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Palladium-Catalyzed Asymmetric Phosphination: Enantioselective Synthesis of a P-Chirogenic Phosphine

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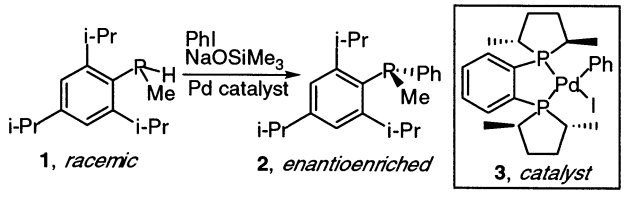
Chiral phosphines, valuable ligands for metal-catalyzed asymmetric reactions,[1] are usually prepared either by resolution or by using a stoichiometric amount of a chiral auxiliary.[2] Surprisingly, metal-catalyzed asymmetric syntheses of these ligands are rare.[3] We report here that Pd-catalyzed asymmetric phosphination (cross-coupling of a secondary phosphine PH(R)(R′) with an aryl halide or triflate)[4] can be used to prepare a P-chirogenic phosphine with control of stereochemistry at phosphorus. Observations of potential intermediates in the catalytic cycle suggest that dynamic resolution of rapidly inverting phosphorus stereocenters is responsible for the enantiomeric excess (ee).

Coupling of racemic PH(Me)(Is) (**1**, Is = 2,4,6-(*i*-Pr)$_3$C$_6$H$_2$)[5] with PhI in the presence of the base NaOSiMe$_3$ and the catalyst Pd((*R*,*R*)-Me-Duphos)(Ph)(I) (**3**)[6] gave enantioenriched P(Ph)(Me)(Is) (**2**, Table 1).[7] Related tertiary methylphosphines are precursors to a family of useful bidentate diphosphines, such as DiPAMP,[8] but incorporation of 2,6-disubstituted aryl groups by standard methods is difficult.[9]



With 5 mol % of **3**, a typical catalytic reaction was complete in about 1 h. ^{31}P NMR monitoring showed quantitative conversion to the tertiary phosphine **2**, which could be isolated in good yields after column chromatography as an oil which solidified on storage in a freezer; its ee was established by NMR after complexation to a chiral Pd amine complex.[10] Toluene was the preferred solvent (entries 1−3), with increase and reduction in ee at lower and higher temperatures (entries 4 and 5). Phenyl bromide and triflate could also be used, although ee's were lower (entries 6 and 7). After this brief survey of reaction conditions, we scaled up the synthesis of **2** and improved its workup to avoid column chromatography.[11] Coupling of 500 mg of **1** (2 mmol) with PhI using 5 mol % of **3** was complete after 2 h. After the solvent was removed, extraction with petroleum ether and filtration through a short pad of silica, followed by washing the silica with 9:1 petroleum ether/THF, gave phosphine **2** in 90% yield and 70% ee (entry 8). Similar results were obtained at lower catalyst loading (2.5 mol %, entry 9).

A study of the individual steps in a potential mechanism for the catalytic reaction (Scheme 1) provided mechanistic information on the origin of the ee.[4] Treatment of Pd(Me-Duphos)(Ph)(I) with PH(Me)(Is) led to broadening of the ^{31}P NMR peaks of the phosphine

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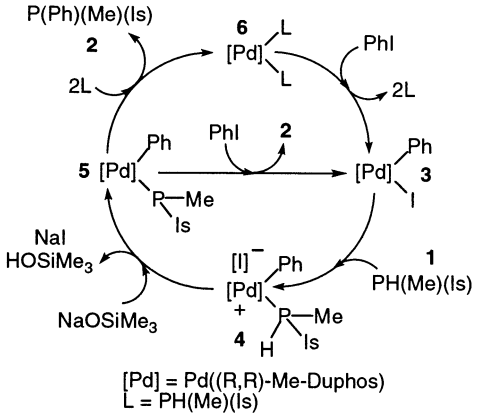
Table 1. Pd-Catalyzed Asymmetric Synthesis of **2** from **1**[a]

entry	PhX	solvent	*T* (°C)	yield (%)	ee (%)
1	PhI	THF	21	69[b]	66
2	PhI	MeCN	21	60[b]	58
3	PhI	toluene	21	71[b]	73
4	PhI	toluene	4	84[c]	78
5	PhI	toluene	50	60[c]	42
6	PhBr	toluene	50	53[c]	38
7	PhOTf	toluene	21	70[c]	50
8	PhI	toluene	21	90[d]	70
9	PhI	toluene	21	88[d]	73

[a] Base = NaOSiMe$_3$ (1.0 M in THF), catalyst = **3** (5 mol %; 7 mol % for entries 1−2, 2.5 mol % for entry 9), 2 equiv of PhX; 1 equiv of PhI for entry 4, 1.05 equiv of PhI for entries 8−9. For experimental details and ee determination, see the Supporting Information. [b] By ^{1}H NMR integration after product isolation by column chromatography. [c] Isolated yield after column chromatography. [d] Isolated yield after workup in the text.

Scheme 1



at room temperature. Low-temperature ^{31}P NMR showed that the phosphine reversibly displaced iodide to form the cation [Pd(Me-Duphos)(Ph)(PH(Me)(Is))][I] (**4**) as a mixture of diastereomers; the equilibrium favored neutral **3**. Cation **4** was independently synthesized as the isolable triflate salt (**4-OTf**) from **3**, phosphine **1**, and AgOTf.[12] Treatment of **4** with NaOSiMe$_3$ at low temperature gave the phosphido complex Pd(Me-Duphos)(Ph)(P(Me)(Is)) (**5**). Because neither iodide complex **3** nor phosphine **1** reacts directly with NaOSiMe$_3$, Pd−PR$_2$ bond formation appears to proceed by the two-step process shown in Scheme 1.[13]

Low-temperature ^{31}P NMR showed that **5**, generated either by deprotonation of cation **4** or directly from **3**, phosphine **1**, and NaOSiMe$_3$, exists as a mixture of diastereomers **5a**−**b** (ratio ca. 40:1, THF/THF-d_8, −60 °C), which presumably interconvert through inversion at phosphorus.[14] The signals due to the minor diastereomer broadened considerably on warming, but coalescence could not be observed because reductive elimination of the tertiary phosphine **2** was also observed starting at −20 °C. After reductive

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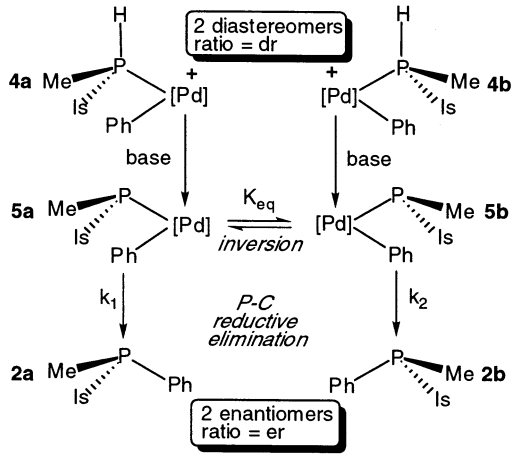
Scheme 2



elimination of **2**, oxidative addition of PhI occurred smoothly to regenerate **3**, consistent with the standard cross-coupling mechanism shown in Scheme 1.

During catalysis with PhI at room temperature, ^{31}P NMR monitoring initially showed the presence of phosphido complex **5** and Pd(Me-Duphos)(PH(Me)(Is))$_2$ (**6**), which undergoes rapid exchange on the NMR time scale with PH(Me)(Is).[15] As catalysis proceeded, complex **3** was also observed; it became the dominant Pd species present near the end of the reaction. In catalysis with PhOTf, the same Pd complexes were observed,[16] but the ratio of **6** to **5** was greater, consistent with faster oxidative addition of PhI.[17] These observations suggest that the rates of oxidative addition and reductive elimination during catalysis are similar and that Pd−P bond formation can be faster than both steps under the appropriate conditions.

The observation of both diastereomers of **5** in an unequal ratio suggests two possible extreme routes to enantioselection. If **5a** and **5b** undergo reductive elimination at similar rates, faster than P inversion, then the ee of product **2** would reflect their thermodynamic ratio (K_{eq}, Scheme 2). Alternatively, if interconversion of **5a** and **5b** is faster than reductive elimination, their relative rates of reductive elimination could control the ee ($k_1 \neq k_2$, Scheme 2).[18]

To probe the relative rates of phosphorus inversion and reductive elimination in intermediates **5a**−**b**, we deprotonated diastereomeric mixtures of cations **4** to give phosphine **2**. If reductive elimination occurs more quickly than inversion, the initial ratio of diastereomers (dr) should be carried through to the product. Instead, if phosphido complexes **5a** and **5b** could interconvert before reductive elimination, their relative abundance and reductive elimination rates might result in an enantiomeric ratio (er) of **2** different from the original dr of cations **4**.[19] Because this was observed (dr = 1:1 or 1:1.4, but er = 6:1), the rate of inversion is greater than or equal to that of reductive elimination under these conditions. Treatment of **3** with phosphine **1** and NaOSiMe$_3$ at room temperature led to analogous results (er = 6:1). The similar product ratio observed in the catalytic reactions provides a rationale for the observed enantioselection, which is apparently controlled by inversion and reductive elimination in phosphido intermediates **5a**,**b**.[20]

In conclusion, the new catalytic asymmetric phosphination is a potentially useful method for the synthesis of P-chirogenic phosphines. In addition to identifying an active catalyst, we have provided information both on the mechanism of the reaction and on the origin of enantioselectivity (via dynamic resolution). We are currently investigating the scope of the catalysis, optimizing yields, ee's, and catalyst loading, and investigating other, structurally related catalysts.

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Supporting Information Available: Experimental procedures and characterization data (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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(11) Because **2** is air-sensitive, chromatography (under N_2) is inconvenient.
(12) Using a stoichiometric amount of PH(Me)(Is) yields a 1:1 mixture of diastereomers of **4**. Heating this material in THF, or use of excess phosphine in the original synthesis, gives **4** in 1:1.4 ratio.
(13) However, we cannot rule out formation, in an unfavorable equilibrium, of the anion [P(Me)(Is)]$^-$, which could displace iodide from **3**.
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(15) Complex **6** was generated free of **5** by running catalysis with a substoichiometric amount of PhI, or by addition of excess PH(Me)(Is) to Pd(Me-Duphos)(*trans*-stilbene). At −40 °C, phosphine exchange in **6** is slow on the NMR time scale, and the expected mixture of four diastereomers was observed.
(16) Reaction mixtures with PhOTf contain 1 equiv of NaI per Pd, derived from precursor **3**. Independent generation of Pd(Me-Duphos)(Ph)(OTf) (from Pd(Me-Duphos)(*trans*-stilbene) and PhOTf) in the presence of NaI gave **3**, consistent with the observations in the catalytic system.
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(20) Deprotonation of diastereomers **4a** and **4b** at different rates to give **5a** and **5b**, which undergo reductive elimination faster than P inversion, might also result in enantioselection if **4a** and **4b** can interconvert before deprotonation is complete, perhaps via reversible proton transfer. However, the observation that different diastereomeric mixtures of **4** lead to the same product ratio in **2** makes this unlikely. Moreover, the ee of **2** in the catalytic reaction does not depend on [NaOSiMe$_3$] (1, 2, 3, or 10 equiv of the base per PH(Me)(Is)).

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