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Double Nucleophilic Addition to Acrolein with Ketene Silyl Acetals and Allylborolanes Catalyzed by Proline

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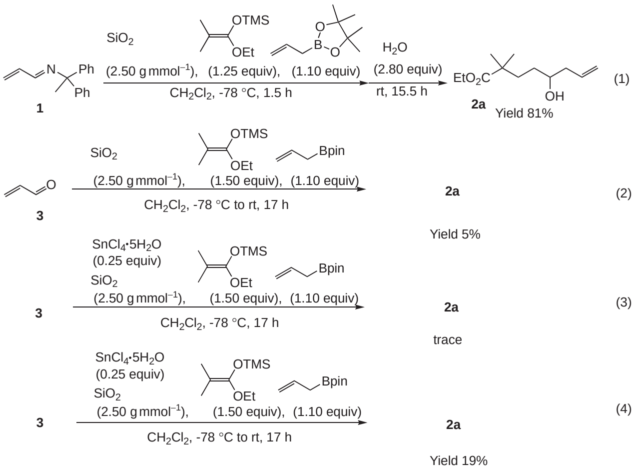
In the presence of a catalytic amount of proline and silica gel, a mixture of ketene silyl acetals and 2-allyl-4,4,5,5-tetramethyl-1,3,2-dioxaborolane underwent 1,4- and subsequently 1,2-addition with acrolein to give δ-hydroxyesters in good yields in a highly diastereoselective manner.

Although acrolein is one of the most useful three-carbon units in organic synthesis, it is not always easy to use this particular compound as a conjugate addition acceptor of carbon nucleophiles.[1] This is due in part to the high reactivity of the carbonyl and olefin functional groups to induce 1,2-addition and/or polymerization. We have recently reported that *N*-allylidene-1,1-diphenylethanamine (**1**) is successfully used as a latent acrolein in the presence of silica gel and a limited amount of water to effect the 1,4- and 1,2- double nucleophilic addition of two different kinds of nucleophiles (eq 1 in Scheme 1).[2a] Since under similar conditions, double addition reactions do not proceed (eqs 2–4 in Scheme 1),[2] this procedure has opened a new entry into an easy use of an acrolein equivalent. However, there still remains an important problem of the waste of a 1,1-diphenylethanamine moiety, and therefore, in an effort to find an efficient system for the use of acrolein itself, catalytic use of an appropriate amine was examined. We have now found that the use of proline and silica gel enables the desired catalytic system.

As summarized in Table 1, the initial examination was carried out using diisopropylamine as a catalyst in the presence of silica gel and water, and the double addition product was obtained in low yield (Entry 1). Among the amines examined proline gave the best result, and the desired adduct was obtained in moderate yield, when the addition was conducted in the presence of silica gel, benzoic acid, and water (Entry 3). Other proline derivatives and pipecolic acid examined were not as effective as proline (Entries 4–10).[3]

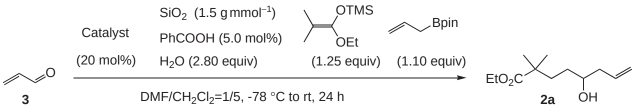


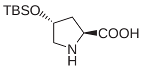
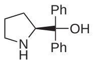
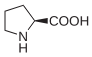
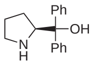
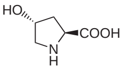
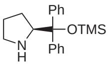
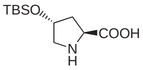
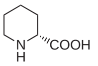
Scheme 1. Double addition to acrolein.

In order to find the optimum reaction conditions additives and the amounts of reagents were examined, and Table 2 summarizes the results.

As can be seen from Table 2, in the absence of silica gel and added acids the reaction gave the adduct in low yield (Entry 1), whereas the acids promoted the addition reaction in the presence of silica gel ($1.5\,g\,mmol^{-1}$) (Entries 2, 3, 5, and 6). However, when increased amounts of silica gel were used, the presence of

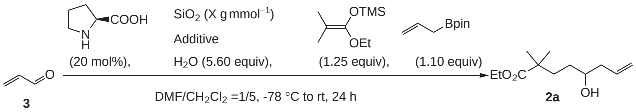
Table 1. Double addition to acrolein in the presence of amine[a]



Entry	Catalyst	**2a**/%[b]	Entry	Catalyst	**2a**/%[b]
1[c,d]	*i*-Pr_2NH	24	6[c]		16
2	Bn_2NH	35	7		26
3		60	8[c]		32
4		24	9		24
5		56	10		25

[a]See a typical procedure in the Supporting Information; SI.[4] [b]Isolated yields. [c]In CH_2Cl_2. [d]In the absence of benzoic acid.

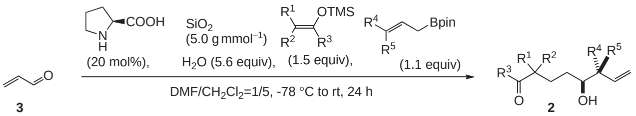
Table 2. Double addition reaction using proline and additives[a]



Entry	Additive (mol %)	SiO_2/g mmol^{-1}	**2a**/%[b]
1	—	0	21
2	—	1.5	45
3	$PhCO_2H$ (5)	1.5	60
4	$PhCO_2H$ (20)	1.5	38
5	$B(OH)_3$ (5)	1.5	56
6	Salicylic acid (5)	1.5	54
7	—	2.5	55
8	—	5.0	70
9[c]	—	5.0	75
10	$PhCO_2H$ (5)	5.0	58
11	—	7.5	61

[a]See a typical procedure in the SI.[4] [b]Isolated yields. [c]Ketene silyl acetal (1.50 equiv) was used.

Table 3. Double addition reaction to acrolein[a]



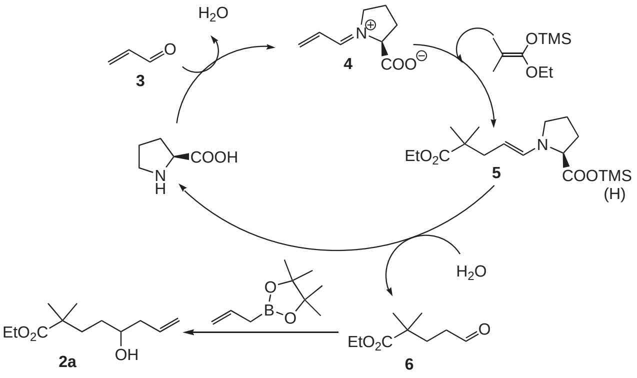
Entry	R^1	R^2	R^3	R^4	R^5	**2**/%[b]	*anti*:*syn*[c]
1	Me	Me	OEt	H	H	**a**: 75[d]	—
2	Me	Me	OBn	H	H	**b**: 40	—
3	Me	Me	OMe	H	H	**c**: 58 (61)[e]	—
4	Me	Me	OCy	H	H	**d**: 61	—
5	H	Me	SPh	H	H	**e**: 0	—
6	H	Me	OCy	H	H	**f**: trace	—
7	H	Me	SCy	H	H	**g**: 27[f]	—
8	H	H	OCy	H	H	**h**: 0	—
9	H	H	SCy	H	H	**i**: 0	—
10	Me	Me	OEt	Me	H	**j**: 52	>99:<1
11	Me	Me	OEt	H	Me	**k**: 58	<1:>99
12	Me	Me	OEt	Me	Me	**l**: 60	—

[a] See a typical procedure in the SI.[4] [b] Isolated yields. [c] Ratio regarding C5/C6 diastereomers.[5] [d] Enantiopurity of the product was 10% ee. [e] In the presence of proline (100 mol %). [f] A 55:45 ratio of diastereomers was obtained.

added acids was not necessary (Entries 7 and 8), indicating that an appropriate acidity of the silica gel would facilitate the formation of the iminium salt. The best conditions were found when the reaction was carried out with ketene silyl acetal (1.50 equiv) and 2-allyl-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (1.10 equiv) in the presence of proline (20 mol %) and silica gel (5.0 g mmol^{-1}), and the 1,4- and 1,2-adduct was obtained in 75% yield (Entry 9). Under the optimum conditions a variety of ketene silyl acetals and allylborolanes were subjected to the double addition reaction, and Table 3 summarizes the results.[4]

Among tetrasubstituted ketene silyl acetals ethoxy derivatives recorded the best result, whereas benzyloxy and methoxy derivatives gave moderate yields of the product. However, in contrast to the results using *N*-allylidene-1,1-diphenylethanamine (**1**) previously reported,[2a] trisubstituted ketene silyl thioacetal gave the adduct in only low yield, where the diastereoselectivity regarding the C2–C5 carbons was not high (Entry 7), and disubstituted derivatives were not successfully employed (Entries 8 and 9). Competing hydrolysis of tri- and disubstituted ketene silyl (thio)acetals may account for the low yields. Use of one equivalent of proline did not noticeably improve the yields of the desired adducts (Entry 3). When crotylborolanes were used as the second nucleophile, the reaction proceeded with excellent diastereoselectivity with respect to the C5–C6 carbons, where the (*E*)-derivative gave *anti*-adducts and the (*Z*)-isomer effected the formation of the *syn*-isomers (Entries 10 and 11). 3-Methylcrotyl derivative could also be employed (Entry 12).

Regarding the reaction pathway, the following Scheme 2 may account for the present reaction. First, the iminium salt **4**[6] is formed from acrolein **3** and proline, and undergoes 1,4-addition with ketene silyl acetal to give the enamine intermediate **5**. Hydrolysis with water present in the reaction system generates the aldehyde **6**, which is attacked by allylborolane to give the double addition product **2a**. Regarding the enantiopurity of the product **2a**, low ee values (8 to 10% ee) were usually obtained, indicating that a major pathway of the 1,2-addition might not include the proline catalysis.



Scheme 2. A possible reaction pathway.

In conclusion, we have developed an efficient system for the double nucleophilic addition to acrolein employing a proline catalyst and silica gel as promoters. Although there is a limitation for the 1,4-nucleophiles, this study opens a direct use of acrolein as an acceptor of plural nucleophiles in a one-pot procedure. Regarding the efficiecy of the proline catalyst as compared with other amines, we have not yet obtained a definite idea, however a sort of double activation of the unsaturated aldehyde by forming the iminium salt coupled with that of the ketene silyl acetal by the attack of the carboxylate anion may be involved in the present system.

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References and Notes

1 a) R. He, C. Ding, K. Maruoka, *Angew. Chem., Int. Ed.* **2009**, *48*, 4559. b) K. Wakabayashi, K. Aikawa, K. Mikami, *Heterocycles* **2009**, *77*, 927. c) B. Srinivas, V. P. Kumar, R. Sridhar, V. P. Reddy, Y. V. D. Nageswar, K. R. Rao, *Helv. Chim. Acta* **2009**, *92*, 1080. d) R. Jana, J. A. Tunge, *Org. Lett.* **2009**, *11*, 971. e) R. W. Bates, R. H. Snell, S. A. Winbush, *Synlett* **2008**, 1042. f) M. Kawatsura, S. Aburatani, J. Uenishi, *Tetrahedron* **2007**, *63*, 4172. g) S. Imachi, M. Onaka, *Chem. Lett.* **2005**, *34*, 708. h) G. Liu, X. Lu, *Tetrahedron Lett.* **2003**, *44*, 127. i) S. Uehira, Z. Han, H. Shinokubo, K. Oshima, *Org. Lett.* **1999**, *1*, 1383. j) Y. Ohgomori, S. Ichikawa, N. Sumitani, *Organometallics* **1994**, *13*, 3758. k) M. Sawamura, H. Hamashima, Y. Ito, *Tetrahedron* **1994**, *50*, 4439. l) B. A. Grisso, J. R. Johnson, P. B. Mackenzie, *J. Am. Chem. Soc.* **1992**, *114*, 5160. m) S. Matsuzawa, Y. Horiguchi, E. Nakamura, I. Kuwajima, *Tetrahedron* **1989**, *45*, 349.

2 a) M. Shimizu, M. Kawanishi, I. Mizota, I. Hachiya, *Org. Lett.* **2010**, *12*, 3571. b) M. Shimizu, T. Nishi, *Synlett* **2004**, 889. c) M. Shimizu, T. Nishi, A. Yamamoto, *Synlett* **2003**, 1469.

3 For recent reviews dealing with conjugate addition to iminium ions, see: a) S. Vera, Y. Liu, M. Marigo, E. C. Escudero-Adán, P. Melchiorre, *Synlett* **2011**, 489. b) B. List, *Synlett* **2011**, 462. c) P. Melchiorre, M. Marigo, A. Carlone, G. Bartoli, *Angew. Chem., Int. Ed.* **2008**, *47*, 6138. d) A. Erkkilä, I. Majander, P. M. Pihko, *Chem. Rev.* **2007**, *107*, 5416. e) S. B. Tsogoeva, *Eur. J. Org. Chem.* **2007**, 1701.

4 For more detailed examination of reaction conditions, see the Supporting Information which is available electronically on the CSJ-Journal Web site, http://www.csj.jp/journals/chem-lett/index.html.

5 For determination of the relative stereochemistry, see: Y. Yamamoto, N. Asao, *Chem. Rev.* **1993**, *93*, 2207, and references cited therein.

6 Our related reactions, see: a) Y. Niwa, M. Shimizu, *J. Am. Chem. Soc.* **2003**, *125*, 3720. b) M. Shimizu, H. Itou, M. Miura, *J. Am. Chem. Soc.* **2005**, *127*, 3296. c) M. Shimizu, *Pure Appl. Chem.* **2006**, *78*, 1867. d) M. Shimizu, Y. Niwa, T. Nagai, I. Hachiya, *Heterocycles* **2007**, *72*, 127. e) T. Iwao, M. Shimizu, *Heterocycles* **2009**, *77*, 767. f) M. Shimizu, I. Hachiya, I. Mizota, *Chem. Commun.* **2009**, 874. g) M. Shimizu, H. Itou, T. Iwao, Y. Umeda, *Chem. Lett.* **2009**, *38*, 732.