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Asymmetric Mannich-Type Reactions of Aldimines with a Chiral Acetate

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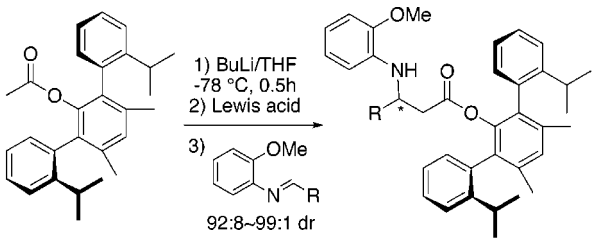
ABSTRACT



We introduce here a strategy that enables effective addition of lithium enolates of acetates to aldimines. The new method depends strongly on the use of *o*-alkoxy (or *o*-fluoro) aniline-derived aldimines which have been found to have a potential effect on the enolate addition. This scope was expanded to the asymmetric process using the chiral acetate. A Lewis acid additive has a complementary role in the pronounced activation of imine functionalities.

Chiral auxiliaries are powerful molecular elements for creating optically active compounds. When covalently attached to the auxiliaries, carboxylic acid derivatives expanded the scope of the asymmetric aldol reaction with aldehydes and have constituted a molecular library of β-hydroxycarbonyl compounds.[1] In contrast, due to the inherent instability of imines (e.g., imine−enamine equilibration) and the poor electrophilicity of stable *N*-substituted imines[2] especially toward *acetate* enolates, there are few reports in the literature[3,4] on the asymmetric Mannich-type reaction using this approach. We address these limitations using 2,6-bis-(2-isopropylphenyl)-3,5-dimethylphenol (**1**)[5] as an effective chiral auxiliary in the diastereoselective Mannich-type reaction of acetate **2**[6] with specialized aldimines (Scheme 1).

Although studies have investigated many aspects of high reactivity of the enolates of propionates and isobutylates,[3a]

(1) (a) Evans, D. In *Asymmetric Synthesis*; Morrison, J. D., Ed.; Academic Press: San diego, CA, 1984; Vol. 3, Chapter 1. (b) *Asymmetric Synthesis*; Procter, G., Ed.; Oxford University Press: Oxford, 1996; Chapter 5. (c) Ager, D. J.; Prakash, I.; Schaad, D. R. *Chem. Rev.* **1996**, *96*, 835.

(2) (a) Arend, M.; Westermann, B.; Risch, N. *Angew. Chem., Int. Ed.* **1998**, *37*, 1044. (b) Denmark, S. E.; Nicaise, O. J.-C. *Chem. Commun.* **1996**, 999. (c) Risch, N.; Arend, M. In *Stereoselective Synthesis (Houben-Weyl), Vol. E21/b*; Helmchen, G., Hoffmann, R. W., Mulzer, J., Schaumann, E., Eds.; Thieme: Stuttgart, 1996; p 1833.

(3) (a) Most examples concerning the asymmetric Mannich-type reaction employ chiral sources appended to the N atom of aldimines. For leading reviews, see: (a) Hart, D. J.; Ha, D.-C. *Chem. Rev.* **1989**, *89*, 1447. (b) *Enantioselective Synthesis of β-Amino Acids*; Juraisti, E., Ed.; Wiley-VCH: New York, 1997. For recent outstanding examples using chiral aldimines and related reactions, see: (c) Tang, T. P.; Ellman, J. A. *J. Org. Chem.* **1999**, *64*, 12. (d) Müller, R.; Goesmann, H.; Waldmann, H. *Angew. Chem., Int. Ed.* **1999**, *38*, 184. (e) Davis, F. A.; Szewczyk, J. M.; Reddy, R. E. *J. Org. Chem.* **1996**, *61*, 2222. For reactions using chiral metal catalysts, see: (f) Hagiwara, E.; Fujii, A.; Sodeoka, M. *J. Am. Chem. Soc.* **1998**, *120*, 2472. (g) Ferraris, D.; Young, B.; Dudding, T.; Lectka, T. *J. Am. Chem. Soc.* **1998**, *120*, 4548. (h) Ferraris, D.; Young, B.; Cox, C.; Drury, W. J., III; Dudding, T.; Lectka, T. *J. Org. Chem.* **1998**, *63*, 6090. (i) Kobayashi, S.; Ishitani, H.; Ueno, M. *J. Am. Chem. Soc.* **1998**, *120*, 431. (j) Ishihara, K.; Miyata, M.; Hattori, K.; Yamamoto, H. *J. Am. Chem. Soc.* **1994**, *116*, 10520.

(4) For asymmetric Mannich-type reactions using a chiral acetate equivalent (chiral iron acyl complex), see: (a) Liebeskind, L. S.; Welker, M. E.; Fengel, R. W. *J. Am. Chem. Soc.* **1986**, *108*, 6328. (b) Liebeskind, L. S.; Welker, M. E.; Goedken, V. *J. Am. Chem. Soc.* **1984**, *106*, 441. Very recent example, see: (c) Palomo, C.; Oiarbide, M.; Concepción, M.; González-Rego, C.; Sharma, A. K.; García, M.; González, A.; Landa, C.; Linden, A. *Angew. Chem., Int. Ed.* **2000**, *39*, 1063.

(5) For preliminary synthesis of **1**, see: (a) Saito, S.; Kano, T.; Hatanaka, K.; Yamamoto, H. *J. Org. Chem.* **1997**, *62*, 5651. For the more efficient synthesis of **1** we developed recently, see: (b) Saito, S.; Kano, T.; Muto, H.; Nakadai, M.; Yamamoto, H. *J. Am. Chem. Soc.* **1999**, *121*, 8943.

(6) Saito, S.; Hatanaka, K.; Kano, T.; Yamamoto, H. *Angew. Chem., Int. Ed.* **1998**, *37*, 3378.

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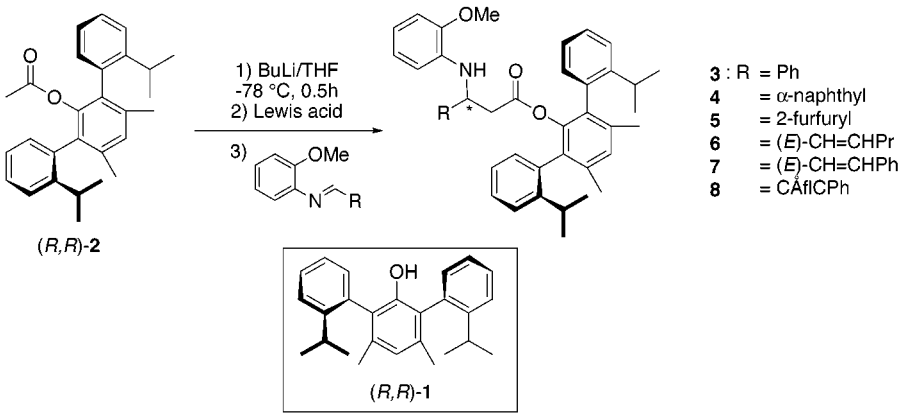
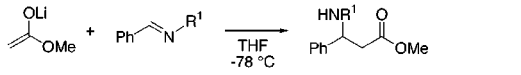
Scheme 1



the lithium enolates of acetates are almost inert to the *N*-phenyl-[7a] and *N*-trimethylsilylaldimines[7b] of benzaldehyde.[7] Thus, our first attempt was to find a potential aldimine partner that reacts smoothly with the acetate enolates. The results are summarized in Table 1, which shows that the aldimines of *o*-anisidine and *o*-fluoroaniline (**9** and **13**) facilitate the reaction most efficiently (entries 3 and 7).[8] The alkoxy and fluoro groups are essential and must be attached to the *ortho*-position of the aniline nitrogen. For example, *m*- and *p*-anisidine derivatives **10** and **11** did not lead to the desired adducts (entries 4 and 5). These results imply that the rather low Lewis acidic Li^+ requires chelation to enable the effective activation of aldimines. Indeed, aldimine **12** with which the chelation control further operates had a similar effect on the addition efficacy (entry 6); dimethoxy derivatives **14** and **15** showed similar productivity (entries 8 and 9). However, *o*,*o*-disubstituted derivatives **16**−**18** were absolutely inert under the present conditions even at higher temperature (0 °C) (entries 10−12).

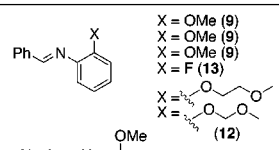
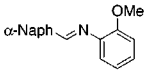
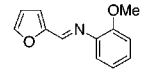
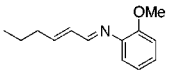
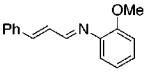
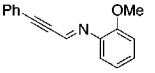
Table 1. Reaction of the Lithium Enolate of Methyl Acetate with Various Aldimines[a]



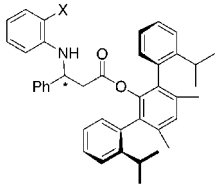
entry	R^1	yield %[b]	entry	R^1	yield %[b]
1	Ph	24[c,d]	9	2,5-$(MeO)_2$-C_6H_3 (**15**)	73
2	Me_3Si	14[c,e]	10	2,6-$(MeO)_2$-C_6H_3 (**16**)	NR
3	2-MeO-C_6H_4 (**9**)	71	11	2-MeO-6-Me-C_6H_4 (**17**)	NR
4	3-MeO-C_6H_4 (**10**)	NR	12	2,6-F_2-C_6H_4 (**18**)	NR
5	4-MeO-C_6H_4 (**11**)	NR	13	Bn	NR
6	2-MOMO-C_6H_4 (**12**)	69	14	MeO	NR
7	2-F-C_6H_4 (**13**)	83	15	Ms	4
8	2,4-$(MeO)_2$-C_6H_3 (**14**)	56			

[a] Unless otherwise specified, reaction was performed using the acetate (1.0 equiv), a THF solution of LDA (1.0 equiv) and aldimine (1.0 equiv) at −78 °C for 3 h. [b] Of isolated *β*-aminoesters. NR = no reaction. [c] The isolated yield of the corresponding *β*-lactam. [d] See ref 7a. [e] See ref 7b.

Table 2

entry	aldimine (RCH=NR^1)	additive	product	yield %[b] (dr, x/1)[c]	absolu config[d]
1	 X = OMe (**9**)	Et_2Zn	**3**	69 (95.5:4.5)	*S*
2	X = OMe (**9**)	Et_2Zn[e]	**3**	82 (95.5:4.5)	*S*
3	X = OMe (**9**)	Me_2Zn	**3**	70 (96:4)	*S*
4	X = F (**13**)	Et_2Zn	**3b**	55 (97:3)	
5	X =	Et_2Zn	**3c**	46 (95.5:4.5)	
6	X = (**12**)	Et_2Zn	**3d**	70 (95:5)	
7		Et_2Zn	**4**	73 (95.5:4.5)	
8		Et_2Zn[e]	**4**	50 (92:8)	
9		Me_2Zn	**5**	62 (92:8)	
10		Et_2Zn	**5**	75 (92:8)	
11		Et_2Zn	**6**	29 (99:1)	
12		Me_2Zn	**7**	70 (96.5:3.5)	*S*
13		Et_2Zn	**7**	72 (95.5:4.5)	*S*
14		*t*-Bu_2Zn[f]	**8**	55 (95.5:4.5)	*S*
15		Et_2Zn	**8**	63 (92.5:7.5)	*S*
16		Et_2Zn[e]	**8**	51 (93:7)[g]	*S*

[a] Unless otherwise specified, reaction was performed using enolate (1.0 equiv), aldimine (1.0 equiv), and R_2Zn (0.5 equiv) at −78 °C for 18−48 h. [b] Of isolated purified product. [c] Determined by HPLC analysis. [d] Absolute configuration of samples. [e] Et_2Zn (1.0 equiv) was used. [f] Salt free reagent. [g] Ethylated product was obtained (10%).

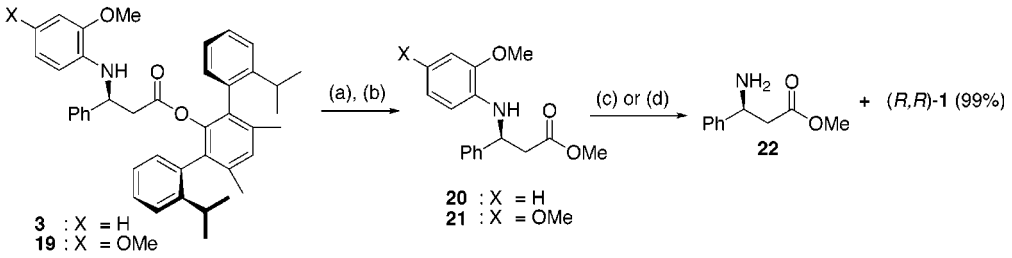


3b : X = F
3c : X = -O(CH_2)$_2$OMe
3d : X = -O(CH_2)OMe (OMOM)

(7) (a) Gluchowski, C.; Cooper, L.; Bergbreiter, D. E.; Newcomb, M. *J. Org. Chem.* **1980**, *45*, 3413. (b) Ha, D.-C.; Hart, D. J.; Yang, T.-K. *J. Am. Chem. Soc.* **1984**, *106*, 4819. The trimethylsilyl ketene acetal of methyl acetate also shows poor reactivity, see: (c) Colvin, E. W.; Macgarry, D. *J. Chem. Soc., Chem. Commun.* **1985**, 539. (d) Colvin, E. W.; Macgarry, D.; Nugent, M. J. *Tetrahedron* **1988**, *44*, 4157.

(8) In the meantime, restraining effects of the *o*-methoxyphenyl substituent of aldimines on the formation of *β*-amino esters, not the *β*-lactams, was reported in the Refomatsky reaction using α-bromoacetate and Zn, see: Adrian, J. C. Jr.; Barkin, J. L.; Hassib, L. *Tetrahedron Lett.* **1999**, *40*, 2457. Moreover, Kobayashi et al. reported a marked influence of aldimines **9** and **17** on the enantioselectivity and reactivity in the Mannich-type reaction using chiral zirconium reagents (ref 3i). Although both aldimines are employable, the reaction mechanism remains totally unclear.

Scheme 2[a]



[a] (a) Bu_4NOH, THF, 0 °C, 99%; (b) $TMSCHN_2$, MeOH, rt, 99%; for **3** and **19**: (c) $AgNO_3$, $(NH_4)_2S_2O_8$. THF−H_2O−MeCN, 60 °C, 53%; for **20**: (d) CAN, H_2O−MeCN, 0 °C, 91%, for **21**.

Unfortunately, the lithium enolate of **2**, generated by treatment with *n*-BuLi in THF at −78 °C for 0.5 h, was almost inert to aldimines **9** and **13** under the above optimized conditions (for aldimine **9**, 15% yield, 93:7 dr). We thus focused on the use of a Lewis acid additive, anticipating the pronounced activation of imine functionalities (Scheme 1). The addition of **2** to aldimine **9** occurred effectively in the presence of 0.5 equiv of R_2Zn (R = Me, Et) at −78 °C to give *β*-aminoester **3** in 70% and 69% yields with diastereomeric ratios (dr) of 95.5:4.5. Using 1.0 equiv of Et_2Zn was generally ineffective in terms of chemical yield due to side reactions, which in some cases generated a considerable amount of ethylated products (entry 16).[9] With the exception of inertness with the 2-hexenal-derived aldimine (entry 11), Table 2 shows that this method proved to be effective in substrate scope, giving high dr up to 99:1. Comparable yields and dr values were obtained whether a Lewis acid was added after or before treatment of aldimine with the enolate. While varying aldimines (entries 4−6) or Lewis acids for **9** (Me_3-Al, 90.5:9.5 dr; *i*-Bu_3Al, 94.5:5.5 dr; Me_3Ga, 97:3 dr) had appreciable effect, absolute *S* configuration at the emerging chiral center was induced throughout. *o*,*o*-Disubstituted aniline-derived aldimines **16**−**18** underwent no addition to give complete recovery of the acetate.

The equilibrium between (*E*)- and (*Z*)-aldimines is known to be involved in the presence of Lewis acid and to affect the stereochemistry of the asymmetric Mannich-type reaction.[10] Thus, there is a possibility that the isomerization to (*Z*)-aldimines could have a potential effect on the rate acceleration of the Mannich addition. In fact, when the $SnCl_4$−(*Z*)-**9** complex[12] was exposed to the lithium enolate of (*R*,*R*)-**2**, adduct **3** was obtained (3*S*:3*R* = 85:15 (= dr)), with the absolute configuration being consistent with the other examples we tested (entries 1−3 and 12−16). It should be pointed out that the reactions showed a general preference for *si* face attack of aldimines, which is opposite to that for the addition of aldehydes.[6]

The chiral auxiliary can readily be recovered (>99%) from Mannich adduct **3** (95.5:4.5 dr) by treatment with NH_4OH in THF,[13] followed by subsequent methylation of the resulting acid with $TMSCHN_2$. Oxidative cleavage of the methoxyphenyl group was effected by catalytic $AgNO_3$ (0.29 equiv) in the presence of excess $(NH_4)_2S_2O_8$ (7.0 equiv)[14] to afford aminoester **22** in 53% yield (90% ee) (Scheme 2). When we used CAN as an alternative oxidant, aminoester **20** underwent considerable dimerization, resulting in negligible formation of **22**.[15] This can be circumvented by use of **14** as an aldimine to give Mannich adduct **19** in 63% yield (96:4 dr). Sequential hydrolysis and methylation were followed by oxidation of **21** with CAN (4 equiv) to give **22** in 91% yield (92% ee), where no dimerization was observed.

In conclusion, this work features a strategy that enables effective addition of acetate enolates to aldimines and expands this scope to the asymmetric process using a chiral auxiliary. We propose that the successful asymmetric reaction originated in part from control of the two possible enolate conformations W-form and U-form,[16] which have been

(9) To explain the difference in the reaction profiles using 0.5 and 1.0 equiv of Et_2Zn, distinctive zincate species (enolate)R_2ZnLi (Li-enolate:R_2Zn = 1:1) and (enolate)$_2R_2ZnLi_2$ (Li-enolate:R_2Zn = 2:1) might be invoked. At present, we have no evidence for the formation of these species and further research is needed. Regarding the search on the reactivity difference between R_3ZnLi and R_4ZnLi_2, see: (a) Uchiyama, M.; Kameda, M.; Mishima, O.; Yokoyama, N.; Koike, M.; Kondo, Y.; Sakamoto, T. J. A*m. Chem. Soc.* **1998**, *120*, 4934.

(10) For example, the reaction of the aldimine derived from 3-trimethylsilyl-2-propynal with a ketene silyl acetal exhibits reversal in the absolute configuration, compared with that of the aldimine derived from benzaldehyde using a chiral boron reagent. This implies that the (*Z*)-structure is the reactive form for the former aldimine, whereas it is (*E*)-isomer for the latter, see ref 3j. In good contrast, the present reaction using the *o*-anisidine-derived aldimines derived from these two types of aldehydes showed an identical *S* configuration.

(11) See Supporting Information for experimental details.

(12) Rasmussen, K. G.; Hazaell, R. G.; Jorgensen, K. A. *Chem. Commun.* **1997**, 1103. (b) Rasmussen, K. G.; Juhl, K.; Hazaell, R. G.; Jorgensen, K. A. *J. Chem. Soc., Perkin Trans. 2* **1998**, 1347.

(13) Hasegawa, T.; Yamamoto, H. *Synlett* **1998**, 882. See also ref 6.

(14) Bhattarai, K.; Cainelli, G.; Panunzio, M. *Synlett* **1990**, 229.

(15) Although it has been reported that aminoester **20** was readily oxidized by CAN to give **22** (ref 8), we were unable to detect the formation of **22** using CAN by varying numerous reaction conditions. No attempt was made here to characterize the exact structure of the dimer. Competitive dimerization is a significant problem in certain cases using CAN, see: Jacob, P., III; Callery, P. S.; Shulgin, A. T.; Castagnoli, N., Jr. *J. Org. Chem.* **1976**, *41*, 3627. We also tried oxidative removal of the *o*-fluorophenyl group from methyl 3-(2-fluorophenyl)amino-3-phenylpropionate (entry 7, Table 1) under conditions similar to those employed for **20** and **21** using CAN. However, product **22** was formed in 14% yield.

(16) It was proposed that the boron enolates of α-unsubstituted ketones favor the more stable U-form by 1−2 kcal/mol than the W-form. Similarly, it is conceivable that the bulky phenoxy group of the enolate of **2** renders the U-form most likely and gives a twist-boat transition structure: (a) Gennari, C.; Todeschini, R.; Beretta, M. G.; Favini, G.; Scolastico, C. *J. Org. Chem.* **1986**, *51*, 612. (b) Hoffmann, R. W.; Ditrich, K.; Froech, S. *Tetrahedron* **1985**, *41*, 5517. (c) Braun, M. *Angew. Chem., Int. Ed. Engl.* **1987**, *26*, 24.

proposed to contribute to the chair and twist boat transition structures, respectively, using the bulky auxiliary. However, an understanding of further mechanistic aspects of the reaction is required to give marked improvement in synthetic efficiency. Efforts toward this end are currently underway in our laboratory.

Supporting Information Available: Experimental details. This material is available free of charge via the Internet at http://pubs.acs.org.

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