

A Phosphine-Catalyzed [3 + 2] Annulation Reaction of Modified Allylic Compounds and *N*-Tosylimines

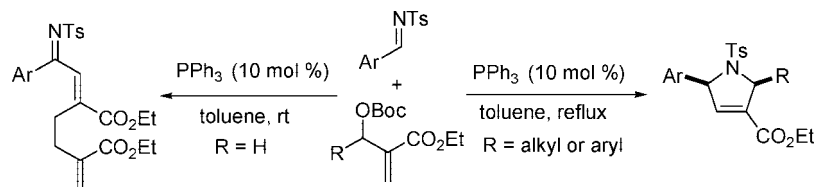
Suqing Zheng and Xiyan Lu*

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

xylu@mail.sioc.ac.cn

Received July 23, 2008

ABSTRACT



A phosphine-catalyzed annulation of modified allylic ylides with various aromatic imines to form 3-pyrrolines was developed. The presence of a substituent in the allylic compound is crucial for this reaction. Without the substituent, (*E*)-dienylimines will be produced via the dimerization of the allylic compounds.

Reports of phosphines as nucleophilic catalysts in the reaction of alkynoates or allenates have grown significantly.^{1,2} Recently, we developed phosphine-catalyzed [3 + 2] and [3 + 6] annulation reactions of carbon–phosphorus ylides with electron-deficient olefins.³

In these reactions, simple allylic compounds, which can be easily obtained by one-step transformation from the product of the Morita–Baylis–Hillman reaction, were used as the three-carbon unit instead of the alkynoates or allenates. Compared with alkynoates or allenates, the allylic compounds have some special reactivities, which stimulated us to explore the new reaction with other kinds of electrophiles.

3-Pyrrolines are a class of compounds, generally used as intermediates for the synthesis of five-membered nitrogen-containing heterocyclic natural products and pharmaceutical compounds.⁴ Among the numerous known methodologies, the [3 + 2] cycloaddition provides the most versatile method for the formation of pyrrolines.⁵ Recently, there are many reports related to the phosphine-catalyzed [3 + 2] annulation reaction of 2,3-butadienoates or 2-butyneates with *N*-tosylimines to form pyrrolines (Scheme 1).^{2,6} Herein, we wish to report the reaction of allylic compounds with *N*-tosylimines under the catalysis of a tertiary phosphine.

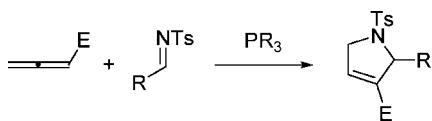
(1) For reviews on phosphine-catalyzed reactions, see: (a) Methot, J. L.; Roush, W. R. *Adv. Synth. Catal.* **2004**, *346*, 1035. (b) Lu, X.; Zhang, C.; Xu, Z. *Acc. Chem. Res.* **2001**, *34*, 535.

(2) Recent reports on phosphine-catalyzed reactions, see: (a) Wurz, R. P.; Fu, G. C. *J. Am. Chem. Soc.* **2005**, *127*, 12234. (b) Wilson, J. E.; Fu, G. C. *Angew. Chem., Int. Ed.* **2006**, *45*, 1426. (c) Virieux, D.; Guillouze, A.-F.; Cristau, H.-J. *Tetrahedron* **2006**, *62*, 3710. (d) Jean, L.; Marinetti, A. *Tetrahedron Lett.* **2006**, *47*, 2141. (e) Nair, V.; Biju, A. T.; Mohanan, K.; Suresh, E. *Org. Lett.* **2006**, *8*, 2213. (f) Lu, X.; Lu, Z.; Zhang, X. *Tetrahedron* **2006**, *62*, 457. (g) Scherer, A.; Gladysz, J. A. *Tetrahedron Lett.* **2006**, *47*, 6335. (h) Mercier, E.; Fonovic, B.; Henry, C. E.; Kwon, O.; Dudding, T. *Tetrahedron Lett.* **2007**, *48*, 3617. (i) Castellano, S.; Fijji, H. D. G.; Kinderman, S. S.; Watanabe, M.; de Leon, P.; Tamanoi, F.; Kwon, O. *J. Am. Chem. Soc.* **2007**, *129*, 5843. (j) Wallace, D. J.; Sidda, R. L.; Reamer, R. A. *J. Org. Chem.* **2007**, *72*, 1051. (k) Henry, C. E.; Kwon, O. *Org. Lett.* **2007**, *9*, 3069. (l) Cowen, B. J.; Miller, S. J. *J. Am. Chem. Soc.* **2007**, *129*, 10988. (m) Tran, Y. S.; Kwon, O. *J. Am. Chem. Soc.* **2007**, *129*, 12632. (n) Sriramurthy, V.; Barcan, G. A.; Kwon, O. *J. Am. Chem. Soc.* **2007**, *129*, 12928. (o) Creech, G. S.; Kwon, O. *Org. Lett.* **2008**, *10*, 429. (p) Fang, Y.-Q.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2008**, *130*, 5660.

(3) (a) Du, Y.; Lu, X.; Zhang, C. *Angew. Chem., Int. Ed.* **2003**, *42*, 1035. (b) Du, Y.; Feng, J.; Lu, X. *Org. Lett.* **2005**, *7*, 1987. (c) Feng, J.; Lu, X.; Kong, A.; Han, X. *Tetrahedron* **2007**, *63*, 6035.

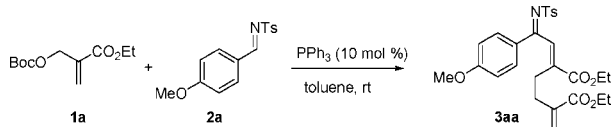
(4) (a) Green, M. P.; Prodger, J. C.; Hayes, C. J. *Tetrahedron Lett.* **2002**, *43*, 6609. (b) Huwe, C. M.; Blechert, S. *Tetrahedron Lett.* **1995**, *36*, 1621. (c) Burley, I.; Hewson, A. T. *Tetrahedron Lett.* **1994**, *35*, 7099.

Scheme 1. [3 + 2] Reaction of Methyl 2,3-Butadienoate with *N*-Tosylimines



To initiate our study, compound **1a** and imine **2a** were stirred in toluene at room temperature under 10 mol % of PPh₃ as the catalyst. Unfortunately, we did not obtain the product pyrroline as expected from the reaction of allenolate and *N*-tosylimine, but only (*E*)-dienylimine **3aa** was obtained in 62% yield (Scheme 2). The structure of compound **3aa**

Scheme 2



was confirmed by X-ray crystallography of the analogous compound **3ad** substituted with a *p*-bromophenyl group.⁷

Varying the ratio of **1a/2a** could not change the product to pyrroline. When the ratio of **1a/2a** was 2:1.5, the yield could be improved to 86% (Table 1, entry 2). Changing PPh₃ to the more nucleophilic phosphine PPh₂Et, the reaction also proceeded smoothly, but no product was obtained when the strong nucleophilic phosphine PBu₃ was used. The reaction proceeded smoothly in many solvents except polar solvents such as acetonitrile or DMF. Toluene was the best solvent.

The reaction could occur with various substituted *N*-tosylimines, and electron-donating group substituted *N*-tosylimines led to better yields (Table 2, entries 1 and 6).

In this reaction, highly substituted (*E*)-dienylimines could be obtained in one step. These compounds are useful in hetero-Diels–Alder reactions⁸ and can be used as intermediates for the synthesis of γ -amino acids.⁹ The synthetic utility of this reaction can be further demonstrated by the Al₂O₃-

Table 1. Effect of Phosphine Catalysts on the Formation of **3aa** from **1a** and **2a**^a

entry	catalyst (10 mol %)	1a/2a	yield ^b (%)
1	PPh ₃	2:1	73
2	PPh ₃	2:1.5	86
3	PPh ₃	1:1	62
4 ^c	PPh ₃	2:1.5	78
5	PBu ₃	2:1.5	— ^d
6	PPh ₂ Et	2:1.5	80

^a Reaction conditions: Under Ar, a mixture of **1a**, **2a**, and catalyst in toluene was stirred at room temperature for 2 days. ^b Isolated yields. ^c 20 mol % of PPh₃ was used. ^d Complicated products.

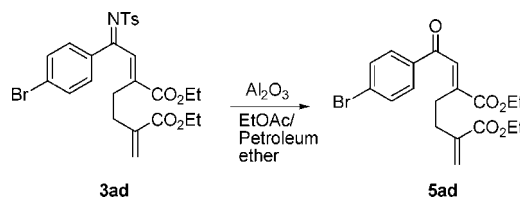
Table 2. Synthesis of **3** from **1a** and *N*-Tosylimines^a

entry	Ar	product	yield ^b (%)
1	<i>p</i> -MeOC ₆ H ₄ (2a)	3aa	86
2	<i>p</i> -MeC ₆ H ₄ (2b)	3ab	71
3	<i>p</i> -ClC ₆ H ₄ (2c)	3ac	78
4	<i>p</i> -BrC ₆ H ₄ (2d)	3ad	64
5	C ₆ H ₅ (2e)	3ae	63
6		3af	90

^a Reaction conditions: Under Ar, a mixture of **1a** (0.20 mmol), **2** (0.15 mmol), and PPh₃ (0.02 mmol) in toluene was stirred at room temperature for 2 days. ^b Isolated yields.

mediated hydrolysis of the imino group to ketone **5ad** (Scheme 3).

Scheme 3



A possible mechanism for this unexpected phosphine-catalyzed reaction is proposed (Scheme 4). The phosphine reacted with modified allylic compound **1a** to form the phosphonium salt **A**. The in situ generated *tert*-butoxide anion deprotonated this salt to afford ylide **B** which was added to another molecule of **1a** to produce **C**. **C** was deprotonated by the in situ generated *tert*-butoxide again to give ylide **D**. The ylide **D** was added to the imine **2** to produce **E**. After hydrogen transfer, **E** was changed to **F**

(5) (a) Padwa, A. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon: New York, 1991; Vol. 4, p 1069. (b) Wade, P. A. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon: New York, 1991; Vol. 4, p 1111. (c) Confalone, P. N.; Huie, E. M. *Org. React.* **1988**, 36, 1. (d) Pearson, W. H. In *Studies in Natural Products Chemistry*; Rahman, A. U., Ed.; Elsevier: Amsterdam, 1988; Vol. 1, p 323. (e) Batia, B. A.; B. N.; Portnoy, M. *Heterocycles* **2006**, 67, 511. (f) Young, I. S.; Williams, J. L.; Kerr, M. A. *Org. Lett.* **2005**, 7, 953.

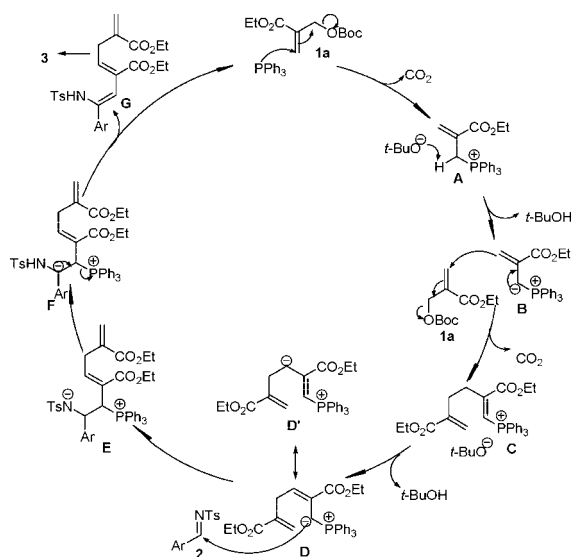
(6) (a) Xu, Z.; Lu, X. *Tetrahedron Lett.* **1997**, 38, 3461. (b) Xu, Z.; Lu, X. *J. Org. Chem.* **1998**, 63, 5031. (c) Zhu, X. F.; Henry, C. E.; Kown, O. *Tetrahedron* **2005**, 61, 6276.

(7) CIF files are included in the Supporting Information.

(8) (a) *Hetero Diels–Alder Methodology in Organic Synthesis*; Boger, D. L., Weinreb, S. M., Eds.; Academic Press: San Diego, 1987. (b) Boger, D. L.; Corbett, W. L.; Wiggins, J. M. *J. Org. Chem.* **1990**, 55, 2999. (c) Boger, D. L.; Corbett, W. L.; Curran, T. T.; Kasper, A. M. *J. Am. Chem. Soc.* **1991**, 113, 1713.

(9) (a) Juaristi, E. *Enantioselective Synthesis of β -Amino Acids*; Wiley-VCH: New York, 1997. (b) Gellman, S. H. *Acc. Chem. Res.* **1998**, 31, 17.

Scheme 4. Proposed Mechanism for the Formation of **3**



which afforded intermediate **G** by elimination of PPh_3 . Finally, **3** was formed by isomerization.

On the basis of the above mechanism, it was suggested that the reason why the reaction could not produce 3-pyrrolines might be due to the high reactivity of **1a** to add to another molecule of **1a** to obtain the dimerized intermediate **C**. It occurred to us that it is possible to facilitate the formation of 3-pyrrolines if the steric bulkiness of **1** is increased. To test the feasibility of this idea, **1b** (1.2 equiv), the phenyl-substituted analogue of **1a**, was used to react with imine **2e** (1 equiv) in refluxing toluene using PPh_3 (10 mol %) as the catalyst. Fortunately, product **4be** was isolated in 85% yield as a single isomer (Table 3, entry 4).

Many phosphines (Table 3) could catalyze this reaction, among which PPh_3 gave the best result. Solvents also were tested, and toluene still was the best solvent. The reaction was found to be general and to occur with different substituted *N*-tosylimines, providing the 2,5-disubstituted 3-pyrrolines in moderate to excellent yields (Table 4). Chloro- and bromo-substituted aryl *N*-tosylimines can afford nearly quantitative yields (Table 4, entries 3 and 4). *N*-Tosylimines with electron-donating aryl substituents gave lower yields (Table 4, entries 1 and 6).

To investigate the scope of this reaction, a variety of modified allylic *tert*-butyl carbonates were used to react with *N*-tosylimine **2e** (Table 5). For various aryl-substituted allylic *tert*-butyl carbonates, reactions could provide moderate yields (Table 5, entries 1–4), while alkyl-substituted allylic *tert*-butyl carbonates gave relatively poor results (Table 5, entries 5 and 6). The reaction of *tert*-butyl ester could also proceed very well (Table 5, entry 7). The *cis*-stereochemistry of these products was confirmed by X-ray crystallography of the analogous compound **4bc** substituted with a *p*-chlorophenyl group.⁷ Thus, this novel reaction potentially provides a new approach to the preparation of multifunctionalized 3-pyrrolines.

Table 3. Effect of Phosphine Catalysts on the Formation of Pyrroline **4be**^a

entry	catalyst (10 mol %)	temperature (°C)	yield ^b (%)
1	PPh_3	rt	—
2	PPh_3	80	12
3	PPh_3	110	72
4 ^c	PPh_3	110	85
5 ^d	PPh_3	110	73
6	PEtPh_2	rt	26
7 ^e	PEtPh_2	rt	47
8	PET_2Ph	rt	24
9 ^e	PET_2Ph	rt	40
10 ^e	P^iBu_3	rt	42

^a Reaction conditions: Under Ar, a mixture of **1b** (76 mg, 0.24 mmol), **2e** (51 mg, 0.2 mmol), and catalyst in toluene (1 mL) was stirred at the temperature indicated. ^b Isolated yields. ^c 2 mL of toluene was used. ^d **1b** (37 mg, 0.12 mmol) in toluene (0.5 mL) was added over 12 h with a syringe pump to a mixture of PPh_3 and **2e** (26 mg, 0.1 mmol) in toluene (0.5 mL) at 110 °C. The mixture was stirred further for 1 h. ^e 20 mol % of catalyst was used.

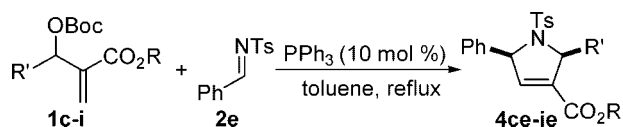
Table 4. Synthesis of 3-Pyrrolines from Various Imines^a

entry	Ar	product	yield ^b (%)
1	<i>p</i> -MeOC ₆ H ₄ (2a)	4ba	38
2	<i>p</i> -MeC ₆ H ₄ (2b)	4bb	75
3	<i>p</i> -ClC ₆ H ₄ (2c)	4bc	99
4	<i>p</i> -BrC ₆ H ₄ (2d)	4bd	98
5	C ₆ H ₅ (2e)	4be	85
6	(2f)	4bf	43
7	(2g)	4bg	85
8	<i>p</i> -CF ₃ C ₆ H ₄ (2h)	4bh	62
9 ^c	<i>p</i> -NO ₂ C ₆ H ₄ (2i)	4bi	75

^a Reaction conditions: Under Ar, a mixture of **1b** (0.24 mmol), **2** (0.2 mmol), and PPh_3 (0.02 mmol) in toluene (2 mL) was stirred at 110 °C. ^b Isolated yields. ^c 4 mL of toluene was used.

A plausible mechanism for this phosphine-catalyzed [3 + 2] annulation reaction of the substituted allylic compounds with *N*-tosylimines is proposed (Scheme 5). The reaction might be initiated by the formation of the phosphonium salt **A** via the addition of PPh_3 to **1b**. **A** was deprotonated by the in situ generated *tert*-butoxide anion affording ylide **B**. Subsequent nucleophilic addition of the ylide **B** to the electron-deficient imine **2e** yielded the intermediate **H**. Intramolecular annulation of the imine to the olefinic double bond occurred with the elimination of PPh_3 to yield the product **4be** and completed the catalytic cycle.

Table 5. Synthesis of 3-Pyrrolines **4** from Different Allylic Compounds^a

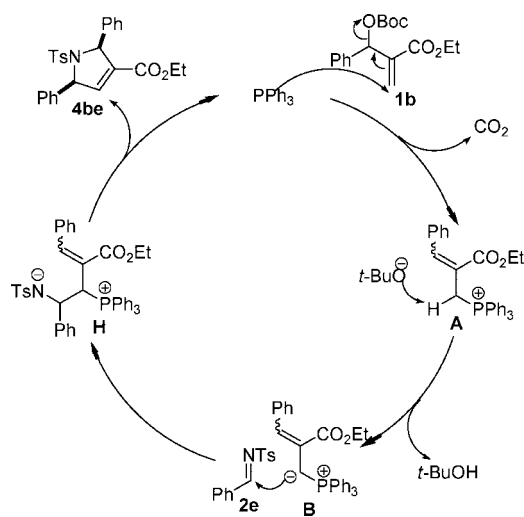


entry	R	R'	product	yield ^b (%)
1	Et	<i>p</i> -MeOC ₆ H ₄ (1c)	4ce	50
2	Et	<i>p</i> -ClC ₆ H ₄ (1d)	4de	68
3	Et	 (1e)	4ee	63
4 ^c	Et	<i>p</i> -NO ₂ C ₆ H ₄ (1f)	4fe	47
5	Et	CH ₃ (1g)	4ge	39
6	Et	<i>n</i> -Pr (1h)	4he	26
7	<i>t</i> -Bu	C ₆ H ₅ (1i)	4ie	86

^a Reaction conditions: Under Ar, a mixture of **1** (0.24 mmol), **2e** (0.2 mmol), and PPh₃ (0.02 mmol) in toluene (2 mL) was stirred at 110 °C. ^b Isolated yields. ^c **1f** (85 mg, 0.24 mmol) in toluene (1 mL) was added over 12 h with a syringe pump to a mixture of PPh₃ and **2e** (52 mg, 0.2 mmol) in toluene (1 mL) at 110 °C. The mixture was stirred further for 1 h.

In conclusion, a novel phosphine-catalyzed reaction of modified allylic *tert*-butyl carbonates with *N*-tosylimines has been developed. The presence of substituents in allylic *tert*-butyl carbonates is crucial for this reaction. For allylic *tert*-butyl carbonates with substituents, a phosphine-catalyzed [3 + 2] annulation of modified allylic *tert*-butyl carbonates with *N*-tosylimines occurred to give 3-ethoxycarbonyl-2,5-*cis*-disubstituted-3-pyrrolines in moderate to good yields with high stereoselectivity. Highly substituted dienylimines **3** were obtained from allylic *tert*-butyl carbonates without any

Scheme 5



substituent. The appealing features of this process involve the availability of the starting materials, the simple manipulation, and the high stereoselectivity of the reaction.

Acknowledgment. We thank the National Natural Science Foundation of China (20572121) and Chinese Academy of Sciences for financial support.

Supporting Information Available: Experimental procedures and characterization data of new compounds. This material is available free of charge via the Internet at <http://pubs.acs.org>.

OL801661Y