Functionalization of Alkynes Catalyzed by *t*-Bu-P4 Base

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Abstract: The addition of O- and N-nucleophiles to alkynes catalyzed by a phosphazene base, *t*-Bu-P4 base, was investigated. Alkynes were easily transformed to enol ethers and enamines in DMSO by the addition of nucleophiles. When phenylacetylene was reacted with diisopropylamine, a unique head-to-head dimerization of phenylacetylene was observed to give the enyne derivative. Terminal proton of phenylacetylene was also catalytically activated by *t*-Bu-P4 base to generate the acetylide anion which was reacted with carbonyl compounds to give phenylpropargylic alcohol derivatives.

Keywords: alkynes; enamines; nucleophilic addition; organic catalysis; phosphazenes; propargyl alcohols

The addition of O- and N-nucleophiles to a carbon-carbon triple bond is one of the important methods for the synthesis of enol ethers and enamines, which represent useful building blocks in organic synthesis. Although various methodologies have been investigated for the transformation, the use of organic catalysts seems to have not been well explored in this area. Conventionally metallic bases and various metal catalysts have been examined for catalytic additions.[1] Recently Knochel reported that CsOH-H_2O is an excellent catalyst for the addition of alcohols and secondary aromatic amines to phenylacetylene in NMP leading to enol ethers and enamines.[2] In terms of the yield, efficiency, and simplicity, the addition in the presence of a metallic catalyst system seems to be making great progress. However, the further development of new catalyst systems, especially of organic catalyst systems, is still considered to be an important subject.

On the other hand, the phosphazene bases developed by Schwesinger are extremely strong, uncharged, metal-free bases.[3] The *t*-Bu-P4 base deprotonates alcohols to give alkoxides and a huge soft cation which is suggested to have its positive charge delocalized over a volume of *ca.* 500 Å.[4] The *t*-Bu-P4 base has been found to generate anionic species of extraordinary reactivity, allowing conversions that have otherwise been difficult.[5] In connection with our recent work on deprotonative functionalization of aromatics with *t*-Bu-P4 base,[6] we became interested in the catalytic use of the phosphazene base for various transformations of alkynes.

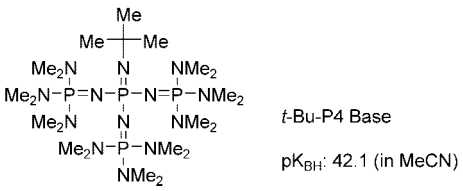
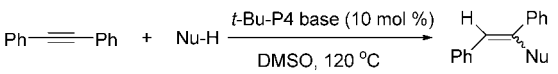


Figure 1. Structure of the *t*-Bu-P4 base.

In a preliminary experiment, a mixture of diphenylacetylene, *t*-Bu-P4 base (10 mol %), and methanol in various organic solvents was heated at 120 °C for 24 h, and the best result was obtained when DMSO was employed as a solvent. The enol ether was obtained in 99% yield as an *E,Z* mixture (50:50). Similarly, other alcohols were reacted with diphenylacetylene in the presence of *t*-Bu-P4 base (10 mol %) in DMSO. *n*-Butanol reacted with diphenylacetylene smoothly to give the enol ether in 99% yield (*E:Z* = 34:66). *n*-Hexanol reacted with diphenylacetylene to give the enol ether in 99% yield (*E:Z* = 26:74). The reaction with benzyl alcohol required a long time (120 h) to give the enol ether in 62% yield. As a secondary alcohol, isopropyl alcohol was also reacted to give the enol ether in 69%, however *t*-butyl alcohol did not add to diphenylacetylene under the same reaction conditions. Diphenylamine reacted smoothly with diphenylacetylene under the same reac-

Table 1. Addition of O- and N-nucleophiles to diphenylacetylene.



Entry	Nu	Time [h]	Yield [%]
1	MeO	24	99
2	n-C_4H_9O	24	99
3	n-$C_6H_{13}O$	24	99
4	$PhCH_2O$	120	62
5	*i*-PrO	48	70
6	Ph_2N	24	100
7	AcNMe	36	79
8	1-pyrrolyl	24	100

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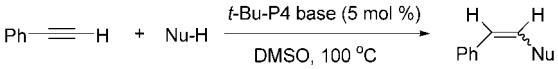
tion conditions to give the enamine in quantitative yield. *N*-Methylacetamide reacted with the alkyne to give the enamine in 79% yield. Pyrrole also reacted with the alkyne to give the *N*-alkenylpyrrole quantitatively.

Secondly, the reaction of a terminal acetylene with nucleophiles was examined. *n*-Butanol reacted with phenylacetylene in the presence of *t*-Bu-P4 base (5 mol %) smoothly to give the enol ether in 82% yield. The nucleophilic attack occurred at the β-carbon of the alkyne, and the product was an *E,Z*-isomeric mixture (*E:Z* = 16:84). The reaction with *n*-hexanol gave the enol ether in 79% yield (*E:Z* = 13:87), and benzyl alcohol gave the enol ether in 32% yield (*E:Z* = 20:80). A secondary alcohol, isopropyl alcohol, also reacted to give the enol ether in 73% (*E:Z* = 31:69). As for N-nucleophiles, diphenylamine reacted smoothly with diphenylacetylene under the same reaction conditions to give the enamine in 98% yield (*E:Z* = 27:73). *N*-Methylacetamide reacted with the alkyne to give the enamine in 65% yield (*E:Z* = 20:80). Pyrrole also reacted with the alkyne to give the *N*-alkenylpyrrole in 61% yield (*E:Z* = 8:92).

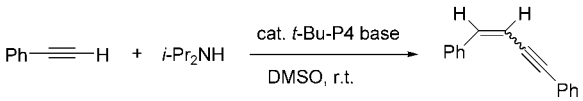
Table 2. Addition of O- and N-nucleophiles to phenylacetylene.



Entry	Nu	Time [h]	Yield [%]
1	*n*-C_4H_9O	12	82
2	*n*-$C_6H_{13}O$	12	79
3	$PhCH_2O$	24	32
4	*i*-PrO	6	73
5	Ph_2N	18	98
6	AcNMe	36	65
7	1-pyrrolyl	36	61

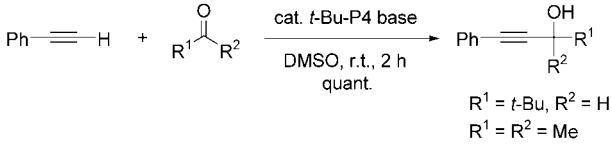
When phenylacetylene was reacted with diisopropylamine in the presence of the catalyst *t*-Bu-P4 base (*ca.* 30 mol %) in DMSO, the desired enamine was not obtained and the formation of the head-to-head enyne (66%, *E:Z* = 58:42) was observed. Conjugated enynes are important building blocks for organic synthesis and significant components in various biologically active compounds.[7] Catalytic dimerization of terminal alkynes is an atom economic and straightforward method for these compounds.[8] Various transition metal catalysts are known to catalyze the dimerization of terminal alkynes, but in most cases a mixture of regio- and stereoisomers was obtained.[9] *t*-Bu-P4 base is found to act as a unique organic catalyst for regioselective head-to-head dimerization of phenylacetylene. This observation indicates the *t*-Bu-P4 base can activate the terminal proton of phenylacetylene catalytically.

Intrigued by the above finding, we next focused our interest on the catalytic activation of the terminal proton



Scheme 1. Head-to head dimerization of phenyacetylene.

with *t*-Bu-P4 base toward the selective alkynylation of carbonyl compounds. The metal-catalyzed addition of terminal alkynes to carbonyl compounds that leads to propargyl alcohols has a considerable synthetic and industrial importance.[10] Conventionally bases such as an organolithium or organomagnesium reagent have been used stoichiometrically to generate an intermediate metal acetylide.[11] Knochel reported the exceptional activity of cesium hydroxide for the catalytic generation of highly reactive species.[12] However, the catalytic activation of an alkyne and subsequent addition to the carbonyl derivatives remain an important subject.[13] *t*-Bu-P4 base was examined for the catalytic activation and it was found that the reaction proceeded smoothly. Phenylacetylene was reacted with pivalaldehyde in the presence of cat. *t*-Bu-P4 base (*ca.* 30 mol %) at room temperature to give the propargylic alcohol in quantitative yield. Similarly, the reaction with acetone also proceeded quantitatively to give the alcohol.



Scheme 2. 1,2-Addition of phenylacetylene to carbonyl compounds.

In conclusion, the catalytic functionalization of alkynes was accomplished by using the addition of O- and N-nucleophiles to alkynes in the presence of *t*-Bu-P4 base catalyst. Unique head-to-head dimerization of phenylacetylene was also catalyzed by *t*-Bu-P4 base. The catalytic activation of the terminal proton by *t*-Bu-P4 base also allows the facile alkynylation of carbonyl compounds. Further investigations to survey the scope and limitation of these catalytic reactions using *t*-Bu-P4 base are in progress.

Experimental Section

Typical Procedure for the Reaction of Diphenylacetylene with Methanol in the Presence of *t*-Bu-P4 Base

Under an argon atmosphere, a mixture of diphenylacetylene (51.7 mg, 0.5 mmol), MeOH (0.06 mL, 1.5 mmol), *t*-Bu-P4 base (1 M solution in hexane, 0.05 mL, 0.05 mmol), and DMSO (0.5 L) was stirred at 120 °C for 24 h. After the reaction,

saturated aqueous NH_4Cl was added to the mixture, and the mixture was extracted with $CHCl_3$. The organic layer was dried over $MgSO_4$ and the solvent was removed under reduced pressure. The residue was purified by SiO_2 column chromatography using *n*-hexane as an eluent to give 1-methoxy-1, 2-diphenylethane as a mixture of *E*- and *Z*-isomers (50:50). ^1H NMR (300 MHz, $CDCl_3$, TMS): δ (*Z*-isomer) = 3.70 (s, 3H), 6.10 (s, 1H), 7.21–7.73 (m, 10H); δ (*E*-isomer) = 3.81 (s, 3H), 5.83 (s, 1H), 6.95–7.13 (m, 5H); IR (neat): ν = 3022, 2829, 1636, 1600, 1235, 1198, 1119, 729, 693 cm^{-1}; MS: *m/z* = 210 (M^+).

Typical Procedure for the Reaction of Phenylacetylene with Acetone in the Presence of *t*-Bu-P4 Base

Under an argon atmosphere, a mixture of phenylacetylene (31.1 mg, 0.3 mmol), acetone (0.04 mL, 0.5 mmol), *t*-Bu-P4 base (1 M solution in hexane, 0.1 mL, 0.1 mmol), and DMSO (0.5 mL) was stirred at 120 °C for 24 h. After the reaction, saturated aqueous NH_4Cl was added to the mixture, and the mixture was extracted with $CHCl_3$. The organic layer was dried over $MgSO_4$ and the solvent was removed under reduced pressure. The residue was purified by SiO_2 column chromatography using hexane-AcOEt (10:1) as an eluent to give 2-methyl-4-phenyl-but-3-yn-2-ol. ^1H NMR (300 MHz, $CDCl_3$, TMS): δ = 1.59 (s, 1H), 1.63 (s, 6H), 7.26–7.31 (m, 3H), 7.40–7.44 (m, 2H); IR (neat): ν = 3350, 2981, 1490, 1160, 960, 754, 689 cm^{-1}; MS: *m/z* = 160 (M^+).

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