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Asymmetric Allylboration of Ketones Catalyzed by Chiral Diols

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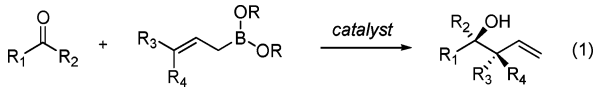
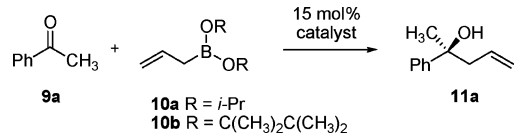
The asymmetric allylation reaction is a powerful method for the construction of chiral building blocks for use in synthesis.[1] Many useful and innovative methods exist for the allylation of aldehydes;[2] however, the enantioselective allylation of ketones to yield chiral tertiary homoallylic alcohols remains a challenge for asymmetric methods.[3] Notable advances in this area include the use of chiral allylsilanes,[4] chiral allylboranes,[5] and boronates,[6] the asymmetric allylation of ketones using allyl stannanes,[7] the asymmetric Cu(I)-catalyzed allylboration reaction,[8] and the Ag(I)-catalyzed asymmetric Sakurai−Hosomi reaction of ketones with allyl silanes.[9] In developing an asymmetric allylation reaction of ketones, we considered two key observations. First, recent reports illustrate that the addition of allylboronates to aldehydes is accelerated by the use of Lewis acids[10] or strong Brønsted acids.[11] The observed rate acceleration is presumably due to Lewis acid activation of the boron atom via coordination to the boronate alkoxy ligand.[12] Second, we sought to capitalize on the facility with which acyclic dialkoxyboranes undergo ligand exchange.[13] We postulated that chiral diols could act as catalytic promoters of asymmetric allylboration reactions (eq 1): exchangeable chiral ligands with Brønsted acidic characteristics. Herein, we report the first example of a highly enantioselective asymmetric allylboration of ketones using chiral BINOL-derived catalysts and allyldiisopropoxyborane.



(1)

We initiated our investigation by evaluating the reaction of allyldiisopropoxyborane **10a** with acetophenone in toluene at 0 °C (Table 1, entry 1). The uncatalyzed reaction afforded the product **11a** in only 13% yield. However, when 15 mol % of (+)-TADDOL **1** was included in the reaction, a greater yield of the tertiary alcohol was obtained (entry 2, 54% yield) but in racemic form. Other chiral diols, such as (*S*,*S*)-1,2-diphenylethane diol **2** and (−)-diethyl tartrate **3**, gave only modest increases in yield over the uncatalyzed reaction (entries 3 and 4). Alternatively, (*S*)-BIPHEN **4** and (*S*)-BINOL **5a** both gave increases in yield over the uncatalyzed reaction (entries 5 and 6), and (*S*)-BINOL afforded **11a** in an enantiomeric ratio (er) of 72:28. Encouraged by this result, we evaluated other BINOL-derived catalysts in the reaction. Catalysts with substitution at the 3,3′-positions (catalysts **5b**,**c**) gave higher enantioselectivities, and the H_8-BINOL catalyst **6b** (entries 7−10) with 3,3′-Br_2-BINOL **5b** afforded the product in the highest er (83:17). The isomeric 6,6′-Br_2-BINOL catalyst afforded **11a** in an er of only 68:32 (entry 11). Using catalyst **5b**, we optimized the reaction for enantioselectivity using temperature and solvent (entries 12−14). Higher er's were achieved at lower temperatures but at a reduced rate (entry 12). Using solvents, such as CH_2Cl_2 and THF, gave lower er's, but α,α,α-trifluorotoluene ($PhCF_3$) gave comparable er's and higher yields at −25 °C as did toluene ($PhCH_3$) at −35 °C (entry 13), the limitation of $PhCF_3$ being that it freezes at −29 °C. A mixture of

Table 1. Asymmetric Allylboration Catalyzed by Chiral Diols[a]



9a **10a** R = *i*-Pr **10b** R = $C(CH_3)_2C(CH_3)_2$ **11a**

entry	catalyst	boronate	temp (°C)	solvent	% yield[b]	er[c]
1		**10a**	0	$PhCH_3$	13	
2	**1**	**10a**	0	$PhCH_3$	54	50:50
3	**2**	**10a**	0	$PhCH_3$	19	50:50
4	**3**	**10a**	0	$PhCH_3$	21	55:45
5	**4**	**10a**	0	$PhCH_3$	58	50:50
6	**5a**	**10a**	0	$PhCH_3$	35	72:28
7	**5b**	**10a**	0	$PhCH_3$	82	83:17
8	**5c**	**10a**	0	$PhCH_3$	78	82:18
9	**6a**	**10a**	0	$PhCH_3$	68	55:45
10	**6b**	**10a**	0	$PhCH_3$	76	71:29
11	**7**	**10a**	0	$PhCH_3$	72	68:32
12	**5b**	**10a**	−35	$PhCH_3$	47	95:5
13	**5b**	**10a**	−25[d]	$PhCF_3$	89	94.5:5.5
14	**5b**	**10a**	−35	$PhCH_3$:$PhCF_3$ 1:3	83	97:3
15	**5b**	**10b**	−35	$PhCH_3$:$PhCF_3$ 1:3	0	
16	**8**	**10a**	−35	$PhCH_3$:$PhCF_3$ 1:3	25	53:47

[a] Reactions were run with 0.25 mmol boronate, 0.375 mmol acetophenone, and 15 mol % of catalyst in organic solvent (0.1 M) for 15 h under Ar, followed by flash chromatography on silica gel. [b] Isolated yield. [c] Enantiomeric ratios determined by chiral HPLC analysis. [d] Freezing point of $PhCF_3$ is −29 °C.

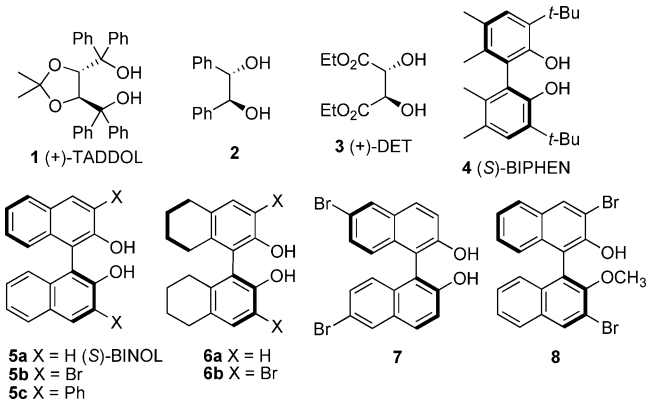


Figure 1. Chiral diols.

$PhCF_3$ and $PhCH_3$ was the most effective solvent system at −35 °C, affording the tertiary homoallylic alcohol in 83% yield and 97:3 er (entry 14). Interestingly, the use of allylpinacol boronate **10b** as the nucleophile under catalytic conditions resulted in no conversion to the product (entry 15), most likely due to the stability of the cyclic boronate. Also of note was the reaction using methyl ether **8** (entry 16); the removal of one hydroxyl group on the catalyst

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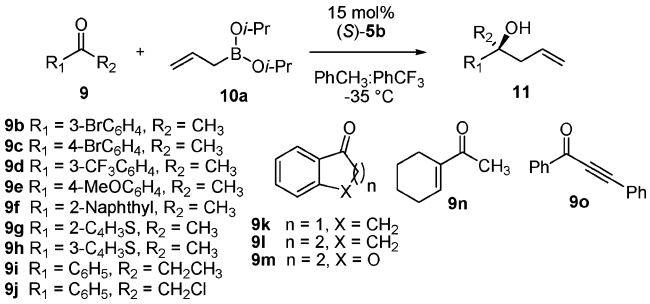
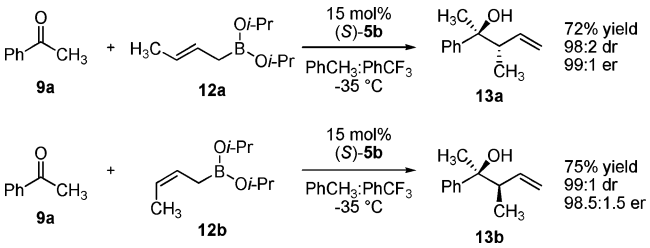
Table 2. Asymmetric Allylboration of Ketones[a]



entry	ketone	product	% yield[b]	er[c]
1[d]	**9a**	**11a**	83	97:3
2[d]	**9b**	**11b**	81	95.5:4.5
3	**9c**	**11c**	86	99.5:0.5
4	**9d**	**11d**	89	95.5:4.5
5	**9e**	**11e**	83	99.5:0.5
6	**9f**	**11f**	81	96.5:3.5
7	**9g**	**11g**	87	97:3
8	**9h**	**11h**	88	97:3
9[d]	**9i**	**11i**	83	97.5:2.5
10	**9j**	**11j**	76	98:2
11	**9k**	**11k**	88	96.5:3.5
12	**9l**	**11l**	87	97.5:2.5
13	**9m**	**11m**	83	96:4
14	**9n**	**11n**	91	96.5:3.5
15[d]	**9o**	**11o**	93	95:5

[a] Reactions were run with 0.125 mmol **10a**, 0.19 mmol ketone, and 15 mol % of catalyst in a $PhCF_3$:$PhCH_3$ (3:1) mixture (0.1 M) for 15 h under Ar, followed by flash chromatography on silica gel. [b] Isolated yield. [c] Determined by chiral HPLC and chiral GC analysis. [d] Reactions were run with 0.5 mmol **10a** and 0.75 mmol acetophenone.

Scheme 1. Asymmetric Crotylboration of Acetophenone



resulted in diminished activity and lower selectivity, highlighting the importance of the diol functionality.

The optimized reaction conditions were effective at promoting the asymmetric allylboration of a variety of ketones in high enantioselectivities (Table 2). Electron-rich and electron-deficient aromatic ketones were tolerated in the reaction (entries 1−6). Heteroaromatic ketones afforded the corresponding homoallylic alcohols in good yields and enantioselectivities (entries 7 and 8). Notably, the ethyl and chloromethyl ketones **9i** and **9j** both cleanly underwent the allylboration in high er's (entries 9 and 10). Cyclic ketones were good substrates for the reaction, as well (entries 11−13). The unsaturated enones **9n** and **9o** only afforded the 1,2-addition products, both in good yields and er's (entries 14 and 15). Catalyst **5b** also promoted the stereoselective crotylboration of acetophenone; (*E*)-crotyl boronate **12a** afforded *anti*-isomer **13a** in high dr and er, and (*Z*)-crotyl boronate **12b** yielded the *syn* product **13b** in good yields and high selectivities (Scheme 1). The observed diastereoselectivities were consistent with a Zimmerman−Traxler transition state model.

Preliminary mechanistic experiments indicate a catalyst-associated boronate complex.[14] Rapid exchange of one isopropoxy ligand was observed by ^{1}H NMR in the reaction of **5b** with **10a**. A similar observation was made when we monitored the asymmetric allylboration reaction catalyzed by **5b**. A positive nonlinear effect was observed when we examined the effect of catalyst er on the enantioselectivity of the reaction.[15] However, the yield of the reaction diminished linearly with catalyst er. The reaction was also found to be first order in catalyst. We attributed the observed nonlinear effect to racemate catalyst aggregation.[16] On the basis of these experiments, we propose a model of selectivity in which the **5b**·boronate complex imparts selectivity by activation of the alkoxy ligand via hydrogen bonding[17] leading to *si* facial attack on the ketone in a chair-like TS‡ (Figure 2).

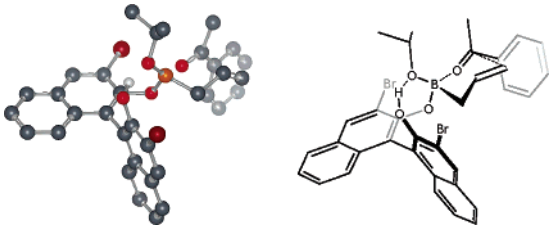


Figure 2. Proposed transition state.

In summary, we have developed a highly enantioselective and diastereoselective allylboration of ketones catalyzed by chiral BINOL-derived catalysts. Ongoing studies include expansion of the scope and utility of the reaction.

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Supporting Information Available: Experimental procedures and HPLC separations for compounds **11a**−**11o**, **13a**, and **13b**. This material is available free of charge via the Internet at http://pubs.acs.org.

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