## Powerful Stereoselective Aldol-type Additions of Phenyl and Phenylthio Esters with Aldehydes or Ketones Mediated by TiCl<sub>4</sub>/Amine Reagent

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Abstract: An efficient TiCl<sub>4</sub>/amine-promoted aldol-type addition of phenyl and phenylthio esters with aldehydes or ketones has been performed. The present method includes a practical merit from the green chemical viewpoint with regard to yields, variations of substrates, availability of reagents, and simple operations.

Key words: aldol reactions, titanium, stereoselectivity, esters, amines

The aldol-type addition of esters with carbonyl acceptors (aldehydes or ketones) has been extensively investigated due to its wide utility in organic syntheses, particularly the straightforward access to useful  $\beta$ -hydroxyl esters.<sup>1</sup> Two methods are representative for this objective: (1) ester metal enolates, which are generated by strong basic reagents such as LDA and Li(K)HMDSO (metal exchanged enolates are also employable), react with the carbonyl acceptors, and (2) esters are converted to reactive ketene silyl acetals, which react with carbonyl acceptors that are promoted by a variety of catalysts (the Mukaiyama protocol).

Direct aldol-type addition of esters with carbonyl acceptors using Lewis acids combined with amines has several advantages: simple procedure, high regio- and stereoselectivity, and tolerance to basic labile functionalities. Due to a lower enolization ability than that of ketones or aldehydes, however, there have been a few successes to this end, namely, the protocols using diazabromoborane (Corey's group),<sup>2</sup> dicyclohexyliodoborane (Brown's group)<sup>3</sup> and boron triflate (Masamune and Abiko's group).<sup>4</sup> These leading achievements prompted us to investigate a direct aldol-type addition of simple esters using a more powerful, accessible and economic agent from the recent green chemical point of view. Consistent with our continuous interests in Ti- or Zr-Claisen and aldol reactions,<sup>5</sup> we report direct, powerful, and stereoselective aldol-type additions of phenyl and phenylthio esters 1, 3 with aldehydes and ketones promoted by a cheap and available TiCl<sub>4</sub>/ amine reagent.

First, we examined the reaction of methyl propanoate with benzaldehyde and the desired  $\beta$ -hydroxyl ester was obtained in 51% yield. Unfortunately, the carbonyl acceptor against methyl propanoate seemed to be limited to alde-

hydes lacking  $\alpha$ -protons, that is, an undesirable side selfaldol addition predominately occurred between the two acceptors possessing  $\alpha$ -protons. To overcome the problem, we chose slightly acidic phenyl esters **1** because of the higher acidity of **1** than that of alkyl esters.<sup>5d</sup> Phenyl esters are readily prepared by several methods and are easily hydrolyzed under milder conditions compared with alkyl esters.<sup>6</sup>

Table 1 lists these results.<sup>7</sup> The salient features are as follows. (1) The present method is very powerful due to the specific character of titanium enolates,<sup>5,8</sup> so that not only aldehydes, but also less reactive ketones act as good acceptors to afford desired  $\beta$ -hydroxyl esters 2. (2) Et<sub>2</sub>N is slightly superior to Bu<sub>3</sub>N with regard to yield (entries 1-4) in contrast to the Ti-aldol addition of ketones.<sup>5b,c</sup> (3) The employed substrates covered  $\alpha, \alpha$ -disubstituted phenyl esters (entries 10–15) including basic labile  $\alpha$ -chloro and  $\alpha$ -mesyloxy esters (entries 16–19), which generally undergo further Darzens-type reactions to form  $\alpha,\beta$ -epoxyesters by means of basic media.<sup>9</sup> (4) The reactions of  $\alpha,\alpha$ -disubstituted phenyl esters were performed at 0–5 °C rather than -78 °C, because in contrast to the Zr-Claisen condensation<sup>5d</sup> the competitive side Ti-Claisen condensation could be adequately suppressed even at such higher temperature. (5) The syn-stereoselectivity with aldehydes was moderate to good. (6) TMSCl co-catalyst, which works as an effective promoter in the related Ti-aldol additions,<sup>5c</sup> did not affect the present reaction. (7) The key intermediate for the synthesis of an useful perfume, a furanone analog of dehydrojasmone, was more easily prepared than in the previously reported method (entry 20).10,11

The use of phenylthio or 4-nitrophenylthio esters **3** instead of phenyl esters **1** has a notable advantage. Table 2 lists these results and the salient features are as follows.<sup>12</sup> (1) These reactions proceeded in excellent yields in every case examined except for a few cases to afford the desired  $\beta$ -hydroxyl thioesters **4**, whose fact suggests a complete Ti-enolate formation. (2) In contrast to the case using phenyl esters **1**, Bu<sub>3</sub>N is slightly superior to Et<sub>3</sub>N with regard to yield (entries 1 and 2). (3)  $\alpha$ , $\alpha$ -Disubstituted phenylthio esters also underwent the additions at 0–5 °C (entries 9– 12). (4) After screening several arylthio propanoates,<sup>13</sup> the reaction using the 4-nitrothiophenyl analog to benzaldehyde proceeded with high *syn*-stereoselectivity (entry 13).

In conclusion, the present protocol includes practical advantages from the viewpoint of green chemistry, for ex-

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R <sup>2</sup>		R <sup>3</sup> R <sup>4</sup> R <sup>3</sup> ,.,		он			
R <sup>1</sup>	℃O <sub>2</sub> Ph	TiCl <sub>4</sub> - Et <sub>3</sub>	N R4	$R^2 R^1$	PI		
1				2	2		
Entry	$\mathbb{R}^1$	R <sup>2</sup>	<b>R</b> <sup>3</sup>	$\mathbb{R}^4$	Yield	syn/anti <sup>b</sup> (%)	
1	Me	Н	Ph	Н	80	82:18	
2					(75) <sup>c</sup>	(85:15)	
3	Me	Н	<i>n</i> -Pr	Н	84	84:16	
4					(76) <sup>c</sup>	(84:16)	
5	Me	Н	<i>i</i> -Pr	Н	79	89:11	
6	Me	Н	Ph	Et	83	64:36	
7	Me	Н	Et	Et	77	_	
8	Me	Н	Ph	CH <sub>2</sub> Cl	77	68:32	
9	Bu	Н	Ph	Н	76	81:12	
10	Me	Me	Ph	Н	87	_	
11	Me	Me	<i>n</i> -Pr	Н	80	_	
12	Me	Me	<i>i</i> -Pr	Н	80	_	
13	Me	Me	Ph	Et	81	_	
14	Me	Me	Et	Et	73	_	
15	Me	Me	Ph	CH <sub>2</sub> Cl	79	_	
16	Me	Cl	Ph	Н	88	(70:30) <sup>d</sup>	
17	Me	Cl	Et	Et	69	_	
18	Me	OMs	Ph	Н	86	(82:18) <sup>d</sup>	
19	Me	OMs	Et	Et	71	_	
20	<i>n</i> -Pr	Н	Me	CH <sub>2</sub> OA	c 60	n.d.	

<sup>a</sup> These reactions were carried out in  $CH_2Cl_2$  at -78 °C (entries 1–9 and 20) and at 0–5 °C (entries 10–19). Molar ratio/1:ketone or alde-hyde:TiCl<sub>4</sub>:Et<sub>3</sub>N = 1:1.2:1.2:1.4.

<sup>b</sup> These ratios were determined by <sup>1</sup>H NMR (300 MHz) of the crude product.

<sup>c</sup> Use of Bu<sub>3</sub>N in the place of Et<sub>3</sub>N.

<sup>d</sup> Syn/anti was not assigned.

ample, yields are good to excellent, the reagents are cheap and available, and the operation can be performed in a single flask method without using less accessible ketene silyl acetals. Table 2Aldol-type Addition of Phenylthio Esters 3 with Aldehydes or Ketones using  $TiCl_4/Bu_3N^a$ 

Δ



3

Entry	$\mathbb{R}^1$	$\mathbb{R}^2$	R <sup>3</sup>	$\mathbb{R}^4$	Yield	syn/anti <sup>b</sup> (%)				
<ar=p< td=""><td colspan="10"><ar=ph></ar=ph></td></ar=p<>	<ar=ph></ar=ph>									
1	Me	Н	Ph	Н	99	86:14				
2					(94) <sup>c</sup>	(86:14)				
3	Me	Н	Ph	Н	94	86:14				
4	Me	Н	<i>n</i> -Pr	Н	98	82:18				
5	Me	Н	<i>i</i> -Pr	Н	96	81:19				
6	Me	Н	CH <sub>2</sub> CH <sub>2</sub> PH	Н	99	83:17				
7	Me	Н	Et	Et	77	-				
8	Me	Н	Ph	Et	98	77:23				
9	Me	Me	Ph	Н	80	-				
10	Me	Me	<i>n</i> -Pr	Н	76	-				
11	Me	Cl	Ph	Н	97	(70:30) <sup>d</sup>				
12	Me	Cl	<i>n</i> -Pr	Н	86	(80:20) <sup>d</sup>				
<ar=4-no<sub>2-Ph&gt;</ar=4-no<sub>										
13	Me	Н	Ph	Н	99	94:6				
14	Me	Н	<i>n</i> -Pr	Н	97	84:16				
15	Me	Н	<i>i</i> -Pr	Н	98	80:20				
16	Me	Н	Et	Et	87	-				

<sup>a</sup> These reactions were carried out in CH<sub>2</sub>Cl<sub>2</sub> at -78 °C (entries 1-8 and 13-16) and at 0-5 °C (entries 9-12). Molar ratio/**3**:ketone or al-dehyde:TiCl<sub>4</sub>:Bu<sub>3</sub>N = 1:1.2:1.2:1.4.

 $^{\rm b}$  These ratios were determined by  $^1{\rm H}$  NMR (300 MHz) of the crude product.

<sup>c</sup> Use of  $Et_3N$  in the place of  $Bu_3N$ .

<sup>d</sup> Syn/anti was not assigned.

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- (7) A typical Experimental Procedure (Table 1, entry 1): TiCl<sub>4</sub> (1.0 M CH<sub>2</sub>Cl<sub>2</sub>; 1.2 mL) and Et<sub>3</sub>N (142 mg, 1.4 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (0.6 mL) were successively added to a stirred solution of phenyl propanoate (150 mg, 1.0 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (2.0 mL) at -78 °C under an Ar atmosphere. After stirring at the same temperature for 30 min, benzaldehyde (127 mg, 1.2 mmol) was added to the mixture, followed by being stirred at -78 °C for 2 h. The mixture was poured onto ice water (2 mL) with stirring, and was extracted twice with ether. The combined organic phase was washed with water, brine, dried (Na<sub>2</sub>SO<sub>4</sub>) and concentrated. The obtained crude oil was purified by SiO2-column chromatography (hexane-EtOAc = 15:1 - 5:1) to give phenyl 3-hydroxy-2-methyl-3phenylpropanoate (205 mg, 80%; syn:anti = 82:18). Colorless oil; <sup>1</sup>H NMR (300 MHz; CDCl<sub>3</sub>):  $\delta = 1.17$  (anti, 0.54 H, d, J = 7.1 Hz, 1.32 (syn, 2.46 H, d, J = 7.1 Hz), 3.04–3.11 (1 H, m), 4.86 (*anti*, 0.18 H, d, J = 8.5 Hz), 5.14 (syn, 0.82 H, d, J = 5.1 Hz), 6.87–7.07 (2 H, m), 7.17–7.27 (1 H, m), 7.25–7.44 (7 H, m); <sup>13</sup>C NMR (75 MHz; CDCl<sub>3</sub>):  $\delta = 11.52, 14.40, 46.95, 47.40, 74.18, 76.41, 121.47, 121.56,$ 125.89, 126.21, 126.67, 127.80, 128.21, 128.40, 128.56, 129.34, 141.39, 150.41, 150.57, 173.88, 174.28; IR(neat):

3484, 3065, 3032, 2983, 2940, 2882, 1753, 1493, 1196, 1163, 702  $\rm cm^{-1}.$ 

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- (11) Reformatsky reaction of ethyl 2-bromoheptanoate with acetoxy acetone proceeded in 40–50%.
- (12) A typical Experimental Procedure (Table 2, entry 1): TiCl<sub>4</sub> (1.0 M CH<sub>2</sub>Cl<sub>2</sub>; 1.2 mL) and Et<sub>3</sub>N (142 mg, 1.4 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (0.6 mL) were successively added to a stirred solution of phenylthio propanoate (83 mg, 0.50 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (1.0 mL) at -78 °C under an Ar atmosphere. After stirring at the same temperature for 30 min, benzaldehyde (58 mg, 0.55 mmol) was added to the mixture, followed by being stirred at -78 °C for 2 h. The mixture was poured onto ice water (2 mL) with stirring, and was extracted twice with ether. The combined organic phase was washed with water, brine, dried (Na<sub>2</sub>SO<sub>4</sub>) and concentrated. The obtained crude oil was purified by SiO2-column chromatography (hexane:EtOAc = 7:1) to give phenylthio 3-hydroxy-2methyl-3-phenylpropanate (135 mg, 99%, syn:anti = 86:14). Colorless oil. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):  $\delta = 1.11$  (*anti*, 0.42 H, d, J = 7.1 Hz), 1.26 (syn, 2.58 H, d, J = 7.1 Hz), 3.05(syn, 0.86 H, dq, J = 4.2, 7.1 Hz), 3.12 (anti, 0.14 H, dq, *J* = 7.1 Hz, 8.3 Hz), 4.84 (*anti*, 0.14 H, d, *J* = 8.3 Hz), 5.14 (*syn*, 0.86 H, d, *J* = 4.2 Hz), 7.30–7.43 (10 H, m).
- (13) Substituents such as 4-*t*-Bu, 4-MeO, 4-Cl, and 2-Cl were examined.