z*)-crotylboronate, respectively, could be readily measured from the ^{19}F NMR spectra of the purified compounds. Comparison of the crude dr to the purified dr by ^{19}F NMR spectroscopy indicated that the major diastereomer was not being isolated as the sole product during column chromatography (e.g. **1f**, see Supporting Information). The enantiomeric excess of the major diastereomer was determined by ^{1}H NMR and occasionally ^{19}F NMR analysis using the literature method with (*R*)- and (*S*)-1,1′-binaphthyl-

2,2′-diylphosphoric acids where the ratio of the diastereomeric salts could be readily measured (Figure 2).[24] These reactions showed good tolerance to variations of the primary amine, including heteroatomic examples. However, no reaction was found using the aromatic primary amine ($PMPNH_2$) for **1j**. Further investigation of this example by ^1H NMR spectroscopy indicated that no imine (**A**–**1**, R^1=Bn, R^2=PMP), or enamine was formed in the course of the reaction. The chiral and more hindered β-substituted aldehyde (*S*)-citronellal was also found to undergo α-fluorination and this intermediate was an appropriate substrate for crotylation with products **1i** and **2f** exhibiting four contiguous stereocentres.

With the *anti*-relative configuration of the β-fluoroamine moiety established based on ^{19}F NMR chemical shifts, the relative configuration of the amino and methyl substituents were determined by NOE spectroscopy of products derived from ring-closing metathesis (RCM) from epimers **1g** and **2d** (Scheme 3). The secondary nitrogen of these amines was found to be resistant to tosylation reactions. This lack of reactivity was understood to be due to the steric effect of the extra β-Me group, where sulfonylation in good yields were possible on related allyl substates (e.g. **3**) in which this substituent was absent.[14] *N*-protection, however, was found to be possible using trifluoroacetic anhydride/Et_3N in THF solution. Unfortunately this protection strategy introduced rotamers to the NMR spectra of the protected and ring-closed products, and determination of the relative configuration between C-2 and C-3 was not possible unless the amine nitrogen was deprotected using $LiAlH_4$. This reaction was performed at r.t., resulting in cleavage of the trifluoroamide rather than reduction to the trifluoroethylamine.

NOESY spectra of these *N*-deprotected RCM derivatives **1ga** and **2da** were used to determine the relative configuration between the C-2 and C-3 stereocentres. For **1ga**, an NOE correlation was observed for protons H_a and H_b, indicating their close proximity in space in the most favourable conformation (the larger -CHFBn group being pseudo-equatorial) and therefore indicating the relative *syn*-configuration between the C-2 amino group and the C-3 Me substituent. Furthermore, a NOE correlation was not observed between H_a and the C-3 Me group, indicating that these substituents were 1,2-diaxially disposed. The reverse was observed in the NOE spectrum of **2da**, where H_a and the C-3 Me group showed a NOE correlation, whereas H_a and H_b did not. These assignments were further supported from the magnitudes of *Ja,b* for these two epimeric compounds, with **1ga** and **2da** having *Jab* = 4.0 and 8.2 Hz, respectively. Therefore, **1g** and **2d** were epimers at the Me substituted stereocentre (C-3), with the (*E*)-crotylboronate reacting to give the 1,2-*anti*-2,3-*syn* products **1a**–**1i**, and the (*Z*)-crotylboronate the 1,2-*anti*-2,3-*anti* products **2a**–**2f**.

To further examine the utility of these crotyl-β-fluoroamines the acylation of **2c** with cinnamoyl chloride was examined (Scheme 4). This was found only possible under reflux conditions over an extended reaction time (30 h), again indicative of the highly hindered nature of the nitrogen atom. The resultant α,β-unsaturated amide **2ca** was obtained in 57% yield and could be converted to the α,β-unsaturated lactam **2cb** using Grubbs II catalyst under reflux conditions (86% yield). Analysis of the NOE spectrum of **2cb** indicated the *syn* stereochemical relationship between H_a and the C-5 methyl group, consistant with the stereochemical assignment made to **2da** (Scheme 3).

The *N*-PMB compounds **1c** and **1h** could be deprotected using ceric ammonium nitrate (CAN) in a 2:1 acetonitrile:water mixture (Scheme 5). Despite the deactivated nature of the resultant deprotected β-fluoroamine, these products were discovered to be unstable and could only be purified by a sequential acid-base extraction procedure. In turn, the compound derived from octanal (**1ca**, R^1 = *n*-Hex, Figure 6) was

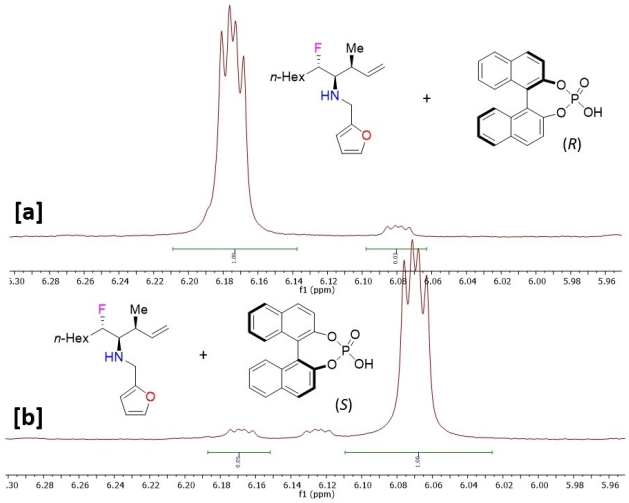
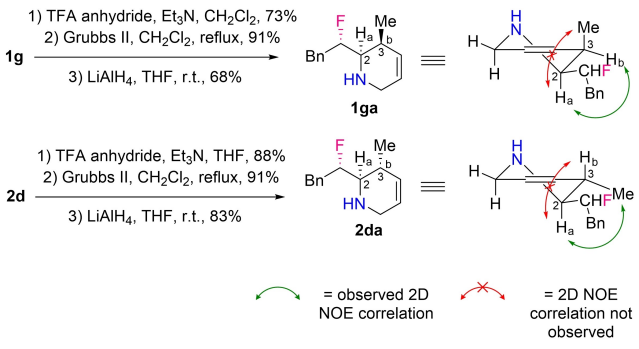
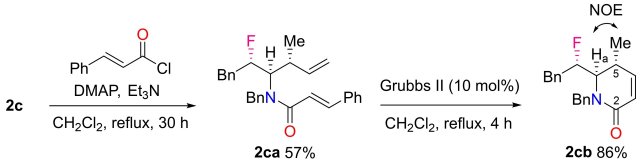


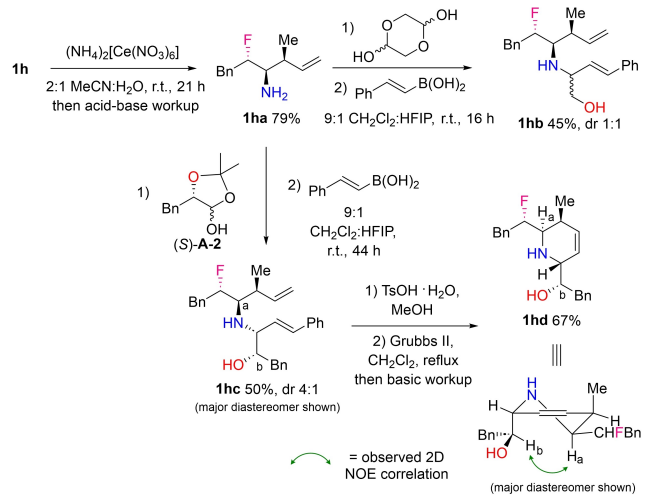
Figure 2. ^1H NMR spectrum of the salt of **1b** derivatised with (*R*)-1,1′-binaphthyl-2,2′-diylphosphoric acid [a]. Comparison of this spectrum with that of the derivative with the (*S*)-acid [b] and comparison of the data allowed for the determination of enantiomeric ratios.



Scheme 3. The synthesis of tetrahydropyridines **1ga** and **2da** and their notable NOE correlations.



Scheme 4. Synthesis and notable NOE correlations of **2cb**.



Scheme 5. Deprotection of the PMB derivative **1 h** using CAN to give **1 ha**, followed by a second classical PBM reaction. Reaction using glycolaldehyde was not diastereoselective, however, that using lactol (*S*)-**A-2** exhibited *anti*-diastereoselectivity at the new stereocentre.

discovered to be too non-polar for the efficient use of this procedure due to the influence of the F atom and alkyl chain and resulted in poor isolated yields. The hydrocinnamaldehyde-derived compound **1 ha** (R^1=Bn) was appreciably more polar, and could be obtained in good yield (79%). Using this compound as a chiral primary amine substrate, a second PBM reaction using glycolaldehyde dimer and (*E*)-styrylboronic acid was attempted. A pilot reaction using classical PBM conditions, that is ethanol over 3 d at r.t.[2a] was unsuccessful and produced a complex mixture of products. Instead conditions using a more polar solvent system 9:1 hexafluoroisopropanol (HFIP):CH_2Cl_2 were successful.[25] The PBM product **1 hb** was obtained in an acceptable yield (45%); however no diastereoselectivity for the new stereocentre was observed (dr 1:1). It may be proposed then that the existing stereocentres are sufficiently distal as to not induce any diastereoselectivity.

However, the same reaction of **1 ha** and (*E*)-styrylboronic acid with lactol (*S*)-**A-2** resulted in PBM product **1 hc** (50%) with 4:1 dr (Scheme 5). RCM of **1 hc** with Grubbs II catalyst produced the tetrahydropyridine **1 hd** (67%), the diastereomers of which could be separated by column chromatography. NOE spectroscopy of the major diastereomer of **1 hd** indicated that in one of the conformational isomers of **1 hd** the CH_bOHBn group is co-facial to H_a, therefore indicating the major diastereomer formed in the reaction of **1 hc** is an *anti*-amino alcohol, in agreement with literature examples of this class of PBM reactions.[5a,9b] The significant portion (~20%) of the epimeric *syn*-diastereomer produced likely results from asymmetric induction from the other stereocentres.

Computational modelling (M062X/def2TZVP/SMD(Methanol)//B3LYP/6-31G(d,p) level of theory) of the transition states (TS) for these reactions supports Cornforth-like TS (with the polar α-F substituent *anti*- to the C=N bond, leading to our experimentally observed major diastereomers, **1** and **2**, see Supporting Information for details) as depicted in Figure 3.

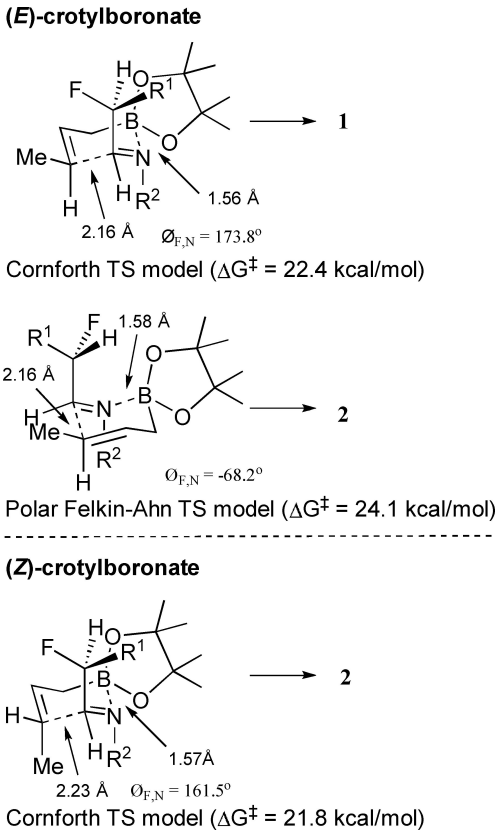


Figure 3. Depictions of Cornforth like transition states leading to the observed products, with solution free energies, distances and dihedral angles ($Ø_{F,N}$) between the F and N on the imine calculated at M062X/def2TZVP/SMD(Methanol)//B3LYP/6-31G(d,p) level of theory. Note: imine **B** (R^1=R^2=Bn) = 0.0 kcal/mol.

In the case of (*E*)-crotylboronate, the TS with the lowest energy barrier was identified as the Cornforth TS ($\Delta G^{\ddagger}$ = 22.4 kcal/mol) with the dihedral angle ($Ø_{F,N}$) between the F and N on the imine calculated as 173.8°. The polar Felkin–Ahn transition state, which would lead to the minor diastereomer **2**, had the second lowest barrier in energy ($\Delta G^{\ddagger}$ = 24.1 kcal/mol; $Ø_{F,N}$ = −68.2°). The polar Felkin–Ahn-like TS[26] places the R^1 group in closer proximity to substituents on the developing chair TS making it less favourable than the Cornforth-like TS with the α-F substituent having an *anti*-relationship with the C=N bond. For the (*Z*)-crotylboronate, the Cornforth TS ($\Delta G^{\ddagger}$ = 21.8 kcal/mol; $Ø_{F,N}$ = 161.5°) also had the lowest in energy barrier, followed by the polar Felkin–Ahn transition state ($\Delta G^{\ddagger}$ = 23.0 kcal/mol, $Ø_{F,N}$ = −65.0°). The stereochemical outcomes of our PBM crotylations are the same as those found in a recent study of the crotylation reactions of α-chiral -OMe and -OBn *N*-sulfonyl imines with in situ generated (*E*)- and (*Z*)-crotyl-BF_2 species.[27] Computational analysis indicated that these reactions were also proceeding through a 6-membered ring chair TS where addition to the imine face occurred via a Cornforth-like conformation,[28] controlling the 1,2-*anti* configuration of the product. The geometry of the crotyl agent however dictated their 2,3-*syn* or 2,3-*anti*-configuration from (*E*)- and (*Z*)-crotyl-BF_2, respectively.

Reactions with chiral α-benzoyloxyaldehydes

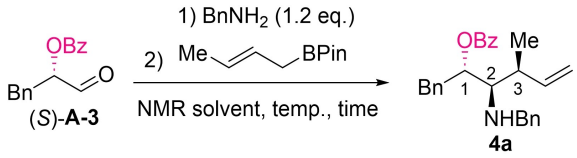
In an earlier communication we reported the PBM crotylation reactions of (2*S*)-(benzoyloxy)-3-phenylpropanal **A-3**[29] with benzylamine and pinacol (*E*)- or (*Z*)-crotylboronate.[15] Under unoptimised conditions these reactions were extremely slow when compared to their corresponding allylation reactions with the reactions employing benzylamine and pinacol (*E*)- or (*Z*)-crotylboronate at r.t. taking 14 d and 28 d, respectively (Table 2 Entries 1 and 1a). The resulting products, **4a** and **3-*epi*-4a**, respectively were obtained with a high dr (95:5 and 99:1 respectively) but in poor isolated yields (30% and 46%, respectively, Table 2). To optimise the yield of **4a**, a reaction solvent screen was made with variations also made to the equivalents of the (*E*)-crotylboronate, as shown in Table 2. These reactions were conveniently monitored by ^{1}H NMR spectroscopy and the reaction times and ^{1}H NMR yields are provided in Table 2.

The use of DMSO (Entry 2), which has been observed to be a good solvent in the investigation of analogous allylation reactions,[15] resulted in a decrease in reaction time and a minor increase in yield. However, using 2.0 equiv. of pinacol (*E*)-crotylboronate with CD_2Cl_2 as solvent achieved the same time reduction, with a greater increase in yield (Entry 3). The reported conditions[30] of trifluoroacetic acid (TFA) in dichloromethane as a rate-accelerating solvent in the PBM reaction were found to be inappropriate, leading to hydrolysis of the imine reactive intermediate (Entry 4). The diol 1,2-addition adduct of **A-3** and the boronate was recovered from this reaction as a mixture of diastereomers. CD_3CN was not found to be a good solvent (Entry 5) and attempting the reaction under reflux conditions did accelerate the reaction, at the expense of hydrolysis of the boronate (Entry 6). The addition of a hydrogen bonding thiourea catalyst, S=C(NH-3,5-$(CF_3)_2$Ph)$_2$, at 20 mol% to activate the imine was not markedly effective (Entry 7).[31] A repeat of Entry 4 with only a sub-stoichiometric amount of TFA in CD_2Cl_2, and 2.0 equiv. of the boronate (Entry 8) resulted in a much cleaner reaction, with no apparent decomposition of the imine. A rate-accelerating effect was observed; however, the yield was not superior to that obtained without the addition of TFA (See Entry 3). The use of HFIP as a co-solvent with 2.0 equiv. of the boronate did have a notable rate-accelerating effect (Entry 9),[25] however the reaction was not as clean as the reaction without HFIP. A reaction with 2.0 equiv. of the boronate in CD_3CN did not exhibit a much faster reaction (Entry 10), nor did the use of HFIP as a 5% co-solvent with CD_3CN (Entry 11).

The reaction conditions described in Entry 3 were chosen as the best conditions based on the purity of the product (i.e. absence of impurities from side reactions), rate and NMR yield. Purification of this reaction mixture by column chromatography resulted in a 56% yield of **4a**, with an excellent 95:5 dr and 93:7 er (determined using chiral phosphoric acids as aforementioned). Under similar reaction conditions except for the use of allylamine, the compounds **4b** and **4c** were synthesised (60% yield, dr 89:7:4 and 44% yield, dr 91:6:3 respectively, Scheme 6) with the ultimate aim of performing a RCM reaction and determining relative configuration of the C-3 -Me group by NOE spectroscopy.

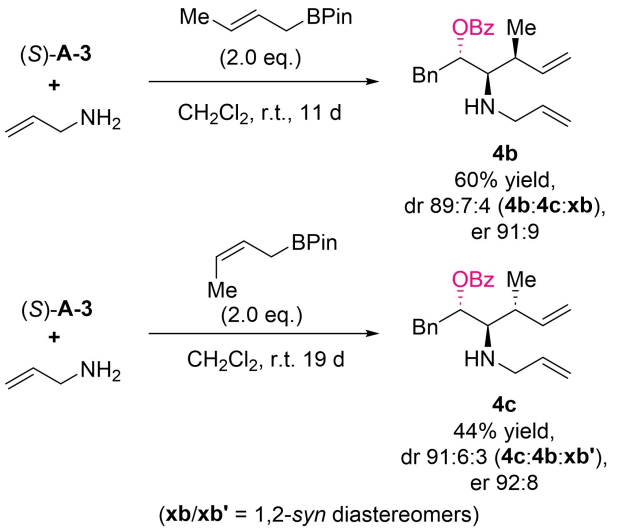
Both epimers were discovered to be resistant to sulfonylation at the secondary nitrogen atom; however, we found that the tosic acid salts of **4b** and **4c** readily underwent RCM with

Table 2. Optimisation reactions of (2*S*)-(benzoyloxy)-3-phenylpropanal (*S*)-**A-3** with benzylamine and pinacol (*E*)-crotylboronate.



Entry	Equiv. of boronate	Solvent	Temp [°C]	Time	NMR yield of **4a** [%][a]	Notes
1	1.2	CD_2Cl_2	r.t.	14 d	40 (32 isol.)	Cpd. **4a** Previously published[15]
1a	1.2	CD_2Cl_2	r.t.	28 d	66 (46 isol.)	Cpd. **3-*epi*-4a**. Previously published reaction with (*Z*)-crotylboronate[15]
2	1.2	DMSO-d_6	r.t.	9 d	45	
3	2.0	CD_2Cl_2	r.t.	9 d	62 (56 isol.)	Best conditions
4	1.2	1:30 CD_2Cl_2/TFA	r.t.	6 d	0	Mixture of diol diastereomers as product
5	1.2	CD_3CN	r.t.	15 d	55	
6	2.0	CH_2Cl_2	reflux	20 h	28	
7	2.0	CD_2Cl_2	r.t.	7 d	41	20 mol% thiourea cat
8	2.0	CD_2Cl_2	r.t.	9 d	50	0.25 equiv. TFA
9	2.0	CD_2Cl_2:HFIP 9:1	r.t.	7 d	72	
10	2.0	CD_3CN	r.t.	10 d	53[b]	
11	2.0	CD_3CN:HFIP 95:5	r.t.	9 d	45	

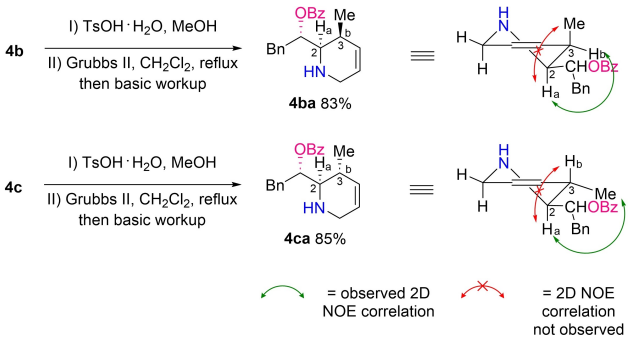
[a] 1,2,3-Trimethoxybenzene (~0.33 equiv.) was used as an internal standard [b] Impurities in the starting material likely compromised the yield.



Scheme 6. Crotylation reactions of pinacol crotylboronates with (*S*)-**A-3** and allylamine.

Grubbs II catalyst. The derivatives **4ba** and **4ca** were obtained in the excellent yields of 83% and 85%, respectively (Scheme 7).

NOE spectroscopy of these ring-closed derivatives was again used to determine the relative configuration at the C-2 and C-3 stereocentres. The relative configuration was revealed to be identical to that found for **1ga** and **2da**, with the (*E*)-crotylboronate giving the 2,3-*syn*-RCM product and producing derivative **4ba**, and the (*Z*)-crotylboronate giving the corresponding 2,3-*anti*-RCM product producing derivative **4ca**. Single crystal X-ray crystallographic analysis of the HBr salt of **4ba** confirmed the stereochemistry shown in Figure 4. Thus, our initially proposed configurations for compounds **4a** and ***3-epi-4a*** in our earlier communication were incorrectly assigned at the Me-substituted carbon.[15]



Scheme 7. RCM of **4b** and **4c** were accomplished using salt derivatives. NOESY spectra of the ring-closed derivatives **4ba** and **4ca** enabled the establishment of relative configuration at the C-3 stereocentre, relative to that at C-2.

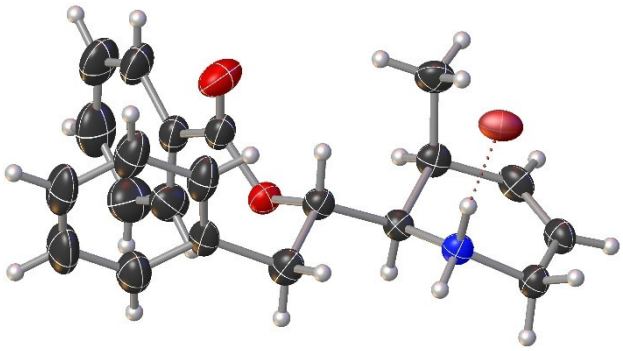


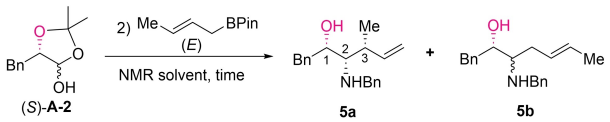
Figure 4. Single crystal X-ray structure of the HBr salt of **4ba**. CCDC 2262184.[32]

Reactions with chiral α-hydroxyaldehydes

In our previous study on the PBM reactions with pinacol allenylboronate and the chiral α-hydroxyaldehyde generated in situ from the lactol (*S*)-**A-2** we observed the synthesis of amino alcohols of *anti*-configuration while allylation reactions with other α-hydroxyaldehydes gave 1,2-*syn*-amino alcohol products (Scheme 1c).[7a] An initial NMR investigation of the reaction of (*S*)-**A-2**, benzylamine and pinacol (*E*)-crotylboronate in CD_2Cl_2 resulted in a mixture of γ- and α-attack products, as major and minor products, respectively (Table 3, Entry 1). A solvent screen revealed CD_2Cl_2 and toluene-d_8 to be the best solvents for maximising formation of the γ-attack product with the dr highest in CD_2Cl_2.

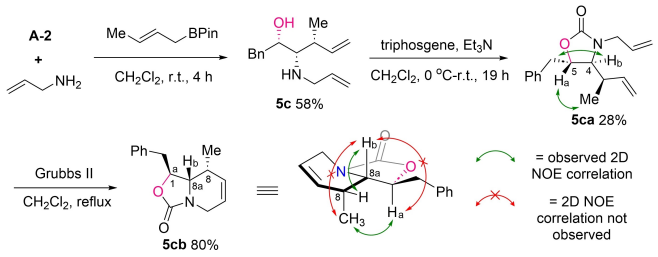
Accordingly, the conditions from Entry 1 were chosen to synthesise amino alcohol **5c**, which was obtained in 58% yield (dr 87:13, γ:α 93:7, Scheme 8). To establish the stereochemistry of **5c** it was converted to the oxazolidinone **5ca**, in which the major diastereomer represented 90% of the product. The NOE spectrum of **5ca** showed NOE correlations between H_a and the

Table 3. Solvent screen of crotylation PBM reactions of acetal-protected chiral α-hydroxyaldehyde (*S*)-**A-2**.



Entry	Solvent	Time	NMR total yield [%][a]	γ:α (**5a**:**5b**)	dr [γ]
1	CD_2Cl_2	4 h	62	91:9	92:8
2	CD_3OD	10 min	80	79:21	77:23
3	CD_3CN	18 h	41	71:29	81:19
4	DMSO-d_6	48 h	94	78:22	79:21
5	toluene-d_8	5 h	61	90:10	88:12

[a] 1,2,3-Trimethoxybenzene (~0.33 equiv.) was used as an internal standard.



Scheme 8. Synthesis of the 3*H*-oxazolo[3,4-*a*]pyridin-3-one **5 cb**.

allylic Me group, and H_b and the benzylic protons. This indicated **5 ca** was a 4,5-*trans*-oxazolidinone and thus **5 c** was a 1,2-*syn* amino alcohol. This stereochemical result is consistent with that observed for reactions of pinacol allylboronate with other α-hydroxyaldehydes (Scheme 1c). The oxazolidinone **5 ca** underwent a RCM reaction, using Grubbs II catalyst under reflux conditions to give the unsaturated 3*H*-oxazolo[3,4-*a*]pyridin-3-one **5 cb** in 80% yield. The NOE spectrum of this bicyclic system was consistent with that seen for the oxazolidinone **5 ca**, notably correlations were observed between H_a and the ring Me group. Additionally, the absence of an NOE correlation between H_b and the Me group indicated that they were on opposite faces of the bicyclic structure, and therefore allowing for the assignment of absolute configuration for amino alcohol **5 c**.

To complement this synthesis we examined the analogous reaction with pinacol (*Z*)-crotylboronate and benzylamine. However, this reaction only generated a trace amount of the desired product. This reaction was then monitored by NMR spectroscopy; the ultimate conclusion being that the (*Z*)-crotylboronate reacts far too slowly with the transient imine before it decays to the α-amino ketone product 1-(benzylamino)-3-phenylpropan-2-one. A repeat of this reaction in CD_3OD yielded a mixture of diastereomers (γ product dr 61 [presumed to be **3-*epi*-5 a**]:22:9:8 [**5 a**]) and regioisomers (approx. 96:4 major γ-diastereomer:major α-diastereomer) of the target product in 55% yield. Protic solvent therefore acts as a better activating medium but significantly erodes the diastereo- and regioselectivity.

The formation of the 1,2-*syn*-2,3-*anti* product **5 a** can be explained by the open transition state **TS-1** involving a 5-membered ring H-bonded imine intermediate, with the crotyl reagent approaching the imine face *anti* to the Bn ring substituent to produce the 1,2-*syn* adduct (Figure 5).[27] The sterically most demanding group of the γ-carbon of the crotyl reagent, the Me group, takes on an antiperiplanar orientation,

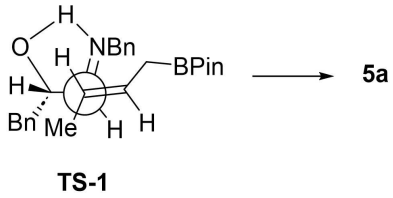


Figure 5. Possible open transition state for the formation of product **5 a**.

relative to the imine moiety, to avoid unfavourable steric interactions with the 5-membered ring methine and the *N*-Bn substituent. This places the smallest γ-carbon substituent, the γ-H, in a-synclinical position over the 5-membered ring and the double bond on the crotyl reagent in a +synclinical position, suitably oriented for the developing secondary amino group to readily capture the BPin that is generated upon cleavage of the C_α-BPin bond.

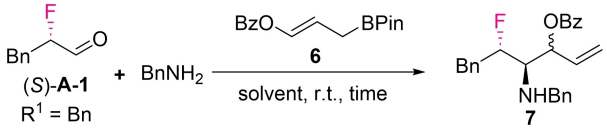
Reactions with pinacol (*E*)-3-benzoyloxyallylboronate

The success of the crotylation PBM reactions encouraged us to study of the reactions of pinacol (*E*)-3-benzoyloxyallylboronate **6** (88:12 *E:Z*)[33] was made, which could provide more highly functionalised products.

An initial study of the PBM reaction using α-fluoroaldehyde (*S*)-**A-1** (R^1=Bn), benzylamine and **6** under the reaction conditions shown in Table 1 was done (Table 4 Entry 1). This resulted in a much longer reaction time to consume the imine, and a lower overall isolated yield of the product. It was posited that the benzoate ester of **6** was decomposing in MeOH via an ester exchange mechanism, therefore a solvent screen was carried out (Entries 2–5). For all these reactions, **6** exhibited a lack of stability, with decomposition occurring before full consumption of the imine, and low recovery of **6** after column chromatography. The low reactivity of **6** was proposed to most likely being a consequence of the electron-withdrawing nature of the benzoate ester.

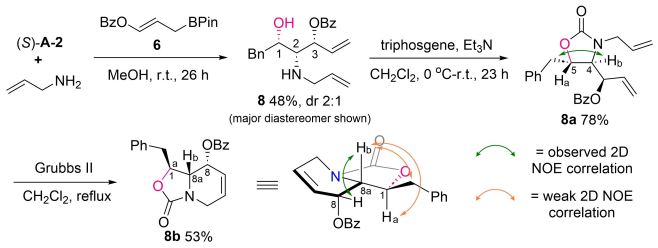
However, a higher degree of reactivity was observed with the lactol (*S*)-**A-2**. A reaction with benzylamine in CD_3OD gave a 22% yield of product only separable by preparative TLC. Much the same as previously outlined in Scheme 8, a PBM reaction of boronate **6** with (*S*)-**A-2** and allylamine in MeOH was performed, resulting in an isolated yield of 48% for amino alcohol **8** (Scheme 9). This compound was largely inseparable from a decomposition product of **6** (See Supporting Information). Nevertheless, this was reacted as a mixture to form the oxazolidinone **8 a** in 78% yield. ^{1}H NMR spectroscopic analysis

Table 4. Reactions of boronate **6** in the PBM reaction with chiral α-fluoroaldehyde (*S*)-**A-1**. The low reactivity observed was attributed to electronic effects and decomposition of **6**.



Entry	Solvent	Time [h]	Yield [%]
1	MeOH	40	11[a]
2	CD_2Cl_2	44	9[a]
3	CD_3CN[a]	42	–
4	DMSO-d_6	43	9[b]
5	THF-d_8	26	–[c]

[a] Isolated yield. [b] NMR yield. [c] No product observed.



Scheme 9. The synthesis of the tetrahydro-3*H*-oxazolo[3,4-*a*]pyridin-8-yl benzoate **8b**.

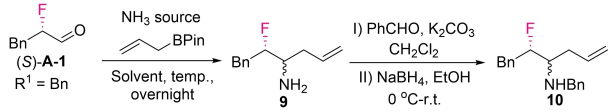
of compound **8a** and the crude reaction mixture indicated the starting amino alcohol **8** to be a 2:1 mixture of diastereomers. A sample of oxazolidinone **8a** (dr 87:13) was analysed by NOE spectroscopy. A correlation was observed between the benzylic protons and H_b, indicating that the oxazolidinone had the relative 4,5-*trans*-configuration, and therefore that the starting major diastereomer of **8** had the 1,2-*syn* configuration. This sample of **8a** was then ring-closed using Grubbs II catalyst to form **8b** in 53% yield and again this was analysed by NOE spectroscopy. For the major diastereomer, a correlation between H_b and the benzylic protons was observed to be weak, as well as that for H_b and H_a, suggesting that H_b and the -OBz group are pseudo-axial. However, a strong correlation was observed between H_b and the proton attached to C-8, therefore indicating they were co-facial and the amine and -OBz groups to have the 2,3-*syn*- configuration for the major diastereomer.

Poor results were observed in reactions of **6** and (*S*)-**A-3**. A reaction of **6** with (*S*)-**A-3** and benzylamine was performed in CD_2Cl_2 and monitored by ^{1}H NMR spectroscopy. Characteristic of this class of reaction, a very long reaction time was observed (9 days), with a product found to form in 26% yield by ^{1}H NMR analysis. Disappointingly, this product could not be isolated using column chromatography.

Allylation and crotylation reactions with NH_3

A study of the allylation and crotylation reactions of representative α-fluoro and α-OBz aldehydes was made using ammonia as the amine component. The allylation reaction of (*S*)-2-fluoro-3-phenylpropanal (*S*)-**A-1** (R^1=Bn) with pinacol allylboronate in a biphasic reaction mixture of 30% aqueous ammonia in ethanol, under similar conditions as described for Scheme 1b[11] gave a low yield (25%) of the desired β-fluoro-*N*-benzylamine **9** with a poor *anti:syn* dr of 42:58, respectively (Table 5, Entry 1). *N*-Benzylation by reductive amination to produce **10** was performed to assist isolation, purification and identification. The relative stereochemistry of these diastereomeric products was identified by ^{19}F NMR analysis when compared to the ^{19}F NMR spectra of the same *anti*-*N*-benzyl-allyl-β-fluoroamines we described previously.[14] Switching the solvent to THF to homogenise the reaction mixture was found to be detrimental to the diastereoselectivity (50:50 dr) and overall yield (Entry 2). Pre-stirring the aqueous ammonia and pinacol allylboronate to pre-form an "aminoallylating reagent"[11] was also attempted

Table 5. Allylation reactions of a chiral α-fluoroaldehyde with different sources of NH_3. All produced a mixture of diastereomers with little selectivity.



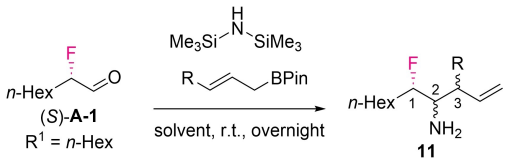
Entry	NH_3 source	Solvent	Temp. [°C]	Yield [%][a]	anti:syn[b]
1	30% aq. NH_3	EtOH	r.t.	25	42:58
2	30% aq. NH_3	THF	r.t.	18	50:50
3	30% aq. NH_3/ allylBPin	EtOH	r.t.	31	44:56
4	Liquid NH_3	EtOH	−63-r.t.	42	54:46

[a] NMR yield of free amine. [b] Ratio pertains to the free amine product before reductive amination.

(Entry 3). Addition of this mixture to the α-fluoroaldehyde had no beneficial influence on diastereoselectivity and resulted in a marginal improvement in yield (Entry 3). A reaction with liquid ammonia condensed from vapour at −63 °C, much like that performed previously,[11] was also poorly diastereoselective (Entry 4, 54:46 *anti:syn*).

Additionally, reactions were carried out using hexamethyldisilazane (HMDS) as potentially an in situ source of ammonia. Much like the prior reactions with ammonia, reactions using HMDS exhibited little diastereoselectivity, in either MeOH (Table 6 Entry 1) or in THF (Entry 2). However, a reaction using pinacol (*E*)-crotylboronate in MeOH exhibited a significant degree of diastereoselectivity (72:22:6 dr, Entry 3). Comparison of the ^{19}F NMR data of the crude product to that of **1ca**, obtained by the deprotection of **1c** suggest that the major

Table 6. Reactions using HMDS as an NH_3 source.



Entry	R	Solvent	Yield [%]	dr[d]	Product
1	H	MeOH	51[a]	46:54	
2	H	THF	70[b]	55:45	11a
3	Me	MeOH	–[c]	72:22:6	11b

[a] Isolated yield of *N*-benzylated derivative after reductive amination and column chromatography. [b] NMR yield of free amine. [c] Yield of free amine not determined. Attempts to purify **11b** as an *N*-benzylated derivative after reductive amination were not successful. [d] Ratio pertains to free amine product.

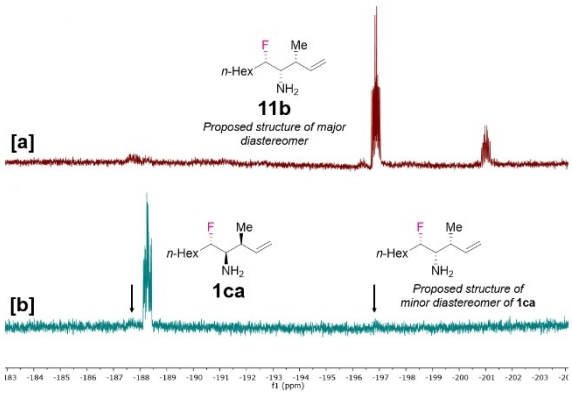
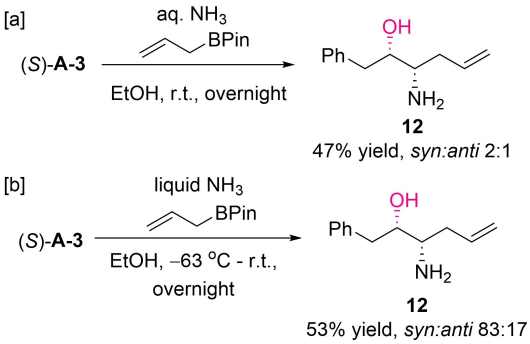


Figure 6. ^{1}H coupled ^{19}F NMR spectra (377 MHz, $CDCl_3$) of [a] the crude reaction mixture of **11b** from Table 6 Entry 3. [b] The crude reaction mixture of **1ca** obtained from the deprotection of PMB compound **1c** with CAN (see Scheme 5). A comparison of these spectra suggest that crotylation reactions with HMDS produce a 1,2-*syn*-2,3-*syn* compound as a major diastereomer (See Figure 1 for discussion on diastereomers of **1** and **2**).



Scheme 10. Reactions of (*S*)-**A-2** with pinacol allylboronate and [a] 30% aqueous NH_3 and [b] liquid NH_3 condensed from vapour at −63 °C.

diastereomer is the opposite of that obtained using primary amines i.e. is of 1,2-*syn*-2,3-*syn* configuration, rather than 1,2-*anti*-2,3-*syn* (Figure 6). The rationalisation of this result is complicated by the uncertainty of the identity of reactive imine intermediate which could be either an *N*-TMS imine or an NH imine, where the former imine may be expected to generate a 1,2-*anti*-2,3-*syn* product as described above and not the observed 1,2-*syn*-2,3-*syn* product.

However, reactions with oxylated substrates exhibited higher levels of diastereoselectivity with a preference for the *syn*-diastereomer **12** (Scheme 10). Reaction of the α-OBz aldehyde (*S*)-**A-3** with 30% aqueous ammonia at r.t. yielded the deprotected alcohol product in a 2:1 *syn:anti* ratio, whereas reaction with liquid ammonia yielded the same product in 83:17 *syn:anti* ratio, concordant with that recorded in the literature.[11] The improvement in dr may be attributed to the lower reaction temperature. The preference for the 1,2-*syn* diastereomer may indicate that the reaction proceeds via a α-hydroxy imine intermediate and not the α-OBz intermediate.

Conclusions

In conclusion, the crotylation reactions of chiral α-heteroatom (F, OBz and OH) aldehydes under Petasis-borono-Mannich reaction conditions using pinacol (*E*)- or (*Z*)-crotylboronate and primary amines have been developed and generally result in γ-addition products in high diastereoselectivity and high enantiomeric ratios. Reactions with ammonia as the amine component were poorly diastereoselective. Chiral α-heteroatom (F and OBz) aldehydes (*S*)-**A-1** and (*S*)-**A-3** react with primary amines and pinacol (*E*)- or (*Z*)-crotylboronate to favour formation of the 1,2-*anti*-2,3-*syn* and 1,2-*anti*-2,3-*anti* products, respectively while the chiral α-hydroxyaldehyde formed in situ from lactol (*S*)-**A-2** gave 1,2-*syn*-2,3-*syn* products. The stereochemical outcomes of the reactions of the chiral α-F and α-OBz aldehydes can be explained using a six-membered ring TS model in which a Cornforth-like conformation is favoured where the α-heteroatom is *anti* to the C=N bond of the imine resulting in 1,2-*anti* products. The 2,3-stereochemical outcome is dependent upon the geometry of the crotylboronate. The stereochemical outcomes of the reactions employing an α-OH aldehyde can be rationalised as occurring via an open-transition state involving H-bonding in the imine intermediate between the α-OH group and the imine N atom. Representative products were converted to highly functionalised tetrahydropyridines and 3*H*-oxazolo[3,4-*a*]pyridine-3-ones that allowed stereochemical assignments to be made. These heterocycles will be valuable scaffolds for the synthesis of natural product-like molecules in the future.

Experimental Section

Full details of the data that support the findings of this study are available in the supplementary material of this article.

General Procedure for preparation of chiral crotyl-β-fluoroamines 1 and 2

Part A: Synthesis of chiral α-fluoroaldehyde (*S*)-**A-1**: Synthesis of the (2*S*)-fluoroaldehyde substrate (*S*)-**A-1** was per the procedure described in Marigo et al. 2005,[23] and replicated in Chevis et al. 2019[14] (Typical scale 0.30 mmol).

Part B: Chiral α-fluoroimine formation (B): To the crude (2*S*)-fluoroaldehyde (*S*)-**A-1** solution in pentane was added CH_2Cl_2 (~2 mL) and the amine component (2.0 equiv.) and the mixture stirred for 10 min. The resultant mixture was concentrated *in vacuo* to afford a crude chiral α-fluoroimine **B** as a fluffy white solid.

Part C: Petasis-Borono-Mannich reaction: To the crude chrial α-fluoroimine **B** from Part 2 was added methanol (0.5 mL) then the boronic ester component (2.0 equiv.). This solution was stirred for 20 h with TLC monitoring. Upon completion, the crude material was concentrated *in vacuo* and purified by flash column chromatography on silica gel to obtain the chiral crotyl-β-fluoroamine product **1** or **2**.

(2*S*,3*R*,4*S*)-*N*-Allyl-2-fluoro-4-methyl-1-phenylhex-5-en-3-amine (1 g)

The title compound was prepared according to the General Procedure using hydrocinnamaldehyde (59.4 μL, 1.5 equiv.) as the aldehyde component, allylamine (45.0 μL, 2.0 equiv.) as the amine component and pinacol (*E*)-crotylboronate (123.0 μL, 2.0 equiv.) as the boronic ester component. Purification by flash column chromatography on silica gel eluting with 1:19 EtOAc/*n*-hexane gave the title product **1 g** (34.9 mg, 46%) as a pale-yellow oil. $\mathbf{R_f}$ = 0.34 (1:9 EtOAc/*n*-hexane). **dr** 93:2:5 (**1 g**:**2 d**:**x**). **er** 96:4. $[\alpha]_D^{25}$ −36.2 (*c* 1.21, $CHCl_3$). **IR (neat)**: ν_{max} 3066 (sp^2 C–H str.), 3029 (sp^3 C–H str.), 1641 (C=C str.), 1604 (Ar C=C str.), 1496 (N–H bend), 1454 (Ar C=C str.), 1379 (CH_3 bend), 995, (sp^2 C–H oop), 914 (C–F str.), 744 (Ar C–H oop), 698 (Ar C–H oop) cm^{-1}. **^{1}H NMR (400 MHz, $CDCl_3$)**: δ 7.35–7.18 (m, 5H, Ar-*H*), 5.94–5.81 (m, 2H, H-5, H-2′), 5.17 (dq, *J* = 17.1, 1.7 Hz, 1H, (*E*)-H-3′), 5.11–5.03 (m, 3H, H-6, (*Z*)-H-3′), 4.60 (dddd, *J* = 47.9 ($^2J_{H,F}$), 9.0, 6.1, 2.6 Hz, 1H, H-2), 3.32 (dt, *J* = 6.0, 1.5 Hz, 2H, H-1′), 3.13 (dd, *J* = 14.6 ($^3J_{H,F}$), 2.7 Hz, 1H, H-1), 3.03 (dd, *J* = 14.6 ($^3J_{H,F}$), 2.7 Hz, 1H, H-1), 2.92 (ddd, *J* = 18.4, 14.6 ($^3J_{H,F}$), 9.2 Hz, 1H, H-1), 2.70 (ddd, *J* = 12.1 ($^3J_{H,F}$), 6.1, 4.8 Hz, 1H, H-3), 2.59–2.49 (m, 1H, H-4), 1.10 (dd, *J* = 6.9, 1.2 ($^5J_{H,F}$) Hz, 3H, H-7). **^{13}C NMR (101 MHz, $CDCl_3$)**: δ 141.6 (C-5), 138.3 (d, $^3J_{C,F}$ = 1.3 Hz, C-1″), 137.1 (C-3′), 129.3 (d, $^4J_{C,F}$ = 0.7 Hz, C-2″), 128.4 (C-3″), 126.4 (C-4″), 115.8 (C-2′), 114.8 (C-6), 95.8 (d, $^1J_{C,F}$ = 175.2 Hz, C-2), 63.2 (d, $^2J_{C,F}$ = 20.8 Hz, C-3), 52.0 (d, $^4J_{C,F}$ = 1.4 Hz, C-1′), 39.0 (d, $^3J_{C,F}$ = 4.6 Hz, C-4), 38.0 (d, $^2J_{C,F}$ = 21.1 Hz, C-1), 15.4 (d, $^4J_{C,F}$ = 2.7 Hz, C-7). **^{19}F NMR (377 MHz, $CDCl_3$)**: δ −183.22 (minor diastereomer), −183.99 (major diastereomer), −191.03 (minor diastereomer). **HRMS (ESI)**: *m/z* calculated for $C_{16}H_{23}NF$ $[M+H]^+$: 248.1815, found 248.1811.

(*S*)-1-Oxo-3-phenylpropan-2-yl benzoate ((*S*)-A-3)

The title compound was prepared according to that outlined in Vaismaa et al. 2009 (1.0 mmol scale),[29a] with the following modifications from Kano et al. 2009.[29b] At the conclusion of the reaction, the reaction mixture was added to a separating funnel with 1 M aq. HCl (~4 mL) and extracted with CH_2Cl_2 (3x~3 mL). The combined organic layers were washed with NaCl brine (~4 mL), then sat. aq. $NaHCO_3$ (~4 mL), then dried over anhydrous K_2CO_3, filtered and concentrated *in vacuo*. The crude material was purified by flash column chromatography eluting with 3:17 EtOAc/*n*-hexane, obtaining the title product **3** (140.5 mg, 55%). The spectroscopic data for **3** was identical to that previously reported. $\mathbf{R_f}$ = 0.23 (1:4 EtOAc/*n*-hexane).

(2*S*,3*R*,4*S*)-3-(Allylamino)-4-methyl-1-phenylhex-5-en-2-yl benzoate (4 b)

To a 10 mL round-bottomed flask was added (*S*)-**A-3** 110.6 mg, 0.435 mmol, 1.0 equiv.) and anhydrous CH_2Cl_2 (2.0 mL), and the mixture stirred until the substrate was dissolved. To this mixture was added allylamine (49.0 μL, 0.6525 mmol, 1.5 equiv.) and the mixture stirred for 5 min. Pinacol (*E*)-crotylboronate (178.4 μL, 0.870 mmol, 2.0 equiv.) was then added and the reaction vessel flushed with nitrogen, sealed and stirred for 11 d at r.t. with TLC monitoring. Upon completion of the reaction, the reaction mixture was added to a separating funnel with sat. aq. $NaHCO_3$ (~5 mL) and extracted with CH_2Cl_2 (3x~4 mL). The combined organic layers were dried over anhydrous K_2CO_3, filtered, concentrated *in vacuo* and purified by flash column chromatography eluting with 3:17 EtOAc/*n*-hexane, obtaining the title product **4 b** (90.5 mg, 60%) as a waxy yellow solid. $\mathbf{R_f}$ = 0.37 (3:17 EtOAc/*n*-hexane). **dr** 89:7:4 (**4 b**:**4 c**:other diastereomer). **er** 91:9. $[\alpha]_D^{23}$ −63.6 (*c* 0.76, $CHCl_3$). **IR (neat)**: ν_{max} 3068 (sp^2 C–H str.), 2923 (sp^3 C–H str.), 1703 (C=O str.), 1641 (C=C str.), 1602 (Ar C=C str.), 1494 (N–H bend), 1452 (Ar C=C str.), 1369 (CH_3 bend), 1270 (C–O str.), 1180 (C–O str.), 995 (sp^2 C–H oop), 914 (sp^2 C–H oop), 739 (Ar C–H oop), 687 (Ar C–H oop) cm^{-1}. **^{1}H NMR (400 MHz, $CDCl_3$)**: δ 8.00–7.93 (m, 2H, H-2″), 7.58–7.49 (m, 1H, H-4″), 7.45–7.38 (m, 2H, H-3″), 7.25–7.10 (m, 5H, H-2‴, H-3‴, H-4‴), 5.98–5.79 (m, 2H, H-5, H-2′), 5.46 (ddd, *J* = 8.0, 5.0, 4.1 Hz, 1H, H-2), 5.13–5.05 (m, 3H, H-6, (*E*)-H-3′), 5.00 (dq, *J* = 10.2, 1.4 Hz, 1H, (*Z*)-H-3′), 3.39 (ddt, *J* = 13.9, 5.8, 1.5 Hz, 1H, CH_AH_B H-1′), 3.30 (ddt, *J* = 13.9, 6.3, 1.4 Hz, 1H, CH_AH_B H-1′), 3.12–3.01 (m, 2H, H-1), 2.83 (dd, *J* = 6.5, 4.2 Hz, 1H, H-3), 2.49–2.38 (m, 1H, H-4), 1.15 (d, *J* = 6.8 Hz, 3H, H-7). **^{13}C NMR (101 MHz, $CDCl_3$)**: δ 165.8 (*C*=O), 141.9 (C-5), 138.2 (C-1‴), 137.2 (C-2′), 132.8 (C-4″), 130.4 (C-1″), 129.5 (C-2″), 129.4 (C-3‴), 128.34 (C-3″), 128.27 (C-2‴), 126.3 (C-4‴), 115.8 (C-3′), 114.6 (C-6), 77.4 (C-2), 62.7 (C-3), 52.3 (C-1′), 40.5 (C-4), 35.9 (C-1), 16.7 (C-7). **HRMS (ESI)**: *m/z* calculated for $C_{23}H_{28}NO_2$ $[M+H]^+$: 350.2120, found 350.2125.

Supporting Information

The authors have cited additional references within the Supporting Information.[34–43]

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Conflict of Interests

The authors declare no conflict of interest.

Data Availability Statement

The data that support the findings of this study are available in the supplementary material of this article.

Keywords: Crotylation · heterocycles · multicomponent reactions · organocatalysis · Petasis-borono-Mannich reaction

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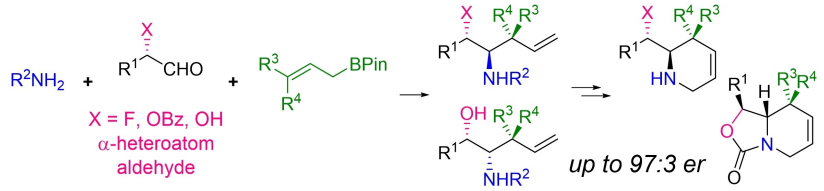

The scope of the Petasis-borono-Mannich reaction has been expanded to include crotylboronates as a variation of boronic ester. These have been examined in reactions of chiral α-heteroatom (F, OBz, OH) aldehydes and primary amines, to produce enantioenriched compounds up to 97 : 3 er. Examples have been converted to heterocyclic scaffolds with proof of absolute configuration.

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