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SHORT COMMUNICATION

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Asymmetric Aldol Reaction Catalyzed by a Chiral Phosphine–Silver Complex

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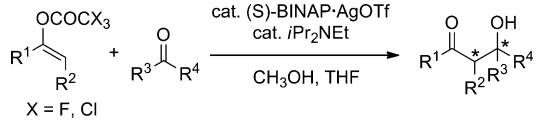
A catalytic asymmetric aldol reaction of alkenyl trihaloacetates or a γ,δ-unsaturated δ-lactone with aldehydes or an α-keto ester was achieved by using a 2,2′-bis(diphenylphosphino)-1,1′-binaphthyl·silver trifluoromethanesulfonate complex as the chiral precatalyst and *N*,*N*-diisopropylethylamine as the base precatalyst in the presence of methanol. Optically active α-alkyl β-hydroxy ketones with enantioselectivities of up to 95 % *ee* were diastereoselectively obtained in moderate to high yields through the in situ generated chiral silver enolates.

Introduction

The β-hydroxy carbonyl moiety is a key synthon for natural products and biologically active organic compounds. Various synthetic methods have been developed for the construction of this functional group. Among them, the aldol reaction is undoubtedly the most efficient and convenient.[1] Many catalytic asymmetric aldol processes have been reported; however, most of them are chiral Lewis acid or chiral Lewis base catalyzed Mukaiyama-type aldol reactions that use silyl enolates as nucleophiles[2,3] or direct aldol reactions involving organocatalysts,[4] and there are no examples of reactions that employ alkenyl esters as latent enolates. We reported that alkenyl trichloroacetates react with dibutyltin dimethoxide to furnish the corresponding tin enolates that have sufficient reactivity toward aldehydes. In addition, in the presence of a catalytic amount of dibutyltin dimethoxide and a stoichiometric amount of methanol, the aldol reaction occurs smoothly to give the desired products.[5] An asymmetric version of the catalytic aldol process has been accomplished as well, which involves the addition of a 2,2′-bis(diphenylphosphino)-1,1′-binaphthyl·silver trifluoromethanesulfonate (BINAP·AgOTf) catalyst.[6] Moreover, not only diverse aldehydes, including α,β-unsaturated aldehydes and aliphatic aldehydes, but also ketones, such as α-keto esters, have shown remarkable reactivity in the reaction.[7] Although the transformation provides a beneficial route to nonracemic β-hydroxy ketones, it has a disadvantage in that the use of a toxic organotin compound is indispensable. To solve the problem, we explored the potential of chiral silver(I)-catalyzed asymmetric aldol synthesis in the absence of organotin reagents.[8] We report herein the asymmetric aldol reaction of alkenyl trihaloacetates with aldehydes or an α-keto ester by using a BINAP·AgOTf complex as the chiral precatalyst and *N*,*N*-diisopropylethylamine as the base precatalyst (Scheme 1).



Scheme 1. Enantioselective aldol reaction of alkenyl trihaloacetates with carbonyl compounds catalyzed by the (*S*)-BINAP·AgOTf complex.

Results and Discussion

As previously mentioned, dibutyltin dimethoxide acts as a catalyst in the aldol reaction of alkenyl trichloroacetates with aldehydes.[5] The reaction takes place via a tin enolate, and the tin dimethoxide is regenerated with the assistance of MeOH. We envisaged that if a BINAP·AgOMe complex could be formed from a BINAP·AgOTf complex and MeOH, the chiral silver(I)-catalyzed asymmetric aldol reaction of alkenyl trichloroacetates without an organotin compound would be possible. Thus, we initially attempted to generate the BINAP·AgOMe complex in the reaction of 1-trichloroacetoxycyclohexene (**1a**)[9] with benzaldehyde. Upon treating a 1.5:1 mixture of **1a** and benzaldehyde with (*S*)-BINAP (8 mol-%) and AgOTf (16 mol-%) in the presence of MeOH (5 equiv.) and 3 Å molecular sieves in THF at –20 °C for 24 h, desired 2-[hydroxy(phenyl)methyl]cyclohexanone (**2aa**) was not obtained at all (Table 1, entry 2), even though the corresponding reaction with $Bu_2Sn(OMe)_2$ (6 mol-%) produced **2aa** in 98% yield with an *anti*/*syn* ratio of 86:14. The *anti* isomer had 92% *ee* and its absolute configuration was determined to be (2*R*,1′*S*) by comparison with reported HPLC analytical data (Table 1, entry 1).[6] Then, we examined the utility of a tertiary amine

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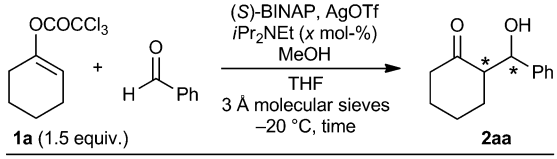
as an additive to facilitate the deprotonation of methanol and increase its nucleophilicity. As a consequence, we found that target product **2aa** was obtained in 66% yield in the presence of 40 mol-% of *N*,*N*-diisopropylethylamine (Table 1, entry 3). Even more significant was that the tertiary amine gave the *anti* product with good diastereoselectivity (*anti*/*syn* = 78:22) and remarkable enantioselectivity (80%*ee*). To attain better results, we further tried to optimize the reaction conditions. Consequently, it turned out that the 3 Å molecular sieves were not necessary for the present asymmetric aldol reaction. In fact, the reaction in the absence of 3 Å molecular sieves at –20 °C for 1 h afforded the desired aldol adduct in 99% yield with high diastereoselectivity (*anti*/*syn* = 89:11) and satisfactory enantioselectivity (90%*ee*; Table 1, entry 4).

Table 1. Enantioselective aldol reaction of alkenyl trichloroacetate **1a** with benzaldehyde catalyzed by (*S*)-BINAP·AgOTf.[a]



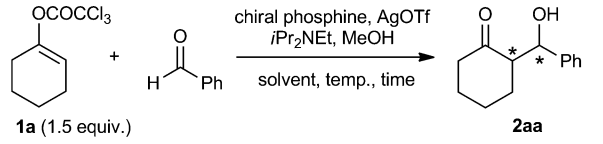
1a (1.5 equiv.) **2aa**

Entry	*x* (mol-%)	Time [h]	Yield[b] [%]	*anti*/*syn*[c]	*ee*[d] [% (*anti*)]
1[e]	0	24	98	86:14	92 (2*R*,1'*S*)
2	0	24	<1	–	–
3	40	24	66	78:22	80 (2*R*,1'*S*)
4[f]	40	1	99	89:11	90 (2*R*,1'*S*)

[a] Unless otherwise specified, the reaction was performed with (*S*)-BINAP (8 mol-%), silver triflate (16 mol-%), alkenyl trichloroacetate **1a** (1.5 equiv.), benzaldehyde (1 equiv.), *N*,*N*-diisopropylethylamine, methanol (5 equiv.), and 3 Å molecular sieves in THF at –20 °C. [b] Yield of isolated product. [c] Determined by ^{1}H NMR spectroscopy. [d] The value corresponds to the *anti* isomer. Determined by HPLC analysis. The absolute configuration is shown in parentheses. [e] The reaction was performed in the presence of $Bu_2Sn(OMe)_2$ (6 mol-%).[6] [f] The reaction was performed without 3 Å molecular sieves.

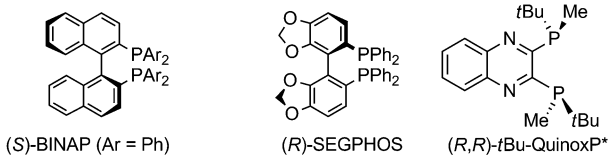
Subsequently, we examined the asymmetric induction ability of chiral phosphines other than BINAP and reconfirmed that BINAP was the chiral ligand of choice (Table 2, entry 1 vs. entries 2–4).[10] Tol-BINAP and SEGPHOS were also promising chiral ligands in terms of *anti* selectivity and enantioselectivity (Table 2, entries 2 and 3). In contrast, the use of *t*Bu-QuinoxP* led to the opposite diastereoselectivity, and the *syn* aldol adduct was predominantly obtained with unsatisfactory optical purity (Table 2, entry 4). Then, we investigated the reaction conditions, specifically the optimum solvent and temperature. First, we checked the suitability of dichloromethane and toluene as solvents instead of THF because less polar solvents were anticipated to be more favorable for realizing a rigid transition-state structure; however, we found that those less polar solvents were inferior in terms of enantioselectivity, *anti*/*syn* selectivity, and yield of the product (Table 2, entries 5 and 6 vs. entry 1). Lowering the reaction temperature to –40 °C raised the enantiomeric excess of **2aa** to 94% (Table 2, entry 7 vs. entry 1). However, there was no further improvement in the enantioselectivity if the reaction was performed at –60 °C (Table 2, entry 8). A significant deceleration of the reaction was observed for the reaction at –78 °C (Table 2, entry 9).

Table 2. Enantioselective aldol reaction of alkenyl trichloroacetate **1a** with benzaldehyde catalyzed by chiral phosphine·AgOTf.[a]



1a (1.5 equiv.) **2aa**

Entry	Chiral phosphine	Solvent	Temp. [°C]	Time [h]	Yield[b] [%]	*anti*/*syn*[c]	*ee*[d] [%]
1	(*S*)-BINAP	THF	–20	1	99	89:11	90
2	(*S*)-Tol-BINAP	THF	–20	3	99	78:22	89
3	(*R*)-SEGPHOS	THF	–20	24	86	83:17	–89
4	(*R*,*R*)-*t*Bu-QuinoxP*	THF	–20	24	83	38:62	56
5	(*S*)-BINAP	CH_2Cl_2	–20	24	82	64:36	59
6	(*S*)-BINAP	toluene	–20	24	86	68:32	70
7	(*S*)-BINAP	THF	–40	2	92	86:14	94
8	(*S*)-BINAP	THF	–60	4	90	90:10	93
9	(*S*)-BINAP	THF	–78	20	84	86:14	94

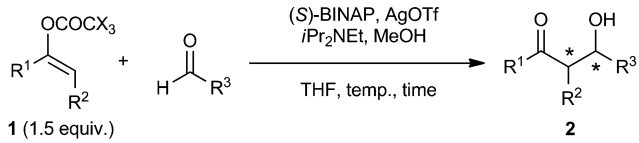


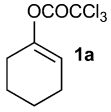
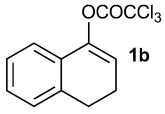
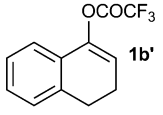
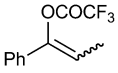
(*S*)-BINAP (Ar = Ph) (*R*)-SEGPHOS (*R*,*R*)-*t*Bu-QuinoxP*
(*S*)-Tol-BINAP (Ar = 4-MeC_6H_4)

[a] Unless otherwise specified, the reaction was performed with chiral phosphine (8 mol-%), silver triflate (16 mol-%), alkenyl trichloroacetate **1a** (1.5 equiv.), benzaldehyde (1 equiv.), *N*,*N*-diisopropylethylamine (40 mol-%), methanol (5 equiv.), and additive in a specified solvent. [b] Yield of isolated product. [c] Determined by ^{1}H NMR spectroscopy. [d] The value corresponds to the major diastereomer. Determined by HPLC analysis.

With the optimum reaction conditions (entry 7 in Table 2) in hand, we performed the chiral silver(I)-catalyzed asymmetric aldol reaction by using various combinations of alkenyl trihaloacetates and aldehydes (Table 3). The introduction of an electron-donating group at the *para* or *ortho* position of benzaldehyde (R^3 = 4-MeOC_6H_4 or 2-MeOC_6H_4) promoted the reaction with 1-trichloroacetoxycyclohexene (**1a**) to yield *anti* adduct **2ab** or **2ac** predominantly with 91 or 89%*ee*, respectively, without decreasing the yield of the isolated product (Table 3, entries 2 and 3). In addition, we executed the reaction of 4-$CF_3C_6H_4CHO$ and found that the electron-deficient aromatic aldehyde also showed remarkable stereoselectivity although the yield of isolated product **2ad** was moderate (Table 3, entry 4). α,β-Unsaturated aldehydes undergo 1,2-addition, and in fact, the reaction of (*E*)-cinnamaldehyde with **1a** gave 2-[(*E*)-1-hydroxy-3-phenylallyl]cyclohexanone (**2af**) almost exclusively (Table 3, entry 6). We also examined the reaction between alkenyl ester **1a** and hydrocinnamaldehyde at –20 °C for 24 h; however, we obtained desired adduct **2ag** in only 16% yield probably as a result of the low reactivity of the aliphatic aldehyde (Table 3, entry 7). The above-mentioned

Table 3. Enantioselective aldol reaction of alkenyl trihaloacetates **1** with aldehydes catalyzed by (*S*)-BINAP·AgOTf.[a]



Entry	Alkenyl ester	R^3	Temp. [°C]	Time [h]	Product	Yield[b] [%]	*anti*/*syn*[c]	*ee*[d] [%]
1	 **1a**	Ph	–40	2	**2aa**	92	86:14	94
2		4-$MeOC_6H_4$	–40	18	**2ab**	91	85:15	91
3		2-$MeOC_6H_4$	–40	12	**2ac**	99	91:9	89
4		4-$CF_3C_6H_4$	–40	20	**2ad**	65	91:9	92
5		2-C_4H_3S	–40	18	**2ae**	95	67:33	78
6		(*E*)-PhCH=CH	–40	18	**2af**	98	68:32	66
7		$PhCH_2CH_2$	–20	24	**2ag**	16	74:26	65
8	 **1b**	Ph	–40	20	**2ba**	81	92:8	75
9		4-$MeOC_6H_4$	–40	20	**2bb**	49	93:7	80
10	 **1b'**	Ph	–78	3	**2ba**	88	96:4	95
11		4-$MeOC_6H_4$	–78	3	**2bb**	78	93:7	90
12	 **1c** (*E*/*Z* = 8:92)	Ph	–78	24	**2ca**	73	1:99	89
13		4-$MeOC_6H_4$	–78	18	**2cb**	94	5:95	73

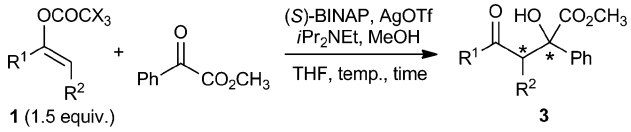
[a] Unless otherwise specified, the reaction was performed with (*S*)-BINAP (8 mol-%), silver triflate (16 mol-%), alkenyl trihaloacetate **1** (1.5 equiv.), aldehyde (1 equiv.), *N*,*N*-diisopropylethylamine (40 mol-%), and methanol (5 equiv.) in THF. [b] Yield of isolated product. [c] Determined by ^{1}H NMR spectroscopy. [d] The value corresponds to the major diastereomer. Determined by HPLC analysis.

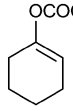
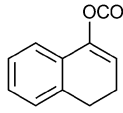
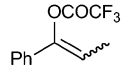
results further encouraged us to employ the alkenyl trifluoroacetates of other cyclic ketones in the asymmetric aldol reaction. 1-Tetralone derivative **1b** afforded target products **2ba** and **2bb** with good optical purities (75–80%*ee*) and predominant *anti* selectivities (*anti*/*syn* = 92:8–93:7) in the reaction with benzaldehyde and *p*-anisaldehyde (Table 3, entries 8 and 9). Then, we examined the ability of alkenyl trifluoroacetates to generate chiral silver enolates. Alkenyl esters have been shown to be superior substrates for an asymmetric protonation that used a cinchona alkaloid as the chiral catalyst.[11] By performing the enantioselective aldol reaction of 1-tetralone-derived alkenyl trifluoroacetate **1b′** with benzaldehyde and *p*-anisaldehyde at a low temperature (–78 °C) for 3 h, we acquired aldol adducts **2ba** and **2bb** in high yields with improved enantiomeric excess values (Table 3, entries 10 and 11). The reaction of acyclic alkenyl trifluoroacetate **1c** (*E*/*Z* = 8:92) with benzaldehyde at –78 °C provided aldol product **2ca** in a satisfactory yield but with opposite *syn* selectivity. The optical purity of the *syn* isomer was 89%*ee* (Table 3, entry 12). Remarkable *syn* selectivity was also noted in the reaction between **1c** and *p*-anisaldehyde (Table 3, entry 13).

The above-mentioned results prompted us to use a ketone as an electrophile for the chiral silver(I)-catalyzed aldol reaction. We previously showed that α-keto esters are good electrophiles for the BINAP·AgOTf-catalyzed asymmetric aldol reaction of alkenyl trichloroacetates in the presence of a catalytic amount of $Bu_2Sn(OMe)_2$.[7] Treatment of methyl benzoylformate with 1-trichloroacetoxy cyclohexene (**1a**) in the presence of (*S*)-BINAP (8 mol-%), AgOTf (16 mol-%), *N*,*N*-diisopropylethylamine (40 mol-%), and MeOH (5 equiv.) in dry THF at –40 °C for 4 h gave a 57:43 diastereomeric mixture of optically active aldol adduct **3a** in almost quantitative yield (Table 4, entry 1). The major diastereomer had 70%*ee*. The utility of the present (*S*)-BINAP·AgOTf-catalyzed asymmetric aldol reaction of methyl benzoylformate was further demonstrated by using alkenyl trifluoroacetates prepared from diverse ketones (Table 4, entries 2 and 3). In addition to cyclic substrate **1b′**, acyclic substrate **1c** was also allowed to react with the α-keto ester enantioselectively, although a long reaction time was necessary for the latter substrate to give a satisfactory yield (Table 4, entry 3). Worthy of note was that the reaction with acyclic substrate **1c** exhibited nearly exclusive diastereoselectivity although the enantioselectivity was moderate (57%*ee*; Table 4, entry 3). In contrast, the reaction with alkenyl trifluoroacetate of α-tetralone **1b′** proceeded with better enantioselectivity (82%*ee*; Table 4, entry 2).

γ,δ-Unsaturated δ-lactones can be used in place of alkenyl trihaloacetate **1** in the present chiral silver(I)-catalyzed

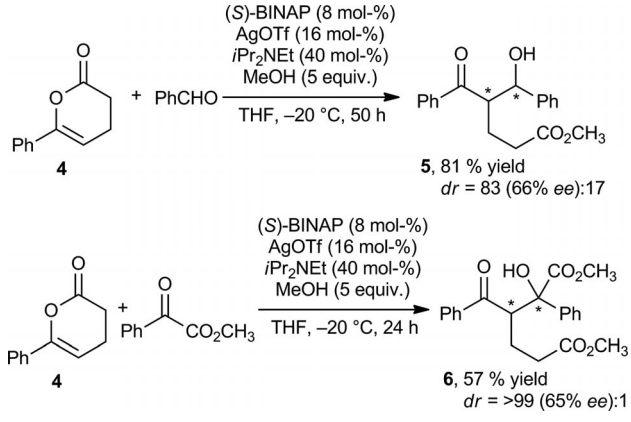
Table 4. Enantioselective aldol reaction of alkenyl trihaloacetates **1** with an α-keto ester catalyzed by (*S*)-BINAP·AgOTf.[a]



Entry	Alkenyl ester	Temp. [°C]	Time [h]	Product	Yield[b] [%]	Major/ minor[c]	*ee*[d] [%]
1	 **1a**	–40	4	**3a**	>99	57:43	70
2	 **1b'**	–78	4	**3b**	37	89:11	82
3	 **1c** (*E*/*Z* = 8:92)	–78	20	**3c**	94	>99:1	57

[a] Unless otherwise specified, the reaction was performed with (*S*)-BINAP (8 mol-%), silver triflate (16 mol-%), alkenyl trihaloacetate **1** (1.5 equiv.), α-keto ester (1 equiv.), *N*,*N*-diisopropylethylamine (40 mol-%), and methanol (5 equiv.) in THF. [b] Yield of isolated product. [c] Determined by ^{1}H NMR spectroscopy. [d] The value corresponds to the major diastereomer. Determined by HPLC analysis.

asymmetric aldol reaction. In fact, the reaction of γ,δ-unsaturated δ-lactone **4** with benzaldehyde provided target aldol adduct **5** in 81% yield. The major diastereomer of **5** had 63%*ee* (Scheme 2). The γ,δ-unsaturated δ-lactone-derived chiral silver enolate also showed satisfactory reactivity toward an α-keto ester. Upon treating methyl benzoylformate with **4** under the same reaction conditions for 24 h, aldol product **6** having a tertiary alcohol moiety was formed in 57% yield as a single diastereomer (65%*ee*, Scheme 2).



Scheme 2. Enantioselective aldol reaction of γ,δ-unsaturated δ-lactone **4** with benzaldehyde and an α-keto ester catalyzed by (*S*)-BINAP·AgOTf.

A plausible catalytic mechanism is shown in Figure 1. Initially, (*S*)-BINAP·AgOTf reacts with methanol in the presence of *N*,*N*-diisopropylethylamine to afford the corresponding (*S*)-BINAP·AgOMe, which is the true catalyst in the present asymmetric aldol reaction. Next, the thus-generated chiral silver methoxide attacks alkenyl trihaloacetate **1** to yield chiral silver enolate **7**. The following addition reaction of chiral silver enolate **7** with carbonyl compound **8** provides chiral silver alkoxide of aldol adduct **9**. Finally, the protonation of **9** with MeOH results in the formation of optically active β-hydroxy ketone **2** or **3** with regeneration of the chiral silver methoxide. The rapid methanolysis of silver alkoxide **9** advances the catalytic cycle efficiently.

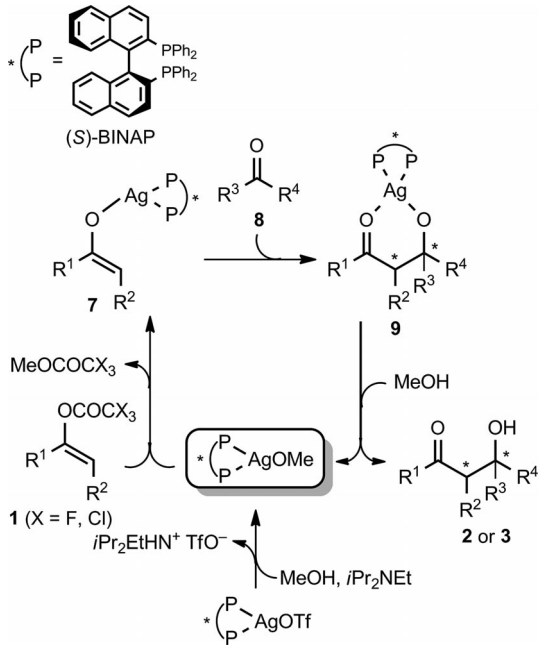


Figure 1. Plausible catalytic cycle for the asymmetric aldol reaction catalyzed by chiral silver methoxide.

The results in Table 3 are evidence that the diastereoselectivity depends on the geometry of a BINAP-coordinated silver enolate and that cyclic transition-state structures (i.e., **A** and **B**) described in Figure 2 are the proposed models. Thus, from the (*E*)-silver enolate, the *anti*-aldol adduct can be obtained via cyclic transition state model **A**, and model **B** connects the (*Z*)-silver enolate to the *syn*-aldol adduct.[12]

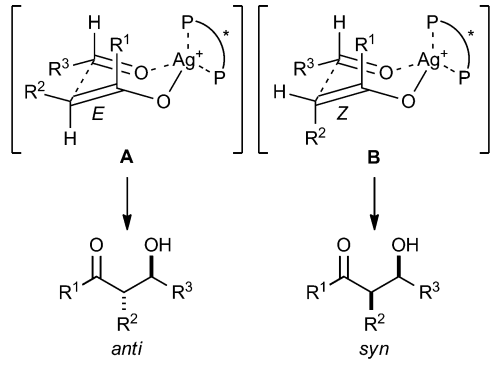


Figure 2. Proposed cyclic transition state structures.

A hypothesis for the enantioface discrimination between an aldehyde and a silver enolate in the present asymmetric aldol reaction catalyzed by (*S*)-BINAP·AgOTf is displayed in Figure 3. An aldehyde approaches the α carbon atom of a chiral silver enolate while avoiding steric repulsion from a phenyl group of the chiral phosphine ligand. Thus, carbon–carbon bond formation occurs selectively between the *Si* face of the silver enolate and the *Si* face of the aldehyde to yield the (2*R*,1′*S*)-β-hydroxy ketone.

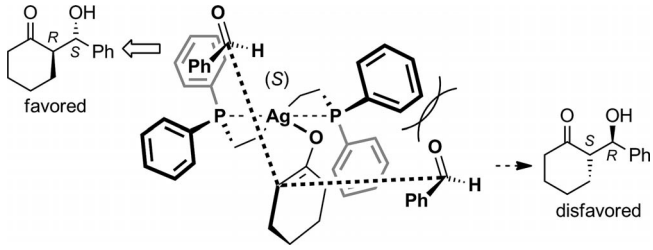


Figure 3. A hypothesis for enantioface discrimination between an aldehyde and a silver enolate.

Conclusions

In summary, we demonstrated a novel example of an asymmetric aldol reaction of alkenyl trihaloacetates or a γ,δ-unsaturated δ-lactone with carbonyl compounds through in situ generated chiral silver enolates catalyzed by BINAP·AgOTf and *N*,*N*-diisopropylethylamine. The procedure is operationally simple, employs readily available chemicals, and produces various optically active α-alkyl-β-hydroxy ketones with enantioselectivities up to 95%*ee* not only from aromatic and α,β-unsaturated aldehydes but also from an α-keto ester. This process is environmentally benign because toxic organotin compounds are not required. Further work is in progress on the asymmetric reaction.

Experimental Section

General Experimental Procedure for the Asymmetric Aldol Reaction Catalyzed by the (*S*)-BINAP·AgOTf Complex and *i*Pr$_2$NEt: A mixture of AgOTf (20.6 mg, 0.08 mmol) and (*S*)-BINAP (24.9 mg, 0.04 mmol) was dissolved in dry THF (3 mL) under an argon atmosphere and with direct light excluded, and the mixture was stirred at room temperature for 20 min. CH_3OH (101 μL, 2.5 mmol) and *i*Pr$_2$NEt (34 μL, 0.20 mmol) were successively added to the resulting solution at the specified temperature (–20, –40, or –78 °C). The mixture was stirred at the specified temperature for 5 min. Then, alkenyl trihaloacetate **1** or γ,δ-unsaturated δ-lactone **4** (0.75 mmol) and aldehyde or α-keto ester (0.5 mmol) were successively added drop by drop to the resulting solution at the specified temperature. After stirring for 2–50 h at that temperature, the mixture was treated with MeOH (2 mL). Then, the mixture was filtered with a glass filter funnel filled with Celite and washed with diethyl ether, and the combined filtrate and washes were concentrated in vacuo. The residual crude product was purified by column chromatography on silica gel to give corresponding β-hydroxy ketones **2**, **3**, **5**, or **6** (see Tables 3 and 4 and Scheme 2). The *anti*/*syn* ratio was determined by ^{1}H NMR spectroscopy and the enantiomeric ratio of the major diastereomer was determined by HPLC analysis.

Supporting Information (see footnote on the first page of this article): Experimental procedures, characterization data, and copies of the ^{1}H NMR and ^{13}C NMR spectra and HPLC traces.

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[1] For reviews, see: a) C. H. Heathcock, *Comprehensive Organic Synthesis* (Eds.: B. M. Trost, I. Fleming, C. H. Heathcock), Pergamon, Oxford, UK, **1991**, vol. 2, p. 133; b) C. Gennari, *Comprehensive Organic Synthesis* (Eds.: B. M. Trost, I. Fleming, C. H. Heathcock), Pergamon, Oxford, UK, **1991**, vol. 2, p. 629; c) M. Braun, *Houben-Weyl: Methods of Organic Chemistry* (Eds.: G. Helmchen, R. W. Hoffmann, J. Mulzer, E. Schaumann), Thieme, Stuttgart, Germany, **1995**, vol. E21, p. 1603; d) C. Palomo, M. Oiarbide, J. M. García, *Chem. Eur. J.* **2002**, *8*, 36; e) R. Mahrwald (Ed.), *Modern Aldol Reactions*, vol. 1, Wiley-VCH, Weinheim, Germany, **2004**; R. Mahrwald (Ed.), *Modern Aldol Reactions*, vol. 2, Wiley-VCH, Weinheim, Germany, **2004**; f) S. E. Denmark, J. R. Heemstra Jr., G. L. Beutner, *Angew. Chem. Int. Ed.* **2005**, *44*, 4682; *Angew. Chem.* **2005**, *117*, 4760; g) L. M. Geary, P. G. Hultin, *Tetrahedron: Asymmetry* **2009**, *20*, 131; h) T. Brodmann, M. Lorenz, R. Schäckel, S. Simsek, M. Kalesse, *Synlett* **2009**, 174; i) X. Ariza, J. Garcia, P. Romea, F. Urpí, *Synthesis* **2011**, 2175; j) S. B. J. Kan, K. K.-H. Ng, I. Paterson, *Angew. Chem. Int. Ed.* **2013**, *52*, 9097; *Angew. Chem.* **2013**, *125*, 9267; k) M. M. Heravi, V. Zadsirjan, *Tetrahedron: Asymmetry* **2013**, *24*, 1149; l) T. Kitanosono, S. Kobayashi, *Adv. Synth. Catal.* **2013**, *355*, 3095.

[2] For reviews on chiral Lewis acid catalyzed asymmetric Mukaiyama-type aldol reactions of silyl enolates, see: a) T. Bach, *Angew. Chem. Int. Ed. Engl.* **1994**, *33*, 417; *Angew. Chem.* **1994**, *106*, 433; b) T. K. Hollis, B. Bosnich, *J. Am. Chem. Soc.* **1995**, *117*, 4570; c) M. Braun, *Houben-Weyl: Methods of Organic Chemistry* (Eds.: G. Helmchen, R. W. Hoffmann, J. Mulzer, E. Schaumann), Thieme, Stuttgart, Germany, **1995**, vol. E21, p. 1730; d) S. G. Nelson, *Tetrahedron: Asymmetry* **1998**, *9*, 357; e) H. Gröger, E. M. Vogl, M. Shibasaki, *Chem. Eur. J.* **1998**, *4*, 1137; f) R. Mahrwald, *Chem. Rev.* **1999**, *99*, 1095; g) E. M. Carreira, *Comprehensive Asymmetric Catalysis* (Eds.: E. N. Jacobsen, A. Pfaltz, H. Yamamoto), Springer, Heidelberg, Germany, **1999**, vol. 3, p. 997; h) P. Arya, H. Qin, *Tetrahedron* **2000**, *56*, 917; i) T. D. Machajewski, C.-H. Wong, *Angew. Chem. Int. Ed.* **2000**, *39*, 1352; *Angew. Chem.* **2000**, *112*, 1406; j) E. M. Carreira, *Modern Carbonyl Chemistry* (Ed.: J. Otera), Wiley-VCH, Weinheim, Germany, **2000**, chapter 8, p. 227; k) H. Yamamoto (Ed.), *Lewis Acids in Organic Synthesis* vol. 1, Wiley-VCH, Weinheim, Germany, **2000**; H. Yamamoto (Ed.), *Lewis Acids in Organic Synthesis* vol. 2, Wiley-VCH, Weinheim, Germany, **2000**; l) T. Mukaiyama, *Angew. Chem. Int. Ed.* **2004**, *43*, 5590; *Angew. Chem.* **2004**, *116*, 5708; m) J. Matsuo, M. Murakami, *Angew. Chem. Int. Ed.* **2013**, *52*, 9109; *Angew. Chem.* **2013**, *125*, 9280; see also ref.[11]

[3] For reviews on chiral Lewis base catalyzed asymmetric aldol reactions by using silyl enolates, see: a) S. E. Denmark, R. A. Stavenger, X. Su, K.-T. Wong, Y. Nishigaichi, *Pure Appl. Chem.* **1998**, *70*, 1469; b) S. E. Denmark, R. A. Stavenger, *Acc. Chem. Res.* **2000**, *33*, 432; c) S. E. Denmark, G. L. Beutner, *Angew.*

Chem. Int. Ed. **2008**, *47*, 1560; *Angew. Chem.* **2008**, *120*, 1584; d) G. L. Beutner, S. E. Denmark, *Angew. Chem. Int. Ed.* **2013**, *52*, 9086; *Angew. Chem.* **2013**, *125*, 9256; e) R. L. Sutar, N. N. Joshi, *Tetrahedron: Asymmetry* **2013**, *24*, 1345; see also ref.[1d–1f]

[4] For reviews on direct catalytic asymmetric aldol reactions of aldehydes with unmodified ketones, see: a) H. Gröger, J. Wilken, *Angew. Chem. Int. Ed.* **2001**, *40*, 529; *Angew. Chem.* **2001**, *113*, 545; b) B. List, *Synlett* **2001**, 1675; c) S. Matsunaga, T. Ohshima, M. Shibasaki, *Adv. Synth. Catal.* **2002**, *344*, 3; d) B. Alcaide, P. Almendros, *Angew. Chem. Int. Ed.* **2003**, *42*, 858; *Angew. Chem.* **2003**, *115*, 884; e) M. Shibasaki, N. Yoshikawa, S. Matsunaga, *Comprehensive Asymmetric Catalysis*, *Supplement 1* (Eds.: E. N. Jacobsen, A. Pfaltz, H. Yamamoto), Springer, Heidelberg, **2004**, p. 135; f) X.-H. Chen, J. Yu, L.-Z. Gong, *Chem. Commun.* **2010**, *46*, 6437; g) U. Scheffler, R. Mahrwald, *Synlett* **2011**, 1660; h) M. Bhanushali, C.-G. Zhao, *Synthesis* **2011**, 1815; i) V. Bisai, A. Bisai, V. K. Singh, *Tetrahedron* **2012**, *68*, 4541; j) M. M. Heravi, S. Asadi, *Tetrahedron: Asymmetry* **2012**, *23*, 1431; see also ref.[1d,1e]

[5] a) A. Yanagisawa, T. Sekiguchi, *Tetrahedron Lett.* **2003**, *44*, 7163; b) A. Yanagisawa, R. Goudu, T. Arai, *Org. Lett.* **2004**, *6*, 4281.

[6] a) S. E. Denmark, R. A. Stavenger, K.-T. Wong, X. Su, *J. Am. Chem. Soc.* **1999**, *121*, 4982; b) A. Yanagisawa, T. Ichikawa, T. Arai, *J. Organomet. Chem.* **2007**, *692*, 550.

[7] A. Yanagisawa, Y. Terajima, K. Sugita, K. Yoshida, *Adv. Synth. Catal.* **2009**, *351*, 1757.

[8] Quite recently, we found that a chiral phosphine·silver(I) complex catalyzed asymmetric Mannich-type reaction of alkenyl trichloroacetates with imines takes place in the presence of a substoichiometric amount of *N*,*N*-diisopropylethylamine without dibutyltin dimethoxide: A. Yanagisawa, Y. Lin, R. Miyake, K. Yoshida, *Org. Lett.* **2014**, *16*, 86.

[9] J. Libman, M. Sprecher, Y. Mazur, *Tetrahedron* **1969**, *25*, 1679.

[10] Employment of SEGPHOS or *t*Bu-QuinoxP* in place of BINAP resulted in a deceleration of the aldol reaction probably because of ligand bite angle effects, which might affect the transition-state structure, see: P. W. N. M. van Leeuwen, P. C. J. Kamer, J. N. H. Reek, P. Dierkes, *Chem. Rev.* **2000**, *100*, 2741.

[11] a) J. Gil, M. Medio-Simon, G. Mancha, G. Asensio, *Eur. J. Org. Chem.* **2005**, 1561; b) A. Claraz, J. Leroy, S. Oudeyer, V. Levacher, *J. Org. Chem.* **2011**, *76*, 6457.

[12] In addition to the latter pathway, the *syn*-aldol adduct can be formed from the (*E*)-silver enolate through another cyclic transition-state structure in which the R^3 group of the aldehyde is directed to the axial position. Therefore, the size of the R^3 group also affects the *anti*/*syn* ratio of the aldol products.

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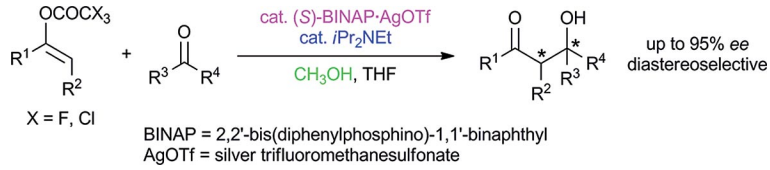

BINAP = 2,2'-bis(diphenylphosphino)-1,1'-binaphthyl
AgOTf = silver trifluoromethanesulfonate

An efficient catalytic enantioselective aldol reaction between alkenyl trihaloacetates and aldehydes or an α-keto ester is described. The use of in situ generated chiral silver methoxide as the chiral catalyst allows the synthesis of various nonracemic α-alkyl β-hydroxy ketones with enantioselectivities of up to 95% *ee*.

Asymmetric Catalysis

Keywords: Synthetic methods / Asymmetric catalysis / Aldol reactions / Silver / Aldehydes

