

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: Allenates 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; allenates; dipolarophiles; synthetic methodology.

INTRODUCTION

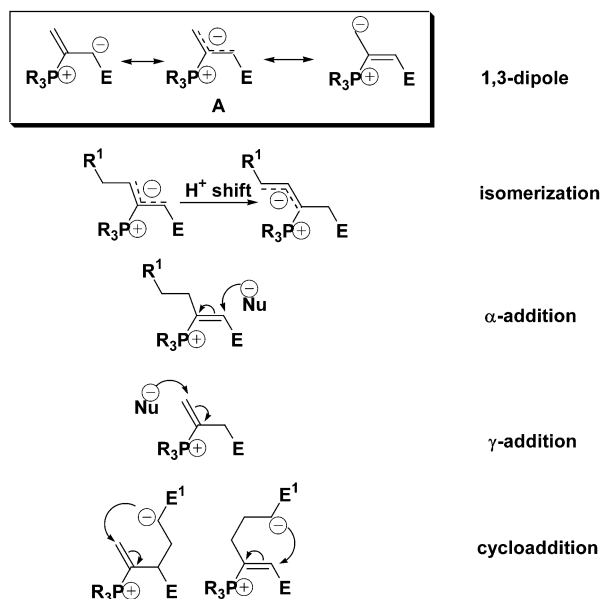
Allenates or 2-alkynoates are known to react with tertiary phosphines to form the phosphine-substituted 1,3-dipoles, which can react with various substrates with the simultaneous elimination of the tertiary phosphine. Recently, some important reactions were discovered in the phosphine-catalyzed reaction 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]

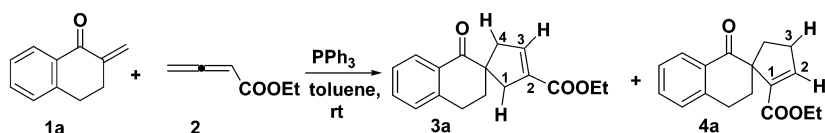
We envisioned that an efficient entry to spiro carbocycles might be achieved by the application of our developed method of the phosphine-catalyzed [3+2] cycloaddition reaction [8]. To initiate our studies, a solution of 2-methylene-3,4-dihydro-2*H*-naphthalen-1-one (**1a**) (1.0 mmol) and ethyl 2,3-butadienoate (**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).

*Paper based on a presentation at the 7th IUPAC International Conference on Heteroatom Chemistry (ICHAC-7), Shanghai, China, 21–25 August 2004. Other presentations are published in this issue, pp. 1985–2132.

[‡]Corresponding author

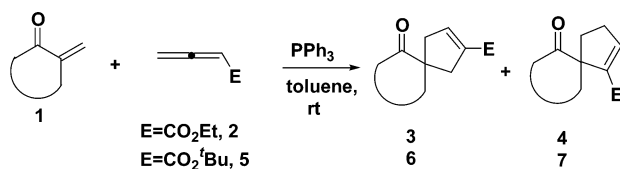


Scheme 1



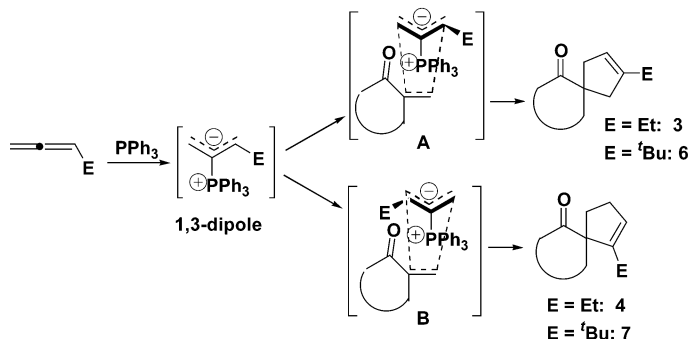
Scheme 2

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

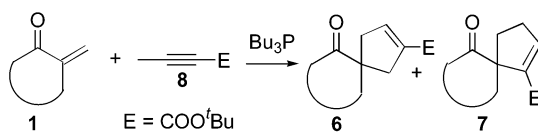
The great enhancement of the regioselectivity by introducing a bulky group into the 2,3-butadienoate might be rationalized by comparing the transition states **A** and **B** of the reaction. The higher energy will occur in **B** due to the steric influence of the bulky group (E) with the skeleton of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



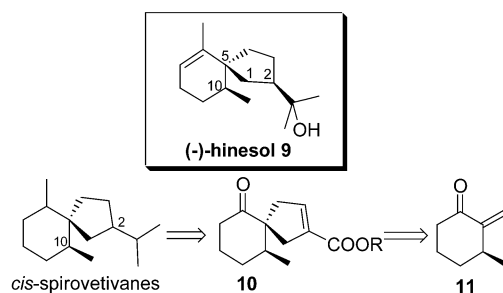
Scheme 4

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



Scheme 6

ACKNOWLEDGMENTS

We thank the Major State Basic Research Program (Grant G20000077502-A). We also thank the National Natural Sciences Foundation of China (29972048, 20072045) and Chinese Academy of Sciences for financial support.

REFERENCES

1. For a recent account on phosphine-catalyzed reactions, see: (a) X. Lu, C. Zhang, Z. Xu. *Acc. Chem. Res.* **34**, 535 (2001); for recent reports on phosphine-catalyzed reactions, see: (b) S. A. Frank, D. J. Mergott, W. R. Roush. *J. Am. Chem. Soc.* **124**, 2404 (2002); (c) L.-C. Wang, A. L. Luis, K. Agapiou, H.-Y. Jang, M. J. Krische. *J. Am. Chem. Soc.* **124**, 2402 (2002); (d) C.-K. Jung, J.-C. Wang, M. J. Krische. *J. Am. Chem. Soc.* **126**, 4418 (2004).
2. B. M. Trost and U. Kazmaier. *J. Am. Chem. Soc.* **114**, 7933 (1992); (b) C. Guo and X. Lu. *J. Chem. Soc., Chem. Commun.* 394 (1993); (c) C. Guo and X. Lu. *J. Chem. Soc., Perkin Trans. 1* 1921 (1993).
3. B. M. Trost and G. R. Dake. *J. Am. Chem. Soc.* **119**, 7595 (1997).
4. (a) B. M. Trost and C.-J. Li. *J. Am. Chem. Soc.* **116**, 3167 (1994); (b) B. M. Trost and C.-J. Li. *J. Am. Chem. Soc.* **116**, 10819 (1994); (c) C. Zhang and X. Lu. *Synlett* 645 (1995); (d) B. M. Trost and G. R. Dake. *J. Org. Chem.* **62**, 5670 (1997).
5. C. Zhang and X. Lu. *J. Org. Chem.* **60**, 2906 (1995); (b) Z. Xu and X. Lu. *Tetrahedron Lett.* **38**, 3461 (1997); (c) G. Zhu, Z. Chen, Q. Jiang, D. Xiao, P. Cao, X. Zhang. *J. Am. Chem. Soc.* **119**, 3836 (1997); (d) Z. Xu and X. Lu. *J. Org. Chem.* **63**, 5031 (1998); (e) Z. Xu and X. Lu. *Tetrahedron Lett.* **40**, 549 (1999).
6. Y. Du, X. Lu, Y. Yu. *J. Org. Chem.* **67**, 8901 (2002).
7. Y. Du and X. Lu. *J. Org. Chem.* **68**, 6463 (2003).
8. Recently, some spiro heterocycles were constructed by Pyne's group using the phosphine-catalyzed [3+2] cycloaddition reaction. See: (a) S. G. Pyne, K. Schafer, B. W. Skelton, A. H. White. *Chem. Commun.* 2267 (1997); (b) A. T. Ung, K. Schafer, K. B. Lindsay, S. G. Pyne, K. Amornraksa, R. Wouters, I. Van der Linden, I. Biesmans, I. A. S. J. Lesage, B. W. Skelton, A. H. White. *J. Org. Chem.* **67**, 227 (2002).
9. Y. Du, X. Lu, C. Zhang. *Angew. Chem., Int. Ed.* **42**, 1035 (2003).
10. C. Lu and X. Lu. *Org. Lett.* **4**, 4677 (2002).