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Communication

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Enantioselective Imine Reduction Catalyzed by Phosphenium Ions

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Supporting Information Placeholder

ABSTRACT: The first use of phosphenium cations in asymmetric catalysis is reported. A diazaphosphenium triflate, prepared in two or three steps on a multi-gram scale from commercially available materials catalyzes the hydroboration or hydrosilation of cyclic imines with enantiomeric ratios of up to 97:3. Catalyst loadings are as low as 0.2 mole percent. Twenty-two aryl/heteroaryl pyrrolidines and piperidines were prepared using this method. Imines containing functional groups such as thiophenes or pyridyl rings that can challenge transition metal catalysts were reduced employing these systems.

Diazaphospholenes are hydridic reagents and catalysts which have recently been shown to be the strongest neutral metal-free hydride donors on the Mayr nucleophilicity scale.[1,2] Diazaphospholenes are attractive catalysts for reductions, since they are tolerant of alkenes, alkynes, and Lewis-basic sites, which may pose issues for metal-based reduction catalysts.[3] Use of diazaphospholenes in asymmetric catalysis is a recent development. Precatalyst **1a**, developed by our group, exhibited enantiomer ratios (e.r.) of up to 88:12 for imine reduction at 2 mol % catalyst loading.[4] Cramer and co-workers subsequently disclosed a strategically designed family of polycyclic diazaphospholenes, exemplified by **1b**, that are more selective than the P-methoxy variant of **1a** for asymmetric conjugate reduction.[5] The synthesis of these catalysts is relatively lengthy compared with that of **1a**. The use of **1b** for imine reductions has not been reported. Both **1a** and **1b** are alkoxy diazaphospholene precatalysts that generate a diazaphospholene hydride during the reaction.[6] This work shows that chiral diazaphosphenium triflates are highly active catalysts for imine reduction, maintain the ease of synthesis of **1a**, and achieve the highest enantioselectivities yet reported in diazaphospholene catalysis.

Phosphenium cations have long been a subject of investigation, but their use in catalysis is a relatively recent development.[7] We have shown that achiral triazaphosphenium cations with chloride counterions are able to catalyze imine reduction.[8] Kinjo and co-workers have demonstrated a general 1,4-reduction of pyridines using achiral diazaphosphenium triflate **2a**.[9]

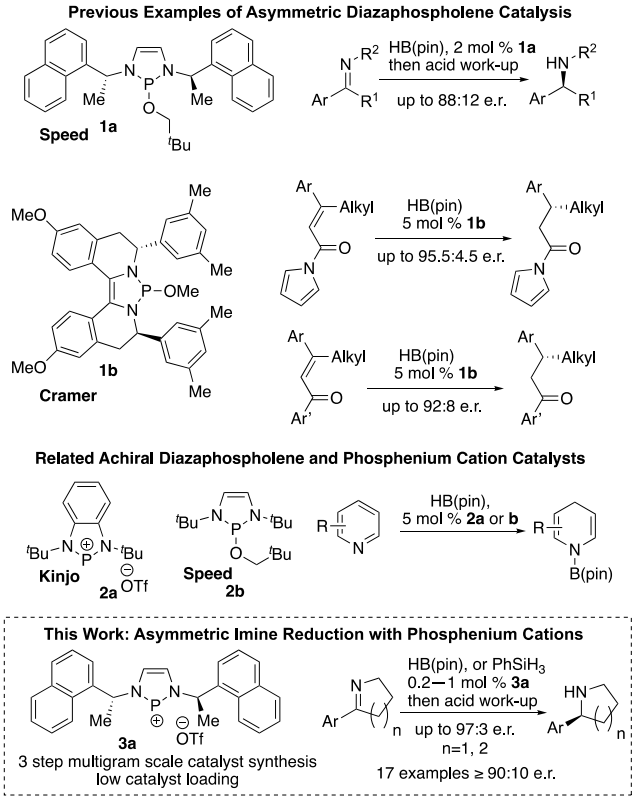


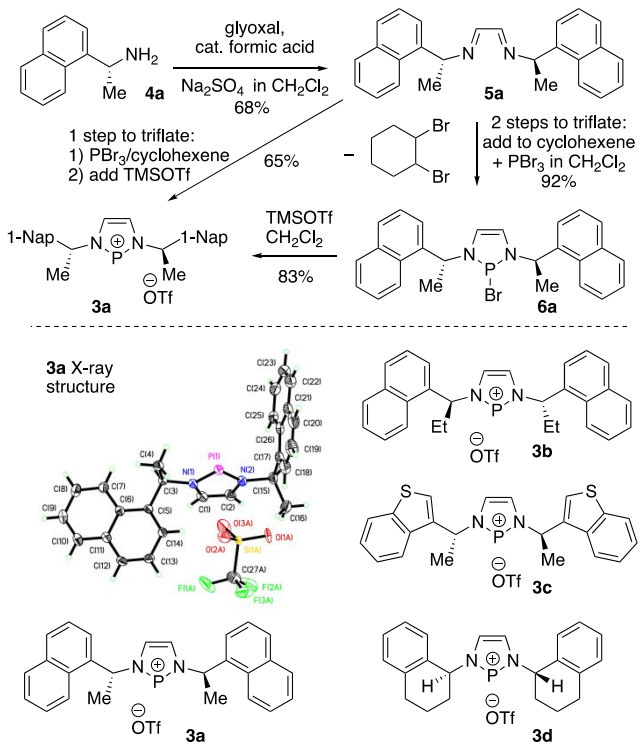
Figure 1. Diazaphospholene-based reduction catalysts

We contemporaneously investigated the 1,4-reduction of pyridines using neutral precatalyst **2b**, which was less active than **2a**, and only functioned when the pyridines bore electron withdrawing groups.[10] We sought to ascertain if moving from neutral catalysts such as **1a** to phosphenium cations such as **3a** for asymmetric imine reduction would exhibit a corresponding increase in

activity. Most importantly, since there is no literature precedent for the use of phosphenium cations in asymmetric catalysis, we also sought to determine if the level of asymmetric induction would be perturbed by the move from a neutral to cationic manifold.

Chiral phosphenium cations are readily accessed via a modification of the protocol originally developed for achiral phosphenium cations by Macdonald and co-workers.[11] Condensation of amine **4a** with glyoxal readily forms diimine **5a** on a 70-gram scale (Scheme 1).[12] Exposure of **5a** to PBr_3 with cyclohexene as a bromine scavenger affords diazaphospholene bromide **6a**. Large scale synthesis of **6a** required modification of the existing procedure since addition of PBr_3 to a mixture of **5a** and cyclohexene gave poor product cleanliness and yields upon scale-up. Premixing PBr_3 and cyclohexene in dichloromethane, followed by addition of a dichloromethane solution of diimine **5a** resulted in clean, scalable cyclization to form **6a**.

Scheme 1. Chiral Phosphenium Triflates 3a–3d

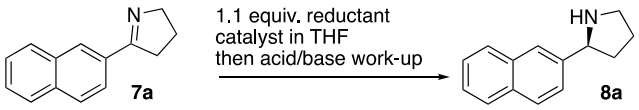


No decrease in yield or purity of **6a** was observed at the largest scale tested (36 grams of **6a** obtained in one batch). We speculate that the beneficial effect of this alteration of addition order arises from minimizing the concentration of diimine present in the oxidative environment of the cyclization process.[13] Bromide **6a** was converted to analytically pure, light beige phosphenium triflate **3a** through treatment with trimethylsilyl (TMS) triflate in dichloromethane on a 15 gram scale.[11] A single crystal of **3a** grown from a THF/ether solution of **3a** confirmed the structure and ionization of the compound in the solid state. Compounds **6a** and **3a** were purified by washing with dry diethyl ether under nitrogen. Alternatively, TMS triflate can be added to the diazaphospholene bromide formation reaction one hour after addition of the diimine allowing a one-pot conversion of **5a** to **3a**. Material prepared in this manner has equivalent catalytic performance to that prepared in two steps from **5a**. The synthesis of **3a** in either two or three steps from commercially available amine **4a** compares favorably in cost, step-count, throughput, and ease of syntheses relative to most chiral phosphine ligands employed in asymmetric catalysis.[14] Related phosphenium cations **3b**, where ethyl groups were used in place of methyl groups, **3c**, where naphthyl was replaced with 3-benzothienyl, and **3d**, derived from (*S*)-1-aminotetralin were also prepared. X-Ray diffraction studies on **3c** and **3d** (See Supporting Information) confirmed their ionic character.

We initially explored reductions of cyclic imines (Table 1) since the product aryl pyrrolidines are common structural motifs in pharmaceuticals and natural products,[3, 15] as well as components of anion-binding organocatalysts.[16] Cyclic imines are readily prepared substrates.[17] Unlike acyclic alkyl imines they are stable to aqueous hydrolysis and chromatography, and there is no possible Z/E isomerism.[18] Because of their utility, a variety of strategies have been developed for the asymmetric synthesis of the product aryl pyrrolidines,[19] including imine and enamine reduction.[20] Stoichiometric sparteine mediated asymmetric lithiation followed by Negishi coupling is especially common,[19a] however practical issues include challenges sourcing sparteine and unequal supply of the enantiomers.[21] Organometallic complex-catalyzed reductions of imines are known, but lengthy or challenging catalyst syntheses present hurdles in these methods,[3,20a,b] Readily accessible catalysts for asymmetric cyclic imine reduction would have immediate utility.

As a baseline result, the reduction of imine **7a** with precatalyst **1a** (entry 1) afforded amine **8a** in 86:14 e.r., comparable to acyclic imine reductions with **1a**.[4] Absolute configuration of **8a** was confirmed by comparison of its optical rotation with literature values,[20c] and was consistent with hydride delivery to the *Re* face of the imine by (*R*,*R*) catalyst, as previously observed with **1a** for acyclic imines.[4] Use of phosphenium triflate **3a** at ambient temperature in THF resulted in the same level and sense of induction (entry 2), verifying that phosphenium cations are capable of asymmetric catalysis. A solvent screen, found in the Supporting Information, confirmed that THF provides the optimal induction for this substrate when using **3a** as the catalyst.[22]

Table 1. Varying Reductant and Catalyst Structure[a,b]



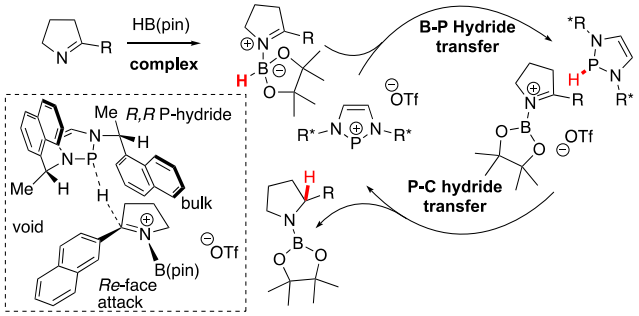
entry	Reductant	Mol % cat	Conv.	e.r.
1[a]	HB(pin)	5 mol % **1a**	>98	86:14
2[a]	HB(pin)	5 mol % **3a**	>98	86:14
3[b]	HB(pin)	5 mol % **1a**	<10	n.d.
4[b]	HB(pin)	5 mol % **3a**	>98	95:5
5[b]	HB(pin)	1 mol % **3a**	>98	**95:5**
6[b,c]	HB(pin)	0.2 mol % **3a**	>98	**95:5**
7[b,c]	HB(pin)	0.1 mol % **3a**	>98	89:11
8[b]	HB(cat)	5 mol % **3a**	>98	86:14
9[a]	Ph_2SiH_2	5 mol % **3a**	>98	84:16
10[b]	Ph_2SiH_2	5 mol % **3a**	<10	n.d.
11[a]	$PhSiH_3$	5 mol % **3a**	>98	87:13
12[b]	$PhSiH_3$	5 mol % **3a**	>98	93:7
13[b]	$PhSiH_3$	1 mol % **3a**	>98	93:7
14[b]	HB(pin)	5 mol % **3b**	>98	5:95
15[b]	HB(pin)	5 mol % **3c**	>98	91:9
16[b]	HB(pin)	5 mol % **3d**	>98	20:80

a) reduction at ambient temperature b) reduction at –35 °C c) reaction conducted with 1 gram of substrate

Cooling neutral **1a** to –35 °C fails to give high conversion (entry 3). Reduction of imine **7a** with ionic **3a** at –35 °C increased the enantiomer ratio to 95:5 with complete conversion (entry 4), demonstrating the superior reactivity of **3a**. Decreasing the catalyst loading to 1 mol % had no impact on conversion or enantioinduction (entry 5). A further decrease to 0.2 mol % was possible (entry 6), but when loading was decreased to 0.1 mol%, the enantioselectivity was lower (entry 7). Catecholborane, which reduces imines without a catalyst, showed inferior selectivity to pinacolborane (entry 8).[23] A brief screen of other reductants revealed **3a** can promote asymmetric imine hydrosilation. Diphenylsilane was used in diazaphospholene catalyzed carbon dioxide reduction.[24] Good conversion and induction were noted with diphenylsilane at room temperature (entry 9), however cooling prevented full conversion (entry 10). Phenylsilane showed similar selectivity to diphenylsilane (entry 11), but higher reactivity at colder temperatures increased asymmetric induction with high conversion (entry 12). The catalyst loading could also be lowered with phenylsilane (entry 13). Existing Lewis-basic catalysts for imine hydrosilation use corrosive trichlorosilane, and require electron deficient aniline-derived imines for turnover, making use of **3a** a complementary process.[25] Catalyst **3b** gave equivalent performance to **3a** (entry 14). Benzothiophene-based **3c** showed slightly less selectivity than that obtained with **3a** (entry 15). Amino-tetralin derived catalyst **3d** also exhibited lower enantioselectivity than **3a** (entry 16).

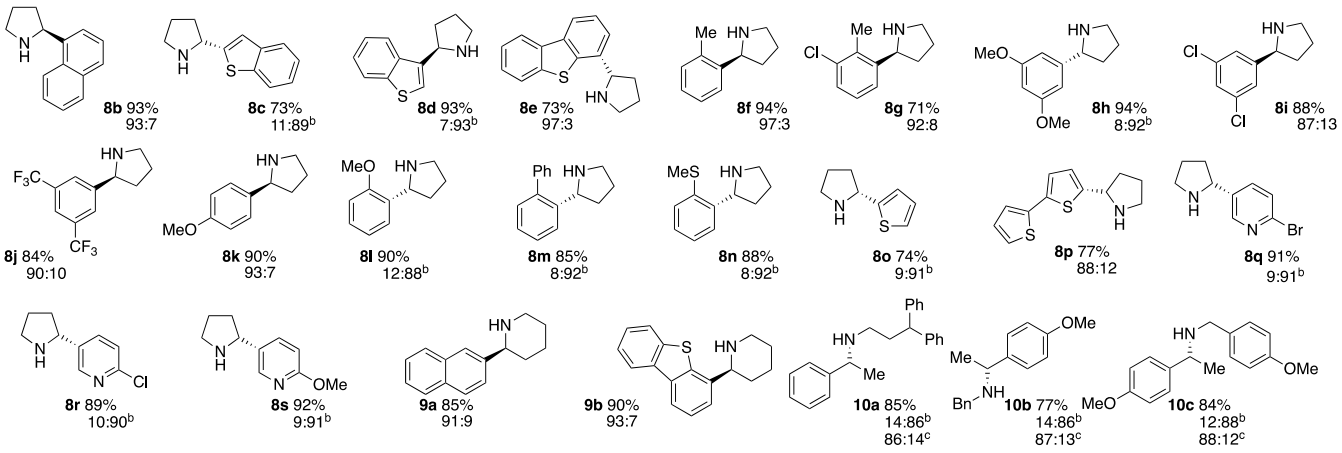
We propose a mechanism for imine hydroboration resembling pyridine reductions by phosphenium cations, where the phosphenium cation abstracts a hydride from a pinacolborane-substrate complex then redelivers the hydride to the resulting imine-borenium (Scheme 2). Given the high enantioinduction, non-enantioselective borenium catalyzed reduction does not appear to be competitive.[26] The selectivity is consistent with minimizing steric interactions between the aryl substituent on the imine and catalyst naphthyl groups.[9,10] While neutral silanes do not complex with imines, a similar mechanism where hydride transfer from the silane to a Lewis acid initiates formation of a silyliminium has been proposed by Piers and coworkers.[27]

Scheme 2. Proposed Hydroboration Mechanism and Induction Model



Silyliminium cations in the Piers mechanism are reduced by back-transfer of the hydride from the Lewis acid-hydride adduct, and this concept could be invoked for our observed silane reductions where **3a** would take on the role of chiral hydride abstractor and donor. Importantly, the high enantioinduction observed with silanes shows that **3a** is not an initiator of racemic silylium ion catalysis as recently articulated by Stephan, Oestreich, and co-workers.[28,29] Further studies to understand the interplay of various reductants, catalyst charge, and structure in diazaphospholene catalyzed reactions are underway in our group. These phosphenium-catalyzed imine reductions contrast with comparably selective metal-free borane and bisborane-based frustrated Lewis pair imine reduction catalysts pioneered by Klankermayer, Repo, and Papai and co-workers,[30] and recently expanded on by Du, and Peng and Wang, and co-workers.[31, 32] While these electrophilic borane systems have been used at loadings of 0.5–5 mol %, electron-deficient aniline derived imines or heterocycles are required as substrates to avoid product inhibition of the electrophilic catalysts, in contrast to the relatively basic cyclic imines used here.

Scheme 3. Scope of asymmetric reduction[a]



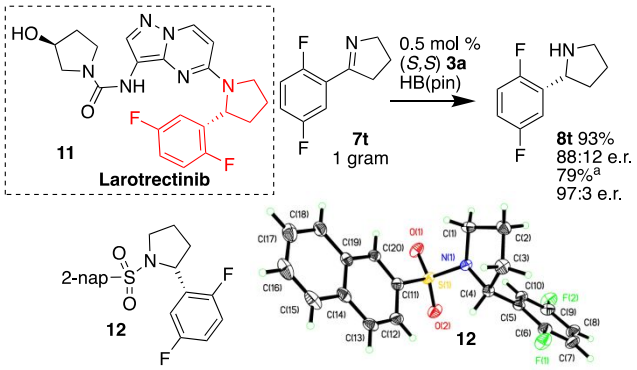
a) Isolated yields and enantiomer ratios for reactions performed on 100 mg scale, using 1 mol % catalyst **3a**, and 1.2 equiv of HB(pin) at –35 °C. Enantiomer ratios determined by HPLC on a chiral stationary phase, configurations assigned by analogy to **8a**. b) Catalyst **ent-3a** used in reduction c) previous e.r. obtained with 2 mol % **1a** at 25 °C in reference 4.

To study scope, substrates were reduced on a 100 mg scale, using a 1 mol % loading of catalyst (Scheme 3). Amine **8b** formed with comparable selectivity to isomeric **8a**. Benzothiophene and dibenzothiophene amines **8c**–**8e** were obtained with good to excellent selectivity. Preparation of **8e**, formerly used as a component of chiral catalysts, previously required stoichiometric sparteine, and 5 mol% palladium catalyst.[16,19a] *Ortho*-methyl substitution patterns **8f** and **8g** and *meta*-substituted **8h**–**8j** were well tolerated. Electron donating groups on the *para* or *ortho* positions of **8k**–**8n** did not interfere. Thiophenes **8o** and **8p** were also well tolerated. Sulfur-containing functional groups can challenge some transition-metal based catalysts.[33] Diazaphospholenes can catalyze the 1,4 hydroboration of certain 3-substituted pyridines,[10] however halogen or methoxy substituents in the 6-position allowed selective reduction of the imine to nornicotine analogues **8q**–**8s**. Substitution of the 6-position to avoid catalyst inhibition was needed in pyridyl imine hydrogenation with an iridium-based catalyst.[3] Two arylpiperidines, **9a** and **9b** were prepared from reduction of the six membered cyclic imines, with slightly lower selectivity than pyrrolidine analogues **8a** and **8e**.

Acyclic amines **10a**, **10b**, and **10c** were prepared by reduction of the corresponding imines catalyzed by 1 mol % of **3a** at –35 °C. These acyclic imine reductions exhibited comparable selectivity to the previously reported reduction with precatalyst **1a** (albeit at lower catalyst loading).[4] It appears for now that cyclic imines are the optimal substrate for reductions with **3a**.

To further demonstrate utility, we prepared **8t**, an intermediate in the synthesis of the tyrosine kinase inhibitor larotrectnib **11** (Scheme 4), on gram scale. Amine **8t** was previously prepared by a 0.4 mol % iridium-complex catalyzed hydrosilation of **7t** with a reported e.r. ranging from 87.5:12.5 to 92.5:7.5.[34] Our catalyst provided a comparable e.r. of 88:12 at 0.5 mol % loading without requiring iridium. An X-ray diffraction study on crystalline derivative **12** provided further proof of configuration.[35]

Scheme 4. Synthesis of larotrectnib intermediate 8t



a) Recovery and e.r. after crystallization with (*R*)-malic acid

In conclusion, we have demonstrated the first example of an asymmetric reaction catalyzed by a phosphenium cation. The synthesis of the catalyst was conducted in three steps on a multi-gram scale. Good to excellent enantioselectivities for preparation of arylpyrrolidones

were obtained at catalyst loadings of 0.2–1 mol %. We anticipate this technology will be useful for the preparation of many cyclic secondary amines. Further developments of cationic catalysts that are highly selective at room temperature, and more selective in acyclic imine reduction will be reported in due course. Both enantiomers of catalyst **3a** will soon be commercially available from Strem Chemicals.

ASSOCIATED CONTENT

Supporting Information

Synthetic procedures, NMR spectra of catalysts, substrates and products, reaction optimization tables, and HPLC traces are available as a PDF file.

CIF files for compounds **3a**, **3c**, **3d** and **12**.

The Supporting Information is available free of charge on the ACS publications website.

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Notes

Competing financial interests: Dalhousie University has filed patents on chiral phosphenium triflates for asymmetric imine reduction, from which royalty payments may be derived.

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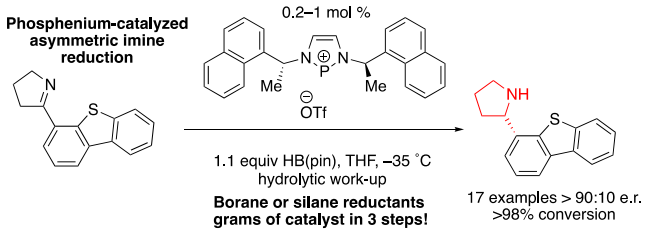
(35) Compound **10** exhibits conglomerate behavior. Crystals that formed in ethyl acetate/hexanes were used for X-ray analysis. HPLC analysis of a solution made from these crystals showed they were almost enantiopure and corresponded to the major enantiomer. The 89:11 ratio was obtained from multiple analyses of an amorphous sample of **10** prepared by concentration of a dichloromethane solution of **10**.



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