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Platinum-Catalyzed Enantioselective Tandem Alkylation/Arylation of Primary Phosphines. Asymmetric Synthesis of P-Stereogenic 1-Phosphaacenaphthenes

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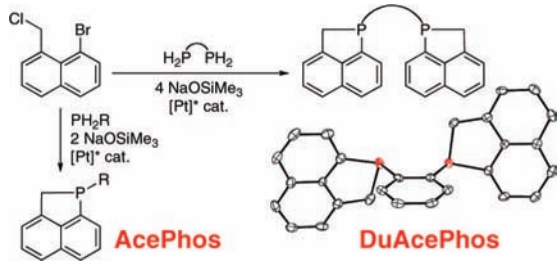
ABSTRACT



Enantioselective tandem alkylation/arylation of primary phosphines with 1-bromo-8-chloromethylnaphthalene catalyzed by Pt(DuPhos) complexes gave P-stereogenic 1-phosphaacenaphthenes (AcePhos) in up to 74% ee. Diastereoselective formation of four P−C bonds in one pot with bis(primary) phosphines gave C_2-symmetric diphosphines, including the *o*-phenylene derivative DuAcePhos, for which the rac isomer was formed with high enantioselectivity. These reactions, which appear to proceed via an unusual metal-mediated nucleophilic aromatic substitution pathway, yield a new class of heterocycles with potential applications in asymmetric catalysis.

Several heteroatom-substituted acenaphthene derivatives **1** are known (Figure 1; E = O, S, NR, SiR_2).[1] Conspicuous by its absence is the analogous phosphine (**3**, E = PR), although this heterocycle is presumably present in the phosphafullerene $C_{59}P$ (**2**), which has been observed by mass spectrometry[2] and analyzed computationally.[3,4] DuPhos and BPE, privileged ligands in asymmetric catalysis, include phospholane rings,[5] while P-stereogenic analogues like TangPhos[6] and BeePhos[7] are also valuable. The 1-phosphaacenaphthene **3** (AcePhos), with reduced conformational flexibility due to the fused naphthalene, might also be a useful ligand.[8]

We recently described a Pd-catalyzed asymmetric synthesis of benzophospholanes via enantioselective cyclization of

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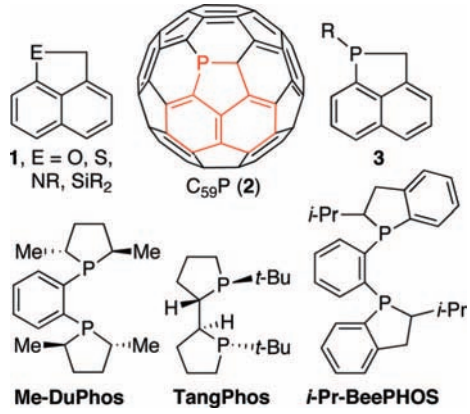
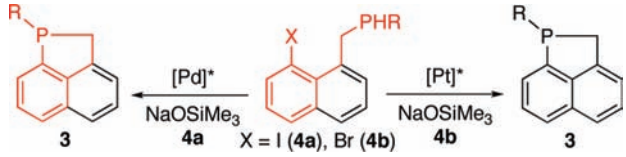


Figure 1. Known 1-heteroatom-acenaphthenes **1**, this ring system in fullerene **2**, target phosphine **3**, and some related bis(phospholane) ligands.

bifunctional aryl iodide/secondary phosphine substrates, shown in red in Scheme 1.[9] These reactions could plausibly

Scheme 1. Metal-Catalyzed Intramolecular Asymmetric Arylation of Secondary Phosphines: Synthesis of Benzophospholanes[9] (in Red, X = I) and Potential Extension to 1-Phosphaacenaphthenes **3**[a]

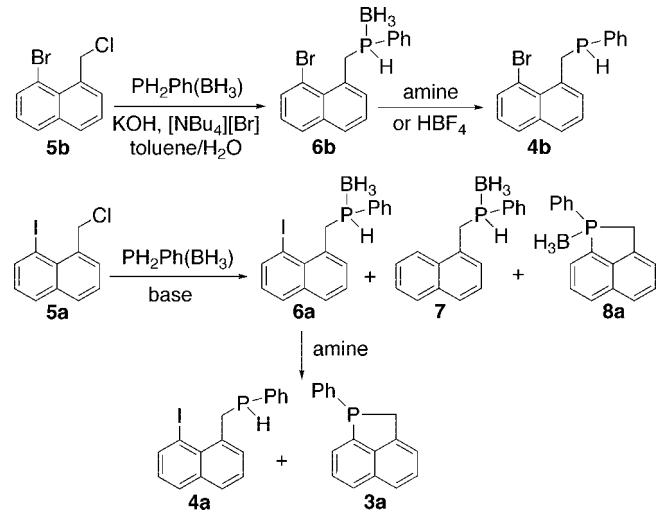


[a][Pd*] = Pd(diphos*)(*trans*-stilbene), [Pt*] = Pt(DuPhos)(Ph)(Cl).

be extended to 1,8-naphthalene derivatives **4** to form **3** (Scheme 1). We report here that, although Pd-catalyzed synthesis of **3** was unselective, novel Pt-catalyzed cyclizations yielded AcePhos ligands enantio- and diastereoselectively (Scheme 1).[10] These reactions, which expand the scope of Pt-catalyzed P−C bond-forming processes,[11] appear to proceed via an unusual metal-mediated nucleophilic aromatic substitution.

Precursors to secondary phosphine substrates **4a**,**b** (R = Ph) were prepared from benzyl chlorides **5** (Scheme 2).[1d]

Scheme 2. Synthesis of Phosphines **4a**,**b**[a]



[a]Base = NaH or KOH (phase-transfer conditions).[12] For **4a**, amine = $NHEt_2$, NEt_3, DABCO, or piperazinomethyl polystyrene.[13] For **4b**, amine = piperazinomethyl polystyrene.

Alkylation of $PH_2Ph(BH_3)$ with bromide **5b** under phase-transfer conditions[12] gave phosphine−borane **6b**, which was deprotected with piperazinomethyl polystyrene[13] or HBF_4 to yield phosphine substrate **4b**.[14]

In contrast, similar alkylations with iodide **5a** were less selective. Deprotonation of $PH_2Ph(BH_3)$ with NaH,[9] followed by treatment with **5a**, gave a mixture of **6a**, the known dehydrohalogenation product **7**,[15] and AcePhos−borane **8a** (see below). Instead, P-alkylation under phase-transfer conditions suppressed ring formation, but dehydrohalogenation still occurred. Phosphine−boranes **6a** and **7** could be separated with difficulty by recrystallization, but deprotection of **6a** gave AcePhos **3a** (R = Ph) in addition to the desired **4a**. This cyclization presumably occurred via deprotonation of **6a** followed by intramolecular nucleophilic attack; no reaction occurred on treatment of the less acidic phosphine **4a** with NEt_3.

Pd(DuPhos)-catalyzed cyclization of **4** gave AcePhos **3a** quickly, but in racemic form (Scheme 1). However, the observations of ring formation under basic conditions in the synthesis of substrates **6a** and **4a** suggested that Pt-mediated nucleophilic activation of **4** might enable enantioselective cyclization.[10] Indeed, this reaction occurred quickly with **4b** and Pt(DuPhos)(Ar)(Cl) catalyst precursors to afford **3a** in up to 6.2:1 er (72% ee, Table 1).

These platinum catalysts mediated alkylation of secondary phosphines with benzyl halides,[10] suggesting that a one-pot AcePhos synthesis from primary phosphines and **5**, via intermediate **4**, might be possible. Indeed, when PH_2Ph and **5b** were treated with 2 equiv of $NaOSiMe_3$ in the presence

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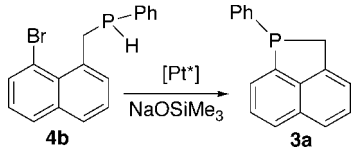
Table 1. Pt-Catalyzed Cyclization of **4b** To Yield **3a**[a]



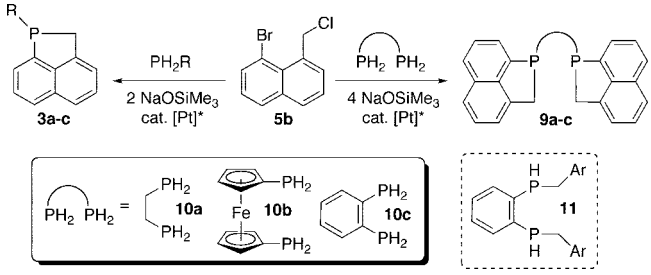
entry	catalyst precursor	yield (%)	er (ee,%)
1	Pt((*R*,*R*)-Me-DuPhos)(Ph)(Cl)	nd[b]	2.0 (33)
2	Pt((*R*,*R*)-*i*-Pr-DuPhos)(Ph)(Cl)	86	−6.2 (−72)[c]
3	Pt((*R*,*R*)-Me-DuPhos)(Phen)(Br)[d]	50	1.6 (23)

[a] Reactions were done in THF with 5 mol % catalyst loading. [b] nd = not determined. [c] The *i*-Pr-Duphos and Me-DuPhos catalyst precursors preferentially yielded opposite enantiomers of **3a**. [d] Phen = 9-phenanthryl.

of a Pt catalyst, secondary phosphine **4b** formed and was then converted to **3a**. Similarly, the alkylphosphines PH_2Cy and PH_2CH_2Fc[16] gave heterocycles **3b**,**c** (Table 2).

Tandem alkylation/arylation was also successful with bis(primary) phosphines, directly yielding C_2-symmetric diphosphines **9a**−**c** (Table 2). This reaction occurred smoothly for unhindered 1,2-bis(phosphino)ethane (**10a**), but was much slower for 1,1′-ferrocene derivative[17] **10b** and bis(phosphino)benzene **10c**, for which bis(secondary) phosphine **11** and other intermediates were observed. While formation of **9a**,**b** occurred with low stereoselectivity, "DuAcePhos" **9c** was formed with good diastereoselection, and the rac isomer was highly enantioenriched.[18]

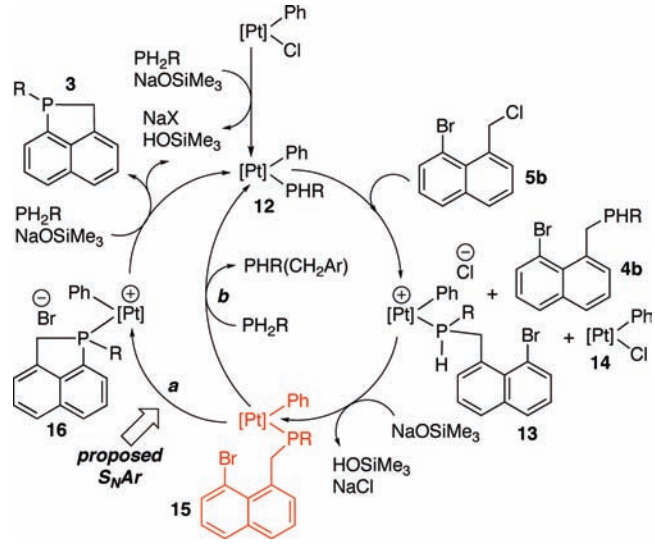
Table 2. Pt-Catalyzed One-Pot Synthesis of Mono- and Bis-1-phosphaacenaphthenes from Primary Phosphines and Bis(primary) Phosphines[a]



entry	substrate (product)	yield (%)	er (ee, %)	dr (de, %)[b]
1	PH_2Ph (**3a**)	80	6.7 (74)	
2	PH_2Cy (**3b**)	85	1.7[c] (26)	
3	PH_2CH_2Fc (**3c**)	85	3.0[d] (50)	
4	$H_2P(CH_2)_2PH_2$ (**9a**)	78	4[e] (60)	1.5 (20)[f]
5	1,1′-Fc$(PH_2)_2$ (**9b**)	69	2.3[e] (39)	1.9 (31)
6	1,2-$C_6H_4(PH_2)_2$ (**9c**)	85	>100[g] (>98)	4.5 (64)

[a] The catalyst precursor was Pt((*R*,*R*)-*i*-Pr-DuPhos)(Ph)(Cl) (entries 1 and 2, 5 mol %), Pt((*R*,*R*)-Me-DuPhos)(Ph)(Cl) (entry 3, 5 mol %, and entry 6, 10 mol %; for entries 4 and 5, the initial loading was 10 mol %, and an additional 4 mol % and 10 mol %, respectively, was added during the reaction). R = Ph (**3a**), Cy (**3b**), $FcCH_2$ (**3c**), Ar (in **11**) = 8-Br-1-naphthyl. Solvent = toluene (entries 1 and 4−6) or THF (entries 2 and 3). [b] dr = rac/meso ratio for the diphosphine. [c] The same er was observed for the mesylate 1-Br-8-CH_2OMs-$C_{10}H_6$. [d] With Pt((*R*,*R*)-*i*-Pr-DuPhos)(Ph)(Cl) (5 mol %), the er was 4.5 (64% ee); the opposite enantiomer was favored. [e] for the rac diphosphine. [f] With Pt((*R*,*R*)-*i*-Pr-DuPhos)(Ph)(Cl) (10 mol %), dr = 1.6 (23% de), er = 4.5 (64% ee); the opposite enantiomer was favored. [g] The minor enantiomer (which was prepared independently as the major product using Pt((*R*,*R*)-*i*-Pr-DuPhos)(Ph)(Cl); dr = 4.3 (62% ee)) was not observed.

Scheme 3. Proposed Mechanism for Pt-Catalyzed Tandem Alkylation/Arylation of Primary Phosphines with **5b**[a]



[a] The intermediates shown in black were observed in stoichiometric and/or catalytic reactions, but **15** (in red) was not observed. [Pt] = Pt(DuPhos), R = Ph or Cy, X = Cl or Br, Ar = 8-bromo-1-naphthyl.

The mechanism proposed in Scheme 3 is consistent with observations on catalytic and stoichiometric reactions with PH_2Ph and PH_2Cy.[10] Treatment of Pt catalyst precursors with a primary phosphine and $NaOSiMe_3$ gave the primary phosphido complexes Pt(DuPhos)(Ph)(PHR) (**12**). Alkylation with **5b** gave a mixture of secondary phosphines **4b**, their cationic Pt complexes **13**, and Pt halide **14**. Deprotonation of **13** with another equiv of base would give secondary phosphido complex **15**, which was not observed, presumably because its subsequent reactions are fast. Intramolecular nucleophilic aromatic substitution by the activated Pt-phosphido group in **15** (path ***a***) would give AcePhos complex **16**,[19] from which product displacement by a phosphine substrate and base would complete the catalytic cycle. Alternatively, proton transfer from a primary phosphine to **15** (path ***b***) could regenerate **12** and yield a secondary phosphine.[20] Competition between paths ***a*** and ***b*** would depend on steric effects and on the nucleophilicity of the phosphido group in **15**.

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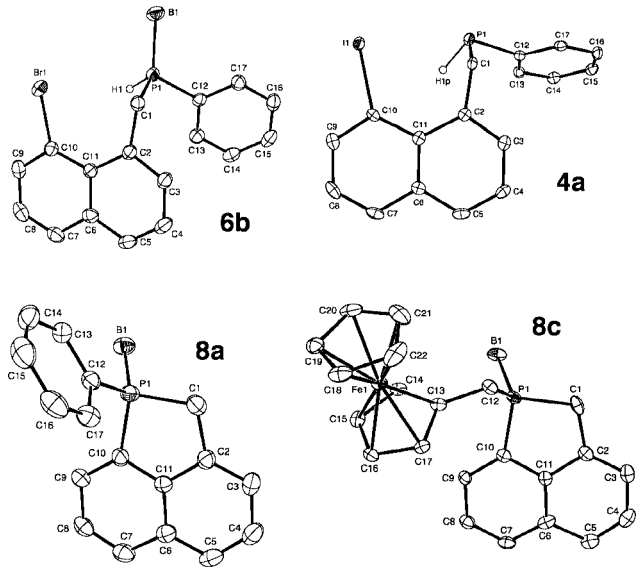

Figure 2. ORTEP diagrams of phosphine−borane **6b**, phosphine **4a**, and AcePhos−borane derivatives **8a** and **8c** (see the abstract for an ORTEP diagram of **9c**, DuAcePhos).

Several of the new phosphacycles and their precursors have been structurally characterized by X-ray crystallography. The structures of **6b** and **4a** (Figure 2) showed features typical of peri-crowding; the 1- and 8-substituents were bent away from each other, and the naphthalene ring was distorted.[21] Details of similar observations on **6a** are given in the Supporting Information. In contrast, in DuAcePhos **9c** and phosphine-boranes **8a** and **8c**,[22] the peri substituents were bent toward each other, distorting the naphthalene in the other direction.[23] Structural constraints of the ring resulted in a small intra-annular CPC bond angle (about 91° for DuAcePhos, 93° in **8a** and **8c**), which may result in unusual properties for these phosphines in coordination chemistry and catalysis.

In summary, we report an asymmetric synthesis of a new class of structurally characterized phosphorus heterocycles (AcePhos) via Pt-catalyzed alkylation of primary phosphines, followed by intramolecular arylation. A convenient one-pot procedure enables the synthesis of C_2-symmetric P-stereogenic diphosphines; these ring-fused phospholanes may be useful ligands in asymmetric catalysis.

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

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