Allylations

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

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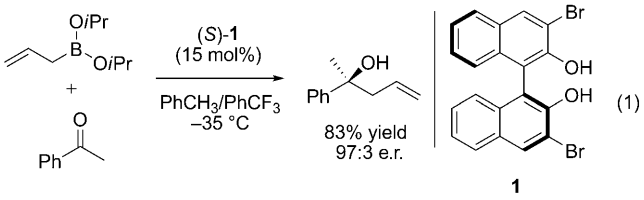
The asymmetric allylboration reaction is an extensively studied synthetic method.[1] The operational simplicity and chiral building blocks afforded readily account for the utility of the reaction.[2] Studies aimed at the development of a catalytic enantioselective allylboration of ketones[3] identified chiral biphenols as effective promoters of the reaction; however, the reaction required the use of relatively high catalyst loadings [Eq. (1)].[4] Reducing catalyst loadings employed in organocatalytic reactions has proven challenging



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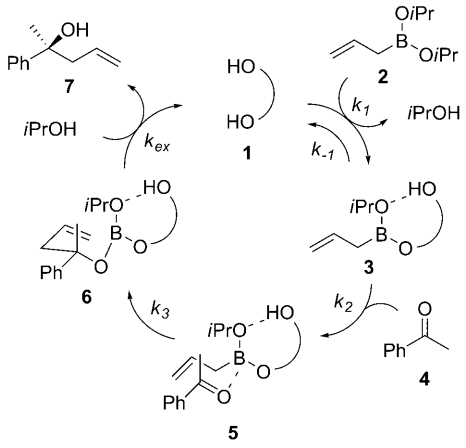

Scheme 1. Proposed catalytic cycle for asymmetric allylboration reaction catalyzed by chiral biphenols.

but recent advances in this area have been successful (2 mol% or lower),[5] especially when coupled with experiments designed to provide insight into the reaction mechanism.[6] We initiated a study of the allylboration reaction mechanism with the aim of simultaneously identifying a reaction which requires less catalyst and also addresses the scope and limitations of the method. Herein we report the results of our mechanistic experiments which led to the development of a reaction that uses 2 mol% of the catalyst under solvent-free reaction conditions at room temperature to afford the products in greater than or equal to 98:2 enantiomeric ratio (e.r.).

Our study began by evaluating the role of both the catalyst and isopropyl alcohol 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] The catalyst **1** reacts with the allylboronate **2** to afford the exchange product **3**, a species that can be detected by direct ESI-MS analysis of the reaction mixture. We presumed this step to be reversible. Spectroscopic analysis of the reaction mixture using ^{1}H NMR methods indicated 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 isopropyl alcohol had not been established. If the overall rate of reaction was dependent on the initial exchange process, the addition of isopropyl alcohol to the reaction should inhibit the observed rate. This dependence 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 isopropyl alcohol on both the rate and enantioselectivity in the allylboration of acetophenone (Figure 1).

The formation of product was monitored by in situ monitoring of the reaction as a function of the isopropyl alcohol concentration ([*i*PrOH]), using IR methods. For operational simplicity the reactions were performed at room temperature using 10 mol% **1**. Under these reaction conditions, and in the absence of *i*PrOH the enantiomeric ratio (e.r.) of the product formed was 2.2:1. As a preliminary study, we chose to monitor the dependence of both the rate and e.r. on [*i*PrOH] over a two-fold concentration range relative to boronate. The observed rate increased almost three-fold (Figure 1); coincident with the rate increase was a substantial increase in the observed enantioselectivity. With the addition of one 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 which was 1.5 times that of [boronate], the reaction rate began to plateau at three-fold

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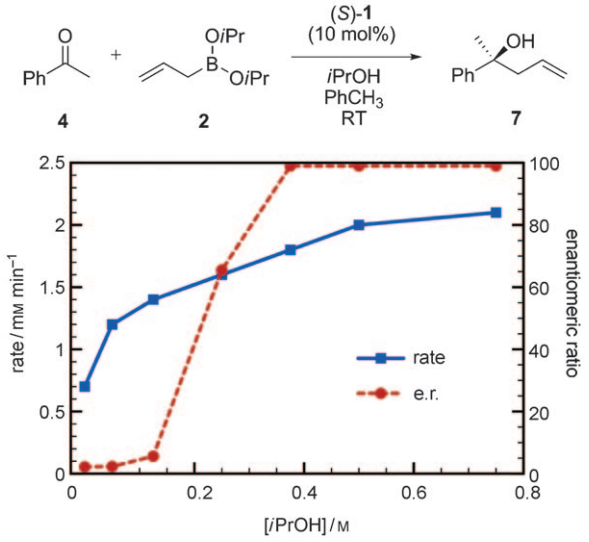


Figure 1. The effect of isopropyl alcohol on reaction rate and enantioselectivity. Reactions were run with 0.075 mmol **1**, 1.5 mmol boronate **2**, and 0.75 mmol acetophenone in $PhCH_3$ (0.25 M) for 15 h under Ar at RT, with subsequent purification by flash chromatography on silica gel (*n*-hexane/EtOAC 50:1). Enantiomeric ratios were determined by chiral HPLC methods.

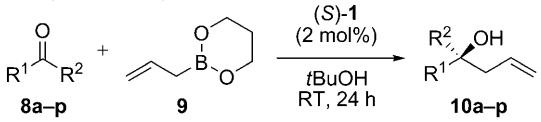
greater than the parent rate and the enantioselectivity was determined to be 99:1 e.r. The inclusion of more than one equivalent *i*PrOH resulted in a substantially improved reaction process exhibiting higher enantioselectivities and increased rates in comparison to the parent reaction at room temperature.

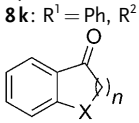
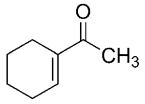
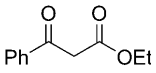
The improved reaction may be understood using the proposed catalytic cycle (Scheme 1). Our observations demonstrate that the rate-determining exchange process is not the initial formation of the active boronate species **3** but the liberation of the catalyst **1** from allylation product **6** (k_{ex}). Although the parent catalyzed reaction was nominally selective (2.2:1 e.r.), there is a four-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 ($[\mathbf{1}] = [cat_{total}] - [\mathbf{3}] - [\mathbf{5}] - [\mathbf{6}]$). The inclusion of *i*PrOH in the catalyzed reaction increases the overall catalyst concentration ([**1**]), thereby increasing the overall rate and 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 ($k_{ex}[\mathbf{6}][i\text{PrOH}]$). 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 additional 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 the 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 periods than acyclic boronates. In addition to the enhancement of stability, cyclic boronates would produce a tethered alcohol upon catalyst exchange, which would more readily liberate the catalyst at the end of a reaction cycle (Scheme 1). Use of the allyldioxaborinane **9** in the allylboration reaction with 15 mol% **1** and 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 hours. We postulated that the addition of another alcohol may facilitate the reaction. Isopropyl alcohol 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 by the 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, but not inhibit the overall rate of the reaction. The addition of *t*BuOH to the reaction in a slight excess (>1 equiv) relative to the boronate concentration ([**9**]) afforded the desired product in near quantitative yields with excellent enantioselectivity (>99:1 e.r.). 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 the allyldioxaborinane **9** required the use of 2 mol% **1** and two 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 grams, achieving similar yields and enantioselectivities. The catalyst could be recovered in 90% yield from the reaction.

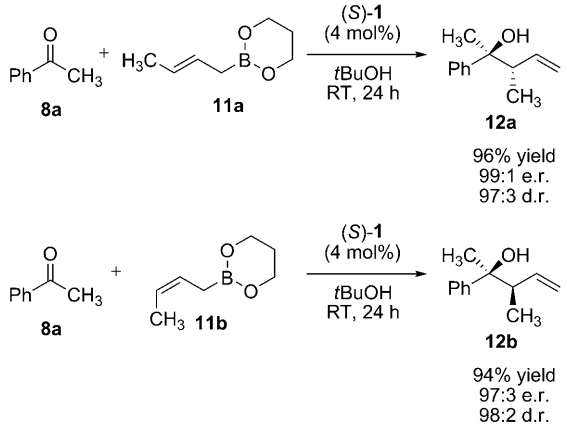
The reaction conditions proved general for a number of substrates (Table 1). Excellent yields and enantioselectivies were achieved for a broad range of ketones (>90% yield, >97:3 e.r.). In some examples, the reaction proved slow. For these substrates, additional catalyst was used to improve the rate (entries 6–8, 11, 13, and 16). The reaction using **9** also exhibited 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. (entry 9). The boronate **9** was also reacted in high enantioselectivities with β-ketoester **8p** (entry 16), a particularly difficult substrate because of facile enolization. Crotylation reactions with **8a** using *E*- (**11a**) and *Z*-crotyldioxaborinane (**11b**) provided products **12a** and **12b**, respectively, in excellent yields with high enantio- and diastereoselectivities (Scheme 2).

Table 1: Asymmetric allylboration of ketones.[a]



Entry	Ketone	Product	Yield [%][b]	E.r.[c]
1	**8a**: R^1 = Ph, R^2 = CH_3	**10a**	96	99:1
2	**8b**: R^1 = 4-$CH_3OC_6H_4$, R^2 = CH_3	**10b**	88	99:1
3	**8c**: R^1 = 4-$NO_2C_6H_4$, R^2 = CH_3	**10c**	93	99:1
4	**8d**: R^1 = 4-BrC_6H_4, R^2 = CH_3	**10d**	97	99:1
5	**8e**: R^1 = 3-FC_6H_4, R^2 = CH_3	**10e**	95	99:1
6[d]	**8f**: R^1 = 2-BrC_6H_4, R^2 = CH_3	**10f**	95	98:2
7[e]	**8g**: R^1 = 2-thienyl, R^2 = CH_3	**10g**	93	>99:1
8[e]	**8h**: R^1 = 3-thienyl, R^2 = CH_3	**10h**	92	99:1
9	**8i**: R^1 = Ph, R^2 = -CH_2Ph	**10i**	98	>99:1
10	**8j**: R^1 = Ph, R^2 = -$(CH_2)_3$Ph	**10j**	93	99:1
11[e]	**8k**: R^1 = Ph, R^2 = -CH_2CH_2Cl	**10k**	95	>99:1
				
12	**8l**: n = 1, X = CH_2	**10l**	95	98:2
13[e]	**8m**: n = 2, X = CH_2	**10m**	97	99:1
14	**8n**: n = 2, X = O	**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, with subsequent purification by flash chromatography on silica gel (*n*-hexane/EtOAC 50:1). [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**.



Scheme 2. Asymmetric crotylboration of acetophenone.

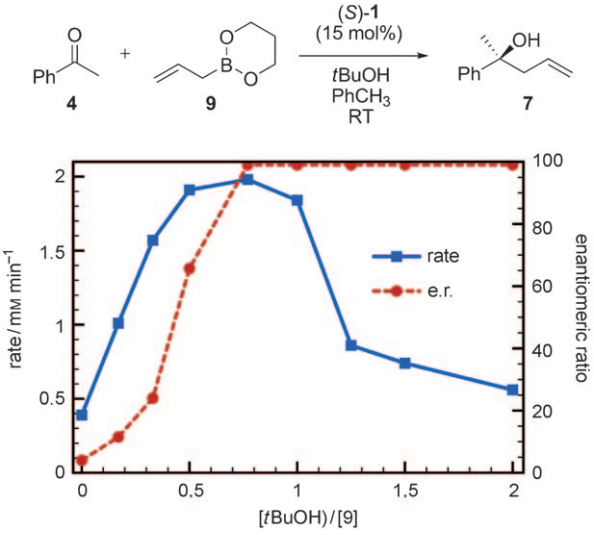


Figure 2. The effect of *tert*-butyl alcohol on reaction rate and enantioselectivity. Reactions were run with 0.15 mmol **1**, 1.5 mmol boronate **9**, and 0.75 mmol acetophenone in $PhCH_3$ (0.3 M) for 15 h under Ar, with subsequent purification by flash chromatography on silica gel (*n*-hexane/EtOAC 50:1). Enantiomeric ratios were determined by chiral HPLC methods.

We performed mechanistic experiments to determine if the allylboration reaction of **9** either proceeded according to the previously proposed reaction mechanism or through 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** by using ESI-MS and ^{1}H NMR methods, which were consistent with our proposed mechanism (Scheme 1).[4,7c,8] The reaction rate and enantioselectivity were 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**] greater than one, 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] Whereas the 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 additional reaction development, application of the method to asymmetric synthesis, and identification of novel catalytic processes.

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Keywords: boron · homogeneous catalysis · reaction mechanisms · synthetic methods

[1] a) W. R. Roush in *Comprehensive Organic Synthesis Vol. 2* (Eds.: B. A. Trost, I. Fleming), Permagon, Oxford, UK, **1991**; b) S. R. Chemler, W. R. Roush, in *Modern Carbonyl Chemistry* (Ed.: J. Otera), Wiley-VCH, Weinheim, **2000**, chap. 11, p. 403; c) S. E. Denmark, N. G. Almstead in *Modern Carbonyl Chemistry* (Ed.: J. Otera), Wiley-VCH, Weinheim, **2000**, chap. 10, p. 299; d) J. W. J. Kennedy, D. G. Hall in *Boronic Acids* (Ed.: D. G. Hall), Wiley-VCH, Weinheim, **2005**, chap. 6, p. 241.

[2] For examples of asymmetric ketone allylations in total synthesis, see: a) D. K. Nielsen, L. L. Nielsen, S. B. Jones, L. Toll, M. C. Asplund, S. L. Castle, *J. Org. Chem.* **2009**, *74*, 1187; b) F. Li, S. S. Tartakoff, S. L. Castle, *J. Am. Chem. Soc.* **2009**, *131*, 6674.

[3] Asymmetric catalytic ketone allylations: a) S. Casolari, D. D'Addario, E. Tagliavini, *Org. Lett.* **1999**, *1*, 1061; b) H. Hanawa, S. Kii, K. Maruoka, *Adv. Synth. Catal.* **2001**, *343*, 57; c) A. Cunningham, S. Woodward, *Synlett* **2002**, *43*; d) A. Cunningham, V. Mokal-Parekh, C. Wilson, S. Woodward, *Org. Biomol. Chem.* **2004**, *2*, 741; e) R. Wada, K. Oisaki, M. Kanai, M. Shibasaki, *J. Am. Chem. Soc.* **2004**, *126*, 8910; f) Y.-C. Teo, J.-D. Goh, T.-P. Loh, *Org. Lett.* **2005**, *7*, 2743; g) J. Lu, M.-L. Hong, S.-J. Ji, Y.-C. Teo, T.-P. Loh, *Chem. Commun.* **2005**, 4217; h) M. Wadamoto, H. Yamamoto, *J. Am. Chem. Soc.* **2005**, *127*, 14556; i) X. Zhang, D. Chen, X. Liu, X. Feng, *J. Org. Chem.* **2007**, *72*, 5227; j) J. J. Miller, M. S. Sigman, *J. Am. Chem. Soc.* **2007**, *129*, 2752; k) U. Schneider, M. Ueno, S. Kobayashi, *J. Am. Chem. Soc.* **2008**, *130*, 13824; l) J. Itoh, S. B. Han, M. J. Krische, *Angew. Chem.* **2009**, *121*, 6431; *Angew. Chem. Int. Ed.* **2009**, *48*, 6313; m) R. Yazaki, N. Kumagai, M. Shibasaki, *J. Am. Chem. Soc.* **2009**, *131*, 3195.

[4] S. Lou, P. N. Moquist, S. E. Schaus, *J. Am. Chem. Soc.* **2006**, *128*, 12660.

[5] a) S. Saaby, M. Bella, K. A. Jørgensen, *J. Am. Chem. Soc.* **2004**, *126*, 8120; b) S. Shirakawa, K. Yamamoto, M. Kitamura, T. Ooi, K. Maruoka, *Angew. Chem.* **2005**, *117*, 631; *Angew. Chem. Int. Ed.* **2005**, *44*, 625; c) M. Kitamura, S. Shirakawa, K. Maruoka, *Angew. Chem.* **2005**, *117*, 1573; *Angew. Chem. Int. Ed.* **2005**, *44*, 1549; d) M. Terada, K. Machioka, K. Sorimachi, *Angew. Chem.* **2006**, *118*, 2312; *Angew. Chem. Int. Ed.* **2006**, *45*, 2254; e) M. Rueping, A. P. Antonchick, T. Theissmann, *Angew. Chem.* **2006**, *118*, 6903; *Angew. Chem. Int. Ed.* **2006**, *45*, 6751; f) S. C. Pan, J. Zhou, B. List, *Angew. Chem.* **2007**, *119*, 618; *Angew. Chem. Int. Ed.* **2007**, *46*, 612; g) T.-Y. Liu, H.-L. Cui, J. Long, B.-J. Li, Y. Wu, L.-S. Ding, Y.-C. Chen, *J. Am. Chem. Soc.* **2007**, *129*, 1878; h) Q.-X. Guo, H. Liu, C. Guo, S.-W. Luo, L.-Z. Gong, *J. Am. Chem. Soc.* **2007**, *129*, 3790; i) M. Terada, K. Machioka, K. Sorimachi, *J. Am. Chem. Soc.* **2007**, *129*, 10336; j) M. Rueping, T. Theissmann, A. Kuenkel, R. M. Koenigs, *Angew. Chem.* **2008**, *120*, 6903; *Angew. Chem. Int. Ed.* **2008**, *47*, 6798; k) C. H. Cheon, H. Yamamoto, *J. Am. Chem. Soc.* **2008**, *130*, 9246.

[6] a) P. Vachal, E. N. Jacobsen, *J. Am. Chem. Soc.* **2002**, *124*, 10012; b) M. Kotke, P. R. Schreiner, *Synthesis* **2007**, 779.

[7] a) T. R. Wu, J. M. Chong, *J. Am. Chem. Soc.* **2005**, *127*, 3244; b) T. R. Wu, J. M. Chong, *J. Am. Chem. Soc.* **2007**, *129*, 4908; c) S. Lou, P. N. Moquist, S. E. Schaus, *J. Am. Chem. Soc.* **2007**, *129*, 15398.

[8] a) T. Ishiyama, T. Ahiko, N. Miyaura, *J. Am. Chem. Soc.* **2002**, *124*, 12414; b) V. Rauniyar, D. G. Hall, *J. Am. Chem. Soc.* **2004**, *126*, 4518; c) V. Rauniyar, H. Zhai, D. G. Hall, *J. Am. Chem. Soc.* **2008**, *130*, 8481; d) K. Sakata, H. Fujimoto, *J. Am. Chem. Soc.* **2008**, *130*, 12519.

[9] R. S. Paton, J. M. Goodman, S. C. Pellegrinet, *Org. Lett.* **2009**, *11*, 37.

[10] a) H. C. Brown, U. S. Racherla, P. J. Pellechia, *J. Org. Chem.* **1990**, *55*, 1868; b) C. D. Roy, H. C. Brown, *J. Organomet. Chem.* **2007**, *692*, 784.

[11] a) M. Tokunaga, J. F. Larrow, F. Kakuichi, E. N. Jacobsen, *Science* **1997**, *277*, 936; b) S. E. Schaus, B. D. Brandes, J. F. Larrow, M. Tokunaga, K. B. Hansen, A. E. Gould, M. E. Furrow, E. N. Jacobsen, *J. Am. Chem. Soc.* **2002**, *124*, 1307; c) J. Long, J. Hu, X. Shen, B. Ji, K. Ding, *J. Am. Chem. Soc.* **2002**, *124*, 10; d) S. J. Dolman, E. S. Sattely, A. H. Hoveyda, R. R. Schrock, *J. Am. Chem. Soc.* **2002**, *124*, 6991; e) Y. Yuan, X. Zhang, K. Ding, *Angew. Chem.* **2003**, *115*, 5636; *Angew. Chem. Int. Ed.* **2003**, *42*, 5478; f) S.-J. Jeon, H. Li, P. J. Walsh, *J. Am. Chem. Soc.* **2005**, *127*, 16416; g) A. J. Wooten, J. G. Kim, P. J. Walsh, *Org. Lett.* **2007**, *9*, 381.

