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J. Am. Chem. Soc., **2007**, 129 (49), 15398-15404 • DOI: 10.1021/ja075204v

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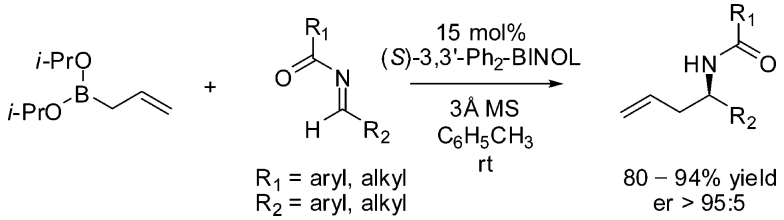

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Asymmetric Allylboration of Acyl Imines Catalyzed by Chiral Diols

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Abstract: Chiral BINOL-derived diols catalyze the enantioselective asymmetric allylboration of acyl imines. The reaction requires 15 mol % (*S*)-3,3′-Ph_2-BINOL as the catalyst and allyldiisopropoxyborane as the nucleophile. The reaction products are obtained in good yields (75−94%) and high enantiomeric ratios (95:5−99.5:0.5) for aromatic and aliphatic imines. High diastereoselectivities (diastereomeric ratio > 98:2) and enantioselectivities (enantiomeric ratio > 98:2) are obtained in the reactions of acyl imines with crotyldiisopropoxyboranes. This asymmetric transformation is directly applied to the synthesis of Maraviroc, the selective CCR5 antagonist with potent activity against HIV-1 infection. Mechanistic investigations of the allylboration reaction including IR, NMR, and mass spectrometry studies indicate that acyclic boronates are activated by chiral diols via exchange of one of the boronate alkoxy groups with activation of the acyl imine via hydrogen bonding.

Introduction

Chiral homoallylic amines are valuable building blocks for use in synthesis.[1] They have found use as precursors for β-amino acids[2] and heterocycles.[3] Chiral homoallylic amines have also served as key intermediates in complex natural product synthesis and pharmacologically relevant compounds.[4] In addition, the structural motif is also present in a variety of bioactive molecules with wide-ranging biological properties.[5]

The asymmetric allylation of imines provides direct access to chiral homoallylic amines.[6] Significant progress has been made in the development of practical approaches to these building blocks using chiral allyl metal reagents such as allyl silanes,[7] allyl boronates,[8] and boranes,[9] as well as diastereoselective allyl metal additions to chiral imines.[10] Innovative catalytic approaches include the development of chiral main group Cu-[11] and Zn-promoted[12] reactions as well as Pd-[13] and Zr-mediated[14] allyl metal additions to imines and, more recently, allylindium reagents generated in the presence of BINOL-derived[15] and chiral thiourea catalysts,[16] which result in enan-

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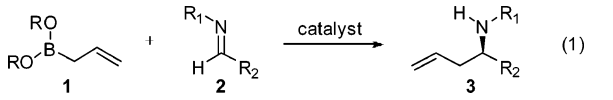
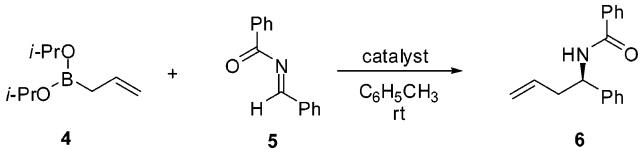


Table 1. Asymmetric Allylboration of Acyl Imines[a]



entry	catalyst	mol %[b]	% yield[c]	er[d]
1			<5	
2	**7a**	15	<5	50:50
3	**7b**	15	<5	55:45
4	**7c**	15	10	60:40
5	**7d**	15	51	50:50
6	**7e**	15	76	68:32
7	**7f**	15	81	93:7
8	**7g**	10	60	96.5:3.5
9	**7h**	15	85	96:4
10	**7h**	10	80	95:5
11	**7h**	5	60	90:10
12	**7i**	15	21	55:45

[a] Reactions were run with 0.125 mmol of borane, 0.125 mmol of acyl imine, 15 mol % catalyst and in toluene (0.1 M) for 16 h under Ar, followed by flash chromatography on silica gel. [b] Catalyst concentration used relative to imine. [c] Isolated yield. [d] Enantiomeric ratios determined by chiral HPLC analysis.

tioselective additions to hydrazones. Despite these creative efforts, the catalytic asymmetric allylation of imines remains a considerable challenge; enantioselective additions to aliphatic imines and diastereoselective additions using substituted allyl metal reagents remain notably difficult using current methods. In an effort to develop a practical approach toward this structural class, we have expanded the scope of the asymmetric allylboration of C═X bonds[17] catalyzed by chiral diols to include imines (eq 1). Herein, we report the enantioselective allylboration of acyl aldimines promoted by BINOL-derived catalysts.

Results and Discussion

Asymmetric Allylboration of Acyl Imines. We initiated our investigation by evaluating the reaction of allyldiisopropoxyborane **4** with a variety of *N*-benzylidene derivatives, including benzamide **5**, *N*-benzylidene benzamine, *N*-benzylidene-4-methoxyaniline, *N*-benzylidene-*p*-toluenesulfonamide, and *N*-benzylidene-*P*,*P*-diphenylphosphinic amide, in toluene at room temperature and 20 mol % (*S*)-BINOL **7e** as catalyst. Benzamide **5** displayed the best reactivity and selectivity and afforded the desired product in 80% yield and in an enantiomeric ratio (er) of 70:30. Other imines generally afforded the corresponding products in lower yield and er.

The allylboration reaction of imine **5** was investigated in the absence and presence of chiral diol catalysts (Figure 1). The reaction performed in the absence of diol afforded the homoallylic amide **6** in ≤5% yield (Table 1, entry 1). Chiral diols such as (*S*,*S*)-1,2-diphenylethane diol **7a**, (+)-diethyl tartrate **7b**, and (*S*,*S*)-3,5-heptanediol **7c** gave only negligible increases in yield over the uncatalyzed reaction (entries 2−4 in Table 1). However, the use of 15 mol % (+)-TADDOL **7d** in the reaction resulted

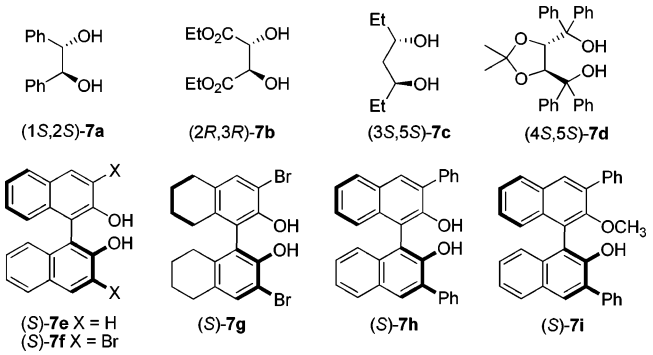
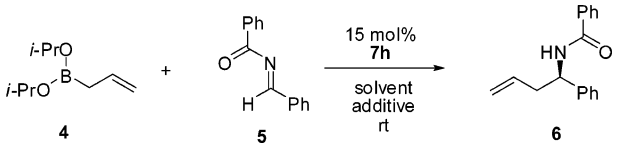


Figure 1. Chiral diols.

Table 2. Asymmetric Allylboration of Acyl Imines[a]



entry	solvent	additive	% yield[b]	er[c]
1	THF		32	58:42
2	Et_2O		28	60:20
3	CH_2Cl_2		75	92:8
4	$C_6H_5CH_3/C_6H_5CF_3$ (3:1)		77	92:8
5	$C_6H_5CH_3$		81	93:7
6	$C_6H_5CH_3$	3 Å molecular sieve	87	99:1
7	$C_6H_5CH_3$	4 Å molecular sieve	85	97:3
8	$C_6H_5CH_3$	5 Å molecular sieve	83	90:10

[a] Reactions were run with 0.125 mmol of borane, 0.125 mmol of acyl imine, 15 mol % catalyst and in toluene (0.1 M) for 16 h under Ar, followed by flash chromatography on silica gel. [b] Isolated yield. [c] Enantiomeric ratios determined by chiral HPLC analysis.

in higher yield (entry 5 in Table 1, 51% yield) but in racemic form. Alternatively, 15 mol % (*S*)-BINOL afforded **6** in 68:32 er and 76% isolated yield. The use of BINOL-derived catalysts bearing substitution at the 3,3′-positions, **7f**−**h**, yielded the product in higher enantioselectivities (entries 7−9 in Table 1) with (*S*)-3,3′-Ph_2-BINOL **7h** affording the highest er (96:4) and yield. Reducing the catalyst loading resulted in diminished enantioselectivity (entries 10 and 11 in Table 1). Use of the BINOL-derived methyl ether **7i** as the catalyst in the allylation reaction afforded the homoallylic amide in significantly lower yield and er, highlighting the importance of the diol functionality of the catalyst.

During the course of our studies to optimize the reaction conditions, a significant solvent effect was observed. Electron donating solvents resulted in slower reaction rates and lower enantioselectivities. One reason for this may be due to the interruption of hydrogen bonding or ligand exchange between boronate **4** and diol **7h** in Lewis basic solvents (Table 2, entries 1 and 2). Polar non-coordinating solvents gave faster rates and higher selectivities (Table 2, entries 3 and 4). However, the key observation was the addition of 3 Å molecular sieves. Their inclusion in the reaction was found to prevent decomposition of the hydrolytically unstable acyl imine from trace amounts of water (Table 2, entry 6). While the size of molecular sieves increased, the beneficial effect diminished (Table 2, entries 7 and 8).

A selection of benzoyl imines was evaluated in the asymmetric allylboration reaction under the general reaction conditions (Table 3). Electron-rich aromatic imines underwent the asymmetric reaction in good yields and er's (Table 3, entries

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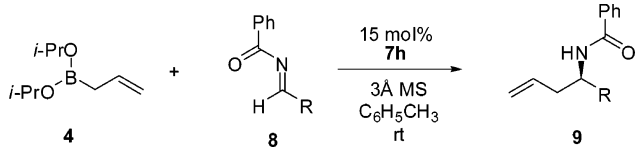
Table 3. Asymmetric Allylboration of Benzoyl Imines[a]



4 8 9

entry	R	product	% yield[b]	er[c]
1	Ph	**9a**	87	99:1
2	*p*-CH_3-C_6H_4	**9b**	83	98:2
3	*p*-Br-C_6H_4	**9c**	86	97.5:2.5
4	*p*-CH_3O-C_6H_4	**9d**	85	95:5
5[d]	*p*-F-C_6H_4	**9e**	94	98:2
6[d]	*o*-F-C_6H_4	**9f**	91	95.5:4.5
7[d]	*m*-CF_3-C_6H_4	**9g**	89	97.5:2.5
8	2-C_4H_3O	**9h**	83	96:4
9	2-C_4H_3S	**9i**	81	95:5
10	2-naphthyl	**9j**	88	96:4
11	(*E*)-PhCH=CH	**9k**	82	95.5:4.5
12	$PhCH_2CH_2$	**9l**	83	99.5:0.5
13	*c*-C_6H_{11}	**9m**	80	98:2
14	*t*-Bu	**9n**	81	99.5:0.5
15	$BnOCH_2$	**9o**	84	96.5:3.5
16	(*Z*)-EtCH=$CH(CH_2)_2$	**9p**	82	95.5:4.5

[a] Reactions were run with 0.5 mmol of **4**, 0.5 mmol of imine, and 15 mol % catalyst and 3 Å 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 10 °C for 48 h.

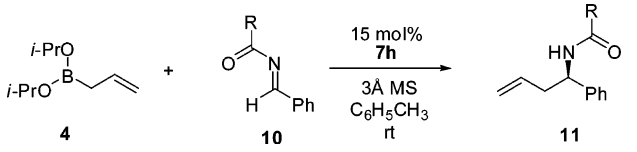
2−4). Electron-deficient aromatic imines were less selective at room temperature; however, better selectivities were attained at lower temperature but at a slower rate (Table 3, entries 5−7). Heteroaromatic imines were also found to be good substrates for the reaction (Table 3, entries 8 and 9) as were 2-naphthyl imine (Table 3, entry 10) and cinnamyl imine (Table 3, entry 11). Aliphatic benzoyl imines were also excellent substrates for the reaction at room temperature achieving some of the highest er's (Table 3, entries 12−14). Similarly, functionalized alkyl benzoyl imines were good substrates for the reaction as well (Table 3, entry 15 and 16).

We next evaluated other types of imines to further explore the scope and limitations of asymmetric allylboration. The reaction of methyl benzylidene carbamate **10a** yielded only 13% desired product in 57:43 er (Table 4, entry 1). The carbamoyl imine decomposed via alcoholysis during the course of the reaction. Yields improved with larger carbamates but did not achieve significantly better levels of enantioselectivity (Table 4, entries 2 and 3). We also investigated how the electronic character of the benzoyl group influenced the reaction. Substitution at the *para*-position with electron-donating groups resulted in slower reaction rates than electron-withdrawing substitution, but in all cases, the enantioselectivities were high (Table 4, entries 5−9). Substitution at the *ortho*-position resulted in significant erosion of the er (Table 4, entry 10). The cinnamoyl imine and cyclohexyl carboxamide imine (Table 4, entry 11 and 12) were also found to be good substrates in the allylboration reaction under optimized conditions. The substrate generality of the asymmetric reaction led us to explore the synthetic utility of this methodology.

Synthesis of Maraviroc. Traditional HIV chemotherapy has relied heavily on the disruption of viral replication.[18] Targeting protease inhibitors and reverse transcriptase inhibitors have increased the lifetime of HIV-infected patients; however, this heavy reliance on the targeting of viral machinery has increased resistance to these drugs.[19] Recently, a new CCR5 entry inhibitor, Maraviroc, has been fast-tracked through clinical trials after showing high success rates.[20] CCR5 entry inhibitors are a new compound class in HIV therapy that targets the human protein responsible for recognition of the virus.

A recent report describing the synthesis of Maraviroc highlights the use of β-phenylalanine acid as the source of chirality for the synthesis.[21] Our approach toward the synthesis of Maraviroc relied on the asymmetric allylation of difluorocyclohexane carboximide imine **13** (Scheme 1). Starting from the corresponding acid, the acyl chloride was accessed by treatment with oxalyl chloride and catalytic DMF. The crude acid chloride was mixed with freshly distilled silyl imine and then refluxed for 3 h. Removal of the solvent and volatiles afforded the acyl amine as viscous oil. Allylation of the imine

Table 4. Asymmetric Allylboration of Benzoyl Imines[a]

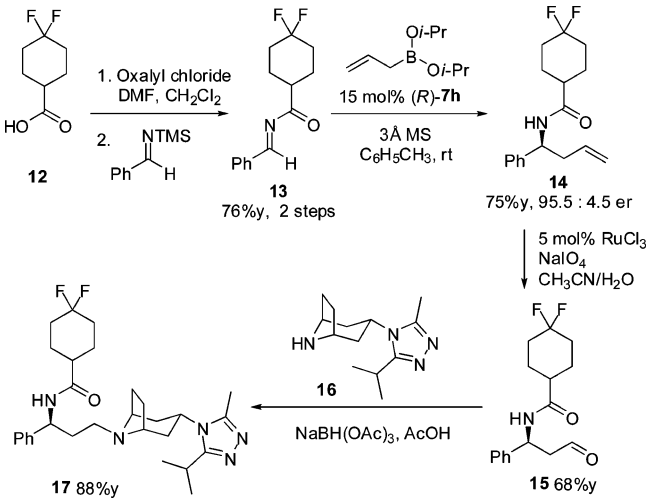


4 10 11

entry	R	product	% yield[b]	er[c]
1	CH_3O	**11a**	13	57:43
2	*t*-BuO	**11b**	25	65:35
3	CH_2=$CHCH_2O$	**11c**	41	65:35
4	CH_3	**11d**	52	70:30
5	*p*-$(CH_3)_2N$-C_6H_4	**11e**	76	97:3
6	*p*-CH_3O-C_6H_4	**11f**	80	97.5:2.5
7	*p*-Br-C_6H_4	**11g**	83	96.5:3.5
8	*p*-F-C_6H_4	**11h**	84	97.5:2.5
9	*p*-NO_2-C_6H_4	**11i**	92	99.5:0.5
10	*o*-F-C_6H_4	**11j**	83	69:31
11	(*E*)-PhCH=CH	**11k**	82	95:5
12	*c*-C_6H_{11}	**11l**	83	97:3

[a] Reactions were run with 0.125 mmol of borane, 0.125 mmol of acyl imine, 15 mol % catalyst and 3 Å 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.

Scheme 1. Synthesis of Maraviroc



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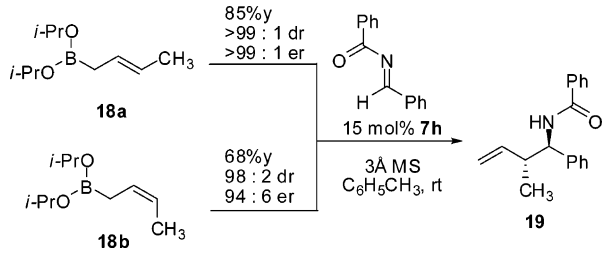
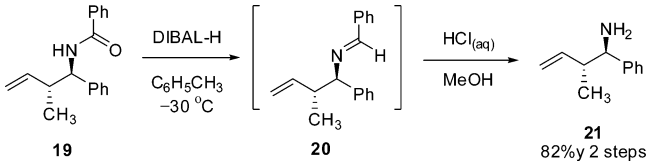
Scheme 2. Asymmetric Crotylboration of Benzoyl Imine



Scheme 3. Removal of the *N*-Benzoyl Group



under standard reaction conditions gave the homoallylic amide in good yield and selectivity (75% yield, 95.5:4.5 er). Oxidation of the olefin with $RuCl_3$ and $NaIO_4$ in a solution of acetonitrile and H_2O (6:1) cleanly gave the aldehyde,[22] and reductive amination with the tropane yielded Maraviroc. The route, while only a few steps shorter than the β-amino acid approach, limits the use of amine protecting group manipulation.

Crotylboration of Acyl Imine. The asymmetric crotylboration of benzoyl imine **5** yielded an interesting result (Scheme 1). The use of (*E*)-crotyl borane **18a** in the reaction resulted in the formation of the anticipated *anti*-addition product **19** in high dr (diastereomeric ratio) and er (99:1). However, using (*Z*)-crotyl boronate **18b** in the reaction also resulted in the formation of **19** in lower yields (68%) and er (94:6). To determine the relative configuration, the benzoyl group was removed via DIBAL-H reduction followed by acid hydrolysis to afford the known homoallylic amine in 82% yield (Scheme 3). Benzylidene **20** was observed as an intermediate in this two step process. The spectroscopic data of amine **21** proved to be identical with previously reported data.[21,23]

Mechanistic Studies. Recent studies involving the catalytic activation of allylboronates have described interesting modes by which the addition to π systems may be accomplished. Beyond the most studied types of Lewis acid activation of carbonyl groups,[1c,24] Hall et al.[25] and Miyaura et al.[26] used Lewis and Brønsted acids to activate the boronate through Lewis acid coordination to the boronate oxygen,[27] Shibasaki illustrated how allylboronates may be used as allyl donors for in situ formation of chiral Cu-allyl species,[11d] and Morken et al. recently described the conjugate addition of allylboronates to benzylidene ketones catalyzed by Ni(0) and Pd(0) complexes.[28] An alternative type of boron activation that we have used for the enantioselective addition of allylboronates to ketones[17] (and Chong and Wu have employed for the asymmetric conjugate addition of organoboronates to benzylidene ketones[29]) is via exchange of the alkoxy boronate ligands to create a more activated allylboronate species. Our mechanistic studies focused on characterizing the boronate species under catalytic conditions, determining the role for the BINOL catalyst, and following the course of the reaction spectroscopically. Key aspects of the asymmetric allylboration reaction catalyzed by diols include the type of boronate used in the reaction, the diol functionality of the catalyst, and the type of imine used in the reaction. Consistent with our previous work, pinacol, ethylene glycol, and 1,3-propanediol-derived allylboronates suffered from slow reaction rates, low yields, and enantioselectivities, whereas diisopropoxy boronate **4** afforded the best results. Similar to our previous studies, the diol functionality of the catalyst was crucial. The allylboration of imine **5** using monomethylated-BINOL catalyst **7i** resulted in significantly lower yields and low er (Table 1, entry 12). Finally, the nature of the imine also proved to be important. Acyl imines were found to be important for rate and selectivity (Table 4). Carbamoyl-derived imines were found to be less reactive and less selective. Benzyl and aryl imines were also not good substrates for the reaction, affording the corresponding homoallylic amine in poor enantioselectivities and in low to moderate yields (<3:2 er, <40% yield). These observations highlight the important characteristics of the imine for achieving good yield and high enantioselectivity.

Boronate Ligand Exchange. Our initial experiments focused on characterizing the boronate species under the catalytic reaction conditions. NMR and electron spray ionization mass spectrometry (ESI-MS) experiments of BINOL-derived diols and boronates were conducted at room temperature in the presence and absence of imines. In the reaction of **4** with (*S*)-3,3′-Br_2-BINOL **7f** (1:1) monitored by ^1H NMR, H_b and H_c at the 4- and 4′-positions of **7f** after 10 h indicated a loss of *C*2 symmetry via exchange of one isopropoxy ligand on the boronate, resulting in the formation of a dissymmetrical boronate complex **22** (Figure 2a), the active complex in the asymmetric allylboration of ketones.[17] A similar observation was made in the reaction of **4** with **7h** (Figure 2b). Resonances corresponding to H_e and H_f in boronate **23** resulted from coupling to the 3- and 3′-phenyl ring of the catalyst-associated complex. Both exchange reactions indicate the formation of a single isopropoxide exchange event.

The exchange reaction was also monitored by ESI-MS. ESI-MS is a relatively mild process that can lead to the qualitative analysis of fleeting structures.[30] With this in mind, we analyzed the mixture of BINOL **7h** and boronate **4** that was allowed to equilibrate at room temperature for 4 h into a MicroMass ZQ 2000 mass spectrometer in positive electrospray ionization mode. Under these conditions, the mass of complex **22** was observed (Figure 3a) without any detectable formation of the corresponding cyclic boronate.

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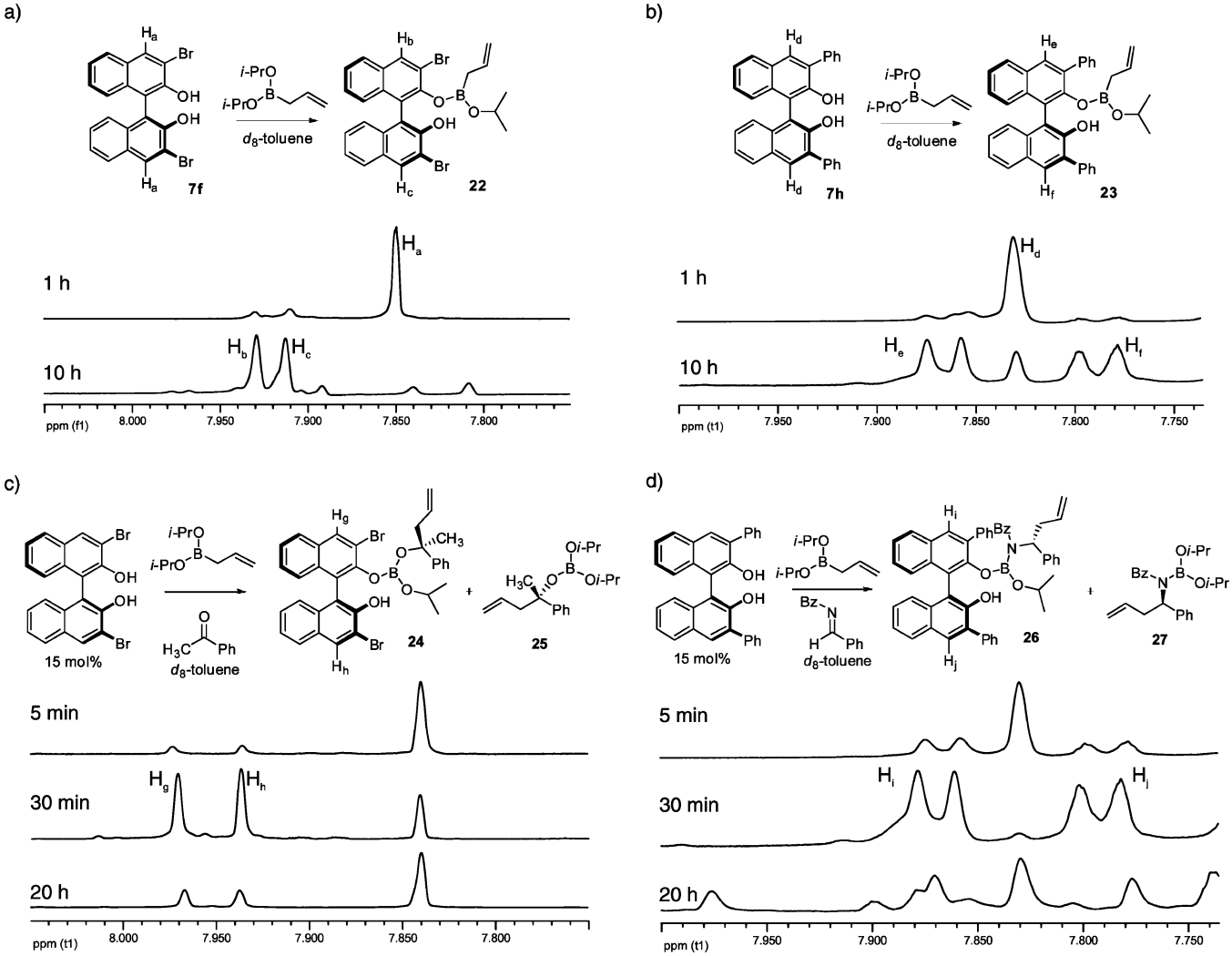


Figure 2. ^{1}H NMR studies for the formation of the BINOL−boronate complex: (a) **7f** + allylboronate **4**, (b) **7h** + allylboronate **4**, (c) **7f** + allylboronate **4** + acetophenone, and (d) **7h** + allylboronate **4** + acyl imine **5**.

Spectroscopic Characterization of the Reaction. We next set out to further characterize the course of the reaction and the role of the diol catalyst by spectroscopic methods. ^{1}H NMR revealed the same exchange process in the asymmetric allylboration of acetophenone and acyl imine **5** (Figure 2c,d). Interestingly, the rate of ligand exchange was significantly enhanced in the presence of an electrophile with complex formation occurring within 30 min. In both the reaction of the ketone and the reaction of the acyl imine, the predominant resting state of the diol appeared to be the product-associated complexes **24** and **26**. Further characterization of intermediate **26** during the course of the reaction was performed using ^{11}B NMR (Figure 4). Disappearance of allyldiisopropoxy borane **4** at 29 ppm with concomitant appearance of product **27** at 17 ppm was observed. However, because of the resolution afforded by ^{11}B NMR, it was difficult to observe other species that may be present at low concentrations such as intermediate **26**. ESI-MS of the crude reaction mixture did reveal the presence of intermediate **26** (Figure 3b) as the predominant intermediate incorporating the diol catalyst.

The dependence of catalyst **7h** concentration on the initial rate of the reaction was determined by *in situ* IR monitoring. Using a Mettler Toledo-AutoChem ReactIR 4000, the appearance of product amide **6a** at 1428 cm^{-1} was monitored during the course of the reaction over a >10-fold range of catalyst concentrations (Figure 5). The linear dependence of observed rates on catalyst concentration is consistent with a model involving an active diol-associated complex **23**. The similar dependence on catalyst was observed for the asymmetric allylboration of acetophenone.[17]

Model for Selectivity. In the asymmetric allylboration of ketones, the (*S*)-homoallylic alcohol is the major enantiomer isolated from the reaction catalyzed by (*S*)-**7h** (Scheme 4). However, using the same catalyst in the allylboration of imine **5**, (*R*)-homoallylic amide **6** was isolated. We postulate that the switch in enantiofacial selectivity is due to an alternative mechanism for activation of the boronate involving a different conformation than that proposed for the asymmetric allylboration of ketones. Another intriguing aspect of the allylboration of imines is the addition of crotyl boronates (Scheme 2). Unlike the high levels of diastereocontrol exhibited by the crotylation of ketones, under similar conditions, both (*E*)- and (*Z*)-crotyl boronates afforded the same diastereomer. The (*E*)-crotyl boronate afforded the product in high er and dr, whereas the (*Z*)-crotyl boronate afforded the product in similarly high dr but lower er. The high degree of *anti*-selectivity afforded by

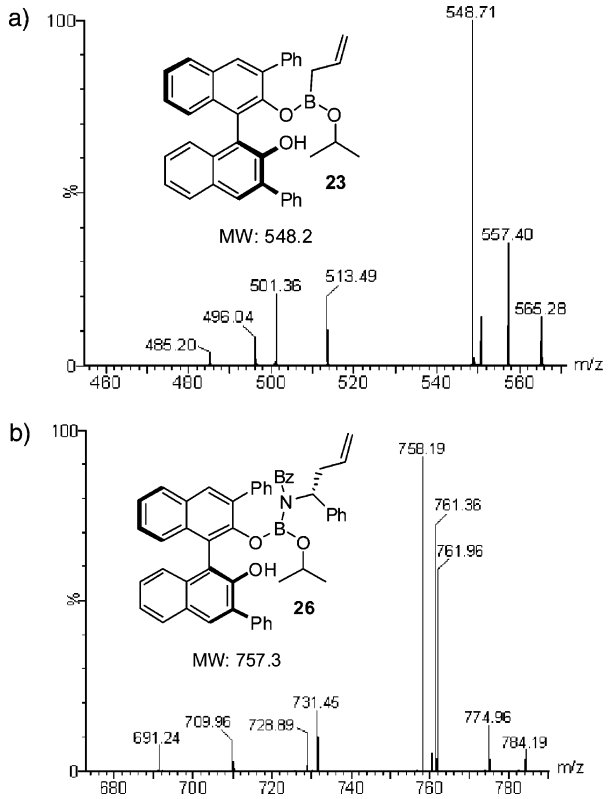


Figure 3. ESI-MS study of boronate intermediates. (a) **7h** + allylboronate **4** for 4 h and (b) **7h** + allylboronate **4** + acyl imine **5**.

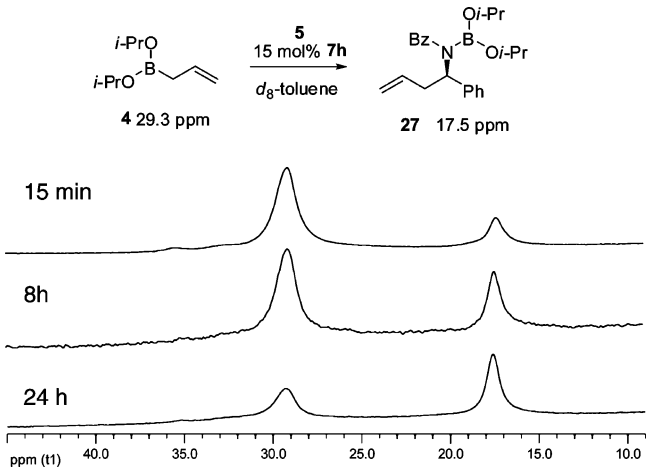


Figure 4. ^{11}B NMR studies of asymmetric allylboration reaction, **7h** + allylboronate **4** + acyl imine **5**.

the (*E*)-crotyl boronate can be rationalized via a chair transition state (Figure 6).[31] However, the *anti*-selectivity afforded by the (*Z*)-crotyl boronate must then arise from the corresponding boat transition state; a preferred conformer due to the pseudo-*trans*-diaxial interaction of the methyl group of the (*Z*)-boronate and acyl substituent of the imine arising from the chair transition state. We propose that the enantiofacial selectivity is the result of catalyst coordination to the (*Z*)-conformer of the acyl imine. While the predominant form of the imine is the (*E*)-configuration, the more reactive (*Z*)-conformer has been proposed by Corey et al.[32] and others[33] for reactions with imines due to steric interactions that arise from boronate reagent coordination. In

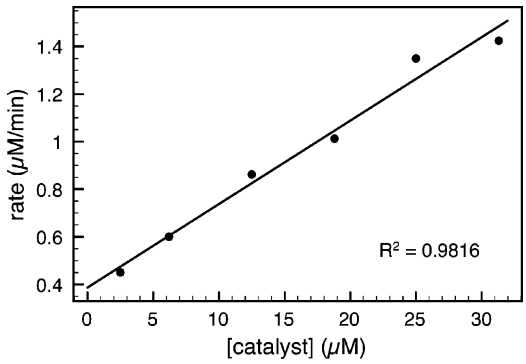
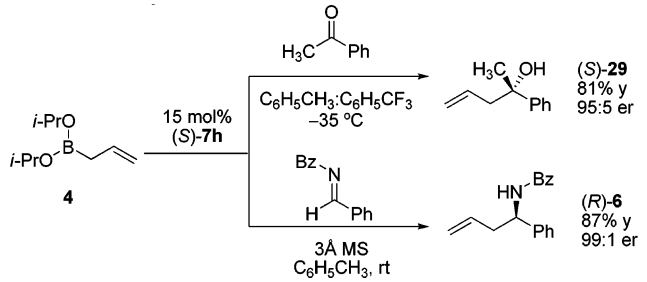


Figure 5. Plot of the observed rate vs [catalyst **7h**] in the reaction of boronate **4** with imine **5** at room temperature. The linear relationship indicates a first-order dependence.

Scheme 4. Enantiofacial Selectivity in Asymmetric Allylboration of Ketones and Acyl Imines



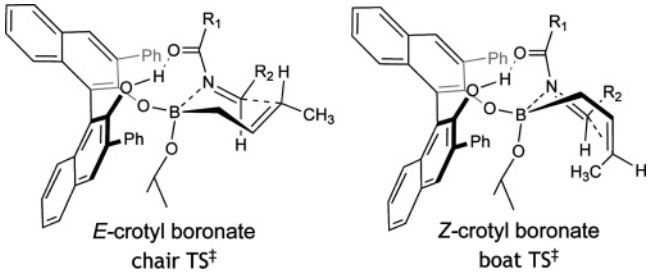


Figure 6. Proposed transition states.

our proposed model for selectivity, the hydrogen-bonding character of the diol−boronate complex facilitates coordination of the imine acyl functionality and could potentially be important for (*E*)/(*Z*)-isomerization. Our proposed model illustrates coordination to the (*Z*)-imine by the boronate complex resulting in the observed *re* enantiofacial selectivity of the allylboration reaction.

Conclusion

In summary, we have developed highly enantioselective allylboration of acyl imines catalyzed by chiral BINOL-derived catalysts. The reaction is highly selective for aryl as well as aliphatic acyl imines. The asymmetric synthesis of the anti-HIV-1 compound Maraviroc was accomplished using the asymmetric allylboration reaction. The reaction of crotyl boronates affords the corresponding *anti*-product in high diastereoselectivity. Mechanistic studies strongly suggest facile exchange between boronate and catalyst giving rise to the active

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allylation reagent. Ongoing studies include expansion of the scope and utility of the reaction.

Experimental Procedures

Enantioselective allylation of acyl imines catalyzed by diols: a 50 mL oven dried round-bottomed flask was charged with a stir bar and flushed with Ar. To the flask was added *N*-benzylidenebenzamide **5** (104 mg, 0.5 mmol), 3 Å molecular sieves (500 mg), and (*S*)-3,3′-Ph_2-BINOL **7h** (33 mg, 0.05 mol). The flask was fitted with a septum and placed under an atmosphere of Ar. To the flask was added toluene (3.0 mL), and the mixture was stirred at room temperature. Allyldiisopropoxyborane **4** in a toluene solution (500 μL, 0.50 mmol, 1 M solution) was added dropwise, and the reaction mixture was stirred at room temperature for 24 h. The reaction was diluted with ether (10 mL) and water (10 mL). The biphasic mixture was stirred at room temperature for 10 min. The organic layer was separated and dried over Na_2SO_4. The organic layer was isolated by filtration, and the filtrate was concentrated in vacuo at 20 °C. The residue was purified by flash chromatography over silica gel (elution with 95:5 − 9:1 hexanes/EtOAc) to afford the homoallylic amide as a white solid (109 mg, 85% yield). The er of the product was determined to be 99:1 by chiral HPLC analysis. t_R minor: 5.9 min, t_R major: 9.1 min (Chiralcel OD column, 24 cm × 4.6 mm i.d., hexanes/IPA 90:10, 1.5 mL/min).

Acknowledgment. The authors acknowledge the CEM Corporation (Matthews, NC) for assistance with microwave instrumentation and Symyx, Inc. (Santa Clara, CA) for chemical reaction planning software support. S.L. gratefully acknowledges a graduate research fellowship from Merck Research Laboratories−Boston. This research was supported by a gift from Amgen, Inc., an NSF CAREER Grant (CHE-0349206), and the NIH (P50 GM067041 and R01 GM078240).

Supporting Information Available: Experimental procedures and HPLC analysis for **9a**−**p**, **11e**−**l**, and **19**; complete reference 20b. This material is available free of charge via the Internet at http://pubs.acs.org.

JA075204V