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Platinum-Catalyzed Asymmetric Alkylation of Secondary Phosphines: Enantioselective Synthesis of P-Stereogenic Phosphines

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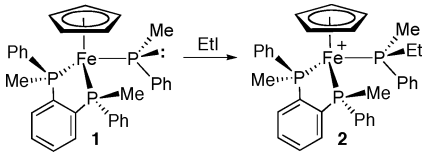
Chiral phosphines, valuable ligands for metal-catalyzed asymmetric reactions,[1] are usually prepared either by resolution or by using a stoichiometric amount of a chiral auxiliary.[2] Surprisingly, metal-catalyzed asymmetric syntheses of these ligands are rare,[3] although P-stereogenic phosphines were prepared via Pt-catalyzed hydrophosphination of activated alkenes[4] and Pd-catalyzed phosphination of aryl halides.[5] Here, we report Pt-catalyzed asymmetric alkylation of secondary phosphines as a new approach to this useful class of compounds.[6]

Terminal metal phosphido complexes (M-PR_2) undergo rapid inversion at phosphorus.[7] With a chiral ancillary ligand, the complexes M(L*)(PRR′) exist as mixtures of rapidly interconverting diastereomers[5a] with different rates of nucleophilic reactivity. For example, alkylation of Fe complex **1** gave complete stereoselectivity at −95 °C (because reaction with EtI was faster than P inversion), but at 20 °C, a 3.2:1 product ratio was observed (because P inversion was now competitive with alkylation, and the diastereomers of **1** reacted with EtI at comparable rates).[8]



Such diastereoselective *stoichiometric* alkylation could be made catalytic if a tertiary phosphine complex like **2** could be converted to a phosphido complex like **1**. Developing such reactions requires overcoming several important hurdles: (1) the background reaction of a secondary phosphine with an electrophile must be much slower than the metal-catalyzed reaction; (2) the equilibrium ratio of phosphido diastereomers and their relative reactivities with the electrophile must be controlled; (3) product inhibition must be avoided; and (4) the chiral ancillary ligand must resist displacement from the metal by the excess phosphine substrate and products. We report here solutions to these problems: Pt(II) complexes catalyze asymmetric alkylation of secondary phosphines in up to 93% ee. We also provide some information on the mechanism of the reaction and the origin of enantioselectivity.

The phosphido complex Pt((*R*,*R*)-Me-Duphos)(Ph)(PMeIs) (**3**) catalyzed the alkylation of PHMe(Is) (**4**) with benzyl chloride or, more quickly, benzyl bromide, in the presence of the base $NaOSiMe_3$ to give PMeIs(CH_2Ph) (**5**, Scheme 1, Is = 2,4,6-(i-Pr)$_3C_6H_2$) in high yield and 70−77% ee (entries 1 and 2, Table 1). Analogous Pt−phosphido complexes also acted as catalysts (entries 3−5). Their air-stable halo precursors[9] were equally active and selective (entries 6−10). The enantiomeric excess improved at lower temperature (entries 6 and 7). (*R*)-Tol-Binap (entries 11 and 12) was also an effective ligand.

Scheme 2 shows a proposed mechanism for the catalysis. Phosphido complex **3** exists as a mixture of diastereomers, which

Scheme 1

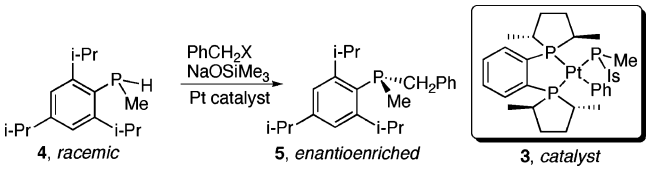
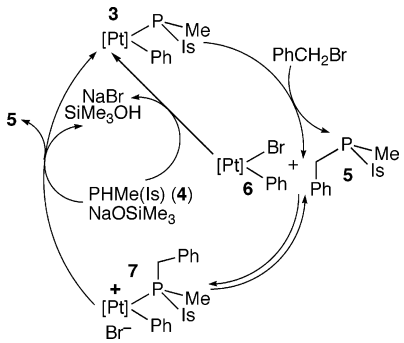


Table 1. Pt-Catalyzed Asymmetric Phosphination of PHMe(Is) with Benzyl Halides[a]

entry	catalyst precursor	time	yield (%)	ee (%)
1[a]	Pt(Me-Duphos)(Ph)(PMeIs)	4 weeks	99	70
2	Pt(Me-Duphos)(Ph)(PMeIs)	3 h	99	77
3	Pt(Me-Duphos)(I)(PMeIs)	4 h	92	31
4[b]	Pt(Me-Duphos)$(PMeIs)_2$	20 h	98	24
5	Pt(i-Pr-Duphos)(Ph)(PMeIs)	24 h	99	−49
6	Pt(Me-Duphos)(Ph)(Cl)	1 h	95	75
7[c]	Pt(Me-Duphos)(Ph)(Cl)	1 day	94	83
8	Pt(i-Pr-Duphos)(Ph)(Cl)	4 h	87	−45
9	Pt(Me-Duphos)(Me)(Cl)	15 min	79	38
10[b]	Pt(Me-Duphos)Cl_2	<20 h	85	22
11	Pt((*R*)-Tol-Binap)(Ph)(Cl)	1 day	90	61
12	Pt((*R*)-Tol-Binap)(Me)(Cl)	1 day	63	52

[a] With 5 mol % catalyst loading, base = $NaOSiMe_3$, solvent = toluene (entries 1 and 2) or THF. Benzyl bromide was used, except for entry 1 (benzyl chloride). All Duphos ligands have *R*,*R*-configuration.[10] Isolated yields (after chromatography) are reported. See Supporting Information for details. [b] With 2.5 mol % catalyst. [c] The reagents were combined at −10 °C, and the reaction was carried out at −25 °C.

Scheme 2 [a]



[a] [Pt] = Pt(Me-Duphos), Is = 2,4,6-(i-Pr)$_3C_6H_2$.

presumably interconvert through rapid inversion at phosphorus, as observed for the Pd analogue.[5a] Treatment of **3** with $PhCH_2Br$ in toluene gave phosphine **5** (70% ee) and Pt(Me-Duphos)(Ph)(Br) (**6**). When **3** was generated from Pt(Me-Duphos)(Ph)(Cl), PHMe(Is), and $NaOSiMe_3$ in toluene, then treated with benzyl bromide, a small amount of the cation [Pt(Me-Duphos)(Ph)(PMeIs(CH_2Ph))][Br] (**7**) was also formed. A mixture of **5** and **6** in CD_2Cl_2 yielded some **7**, consistent with formation of this cation at equilibrium favored by a polar medium.[11] Cation **7** was also the resting state

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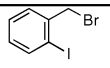
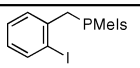
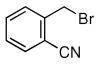
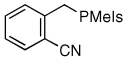
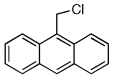
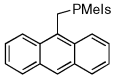
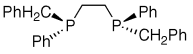
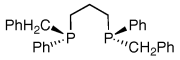
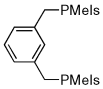
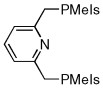
Table 2. Pt-Catalyzed Asymmetric Phosphination of Benzylic Substrates[a]

entry	substrate	product	yield (%)	ee (%)
1			88	55
2			86	50
3[b]			77	66
4	$PhCH_2Br$	$PMe(Phes)(CH_2Ph)$	86	81
5	$PhCH_2Br$	$PMe(Mes)(CH_2Ph)$	86	69
6	$PhCH_2Br$	$PMe(Ph)(CH_2Ph)$	84	35
7	$PhCH_2Br$	$PMe(Men)(CH_2Ph)$	87	56% de
8	$PhCH_2Br$	$PPh(o\text{-}An)(CH_2Ph)$	85	9
9	$PhCH_2Br$	$PPh(Cy)(CH_2Ph)$	93	48
10	$PhCH_2Br$	$PPh(t\text{-}Bu)(CH_2Ph)$	90	42
11[c]	$PhCH_2Br$		81	47% de 91% ee
12	$PhCH_2Br$		87	59% de 93% ee
13[b]			86	55% de 69% ee
14[b]			90	17% de 72% ee

[a] Catalyst precursor = Pt(Me-Duphos)(Ph)(Cl) (5 mol %), base = $NaOSiMe_3$, solvent = THF, room temperature. Product yields are for isolated materials (after chromatography) of >97% purity (NMR), except for entries 13 and 14 (87 and 90% purity). For experimental details, see Supporting Information. Phes = 2,4,6-$Ph_3C_6H_2$, Mes = 2,4,6-$Me_3C_6H_2$, *o*-An = *o*-$MeOC_6H_4$, Cy = cyclo-C_6H_{11}, Men = (−)-menthyl, de = diastereomeric excess. [b] Catalyst precursor = complex **3**, in toluene. [c] With 2.5 mol % catalyst precursor, at −5 °C for 4 h, then −15 °C for 4 days. The catalyst precursor Pt(*i*-Pr-Duphos)(Ph)(Cl) (5 mol %, 21 °C) gave the opposite enantiomer in 98% yield (48% de, 86% ee).[10]

during catalysis. Its BF_4 salt reacted with PHMe(Is)/$NaOSiMe_3$ to yield **3**, as did bromide **6** and these reagents.

We hypothesize that interconversion of the phosphido diastereomers **3a** and **3b** by P inversion is much faster than the enantioselectivity-determining alkylation.[5a] Under these Curtin−Hammett conditions, the enantiomeric excess of product **5** would depend on K_{eq} for the **3a**/**3b** equilibrium and the relative rates of alkylation of these diastereomers.[12]

Similar reactions with diverse benzylic halides and secondary phosphines gave other tertiary phosphines in enantioenriched form (Table 2). *ortho*-Substituted benzyl groups (entries 1 and 2) or an anthracenylmethyl group (entry 3) could be used. A range of secondary phosphines, including PHMe(Ar) with different aryl groups (entries 4−6), the chiral dialkylphosphine PHMe(Men) (Men = (−)-menthyl, entry 7), and phenylphosphines with aryl or alkyl substituents (entries 8−10), was possible. Alkylation of bis(secondary) phosphines directly yielded chiral bidentate ligands,[13] including DiPAMP analogues (entries 11 and 12)[14] and potential precursors for chiral pincer complexes (entries 13 and 14).[15]

In summary, we have developed a novel method for the catalytic asymmetric synthesis of monodentate or bidentate P-stereogenic phosphines. It relies on the enhanced nucleophilicity and reduced inversion barrier in the diastereomeric Pt−phosphido intermediates. The scope of the reaction (several benzylic halides and secondary phosphines may be used) and the possibility of tuning the catalyst by choice of the ancillary ligands (chiral diphosphine and Pt−R group) suggest that further development may result in a practical method for preparation of this valuable class of compounds.

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

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(10) From the Cahn−Ingold−Prelog rules, (*R*,*R*)-Me-Duphos and (*R*,*R*)-*i*-Pr-Duphos have opposite stereochemistry,[3a] explaining the apparent enantioselectivity reversal.
(11) This is consistent with the equilibrium observed in ref 5a between Pd(Me-Duphos)(Ph)(I), PHMe(Is), and the cation [Pd(Me-Duphos)(Ph)(PHMe(Is))][I], which favored the neutral iodo complex. Treatment of **7**−BF_4 with excess $NOct_4Br$ in toluene gave bromide **6**.
(12) Product racemization via pyramidal inversion should be slow under these conditions (Mislow, K. *Trans. N.Y. Acad. Sci.* **1973**, *35*, 227−242).
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