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Asymmetric Catalytic Synthesis of *P*-Stereogenic Phosphines via a Nucleophilic Ruthenium Phosphido Complex

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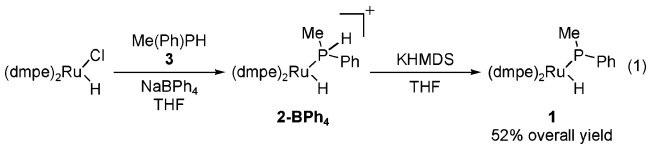
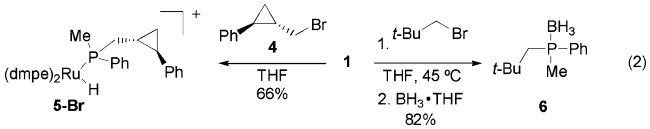
Many reactions rely upon the activation of an electrophile via coordination to a Lewis acidic metal catalyst, followed by attack of an external nucleophile. The inverse situation—the activation of a nucleophile via coordination to an electron-rich metal center—remains a largely unexplored area of catalysis.[1] The high nucleophilicity at phosphorus of late transition metal phosphido ($M-PR_2$) complexes[2] provides an excellent opportunity to investigate this reactivity. We therefore sought to synthesize electron-rich metal phosphido species and investigate their substitution chemistry. After establishing its enhanced nucleophilicity, we hoped to utilize these compounds in the asymmetric catalytic synthesis of *P*-stereogenic phosphines.[2b] These enantioenriched phosphines are employed as ligands in late transition-metal-catalyzed asymmetric reactions,[3] but have seen little use to date, due to the dearth of efficient methods for their preparation.[4] Herein, we report the synthesis and reactivity of a highly nucleophilic Ru(II) phosphido complex and its application in a novel catalytic enantioselective alkylation reaction.



On the basis of the strong basicity and nucleophilicity of previously reported iron and ruthenium amido complexes, particularly $(dmpe)_2M(H)NH_2$ (dmpe = 1,2-bis(dimethylphosphino)ethane, M = Fe,[5] Ru[6]), an analogous phosphido complex $(dmpe)_2Ru(H)$(PMePh) **1** was synthesized (eq 1).[7] Abstraction of the chloride ligand from $(dmpe)_2Ru(H)(Cl)$, followed by addition of 1 equiv of methylphenylphosphine **3**, afforded cationic phosphine complex **2-BPh$_4$**. Deprotonation of this complex with KHMDS afforded ruthenium phosphido complex **1**.

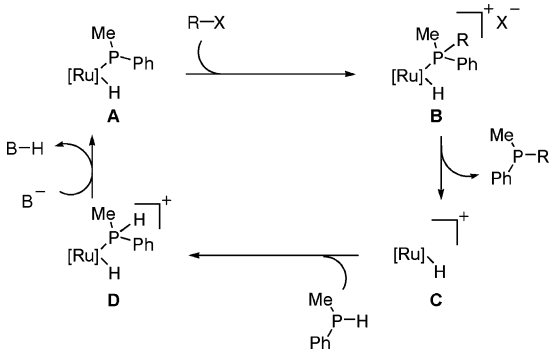
Crystals of **1** and **2-BPh$_4$** suitable for X-ray diffraction analysis were obtained from concentrated THF solutions cooled to −35 °C. The Ru−P bond in the cationic complex **2-BPh$_4$** is lengthened from 2.342 to 2.513 Å upon deprotonation to form **1**. This bond lengthening is consistent with a filled−filled dπ−pπ repulsive interaction[2a] between the phosphido moiety and the electron-rich and π-basic ruthenium atom. The sum of the angles around the phosphido phosphorus in **1** (327.1°) provides evidence that there is minimal back-bonding to the ruthenium center from the phosphido ligand.

Having synthesized the desired phosphido complex, experiments were conducted to evaluate its nucleophilicity at phosphorus. Ruthenium phosphido **1** displaces halides and tosylates from a wide variety of electrophiles.[8] Two informative examples are discussed (eq 2). Addition of 1 equiv of the bromomethylcyclopropane **4** to a solution of **1** in THF afforded complex **5-Br**; no cyclopropane ring scission was detected, providing strong evidence against a radical pathway for the substitution. **1** also underwent substitution with neopentyl bromide, a traditionally poor S_N2 substrate, within 36 h at 45 °C; the resulting methylneopentylphenylphosphine dissociated from the ruthenium center to yield **6** (isolated as the borane complex).



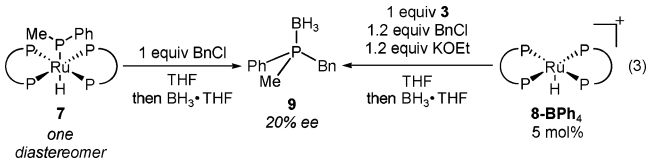
Two of the transformations discussed above—deprotonation (eq 1) and alkylation (eq 2)—provide the basis for a proposed catalytic cycle. As depicted in Scheme 1, phosphido complex **A** undergoes

Scheme 1



alkylation with an electrophile. As observed in the reaction of **1** with neopentyl bromide, the tertiary phosphine of cationic complex **B** can dissociate from the metal center, providing coordinatively unsaturated Ru−H complex **C**. Association of a secondary phosphine to **C** generates complex **D**. Deprotonation of **D** regenerates metal phosphido complex **A**, closing the catalytic cycle.

In developing a catalytic asymmetric alkylation reaction, the 1,2-bis((2*R*,5*R*)-2,5-dimethylphospholano)ethane ((*R*,*R*)-Me-BPE) analogue of **1** was synthesized as a single diastereomer.[9] The stoichiometric alkylation of diastereopure (*R*,*R*)-Me-BPE phosphido complex **7** with benzyl chloride afforded the corresponding tertiary phosphine **9** (following borane protection) with low, but promising, enantioselectivity (eq 3).



Satisfyingly, a catalytic amount of $[((R,R)\text{-Me-BPE})_2Ru(H)][BPh_4]$ **8-BPh$_4$** also afforded phosphine borane **9** with enantioselectivity. Thus, the proposed catalytic cycle is a potentially viable method for the asymmetric alkylation of secondary phosphines.

In optimizing the catalytic, asymmetric phosphido alkylation, sodium *tert*-amyloxide was selected as the most suitable base with regard to two critical criteria: (1) its ability to regenerate a Ru

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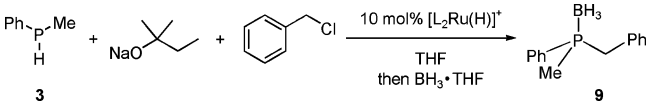
Table 1. Catalyst Optimization



3 **9**

entry	ligand	temp (°C)	time	% ee[a]
1	(*R*,*R*)-Me-BPE	23	20 min	−21 (−19[b])
2	(*R*)-Me-PHOX	23	1 h	−24
3	(*R*)-Ph-PHOX	23	1 h	10
4	(*S*)-Bn-PHOX	23	1 h	7
5	(*R*)-*i*-Pr-PHOX (**10**)	23	1 h	27 (8[c])
6	(*R*,*R*)-Me-BPE	−30	48 h	19
7	(*R*)-Me-PHOX	−30	60 h	11
8	(*R*)-*i*-Pr-PHOX (**10**)	−30	60 h	−79[d]
9	(*S*)-*i*-Pr-PHOX	−30	60 h	75

[a] Measured by chiral HPLC. Negative ee denotes opposite enantiomer. [b] With 2 mol % catalyst loading. [c] Reaction with benzyl bromide. [d] The % ee reported as an average of four trials.

phosphido complex (**D** to **A** in Scheme 1), and (2) its noncompetitive background reaction.

Having demonstrated proof of principle (eq 3), the catalytic alkylation of **3** with benzyl chloride was examined with a variety of chiral hydrido ruthenium complexes (Table 1). The substituted phosphine was isolated as the air-stable benzylmethylphenylphosphine borane **9**. Ruthenium catalysts with C_2-symmetric diphosphine ligands overall gave low enantioselectivities.[10] Notably, reducing the catalyst loading from 10 to 2 mol % resulted in only a slight decrease in the enantiomeric excess, demonstrating the efficiency of the metal-catalyzed reaction (entry 1). Phosphino-oxazoline (PHOX) ligands also resulted in low enantioselectivities (entries 2−5). Reaction with the more reactive benzyl bromide gave a significant decrease in the enantioselectivity (entry 5). Upon lowering the reaction temperatures to −30 °C, however, the *i*-Pr-PHOX catalyst **10** afforded phosphine borane **9** in 79% ee (entry 8).

The temperature-optimized conditions with catalyst **10** were then applied to the asymmetric alkylation of secondary phosphine **3** with a variety of substituted benzylic chlorides (Table 2). The reaction tolerates *para*-substitution, particularly electron-donating groups (entries 3 and 4). Chloro substitution was also tolerated in the reaction (entry 2). Substrates with substitution in the *ortho* position reacted efficiently, although with lower enantioselectivities (entries 5−7). Chelating bisphosphines were efficiently synthesized (entries 7 and 8); a chiral pincer ligand (entry 8) was obtained from the double substitution in 95% ee. Heteroaryl substrates were tolerated (entries 9−11), giving a chiral pyridyl−pincer ligand in 84% ee (entry 9). The reaction was demonstrated to take place efficiently with a nonbenzylic electrophile to give ethylmethylphenylphosphine borane in 57% ee (entry 12).

In conclusion, the enhanced nucleophilicity of electron-rich ruthenium phosphido complexes was exploited in the development of a catalytic system for the asymmetric synthesis of *P*-stereogenic phosphines. This enantioselective alkylation reaction provides access to useful and synthetically challenging phosphine ligands in a single step from secondary phosphines and alkyl halides. In a broader sense, this reaction represents the activation of a nucleophile via coordination to an electron-rich transition metal; this reactivity, which differs from typical Lewis acid activation of an electrophile, offers many new exciting avenues in catalysis.[11]

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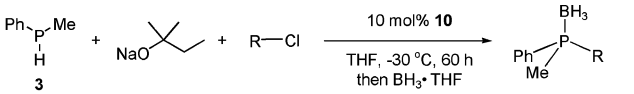
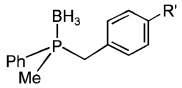
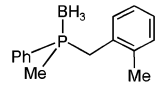
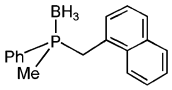
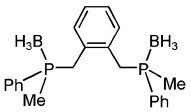
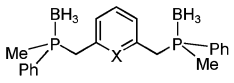
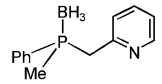
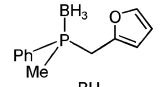
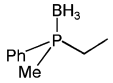
Table 2. Enantioselective Alkylation with Alkyl Chlorides



3

entry	product		% yield[a]	% ee[b]
1		R' = H (**9**)	91	75 (92[c])
2		R' = Cl	96	41
3		R' = Me	80	83
4		R' = OMe	85	85
5			92	57
6			96	59
7			87	74[d]
8		X = CH	86	95[e]
9		X = N	89	84[f]
10			94	48
11			80	68
12			70	57[g]

[a] Isolated yields. [b] Measured by chiral HPLC. [c] The % ee after a single recrystallization. [d] A 33:67 mixture of C_2:meso diastereomers determined by HPLC. [e] A 74:26 C_2:meso dr. [f] A 58:42 C_2:meso dr. [g] Reaction with ethyl bromide.

Supporting Information Available: XRD for **1** and **2-BPh$_4$**, experimental procedures, and characterization data are available. This material is available free of charge via the Internet at http://pubs.acs.org.

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(7) An alternative method of preparing **1** from (dmpe)$_2$RuH$_2$ is described in the Supporting Information.
(8) The full scope of electrophiles that react with **1** will be reported in due course.
(9) Metal phosphido complexes typically exhibit low barriers to pyramidal inversion: Rogers, J. R.; Wagner, T. P. S.; Marynick, D. S. *Inorg. Chem.* **1994**, *33*, 3104−3110. We are currently investigating the barrier to pyramidal inversion in **7**.
(10) Other diphosphine ligands afforded **9** with low or no enantiomeric excess: (*R*,*R*)-DIOP (0%); (*R*,*R*)-*i*-Pr-DuPhos (0%); (*R*,*R*)-Me-DuPhos (−10%); (*R*,*R*)-Et-DuPhos (−9%).
(11) By agreement of the authors, this paper should have appeared simultaneously on the ASAP version of the journal with the paper by Scriban and Glueck that immediately follows this one in the paginated version of the journal (Scriban, C.; Glueck, D. S. *J. Am. Chem. Soc.* **2006**, *128*, 2788−2789.

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