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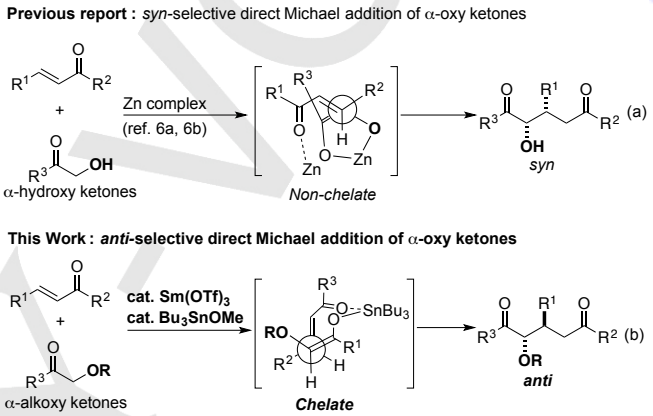
First *anti*-Selective Direct Michael Addition of α-Alkoxyketones to Enones by Cooperative Catalysis of $Sm(OTf)_3$ and Bu_3SnOMe

Naoto Esumi,[a] Yoshihiro Nishimoto,*[b] and Makoto Yasuda*[a]

Abstract: A new highly *anti*-diastereoselective Michael addition of α-alkoxyketones to α,β-unsaturated ketones was achieved. This method features a dual-catalyst protocol that combines $Sm(OTf)_3$ and Bu_3SnOMe. The combination of these two catalysts effectively generates enolate species from α-alkoxyketones and produces Michael adducts in high yields with high *anti*-diastereoselectivity. A variety of enones and α-alkoxyketones were applied to this system to give the *anti*-products. The one-pot domino Michael/aldol reactions effectively afford cyclic enones with defined configuration.

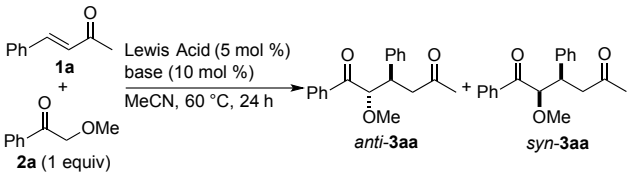
The diastereoselective Michael addition reaction is a powerful and versatile tool in organic synthesis.[1, 2] In particular, much effort has been extended to develop the reaction of enolates as nucleophiles with α,β-unsaturated carbonyl compounds, which is one of the most useful methods for the construction of 1,5-dicarbonyl units.[3] Especially, the ability to directly use carbonyl compounds as nucleophiles is desired for atom- and step-economical reactions. α-Functionalized ketones are applied to various direct catalytic diastereoselective Michael reactions with enones to provide functionalzed 1,5-dicarbonyl compounds. In many cases, however, the functional groups that can be used at the α-position of the carbonyl group has been limited to electron-withdrawing groups because of the ease of enolization.[4] Therefore, demands to extend the diversity of available functional groups have increased. In particular, the application of α-oxycarbonyl compounds such as α-hydroxy- and α-alkoxyketones to yield 2-oxy-1,5-dicarbonyl compounds, which are important building blocks for bioactive compounds,[5] remains a challenging issue. Previous reports have described the *syn*-selective direct catalytic 1,4-addition of α-hydroxyketones to enones catalyzed by dinuclear Zn complexes (Scheme 1a).[6] A catalytic reaction system that could selectively give an *anti*-product, however, has never been reported.[7] Therefore, a methodology for the control of diastereoselectivity is needed, especially for the production of an *anti*-form. In the present study, we present the first highly *anti*-selective direct catalytic Michael addition of α-alkoxyketones to α,β-unsaturated ketones via the combination of a catalytic amount of $Sm(OTf)_3$ and Bu_3SnOMe (Scheme 1b).[8,9] In this reaction system, control of both the geometry of generated metal enolates and the chelated transition state via the combination of catalysts achieved high *anti*-selectivity.



Scheme 1. Catalytic diastereoselective Michael additions by the α-oxy ketones to enones.

The optimization of the reaction conditions of a Michael addition of benzylideneacetone (**1a**) with α-methoxyacetophenone (**2a**) was conducted in the presence of various types of Lewis acids and basic additives (Table 1). The combination of $Sm(OTf)_3$ as a Lewis acid and Bu_3SnOMe as a base[10] afforded the product **3aa** in high yield and high diastereoselectivity (88% yield, *anti*/*syn* = 93:7) (entry 1). Using other lanthanide triflate catalysts such as $La(OTf)_3$, $Yb(OTf)_3$, and $Sc(OTf)_3$ gave the product **3aa** in lower yields (entries 2–4), but some main group metal and transition metal catalysts were not effective (entries 5–9). The addition reaction was significantly suppressed in the absence of either $Sm(OTf)_3$ or Bu_3SnOMe (entries 10 and 11). When other basic additives such as an amine or sodium alkoxide were used, the reactions resulted in only moderate yields and moderate diastereoselectivities (entries 12–14). These results clearly show that the combination of $Sm(OTf)_3$ and Bu_3SnOMe contributed to both high yield and high diastereoselectivity.

Table 1. Optimization of reaction conditions of the *anti*-selective Michael addition.[a]



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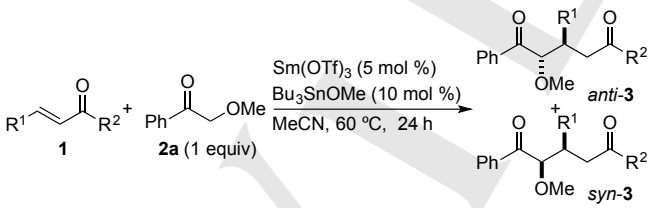
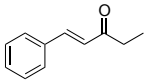
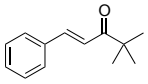
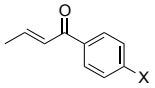
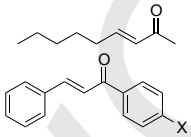
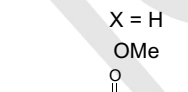
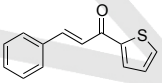
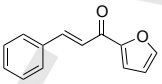
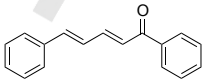
Entry	Lewis acid	basic additives	Yield [%][b]	*anti/syn*[c]
1	$Sm(OTf)_3$	Bu_3SnOMe	88(84)[d]	93:7
2	$La(OTf)_3$	Bu_3SnOMe	79	90:10
3	$Yb(OTf)_3$	Bu_3SnOMe	42	94:6
4	$Sc(OTf)_3$	Bu_3SnOMe	50	89:11
5	$In(OTf)_3$	Bu_3SnOMe	<5	Nd
6	$Sn(OTf)_2$	Bu_3SnOMe	0	Nd
7	$Zn(OTf)_2$	Bu_3SnOMe	7	Nd
8	AgOTf	Bu_3SnOMe	<5	Nd
9	$Cu(OTf)_2$	Bu_3SnOMe	<5	Nd
10	none	Bu_3SnOMe	0	Nd
11	$Sm(OTf)_3$	none	11	85:15
12	$Sm(OTf)_3$	*i*Pr_2NEt	61	75:25
13	$Sm(OTf)_3$	NaOMe	73	78:22
14	$Sm(OTf)_3$	NaO*t*-Bu	70	83:17

[a] Reaction conditions: **1a** (1.0 mmol), **2a** (1.0 mmol), Lewis acid (0.050 mmol), basic additives (0.10 mmol), MeCN (1.0 mL), 60 °C, 24 h. [b] Determined by ^{1}H NMR analysis using 1,1,2,2-tetrachloroethane as the internal standard. [c] Determined by ^{1}H NMR analysis of the crude products. [d] Isolated yield.

With the optimized reaction conditions in hand (Table 1, entry 1), various enones **1** were applied to the reaction of α-methoxyacetophenone (**2a**), as shown in Table 2. β-Aryl substituted enones **1a**–**1e** furnished the corresponding products in high yields and high *anti*-selectivity (entries 1–5).[11] The sterically hindered enone **1f** was also applicable to afford the product **3fa** (entry 6). Excellent yields were obtained in the reactions of aromatic enones bearing electron-withdrawing and electron-donating groups **1g**–**1i** (entries 7–9). It is noteworthy that aliphatic enone **1j** was also applied to this reaction system to give **3ja** in high yield and high selectivity (entry 10). Chalcone derivatives **1k** and **1l** furnished the corresponding products **3ka** and **3la**, respectively, in a high yield with a high level of diastereoselectivity (entries 11 and 12). The heteroaryl-substituted enones **1m** and **1n** were smoothly converted to the corresponding Michael addition products **3ma** and **3na**, respectively (entries 13 and 14). The reaction of highly conjugated enone **1o** also proceeded to provide the corresponding 1,4-addition product **3oa** (entry 15). Unfortunately, the reaction of cyclic enone **1p** resulted in a very low yield (entry 16).

Table 2. Substrate scope of enones **1**.[a]

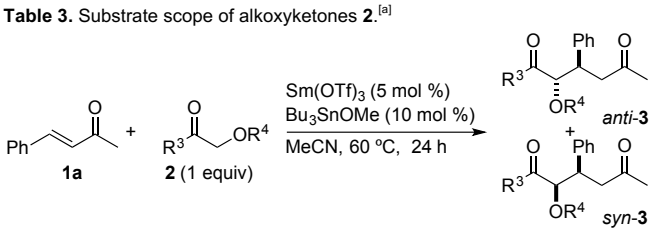


Entry	1		Product	Yield [%][b]	*anti/syn*[c]
1	X = H	**1a**	**3aa**	84	93:7
2	Cl	**1b**	**3ba**	83	92:8
3	Me	**1c**	**3ca**	83	93:7
4	OMe	**1d**	**3da**	76	91:9
5		**1e**	**3ea**	70	94:6
6[d]		**1f**	**3fa**	80	95:5
7	 X = H	**1g**	**3ga**	84	96:4
8	Cl	**1h**	**3ha**	91	94:6
9	OMe	**1i**	**3ia**	85	95:5
10[e]		**1j**	**3ja**	75	93:7
11[f]	 X = H	**1k**	**3ka**	89	91:9
12[f]	OMe	**1l**	**3la**	87	92:8
13[f]		**1m**	**3ma**	89	96:4
14[f]		**1n**	**3na**	89	95:5
15[d,f]		**1o**	**3oa**	79	95:5
16		**1p**	**2pa**	<5	nd

[a] Reaction conditions: **1** (1.0 mmol), **2a** (1.0 mmol), Bu_3SnOMe (0.10 mmol), $Sm(OTf)_3$ (0.050 mmol), MeCN (1.0 mL), 60 °C, 24 h. [b] Isolated products. [c] Determined by ^{1}H NMR analysis of the crude products. [d] $Sm(OTf)_3$ (10 mol %) was used. [e] THF was used instead of MeCN. [f] The reaction was performed at 40 °C.

Next, the reactions of various α-alkoxyketones **2** with benzylideneacetone (**1a**) were investigated, as shown in Table 3. In the reactions of *o*-, *m*-, and *p*-methylated α-methoxyacetophenones **2b**–**2d**, the position of Me group on the aryl ring of methoxyacetophenones had little effect on either yield or diastereoselectivity (entries 1–3). Naphthyl substituted ketone **2e** provided high yield and high *anti*-selectivity (entry 4). Although the yield of **3af** was low, aliphatic methoxyketone **2f** was also applicable to this reaction system (entry 5). The reaction of isopropoxy ketone **2g**, which has the greater steric hindrance of an alkoxy group, afforded the corresponding product **3ag** with high diasteoselectivity, although the yield was moderate (entry 6).

Table 3. Substrate scope of alkoxyketones **2**.[a]



Entry	2	Product	Yield [%][b]	*anti/syn*[c]

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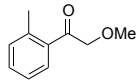
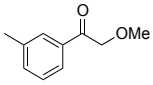
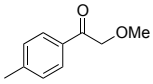
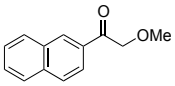
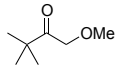
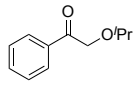
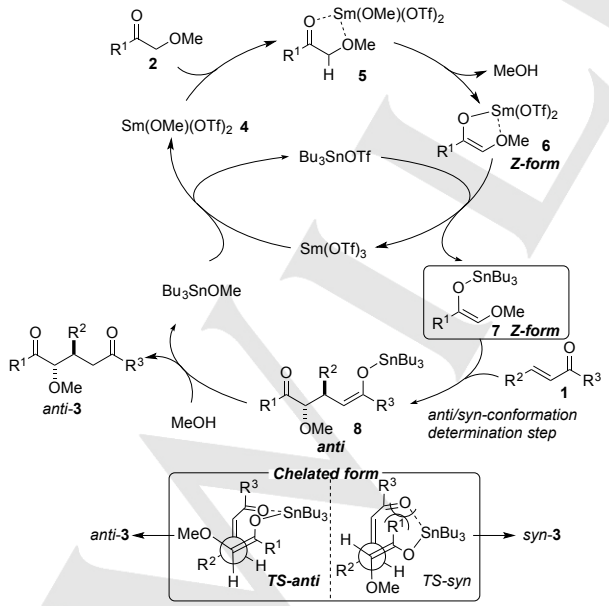
1[d]		**2b**	**3ab**	82	96:4
2		**2c**	**3ac**	79	93:7
3		**2d**	**3ad**	74	94:6
4[d]		**2e**	**3ae**	81	93:7
5		**2f**	**3af**	24	94:6
6		**2g**	**3ag**	30	92:8

[a] Reaction conditions: **1a** (1.0 mmol), **2** (1.0 mmol), Bu_3SnOMe (0.10 mmol), $Sm(OTf)_3$ (0.050 mmol), MeCN (1.0 mL), 60 °C, 24 h. [b] Isolated products. [c] Determined by ^1H NMR analysis of the crude products. [d] The reaction was performed at 50 °C.

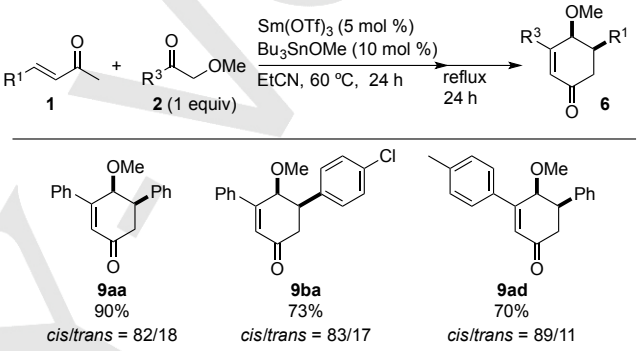
A plausible reaction mechanism is shown in Scheme 2. First, the transmetalation between Bu_3SnOMe and $Sm(OTf)_3$ proceeds to give the samarium methoxide **4** and Bu_3SnOTf.[12] Samarium methoxide **4** is coordinated by alkoxyketone **2** to form the chelate complex **5**, which increases the acidity of the α-proton.[13] Then, a proton abstraction of the methoxy group on the samarium atom effectively affords the samarium enolate species **6** in *Z*-form, because of the chelation effect. In the transmetallation between Bu_3SnOTf and **6**, (*Z*)-tin enolate **7** is formed,[14] and the reaction of **7** with (*E*)-enone **1** affords the corresponding Michael adduct **8** in *anti*-selectivity through the chelated transition state, **TS-*anti***.[15,16,17] The *syn* product is suppressed by the steric repulsion between enone **1** and R^1 in **TS-*syn***. Finally, the protonation of **8** by MeOH yields the product *anti*-**3**, and Bu_3SnOMe is regenerated.



Scheme 2. Plausible reaction mechanism of the *anti*-selective Michael addition of alkoxyketone **2** with enone **1**.

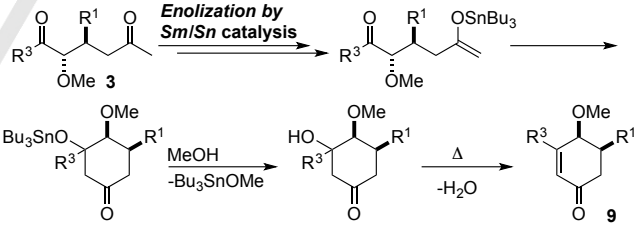
The cooperative $Sm(OTf)_3/Bu_3SnOMe$ system includes two important points that allow the realization of a selective reaction for the *anti*-form, **3**: 1) samarium triflate can have a higher coordination number to give the chelated *Z*-form **6**; and, 2) the chelated transition state ***TS-anti*** includes highly coordinated tin enolates, which is favorable.

During the course of the present study, we found that a direct Michael addition followed by heating at high temperature gave cyclic enones (Scheme 3).[2j, 18] The reaction of enone **1a** with methoxyketone **2a** was conducted under the optimized catalyst system in propionitrile for 24 h, and then the reaction mixture was heated to reflux (ca.115 °C) to afford a *cis*-isomer of cyclic enone **9ba** in a 90% yield.[19, 20] Reaction using either enone **1b** or α-methoxyketone **2d** also gave the corresponding *cis*-isomers **9ba** and **9ad**, respectively, in high yields with high diastereoselectivity.



Scheme 3. Michael/aldol cyclization reaction of enone **1** with alkoxyketone **2**.

A possible reaction mechanism is shown in Scheme 4. The acetyl moiety of Michael adduct **3** is converted into a tin enolate unit by $Sm(OTf)_3/Bu_3SnOMe$. Subsequently, an intramolecular aldol reaction and a dehydration reaction proceed to give the corresponding *cis*-isomer of a cyclic enone.



Scheme 4. Possible mechanism of cyclization reaction of Michael adduct **3**.

In summary, we have developed the first *anti*-selective direct diastereoselective Michael addition reaction of α-alkoxyketones to enones using $Bu_3SnOMe/Sm(OTf)_3$ cooperative catalysis. This reaction is applicable to various types of enones to afford 1,5-dicarbonyl compounds in a high level of *anti*-product. Moreover, the direct Michael addition/intramolecular aldol condensation sequence effectively provided a variety of cyclic enones.

Experimental Section

Typical procedure (Table 2): To a suspended solution of $Sm(OTf)_3$ (0.050 mmol) in acetonitrile (1.0 mL), enone **1** (1.0 mmol), α-methoxyketone **2** (1.0 mmol), and Bu_3SnOMe (0.10 mmol) was added. The reaction mixture

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was stirred for 24 h at 60 °C, and then quenched by NH_4F aq (10%, 10 mL). The mixture was extracted with diethyl ether (10 mL x 3). The collected organic layers were dried over $MgSO_4$, and evaporation of volatiles gave the crude product, which was analyzed by ^1H NMR spectroscopy to decide diastereomeric ratio. The crude product was purified by column chromatography to give the product.

Acknowledgements

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Keywords: Michael addition • tin • samarium • methoxyketones • diastereoselectivity

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[11] The configuration of **3ea** was determined by X-ray structural analysis, see supporting information.

[12] The transmetalation between Bu_3SnOMe and $Sm(OTf)_3$ smoothly proceeded at ambient temperature and the process was observed by ^{13}C NMR, see supporting information.

[13] The coordination of alkoxyketone by samarium methoxide was observed by ^{13}C NMR, see, supporting information.

[14] When Me_3SnOMe was used instead of Bu_3SnOMe, the *anti*-selectivity was quite changed (75% yield, anti/syn = 77/23). This result suggested that the tin enolate generated in *situ* acted as a reactive species of Michael addition step, see supporting information.

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[19] The configuration of major isomer was determined by X-ray structural analysis of **9ba**.

[20] The reaction of **1b** with **2a** in EtCN at 60 °C for 24 h gave the corresponding product **3ab** (91% yield, *anti*/*syn* = 93/7).

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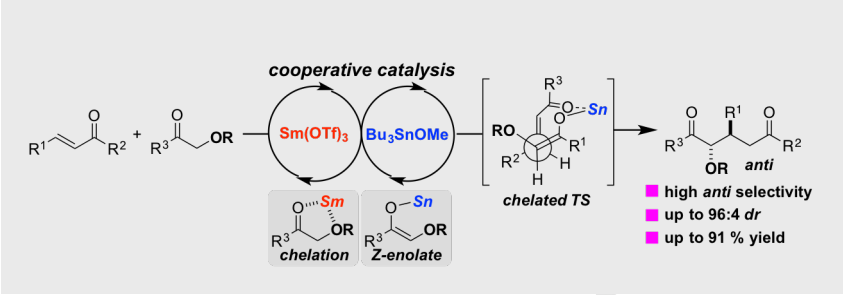

A cooperative Sm/Sn-catalyzed highly *anti*-selective Michael reaction of α-alkoxyketone with enone was achieved. Key to this *anti*-selectivity was the effective generation of (*Z*)-tin enolates by the combination of $Sm(OTf)_3$ and Bu_3SnOMe and the eight-membered chelated transition state. This reaction also provided an efficient access to diastereoselective cyclic enones.

Naoto Esumi,[a] Yoshihiro Nishimoto,[b] and Makoto Yasuda*[a]*

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First *anti*-Selective Direct Michael Addition of α-Alkoxyketones to Enones by Cooperative Catalysis of $Sm(OTf)_3$ and Bu_3SnOMe

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