Published in final edited form as:
Angew Chem Int Ed Engl. 2009 ; 48(46): 8679. doi:10.1002/anie.200904715.

Mechanism and an Improved Asymmetric Allylboration of Ketones Catalyzed by Chiral Biphenols**

David S. Barnett, **Philip N. Moquist**, and **Scott E. Schaus [Prof.]***
Department of Chemistry, Center for Chemical Methodology and Library Development at Boston University (CMLD-BU) Life Science and Engineering Building, Boston University 24 Cummington Street, Boston, Massachusetts, 02215 (USA), Fax: (+1) 617-353-6466, seschaus@bu.edu

Abstract

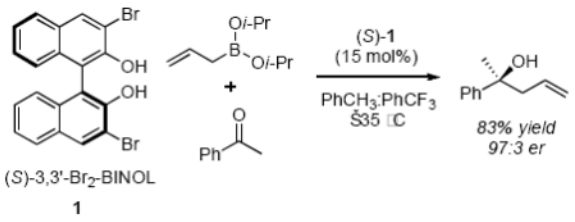
A mechanistic study of the enantioselective asymmetric allylboration of ketones with allyldiisopropoxyborane catalyzed by chiral biphenols resulted in the development of improved reaction process. In a ligand exchange process involving the chiral biphenol and the boronate to liberate isopropanol as the key step, addition of isopropanol to the reaction was found to increase the overall rate and enantioselectivity. In the design of an improved reaction, a boronate possessing a tethered alcohol would more readily liberate catalyst at the end of a reaction. The use of allyldioxaborinane with 2 mol% (S)-3,3′-Br2-BINOL and 2 equivalents t-BuOH relative to ketone at room temperature results in high yields and enantioselectivities. Insight gathered from the mechanistic investigation resulted in the development of a reaction process that uses less catalyst (from 15 mol% to 2 mol%) at warmer temperatures (from -35 °C to room temperature).

The asymmetric allylboration reaction is an extensively studied synthetic method.[1] The operational simplicity and chiral building blocks afforded readily account for the utility of the reaction.[2] Studies aimed at the development of a catalytic enantioselective allylboration of ketones[3] identified chiral biphenols as effective promoters of the reaction; however, the reaction required the use of relatively high catalyst loadings (0.15 equivalent, equation 1).4 Reducing catalyst loadings employed in organocatalytic reactions has proven challenging but recent advances in this area have been successful (2 mole % or lower),5 especially when coupled with experiments designed to provide insight into the reaction mechanism.6 We initiated a study of the reaction mechanism with the aim of indentifying a reaction that requires less catalyst and would also simultaneously address the scope and limitations of the method. Herein we report the results of our mechanistic experiments that led to the development of a reaction that uses 2 mole % of the catalyst under solvent free reaction conditions at room temperature to afford the products in ≥98:2 enantiomeric ratio (e.r.).

**This research was supported by the NIH (R01 GM078240)

*seschaus@bu.edu.

Supporting information for this article is available on the WWW under http://www.angewandte.org or from the author.



(1)

Our study began by evaluating the role of the catalyst and isopropanol in the catalytic cycle. The key steps include a crucial ligand exchange processes at the beginning and end of the catalytic cycle; a process crucial for activation of the boronate (Scheme 1).[4,7,8] Catalyst **1** reacts with allylboronate **2** to afford exchange product **3**, a species that can be detected via direct ESI-MS analysis of the reaction mixture. We presumed this step is reversible. Spectroscopic analysis of the reaction mixture using ^{1}H NMR indicates the formation of **3** along with free catalyst **1**. Our previous studies determined the rate dependence on catalyst **1** to be first order.[4] However, the order in isopropanol had not been established. If the overall rate of reaction was dependent on the initial exchange process, the addition of isopropanol to the reaction should inhibit the observed rate. This would indeed be the case for a single or double exchange process leading to **3** or a cyclic boronate.[9] We performed experiments designed to ascertain the effect of isopropanol on rate and enantioselectivity in the allylboration of acetophenone (Figure 1).

The formation of product was monitored using *in situ* ReactIR monitoring of the reaction as a function of isopropanol concentration ([*i*-PrOH]). For operational simplicity the reactions were performed at room temperature using 10 mol% **1**. Under these conditions, the enantiomeric ratio (e.r.) of the product formed was 2.2:1 without *i*-PrOH. As a preliminary study, we chose to monitor the dependence of rate and e.r. on [*i*-PrOH] over a 2-fold concentration range relative to boronate. The observed rate increased almost 3-fold (Figure 1); coincident with the rate increase was a substantial increase in the observed enantioselectivity. With the addition of 1 equivalent *i*-PrOH relative to boronate the reaction rate doubled and the enantioselectivity increased to 65:1 e.r. At a concentration of *i*-PrOH 1.5 times [boronate], the reaction rate began to plateau at 3-fold greater than the parent rate and the enantioselectivity was determined to be 99:1 e.r. The inclusion of >1 equivalent *i*-PrOH resulted in a substantially improved reaction process exhibiting higher enantioselectivities and increased rates in comparison to the parent reaction at room temperature.

The improved reaction may be understood using the proposed catalytic cycle (Scheme 1). Our observations demonstrate that the rate determining exchange process is not the initial formation of active boronate species **3** but liberation of catalyst **1** from allylation product **6** (k_{ex}). Although the parent catalyzed reaction was nominally selective (e.r. = 2.2:1), there is a 4-fold increase over the reaction run in the absence of catalyst. The catalyst **1** serves to increase the overall rate of reaction; however, the effective catalyst concentration is reduced by the formation of **6** in addition to the other species in the reaction ([**1**] = [cat_{total}] − [**3**] − [**5**] − [**6**]). The inclusion of *i*-PrOH to the catalyzed reaction increases the overall catalyst concentration ([**1**]) thereby increasing the overall rate; consequently changing the rate-limiting step of the reaction process. The effective catalyst concentration approaches the actual catalyst concentration as the exchange rate increases by the addition of *i*-PrOH (k_{ex}[**6**][*i*-PrOH]). The apparent rate of reaction is the maximum rate possible for the allylboration bond formation process. Observations made from our investigations led us to consider further improvements of the reaction.

We focused our attention on the identity of the boronate utilized in the reaction and catalyst concentration as areas for improvement. The characteristic of allyldiisopropoxyboronate **2** that makes it ideal for use in the catalytic reaction is the same characteristic that makes it a difficult reagent to prepare and store; the lability of the isopropoxy groups result in a hydrolytically unstable boronate reagent. We sought to identify a boronate possessing a desirable balance of kinetic reactivity and thermodynamic stability. Cyclic boronates such as dioxaborolanes and dioxaborinanes are substantially more stable.[10] They can be prepared and purified with greater ease and stored for longer times than acyclic boronates. In addition to the enhancement of stability, cyclic boronates would produce a tethered alcohol upon catalyst exchange that would more readily liberate the catalyst at the end of a reaction cycle (Scheme 1). Use of allyldioxaborinane **9** in the allylboration reaction with 15 mol% **1** with acetophenone **8a** (0.1 M in $PhCH_3$) at room temperature resulted in good yields of the product in 4:1 e.r. after 24 h. We postulated that the addition of another alcohol may facilitate the reaction. Isopropanol was added to the reaction of **8a** and **9** to yield the product **10a** with low yields (60% after 3 days) but high enantiopurity (99:1 e.r.). The addition of *i*-PrOH effectively reduced the background reaction while coincidentally inhibiting the catalytic reaction. This observation can be understood *via* a Lewis acid-base coordination of *B*-allyldioxaborinane and *i*-PrOH. We reasoned that a less coordinating alcohol such as *t*-BuOH would still accelerate the catalyzed reaction by facilitating ligand exchange while not inhibiting the overall rate of reaction. The addition of *t*-BuOH to the reaction in slight excess relative to boronate concentration ([**9**]) afforded the desired product in near quantitative yields with excellent enantioselectivity (e.r. > 99:1). While investigating the reaction of **8a** and **9** we found that the reaction proceeded well in the absence of solvent[11] with complete conversion and no loss in enantioselectivity. The optimized reaction conditions using allyldioxaborinane **9** required the use of 2 mol% **1** and 2 equivalents *t*-BuOH relative to ketone at room temperature. The catalyst concentration should be noted. The catalyst loading is calculated based on ketone concentration. Since the catalyst activates the boronate, relative to [boronate] the catalyst loading is 1.3 mol%. The use of lower catalyst loadings resulted in lower rates of reaction with no loss in enantioselectivity. Finally, the reaction of acetophenone could be scaled to 5 g achieving similar yields and enantioselectivities. The catalyst could be recovered in 90% yield from the reaction.

The reaction conditions proved general for a number of substrates (Table 1). Excellent yields and enantioselectivies were achieved for a broad range of ketones (>90% yield, >97:3 e.r.). In some examples, the reaction proved slow. For these substrates, additional catalyst was used to improve the rate (Table 1, Entries 6–8, 11, 13, 16). The reaction using **9** also exhibits a broader scope than the previous reaction. Phenyl acetophenone **8i** was found to be a poor substrate under the previous reaction conditions (<15% yield, low enantioselectivities). However, the reaction of **8i** with **9** afforded the allylboration product in 98% yield and 99:1 e.r. (Table 1, Entry 9). Boronate **9** was also reacted in high enantioselectivities with β-ketoester **8p** (Entry 16), a particularly difficult substrate due to facile enolization. Crotylation reactions with **8a** using *E*- and *Z*-crotyldioxaborinane, **11a** and **11b** respectively, provided products **12a** and **12b** in excellent yields with high enantio- and diastereoselectivities (Scheme 2).

We performed mechanistic experiments to determine if the allylboration reaction of **9** follows the previously proposed reaction mechanism or *via* an alternative reaction process. The reaction exhibited a first-order rate dependence on [**1**], consistent with our previous findings. We also observed the formation of the corresponding exchange product complex of boronate **8** and **1** *via* ESI-MS and ^{1}H NMR, similarly consistent with our proposed mechanism (Scheme 1).[4, 7c,8] The reaction rate and enantioselectivity was also monitored as a function of [*t*-BuOH] (Figure 2). Similar to the observations obtained using boronate **2** and *i*-PrOH, there was a coincident increase in rate and enantioselectivity with increasing concentrations of *t*-BuOH. However, at [*t*-BuOH]/[**9**] > 1 the rate became slower. Based on our previous observations using *i*-PrOH with **9**, the rate may be inhibited by a weakly coordinating Lewis acid-base

coordination of *B*-allyldioxaborinane.[10] While cyclic boronate **9** appears to be more sensitive to Lewis base coordination, the mechanism by which **9** proceeds is consistent with our previous observations.

In summary, a mechanistic investigation of the asymmetric allylboration reaction of ketones catalyzed by chiral biphenols has resulted in the development of a highly optimized reaction. Key observations about the ligand exchange process aided the design of a reaction that uses less catalyst (from 15 mol% to 2 mol%) at ambient temperatures (from -35 °C to room temperature). The new reaction exhibits similar mechanistic characteristics to the original with a first-order rate dependence on catalyst concentration and chiral biphenol-boronate complex formation. Insight afforded by this study will enable further reaction development, application of the method to asymmetric synthesis, and identification of novel catalytic processes.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

References

1. Roush, WR. Comprehensive Organic Synthesis. Trost, BA.; Fleming, I., editors. Vol. 2. Permagon Press; Oxford, U.K.: 1991. (b) Chemler, SR.; Roush, WR. Modern Carbonyl Chemistry. Otera, J., editor. Wiley-VCH; Weinheim: 2000. p. 403Chapter 11(c) Denmark, SE.; Almstead, NG. Modern Carbonyl Chemistry. Otera, J., editor. Wiley-VCH; Weinheim: 2000. p. 299Chapter 10(d) Kennedy, JWJ.; Hall, DG. Boronic Acids. Hall, DG., editor. Wiley-VCH; Weinheim: 2005. p. 241Chapter 6
2. For examples of asymmetric ketone allylations in total synthesis, see: (a) Nielsen DK, Nielsen LL, Jones SB, Toll L, Asplund MC, Castle SL. J Org Chem 2009;74:1187. [PubMed: 19072324] (b) Li F, Tartakoff SS, Castle SL. J Am Chem Soc 2009;131:6674. [PubMed: 19397370]
3. Asymmetric catalytic ketone allylations: (a) Casolari S, D'Addario D, Tagliavini E. Org Lett 1999;1:1061. (b) Hanawa H, Kii S, Maruoka K. Adv Synth Catal 2001;343:57. (c) Cunningham A, Woodward S. Synlett 2002:43. (g) Cunningham A, Mokal-Parekh V, Wilson C, Woodward S. Org Biomol Chem 2004;2:741. [PubMed: 14985815] (d) Wada R, Oisaki K, Kanai M, Shibasaki M. J Am Chem Soc 2004;126:8910. [PubMed: 15264818] (e) Teo YC, Goh JD, Loh TP. Org Lett 2005;7:2743. [PubMed: 15957936] (f) Lu J, Hong ML, Ji SJ, Teo YC, Loh TP. Chem Commun 2005:4217. (g) Wadamoto M, Yamamoto H. J Am Chem Soc 2005;127:14556. [PubMed: 16231892] (h) Zhang X, Chen D, Liu X, Feng X. J Org Chem 2007;72:5227. [PubMed: 17559275] (i) Miller JJ, Sigman MS. J Am Chem Soc 2007;129:2752. [PubMed: 17309263] (j) Schneider U, Ueno M, Kobayashi S. J Am Chem Soc 2008;130:13824. [PubMed: 18816118] (k) Itoh J, Han SB, Krische MJ. Angew Chem 2009;121:6431.Angew Chem Int Ed 2009;48:6313. (l) Yazaki R, Kumagai N, Shibasaki M. J Am Chem Soc 2009;131:3195.
4. Lou S, Moquist PN, Schaus SE. J Am Chem Soc 2006;128:12660. [PubMed: 17002355]
5. (a) Saaby S, Bella M, Jørgensen KA. J Am Chem Soc 2004;126:8120. [PubMed: 15225045] (b) Shirakawa S, Yamamoto K, Kitamura M, Ooi T, Maruoka K. Angew Chem 2005;117:631.Angew Chem, Int Ed 2005;44:625. (c) Kitamura M, Shirakawa S, Maruoka K. Angew Chem 2005;117:1573.Angew Chem, Int Ed 2005;44:1549. (d) Terada M, Machioka K, Sorimachi K. Angew Chem 2006;118:2312.Angew Chem, Int Ed 2006;45:2254. (e) Rueping M, Antonchick AP, Theissmann T. Angew Chem 2006;118:6903.Angew Chem, Int Ed 2006;45:6751. (f) Pan SC, Zhou J, List B. Angew Chem 2007;119:3028.Angew Chem, Int Ed 2007;46:612. (g) Liu TY, Cui HL, Long J, Li BJ, Wu Y, Ding LS, Chen YC. J Am Chem Soc 2007;129:1878. [PubMed: 17263539] (h) Guo QX, Liu H, Guo C, Luo SW, Gong LZ. J Am Chem Soc 2007;129:3790. [PubMed: 17358062] (i) Terada M, Machioka K, Sorimachi K. J Am Chem Soc 2007;129:10336. [PubMed: 17676850] (j) Rueping M, Theissmann T, Kuenkel A, Koenigs RM. Angew Chem 2008;120:6903.Angew Chem, Int Ed 2008;47:6798. (k) Cheon CH, Yamamoto H. J Am Chem Soc 2008;130:9246. [PubMed: 18582053]
6. Vachal P, Jacobsen EN. J Am Chem Soc 2002;124:10012. [PubMed: 12188665] (b) Kotke M, Schreiner PR. Synthesis 2007:779.

7. Wu TR, Chong JM. J Am Chem Soc 2005;127:3244. [PubMed: 15755118] (b) Wu TR, Chong JM. J Am Chem Soc 2007;129:4908. [PubMed: 17402741] (c) Lou S, Moquist PN, Schaus SE. J Am Chem Soc 2007;129:15398. [PubMed: 18020334]

8. (a) Ishiyama T, Ahiko T, Miyaura N. J Am Chem Soc 2002;124:12414. [PubMed: 12381174] (b) Rauniyar V, Hall DG. J Am Chem Soc 2004;126:4518. [PubMed: 15070360] (c) Rauniyar V, Zhai H, Hall DG. J Am Chem Soc 2008;130:8481. [PubMed: 18540580] (d) Sakata K, Fujimoto H. J Am Chem Soc 2008;130:12519. [PubMed: 18712868]

9. Paton RS, Goodman JM, Pellegrinet SC. Org Lett 2009;11:37. [PubMed: 19035769]

10. (a) Brown HC, Racherla US, Pellechia PJ. J Org Chem 1990;55:1868. (b) Roy CD, Brown HC. J Organomet Chem 2007;692:784.

10. (a) Tokunaga M, Larrow JF, Kakuichi F, Jacobsen EN. Science 1997;277:936. [PubMed: 9252321] (b) Schaus SE, Brandes BD, Larrow JF, Tokunaga M, Hansen KB, Gould AE, Furrow ME, Jacobsen EN. J Am Chem Soc 2002;124:1307. [PubMed: 11841300] (c) Long J, Hu J, Shen X, Ji B, Ding K. J Am Chem Soc 2002;124:10. [PubMed: 11772048] (d) Dolman SJ, Sattely ES, Hoveyda AH, Schrock RR. J Am Chem Soc 2002;124:6991. [PubMed: 12059222] (e) Yuan Y, Zhang X, Ding K. Angew Chem 2003;115:5636.Angew Chem, Int Ed 2003;42:5478. (f) Jeon SJ, Li H, Walsh PJ. J Am Chem Soc 2005;127:16416. [PubMed: 16305227] (g) Wooten AJ, Kim JG, Walsh PJ. Org Lett 2007;9:381. [PubMed: 17249767]

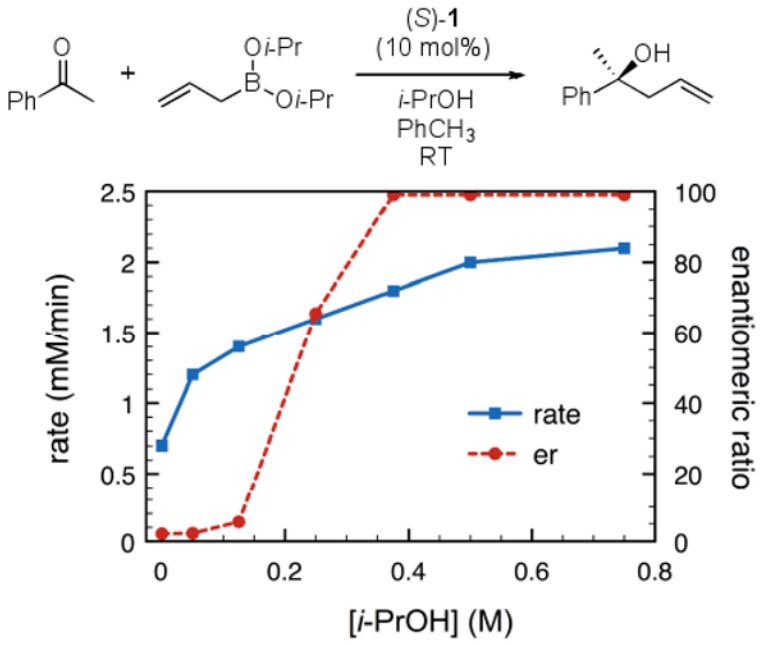


Figure 1. Effect of isopropanol on rate and enantioselectivity[a]

[a] Reactions were run with 0.075 mmol **1**, 1.5 mmol boronate **2**, and 0.75 mmol acetophenone in $PhCH_3$ (0.25 M) for 15 h under Ar at RT, followed by flash chromatography on silica gel. Enantiomeric ratios were determined by chiral HPLC methods.

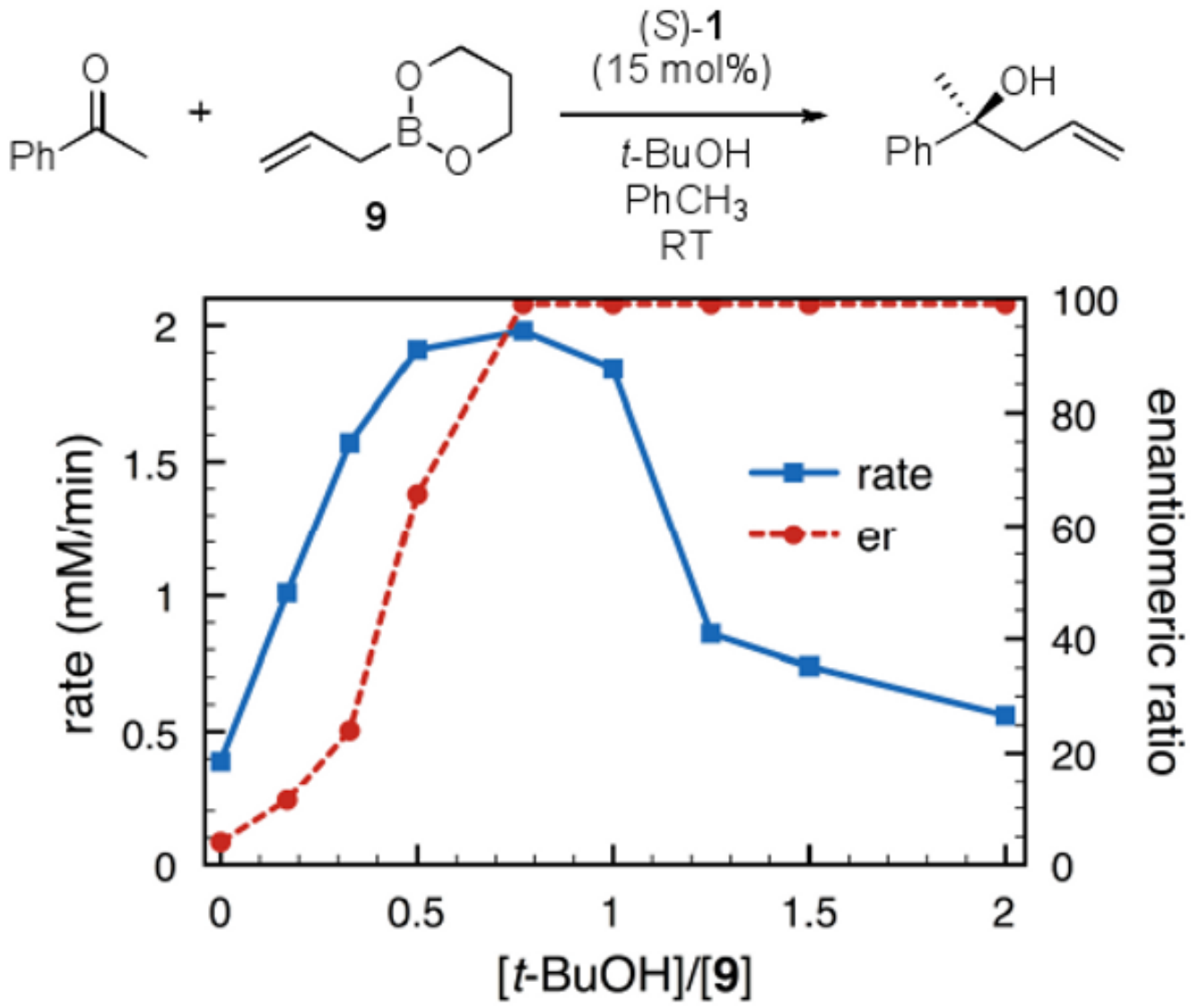
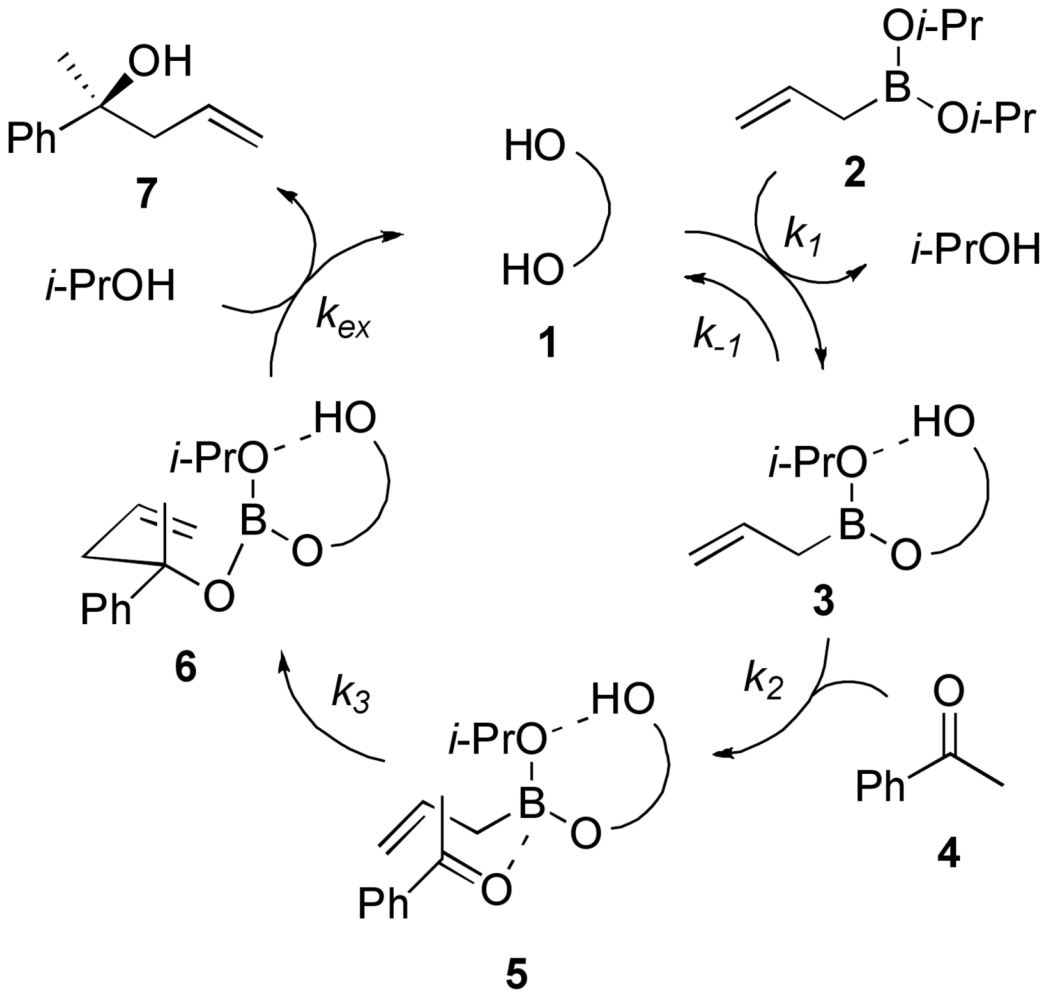
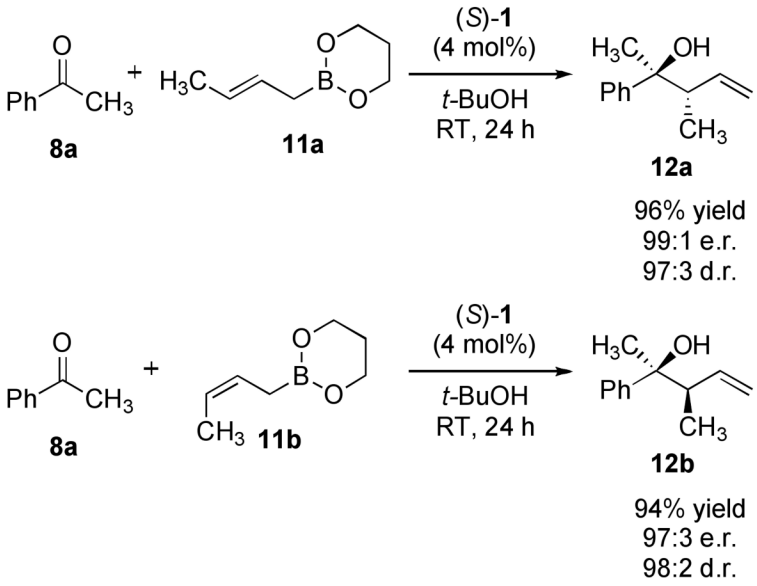


Figure 2. Effect of t-butanol on rate and enantioselectivity[a]

[a] Reactions were run with 0.15 mmol **1**, 1.5 mmol boronate **9**, and 0.75 mmol acetophenone in $PhCH_3$ (0.3 M) for 15 h under Ar, followed by flash chromatography on silica gel. Enantiomeric ratios were determined by chiral HPLC methods.



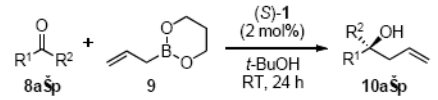
Scheme 1. Proposed Catalytic Cycle for Asymmetric Allylboration Reaction Catalyzed by Chiral Biphenols



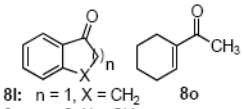
Scheme 2. Asymmetric crotylboration of acetophenone

Table 1

Asymmetric allylboration of ketones[a]

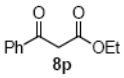


8a: R^1 = Ph, R^2 = CH_3
8b: R^1 = 4-CH_3O-Ph, R^2 = CH_3
8c: R^1 = 4-NO_2-Ph, R^2 = CH_3
8d: R^1 = 4-Br-Ph, R^2 = CH_3
8e: R^1 = 3-F-Ph, R^2 = CH_3
8f: R^1 = 2-Br-Ph, R^2 = CH_3
8g: R^1 = 2-C_4H_3S, R^2 = CH_3
8h: R^1 = 3-C_4H_3S, R^2 = CH_3
8i: R^1 = Ph, R^2 = -CH_2Ph
8j: R^1 = Ph, R^2 = -$(CH_2)_3CH_3$
8k: R^1 = Ph, R^2 = -CH_2CH_2Cl



8l: n = 1, X = CH_2
8m: n = 2, X = CH_2
8n: n = 2, X = O

8o



8p

Entry	ketone	product	Yield [%][b]	e.r.[c]
1	8a	10a	96	99:1
2	8b	10b	88	99:1
3	8c	10c	93	99:1
4	8d	10d	97	99:1
5	8e	10e	95	99:1
6[d]	8f	10f	95	98:2
7[e]	8g	10g	93	>99:1
8[e]	8h	10h	92	991
9	8i	10i	98	>99:1
10	8j	10j	93	99:1
11[e]	8k	10k	95	>99:1
12	8l	10l	95	98:2
13[e]	8m	10m	97	99:1
14	8n	10n	95	99:1
15	8o	10o	96	98:2
16[e]	8p	10p	98	99:1

[a] Reactions were run with 0.02 mmol (*S*)-**1**, 2.0 mmol *t*-BuOH, 1.0 mmol of ketone **8**, and 1.5 mmol *B*-allyl-1,3,2-dioxaborinane **9** at RT for 24 h under Ar, followed by flash chromatography on silica gel.

[b] Yield of isolated product.

[c] Determined by chiral HPLC methods.

[d] Reaction was run in $PhCH_3$ (0.25 M) with 0.075 mmol (*S*)-**1**.

[e] Reaction was run with 0.04 mmol (*S*)-**1**.