Homogeneous Catalysis

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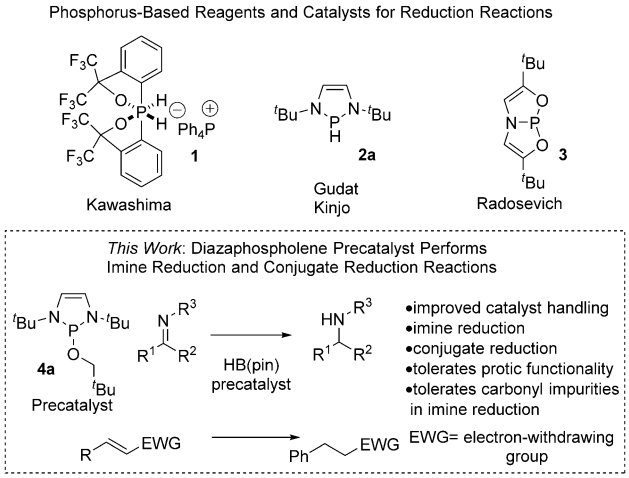
Diazaphospholene Precatalysts for Imine and Conjugate Reductions

*Matt R. Adams, Chieh-Hung Tien, Blake S. N. Huchenski, Michael J. Ferguson, and Alexander W. H. Speed**

Abstract: *The first examples of 1,3,2-diazaphospholene-catalyzed imine reduction and conjugate reduction reactions are reported. This approach employs readily synthesized alkoxydiazaphospholene precatalysts that can be handled in open air. Reduction of substrates containing Lewis basic functionality, isolated unsaturation, and protic functional groups was accomplished. The synthetic utility of this approach is demonstrated by the synthesis of the important antiparkinson medicine rasagiline and the natural product zingerone.*

Amine functional groups are ubiquitous in natural products and drug molecules. The reduction of imines represents one of the most important methods for accessing amines, owing to the ease of preparation of imines from readily available ketones and aldehydes. Use of catalysis for the reduction of imines affords opportunities to control selectivity, especially in the reduction of substrates containing multiple reactive functional groups. Platinum-group metal-complex catalyzed hydrogenations of imines are well-established methods,[1] however the expense and scarcity of precious metals provides impetus for the development of alternative methods. Metal-free catalytic reduction is an emerging field.[2] Imine reduction using frustrated Lewis pairs and dihydrogen is a burgeoning area of investigation in main-group catalysis.[3] In small-scale exploratory work such as drug discovery or total synthesis, where scope and reliability are of prime concern, imine reduction by hydroboration has several attractive aspects. Common hydroboration reagents such as pinacolborane, [HB(pin)] are readily handled liquids that do not require the use of high-pressure equipment. The resultant amines are also transiently protected as boron adducts, thus minimizing catalyst inhibition by the amine products. Despite the importance of imine reduction, examples of catalyzed imine hydroboration are scarce. Seminal reports of imine hydroboration involved coinage-group metals,[4] and there are very recent reports with nickel and ruthenium.[5] A chiral phosphoric acid catalyzed imine reduction employing catecholborane has also been reported.[6] In the main-group area, both *s*- and *p*-block catalysts have recently emerged as being well-suited for imine hydroboration. Two examples are a borenium cation catalyzed imine hydroboration reported by Crudden and co-workers,[7] and a magnesium diketiminato catalyzed imine hydroboration reported by Hill and co-workers.[8]

Phosphorus-based reductive catalysts have potential for providing alternative types of selectivity to the aforementioned acidic catalysts, because of the low Lewis acidity of neutral phosphorus(III) centers and consequent reduced sensitivity to Lewis basic reaction components and impurities. The development of phosphorus-based catalysts has undergone a surge of interest in recent years. Kawashima and co-workers demonstrated stoichiometric hydridic character at an anionic P^V center through the reduction of benzaldehydes (**1**, Scheme 1),[9] while Gudat and co-workers demonstrated the hydridic character of the P–H bond of P^{III} diazaphospholene **2a** in stoichiometric reactions, including reductions of benzaldehyde and cinnamaldehyde.[10] In the catalytic manifold, Radosevich and co-workers have shown the ability of phosphorus pincer complexes such as **3** to mediate diazene reduction by ammonia borane.[11] Catalytic hydride delivery from phosphorus(V) species in electrophilic fluorophosphonium-based Lewis pairs has recently been reported for olefin hydrogenation by Stephan and co-workers.[12] With the P^{III} system, Kinjo and co-workers have shown that **2a** can be employed in catalytic carbonyl hydroboration reactions, using HB(pin) to regenerate the P–H bond from the P–O bond formed during carbonyl reduction.[13] Both diazaphospholenes and tertiary phosphines have also been used in the hydroboration of carbon dioxide.[14]



Scheme 1. Comparison of existing technologies for reductions catalyzed by phosphorus complexes.

[*] M. R. Adams, C.-H. Tien, B. S. N. Huchenski, Prof. Dr. A. W. H. Speed
Department of Chemistry, Dalhousie University
Halifax, Nova Scotia B3H 4R2 (Canada)
E-mail: aspeed@dal.ca
Dr. M. J. Ferguson
X-ray Crystallography Laboratory, Department of Chemistry
University of Alberta, Edmonton, Alberta T6G 2G2 (Canada)
Supporting information and the ORCID identification number(s) for the author(s) of this article can be found under: http://dx.doi.org/10.1002/anie.201611570.

Despite this progress, no examples of imine hydroboration by phosphorus(III)-based catalysts have been reported. Herein, we disclose imine reduction and conjugate reduction reactions enabled by the readily handled precatalyst **4a**.

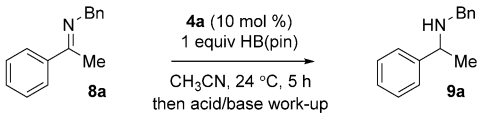
Our initial studies toward imine reduction by diazaphospholenes began with the development of a simple way to generate and handle **2a**, which is a highly air- and moisture-sensitive liquid, thus making routine use in exploratory organic synthesis challenging.[10a] We surmised on the basis of the work of the Kinjo group that an alkoxydiazaphospholene would be an appropriate entry point for catalysis.[13b]

According to a reported procedure, diimine **5** was converted into bromodiazaphospholene **6**,[15,16] (Scheme 2). Treatment of **6** with benzyl alcohol and triethylamine afforded known benzyloxydiazaphospholene **4b**, which is a solid with a low melting point. An analogous reaction with neopentyl alcohol gave **4a**, a readily handled, pentane-soluble, sublimable white solid. Exposure of a 30 mg sample of solid **4a** to ambient atmosphere for 30 minutes resulted in only 10% decomposition, as ascertained by ^{1}H and ^{31}P NMR, meaning that **4a** can be handled in open air. The mesityl variant **4c** was prepared from the corresponding bromodiazaphospholene by an analogous route.[17] To explore the role of unsaturation in the backbone, saturated compound **7** was also prepared in two steps from the corresponding diamine (see the Supporting Information for details).[18] We chose not to pursue **4b** in further studies because its melting point around ambient temperature made it less convenient to transfer in small quantities than solids **4a** and **4c**.

Exposure of diazaphospholenes **4a** and **4c** to one equivalent of HB(pin) in dry acetonitrile caused P–O to P–H bond conversion as evidenced by ^{31}P NMR, resulting in the formation of **2a** and **2b**. Diazaphospholane **7** did not undergo this transformation, thus indicating that unsaturation in the backbone is necessary for reactivity. Exposure of **4a** to excess HB(pin) in acetonitrile resulted in initial formation of **2a**, followed by the appearance of a triplet in the ^{31}P NMR spectrum at −42.9 ppm (J_{PH} = 195.9 Hz), thus indicating the formation of a compound with two P–H bonds through endocyclic cleavage. This was followed by formation of phosphine (PH_3), as evidenced by a quartet at −243.6 ppm. Compound **4c** underwent an analogous decomposition.[19] The two-step preparation of **4a** and **4c** from the corresponding diimines can be conducted on a multigram scale, and they represent convenient precatalysts for **2a** and **2b**.

With precatalysts **4a** and **4c** in hand, we turned our attention to the development of imine reduction with **8a** as a test substrate (Table 1). Hydroboration of **8a** with HB(pin) was complete in 5 hours when using 10 mol% **4a** at ambient temperature (entry 1). Work-up with acid and then base provided amine **9a**. In the absence of catalyst **4a**, or when using saturated diazaphospholane **7** in the place of **4a**, negligible conversion of **8a** was observed (entries 2 and 3). Far less reduction was observed with aged solutions of HB(pin) and **4a**, which contain PH_3 as the predominant phosphorus containing species (entry 4).

Table 1: Development and optimization of the imine reduction.

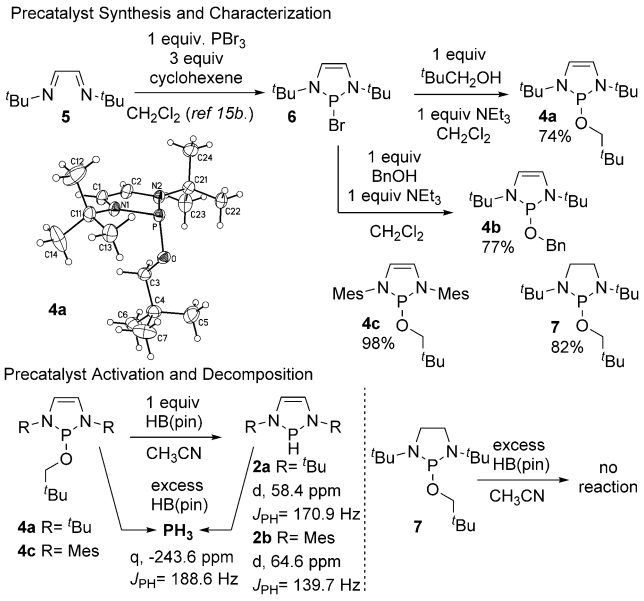


Entry	Deviation from standard conditions	Conv. [%][a]	Yield[b]
1	none	>98	95
2	no catalyst	<2	na
3	**7** instead of **4a**	<2	na
4	**4a** + HB(pin) aged 24 h before adding **8a**	36	nd
5	**4c** instead of **4a**	25	nd
6	HB(cat) instead of HB(pin)	67	nd
7	2 mol% loading of **4a** (12 h)	>98	95
8	1 mol% loading of **4a** (12 h)	66	nd
9	2 mol% loading (12 h, gram scale for **8a**)	>98	97

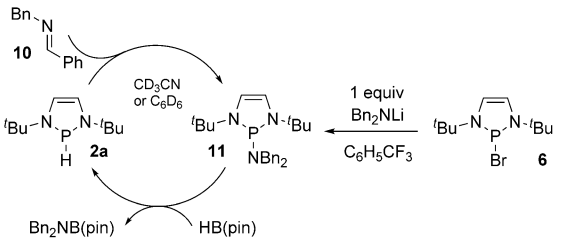
[a] Conversion based on NMR analysis of starting material and product. [b] Yields of isolated product arere after acidic work-up and then basification and basic alumina chromatography.

Mesityl diazaphospholene **4c** provided inferior conversion in the reduction (entry 5). The use of catecholborane, [HB(cat)] with **4a** resulted in lower conversion (entry 6). NMR studies suggest that exocyclic cleavage to PH_3 is especially rapid with this reagent. The catalyst loading could be reduced to 2 mol% (entry 7); however a drop in conversion was observed at 1 mol% loading (entry 8). The reaction could be conducted on a gram scale with no loss of efficiency (entry 9). A final important feature of this reaction is that the presence of the corresponding ketone as an impurity in the imine is not detrimental to the imine reduction.

Preliminary insight into a mechanism was provided by stoichiometric reactions (Scheme 3). A purified sample of **2a**



Scheme 2. Precatalyst synthesis, crystal structure of **4a**,[a] and activation and decomposition pathways for **4a** and **4c**. [a] Non-hydrogen thermal ellipsoids are shown at 30% probability. Hydrogen atoms are shown with arbitrarily small thermal parameters. Selected interatomic distances for **4a:** [Å] P–O 1.6470(11), P–N1 1.7072(13), P–N2 1.7060(13), C1–C2 1.323(2).



Scheme 3. Observation of intermediates in the proposed catalytic cycle.

was exposed to imine **10**. Formation of the P–N compound **11** was observed on the basis of ^{1}H and ^{31}P NMR data. A sample of **11**, independently generated through reaction of **6** with lithiated dibenzylamine, possessed identical spectral properties.[20] Exposure of **11** to HB(pin) in acetonitrile resulted in the reformation of **2a**. These results show that **2a** can reduce imines and can be regenerated through cleavage of the resulting P–N bond, thus suggesting the cycle shown in Scheme 3, which is analogous to the catalytic cycle proposed by Kinjo for carbonyl reduction, is possible.[13b]

We further explored the scope of the imine reduction (Figure 1). In an extension from imine **8a**, reduction of a more hindered indanone-derived imine yielded amine **9b**. Amine **9c**, the monoamine oxidase inhibitor rasagiline, was cleanly produced from the corresponding imine, with no observed alkyne hydroboration, thus showing that imines other than benzyl imines, and alkynes are both tolerated.[21] A *p*-methoxybenzyl protecting group is tolerated in product **9d**. A Lewis basic pyridyl group did not have a detrimental effect on the reaction, as evidenced by the clean formation of **9e**, and additionally, no reduction of the pyridyl ring was observed.[22] Aldimines exhibiting different steric demand were reduced, producing amines **12a**, **12b**, and **12c**. Diamine

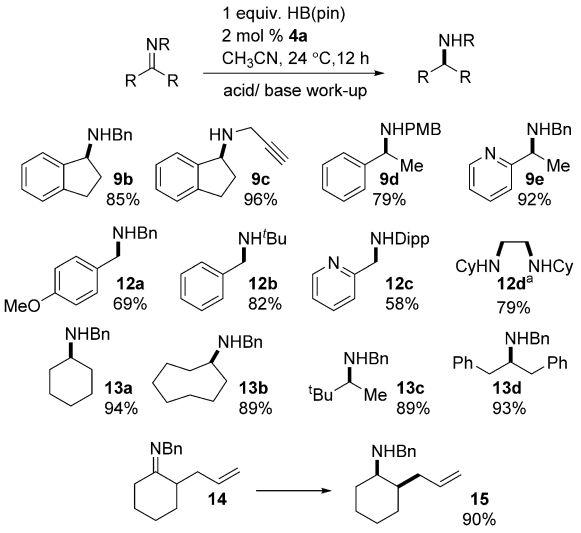


Figure 1. Amines successfully formed through imine reduction. Bonds shown in bold indicate former imine position except for **15**, where they denote relative stereochemistry. [a] 10 mol% **4a** employed. Yields refer to isolated products after work-up.

12d resulted from the reduction of the corresponding diimine in the presence of 2 equivalents of HB(pin). An attempted monoreduction was not successful. Imines derived from cyclic aliphatic ketones were reduced, leading to amines **13a** and **13b**. Imines derived from acyclic aliphatic ketones were also reduced, yielding imines **13c** and **13d**.

Finally, racemic chiral imine **14** was reduced to **15** with high diastereoselectiviy.[23] A tert-butyl sulfenylimine of acetophenone,[24] the benzyl imine of trifluoroacetophenone, and the phenyl imine of acetophenone were not successful substrates. We hypothesize that these electron-withdrawing groups inhibit the regeneration of the P–H bond from the P–N intermediate. Computational studies have suggested that electron-poor diazaphospholenes possess less polarized exocyclic bonds.[25]

We wished to investigate the potential of our precatalyst in other reduction reactions. Gudat reported that stoichiometric **2a** reduced cinnamaldehyde in a 1,4 fashion, prompting our exploration of catalyzed conjugate reductions (Figure 2).[10b] Conjugate reduction reactions are commonly performed using reagents such as copper-based Stryker's reagent[26] or L-Selectride.[27] Catalytic copper-based reduction using various terminal reductants, especially silanes, is an active area of study.[28] A notable catalytic hydroboration method involves rhodium-catalyzed hydroboration with HB(cat).[29]

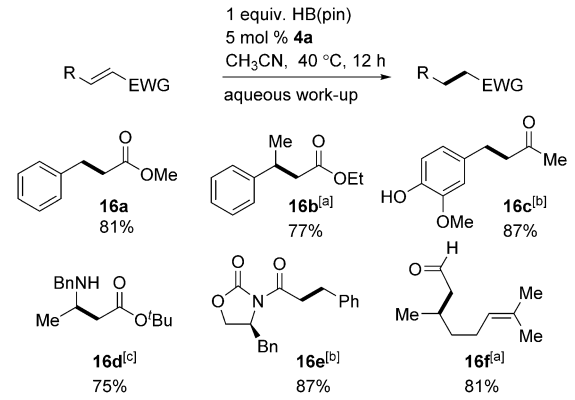


Figure 2. Substrate scope of the conjugate reduction. Bonds shown in bold indicate former alkene positions. Yields refer to isolated products after B(pin) cleavage. [a] 10 mol% **4a** used; [b] reaction conducted at 24 °C; [c] reaction conducted at 50 °C.

Combination of precatalyst **4a** (10 mol%), cinnamaldehyde, and HB(pin) in acetonitrile resulted in the formation of a complex mixture. Since cinamaldehyde is a potent bifunctional electrophile, we surmised that side products arise from the reaction of enolate intermediates with highly reactive starting material. Accordingly, we switched to less electrophilic methyl cinnamate and observed clean reduction to methyl hydrocinnamate **16a** with 10 mol% catalyst upon modest heating in acetonitrile (40 °C). No reduction was observed in acetonitrile in the absence of catalyst. A trisubstituted olefin (> 95% *E*) was also a viable partner, giving product **16b**. Ketones proved to be excellent conjugate

acceptors, undergoing reduction at room temperature and permitting the synthesis of the natural product Zingerone **16c**. A protected β-amino ester (**16d**) was synthesized from the corresponding enamide. Notably, the phenol in ketone **16c** and amine in **16d** represent protic functionalities, however, no dehydrocoupling of the pinacolborane with these moieties was observed.[30] Finally, dihydrocinnamoyl oxazolidinone **16e** and citronellal **16f** (from the reduction of a 1:2 mixture of *Z* and *E* isomers of commercial citral) could also be prepared under these conditions, which shows that the reaction is tolerant of a diverse set of electron-withdrawing groups.

In conclusion, a convenient route to 2-alkoxy-1,3,2-diazaphospholenes was developed, and the use of these entities as precatalysts for imine and conjugate reductions by HB(pin) was demonstrated. We anticipate that this method will find utility in synthesis. Efforts towards a deeper understanding of the mechanism of this transformation, and the synthesis of diazaphospholenes capable of asymmetric catalysis, are underway in our laboratory.

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Conflict of interest

The authors declare no conflict of interest.

Keywords: homogeneous catalysis · diazaphospholenes · imines · phosphorus hydrides · reduction

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M. R. Adams, C.-H. Tien,
B. S. N. Huchenski, M. J. Ferguson,
A. W. H. Speed* _____ ■■■■–■■■■

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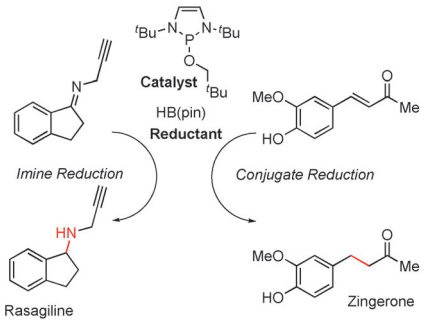

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