TTMPP Catalyzed One-pot Silyl Ketene Acetal–Imine Condensation Route to β-Lactams

Satoru Matsukawa* and Kayoko Obu

Department of Science, Faculty of Education, Ibaraki University, Mito, 310-8512

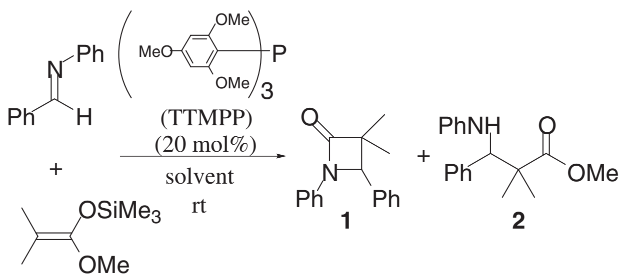
(Received September 28, 2004; CL-041143)

Highly nucleophilic phosphine, tris(2,4,6-trimethoxy phenyl) phosphine (TTMPP) catalyzes a unique one-pot cyclization reaction between silyl ketene acetal and aldimine, resulting in β-lactam.

The addition of silyl ketene acetals to aldimines is an important synthetic method for the preparation of β-lactams.[1,2] Therefore, numerous kinds of activators have been developed,[3] and highly enantioselective reactions have been reported.[4] In these reactions, β-amino ester is obtained as a precursor of β-lactam. On the other hand, reactions using metal-free and uncharged organic molecules as activators have recently attracted attention from the viewpoint of their environmentally benign nature.[5] In our previous study, highly nucleophilic phosphine, tris(2,4,6-trimethoxyphenyl)phosphine (TTMPP)[6] was shown to catalyze the aldol reaction of silyl ketene acetal and aldehydes.[7] Herein, we report an unprecedented one-pot cyclization reaction between silyl ketene acetal and aldimine catalyzed by TTMPP to afford β-lactam.

Initially, the reaction of *N*-phenylaldimine and trimethylsilyl ketene acetal, derived from methyl isobutylate, was examined in various solvents (Table 1, Entries 1–5). Interestingly, β-lactam along with β-amino ester is obtained in THF. Furthermore, with the use of DMF as the solvent, mainly β-lactam was formed. Only trace amounts of product were obtained using Et_2O, CH_3CN, and CH_3OH. Thus, in DMF, the TTMPP catalyzed aldol reaction proceeded smoothly, and the one-pot formation of β-lactam was observed.[8]

Table 1. Optimization of the reaction conditions



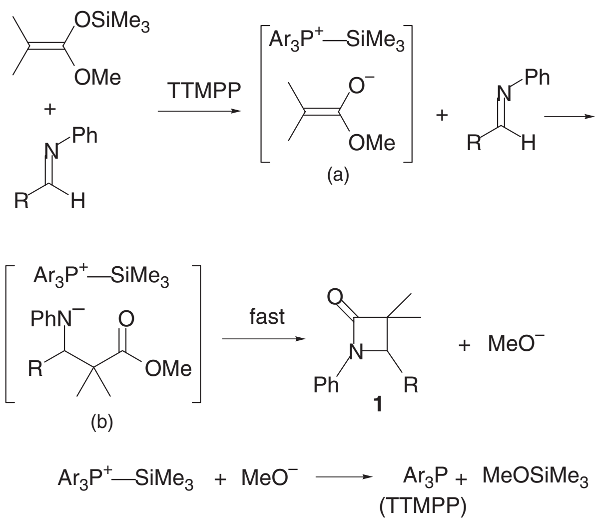
Entry	Solvent	Time	Yield / %	(**1**:**2**)[a]
1	THF	1 h	92	44:56
2	DMF	1 h	96	92:8
3	Et_2O	12 h	0	
4	CH_3OH	12 h	0	
5	CH_3CN	12 h	8	24:76
6	DMF	5 min	33	88:12
7	DMF	15 min	78	92:8
8	DMF	18 h	95	89:11
9[b]	DMF	1 h	42	84:16
10[c]	DMF	1 h	88	90:10

[a]Ratio was determined by ^{1}H NMR analysis. [b]at 0 °C. [c]50 °C.

Next, we investigated the mechanism of this one-pot formation of β-lactam. It is well recognized that β-lactams are directly formed from metal enolates and aldimines.[1a] Under these conditions, β-amino ester was generally obtained in shorter reaction times and/or at lower temperatures, whereas β-lactam was obtained in longer reaction times and/or at higher temperatures. These results were interpreted as evidence for a two-step condensation-cyclization mechanism in which cyclization was rate determining. To confirm the mechanism, this TTMPP catalyzed reaction was carried out under various conditions. The product was obtained in lower yields when the reaction time was reduced, but the selectivity remained fairly constant. Longer reaction times did not increase the selectivity (Table 1, Entries 2 vs 6–8). Furthermore, the β-lactam selectivity was found to be almost the same, regardless of the temperature(Table 1, Entries 2 vs 9, 10).

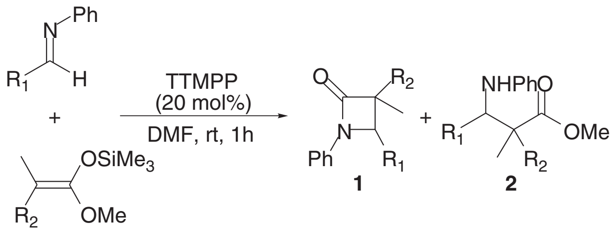
On the basis of these results, it seems that cyclization is not rate determining for this TTMPP catalyzed reaction. In the present reaction, naked enolate (a)[9] was produced via nucleophilic O–Si bond cleavage by TTMPP.[7] Then reacted with aldimine to produce naked anion intermediate (b). This anion intermediate is unstable, so that it rapidly cyclize to afford β-lactam (Scheme 1). In this reaction, we consider that the condensation step, espacially in the O–Si bond cleavage step, is rate determining, unlike in the reaction of metal enolate.

In order to clarify the scope of this TTMPP catalyzed β-lactam selective reaction, several aldimines were examined in the presence of TTMPP (Table 2). β-Lactam was obtained in good yields and with a high level of selectivity. Moderate *trans* selectivity was observed irrespective of the geometry of the silyl



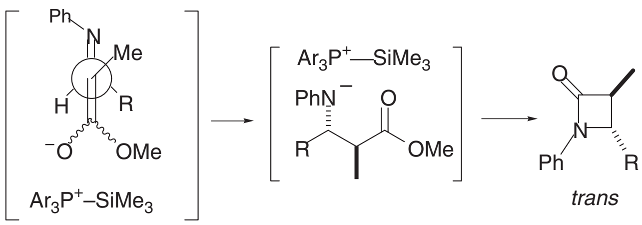
Scheme 1.

Table 2. TTMPP catalyzed one-pot formation of β-lactams



Entry	R_1	R_2	Yield / %	(**1**:**2**)[a]
1	*p*-Tol	Me	92	84:16
2	4-CF_3Ph	Me	96	92:8
3	4-ClPh	Me	94	91:9
4	4-MeOPh	Me	100	80:20
5	4-NO_2Ph	Me	77	84:16
6	1-Naphtyl	Me	85	90:10
7	3-Pyridyl	Me	96	78:22
8[b]	Ph	H	46	80[c]:20
9[d]	Ph	H	55	76[e]:24

[a]Ratio was determined by ^{1}H NMR analysis. [b]75% *E*. [c]*cis*/*trans* = 34:66. [d]88% *Z*. [e]*cis*/*trans* = 37:63.



Scheme 2.

ketene acetal, which was derived from methyl propionate (Table 2, Entries 8, 9). This observed stereoselectivity was determined in the condensation step. It can be reasonably explained by considering an extended transition state (Scheme 2). A typical experimental procedure is as follows: To a solution of aldimine (1 mmol) and TTMPP (0.2 mmol) in DMF (2 mL), silyl ketene acetal (1.5 mmol) was added at room temperature. The reaction was monitored by TLC. After one hour, the mixture was quenched with water. A general work-up and purification by flash column chromatography resulted in the desired product.

In summary, we disclose that TTMPP catalyzes a unprecedented one-pot cyclization reaction between silyl ketene acetal and aldimine to afford β-lactam. Further investigations along these lines, including stereoselective reactions, are currently underway.

References and Notes

1 Reviews: a) D. J. Hart and D.-C. Ha, *Chem. Rev.*, **89**, 1447 (1989). b) M. J. Brown, *Heterocycles*, **29**, 2225 (1989). c) E. F. Kleinman, in "Comprehensive Organic Synthesis," ed. by C. H. Heathcock, Pergamon Press, Oxford (1991). d) G. A. Coppel, in "Small Ring Heterocycles," ed. by A. Hassner, Wiley, New York (1983), Vol. 42, p 219. e) N. DeKimpke, in "Comprehensive Heterocyclic Chemistry II," ed. by A. Padwa, Elsevier, Oxford (1996).

2 a) I. Ojima, S. Inaba, and K. Yoshida, *Tetrahedron Lett.*, **18**, 3643 (1977). b) I. Ojima, S. Inaba, and M. Nagai, *Synthesis*, **1981**, 545.

3 a) K. Ikeda, K. Achiwa, and M. Sekiya, *Tetrahedron Lett.*, **24**, 4707 (1983). b) E. W. Colvin and D. G. Mckarry, *J. Chem. Soc., Chem. Commun.*, **1985**, 539. c) R. A. Pilli and D. J. Russowsky, *J. Chem. Soc., Chem. Commun.*, **1987**, 1053. d) T. Mukaiyama, K. Kashiwagi, and S. Matsui, *Chem. Lett.*, **1989**, 1397. e) T. Mukaiyama, H. Akamatsu, and J. S. Han, *Chem. Lett.*, **1990**, 889. f) M. Onaka, R. Ohno, N. Yanagiya, and Y. Izumi, *Synlett*, **1993**, 141. g) K. Ishihara, M. Funahashi, N. Hanaki, M. Miyata, and H. Yamamoto, *Synlett*, **1994**, 963. h) S. Kobayashi, M. Araki, H. Ishitani, and I. Hachiya, *Synlett*, **1995**, 233. i) S. Kobayashi and S. Nagayama, *J. Am. Chem. Soc.*, **119**, 10049 (1997). j) R. Hayakawa and M. Shimizu, *Chem. Lett.*, **1999**, 591. k) T. Akiyama, J. Takaya, and H. Kagoshima, *Synlett*, **1999**, 1045. l) K. Miura, K. Tamaki, T. Nakagawa, and A. Hosomi, *Angew. Chem., Int. Ed.*, **39**, 1958 (1999). m) H. Fujisawa, E. Takahashi, T. Nakagawa, and T. Mukaiyama, *Chem. Lett.*, **32**, 1036 (2003).

4 For asymmetric reactions, see: a) K. Ishihara, M. Miyata, K. Hattori, T. Tada, and H. Yamamoto, *J. Am. Chem. Soc.*, **116**, 10520 (1994). b) H. Ishitani, M. Ueno, and S. Kobayashi, *J. Am. Chem. Soc.*, **119**, 7153 (1997). c) S. Kobayashi, H. Ishitani, and M. Ueno, *J. Am. Chem. Soc.*, **120**, 431 (1998). d) R. Müller, H. Goesmann, and H. Waldmann, *Angew. Chem., Int. Ed.*, **38**, 184 (1999). e) E. Hagiwara, A. Fujii, and M. Sodeoka, *J. Am. Chem. Soc.*, **120**, 2474 (1998). f) D. Ferraris, B. Young, T. Dudding, and T. Lectka, *J. Am. Chem. Soc.*, **120**, 4548 (1998). g) S. Xue, S. Yu, Y. Deng, and W. D. Wulff, *Angew. Chem., Int. Ed.*, **40**, 2271 (2001). h) S. Kobayashi, T. Hamada, and K. Manabe, *J. Am. Chem. Soc.*, **124**, 5640 (2002). i) B. M. Trost and L. R. Terrell, *J. Am. Chem. Soc.*, **125**, 338 (2003). j) S. Matsunaga, N. Kumagai, S. Harada, and M. Shibasaki, *J. Am. Chem. Soc.*, **125**, 4712 (2003). k) T. Akiyama, J. Itoh, K. Yokota, and K. Fuchibe, *Angew. Chem., Int. Ed.*, **43**, 1566 (2004).

5 a) S. Kobayashi, C. Ogawa, H. Konishi, and M. Sugiura, *J. Am. Chem. Soc.*, **125**, 6610 (2003). b) C. Ogawa, M. Sugiura, and S. Kobayashi, *Chem. Commun.*, **2003**, 192.

6 a) M. Wada and S. Higashizaki, *J. Chem. Soc., Chem. Commun.*, **1984**, 482; Recent report of the reaction using TTMPP, see: b) S. Röper, R. Wartchow, and M. R. Hoffmann, *Org. Lett.*, **4**, 3179 (2002). c) H. Kawabata and M. Hayashi, *Tetrahedron Lett.*, **43**, 5645 (2002). d) K. Yoshimoto, H. Kawabata, N. Nakamichi, and M. Hayashi, *Chem. Lett.*, **2001**, 934. e) S. M. Maddock and M. G. Finn, *Organometallics*, **19**, 2684 (2000).

7 S. Matsukawa, N. Okano, and T. Imamoto, *Tetrahedron Lett.*, **41**, 103 (2000).

8 Other phsophines, such as triphenylphosphine, tricyclohexyl phosphine, tributylphosphine and triisopropylphosphine, did not catalyze this reaction.

9 a) I. Kuwajima and E. Nakamura, *J. Am. Chem. Soc.*, **97**, 3257 (1975). b) R. Noyori, K. Yokoyama, J. Sakata, I. Kuwajima, E. Nakamura, and M. Shimizu, *J. Am. Chem. Soc.*, **99**, 1265 (1977). c) R. Noyori, I. Nishida, J. Sakata, and M. Nishizawa, *J. Am. Chem. Soc.*, **102**, 1223 (1980). d) R. Noyori, I. Nishida, and J. Sakata, *J. Am. Chem. Soc.*, **103**, 2106 (1981). e) I. Kuwajima and E. Nakamura, *Acc. Chem. Res.*, **18**, 181 (1985). f) R. J. P. Corriu, R. Perz, and C. J. J. Reyé, *Tetrahedron*, **39**, 999 (1983).

Published on the web (Advance View) November 20, 2004; DOI 10.1246/cl.2004.1626