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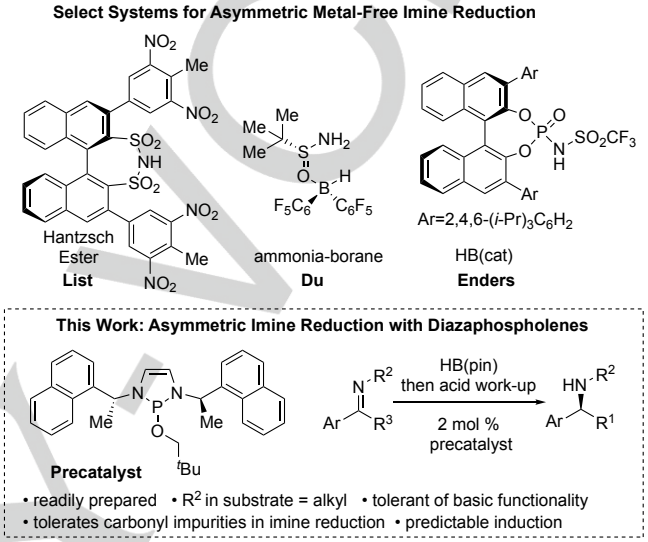
Asymmetric Imine Hydroboration Catalyzed by Chiral Diazaphospholenes

Matt R. Adams,[a] Chieh-Hung Tien,[a] Robert McDonald[b] and Alexander W. H. Speed*[a]

Abstract: *The first use of diazaphospholenes as chiral catalysts has been demonstrated with enantioselective imine hydroboration. A chiral diazaphospholene prepared in a simple three-step synthesis from commercial materials has been shown to achieve the highest enantioselectivity for hydroboration of alkyl imines with pinacolborane reported to date. Enantiomer ratios of up to 88:12 were obtained with low (2 mol %) catalyst loadings. Shown are 20 examples of asymmetric reduction employing this main-group catalysis protocol, including the synthesis of the pharmaceuticals ent-rasagiline and fendiline.*

The preparation of enatioenriched amines is of vital importance for the preparation of pharmaceuticals and agrochemicals.[1] While enzymatic resolution of primary amines by lipases is a practical method, these types of resolutions are not effective for preparation of enantioenriched secondary amines.[2] Hydrogenation of imines to form enantioenriched secondary amines by chiral transition metal catalysts is a well developed field.[3] Despite the performance of transition metal catalysts in homogenous hydrogenation, development of alternative procedures employing main-group element-based catalysts is currently of great interest, both to reduce usage of precious metal catalysts, and to uncover alternate selectivity and reactivity patterns to metal complexes.[4,5] Chiral frustrated Lewis pairs have been used for hydrogenation of imines to form enantioenriched amines.[6] Reductants other than hydrogen have been widely explored. Chiral Lewis base activation of trichlorosilane allows asymmetric reduction of aniline-derived imines.[7] A number of chiral Brønsted acid based catalysts employ Hantzsch esters or dihydrobenzothiazoles as terminal reductants, with a chiral sulfonic acid developed by List and co-workers (Scheme 1) proving especially effective for the synthesis of secondary alkylamines.[8,9] Surprisingly, reports employing boranes as terminal reductants are scarce. Reports of asymmetric reductive amine formation with CBS catalyst/Itsuno type reagents frequently require stoichiometric quantities of amino alcohol ligand, or very electron poor imines for high conversion or enantioselectivity unless the substrate is an oxime.[10,11,12] In a more recent development, Du and co-workers reported the asymmetric reduction of aryl imines with ammonia borane, employing 10 mol % of an adduct between Ellman's chiral sulfinimide and Piers' borane as a catalyst (Scheme 1).[13] A report by Enders and co-workers describes the use of a chiral Brønsted acid for imine reduction employing catecholborane as the terminal reductant (Scheme 1), with aryl α imino ester substrates giving optimal enantioinduction.[14]



Scheme 1. Systems for Metal Free Synthesis of Secondary Amines

Hydridic diazaphospholenes are an emerging class of reductive catalysis. Follwing Gudat and co-workers' original demonstration of diazaphospholene hydridicity in stoichiometric transformations,[15] Kinjo and co-workers demonstrated catalytic carbonyl and diazene reductions.[16] Our group recently demonstrated the application of neopentoxy diazaphospholene precatalysts for imine reduction with low catalyst loadings at ambient temperatures (2 mol %).[17] Attracted by this efficiency, we sought to develop an asymmetric variant. While a diazaphospholene bearing chiral alkyl groups on nitrogen has been synthesized,[18] *no examples of asymmetric reactions catalyzed by diazaphospholenes have yet been reported.*

Inspired by C_2 symmetric carbenes developed by Herrmann and co-workers,[19] and Cramer and co-workers' recent use of pseudo C_2 symmetric diaminophospholanes as ligands for metal-catalyzed processes,[20] we investigated the preparation of pseudo C_2 symmetric chiral diazaphospholenes (Scheme 2). Our previous studies showed that unsaturation in the backbone is required for reductive activity, precluding the use of a similar route to Cramer.[17]

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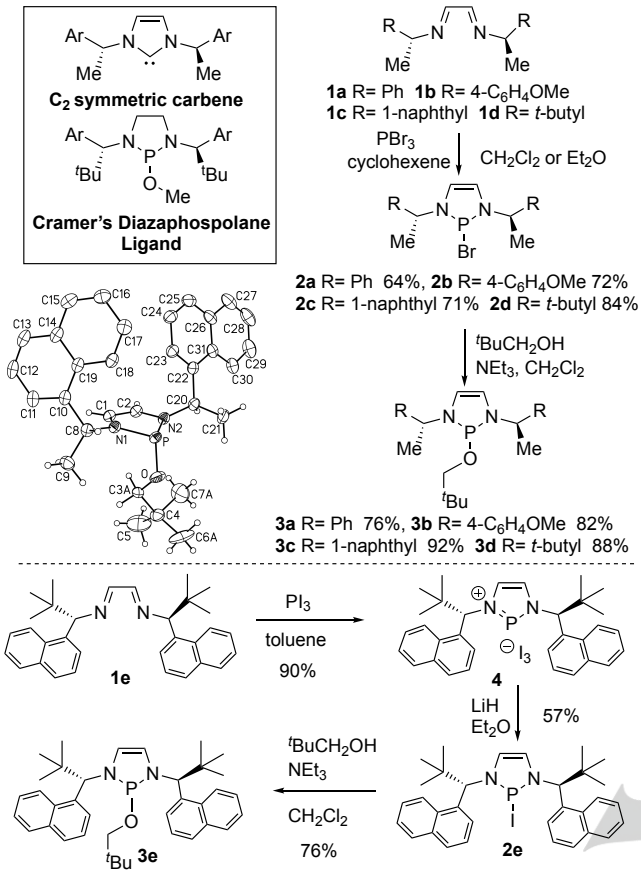
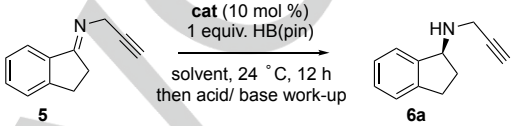


Scheme 2. Strategy for synthesis of chiral diazaphospholenes and crystal structure of precatalyst **3c**. Non-hydrogen thermal ellipsoids are scaled at the 30% probability level. Hydrogen atoms are shown with arbitrarily small thermal parameters. Selected Interatomic distances for **4a** (Å) P–O 1.636(2), P–N1 1.702(2), P–N2 1.705(2), C1–C2 1.323(4).

We investigated several diazaphospholenes with varying chiral groups. Known diimines **1a**, [21] **1b**,[22] **1c**,[23] and **1d**[24] underwent reductive cyclization with PBr_3 in the presence of cyclohexene to give bromides **2a-2d** according to the procedure developed by Macdonald and co-workers for achiral diimines.[25],[26] Bromides **2a**-**2d** were converted to the corresponding neopentyloxides **3a**-**3d** by treatment with neopentyl alcohol and triethylamine. A single crystal of **3c**, grown from acetonitrile, exhibited a conformation where the naphthyl groups avoid the neopentoxy group. Diimine **1e** did not undergo cyclization according to the PBr_3 protocol. [20] Switching to use of PI_3 as reported by Cowley and co-workers resulted in cyclization to phosphenium triiodide **4**.[27] Exposure **4** to an alkoxide was not fruitful, an observation precedented by Gudat, Nyulászi, and co-workers' difficulties of adding metal amides to related pyridoannelated phosphenium cations.[28] It was found lithium hydride in diethyl ether could convert **4** to diazaphospholene iodide **2e** which was uneventfully converted to precatalyst **3e**.

We next sought to explore these precatalysts' ability to conduct asymmetric reduction reactions (**Table 1**). Imine **5**, the precursor to the therapeutic ent-rasagiline, **6a**, was employed as a test substrate since the alkyne in **5** would present a selectivity challenge for many transition metal catalysts. A brief solvent screen showed that THF gave the optimal induction for all precatalysts. In an initial reaction, precatalyst **3a** gave predominantly (*S*) amine **6a** (configuration determined by sign of optical rotation) in 72:28 e.r. (entry 1). All alkyl precatalyst **3d** gave (*S*) imine with an inferior e.r. (entry 2). Electron-rich pre-catalyst **3b** also provided inferior stereoselection to catalyst **3a** (entry 3). We next attempted reduction with catalyst **3c** bearing larger and more rigid 1-naphthyl aromatic side chains.

Table 1. Optimization of Asymmetric Induction



Entry	Catalyst	Solvent	Conversion[a]	e. r.[b]
1	**3a**	THF	>98	72:28
2	**3d**	THF	>98	60:40
3	**3b**	THF	>98	62:38
4	**3c**	**THF**	**>98**	**85:15**
5	**3e**	THF	>98	35:65
6	**3c**	CH_3CN	>98	62:38
7	**3c**	CH_2Cl_2	63	73:27
8	**3c**	Toluene	>98	76:24

[a] Determined by ^{1}H NMR spectrometry. [b] Determined by HPLC on a chiral stationary phase.

Reduction of **5** employing catalyst **3c** resulted in amine **6a** in 85:15 e.r. (entry 4). Replacing the methyl groups with *tert*-butyl groups (**3e**) resulted in a reduction in stereoselectivity. Measured enantiomer ratios produced by optimal catalyst **3c** in three other select solvents are included for comparative purposes (entries 6-8).

We developed a predictive model for induction based on the observed stereochemical outcome. In a conformation where the H substituents on the stereogenic centres point toward the phosphorus, a sterically controlled substrate approach based on minimizing interaction between the substituents on the imine and the large aryl groups produces the observed configuration (Figure 1). Minimization of $A^{1,3}$ strain between the *peri* position of the naphthalene ring and the stereogenic centre increase the protrusion of the naphthyl ring into the space where the substrate would approach the P-H bond, potentially explaining the higher induction observed with catalyst **3c**.[29] Catalyst **3e** may have decreased steric differentiation between the void and filled quadrants relative to **3c**, because of the increased steric bulk of the *tert*-butyl groups, potentially explaining the diminished enantioselectivity.

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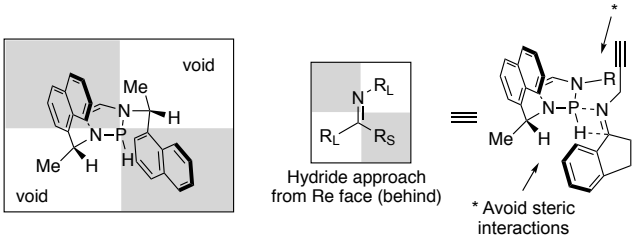
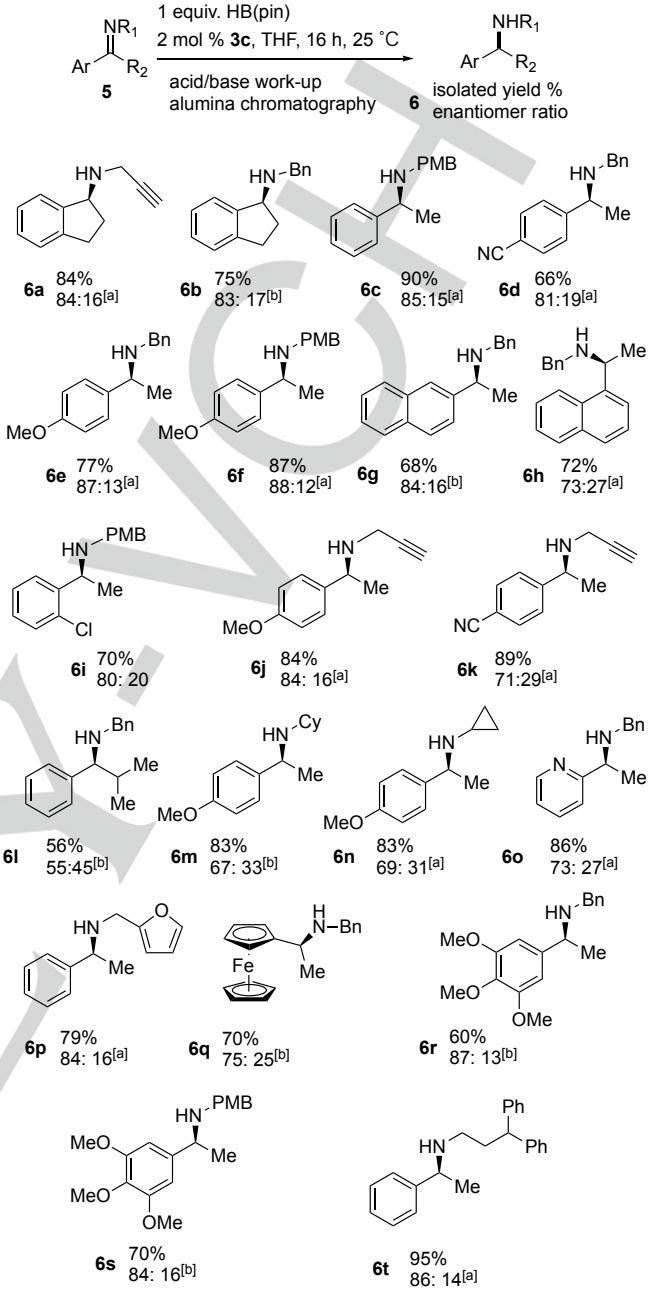


Figure 1. Quadrant model for asymmetric induction.[30]

A series of amines were formed in investigation of substrate scope (Scheme 3), employing a reduced loading of 2 mol % of **3c**, with essentially no erosion of e.r. obtained for **6a** at this loading. High conversions were generally observed after 16 hours of reaction time. Substitution of the propargyl group with benzyl gave **6b** with similar selectivity. A PMB group in **6c** also gave similar selectivity. Investigation of electron withdrawing and donating groups in **6d** and **6e**, showed the electron withdrawing group resulted in a slight reduction of enantioselectivity. An imine derived from methoxyacetophenone and PMB amine gave amine **6f** with slightly higher enantioselectivity. Amine **6g**, containing a 2-naphthyl group was formed with higher selectivity than 1-naphthyl-bearing amine **6h**. Ortho–substitution was tolerated in the formation of **6i**. Propargylamines **6j** and **6k** again showed that an electron withdrawing group was detrimental to selectivity. Reduction of an imine derived from an isopropyl ketone to give amine **6l** resulted in low induction, implying that imines with less steric differentiation between the substituents are poor substrates, in line with the quadrant model presented in Figure 1. Branching on the nitrogen substituent, in amines **6m** and **6n** also gave modest enantioselectivity. Pyridyl (**6o**), furyl (**6p**) and ferrocenyl (**6q**) were tolerated with varying selectivities. Very electron rich aryl groups (**6r** and **6s**) gave comparable selectivity to unadorned **6c**. Finally, the pharmaceutical fendiline (**6t**) could be prepared with good enantioselectivity. The absolute (*S*) configuration for several of these products was confirmed by comparison of observed optical rotation to literature values.

While the enantioselectivities for alkyl imine reduction observed with **3c** do not equal the highest inductions obtained with chiral Brønsted acids such as those shown in Scheme 1, **3c** has a number of attractive features, which should encourage further development and exploration of chiral diazaphospholenes in catalysis. The preparation of **3c** is simpler than the Brønsted acid and Piers borane based catalysts shown in Scheme 1, requiring only three steps from commercially available 1-(1-naphthyl)ethylamine, no organometallic intermediates, and no chromatographic purification.[31] The 2 mol % loading of **3c** and 16 h reaction times compares favorably with 5-10 mol % loadings required for imine reduction with catalysts shown in Scheme 1. While Hantzsch esters do not function as reductants with **3c**, use of pinacolborane may confer advantages for product purification.[32] Additionally, pinacolborane is approximately half the molecular weight of typically used Hantzsch ester reductants.



Scheme 3. Substrate Scope for Reduction. [a] Enantiomer ratio determined by HPLC of the amine on a chiral stationary phase. [b] Enantiomer ratio determined by HPLC of the BOC protected amine on a chiral stationary phase. Bn= benzyl, PMB=4-methoxybenzyl, Cy= cyclohexyl.

In conclusion, we have shown chiral diazaphospholenes are a new and practical class of catalyst for asymmetric synthesis. The use of chiral diazaphospholenes with commercially available HB(pin) as the terminal reductant has been shown to be competitive with existing metal-free technologies for reduction of imines because of simple catalyst preparation, and low catalyst loading. A broad substrate scope among imines

flanked by aromatic groups was demonstrated, and enantiomeric ratios are best-in-class for alkyl imine hydroborations with pinacolborane. Efforts to explore chiral diazaphospholene architecture in other classes of reactions are underway, and will be reported in due course.

Acknowledgements

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Conflict of Interest

A provisional patent encompassing this work has been filed.

Keywords: Asymmetric reduction • diazaphospholene • chiral hydride • hydroboration • imine

[1] T. C. Nugent, M. El-Shazly, *Adv. Synth. Catal.* **2010**, *352*, 753-819.

[2] A) M. T. Reetz, *J. Am. Chem. Soc.* **2013**, *135*, 12480-12496. B) S.-Y. Hsieh, B. Wanner, P. Wheeler, A. M. Beauchemin, T. Rovis, J. W. Bode, *Chem. Eur. J.* **2014**, *20*, 7228-7231.

[3] A) Z. Han, Z. Wang, X. Zhang, K. Ding, *Angew. Chem. Int. Ed.* **2009**, *48*, 5345-5349. B) F. Chen, T. Wang, Y. He, Z. Ding, Z. Li, L. Xu, Q.-H. Fan, *Chem. Eur. J.* **2011**, *17*, 1109-1113. C) D. J. Ager, A. H. M. de Vries, J. G. de Vries, *Chem. Soc. Rev.* **2012**, *41*, 3340-3380.

[4] S. Rossi, M. Benaglia, E. Massolo, L. Raimondi, *Catal. Sci. Technol.* **2014**, *4*, 2708-2723.

[5] L. C. Wilkins, R. L. Melen, *Coordination Chemistry Reviews*, **2016**, *324*, 123-139.

[6] A) D. Chen, Y. Wang, J. Klankermayer, *Angew. Chem. Int. Ed.* **2010**, *49*, 9475-9478. B) Y. Liu, H. Du, *J. Am. Chem. Soc.* **2013**, *135*, 6810-6813. C) M. Lindqvist, K. Borre, K. Axenov, B. Kótai, M. Nieger, M. Leskelä, I. Pápai, T. Repo, *J. Am. Chem. Soc.* **2015**, *137*, 4038-4041.

[7] A) A. V. Malkov, A. Mariani, K. N. MacDougall, P. Kočovský, *Org. Lett.* **2004**, *6*, 2253-2256. B) Z. Wang, X. Ye, S. Wei, P. Wu, A. Zhang, J. Sun, *Org. Lett.* **2006**, *8*, 999-1001. C) Y. Matsumura, K. Ogura, Y. Kouchi, F. Iwasaki, O. Onomura. **2006**, *8*, 3789-3792. D) A. V. Malkov, K. Vranková, S. Stončius, P. Kočovský. *J. Org. Chem.* **2009**, *74*, 5839-5849. E) C. Wang, X. Wu, L. Zhou, J. Sun, *Org. Biomol. Chem.* **2015**, *13*, 577-582. F) X. Li, A. T. Reeder, F. Torri, H. Adams, S. Jones. *Org, Biomol. Chem.* **2017**, *15*, 2422-2435.

[8] A) C. Zhu, T. Akiyama, *Org. Lett.* **2009**, *11*, 4180-4183. B) C. Zhu, K. Saito, M. Yamanaka, T. Akiyama, *Acc. Chem. Res.* **2015**, *48*, 388-398.

[9] V. N. Wakchaure, P. S. J. Kaib, M. Leutzsch, B. List, *Angew. Chem. Int. Ed.* **2015**, *54*, 11852-11856.

[10] A) S. Itsuno, Y. Sakurai, K. Ito, A. Hirao, S. Nakahama. *Bull. Chem. Soc. Jpn.* **1987**, *60*, 395-396. B) B. T. Cho, Y. S. Chun, *J. Chem. Soc. Perkin. Trans. 1.* **1990**, 3200-3201. C) M. Shimizu, M. Kamei, T. Fujisawa, *Tet. Lett.* **1995**, *36*, 8607-8610. D) E. H. M. Kirton, G. Tughan, R. E. Morris, R. A. Field, *Tet. Lett.* **2004**, *45*, 853-855. E) F. Gosselin, P. D. O'Shea, S. Roy, R. A. Reamer, C. Chen, R. P. Volante, *Org. Lett.* **2005**, *7*, 355-358.

[11] X. Huang, M. Ortiz-Marciales, K. Huang, V. Stepanenko, F. G. Merced, A. M. Ayala, W. Correa, M. De Jesús, *Org. Lett.* **2007**, *9*, 1793-1795.

[12] J. M. Brunel, G. Buono, *Synlett* **1996**, 177-178. Enantiomeric excesses in this work were determined by optical rotation.

[13] S. Li, G. Li, W. Meng, H. Du, *J. Am. Chem. Soc.* **2016**, *138*, 12956-12962.

[14] A) D. Enders, A. Rembiak, M. Seppelt, *Tet. Lett.* **2013**, *54*, 470-473. B) D. Enders, A. Rembiak, B. A. Stöckel. *Adv. Synth. Catal.* **2013**, *355*, 1937-1942.

[15] D. Gudat, A. Haghverdi, M. Nieger, *Angew. Chem. Int. Ed.* **2000**, *39*, 3084-3086.

[16] a) Reduction of Diazene: C. C. Chong, H. Hirao, R. Kinjo, *Angew. Chem. Int. Ed.* **2014**, *53*, 3342-3346 b) Carbonyl Reduction: C. C. Chong, H. Hirao, R. Kinjo, *Angew. Chem. Int. Ed.* **2015**, *54*, 190-194.

[17] M. R. Adams, C.-H. Tien, B. S. N. Huchenski, M. J. Ferguson, A. W.H. Speed, *Angewandte Chem. Int. Ed.* **2017**, *56*, 6268-6271.

[18] D. Förster, I. Hartenbach, M. Nieger, D. Gudat, *Z. Naturforsch.* **2012**, *67b*, 765-773.

[19] W. A. Herrmann, L. J. Goossen, C. Köcher, G. R. J. Artus, *Angew. Chem. Int. Ed.* **1996**, *35*, 2805-2807.

[20] a) P. A. Donets, N. Cramer, *J. Am. Chem. Soc.* **2013**, *135*, 11772-11775. B) J. Pedroni, N. Cramer, *J. Am. Chem. Soc.* **2017**, *139*, 12398-12401.

[21] H. Tom Dieck, J. Dietrich, *Chem. Ber.* **1984**, *117*, 694-701.

[22] D. Balestri, S. Grilli, C. Romano, D. Savoia, *Eur. J. Org. Chem.* **2014**, 8021-8025.

[23] C. L. Winn, F. Guillen, J. Pytkowicz, S. Roland, P. Mangeney, A. Alexakis, *J. Organomet. Chem.* **2005**, *690*, 5672-5695.

[24] L. Carroccia, M. Delfini, S. Fioravanti, L. Pellacani, F. Sciubba, *J. Org. Chem.* **2012**, *77*, 2069-2073.

[25] J. W. Dube, G. J. Farrar, E. L. Norton, K. L. S. Szekely, B. F. T. Cooper, C. L. B. Macdonald, *Organometallics* **2009**, *28*, 4377-4384.

[26] We have observed cleanliness of cyclization appears to correlate with bulk of diimine substituents, with **3d** and **3c** providing clean products, and **3a** being of marginal purity. Fortunately the cyclization of the optimal catalyst, **3c** is well behaved.

[27] G. Reeske, C. R. Hoberg, A. H. Cowley, *Inorg. Chem.*, **2007**, *46*, 4358-4358.

[28] Z. Benkó, S. Burck, D. Gudat, M. Nieger, L. Nyulászi, N. Shore, *Dalton Trans.* **2008**, *36*, 4937-4945.

[29] W. H. Pirkle, C. J. Welch, M. H. Hyun, *J. Org. Chem.* **1983**, *48*, 5022-5026.

[30] Formation of a P-H bond is observed by ^{31}P NMR upon combination of **3c** with HB(pin) in THF. See supporting information for details.

[31] The (*R*) enantiomer of this amine is used in preparation of the pharmaceutical Cinacalcet. The (*R*) enantiomer is approximately $1/ gram from Oakwood Chemical, while the (*S*) enantiomer is approximately $1.50/ gram at time of submission.

[32] We explored a Hantzsch ester as reductant for **5** with both **2c** and **3c**. No reduction was observed.

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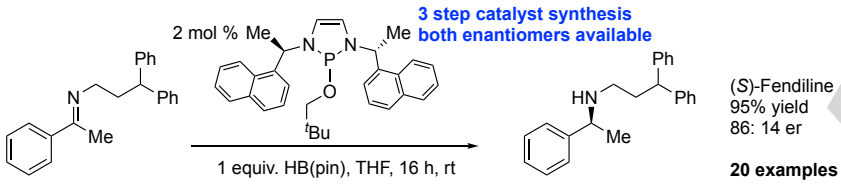

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Asymmetric Imine Hydroboration Catalyzed by Chiral Diazaphospholenes

The first use of chiral diazaphospholenes as catalysts is reported. A conveniently synthesized diazaphospholene catalyzes the asymmetric reduction of imines with pinacolborane to secondary amines with low catalyst loadings (2 mol %) at ambient temperature.