THE CHEMICAL RECORD

Development of Asymmetric Reactions Catalyzed by Chiral Organotin-Alkoxide Reagents

AKIRA YANAGISAWA* AND KAZUHIRO YOSHIDA
Department of Chemistry, Graduate School of Science, Chiba University, Inage, Chiba 263-8522 (Japan)
E-mail: ayanagi@faculty.chiba-u.jp

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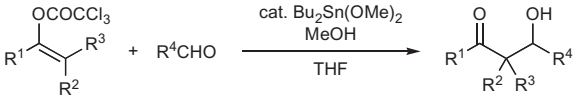
ABSTRACT: Asymmetric catalysis under almost-neutral reaction conditions is key for the efficient synthesis of optically active polar molecules. We have developed catalytic enantioselective reactions of acyclic or cyclic alkenyl esters by using an (*S*)-BINOL-derived chiral tin-dibromide reagent that possesses a bulky aryl group at the 3 or 3′ position as the chiral pre-catalyst in the presence of a sodium alkoxide and an alcohol, in which a chiral tin alkoxide bromide is generated in situ and recycled with the assistance of an alcohol. In this Personal Account, we describe three types of asymmetric transformation that proceed through a chiral tin enolate: 1) The asymmetric aldol reaction of alkenyl esters or unsaturated lactones with aldehydes or isatins; 2) the asymmetric three-component Mannich-type reaction of alkenyl esters and related cycloaddition reactions; and 3) the asymmetric *N*-nitroso aldol reaction of unsaturated lactones with nitrosoarenes. **DOI 10.1002/tcr.201200019**

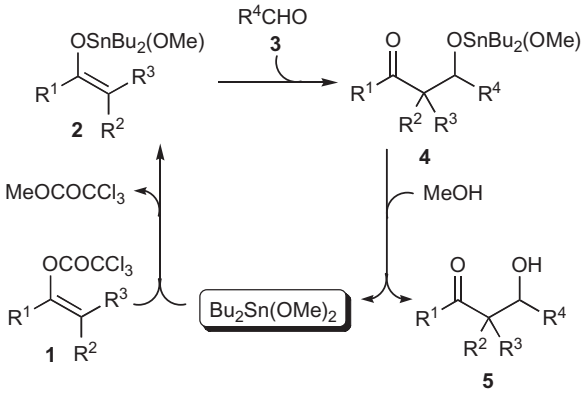
Keywords: aldol reaction, alkoxides, asymmetric catalysis, ligand effects, tin

1. Introduction

The development of highly enantioselective methods for the synthesis of optically active natural products and biologically active compounds is one of the most important research topics in modern synthetic chemistry. The asymmetric aldol reaction and the asymmetric Mannich-type reaction, which employ catalytic amounts of a chiral Lewis acid, are useful routes to non-racemic β-hydroxy-carbonyl compounds[1] and non-racemic β-amino-carbonyl compounds,[2] respectively, and they have attracted a great deal of attention from organic chemists. Numerous chiral Lewis acid catalysts have been designed and prepared in an effort to develop aldol and Mannich processes that have superior stereoselectivity and chemical yield. However, in the case of a strong Lewis acid catalyst, there is an intrinsic problem that the catalytic activity is decreased owing to the coordination of the catalyst with the aldol product or the Mannich product, which is more polar than the starting materials (i.e., product inhibition).[2a,3] Furthermore, Lewis acid catalysts are generally moisture sensitive and, thus, cannot be used in a solvent that contains water or alcohol. We have found that dibutyltin dimethoxide [$Bu_2Sn(OMe)_2$] catalyzes the aldol reaction between alkenyl trichloroacetates and aldehydes, including aliphatic aldehydes, in the presence of MeOH (Scheme 1).[4] A probable catalytic mechanism for this reaction is shown in Scheme 2. First, alkenyl trichloroacetate **1** reacts with $Bu_2Sn(OMe)_2$ to afford tin enolate **2** and methyl trichloroacetate. Subsequently, aldehyde **3** is added to tin enolate **2** to provide the tin alkoxide of aldol adduct **4**. The catalytic cycle is completed by the alcoholysis of tin alkoxide **4** with MeOH to

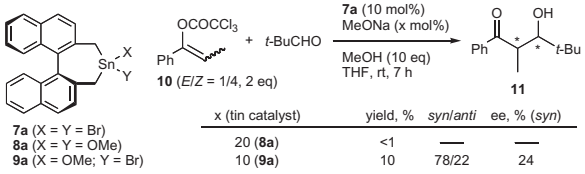


Scheme 1. Aldol reaction of alkenyl trichloroacetates with aldehydes catalyzed by $Bu_2Sn(OMe)_2$.



Scheme 2. Proposed catalytic cycle for the aldol reaction of alkenyl trichloroacetates with aldehydes catalyzed by $Bu_2Sn(OMe)_2$.

yield the regenerated $Bu_2Sn(OMe)_2$ and the desired aldol product (**5**). The slow protonation of tin enolate **2** with MeOH, compared to the rate of reaction of tin enolate **2** with aldehyde **3**, is key to the success of the catalytic cycle. We envisaged that, if a chiral organotin dimethoxide, $R^*_2Sn(OMe)_2$, were applied as a chiral catalyst to this catalytic system, an asymmetric version of the catalytic aldol reaction would be possible in which an optically active aldol product would be obtained through a chiral tin enolate. In this Personal Account, we describe the synthesis of binaphthol-based chiral organotin(IV) dibromides and the asymmetric reactions of



Scheme 3. Evaluation of BINOL-derived tin-methoxide reagents as chiral catalysts.

alkenyl esters or unsaturated lactones by using the chiral tin compound as the chiral pre-catalyst in the presence of a sodium alkoxide and an alcohol.

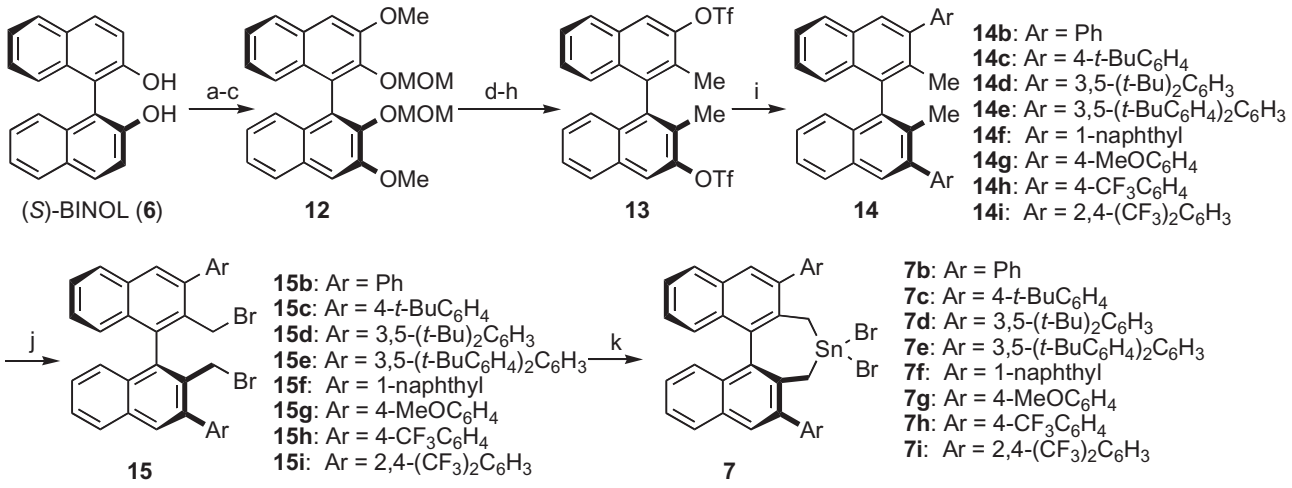
2. Synthesis of Chiral Organotin(IV) Dibromides

As the chiral tin catalyst, we chose a binaphthol-derived organotin(IV) compound because a number of chiral catalysts that contain the binaphthyl motif have been found to be efficacious in diverse asymmetric transformations.[5] First, we attempted to synthesize chiral tin dimethoxide **8a** from (*S*)-BINOL (**6**). According to the literature,[6] chiral tin dibromide **7a** can be prepared from compound **6** in 20% overall yield; however, we failed to obtain targeted tin dimethoxide **8a** by treating tin dibromide **7a** with two equivalents of MeONa in MeOH, owing to the instability of compound **8a** (Scheme 3).[7]

Consequently, we attempted to generate compound **8a** in situ from a 1:2 mixture of compound **7a** and MeONa and to apply it as a chiral catalyst to the aldol reaction of alkenyl trichloroacetate **10** with pivalaldehyde. However, no target aldol adduct (**11**) was obtained at all (Scheme 3). In contrast, chiral tin bromide methoxide **9a**, which was prepared from a 1:1 mixture of compound **7a** and MeONa in MeOH, displayed definite reactivity and the reaction actually furnished

Kazuhiro Yoshida received his PhD from Kyoto University in 2003 under the supervision of Professor Tamio Hayashi. He then became a postdoctoral fellow at the Scripps Research Institute under the guidance of Professor Kim. D. Janda (2003–2004). In 2004, he became an Assistant Professor at Chiba University, where he was promoted to Associate Professor in 2009. His main research interests lie in the field of transition-metal-catalyzed reactions.

Akira Yanagisawa received his PhD from Nagoya University. He became an Assistant Professor at Nagoya University and, later, an Associate Professor there. In 2001, he moved to take up the position of Professor at Chiba University. His research interests focus on the development of new synthetic methods by using allylic organometallic reagents, such as allylic barium reagents, and asymmetric synthesis, including BINAP-silver(I)-catalyzed asymmetric carbon-carbon bond-forming reactions and the asymmetric protonation of metal enolates.



(a) i) NaH, THF, 0 °C ~ rt, ii) MOMCl, THF, 0 °C ~ rt; (b) i) BuLi, THF, rt, ii) $B(OMe)_3$, THF, -78 °C ~ rt, iii) H_2O_2 aq., $CHCl_3$, reflux; (c) MeI, K_2CO_3, acetone, reflux; (d) *conc*. HCl aq., dioxane, 50 °C; (e) Tf_2O, Et_3N, $CHCl_3$, 0 °C ~ rt; (f) MeMgBr, $Ni(dppp)Cl_2$, Et_2O, reflux; (g) BBr_3, $CHCl_3$, 0 °C; (h) Tf_2O, Et_3N, $CHCl_3$, 0 °C ~ rt; (i) $ArB(OH)_2$, $Pd(OAc)_2$, PPh_3, K_3PO_4, THF/H_2O, reflux; (j) NBS, BPO, CCl_4, reflux; (k) Sn, H_2O, toluene, reflux.

Scheme 4. Synthesis of chiral tin dibromides **7b**-**7i**. MOM=methoxymethyl, NBS=*N*-bromosuccinimide, BPO=benzoyl peroxide.

compound **11** in 10% yield, even though the enantiomeric excess of the major *syn* isomer was low (Scheme 3).

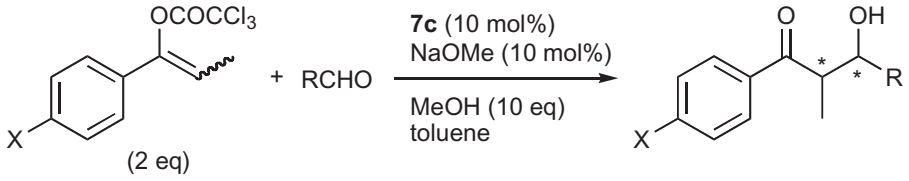
Because this second set of reaction conditions that we tested were found to be promising, we tried to synthesize various chiral tin dibromides that contained aryl groups at the 3,3′ positions, which were expected to induce high asymmetric induction in this aldol reaction.[8] The synthesis of compounds **7b**-**7i** from (*S*)-BINOL (**6**) is shown in Scheme 4. MOM protection of compound **6**, followed by a hydroxylation/methylation sequence, gave 3,3′-dimethoxy BINOL derivative **12**. The next five-step transformation of compound **12** by 1) deprotection of the MOM groups, 2) trifluoromethanesulfonylation of the 2,2′-OH groups, 3) Ni-catalyzed cross-coupling with a methyl-Grignard reagent, 4) demethylation, and 5) trifluoromethanesulfonylation of the 3,3′-OH groups provided ditriflate **13**. Then, ditriflate **13** underwent Suzuki-Miyaura coupling with arylboronic acids to afford the corresponding coupling products (**14b**-**14i**). Benzylic bromination[9] and subsequent oxidative addition of the resulting products (**15b**-**15i**) by tin metal completed the synthesis of the target chiral tin dibromides (**7b**-**7i**).

3. Catalytic Asymmetric Aldol Reaction of Alkenyl Esters and Unsaturated Lactones

With chiral tin dibromides **7** in hand, we studied the catalytic activity of their corresponding tin bromide methoxides in the aldol reaction of alkenyl trichloroacetate **10** with pivalaldehyde. The anticipated aldol adduct (**11**) was produced in 70% yield with a *syn/anti* ratio of 94:6 through a reaction that employed compound **7c** as the pre-catalyst in toluene at 40 °C for 1.5 h (Table 1, entry 1); the *syn* isomer was formed in 85% *ee*. Then, we performed the chiral-tin-catalyzed enantioselective aldol reaction of diverse combinations of acyclic alkenyl trichloroacetates and aldehydes under the optimized reaction conditions; the results are shown in Table 1. The introduction of a phenyl group at the *para* position of alkenyl trichloroacetate **10** allowed the reaction to take place smoothly at low temperatures and, indeed, the non-racemic aldol products were furnished *syn*-selectively in approximately 70% yield and 94–98% *ee* in the reactions with different aliphatic aldehydes, even at room temperature (Table 1, entries 3–5). The reaction of 2-methyl-2-phenylpropanal at 0 °C provided an almost enantiomerically pure product (Table 1, entry 6). From these aforementioned results, BINOL-derived chiral tin bromide methoxides that contained bulky substituents at the 3,3′ positions were found to be effective in affording high enantioselectivities in this asymmetric aldol reaction.

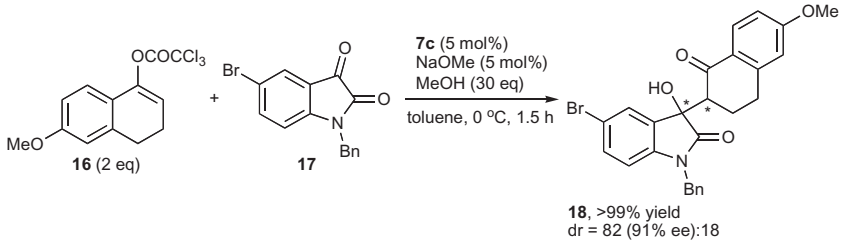
Isatin derivatives could be also employed as electrophiles in the chiral-tin-methoxide-catalyzed asymmetric aldol reaction. Isatin and its derivatives are beneficial synthetic intermediates of various biologically active molecules.[10] To accomplish their asymmetric transformation, numerous chiral organocatalysts[11] have been developed, in contrast to the few examples of reactions that utilize chiral Lewis acid catalysts.[12] We

Table 1. Catalytic asymmetric aldol reaction of alkenyl trichloroacetates with aldehydes by using chiral tin dibromide **7c** and sodium methoxide as pre-catalysts.



Entry	X	R	Conditions	Yield[a] [%]	*syn/anti*[b]	*ee* [%][c] (*syn*)
1	H (**10**, *E/Z* = 1:4)	*t*-Bu	40 °C, 1.5 h	70 (**11**)	94:6	85
2	H (**10**, *E/Z* = 1:4)	Me_2PhC	40 °C, 4 h	80 (**11**)	95:5	93
3	Ph (*E/Z* = 1:99)	*i*-Pr	r.t., 18 h	80	>99:1	94
4	Ph (*E/Z* = 1:99)	*t*-Bu	r.t., 16 h	65	>99:1	97
5	Ph (*E/Z* = 1:99)	Me_2PhC	r.t., 14 h	75	85:15	98
6	Ph (*E/Z* = 1:99)	Me_2PhC	0 °C, 30 h	41	89:11	99
7	MeO (*E/Z* = 9:91)	Me_2PhC	40 °C, 4 h	63	96:4	88
8	Br (*E/Z* = 1:4)	*t*-Bu	r.t., 14 h	54	99:1	95

[a]Yield of the isolated product. [b]Determined by ^{1}H NMR spectroscopy. [c]Value corresponds to the *syn* isomer; determined by HPLC.

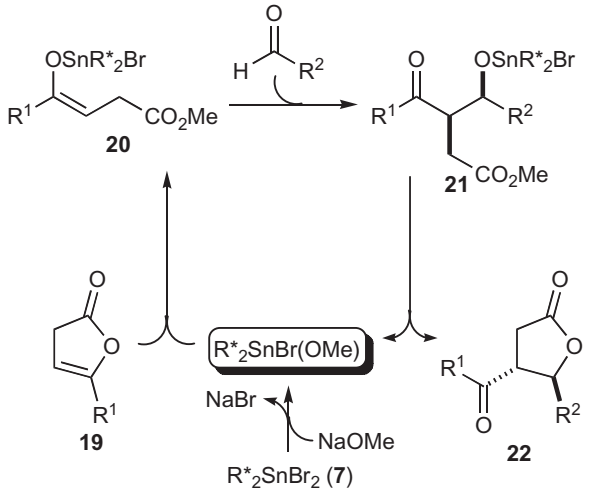


Scheme 5. Catalytic asymmetric aldol reaction of alkenyl trichloroacetate **16** with isatin **17**.

attempted to react 6-methoxy-1-tetralone-derived alkenyl trichloroacetate **16** with *N*-benzyl isatin derivative **17** by using chiral tin dibromide **7c** and sodium methoxide as pre-catalysts and, as a result, the anticipated aldol product (**18**) was afforded with noticeable asymmetric induction. For example, the treatment of a mixture of compounds **16** (2 equiv) and **17** (1 equiv) with chiral tin dibromide **7c** (5 mol%) and NaOMe (5 mol%) in the presence of MeOH (30 equiv) in toluene at 0 °C for 1.5 h resulted in the formation of an 82:18 diastereomeric mixture of compound **18** in quantitative yield (Scheme 5);[13] the major diastereomer of compound **18** was formed in 91% ee. The corresponding alkenyl trifluoroacetate[14] could be also used as a substrate for the generation of a chiral tin enolate.

In addition to ketone-derived alkenyl esters, unsaturated lactones could be also applied as enolate precursors to the chiral-tin-bromide-methoxide-catalyzed asymmetric aldol reaction. With these former substrates, there was the drawback that MeOH was essential as an additive for recycling the corresponding chiral tin enolates, in addition to the fact that undesired methyl trichloroacetate was produced. In contrast, the aldol reaction of unsaturated lactones could proceed in the absence of MeOH because the subsequent lactonization of the generated tin alkoxide of β-hydroxy ketones that contained an ester group regenerated the chiral tin bromide methoxide. A plausible catalytic mechanism for the chiral-tin-catalyzed tandem asymmetric aldol-reaction/cyclization by using γ-substituted β,γ-didehydro-γ-butyrolactone **19** as the enolate precursor is shown in Scheme 6. First, chiral tin dibromide **7** reacted with an equimolar amount of sodium methoxide to give the corresponding chiral tin bromide methoxide. The thus-generated chiral tin bromide methoxide was subsequently added to β,γ-didehydro-γ-butyrolactone **19** to form chiral tin enolate **20**. The following aldol reaction of an aldehyde with chiral tin enolate **20** afforded the tin alkoxide of β-hydroxy ketone **21**. Lastly, tin alkoxide **21** underwent lactonization through participation of its ester portion to give non-racemic β,γ-disubstituted γ-butyrolactone **22** with regeneration of the chiral tin bromide methoxide. The methoxycarbonyl group of intermediates **20** and **21** played a key role in the catalytic cycle.

To confirm of the validity of this catalytic mechanism, various γ-substituted β,γ-didehydro-γ-butyrolactones (**19**) were transformed into their corresponding optically active β,γ-disubstituted γ-butyrolactones (**22**).[15] For instance, when a 1:1 mixture of 5-(4-methoxyphenyl)furan-2(3*H*)-one (**19a**) and pivalaldehyde was treated with chiral tin dibromide **7c** (10 mol%) and NaOMe (10 mol%) in toluene at room temperature for 19 h, *trans*-5-(*tert*-butyl)-4-(4-methoxybenzoyl)dihydrofuran-2(3*H*)-one (**22a**) was obtained exclusively in 76% yield and >99% *ee* (Scheme 7). Non-racemic γ-butyrolactones **22b** and **22c** were also prepared from their corresponding β,γ-didehydro-γ-butyrolactones (**19**) and aldehydes. Enantiomerically enriched γ-lactones are useful chiral synthons for the synthesis of a variety of biologically active natural products or synthetic drugs.[16] Numerous methods are available to obtain such versatile synthetic intermediates;[17] however, as far as we know, there are no reports of catalytic pathways that involve this aldol approach.

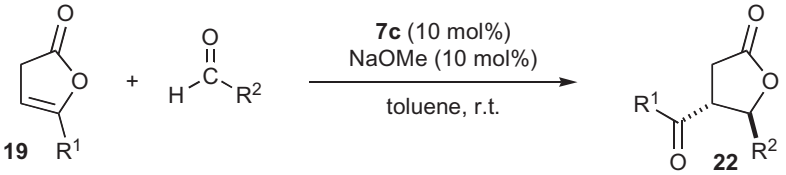


Scheme 6. Plausible catalytic cycle for the tandem asymmetric aldol-reaction/cyclization by using unsaturated lactone **19**.

4. Catalytic Asymmetric Mannich-Type Reaction of Alkenyl Esters and Related Cycloaddition Reaction

The asymmetric Mannich-type reaction is a convenient route to optically active β-amino-carbonyl compounds, which can be further converted into useful chiral organic molecules, such as β-lactams.[2] A three-component procedure that employs an enolate, an amine, and an aldehyde is much more preferable than a two-component one that uses an enolate and an imine because the former method does not require the prior preparation of imines and can be applied to less-stable aliphatic imines.[18] We found that dibutyltin dimethoxide behaves as a catalyst in the three-component Mannich-type reaction between 1-trichloroacetoxycyclohexene, aldehydes, and anilines, thereby yielding racemic β-amino ketones.[19] Notably, the tin dimethoxide exhibits remarkable catalytic activity, even in the presence of water or an alcohol. Thus, we explored the possibility of developing an asymmetric version of this three-component Mannich-type reaction by using an in situ generated chiral tin alkoxide that possesses a binaphthyl structure as the chiral catalyst and we found that the desired non-racemic β-amino ketones were produced in high yields with significant enantioselectivities.[20]

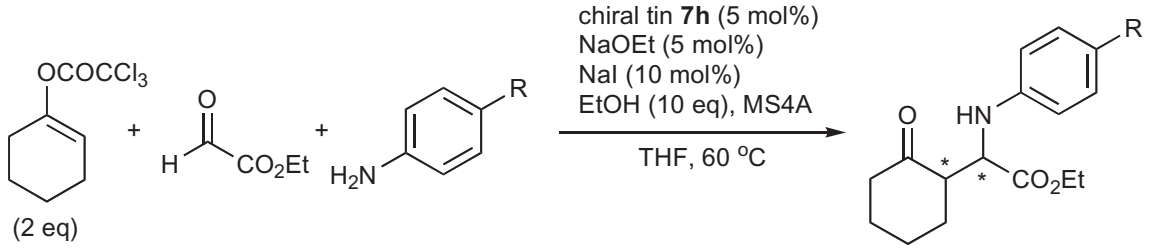
First, we optimized the reaction conditions for chiral tin catalyst **7**, sodium alkoxide, alcohol, and additives. The combination of chiral tin dibromide **7h** and NaOEt/EtOH in the presence of MS4A was found to be superior to **7c**/NaOMe/MeOH in terms of reactivity and enantioselectivity. Moreover, the *syn/anti* selectivity and the enantiomeric excess of the *syn* product were improved when a catalytic amount of NaI was added. With the optimal reaction conditions in hand, we examined the catalytic asymmetric three-component Mannich-type reaction of 1-trichloroacetoxycyclohexene, ethyl glyoxalate, and various anilines; selected examples are summarized in Table 2. One point worth noting is that the presence of a phenolic hydroxy, an amino, or an amide substituent on the

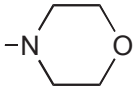


R^1	R^2	Time, h	Product	Yield [%]	*trans*/*cis*
4-$MeOC_6H_4$ (**19a**)	*t*-Bu	19	**22a**	76	>99 (99% ee)/1
4-FC_6H_4 (**19b**)	Me_2CH	23	**22b**	76	93 (94% ee)/7
2-naphthyl (**19c**)	Me_2PhC	22	**22c**	87	>99 (94% ee)/1

Scheme 7. Tandem catalytic asymmetric aldol-reaction/cyclization with γ-substituted β,γ-didehydro-γ-butyrolactones (**19**) and aldehydes.

Table 2. Catalytic asymmetric three-component Mannich-type reaction of 1-trichloroacetoxycyclohexene, ethyl glyoxalate, and various anilines.



Entry	R	Time, h	Yield[a] [%]	*syn/anti*[b]	*ee* [%][c] (*syn*)
1	OMe	0.5	>99	74/26	83
2	OH	1	>99	77/23	84
3	NMe_2	1.5	98	72/28	93
4	NHPh	2	>99	76/24	81
5	$NHCOCH_3$	1.5	>99	75/25	67
6		1	86	67/33	86

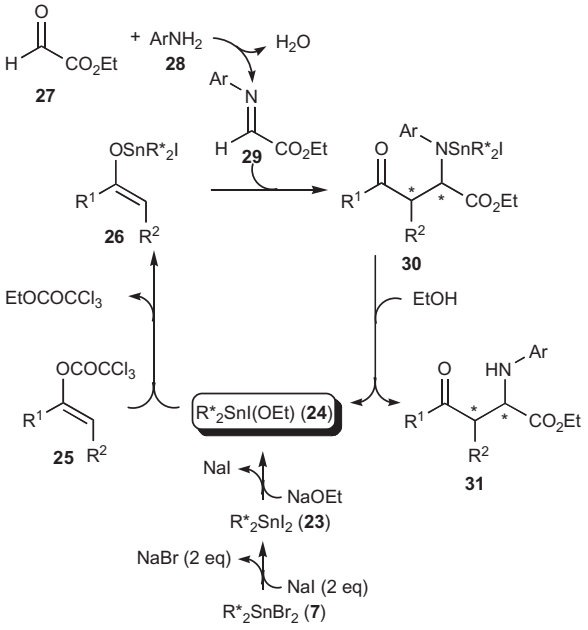
[a]Yield of the isolated product. [b]Determined by ^{1}H NMR spectroscopy. [c]Value corresponds to the *syn* isomer; determined by HPLC.

aniline derivative did not retard the reaction. In fact, each reaction was completed within 2 h (Table 2, entries 2–5). In the case of an aniline derivative that contained a Me_2N group, the optical purity of the *syn* product reached 93% *ee* (Table 2, entry 3). These results clearly show that in situ generated chiral tin ethoxide iodide can better tolerate polar substituents than representative Lewis acids.[21]

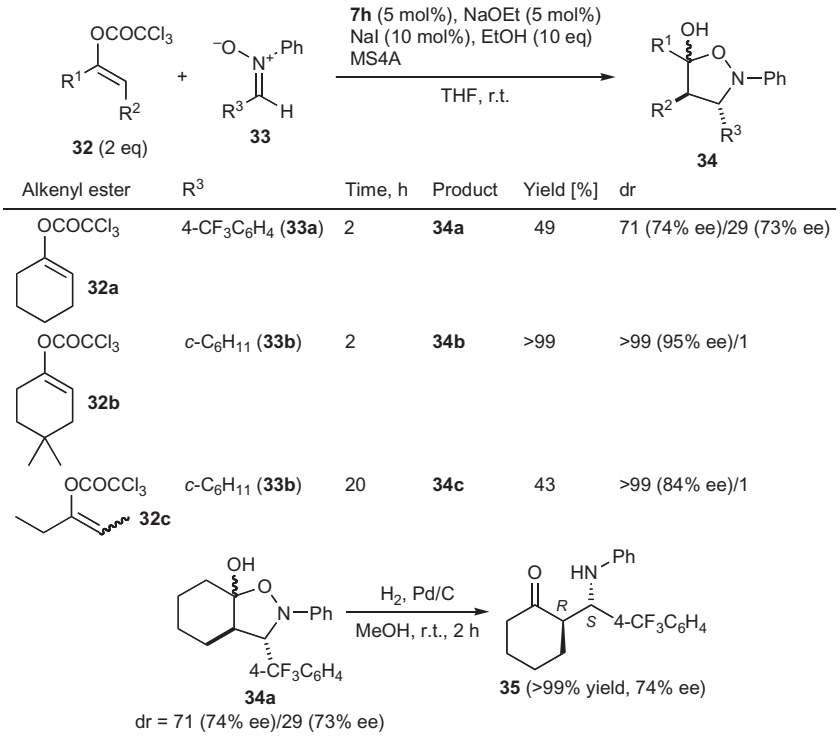
Various alkenyl trichloroacetates can be employed in this asymmetric Mannich-type reaction; not only cyclic ketone derivatives but also acyclic ketone derivatives have been efficiently transformed into their corresponding enantiomerically enriched β-amino ketones in satisfactory yields with notable enantioselectivities of up to 98% *ee*. In this three-component system, the aldol reaction does not intervene and no products are formed at all. In addition, no β-elimination of the Mannich product occurs under the optimized reaction conditions.

The probable catalytic cycle is presented in Scheme 8. Chiral tin ethoxide iodide **24**, which is generated from chiral tin dibromide **7** through chiral tin diiodide **23**, reacts with alkenyl trichloroacetate **25** to produce chiral tin enolate **26**. Then, enolate **26** undergoes an addition reaction with imine **29**, which is formed by reacting ethyl glyoxalate (**27**) with aromatic amine **28**, thus providing the chiral tin amide of Mannich product **30**. The subsequent protonation of tin amide **30** with EtOH completes the catalytic cycle by furnishing non-racemic β-amino ketone **31** and regenerating chiral tin ethoxide iodide **24**.

This chiral-tin-alkoxide-catalyzed asymmetric transformation was extended to enantio- and diastereoselective cycloaddition reactions between alkenyl trichloroacetates **32** and nitrones **33**.[22] Initially, we envisaged that a nitrone would undergo the aforementioned asymmetric Mannich-type reaction to afford non-racemic β-hydroxyamino ketones; however, instead, the electrophile reacted with an alkenyl trichloroac-



Scheme 8. Probable catalytic cycle for the asymmetric Mannich-type reaction catalyzed by chiral tin ethoxide iodide.



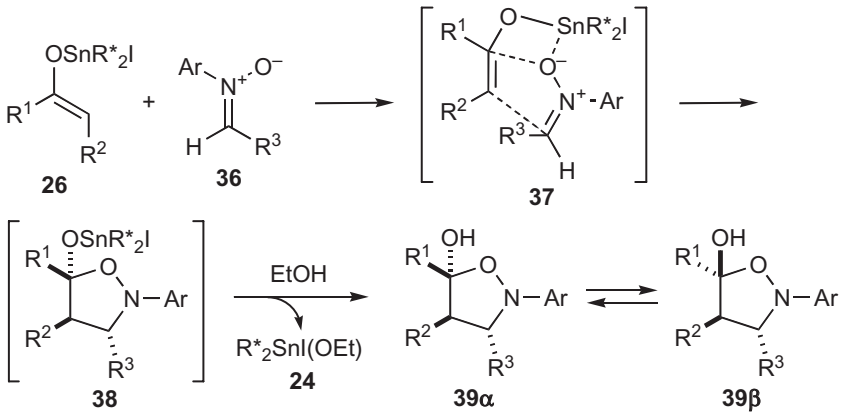
Scheme 9. Catalytic asymmetric cycloaddition reaction and subsequent reductive N-O cleavage of cycloadduct **34a**.

etate to produce an unanticipated cycloadduct. For example, when a mixture of cyclohexanone-derived alkenyl trichloroacetate **32a** (2 equiv) and nitrone **33a** (1 equiv) was treated with chiral tin dibromide **7h** (5 mol%), NaOEt (5 mol%), and NaI (10 mol%) in the presence of EtOH (10 equiv) in THF at room temperature for 2 h, a 71:29 diastereomeric mixture of isoxazolidine **34a** was obtained in 49% yield (Scheme 9); the major diastereomer was formed in 74% *ee*. Aliphatic-aldehyde-derived nitrone **33b** was a more suitable 1,3-dipole for realizing higher yields, diastereomeric ratios, and enantiomeric excess. Not only cyclic alkenyl esters **32a** and **32b** but also acyclic analogue **32c** could be used as the precursor of chiral tin enolate. Cycloadduct **34a** further underwent reductive N-O cleavage by Pd/C under a hydrogen atmosphere to give *anti* β-amino ketone **35** as a single diastereomer in 74% *ee*. This result unequivocally confirmed that the diastereomers of compound **34a** originated from a stereogenic center at the hemiketal portion. The absolute configuration of β-amino ketone **35** was determined by HPLC to be 2*R*,3*S*.[23]

Based on the observed *syn* selectivity in the chiral-tin-alkoxide-catalyzed asymmetric Mannich-type reaction, irrespective of the *E/Z* ratio in the alkenyl trichloroacetate,[20] and the fact that opposite *anti*-Mannich product **35** was formed from cycloadduct **34** (Scheme 9), a 1,3-dipolar cycloaddition mechanism (Scheme 10) was proposed for the cyclization reaction. In the [3+2] mechanism, nitrone **36** was assumed to be activated by a Lewis acidic chiral tin compound in transition-state structure **37**, thus generating products **39α** and **39β** through cyclized intermediate **38**. In the case of aromatic-aldehyde-derived nitrones (R^3 = Ar), an equilibrium between compounds **39α** and **39β** was considered to occur more easily. This is a new example of a catalytic enantioselective 1,3-dipolar cycloaddition reaction of nitrones by using electron-rich alkenes, such as dipolarophiles.[24]

5. Catalytic Asymmetric *N*-nitroso Aldol Reaction of Cyclic Alkenyl Esters

The asymmetric nitroso aldol reaction is a useful C-O/C-N bond-forming reactions that affords optically active α-aminooxy-carbonyl compounds and/or α-hydroxyamino-carbonyl compounds.[25] A central issue in this transformation is how to control the O/N regioselectivity. The enantioselective *O*-nitroso aldol reaction (aminoxylation) can be readily carried out by employing simple organocatalysts, including proline; however, it is still not easy to obtain the opposite α-hydroxyamino-carbonyl compounds with high regio- and enantioselectivities. We previously found that dibutyltin dimethoxide catalyzed the *N*-nitroso aldol reaction between



Scheme 10. A plausible reaction pathway for the asymmetric cycloaddition reaction.

alkenyl trichloroacetates and nitrosobenzene, in which a tin enolate was generated in situ and the tin dimethoxide was recycled with the assistance of MeOH.[26] We envisaged that, if a chiral tin enolate were produced from a suitable chiral tin alkoxide and the enolate could activate a nitrosoarene, the asymmetric version of the *N*-nitroso aldol reaction would occur. To this end, we chose γ,δ-unsaturated δ-lactones as the enolate precursors for the asymmetric *N*-nitroso aldol reaction because related unsaturated lactones were found to be superior substrates in the chiral-tin-alkoxide-catalyzed tandem asymmetric aldol-reaction/cyclization.[15] We attempted to react δ-substituted γ,δ-didehydro-δ-valerolactones with nitrosoarenes by using chiral tin dibromide **7** and a sodium alkoxide as pre-catalysts and, consequently, the anticipated *N*-nitroso aldol adducts were afforded with remarkable asymmetric induction.[27] For example, when a mixture of 3,4-dihydro-6-phenylpyran-2-one (**40a**, 2 equiv) and 1-isopropyl-2-nitrosobenzene (**41a**, 1 equiv) was treated with chiral tin dibromide **7c** (10 mol%) and NaOEt (10 mol%) in toluene at 0 °C for 12 h, the desired product (**42aa**) was produced in 82% yield (Table 3, entry 1); the *N*-adduct was formed in 90% *ee* and the corresponding O adduct was not observed at all.

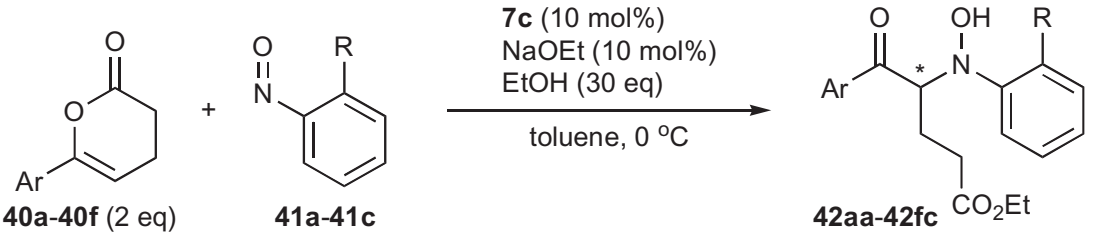
The results of reactions that employed various combinations of δ-substituted γ,δ-didehydro-δ-valerolactone and nitrosoarene are summarized in Table 3. Not only electron-rich-aromatic-group-substituted lactones but also electron-deficient-aromatic-group-substituted lactones showed significant reactivity as masked enolates and the enantioselectivities surpassed 90% *ee* in all cases (Table 3, entries 2–5). In addition, γ,δ-disubstituted-γ,δ-didehydro-δ-valerolactone (**40f**) was a favorable substrate for the α-hydroxyamination reaction (Table 3, entry 6). However, the use of *tert*-butyl–substituted nitrosobenzene **41b** as the electrophile was more effective in improving the extent of the asymmetric induction, although the electrophilicity decreased owing to the steric bulkiness of the *tert*-butyl group (Table 3, entries 7–9). From γ,δ-disubstituted substrate **40f**, target product **42fb**, which had almost-perfect enantiomeric excess (99% *ee*), was obtained (Table 3, entry 9). If compound **40f** was chosen as the enolate precursor, even relatively small nitrosoarene **41c** showed remarkable reactivity and enantioselectivity (Table 3, entry 10). The absolute configuration of α-hydroxyamino ketone **42eb** was determined to be *S* by single-crystal X-ray analysis.[27]

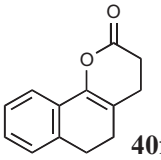
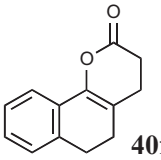
The suggested catalytic cycle appears in Scheme 11. Initially, chiral tin dibromide **7** undergoes an exchange reaction with an equimolar amount of NaOEt to afford the corresponding chiral tin bromide ethoxide. Then, the as-formed chiral tin species reacts with γ,δ-didehydro-δ-valerolactone **43** to provide chiral tin enolate **44**. The following *N*-nitroso aldol reaction of chiral tin enolate **44** with nitrosoarene **45** gives the tin alkoxide of α-hydroxyamino ketone **46**. In the end, ethanolysis of tin alkoxide **46** produces enantiomerically enriched α-hydroxyamino ketone **47** with regeneration of the chiral tin-alkoxide catalyst. The rapid protonation of tin alkoxide **46** with EtOH is key to the catalytic mechanism.

6. Conclusion

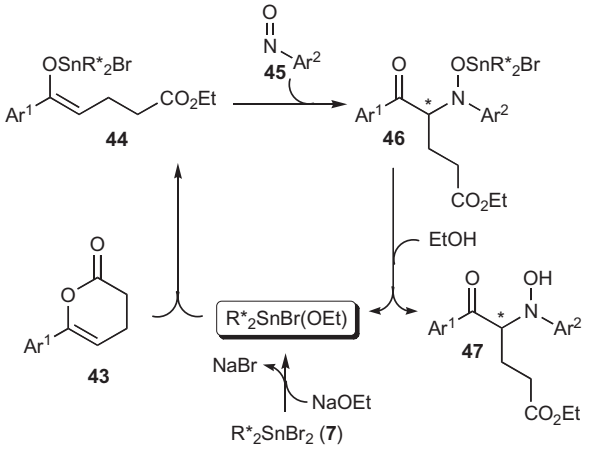
Herein, we have described several new examples of asymmetric transformations under almost-neutral conditions by using an (*S*)-BINOL-derived chiral organotin(IV) dibromide that contains bulky aryl groups at the 3,3′ positions as the chiral pre-catalyst, which is then converted in situ into the corresponding chiral tin alkoxide by treatment with sodium alkoxide.[28] Alkenyl esters and unsaturated lactones are efficiently transformed into chiral tin enolates in the presence of the chiral tin alkoxide and the chiral tin catalyst is regenerated from the reaction products under the influence of an alcohol. This catalytic system is more environmentally friendly because the

Table 3. Catalytic asymmetric *N*-nitroso aldol reaction of γ,δ-unsaturated δ-lactones.



Entry	Ar	R	*t* [h]	Product	Yield [%][a]	*ee* [%][b]
1	Ph (**40a**)	*i*-C_3H_7 (**41a**)	12	**42aa**	82	90
2	4-MeC_6H_4 (**40b**)	*i*-C_3H_7 (**41a**)	12	**42ba**	94	95
3	4-$MeOC_6H_4$ (**40c**)	*i*-C_3H_7 (**41a**)	12	**42ca**	97	92
4	2-FC_6H_4 (**40d**)	*i*-C_3H_7 (**41a**)	18	**42da**	75	>99
5	4-BrC_6H_4 (**40e**)	*i*-C_3H_7 (**41a**)	12	**42ea**	92	95
6	 **40f**	*i*-C_3H_7 (**41a**)	16	**42fa**	>99	90
7	Ph (**40a**)	*t*-C_4H_9 (**41b**)	12	**42ab**	37	99
8	4-BrC_6H_4 (**40e**)	*t*-C_4H_9 (**41b**)	12	**42eb**	73	96
9	 **40f**	*t*-C_4H_9 (**41b**)	17	**42fb**	52	>99
10		Me (**41c**)	15	**42fc**	75	92

[a]Yield of the isolated product; [b]determined by ^{1}H NMR spectroscopy.



Scheme 11. Plausible catalytic cycle for the asymmetric *N*-nitroso aldol reaction.

amount of toxic organotin compounds is decreased to a catalytic amount. These chiral tin catalysts have been utilized in aldol reactions, Mannich-type reactions, cycloaddition reactions, and *N*-nitroso aldol reactions, to name a few. Optically active products are obtained in high yields with high *ee* values, even from electrophiles that contain a polar substituent, such as an amino group. These aforementioned reactions unambiguously indicate that chiral tin alkoxides have much potential as asymmetric Lewis acid catalysts and, in the near future, the emergence of unprecedented reactions that are catalyzed by these organometallic reagents is greatly anticipated.

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