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The Asymmetric Catalytic Aldol Reaction of Allenolates with Aldehydes Using *N*-Fluoroacyl Oxazaborolidine as the Catalyst

Guigen Li,* Han-Xun Wei, Brian S. Phelps, David W. Purkiss, and Sun Hee Kim

Department of Chemistry and Biochemistry, Texas Tech University, Lubbock, Texas 79409-1061
qeggl@ttu.edu

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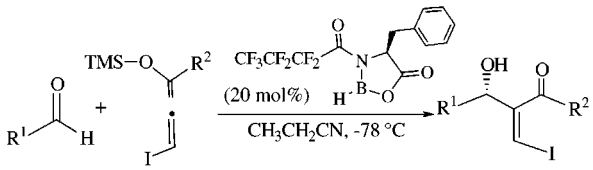
ABSTRACT



(60 - 75 %, 61 - 98 %ee, *E*/*Z* 1:1.8 - <1:20)

The asymmetric catalytic aldol reaction of silyl allenolates with aldehydes has been achieved by using *N*-C_3F_7CO oxazaborolidine as the catalyst. The fluoroacyl group of the catalyst was found to be crucial for control of enantioselectivity. The reaction provides the first enantioselective approach to *β*-halo Baylis−Hillman-type adducts.

The asymmetric catalytic aldol reaction is among the most important C−C bond-forming reactions in organic chemistry and has been an active research topic for several decades.[1−3] Unfortunately, an asymmetric catalytic aldol reaction using allenolates as nucleophiles to form C(sp^3)−C(sp^2) bonds has not been established thus far. Such a reaction could conceivably act as a powerful tool for the asymmetric synthesis of multifunctionalized organic compounds, particularly α-1-hydroxyalkyl-*β*-iodo enones which belong to Baylis−Hillman-type adducts and can be used as versatile building blocks for a variety of chemical and biological purposes.[4,5] Baylis−Hillman-type adducts were found to directly inhibit the growth of tumor cells.[6] In fact, the Baylis−Hillman reaction has been used for the synthesis of these important compounds and has attracted considerable interest in the synthetic community in the past few years.[4−8]

Several asymmetric C(sp^3)−C(sp^2) formation processes have been carried out under asymmetric Baylis−Hillman conditions using chiral auxiliary-anchored substrates[5a] or by replacing DABCO catalysts with special chiral amines,[5b,c] BINAP,[6a] and chalcogenide−$TiCl_4$ complexes.[6b] Very recently, the Pd complex-catalyzed deracemization was de-

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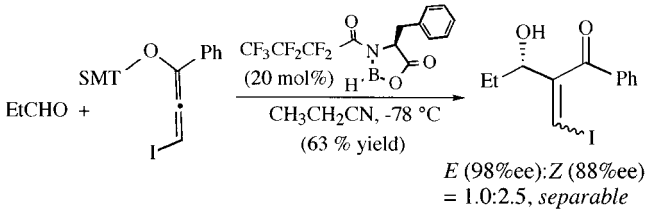
veloped by Trost and co-workers for asymmetric synthesis of Baylis−Hillman-type adducts.[8] Unfortunately, only a limited number of Baylis−Hillman-type adducts can be prepared by using these known methods due to serious scope limitations. In this Letter, we present a novel asymmetric carbon−carbon bond formation between silyl allenolates and aldehydes using *N*-heptafluorobutyryl oxazaborolidines as catalysts, as represented in Scheme 1. The reaction provides a straightforward approach to β-halo Baylis−Hillman-type adducts.[9] These products can be readily converted into β-alkyl Baylis−Hillman-type adducts and other useful building blocks.[10]

Scheme 1



As mentioned earlier, the aldol reaction acts as the key step of the original Baylis−Hillman reaction, which indeed inspired us to develop alternative approaches to Baylis−Hillman-type adducts. The use of silyl allenolates, metal allenolates or allenoates, and vinyl anionic species pioneered by Kishi,[9] Marino,[11] and Tsuda[12] has previously been proven to be successful for the synthesis of a variety of β-substituted Baylis−Hillman-type adducts. The two-step Michael-type addition followed by elimination has also been utilized for the synthesis of these adducts.[13] In the past few years, we have been involved in exploring reactions of vinyl anions and/or metal allenolates with aldehydes[7,10c−d] and believe that their asymmetric catalytic versions could be achieved by using chiral Lewis acids to activate the aldehydes or by using Lewis bases to push anionic species onto aldehydes.

At first, enantiomerically pure titanium(VI) Lewis acids such as Ti(O^{i}Pr)$_2$[BINOL], TiCl$_2$[BINOL], TiO[BINOL], etc.[2,14] which have been widely used in asymmetric aldol reactions, were tested to activate aldehydes. Unfortunately, all of these Lewis acids failed to give enantiomeric excesses even when they were used in a stoichiometric amount. We then studied another aldol catalyst series, oxazaborolidines, under similar conditions.[3a−b,15] Still no enantioselectivity was observed when Ti and Al metal allenolates were employed as the nucleophiles to react with benzaldehyde. Our attention was thereafter turned to the use of Kishi's β-iodo allenolates.[9a−c] The effort to render this asymmetric process became extremely challenging because its racemic version can proceed smoothly at 0 °C in CH$_2$Cl$_2$ in the absence of any catalysts. We were also challenged by the fact that a low-temperature system should be found for in situ generation of both allenolates and catalysts, as well as for the subsequent carbonyl addition. Our next attempt was a thorough search to find and modify suitable catalysts, carefully choose certain allenolates, catalysts, and solvents or cosolvents, and concurrently decrease the reaction rate through slow addition of reactants with a syringe pump.

While other Lewis acid catalysts failed to give any enantioselectivity for the carbonyl reaction of Kishi's β-iodo allenolates with aldehydes, *N*-sulfonyl oxazaborolidine catalysts[15,17] gave promising results. The first encouraging experiments (entry 1 of Table 3) were performed in dichloromethane at −78 °C using two *N*-sulfonyl oxazaborolidines which were derived from (*S*)-tryptophane and (*S*)-phenylalanine. The enantioselectivity of the *E* isomer controlled by these two catalysts was determined to be 11 and 40 ee %, respectively. These results led us to favor phenylalanine-derived oxazaborolidine as the candidate for further refinements of the catalyst and catalytic system. The *N*-tosyl group of phenylalanine-derived oxazaborolidine was then replaced with several other electron-deficient counterparts such as *N*-trifluoromethanesulfonyl[16a] and 4-nosyl and 2-nosyl groups.[16b,c] In fact, *N*-subunits of oxazaborolidines have already been proven by Corey and co-workers to be important in controlling the orientation of boron−aldehyde coordination.[17] To our surprise, the ee % was diminished

Table 1. Effects of *N*-Protecting Groups on Enantioselectivity in CH$_2$Cl$_2$ at −78 °C

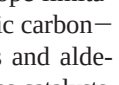
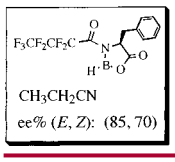
R					
ee% (*E*, *Z*)	(41, 19)	(10, 4)	(8, 0)	no product	(60, 27)

Table 2. Solvent Effects on ee % Using *N*-Trifluoroacetyl Oxazaborolidine as the Catalyst



Solvent	CH_3CH_2CN	CH_2Cl_2	$CH_3CH_2NO_2$	CH_3CH_2CN/$CH_3CH_2NO_2$ (v/v = 1:1)
ee% (*E*, *Z*)	(75, 63)	(48 21)	(45, 18)	(48, 48)

(7) (a) Hayase, T.; Shibata, T.; Soai, K.; Wakatsuki, Y. *Chem. Commun.* **1998**, 1271. (b) Kataoka, T.; Iwama, T.; Tsujiyama, S.; Watanable, S. *Chem. Lett.* **1999**, *3*, 257.

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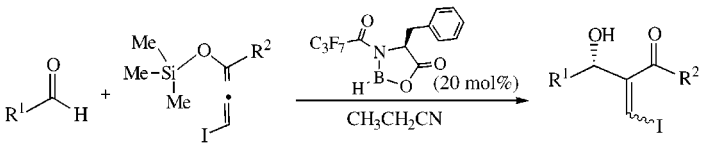
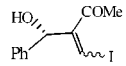
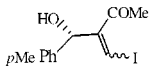
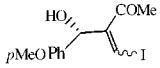
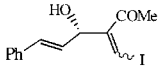
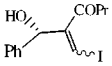
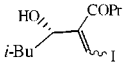
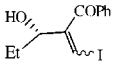
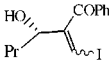
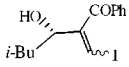
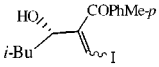
(13) (a) Nagaoka, Y.; Tomioka, K. *J. Org. Chem.* **1998**, *63*, 6468. (b) Barrett, A. G. M.; Kamimura, A. *Chem. Commun.* **1995**, 1755.

Table 3. Results of the New Asymmetric Catalytic C−C Bond Formation[a]



entry	R^1	R^2	product	E/Z^b	% ee[c] E	% ee[c] Z	yield (%)[d]
1	Ph	Me		1.0/2.0	85	70	71
2	*p*-MePh	Me		1.0/1.9	98	66	68
3	*p*-MeOPh	Me		1.0/1.8	94	69	67
4	(*E*) PhCH=CH-	Me		<1.0/20	–	72	75
5	Ph	Pr		1.0/6.3	81	61	65
6	*i*-Bu	Pr		<1.0/20	–	97	63
7	Et	Ph		1.0/2.5	98	88	63
8	Pr	Ph		1.0/5.0	97	73	62
9	*i*-Bu	Ph		<1.0/20	–	98	60
10	*i*-Bu	*p*-MePh		<1.0/20	–	97	61

[a] Reactions were run at −78 °C by adding aldehyde into the preformed mixture of catalyst and silyl allenolate in propionitrile over a period of 10 h via a syringe pump. After addition was finished, the reaction was stirred for additional 7 h before being quenched with dilute HCl. The catalyst was generated by adding BH_3·THF into the propionitrile solution of *N*-heptafluoropropyl phenylalanine at rt.[3a,b] TMS-allenolates were obtained by adding TMS-I to acetylenic ketones also in propionitrile at −78 °C stirring for 1 h. [b] Estimated by crude ^{1}H NMR determination. [c] Both *Z* and *E* isomers were determined to have *S* chirality which is shown in ref 19. Enantiomeric excesses were determined by Chiralcel OD-H, AD, and OG HPLC columns (see Supporting Information). [d] The combined yields of *Z* and *E* isomers after column chromatography; 20 mol % of catalyst was used for all cases. Similar ee % and yields were obtained with 50 mol % of catalyst for case 1.

with the two nosyl replacements but retained with the *N*-trifluoromethanesulfonyl modification. We then evaluated the *N*-carbonyl moieties instead of *N*-sulfonyl groups for possible enantioselectivity enhancement. It was found that the *N*-acetyl oxazaborolidine did not give any aldol products. However, *N*-trifluoroacetyl oxazaborolidine catalyst did increase enantioselectivity to 60 and 27 ee % for *E* and *Z* isomers, respectively (Table 1).

The reason to use dichloromethane as the first solvent is that it has been proven to be effective for in situ preparation of β-iodo TMS-allenolates and the subsequent carbonyl additions. However, for the oxazaborolidine-catalyzed aldol reaction, propionitrile and nitroethane are normally chosen,[3a,b,18] even though they have not been utilized for in situ preparation of β-iodo TMS-allenolates as yet. To further improve the reaction, parallel optimization experiments were then set up with three solvents, CH_2Cl_2, EtCN, and $EtNO_2$. As shown in Table 2, the use of propionitrile resulted in improved

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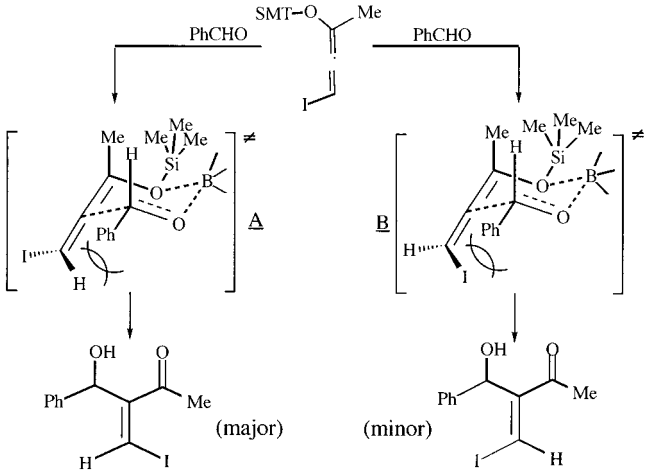
enantioselectivity for both *E* and *Z* isomers (75 ee % for *E* and 63 ee % for *Z*, respectively). We then reconsidered the importance of the *N*-substituent of the catalyst and replaced the *N*-trifluoroacetyl group with its *N*-heptafluorobutyryl counterpart. We found that this replacement can give greater enantioselectivity for both *Z* and *E* isomers (85 ee % for *E* and 70 ee % for *Z*, respectively). Obviously, it is crucial that all three in situ preparations for catalysts, β-iodo TMS-allenolates, as well as the subsequent carbonyl additions can be performed in propionitrile at −78 °C.

With these conditions in hand, a series of substrates were thus extensively investigated. The preliminary results listed in Table 3 indicate that a broad scope of substrates can be used for this new reaction. Both aromatic and aliphatic aldehydes can serve as the electrophilic acceptors. Furthermore, both aromatic and aliphatic α,β-acetylenic ketones can be employed as Michael-type acceptors to generate TMS-allenolates prior to carbonyl additions. Modest to excellent *Z*/*E* selectivity (>20:1−1.8:1) has been obtained for all cased examined. The resulting *Z*/*E* isomers of each case can be readily separated by routine column chromatography. The *Z*/*E* selectivity was measured by ^{1}H NMR analysis of crude products. The geometry was determined by NOE experiments of ^{1}H NMR spectroscopy in which 5% NOE was observed between the signals of vinyl proton and methyl protons of the *E* isomer of product **1**. In contrast to *N*-trifluoroacetyl oxazaborolidine, the *N*-pentafluorobutyryl-modified catalyst resulted in consistent and reproducible *Z*/*E* selectivity. Increasing reaction temperature or adding aldehyde in one portion diminished *Z*/*E* selectivity and enantioselectivity.

Using deuterium solvents enabled us to directly observe β-iodo TMS-allenolate. After the reaction, no such intermediate was detected in the reaction mixture by ^{1}H NMR determination, which means that both enantiomers of silyl allenolate were consumed. The facial selectivity of the carbonyl addition is obviously controlled by the catalyst. Further study will be conducted on the use of chiral aldehydes or alternative catalysts to ascertain the asymmetric kinetic resolution of β-iodo silyl allenolates. Since the present reaction was carried out at −78 °C, the resulting isomeric products are believed to result from kinetical control. Two possible transition states (A and B) for forming individual *Z* and *E* isomers are shown in Scheme 2. Transition state A is obviously the predominant one; the steric effect between the iodine and the hydrogen of the aldehyde is smaller than the corresponding interaction in transition state B.

The absolute structure was determined by transforming the *E* isomer of product **1** to methyl (*S*)-α-methoxyphenylacetate which is derived from an authentic sample of (*S*)-menthyl mandelate.[18−21] The resulting chirality controlled by oxazaborolidines derived from *N*-trifluoroacetyl and *N*-heptafluoropropyl phenyalanine as well as *N*-trifluoro acetyl tryptophane is consistent with that of the aldol reaction catalyzed by Corey's oxazaborolidine catalyst.[3b,22] Therefore, the asymmetric induction of the current reaction can be suggested by using Corey's oxazaborolidine−aldehhyde complexation model.[3b]

Scheme 2



In conclusion, the first asymmetric carbonyl addition of allenolates to aldehydes has been established using *N*-heptafluoropropyl oxazaborolidine as the catalyst. The reaction provides an unprecedented enantioselective approach to individual *Z* and *E* isomers of β-halo Baylis−Hillman-type adducts. Further optimizations of this new asymmetric reaction and scope extension as well as its synthetic applications will be studied in the future.

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Supporting Information Available: Experimental, HPLC analysis and ^{1}H and ^{13}C NMR spectra for all pure *Z* and *E* isomers. This material is available free of charge via the Internet at http://pubs.acs.org.

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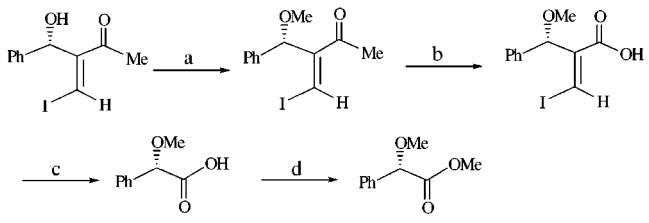
(19) Synthetic transformations for absolute structure determination: (a) MeI, Ag_2O, MeCN, reflux. (b) i, KOCl, 0 °C, 12 h then rt 3 h; ii, H_3O^+. (c) $RuCl_2 \cdot 3H_2O$ (cat.), H_5IO_6 (3 equiv), CCl_4/MeCN/H_2O (1/1/1.4, v/v/v). (d) Me_3SiCl, MeOH, rt, overnight.



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