ORGANIC LETTERS

2008
Vol. 10, No. 21
4999−5001

Asymmetric Mukaiyama Aldol Reaction of Nonactivated Ketones Catalyzed by *allo*-Threonine-Derived Oxazaborolidinone

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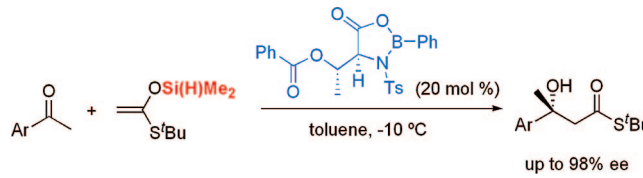
Received September 5, 2008

ABSTRACT



Asymmetric Mukaiyama aldol reaction of nonactivated ketones is realized for the first time by using an oxazaborolidinone catalyst derived from *O*-benzoyl-*N*-tosyl-*allo*-threonine. By employing a dimethylsilyl ketene *S*,*O*-acetal as a nucleophile, a variety of acetophenone derivatives afford the corresponding tertiary β-hydroxy carbonyl compounds with high enantioselectivity up to 98% ee.

Chiral tertiary alcohols are important subunits frequently found in biologically active compounds. Recently, catalytic asymmetric aldol addition to ketone acceptors has received growing attention since the resulting tertiary aldols are valuable building blocks for these subunits. A number of efficient Lewis acid catalysts have been developed for the asymmetric Mukaiyama aldol reaction of aldehyde acceptors.[1] However, for the reaction of ketones, successful examples are so far limited to those of highly reactive α-ketoesters and α-diketones.[2,3] The catalytic asymmetric reaction of simple ketones has been realized based upon different approaches.[4−8] The first successful reaction was reported by Denmark and co-workers,[4] employing a trichlorosilyl ketene acetals with chiral Lewis base catalysts. Shibasaki and co-workers[5] have developed an efficient catalytic reaction involving a chiral copper enolate intermediate, by using trimethylsilyl ketene acetals with chiral copper(I) fluoride-phosphine catalysts.[6] Very recently, a new strategy that relies on domino reduction/aldol reaction

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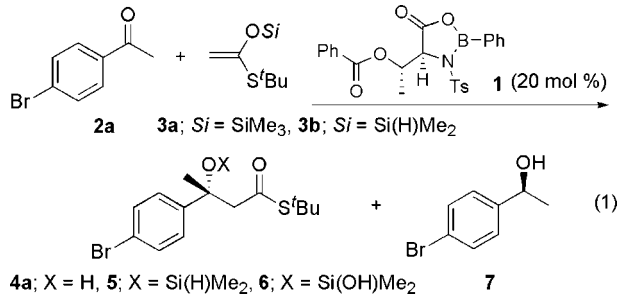
10.1021/ol802087u CCC: $40.75
Published on Web 09/26/2008

sequence between α,β-unsaturated esters and ketones has been developed for the preparation of tertiary aldols with an α-methyl group.[7]

We have recently reported that *allo*-threonine-derived oxazaborolidinone (OXB) **1** is an efficient catalyst for the asymmetric Michael reaction[9a−c] and Diels−Alder reaction[9d,e] of acyclic α,β-unsaturated ketones.[9f] The characteristic feature of the OXB catalyst for the enantioselective activation of the less reactive ketone carbonyl groups prompted us to employ it in the ketone aldol reaction. Herein, we wish to report the first example of the asymmetric Mukaiyama aldol reaction of nonactivated ketones by employing a dimethylsilyl ketene *S*,*O*-acetal as a nucleophile with OXB **1**.

The potential of OXB catalyst **1** in ketone aldol reaction was first evaluated in the reaction of *p*-bromoacetophenone (**2a**) with silyl ketene *S*,*O*-acetals **3a**,**b** (eq 1). The reaction



(1)

with trimethylsilyl derivative **3a** in the presence of **1** (20 mol %) in dichloromethane at −40 °C for 24 h gave aldol product **4a** in 20% yield and 84% ee (Table 1, entry 1). When

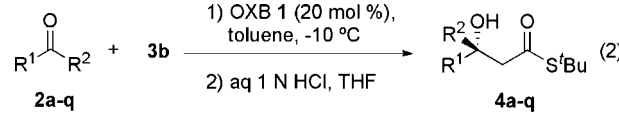
Table 1. Asymmetric Aldol Reaction of *p*-Bromoacetophenone (**2a**) with Silyl Ketene *S*,*O*-Acetals **3a**,**b** Catalyzed by OXB **1**[a]

				yield (%) (ee (%))			
entry	solvent	time (h)	temp (°C)	**4a**[a]	**5**	**6**	**7**
1[b]	CH_2Cl_2	24	−40	20 (84)			
2	CH_2Cl_2	24	−40	19 (90)	9[c]	8[d]	17
3	Et_2O	24	−40	23 (94)	18	5	6
4	Et_2O	97	−10	17 (96)	0	15	31
5	toluene	2	−40	21 (94)	0	0	0
6	toluene	24	−40	25 (93)	0	0	0
7	toluene	48	−10	28 (94)	17	4	5
8	toluene[e]	48	−10	27 (93)	27	14	15
9[f]	toluene[e]	48	−10	68 (94)			13[g]
10[b]	toluene	48	−10	19 (94)			

[a] Unless otherwise noted, reactions were carried out by using **2a** (1.0 mmol), **3b** (1.5 equiv), and OXB **1** (20 mol %) in a solvent (2 mL). [b] **3a** was used as a nucleophile. [c] 91% ee. [d] 90% ee. [e] 0.5 mL of toluene was used. [f] The crude products were treated with aqueous 1 N HCl in THF at room temperature. [g] 44% ee. The absolute configuration was determined to be *S* (see Supporting Information).

dimethylsilyl derivative **3b** was used as a nucleophile under similar conditions, **4a** (90% ee) and its silyl derivatives, **5** (91% ee) and **6** (90% ee), were obtained in 36% combined yield, together with reduction product **7** (entry 2). Encouraged by the improvement in conversion and enantioselectivity, reaction conditions were surveyed for the reaction with **3b**.[10] The reactions in diethyl ether and in toluene exhibited enhanced selectivity at −40 °C (entries 3 and 6). While byproduct formation of **7** became significant at −10 °C in diethyl ether (entry 4), the combined yield of the aldol derivatives **4a**, **5**, and **6** was improved without degrading high enantioselectivity by carrying out the reaction in toluene at −10 °C (entry 7) and at higher concentration (entry 8). Upon treatment with aqueous 1 N HCl in THF, silyl derivatives **5** and **6** were cleanly converted into **4a** without lowering the enantioselectivity. Thus, the reaction mixture of entry 8, after such treatment, afforded **4a** of 94% ee in 68% yield (entry 9).

The scope of the OXB-catalyzed ketone aldol reaction was examined in toluene at −10 °C (eq 2, Table 2). A variety of



(2)

Table 2. Asymmetric Aldol Reaction of Ketones **2a**−**q** with **3b**[a]

entry		ketone R^1	R^2	product	yield (%)	ee (%)
1	**2a**	*p*-BrC_6H_4	Me	**4a**	68	94
2	**2b**	C_6H_5	Me	**4b**	61	91
3[b]	**2c**	*m*-BrC_6H_4	Me	**4c**	76	91
4[b,c]	**2d**	3,5-$Br_2C_6H_3$	Me	**4d**	78	94
5	**2e**	*o*-BrC_6H_4	Me	**4e**	36	92
6[b,d]	**2f**	*p*-ClC_6H_4	Me	**4f**	65	93
7[b,d]	**2g**	*m*-ClC_6H_4	Me	**4g**	65	95
8[b,d]	**2h**	*p*-$CF_3C_6H_4$	Me	**4h**	68	92
9[b,d]	**2i**	*m*-$CF_3C_6H_4$	Me	**4i**	65	94
10[b,d]	**2j**	*p*-$EtOCOC_6H_4$	Me	**4j**	68	94
11[e]	**2k**	*p*-$NO_2C_6H_4$	Me	**4k**	53	98
12	**2l**	*p*-MeC_6H_4	Me	**4l**	53	92
13	**2m**	*p*-$MeOC_6H_4$	Me	**4m**	54	81
14	**2n**	2-naphthyl	Me	**4n**	44	97
15	**2o**	2-thienyl	Me	**4o**	40	55
16	**2p**	$C_6H_5CH_2CH_2$	Me	**4p**	51	52
17	**2q**	C_6H_5	Et	**4q**	23	66

[a] Unless otherwise noted, reactions were carried out with **2** (1.0 mmol), **3b** (1.5 mmol), and **1** (0.2 mmol) in toluene (0.5 mL) at −10 °C for 48 h. [b] 1.5 mL of toluene was used. [c] The reaction was carried out for 9 h. [d] The reaction was carried out for 21 h. [e] The reaction was carried out at room temperature.

acetophenone derivatives bearing substituents at the *para*-, *meta*-, or *ortho*-position underwent reaction with **3b** to give the corresponding aldol products **4** in high enantioselectivity (91−98% ee) and in satisfactory yield (entries 1−12). Specifically, aldol products **4j** and **4k** bearing ethoxycarbonyl and nitro groups, respectively, could be prepared

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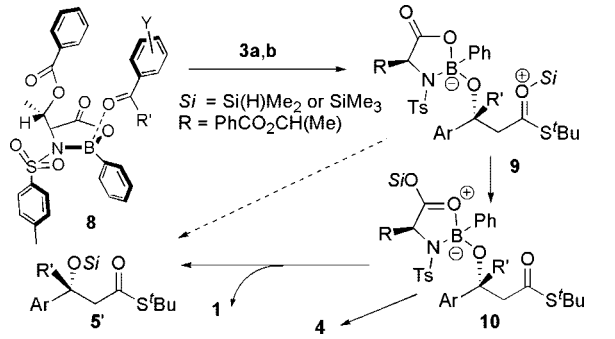
(10) For the advantageous use of dimethylsilyl enolates, see ref 9b and references therein.

enantioselectively (entries 10 and 11). High selectivity was also obtained in the reaction of 2-naphthophenone (**2n**) (entry 14), while on the other hand the reactions of heteroaromatic ketone **2o**, aliphatic ketone **2p**, and ethyl ketone **2q** resulted in lower selectivity (entries 15−17). The reactions were sluggish for *o*-bromo derivative **2e** (entry 5) and **2l** and **2m** with electron-donating substituents at the *para*-position (entries 12 and 13).

The absolute stereochemical course of the present reaction[11] is rationalized in terms of an activated complex model **8**, in which nucleophile **3b** attacks selectively from the open *re* face of a ketone (Scheme 1). The attack of ketene silyl

Scheme 1. Plausible Reaction Pathway



acetal **3a,b** to activated enone **8** first generates unstable intermediate **9**. A pathway involving direct silyl-group migration of **9** to give **5′** is less likely from the following observation. In the reaction of **2a** with **3b**, the formation of **4a** (21%) was relatively fast at −40 °C (entry 5 in Table 1). However, prolonged reaction time and higher temperature were required for the reaction to proceed in a catalytic manner, leading to the formation of the silyl derivatives **5** and **6** as well as **4a** (entries 7 and 8). The result can be rationalized by assuming a stepwise silyl-group migration via silyl ester **10**;[12] initial rapid migration to form **10** followed by slow formation of **5′** with regeneration of OXB **1**. According to this pathway, at the low temperature, the reaction stopped at **10** to give **4** after hydrolysis as an exclusive aldol product. At higher temperature, transformation of **10** to **5′** proceeded slowly to afford the observed mixture of products after workup.[13] In the reaction with trimethylsilyl derivative **3a**, the formation of the corresponding silyl product **5′** was not observed even at −10 °C after 48 h (entry 10). The result suggests that the crucial conversion of silyl ester **10** into **5′** is accelerated significantly for the dimethylsilyl derivative in comparison with the trimethylsilyl derivative.

In summary, we have developed an OXB-catalyzed asymmetric aldol reaction of nonactivated aromatic ketones, providing tertiary β-hydroxy carbonyl compounds with high enantioselectivity. The use of dimethylsilyl ketene *S*,*O*-acetal **3b**, in place of the conventional trimethylsilyl derivative **3a**, is shown to be essential to achieve catalytic reaction and high selectivity.

Acknowledgment. This work was supported partially by a grant from the Ministry of Education, Science, Sports and Culture of the Japanese Government (Grant-in-Aid for Scientific Research no. 17550101).

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

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(11) For the absolute structure determination of **4b** and **4q**, see Supporting Information.

(12) An analogous silyl ester intermediate was proposed previously for a oxazaborolidinone-catalyzed aldol reaction: Parmee, E. R.; Tempkin, O.; Masamune, S.; Abiko, A. *J. Am. Chem. Soc.* **1991**, *113*, 9365–9366.

(13) Treatment of **5** (93% ee) with an equimolar amount each of **2a** and **1** in toluene at −10 °C for 18 h gave **6** (30% yield, 93% ee) and **7** (28% yield, 34% ee). The result suggests that, during the reaction, a part of **5** is converted into the hydroxydimethylsilyl derivative by the reaction with **2a**.