Asymmetric Catalysis

DOI: 10.1002/anie.201103883

Asymmetric Reduction of Ketones by Phosphoric Acid Derived Catalysts**

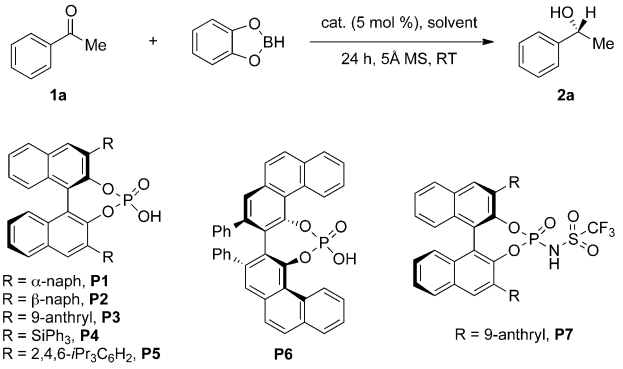
*Zuhui Zhang, Pankaj Jain, and Jon C. Antilla**

Enantioenriched secondary alcohols represent an important class of molecules found in numerous intermediates, chiral building blocks, and biologically active compounds.[1] Asymmetric reduction of prochiral ketones constitutes the most straightforward way to form these important moieties. Traditionally, stoichiometric amounts of chiral ligands were used together with an aluminium or a boron hydride to achieve high levels of enantioselectivity.[2] Various catalytic processes have been developed in the past three decades in an effort to eliminate the use of stoichiometric amounts of chiral regents.[2] The Corey–Bakshi–Shibata (CBS) catalyst[2b] and Noyori's ruthenium catalyst[2a] represent two of the most well-known methods for this purpose. Both catalytic systems have been further developed by altering the ligand or by employing different metals in efforts to enhance the selectivity or improve practicality.[3–5] Despite extensive research, the utilization of simple chiral Brønsted acids as precatalysts for this asymmetric process is still unknown.

Chiral phosphoric acids have emerged as highly efficient and selective catalysts for a variety of transformations since their first reports, through independent studies by Akiyama and Terada.[6,7] Early publications using these catalysts relied on the activation of imine electrophiles. Recently, additional discoveries have shown an ability for these catalysts to activate vinyl ether,[8] aziridines,[9] nitroso compounds,[10] enones,[11] and glyoxylates.[12] However, general carbonyl compounds, like ketones, have not been used as substrates in the presence of chiral phosphoric acid. Recently, our group reported the first highly enantioselective allylboration of aldehydes catalyzed by a chiral phosphoric acid.[13] Protonation of the boronate oxygen by the catalyst was proposed to rationalize both the activation and the enantioselectivity.[14] The broadening of the limited scope of this type of activation is highly desired. Herein, we describe, to the best of our knowledge, the first example of highly enantioselective reduction of ketones catalyzed by a chiral phosphoric acid derivative. However, this chemistry is believed to differ mechanistically in comparison to our previous allylboration. The formation of a new phosphoryl catechol boronate is proposed based on preliminary spectroscopic evidence. The phosphoryl borate formed in situ is believed to act as a novel chiral bifunctional catalytic system.

The reduction of acetophenone (**1a**) with catecholborane was chosen as the starting point for optimization of the reaction conditions. A series of binol-derived phosphoric acids were screened in toluene at room temperature in the presence of 5 Å molecular sieves (Table 1, entries 1–6). Catalyst **P3**, with a 9-anthryl group in the 3,3′-position of binol, provided the product with the highest enantioselectivity (Table 1, entry 3). Chiral *N*-triflyl phosphoramide **P7**, which is a stronger Brønsted acid than its phosphoric acid counterpart, provided the product with reverse absolute configuration and low *ee* (Table 1, entry 7).[15] Further solvent

Table 1: Optimization of reaction conditions.[a]



Entry	Solvent	Catalyst[b]	Yield [%]	*ee* [%]
1	toluene	**P1**	96	1
2	toluene	**P2**	94	12
3	toluene	**P3**	95	46
4	toluene	**P4**	93	10
5	toluene	**P5**	97	28
6	toluene	**P6**	92	−31
7	toluene	**P7**	94	−17
8	benzene	**P3**	95	33
9	CH_2Cl_2	**P3**	94	39
10	EtOAc	**P3**	93	38
11	Et_2O	**P3**	95	7
12[c]	toluene	**P3**	94	78
13[d]	toluene	**P3**	95	67

[a] Reaction conditions: **1a** (0.10 mmol), catecholborane (0.16 mmol, 1.6 equiv), catalyst (5 mol%), 5 Å MS (50 mg), solvent (1 mL, 0.1 M) under argon. Yields refer to isolated product. Enantiomeric excess was determined by chiral HPLC analysis using a chiral column. [b] The catalysts in entries 1–12 were washed with HCl after purification by silica gel chromatography. [c] $T = -20$ °C. [d] **P3** was purified on silica gel without re-acidification with HCl, $T = -20$ °C.

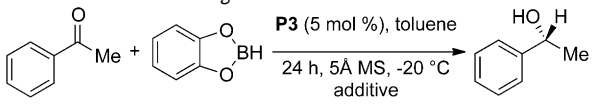
[*] Dr. Z. Zhang, P. Jain, Prof. Dr. J. C. Antilla
Department of Chemistry, University of South Florida
4202 E. Fowler Avenue, CHE 205A, Tampa, FL 33620 (USA)
E-mail: jantilla@usf.edu
Homepage: http://chemistry.usf.edu/faculty/antilla/

[**] We thank the National Institutes of Health (NIH GM-082935) and the National Science Foundation CAREER program (NSF-0847108) for financial support. We also thank the referees very valuable suggustions.

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/anie.201103883.

screening using benzene, dichloromethane, ethyl acetate, or diethyl ether gave inferior selectivities when compared to the use of toluene as solvent (Table 1, entries 8–11). To our delight, an increase to 78% *ee* was obtained by lowering the reaction temperature to −20 °C (Table 1, entry 12). Interestingly, the catalyst purified by silica gel chromatography, which is known to be contaminated by metal impurities, as shown by Ishihara,[16] List,[17] and our group,[18] can also catalyze the reaction, albeit with slightly lower levels of enantioselectivity (Table 1, entry 13). This result prompted us to investigate different phosphate salts, in an attempt to further improve the enantioselectivity. **P3** metal phosphates of calcium, magnesium and lithium afforded similar selectivities as the catalyst obtained from reacidification by HCl (Table 2, entries 1–3).

Table 2: Additives screening.[a]



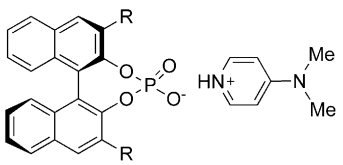
1a **2a**

Entry	Additive (mol%)	Yield [%]	*ee* [%]
1	$Ca(OMe)_2$ (2.5)	96	80
2	$Mg(tBu)_2$ (2.5)	94	79
3	*n*BuLi (5)	94	83
4	pyridine (5)	95	83
5	2,2′-bipyridine (2.5)	96	58
6	4,4′-bipyridine (2.5)	92	67
7	quinoline (5)	93	83
8	**DMAP (5)**	**93**	**92**
9	pyrrolidine (5)	97	48
10	Et_3N (5)	95	63
11	(+)-cinchonine (5)	94	25
12	(−)-cinchonine (5)	95	7

[a] Reaction conditions: **1a** (0.20 mmol), catecholborane (0.32 mmol, 1.6 equiv), **P3** (5 mol%), additive (*x* mol%), 5 Å MS (100 mg), toluene (2 mL, 0.1 M) under argon.

When pyridine was used as an additive, a higher selectivity (83% *ee*) was obtained, presumably due to the formation of the pyridium phosphate salt (Table 2, entry 4).[19] Pyridine deviratives, such as 2,2′-bipyridine, 4,4′-bipyridine and quinoline, did not further improve the *ee* (Table 2, entries 5–7). However, excellent enantioselectivity was obtained using 4-(dimethylamino)pyridine (DMAP) as an additive (Table 2, entry 8). It was proposed that **P8**, a very weak acid, is formed (Figure 1).[20] Other amine additives evaluated included pyrrolidine (secondary), triethylamine (tertiary), and cinchodine (chiral). In each case lower *ee* values were observed (Table 2, entries 9–12).

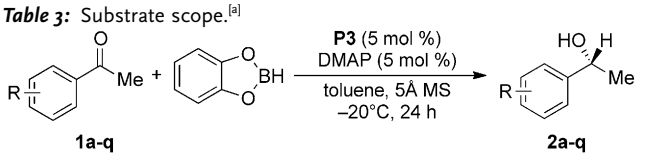
With the optimized conditions in hand, the scope of the reaction was studied. As shown in Table 3, the substrates bearing either electron-donating or electron-withdrawing groups on the phenyl ring furnished the resulting chiral alcohols with good selectivity (Table 3, **2b**–**2l**). Labile functional groups, such as nitrile, nitro, ester, iodide and bromide,



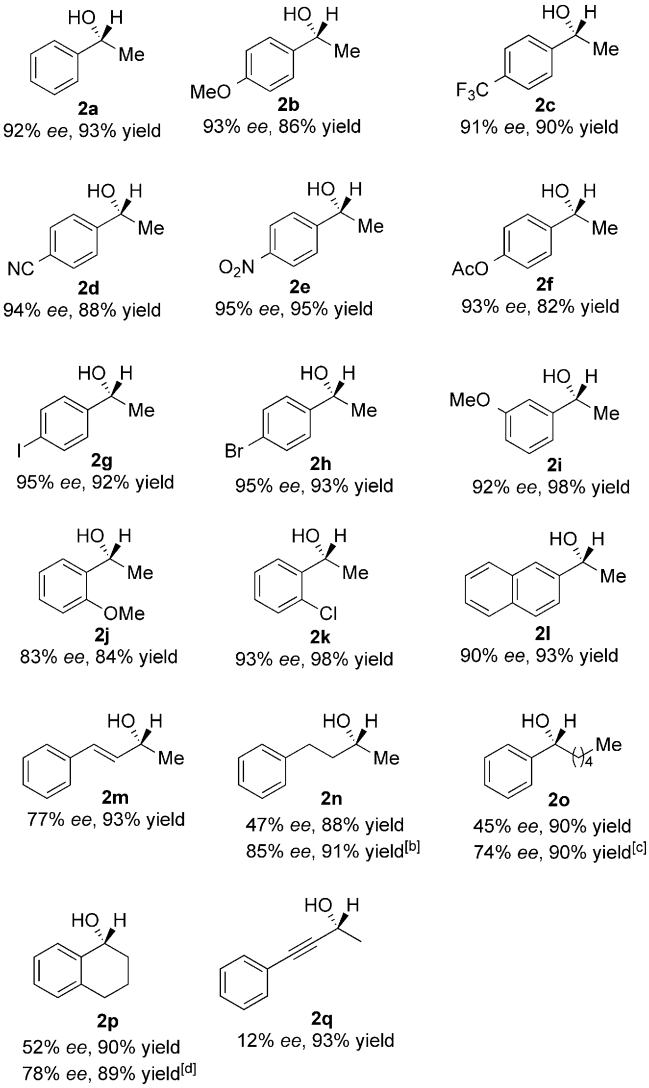
R = 9-anthryl, **P8**

Figure 1. Phosphoric acid–DMAP complex.

Table 3: Substrate scope.[a]



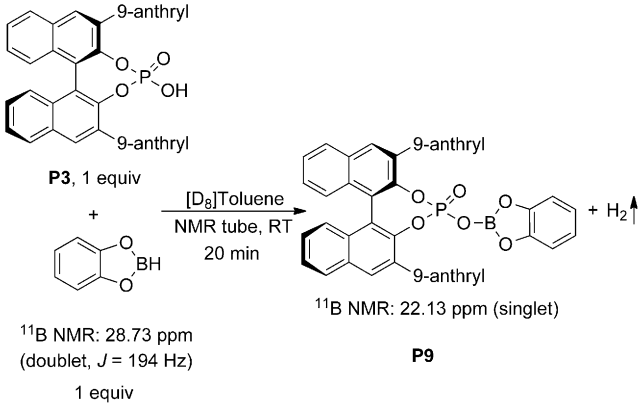
1a-q **2a-q**



[a] Reaction conditions: **1a**–**1o** (0.20 mmol), catecholborane (0.32 mmol, 1.6 equiv), **P3** (5 mol%), DMAP (5 mol%), 5 Å MS (100 mg), toluene (2 mL, 0.1 M) at −20 °C under argon. Yields refer to isolated product. Enantiomeric excess was determined by chiral HPLC analysis using a chiral column. [b] The reactions were run at −78 °C without DMAP. [c] The reaction was run using LiO*i*Pr (5 mol%) instead of DMAP as additive. [d] The reactions were run at −55 °C without DMAP.

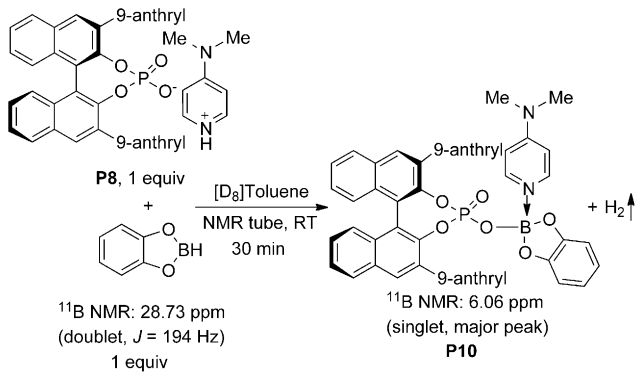
were well tolerated (Table 3, **2d**–**2h**). When employing the above conditions, moderate selectivity was obtained for an alkyl methyl ketone (47% *ee*), which could be improved to 85% *ee* using **P3** at −78°C (Table 3, **2n**).[21] The lithium salt of **P3** proved to be a better catalyst for the reduction of phenyl pentyl ketone (74% *ee*) compared to **P8** which only give 45% *ee* (Table 3, **2o**).[21] Likewise, the selectivity for the cyclic ketone 1-tetralone can be improved from 52% *ee* under the standard conditions to 78% *ee* using **P3** at −55°C (Table 3, **2p**).[21] However, a low *ee* was obtained in the case of alkynyl ketone (Table 3, **2q**).

In order to examine the mechanism of this new catalytic system, ^{11}B NMR experiments were carried out. As shown in Scheme 1, a [D_8]toluene solution of **P3** was placed in a NMR



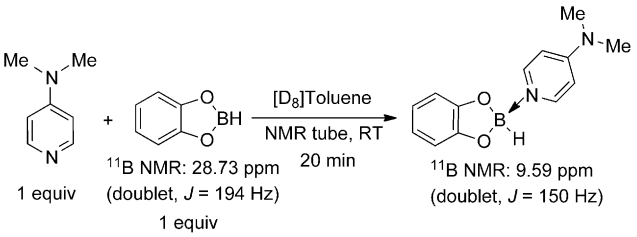
Scheme 1. ^{11}B NMR study of the reaction of **P3** with catecholborane.

tube under Ar, and was treated with an equal amount of catecholborane. Interestingly, evolution of gas was observed after the addition of catecholborane. 20 min later, the ^{11}B NMR spectrum (^{1}H-coupled) clearly showed that the resonance for catecholborane ($\delta = 28.73$ ppm, doublet, $J =$ 194 Hz) shifted upfield to 22.13 ppm as a singlet. Based on these results, it was proposed that the phosphoric acid interacted with the catecholborane to form hydrogen gas and a new boron species, **P9**. In the case of **P8**, the same experiment was studied (Scheme 2). The gas evolution was also observed with a major peak at 6.06 ppm in the ^{11}B NMR spectrum (^{1}H-coupled). Compared with the chemical shift of



Scheme 2. ^{11}B NMR study of the reaction of **P8** with catecholborane.

DMAP–catecholborane complex as shown in Scheme 3 ($\delta =$ 9.59 ppm, doublet, $J = 150$ Hz), the major boron signal was tentatively assigned to **P10**. With the proposed catalyst



Scheme 3. ^{11}B NMR study of the reaction of DMAP with catecholborane.

structure, we envision a transition state shown in Figure 2. The boron center is believed to act as a Lewis acid to activate the carbonyl, while the P=O moiety can act as a Lewis base to increase the nucleophilicity of catecholborane.[22] Simultaneously, the hydride from unreacted catecholborane is added to the activated carbonyl in a chiral environment to form the enantioenriched hydroboration product and regenerate the catalyst. However, since many additives were explored and each can induce a myriad of different possible mechanisms, an in-depth investigation is required to completely understand the mechanistic pathway.

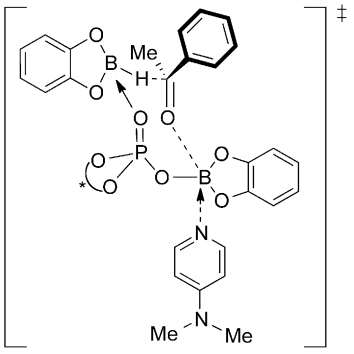


Figure 2. Proposed transition state.

In conclusion, we have developed a catalyst system for the asymmetric reduction of ketones using a phosphoric acid derivative (**P8**) as the precatalyst. Using catecholborane as a reducing agent, chiral secondary alcohols were produced with high levels of enantioselectivities over a reasonably broad substrate scope. Preliminary ^{11}B NMR studies suggest the reaction of the Brønsted acid with catecholborane forms the phosphoryl catechol borate as the active catalyst, which is a potentially powerful bifunctional catalyst that could find application to further reactions. Mechanistic investigations and applications of the catalyst are currently underway in our laboratory and will be reported in due course.

Experimental Section

General procedure: To a flame-dried test tube was added **P3** (7.0 mg, 0.010 mmol, 5 mol%), 4-(dimethylamino)pyridine (DMAP, 1.2 mg, 0.010 mmol, 5 mol%) and activated 5 Å MS (100 mg). The vessel was placed under vacuum and the atmosphere exchanged with argon three times before the addition of toluene (2.0 mL). The mixture was allowed to stir for 20 min and then cooled to −20 °C. Ketone **1** (0.20 mmol) and catecholborane (0.32 mmol, 1.6 equiv) were subsequently added. After stirring for 24 h at −20 °C, MeOH (0.5 mL) followed by 1N NaOH solution (0.5 mL) were each added. The mixture was allowed to warm to room temperature gradually and stirring was continued for another 1 h before the mixture was extracted with EtOAc (10 mL × 3), dried over Na_2SO_4 and concentrated in vacuo. The residue was purified by silica gel column chromatography (eluent: hexanes/ethyl acetate = 6/1) to afford pure product **2**.

Received: June 7, 2011
Revised: August 8, 2011
Published online: September 22, 2011

Keywords: asymmetric catalysis · chiral alcohol · ketone · phosphoric acids · reduction

[1] a) *Transition Metals for Organic Synthesis: Building Blocks and Fine Chemicals*, *Vols. 1 and 2* (Eds.: M. Beller, C. Bolm), Wiley-VCH, Weinheim, **1998**; b) *Chirality in Industry: The Commercial Manufacture and Applications of Optically Active Compounds* (Eds.: A. N. Collins, G. N. Sheldrake, J. Crosby), Wiley, Chichester, **1992**.

[2] a) R. Noyori, *Asymmetric Catalysis in Organic Synthesis*, Wiley, New York, **1994**; b) E. J. Corey, C. J. Helal, *Angew. Chem.* **1998**, *110*, 2092–2118; *Angew. Chem. Int. Ed.* **1998**, *37*, 1986–2012.

[3] For reviews, see: a) B. T. Cho, *Chem. Soc. Rev.* **2009**, *38*, 443–452; b) W. Tang, X. Zhang, *Chem. Rev.* **2003**, *103*, 3029–3069; c) A. J. Minnaard, B. L. Feringa, L. Lefort, J. G. de Vries, *Acc. Chem. Res.* **2007**, *40*, 1267–1277; d) R. H. Morris, *Chem. Soc. Rev.* **2009**, *38*, 2282–2291.

[4] For recent hydrogenations of ketones using metals, see: a) M. T. Reetz, X. Li, *J. Am. Chem. Soc.* **2006**, *128*, 1044–1045; b) T. Ohkuma, C. A. Sandoval, R. Srinivasan, Q. Lin, Y. Wei, K. Muñiz, R. Noyori, *J. Am. Chem. Soc.* **2005**, *127*, 8288–8289; c) N. S. Shaikh, S. Enthaler, K. Junge, M. Beller, *Angew. Chem.* **2008**, *120*, 2531–2535; *Angew. Chem. Int. Ed.* **2008**, *47*, 2497–2501; d) B. K. Langlotz, H. Wadepohl, L. H. Gade, *Angew. Chem.* **2008**, *120*, 4748–4752; *Angew. Chem. Int. Ed.* **2008**, *47*, 4670–4674; e) A. Mikhailine, A. J. Lough, R. H. Morris, *J. Am. Chem. Soc.* **2009**, *131*, 1394–1395.

[5] For the reduction using an organocatalytic bifunctional catalyst, see: D. R. Li, A. He, J. R. Falck, *Org. Lett.* **2010**, *12*, 1756–1759.

[6] a) T. Akiyama, J. Itoh, K. Yokota, K. Fuchibe, *Angew. Chem.* **2004**, *116*, 1592–1594; *Angew. Chem. Int. Ed.* **2004**, *43*, 1566–1568; b) D. Uraguchi, M. Terada, *J. Am. Chem. Soc.* **2004**, *126*, 5356–5357.

[7] For reviews, please see: a) T. Akiyama, *Chem. Rev.* **2007**, *107*, 5744–5758; b) M. Terada, *Synthesis* **2010**, 1929–1982; c) M. Terada, *Chem. Commun.* **2008**, 4097–4112; d) A. D. Doyle, E. N. Jacobsen, *Chem. Rev.* **2007**, *107*, 5713–5743; e) J. Yu, F. Shi, L.-Z. Gong, *Acc. Chem. Res.* **2011**, DOI: 10.1021/ar2000343.

[8] a) M. Terada, H. Tanaka, K. Sorimachi, *J. Am. Chem. Soc.* **2009**, *131*, 3430–3431; b) Q.-W. Zhang, C.-A. Fan, H.-J. Zhang, Y.-Q. Tu, Y.-M. Zhao, P. Gu, Z.-M. Chen, *Angew. Chem.* **2009**, *121*, 8724–8726; *Angew. Chem. Int. Ed.* **2009**, *48*, 8572–8574; c) I. Čorić, S. Vellalath, B. List, *J. Am. Chem. Soc.* **2010**, *132*, 8536–8537.

[9] a) E. B. Rowland, G. B. Rowland, E. Rivera-Otero, J. C. Antilla, *J. Am. Chem. Soc.* **2007**, *129*, 12084–12085; b) S. E. Larson, J. C. Baso, G. Li, J. C. Antilla, *Org. Lett.* **2009**, *11*, 5186–5189.

[10] a) M. Lu, D. Zhu, Y. Lu, X. Zeng, B. Tan, Z. Xu, G. Zhong, *J. Am. Chem. Soc.* **2009**, *131*, 4562–4563; b) M. Lu, Y. Lu, D. Zhu, X. Zeng, X. Li, G. Zhong, *Angew. Chem.* **2010**, *122*, 8770–8774; *Angew. Chem. Int. Ed.* **2010**, *49*, 8588–8592.

[11] a) Q. Gu, Z.-Q. Rong, C. Zheng, S.-L. You, *J. Am. Chem. Soc.* **2010**, *132*, 4056–4057; b) T. Akiyama, T. Katoh, K. Mori, *Angew. Chem.* **2009**, *121*, 4290–4292; *Angew. Chem. Int. Ed.* **2009**, *48*, 4226–4228.

[12] a) M. Terada, K. Soga, N. Momiyama, *Angew. Chem.* **2008**, *120*, 4190–4193; *Angew. Chem. Int. Ed.* **2008**, *47*, 4122–4125; b) N. Momiyama, H. Tabuse, M. Terada, *J. Am. Chem. Soc.* **2009**, *131*, 12882–12883.

[13] P. Jain, J. C. Antilla, *J. Am. Chem. Soc.* **2010**, *132*, 11885–11886.

[14] For the same type of activation, see: a) T. G. Elford, Y. Arimura, S. H. Yu, D. G. Hall, *J. Org. Chem.* **2007**, *72*, 1276–1284; b) J. W. J. Kennedy, D. G. Hall, *J. Am. Chem. Soc.* **2002**, *124*, 11586–11587; c) D. S. Barnett, P. N. Moquist, S. E. Schaus, *Angew. Chem.* **2009**, *121*, 8835–8838; *Angew. Chem. Int. Ed.* **2009**, *48*, 8679–8682.

[15] D. Nakashima, H. Yamamoto, *J. Am. Chem. Soc.* **2006**, *128*, 9626–9627.

[16] M. Hatano, K. Moriyama, T. Maki, K. Ishihara, *Angew. Chem.* **2010**, *122*, 3911–3914; *Angew. Chem. Int. Ed.* **2010**, *49*, 3823–3826.

[17] M. Klussmann, L. Ratjen, S. Hoffmann, V. Wakchaure, R. Goddard, B. List, *Synlett* **2010**, 2189–2192.

[18] a) Z. Zhang, W. Zheng, J. C. Antilla, *Angew. Chem.* **2011**, *123*, 1167–1170; *Angew. Chem. Int. Ed.* **2011**, *50*, 1135–1138; b) W. Zheng, Z. Zhang, M. J. Kaplan, J. C. Antilla, *J. Am. Chem. Soc.* **2011**, *133*, 3339–3341; c) G. K. Ingle, Y. Liang, M. Mormino, G. Li, F. R. Fronczek, J. C. Antilla, *Org. Lett.* **2011**, *13*, 2054–2057; d) S. E. Larson, G. Li, G. B. Rowland, D. Junge, R. Huang, H. L. Woodcock, J. C. Antilla, *Org. Lett.* **2011**, *13*, 2188–2191.

[19] Pyridinium salts of phosphoric acids have been reported by Akiyama, see: J. Itoh, K. Fuchibe, T. Akiyama, *Angew. Chem.* **2006**, *118*, 4914–4916; *Angew. Chem. Int. Ed.* **2006**, *45*, 4796–4798.

[20] a) In water, the pK_a value of phosphoric acid is 1, see: reference [7d]; b) in water, the pK_a value of pyridinium is 5.21 and the pK_a value of 4-(dimethylamino)pyridinium is 9.2, see: *Evans pK_a Table* (http://www2.lsdiv.harvard.edu/labs/evans).

[21] For the optimization of **2n**, **2o** and **2p**, see the Supporting Information.

[22] An alternate mechanism involving the DMAP as a Lewis base that may combine with the reacting boron center was indicated by a ^{11}B NMR experiment: when 2 equiv of catecholborane was combined with 1 equiv of **P8** the ^{11}B NMR spectrum did show the presence of **P9**. See the Supporting Information for spectral details.

