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Dimethylsilyl Ketene Acetal as a Nucleophile in Asymmetric Michael Reaction: Enhanced Enantioselectivity in Oxazaborolidinone-Catalyzed Reaction

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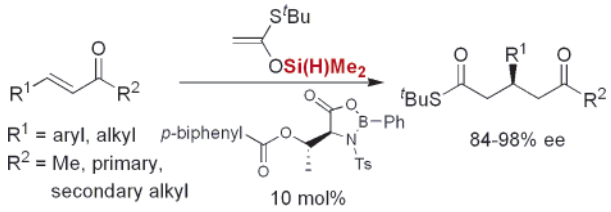
ABSTRACT



Dimethylsilanyl [$Me_2Si(H)$] ketene *S,O*-acetal 6b is an effective nucleophile that retards the undesirable Si^+-catalyzed racemic pathway in the oxazaborolidinone-catalyzed asymmetric Michael reaction. Through the further suppression of the Si^+-catalyzed pathway by carrying out the reaction in the presence of 2,6-diisopropylphenol and *t*-BuOMe as additives, enantioselectivity up to 98% ee could be achieved for a variety of acyclic enones.

The Michael reaction is one of the fundamental methods used for constructing 1,5-dicarbonyl skeletons in organic synthesis. Recently, catalytic asymmetric versions of this reaction have received extensive attention in this regard,[1] and major progress has been made in effecting asymmetric Michael reactions using enolate anions generated in situ.[2,3] A limitation of this approach, however, is the fact that the process is often limited to nucleophilic partners that readily enolize, such as active methylene compounds and nitromethane. For the much less acidic ketone and carboxylic acid derived nucleophiles, alternative approaches must be used that exploit silyl enolates as the active nucleophiles in the presence of chiral Lewis acids. Indeed, the Mukaiyama−Michael reaction is now of major synthetic importance.[4,5]

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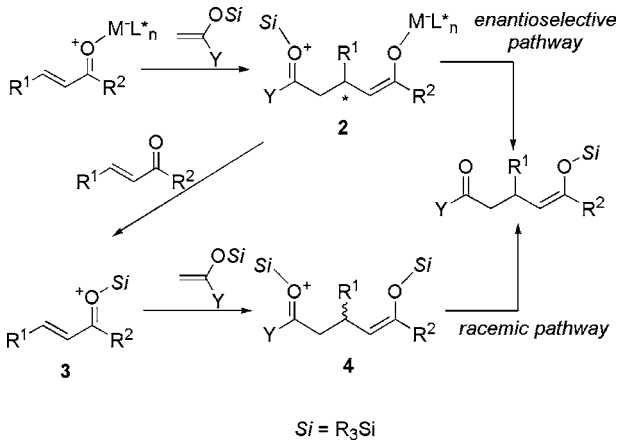
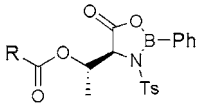
Scheme 1. Enantioselective versus Racemic Pathway in Asymmetric Michael Reaction



Despite recent advances, application of the asymmetric Mukaiyama−Michael reaction to simple acyclic enones has remained a challenging issue in this field. Recently, we found that the chiral oxazaborolidinone (OXB) catalysts **1** were highly effective for promoting the Mukaiyama−Michael reaction on acyclic enones.[6] By using 10 mol % of these catalysts in the presence of 2,6-diisopropylphenol and *t*-BuOMe as additives, the reactions of alkenyl methyl ketones with a trimethylsilyl (TMS) ketene *S,O*-acetal afforded Michael adducts in up to 90% ee.

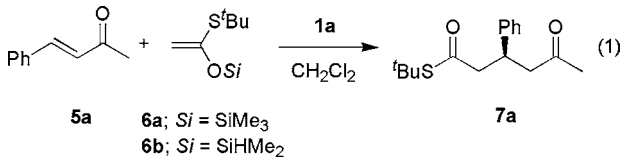
Herein we wish to report that the use of a dimethylsilanyl ($Me_2Si(H)$) ketene *S,O*-acetal as a nucleophile,[7] in place of the conventional TMS derivative, not only enhances the enantioselectivity of the OXB-catalyzed asymmetric Michael reaction but also expands the scope of the reaction with respect to the enone structure.



1a; R = *p*-biphenyl
1b; R = 2-naphthyl

Along a plausible reaction pathway for a chiral Lewis acid catalyzed Mukaiyama−Michael reaction, the silyl group of the intermediate **2** needs to migrate to a relatively remote enolate oxygen atom in order to regenerate the active catalyst (ML^*_n) (Scheme 1). In competition with this, the silyl group tends to be transferred intermolecularly to the starting enone to form intermediate **3**, leading to the formation of racemic enolsilane product through **4**.[8]

Indeed, the Si^+-catalyzed racemic pathway is predominant when the OXB-catalyzed reaction is carried out in the absence of the phenolic and ethereal additives. Thus, the reaction of benzalacetone (**5a**) and TMS ketene *S,O*-acetal **6a** (1.5 equiv) catalyzed by OXB **1a** (20 mol %) gave adduct **7a** of only in 18% ee (82% yield) (eq 1). In sharp contrast to this, the reaction using dimethylsilanyl ketene acetal **6b** as a nucleophile afforded **7a** in 62% ee and 71% yield. The observed improvement in enantioselectivity suggested that the dimethylsilanyl group is less prone to catalyze the racemic pathway than the conventionally used trimethylsilyl group.



5a **6a**; *Si* = $SiMe_3$ **7a**
6b; *Si* = $SiHMe_2$

As reported previously,[6] the Si^+-catalyzed racemic pathway in the OXB-catalyzed asymmetric Michael reaction with the TMS ketene acetal can be suppressed by the use of 2,6-diisopropylphenol as an additive, which traps intermediate **2** (ML^*_n = OXB) to form the Michael adduct and 2,6-diisopropylphenyl trimethylsilyl ether with regeneration of the catalyst. The superior result observed for $Me_2Si(H)$ derivative **6b** encouraged us to optimize the reaction conditions using the phenolic additive.

An enantioselectivity of 91% ee was observed when the reaction of **5a** was carried out with $Me_2Si(H)$ derivative **6b** in the presence of 2,6-diisopropylphenol (1 equiv) (Table 1, entry 2). In accord with our previous observations that the effect of the phenolic additive is enhanced by using *t*-BuOMe as a second additive,[6b] the combined use of the phenol (1 equiv) and the ether (2 equiv) improved the enantioselectivity to 96% ee (entry 4). The advantage of $Me_2Si(H)$ derivative is shown by lower ee observed for the TMS derivative **6a** under the similar conditions (entry 5). The use of *t*-BuOMe in the absence of the phenol was not effective (entry 3).

The observed high enantioselectivity was maintained when the catalyst load was reduced to 10 mol %, but the level of conversion was lower (entry 6). This result suggested ketene acetals had lower reactivity compared to that of their TMS counterparts. According to the previously optimized protocol,[6c] these reactions were best carried out by adding a mixture of enone **5a** and the phenol slowly over 6 h to a solution of the nucleophile and the OXB and by quenching immediately after the completion of the addition. Complete conversion of the enone to the product was achieved without lowering of the enantioselectivity by carrying out the reaction for an additional 12 h after the slow addition was complete (entry 7). However, even without using the slow addition procedure, relatively high selectivity was still obtained in the reaction of **6b** (entries 8 and 9).

The scope of the OXB-catalyzed asymmetric Michael addition of various acyclic enones **5a**−**m** with **6b** was investigated under the optimized conditions (eq 2, Table 2). In contrast to the reaction with TMS derivative **6a**, superior

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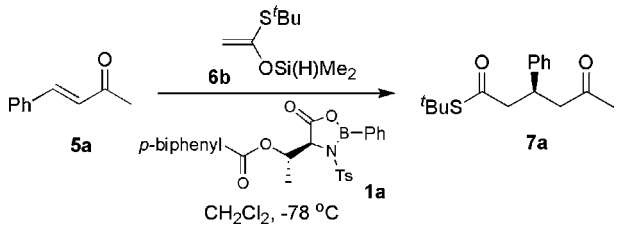
Table 1. Asymmetric Michael Reaction of Benzalacetone with $Me_2Si(H)$ Ketene Acetal **6b** Catalyzed by OXB **1a**[a]



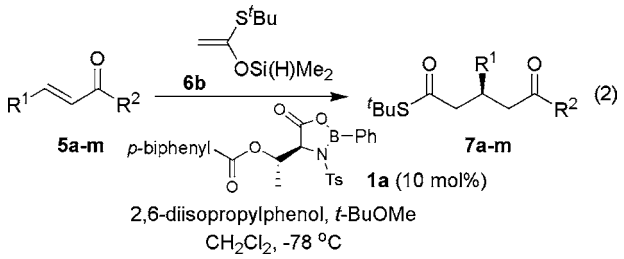
entry	**1a** (mol %)	diisopropyl-phenol (equiv)	*t*-BuOMe (equiv)	yield (%)	ee[b] (%)
1	20	0	0	71	62
2	20	1	0	71	91
3	20	0	2	73	62
4	20	1	2	70	96
5[c]	20	1	2	88	89
6	10	1	1	52	95
7[d]	10	1	1	78	94
8[e]	10	1	0	40	93
9[f]	10	1	0	42	90

[a] Unless otherwise noted, reactions were carried out at −78 °C by adding a CH_2Cl_2 solution of **5a** (1 M) and 2,6-diisopropylphenol to a CH_2Cl_2 solution of OXB **1a** (0.1 M), **6b** (1.5 equiv), and *t*-BuOMe over 6 h. [b] Determined by chiral phase HPLC using a Chiralpak AD column. [c] TMS derivative **6a** was used as a nucleophile. [d] Additional 12 h of stirring after the completion of slow addition. [e] Slow addition for 2 h. [f] Slow addition procedure was not applied. The reaction mixture was stirred for 6 h.

enantioselectivities (>90% ee) were obtained for a variety of alkenyl methyl ketones **5a**−**j** (R^2 = Me) with β-aryl (entries 1−7), -alkyl (entry 8), and functionalized substituent (entry 9). Of these, the high selectivity (98% ee) observed for **5h** (R^1 = Me) is particularly noteworthy. In the reaction with TMS derivative **6a**, enantioselectivity was moderate for ethyl and isopropyl ketones **5j**,**m**.[6] As revealed in entries 10−13, the reaction with **6b** was tolerant of variation in the alkyl group R^2 (primary and secondary), exhibiting high selectivity (84−94% ee). Therefore, the use of $Me_2Si(H)$ derivative **6b** as a nucleophile significantly expands the scope of the OXB-catalyzed asymmetric reaction. To demonstrate the preparative utility of this process, the reaction of enone **5a** with **6b** was carried out on a 10 mmol scale to afford adduct **7a** (2.3 g, 83% yield) in 95% ee (entry 1).

In summary, the use of $Me_2Si(H)$ ketene acetal **6b** as a nucleophile, in place of the conventional TMS ketene acetal, is demonstrated to enhance the enantioselectivity of the OXB-catalyzed asymmetric Michael reaction together with

Table 2. OXB-CatalyzedAsymmetric Michael Reaction of Enones **5a**−**m** with $Me_2Si(H)$ Ketene Acetal **6b**



entry	enone **5**	R^1	R^2	yield of **7** (%)	ee[b,c] (%)
1[d]	**5a**	C_6H_5	Me	83	95 (89)
2	**5b**	*p*-MeC_6H_4	Me	75	95 (86)
3	**5c**	*p*-$MeOC_6H_4$	Me	54	92 (85)
4	**5d**	*p*-ClC_6H_4	Me	72	95 (85)
5	**5e**	*p*-FC_6H_4	Me	63	93 (90)
6	**5f**	*p*-$CF_3C_6H_4$	Me	81	92 (80)
7	**5g**	*m*- $CF_3C_6H_4$	Me	68	95 (89)
8	**5h**	Me	Me	75	98 (89)
9	**5i**	$BnOCH_2$	Me	60	90
10	**5j**	Ph,	Et	85	84 (59)
11	**5k**	Me	Et	79	94
12	**5l**	Ph	Bu	82	88
13	**5m**	Ph	*i*-Pr	64	88 (72)

[a] Unless otherwise noted, reactions were carried out by using enone **5** (1 mmol), OXB **1a** (10 mol %), **6b** (1.5 equiv), 2,6-diisopropylphenol (1 equiv), and *t*-BuOMe (1 equiv) in CH_2Cl_2 at −78 °C. [b] Determined by chiral phase HPLC analysis. [c] ee values obtained in the reaction with TMS ketene acetal **6a** under similar conditions (ref 6c) are shown in parentheses. [d] The reaction was carried out on a 10 mmol scale.

the expansion of the scope of the reaction with respect to the enone structure. The study suggested that the dimethylsilanyl group is effective in retarding the undesirable Si^+-catalyzed racemic pathway. The observation might be utilized in other Lewis acid catalyzed asymmetric reactions.

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Supporting Information Available: Experimental procedure and spectra data for new products. This material is available free of charge via the Internet at http://pubs.acs.org.

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