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Hydrophosphination of Propargylic Ethers with Diphenylphosphine in the Presence of LiHMDS, *N*-Heterocyclic Carbene, and $Ti(NMe_2)_4$

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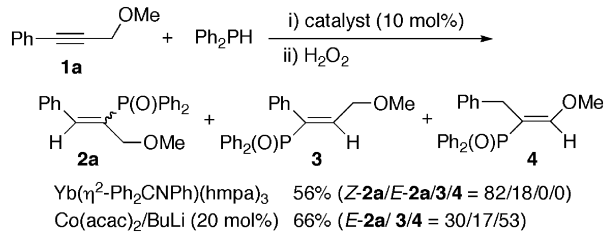
Regio- and stereoselective hydrophosphination of propargylic ethers with diphenylphosphine has been achieved using three-component catalyst, $LiN(SiMe_3)_2$/1,3-dimethylimidazol-2-ylidene/$Ti(NMe_2)_4$ (10 mol % of each).

Hydrophosphination, phosphinylation, and phosphonylation of alkynes have been frequently used for the synthesis of α,β-unsaturated phosphorus compounds, which are valuable materials as biologically active compounds, ligands, and synthetic reagents.[1] Promoters and catalysts for the reaction of trivalent hydrophosphines have been limited, compared with pentavalent phosphorus compounds.[2] Beside radical initiators, a few metal catalysts such as La,[3] Co,[4] Ni,[5] and Pd[5] have been reported for the hydrophosphination of unactivated alkynes. Moreover titanium phosphinidene complex, [Ti=PR], also catalyzes the reaction of diphenylacetylene with $PhPH_2$.[6] However, these catalysts are not always applicable to the reaction of a wide range of alkynes and thus a search for new catalysts has been continued. For example, hydrophosphination of propargylic alcohols and that of 1-alkynylphosphines succeeded using Ru[7] and Cu catalysts,[8] respectively.

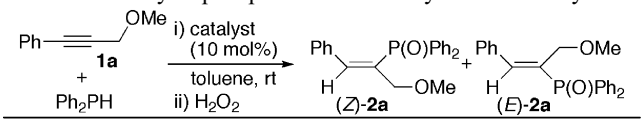
When we carried out the hydrophosphination of 3-methoxy-1-phenyl-1-propyne (**1a**) with Ph_2PH by Yb–imine catalyst,[3b] the expected product **2a** was formed in only 56% yields with a low stereoselectivity (Scheme 1). The sophisticated $Co(acac)_2$/BuLi catalyst[4] gave the three regioisomers, **2a**, **3**, and **4**, though with a perfect syn-selectivity. In order to overcome these limitations, we tested various catalysts for this reaction, and found that regio- and stereoselective hydrophosphination of propargylic ethers can be conducted under mild conditions by three-component catalyst, $LiN(SiMe_3)_2$/*N*-heterocyclic carbene/$Ti(NMe_2)_4$.[9] We report herein these results.

Surprisingly, treatment of propargylic ether **1a** with equimolar amounts of Ph_2PH in toluene at room temperature for 5 min in the presence of lithium hexamethyldisilazide (LiHMDS), 1,3-dimethylimidazol-2-ylidene (IMe), and $Ti(NMe_2)_4$ (10 mol % of each; catalyst **D**) gave the product **2a**



Scheme 1. Hydrophosphination of **1a** by the conventional catalysts.

Table 1. Hydrophosphination of **1a** by various catalyst[a]



Run	Catalyst	Time/h	Yield of **2a**[b]/%	*Z*/*E* ratio[b]
1	LiHMDS (**A**)	24	3	nd[c]
2	$Ti(NMe_2)_4$	24	8	nd[c]
3	IMes	24	5	nd[c]
4	$Ti(NMe_2)_4$/IMes	24	7	nd[c]
5	LiHMDS/$Ti(NMe_2)_4$ (**B**)	24	81	95/5
6	LiHMDS/IMe (**C**)	30 min	91	83/17
7	LiHMDS/IMe/$Ti(NMe_2)_4$ (**D**)	5 min	97	97/3

[a]Reaction conditions: **1a** (1 mmol), Ph_2PH (1 mmol), and toluene (1 mL). [b]Determined by ^1H NMR. [c]Not determined.

in 97% yield with a *Z*/*E* ratio of 97/3 after oxidative work-up (Table 1, Run 7). Toluene solvent can be substituted by cyclohexane, but THF and MeCN slightly decreased the yield and stereoselectivity. Then, the reaction was repeated under similar conditions using one or two components of **D** to investigate which one really contribute to the good performance. The reaction with LiHMDS alone (catalyst **A**) afforded **2a** in very low yields (Run 1). Similarly, isolated 1,3-dimesitylimidazol-2-ylidene (IMes),[10] $Ti(NMe_2)_4$, and their mixture (1/1) showed nearly no catalyst activity (Runs 2–4). In contrast, the reaction using a mixed catalyst of the LiHMDS and $Ti(NMe_2)_4$ (catalyst **B**) gave **2a** in 81% yield (*Z*/*E* = 95/5), although longer reaction time was necessary (Run 5). A complex of the LiHMDS and IMe (catalyst **C**) reduced the reaction period and resulted in good yield (91%), but the *Z*/*E* ratio decreased to 83/17 (Run 6). Similar effects were confirmed in the reaction of 1-(4-chlorophenyl)-3-methoxy-1-propyne (**1j**) using the four catalysts **A**–**D**. Based on these results, it is apparent that all individual components of **D** take part in the reaction, and efficiency and selectivity decrease drastically by lack of one or two catalytic components, vide infra.

Next, hydrophosphination of various propargylic ethers was carried out with the three-components catalyst **D** (Table 2). Substitution of the methyl ether moiety by other protecting groups like *t*-butyldimethylsilyl, benzyl, and 2-tetrahydropyranyl ethers did not affect the reaction efficiency to give the products **2b**–**2d** in high yields with nearly perfect *Z*-stereoselectivity (Runs 2–4). The alkyne **2e** having methoxymethyl substituent, which has been known as a good substrate for carbolithiation of alkyne,[11] showed inferior results (Run 5). Both

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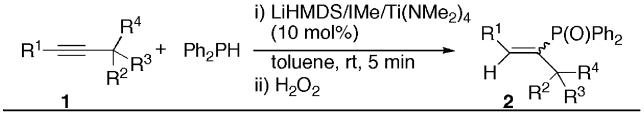
Table 2. Hydrophosphination of various propargylic alkynes by the three-component catalyst **D**[a]



Run	Propargylic ether					2	Yield[b] /%	Z/E ratio[b]
	1	R_1	R_2	R_3	R_4			
1	**1a**	Ph	H	H	OMe	**2a**	97	97/3
2	**1b**	Ph	H	H	OTBDMS	**2b**	98	99/1
3	**1c**	Ph	H	H	OBn	**2c**	96	98/2
4	**1d**	Ph	H	H	OTHP	**2d**[c]	95	95/5
5[d]	**1e**	Ph	H	H	MOM	**2e**	43	83/17
6	**1f**	2-MeC_6H_4	H	H	OMe	**2f**	95	99/1
7	**1g**	4-MeC_6H_4	H	H	OMe	**2g**	98	99/1
8	**1h**	4-MeOC_6H_4	H	H	OMe	**2h**	98	99/1
9	**1i**	2-ClC_6H_4	H	H	OMe	**2i**	99	96/4
10	**1j**	4-ClC_6H_4	H	H	OMe	**2j**	98	97/3
11	**1k**	4-BrC_6H_4	H	H	OMe	**2k**	95	94/6
12[e]	**1l**	Ph	Et	H	OMe	**2l**	86	77/23
13[f]	**1m**	Ph	Me	Me	OMe	**2m**	91	95/5

[a]Reaction conditions: **1** (1 mmol), Ph_2PH (1 mmol), and toluene (1 mL). [b]Determined by ^1H NMR. [c]Isolated as 2-diphenylphosphinyl-3-phenyl-2-propen-1-ol (**2d′**). [d]Reaction was carried out at 100 °C for 24 h. [e]Reaction period was 3 h. [f]Reaction period was 6 h.

electron-donating and -withdrawing aromatic alkynes gave exclusively the *Z*-alkenylphosphine oxides **2f**–**2k** in quantitative yields (Runs 6–11). Secondary and tertiary propargylic ethers **1l** and **1m** gave satisfactory product yields, though longer reaction time was necessary to complete the reaction and stereoselectivity was decreased in the former case (Runs 12 and 13). Unfortunately, merits of the three-component catalyst **D** did not appear in the reaction of 1-phenyl-1-propyne, wherein 2-diphenylphosphinyl-1-phenyl-1-propene was obtained in similar yields and selectivities (ca. 60%, $Z/E = 70/30$) with the catalysts **B**–**D**.

In spite of the good performance of the catalyst **D**, the role of the individual component is unclear. Thus, in order to get some information on the active species generated in situ, NMR tube reaction of Ph_2PH with equimolar amounts of **A**–**D** was carried out in THF and measured by ^{31}P NMR (Figure 1). Treatment with LiHMDS (**A**) changed a signal of Ph_2PH at −40 ppm to the broad one of the aggregated Ph_2PLi at −26 ppm. With LiHMDS/$Ti(NMe_2)_4$ (**B**), a sharp signal appeared at −19 ppm in addition to the broad one. Because the sharp signal was only observed in the presence of $Ti(NMe_2)_4$, it may be assignable to the titanium phosphido species. With LiHMDS/IMe (**C**), the broad signal of Ph_2PLi shifted to lower field at −22 ppm probably because of the coordination of IMe to Li cation. On the treatment with the three component catalyst **D**, two signals were observed at −22 and −19 ppm. Combining the results shown above and those given in Table 1, it is likely that the two phosphido species appearing at −22 and −19 ppm are responsible for the fast reaction rate and high stereoselectivity, respectively, that is, the *N*-heterocyclic carbene seems to act as an activator of the Ph_2PLi nucleophile, and $Ti(NMe_2)_4$ as a controller of the stereochemistry.

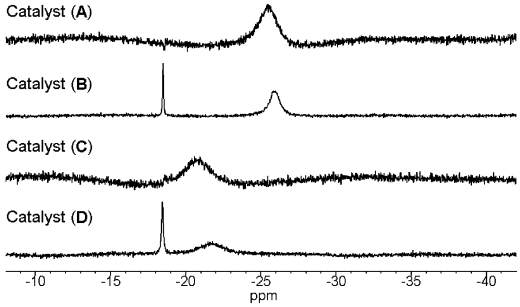


Figure 1. ^{31}P NMR spectra of the mixture of Ph_2PH and the catalysts **A**–**D**.

In summary, we have demonstrated regio- and stereoselective hydrophosphination of propargylic ethers with Ph_2PH by use of the three-component catalyst, LiHMDS/*N*-heterocyclic carbene/$Ti(NMe_2)_4$.[12] Further studies on mechanistic aspects and scope and limitation are in progress.

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