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Catalytic Asymmetric Three-Component Mannich-Type Reaction of Alkenyl Trichloroacetates

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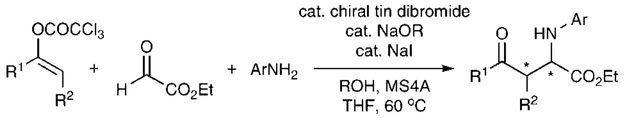
ABSTRACT

A catalytic enantioselective three-component Mannich-type reaction of alkenyl trichloroacetates, ethyl glyoxalate, and aniline derivatives was achieved using an (*S*)-BINOL-derived chiral tin dibromide possessing a 4-trifluoromethylphenyl group at the 3- and 3′-positions as the chiral precatalyst in the presence of sodium ethoxide, sodium iodide, and ethanol. Optically active β-amino ketones with up to 98% ee were *syn*-selectively obtained in high yields even from imines possessing a polar amino group under the influence of the in situ generated chiral tin bromide ethoxide.

The asymmetric Mannich-type reaction is a beneficial method for preparing optically active β-amino carbonyl compounds.[1] Especially, the three-component coupling procedure that uses an enolate (or a ketone), an amine, and an aldehyde is more favorable than the two-component version that uses an enolate (or a ketone) and an imine because it does not require the tedious preparation of imines and is applicable also to aliphatic imines, which are difficult to isolate and purify.[2−4] The three-component method does have a disadvantage in that a moisture-sensitive Lewis acid cannot be used to catalyze the reaction as a stoichiometric amount of water is generated when an imine is formed from an amine and an aldehyde. Furthermore, in the case of a strong Lewis acid catalyst, there is an intrinsic problem that the catalytic activity is decreased due to the coordination of the catalyst with the Mannich product, which is more polar than the starting materials (i.e., product inhibition).[1a,5] We found that an in situ generated chiral tin bromide alkoxide possessing a binaphthyl structure catalyzes the asymmetric three-component Mannich-type reaction of alkenyl trichloroacetate, amine, and aldehyde smoothly even in the presence of water or alcohol as well as a polar substituent, such as an amino group or a phenolic hydroxyl group, in the substrate (Scheme 1).[6] Reported herein are the preliminary results of a novel Mannich-type transformation.

Scheme 1. Chiral Tin-Catalyzed Asymmetric Three-Component Mannich-Type Reaction



First, using chiral tin dibromide **1a**[7] as a chiral precatalyst, we attempted to perform the reaction of 1-trichloroacetoxycyclohexene[8] with ethyl glyoxalate and 4-methoxyaniline. When these substrates were exposed to chiral tin dibromide **1a** (10 mol %), NaOMe (10 mol %), and MeOH (10 equiv) in THF at 60 °C for 0.5 h, the targeted Mannich adduct was obtained in 83% yield with *syn* selectivity, although the enantiomeric excess was low (Table 1, entry 1). To improve the asymmetric induction, some drying agents were tested as an additive, and consequently, Drierite and MS 4A were found to effect higher enantioselectivity (entries 2 and 3). Use of an NaOEt/EtOH combination further increased the

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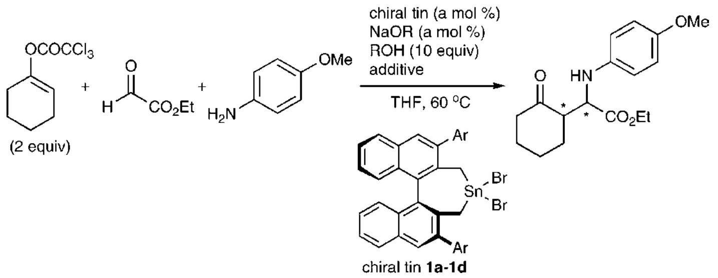
Table 1. Optimization of Catalytic Asymmetric Three-Component Mannich-Type Reaction of Alkenyl Trichloroacetates[a]



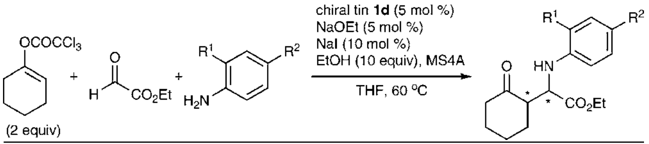
entry	Ar	a	R	additive	time, h	yield, %[b]	*syn*/*anti*[c]	ee, % (*syn*)[d]
1	4-*t*-BuC$_6$H$_4$ (**1a**)	10	Me	–	0.5	83	73/27	4
2	4-*t*-BuC$_6$H$_4$ (**1a**)	10	Me	Drierite	0.25	91	70/30	59
3	4-*t*-BuC$_6$H$_4$ (**1a**)	10	Me	MS4A	0.25	90	70/30	62
4	4-*t*-BuC$_6$H$_4$ (**1a**)	10	Et	MS4A	0.25	>99	70/30	65
5	H (**1b**)	10	Et	MS4A	0.25	97	84/16	22
6	Ph (**1c**)	10	Et	MS4A	0.25	99	71/29	73
7	4-CF$_3$C$_6$H$_4$ (**1d**)	10	Et	MS4A	0.25	>99	70/30	78
8	4-CF$_3$C$_6$H$_4$ (**1d**)	5	Et	MS4A	0.5	>99	70/30	78
9	4-CF$_3$C$_6$H$_4$ (**1d**)	5	Et	MS4A, NaI (10 mol %)	0.5	>99	74/26	83

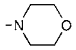
[a] Unless otherwise specified, the reaction was carried out using chiral tin **1a**−**1d** (5 or 10 mol %), sodium alkoxide (5 or 10 mol %), alkenyl trichloroacetate (2 equiv), ethyl glyoxalate (1 equiv), 4-methoxyaniline (1 equiv), alcohol (10 equiv), and additives in THF at 60 °C for the specified reaction time. [b] Isolated yield. [c] Determined by ^{1}H NMR analysis. [d] The value corresponds to the *syn* isomer. Determined by HPLC analysis.

enantiomeric excess of the *syn* isomer to 65% (entry 4). We hereupon examined the catalytic ability of chiral tins other than **1a** and as a result found that **1d** was superior to **1a** with regard to enantioselectivity (entries 4−7). Reducing the amount of the precatalyst to 5 mol % did not affect the chemical yield or the stereoselectivity (entry 8). The optical purity of the *syn* isomer finally reached 83% ee when a catalytic amount of NaI was added (entry 9).

With the optimized reaction conditions in hand, we investigated the catalytic asymmetric three-component Mannich-type reaction using diverse anilines (Table 2). Noteworthy was the fact that the existence of a phenolic OH group, a dialkylamino group, a phenylamino group, or an amide group on the aromatic ring did not significantly lower the reaction rate, and indeed, every reaction was completed within 2 h (entries 2−5). What was even more significant is that an aniline derivative possessing a dimethylamino group afforded the *syn* product with 93% ee (entry 3). These

Table 2. Catalytic Asymmetric Three-Component Mannich-Type Reaction Using Various Anilines[a]



entry	R^1	R^2	time, h	yield, %[b]	*syn*/*anti*[c]	ee, % (*syn*)[d]
1	H	OMe	0.5	>99	74/26	83
2	H	OH	1	>99	77/23	84
3	H	NMe$_2$	1.5	98	72/28	93
4	H	NHPh	2	>99	76/24	81
5	H	NHCOCH$_3$	1.5	>99	75/25	67
6	H		1	86	67/33	86
7	OMe	OMe	1	86	81/19	88

[a] The reaction was carried out using chiral tin **1d** (5 mol %), sodium ethoxide (5 mol %), sodium iodide (10 mol %), alkenyl trichloroacetate (2 equiv), ethyl glyoxalate (1 equiv), an aniline derivative (1 equiv), ethanol (10 equiv), and MS4A in THF at 60 °C for the specified reaction time. [b] Isolated yield. [c] Determined by ^{1}H NMR analysis. [d] The value corresponds to the *syn* isomer. Determined by HPLC analysis.

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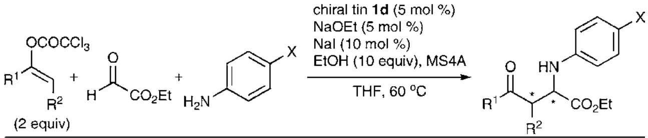
(1) For reviews of catalytic asymmetric Mannich-type reactions, see: (a) Kobayashi, S.; Ishitani, H. *Chem. Rev.* **1999**, *99*, 1069. (b) Córdova, A. *Acc. Chem. Res.* **2004**, *37*, 102. (c) Friestad, G. K.; Mathies, A. K. *Tetrahedron* **2007**, *63*, 2541.

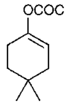
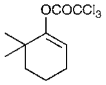
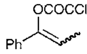
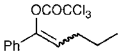
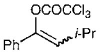
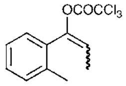
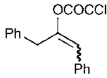
(2) For recent notable examples of catalytic asymmetric two-component Mannich-type reactions, see: (a) Mauksch, M.; Tsogoeva, S. B.; Martynova, I. M.; Wei, S. *Angew. Chem., Int. Ed.* **2007**, *46*, 393. (b) Yang, J. W.; Stadler, M.; List, B. *Angew. Chem., Int. Ed.* **2007**, *46*, 609. (c) Suto, Y.; Kanai, M.; Shibasaki, M. *J. Am. Chem. Soc.* **2007**, *129*, 500. (d) Morimoto, H.; Lu, G.; Aoyama, N.; Matsunaga, S.; Shibasaki, M. *J. Am. Chem. Soc.* **2007**, *129*, 9588. (e) Hashimoto, T.; Maruoka, K. *J. Am. Chem. Soc.* **2007**, *129*, 10054. (f) Cutting, G. A.; Stainforth, N. E.; John, M. P.; Kociok-Köhn, G.; Willis, M. C. *J. Am. Chem. Soc.* **2007**, *129*, 10632. (g) Chen, Z.; Morimoto, H.; Matsunaga, S.; Shibasaki, M. *J. Am. Chem. Soc.* **2008**, *130*, 2170. (h) Zhang, Y.; Liu, Y.-K.; Kang, T.-R.; Hu, Z.-K.; Chen, Y.-C. *J. Am. Chem. Soc.* **2008**, *130*, 2456. (i) Nojiri, A.; Kumagai, N.; Shibasaki, M. *J. Am. Chem. Soc.* **2008**, *130*, 5630. (j) Yalalov, D. A.; Tsogoeva, S. B.; Shubina, T. E.; Martynova, I. M.; Clark, T. *Angew. Chem., Int. Ed.* **2008**, *47*, 6624. (k) Lu, G.; Morimoto, H.; Matsunaga, S.; Shibasaki, M. *Angew. Chem., Int. Ed.* **2008**, *47*, 6847. (l) Uraguchi, D.; Koshimoto, K.; Ooi, T. *J. Am. Chem. Soc.* **2008**, *130*, 10878. (m) Gianelli, C.; Sambri, L.; Carlone, A.; Bartoli, G.; Melchiorre, P. *Angew. Chem., Int. Ed.* **2008**, *47*, 8700. (n) Morimoto, H.; Yoshino, T.; Yukawa, T.; Lu, G.; Matsunaga, S.; Shibasaki, M. *Angew. Chem., Int. Ed.* **2008**, *47*, 9125. (o) Du, Y.; Xu, L.-W.; Shimizu, Y.; Oisaki, K.; Kanai, M.; Shibasaki, M. *J. Am. Chem. Soc.* **2008**, *130*, 16146. (p) Hernández-Toribio, J.; Arrayás, R. G.; Carretero, J. C. *J. Am. Chem. Soc.* **2008**, *130*, 16150. (q) Hatano, M.; Maki, T.; Moriyama, K.; Arinobe, M.; Ishihara, K. *J. Am. Chem. Soc.* **2008**, *130*, 16858. (r) Kano, T.; Yamaguchi, Y.; Maruoka, K. *Angew. Chem., Int. Ed.* **2009**, *48*, 1838. (s) Chandler, C.; Galzerano, P.; Michrowska, A.; List, B. *Angew. Chem., Int. Ed.* **2009**, *48*, 1978. (t) Xu, Y.; Lu, G.; Matsunaga, S.; Shibasaki, M. *Angew. Chem., Int. Ed.* **2009**, *48*, 3353.

results proved that chiral tin alkoxides were virtually unaffected by polar products, in marked contrast to classical Lewis acids.[9] The introduction of an additional MeO group to the *o*-position of 4-methoxyaniline resulted in a better *syn*/*anti* ratio as well as a higher enantiomeric excess (compare entries 1 and 7).

The usefulness of the present asymmetric Mannich-type reaction was further exemplified by employing various alkenyl trichloroacetates of ketones as shown in Table 3.

Table 3. Catalytic Asymmetric Three-Component Mannich-Type Reaction Using Various Alkenyl Esters[a]



entry	alkenyl ester	X	time, h	yield, %[b]	*syn*/*anti*[c]	ee, % (*syn*)[d]
1		OMe	1	99	77/23	88
2		NMe$_2$	1	96	75/25	94
3		OMe	20	60	57/43	94
4	 *E*/*Z* = 19/81	OMe	20	89	57/43[e]	94
5	 *E*/*Z* = 27/73	OMe	20	89	68/32[e]	97
6		NMe$_2$	20	73	71/29[e]	98
7[f]	 *E*/*Z* = 30/70	OMe	20	73	77/23[e]	98
8	 *E*/*Z* = 70/30	OMe	20	63	73/27[e]	96
9	 *E*/*Z* = 55/45	OMe	20	77	65/35[e]	97

[a] The reaction was carried out using chiral tin **1d** (5 mol %), sodium ethoxide (5 mol %), sodium iodide (10 mol %), alkenyl trichloroacetate (2 equiv), ethyl glyoxalate (1 equiv), an aniline derivative (1 equiv), ethanol (10 equiv), and MS4A in THF at 60 °C for the specified reaction time. [b] Isolated yield. [c] Determined by ^{1}H NMR analysis. [d] The value corresponds to the *syn* or major diastereomer. Determined by HPLC analysis. [e] The diastereomeric ratio. [f] Chiral tin **1d** (10 mol %), sodium ethoxide (10 mol %), and sodium iodide (20 mol %) were used.

Not only cyclic alkenyl esters but also acyclic ones underwent the three-component coupling, although prolonged reaction times were necessary to obtain satisfactory isolated yields (entries 4−9). As for cyclohexanone derivatives, the inclusion of bulky substituents at the appropriate position seemed to contribute to effective enantioface discrimination (entries 1−3). In contrast, acyclic alkenyl esters generally showed superior enantioselectivity of up to 98% ee despite the fact that a mixture of *E*/*Z* stereoisomers was used (entries 4−9). Dimethylamino-substituted aniline furnished the corresponding optically active Mannich products with enantioselectivities that were much higher than those furnished by 4-methoxyaniline without significant loss of the chemical yield (compare entries 1, 2, 5, and 6).

The proposed catalytic mechanism is shown in Figure 1. First, an in situ generated chiral tin bromide ethoxide, R*$_2$SnBr(OEt), reacts with alkenyl trichloroacetate **2** to yield chiral tin enolate **3** accompanied by ethyl trichloroacetate.

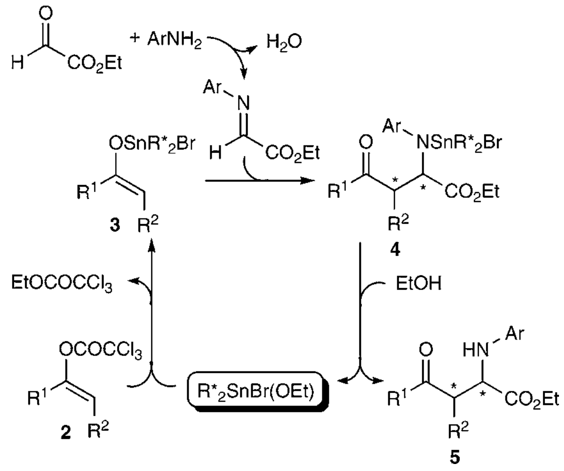


Figure 1. Plausible catalytic cycle for the asymmetric Mannich-type reaction catalyzed by chiral tin bromide ethoxide.

Chiral tin enolate **3** then undergoes addition reaction with an imine that is generated from ethyl glyoxalate and an aromatic amine, affording chiral tin amide of Mannich adduct **4**. Finally, protonation of tin amide **4** with ethanol results in the formation of targeted nonracemic β-amino ketone **5** along with the regeneration of chiral tin bromide ethoxide. The rapid alcoholysis of tin amide **4** makes the catalytic cycle possible.

In summary, we have demonstrated a catalytic enantioselective three-component Mannich-type reaction of alkenyl

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(3) For recent notable examples of catalytic asymmetric three-component Mannich-type reactions, see: (a) Ramasastry, S. S. V.; Zhang, H.; Tanaka, F.; Barbas, C. F., III *J. Am. Chem. Soc.* **2007**, *129*, 288. (b) Guo, Q.-X.; Liu, H.; Guo, C.; Luo, S.-W.; Gu, Y.; Gong, L.-Z. *J. Am. Chem. Soc.* **2007**, *129*, 3790. (c) Hayashi, Y.; Urushima, T.; Aratake, S.; Okano, T.; Obi, K. *Org. Lett.* **2008**, *10*, 21. (d) Dziedzic, P.; Ibrahem, I.; Córdova, A. *Tetrahedron Lett.* **2008**, *49*, 803. (e) Teo, Y.-C.; Lau, J.-J.; Wu, M.-C. *Tetrahedron: Asymmetry* **2008**, *19*, 186. (f) Mandai, H.; Mandai, K.; Snapper, M. L.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2008**, *130*, 17961. (g) Chen, S.; Hou, Z.; Zhu, Y.; Wang, J.; Lin, L.; Liu., X.; Feng, X. *Chem.—Eur. J.* **2009**, *15*, 5884.

(4) For examples of three-component Mannich-type reactions using aliphatic aldehydes as precursors for aldimines, see: (a) Chen, S.-L.; Ji, S.-J.; Loh, T.-P. *Tetrahedron Lett.* **2003**, *44*, 2405. (b) Iimura, S.; Nobutou, D.; Manabe, K.; Kobayashi, S. *Chem. Commun.* **2003**, 1644. (c) Ollevier, T.; Nadeau, E. *J. Org. Chem.* **2004**, *69*, 9292. (d) Cozzi, P. G.; Rivalta, E. *Angew. Chem., Int. Ed.* **2005**, *44*, 3600. (e) Akiyama, T.; Suzuki, A.; Fuchibe, K. *Synlett* **2005**, 1024. (f) Enders, D.; Grondal, C.; Vrettou, M.; Raabe, G. *Angew. Chem., Int. Ed.* **2005**, *44*, 4079.

(5) (a) Kobayashi, S.; Kiyohara, H.; Nakamura, Y.; Matsubara, R. *J. Am. Chem. Soc.* **2004**, *126*, 6558. (b) Evans, D. A.; Scheidt, K. A.; Johnston, J. N.; Willis, M. C. *J. Am. Chem. Soc.* **2001**, *123*, 4480.

(6) We have previously reported that dibutyltin dimethoxide acts as a catalyst for the three-component coupling reaction of 1-trichloroacetoxycyclohexene, aldehydes, and anilines providing racemic β-amino ketones: Yanagisawa, A.; Saito, H.; Harada, M.; Arai, T. *Adv. Synth. Catal.* **2005**, *347*, 1517.

trichloroacetates, ethyl glyoxalate, and aniline derivatives. The main characteristics of this reaction are as follows: (1) optically active β-amino ketones with up to 98% ee are *syn*-selectively obtained in high yields even from imines possessing a polar amino group under the influence of the in situ generated chiral tin bromide ethoxide; (2) this method is environmentally friendly because the amount of toxic organotin compound is reduced to a catalytic amount; (3) in the present three-component system no aldol reaction occurs and corresponding β-hydroxy ketones are not formed; and (4) no β-elimination of the product takes place under conventional reaction conditions. This is a novel example of a catalytic asymmetric Mannich-type reaction that proceeds via a chiral tin enolate according to a catalytic mechanism different from those of conventional Mannich processes. Further studies on the extension of the present catalytic system to other asymmetric reactions are underway.

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Supporting Information Available: Experimental procedures, spectral data for compound **1d**, and products in Table 1−3. This material is available free of charge via the Internet at http://pubs.acs.org.

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(8) Libman, J.; Sprecher, M.; Mazur, Y. *Tetrahedron* **1969**, *25*, 1679.

(9) (a) Ojima, I.; Inaba, S.; Yoshida, K. *Tetrahedron Lett.* **1977**, *18*, 3643. (b) Veenstra, S. J.; Schmid, P. *Tetrahedron Lett.* **1997**, *38*, 997.