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Palladium-Catalyzed Insertion of Isocyanides into P(O)−H Bonds: Selective Formation of Phosphinoyl Imines and Bisphosphinoylaminomethanes

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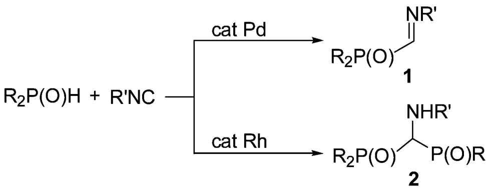
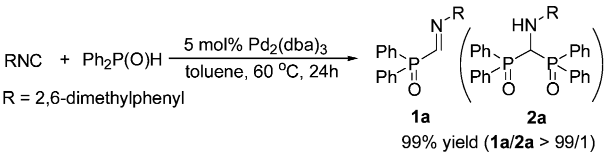
We report herein a direct, selective synthesis of α-iminophosphine oxides **1**[1] and bisphosphinoylaminomethanes **2**[1,2] via metal-mediated insertions of isocyanides to P(O)−H bonds (eq 1). Compounds bearing a P−C−N or a P−C(N)−P unit often show unique biological activity and are of current interest. For example, α-aminophosphonates can mimic the action of natural amino acids and act as inhibitors of enzymes,[3] while the methylene bisphosphonates are mediators of bone metabolism.[4] α-Iminophosphorus compounds are potentially versatile synthetic intermediates for the preparation of these compounds.[5] However, currently only a few methods for their preparation are known.[1,6] Successes in discovering a series of transition-metal-mediated regio- and stereoselective additions of P(O)−H bonds to carbon−carbon unsaturated bonds[7] prompted us to ascertain a new strategy for the preparation of **1** by the metal-mediated direct insertion of isocyanides to P(O)−H bonds. As shown in eq 1, we found that a palladium catalyst and a rhodium catalyst can selectively produce α-iminophosphine oxides **1** and bisphosphinoylaminomethanes **2**, respectively. To the best of our knowledge, this finding represents a rare example of selective addition of a H-heteroatom bond to a isocyanide by group 10 metal catalysts since oligomerization of isocyanides usually competes severely under these conditions.[8−11]



(1)

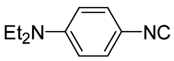
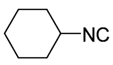
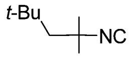
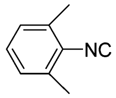
The reaction of $Ph_2P(O)H$ (0.5 mmol) with $2,6\text{-}Me_2NC_6H_3NC$ (0.5 mmol) in the presence of a catalytic amount of $Pd_2(dba)_3$ (5 mol %) in toluene (2.5 mL) at 60 °C proceeded efficiently to give the 1:1 adduct **1a** selectively in a high yield (eq 2). Another possible adduct **2a** (2:1 adduct of $Ph_2P(O)H$ to the isocyanide) could be hardly detected.[12]



(2)

This palladium catalyst is essential for this addition reaction; that is, in the absence of the catalyst, no adduct could be obtained under similar reaction conditions. As for other zero-valent palladium species, $Pd(PPh_3)_4$ also produced a high yield of **1a** (95% yield **1a**/**2a** = 95/3). Moreover, the addition of a large amount of PEt_3 did not affect the reaction (Pd_2dba_3/PEt_3; Pd/PEt_3 = 1/20, 93% yield, **1a**/**2a** = 93/2). On the contrary, palladium(II) complexes showed low catalytic activity under similar reaction conditions: $Pd(OAc)_2$ (11%), $PdCl_2$ (0%), $Pd(PPh_3)_2Cl_2$ (0%). Allylpalladium chloride dimer $[C_3H_5PdCl]_2$ and other group 10 metals [$Ni(cod)_2$, $Ni(cod)_2$/$4PPh_3$, and $Pt(PPh_3)_2(CH_2{=}CH_2)$] did not catalyze the addition at all.

Table 1. Palladium-Catalyzed Selective Addition of Secondary Phosphine Oxides to Isocyanides Forming Iminophosphine Oxides[a]

entry	H-phosphine oxide	isocyanide	% yield of **1** (**1/2**)[b]
1	$Ph_2P(O)H$		91 (88)[c] (**1b**) (98/2)
2			90 (88)[c] (**1c**) (99/1)
3			74 (70)[c] (**1d**) (99/1)
4	$(4\text{-}CF_3C_6H_4)_2P(O)H$		91 (86)[c] (**1e**) (95/5)
5	$(4\text{-}ClC_6H_4)_2P(O)H$		96 (90)[c] (**1f**) (98/2)
6	$(4\text{-}MeOC_6H_4)_2P(O)H$		94 (89)[c] (**1g**) (98/2)
7	PhMeP(O)H		92 (87)[c] (**1h**) (100/0)
8	Ph(*t*-Bu)P(O)H		41 (39)[c] (**1i**) (100/0)
9	$Me_2P(O)H$		43 (41)[c] (**1j**) (100/0)
10	*n*-$Bu_2P(O)H$		81 (80)[c] (**1k**) (100/0)
11	$(cyclohexyl)_2P(O)H$		trace

[a] Reaction conditions: H-phosphine oxide (0.5 mmol), isocyanide (0.5−0.7 mmol), $Pd_2(dba)_3$ (2.5−5 mol % based on H-phosphine oxide) in toluene-d_8 (2.5 mL) at 60 °C, 12−24 h. [b] Determined by ^{31}P NMR. [c] Isolated yields.

By employing the reaction conditions of eq 2, the reaction of secondary phosphine oxides with isocyanides was investigated thoroughly (Table 1). In addition to the bulky $2,6\text{-}Me_2C_6H_3NC$, aromatic isocyanides, such as $4\text{-}(Et_2N)C_6H_3NC$, can also give high yield of **1b** with high selectivity. Aliphatic isocyanides also worked well. Thus cyclohexylisocyanide and 1,1,3,3-tetramethylbutylisocyanide produced the corresponding **1** in 90 and 74% yields with excellent selectivities, respectively (entries 2 and 3). As for aromatic secondary phosphine oxides, substrates with an electron-withdrawing group (CF_3, entry 4) or an electron-donating group (MeO, entry 6) on the benzene ring all gave high yields of the corresponding **1** with good selectivity. In addition to aromatic substrates, H-phosphine oxides bearing an aromatic and an aliphatic substituent (entries 7 and 8) or aliphatic H-phosphine oxides can also be employed (entries 9−11). It appears that steric factors determine the reactivity of these H-phosphine oxides. Thus, while PhMeP(O)H gave **1h** in 92% yield, the crowded Ph(*t*-Bu)P(O)H only produced **1i** in 41% yield. A similar phenomenon was observed with aliphatic H-phosphine oxides.[13] Thus, while $(n\text{-}Bu)_2P(O)H$

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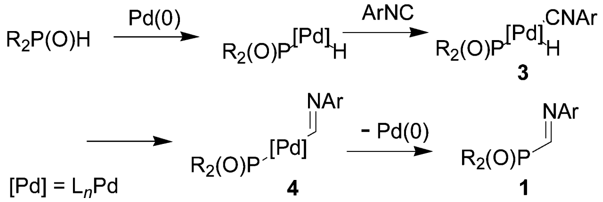
Table 2. Rh-Catalyzed Selective Addition of Secondary Phosphine Oxides to Isocyanides Forming **2**[a]

entry	R′$_2$P(O)H	catalyst	% yield of **2**[b]
1	Ph$_2$P(O)H	Rh(PPh$_3$)$_3$Cl	95 (**2a**)[d]
2	Ph$_2$P(O)H	Rh(PPh$_3$)$_3$Br	88 (**2a**)[d]
3	Ph$_2$P(O)H	Rh(PPh$_3$)$_3$I	69 (**2a**)[d]
4[c]	Ph$_2$P(O)H	Rh$_2$(cod)$_2$Cl$_2$	94 (**2a**)[d]
5	Ph$_2$P(O)H	RhCl$_3$	0 (**2a**)
6	(4-CF$_3$C$_6$H$_4$)$_2$P(O)H	Rh$_2$Cl$_2$cod$_2$	68 (**2b**)[d]
7	(4-ClC$_6$H$_4$)$_2$P(O)H	Rh(PPh$_3$)$_3$Cl	72 (**2c**)[d]
8	(4-MeOC$_6$H$_4$)$_2$P(O)H	Rh(PPh$_3$)$_3$Cl	47 (**2d**)[d]

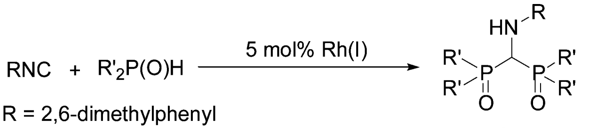
[a] Reaction conditions: H-phosphine oxide (1.0 mmol), isocyanide (0.5 mmol), Rh(I) (5 mol % based on isocyanide) in toluene (2.5 mL) at 80 °C, 4 days. [b] Determined by ^{31}P NMR. [c] At 60 °C. [d] Isolated yields: entry 1, 92%; entry 6, 65%; entry 7, 71%; entry 8, 43%.

Scheme 1. A Proposed Pathway for the Addition of R$_2$P(O)H to Isocyanides Forming α-Iminophosphine Oxides **1** (ligands on Pd were omitted for clarity)



gave 81% yield of **1k**, the bulky biscyclohexylphosphine oxide only produced a trace amount of **1** (<5% yield).

Remarkably, the minor 2:1 adduct of Ph$_2$P(O)H to isocyanide in eq 2 could be selectively generated by using rhodium catalysts.[12] Thus, under similar reaction conditions, when the catalyst Pd$_2$(dba)$_3$ in eq 2 was replaced with Rh(PPh$_3$)$_3$Cl (5 mol %), **2a** was predominantly formed in 41% yield based on Ph$_2$P(O)H (**1a**/**2a** = 1/41); although slowly, the yield of **2a** could increase to 95% after 4 days (eq 3 and entry 1 in Table 2). Under similar conditions, other rhodium(I), but not the rhodium(III), complexes also produce **2a** selectively (catalyst, yields of **2a**): Rh(PPh$_3$)$_3$Br, 88%; Rh(PPh$_3$)$_3$I, 69%; [Rh(cod)Cl]$_2$, 94%; RhCl$_3$, 0% (entries 2−5). Representative examples of the selective formation of **2** via the rhodium-catalyzed addition of aromatic phosphine oxides to 2,6-Me$_2$NC$_6$H$_3$NC are shown in Table 2 (entries 6−8). Alkylphosphine oxides, such as *n*-Bu$_2$P(O)H, only gave a trace amount of bisphosphinoylaminomethane **2** under similar conditions.



(3)

R = 2,6-dimethylphenyl

2

Although the detailed reaction mechanism remained to be clarified, we rationalized that the palladium-catalyzed addition perhaps proceeds via the oxidative addition of the P(O)−H bond of R$_2$P(O)H to Pd(0) to give a hydridopalladium **3**, which reacts with isocyanide to give **4** via the Pd−H addition.[14] Subsequent P−C bond-forming reductive elimination from **4** produced **1** with the regeneration of Pd(0) (Scheme 1).[14a,15,16]

In summary, we have successfully revealed the first highly selective palladium- and rhodium-catalyzed additions of secondary phosphine oxides to isocyanides, leading to α-iminophosphine oxides **1** and bisphosphinoylaminomethanes **2**, respectively. Studies on the reaction mechanism and applications to other H-phosphorus compounds are now in progress.

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

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(12) The reaction proceeded faster at an elevated temperature (100 °C, 90 min, 96% NMR yield of **1a**), though a trace amount of byproducts was detected. It was confirmed that noncatalytic additions of Ph$_2$P(O)H to **1a** can take place, and this may contribute to the formation of **2a** in eq 2 since, unlike its rhodium counterpart (eq 3), palladium does not catalyze this addition.

(13) Me$_2$P(O)H gave unidentified products, which may be partially due to the instability of this substrate.

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(16) The rhodium-catalyzed reaction was thought to proceed in a similar way (ref 14b). Although **4** has not been successfully isolated, our preliminary mechanistic study shows that a stoichiometric reaction of HPt[Ph$_2$P(O)][Ph$_2$P(OH)](PEt$_3$) with 2,6-Me$_2$C$_6$H$_4$NC generates a new signal at 9.8 ppm (J_{P-H} = 23.1 Hz, J_{Pt-H} = 115.9 Hz) in ^{1}H NMR spectroscopy, which may be assignable to [Ph$_2$P(O)]PtCH=NAr (the platinum analogue of **4**).

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