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Synthetic methodology using tertiary phosphines as nucleophilic catalysts*

Xiyan Lu[‡], Yishu Du, and Cheng Lu

State Key Laboratory of Organometallic Chemistry, Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, 354 Fenglin Lu, Shanghai 200032, China

Abstracts: Allenoates or 2-alkynoates are known to react with tertiary phosphines to form the phosphine-substituted 1,3-dipoles, which can react with various substrates with the simultaneous elimination of the tertiary phosphine. The reaction is catalytic to the tertiary phosphine used. The investigation of the appropriate dipolarophiles and the further extension of this reaction are discussed.

Keywords: Tertiary phosphines; nucleophilic catalysts; allenoates; dipolarophiles; synthetic methodology.

INTRODUCTION

Allenoates or 2-alkynoates are known to react with tertiary phosphines to form the phosphine-substituted 1,3-dipoles, which can react with various substrates with the simultaneous elimination of the tertiary phosphine. Recently, some important reactions were discovered in the phosphine-catalyzed reaction of 2,3-butadienoates or 2-butynoates [1], such as isomerization [2], α -addition [3], γ -addition [4], and [3+2] cycloaddition [5] (Scheme 1). Herein, we wish to report the new synthetic methodology using tertiary phosphines as nucleophilic catalysts developed in our laboratory.

HIGHLY REGIOSELECTIVE CONSTRUCTION OF SPIROCYCLES [6,7]

We envisioned that an efficient entry to spiro carbocycles might be achieved by the application of our developed method of the phosphine-catalyzed [3+2] cycloaddition reaction [8]. To initiate our studies, a solution of 2-methylene-3,4-dihydro-2H-naphthalen-1-one (1a) (1.0 mmol) and ethyl 2,3-buta-dienoate (2) (1.2 mmol) in dry toluene (10 mL) was treated with Ph₃P (10 mol %) at room temperature for 11 h. Two regioisomers were obtained in total yield of 93 % with moderate selectivity (3a:4a = 79:21) (Scheme 2).

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[‡]Corresponding author

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$$R_3P \oplus E$$
 $R_3P \oplus E$
 $R_3P \oplus E$

Scheme 1

Scheme 2

Under similar conditions as shown in Scheme 2, other exo-methylenecycles underwent addition of ethyl 2,3-butadienoate to obtain regioisomeric spirocycles in total yields of 28-98% with low to moderate selectivity (3:4 = 58:42 to 84:16) (Scheme 3) [6]. The regioselectivity of the reaction was greatly improved by introducing a bulky group into the 2,3-butadienoate. When tert-butyl 2,3-butadienoate (5) was used as a three-carbon synthon instead of ethyl 2,3-butadienoate, the reaction proceeded smoothly to afford spirocycles 6 and 7 in high yields (63-99 %) with moderate to high selectivities (6:7 = 74:26 to 95:5) (Scheme 3) [6].

Scheme 3

The great enhancement of the regioselectivity by introducing a bulky group into the 2,3-butadienoate might be rationalized by comparing the transition states **A** and **B** of the reaction. The higher energy will occur in **B** due to the steric influence of the bulky group (E) with the skeleton of C2 components, making products **3** or **6** more preferable (Scheme 4) [6].

Scheme 4

When *tert*-butyl 2-butynoate (**8**) was used instead of *tert*-butyl 2,3-butadienoate (**5**) in the tributylphosphine-catalyzed [3+2] cycloaddition reaction, the regioselectivity was further improved in some cases (>97:3). Especially, improved high regioselectivities were observed for the simple α -methylene-cycloalkanones (entries 6–7, **6**:7 = 89:11 to 92:8) (Scheme 5) [6], which were of considerable interest as a synthetic route to naturally occurring spiro[4.5]decane sesquiterpenes and spiro[4.4]nonanes.

A highly efficient approach to construct the skeleton of *cis*-spirovetivanes, via a phosphine-catalyzed [3+2] cycloaddition reaction was developed. The utility of this method was exemplified by the first total synthesis of natural product (–)-hinesol **9** (Scheme 6) [7], which features a rapid and efficient construction of the spiro carbocyclic skeleton.

Scheme 5

$$(-)$$
-hinesol 9 COOR $(-)$ -cis-spirovetivanes $(-)$ -hinesol $(-)$ -hines

Scheme 6

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CATALYTIC REACTION OF CARBON-PHOSPHORUS YLIDE [9]

The major reason for the success of the phosphine-catalyzed isomerization, α -, γ -addition and [3+2] cycloaddition of electron-deficient allenes or alkynes, was ascribed to the presence of electron-with-drawing groups, which facilitated the nucleophilic additions and the elimination of phosphines to complete the catalytic cycles [1a]. With this in mind, it was thought that phosphine-catalyzed reactions might be realized via a modified allylic phosphorus ylide **12** (Scheme 7). Thus, a novel phosphine-catalyzed annulation reaction of modified allylic compounds with electron-deficient alkenes was developed (Scheme 8) [9].

Scheme 7

Scheme 8

To initiate our study, phosphonium salt **18**, compound **19**, and potassium carbonate in toluene were stirred at 90 °C, affording an adduct **20** in 74 % yield and triphenylphosphine (Scheme 9). Since phosphonium salt **18** was prepared from ethyl 2-bromomethyl-2-propenoate (**21**) and triphenylphosphine, it was expected that the above reaction might occur starting from **21** by utilizing a catalytic amount of triphenylphosphine. The result showed that the phosphine-catalyzed annulation reaction of the ylides did proceed (Scheme 9), implying that a novel catalytic ylide reaction is possible to occur [9].

The scope of this novel ylide reaction with respect to the C_2 and C_3 components was also investigated. Further investigation revealed that the key intermediate (ylide 12) of this novel catalytic annulation reaction of the ylides could be generated not only from the corresponding bromides 13 but also from the acetates 14 (Scheme 7). We also found that the reaction could be modified from heterogeneous conditions to homogeneous conditions by using *tert*-butyl carbonate 15 from which the *tert*-butoxide anion was generated as a base in situ (Scheme 7) [9].

Scheme 9

TANDEM REACTIONS TO CONSTRUCT HETEROCYCLES [10]

Tandem reactions involving the umpolung addition and the conjugate addition of a bifunctional nucleophile to an electron-deficient alkyne or allene catalyzed by triphenylphosphine were developed [10]. If a bifunctional nucleophile was used in the addition reaction with an electron-deficient alkyne or allene, the resulting umpolung adduct would have not only a nucleophilic center, but also an electrophilic center (the electron-deficient double bond) required for an intramolecular conjugate addition, implying that the heterocycles could be formed by the phosphine-catalyzed tandem reactions (Scheme 10) [10].

Scheme 10

Reaction of 1,3-dicarbonyl compounds with electron-deficient allenes catalyzed by triphenylphosphine afforded the dihydrofuran derivatives with good yields. Electron-deficient alkynes, synthetically equivalent to the electron-deficient allenes in the phosphine-catalyzed umpolung addition reactions [1a], were subject to the similar reaction condition and gave the cyclized products with good to excellent yield. Reaction of bifunctional nitrogen-nucleophile 1,2-bis(p-toluenesulfonylamino) ethane with electron-deficient alkynes afforded the piperazine derivatives in good to excellent yields. When the nitrogen-oxygen bifunctional nucleophile, 2-(p-toluenesulfonylamino) ethanol was used, morpholine derivatives were obtained in moderate yields. Tandem α - and β -additions were also realized by the reaction of 1-hexyn-3-one or ethyl propiolate with the bifunctional nucleophile. It is noteworthy that the seven-membered heterocycle, a diazepane derivative, was also obtained in high yield using this strategy [10].

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