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Powerful Amino Diol Catalyst for Effecting the Direct Asymmetric Conjugate Addition of Aldehydes to Acrylates

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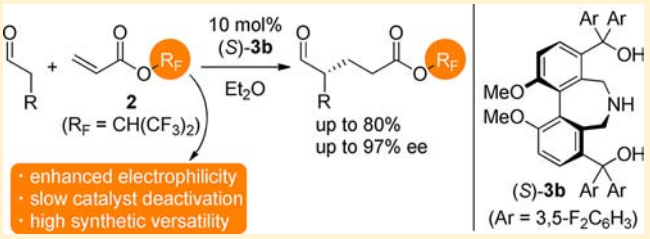
Supporting Information

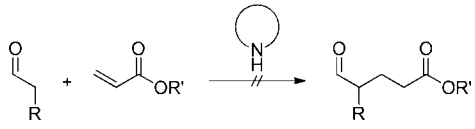
ABSTRACT: Di-*tert*-butyl methylenemalonate (**1**) could be employed as a reactive equivalent of a three-carbon Michael acceptor such as acrylate in a direct asymmetric conjugate addition of aldehydes catalyzed by an axially chiral amino diol (*S*)-**3a**. Furthermore, acrylate, an unexplored and challenging substrate in enamine catalysis, has also been successfully employed in asymmetric conjugate addition reaction. Relatively inert acrylate is doubly activated by polyfluoroalkyl group of **2** and the hydroxyl group on the axially chiral amino diol catalyst (*S*)-**3b**, giving corresponding conjugate adducts in high yield with excellent enantiomeric excess. The obtained conjugate addition products were readily converted to synthetically useful and important chiral building blocks.



INTRODUCTION

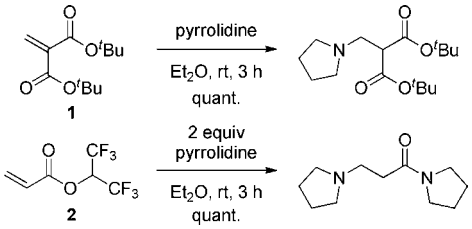
The catalytic asymmetric conjugate addition of carbon nucleophiles to electron-deficient olefins is one of the most fundamental and reliable C−C bond-forming reactions in synthetic organic chemistry.[1] In the area of organocatalysis, a large number of asymmetric conjugate addition reactions have been developed to date.[2,3] Consequently, a wide variety of electron-deficient olefins are now applicable as acceptor to the amine-catalyzed conjugate additions through an enamine intermediate.[3,4] In light of the versatility of these reactions, it is surprising that one of the simplest three-carbon Michael acceptors, alkyl acrylate, has not been utilized in enamine catalysis (Scheme 1).[5,6] This might be due to the combination

Scheme 1. Challenging Amine-Catalyzed Conjugate Addition



of relatively low nucleophilicity of the enamine intermediate and low electrophilicity of acrylate.[7,8] On the other hand, highly reactive modified acrylates such as dialkyl methylenemalonates[9] and polyfluoroalkyl acrylates can lead to the catalyst deactivation by the undesired conjugate addition and amidation (Scheme 2). To overcome this intrinsic dilemma, we became interested in using the amine catalyst with enzyme-like active site, which can further activate the reactive dialkyl methylenemalonate and polyfluoroalkyl acrylate at the appropriate position by the acidic proton (Scheme 3). At the same time, the catalyst amine moiety in the cavity is expected to allow selective

Scheme 2. Consumption of Pyrrolidine by Highly Reactive Acrylate Derivatives



interaction with an aldehyde to generate the enamine intermediate while keeping a dialkyl methylenemalonate and polyfluoroalkyl acrylate out of the catalyst cavity. Herein, we wish to report a highly enantioselective conjugate addition reaction of aldehydes to the dialkyl methylenemalonate and polyfluoroalkyl acrylate catalyzed by an axially chiral amino diol of type (*S*)-**3**.

RESULTS AND DISCUSSION

We first investigated the conjugate addition of 3-phenylpropanal to di-*t*-butyl methylenemalonate **1** as a reactive equivalent of acrylates in tetrahydrofuran (THF) in the presence of various secondary amine catalysts (10 mol %), and the results are shown in Table 1.[5g] The use of pyrrolidine as a catalyst did not afford the desired conjugate addition product due to the undesired conjugate addition of pyrrolidine to **1** as shown in Scheme 2 (entry 1).[10] On the other hand, both sterically hindered amine catalysts (*S*)-**3a**[5g] having hydroxydiphenylmethyl groups[11] and (*S*)-**4b**[12] gave the

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Scheme 3. Catalyst Design for Conjugate Addition of Aldehydes to Highly Reactive Acrylate Derivatives

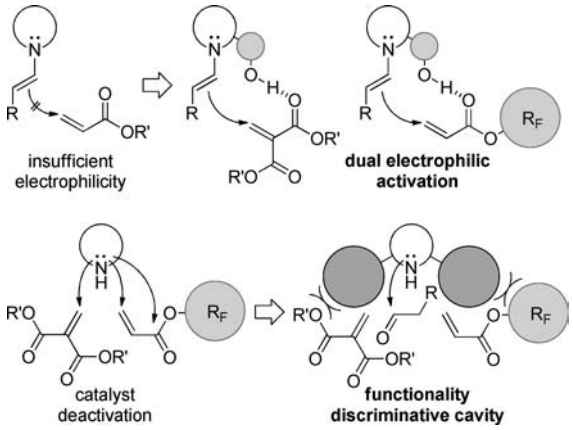
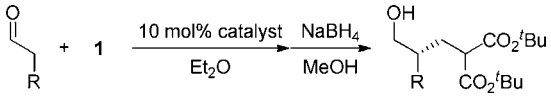


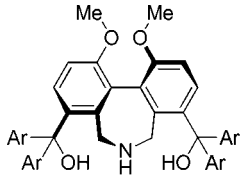
Table 1. Conjugate Addition of Aldehydes to 1[a]



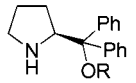
entry	catalyst	R	conditions (°C, h)	yield (%)[b]	ee (%)[c]
1[d]	pyrrolidine	Bn	rt, 4	n.d.	-
2[d]	L-proline	Bn	rt, 4	48	−6
3[d]	(*S*)-**4b**	Bn	rt, 4	69	−89
4[d]	(*S*)-**3a**	Bn	rt, 4	93	76
5[d]	(*S*)-**3a**	Bn	0, 4	74	87
6	(*S*)-**3a**	Bn	0, 4	94	94
7[e]	(*S*)-**3a**	Bn	0, 4	83	95
8[e]	(*S*)-**4b**	Bn	0, 4	38	−97
9	(*S*)-**3a**	Me	0, 4	80	96
10[e]	(*S*)-**3a**	Me	0, 4	79	96
11[f]	(*S*)-**3a**	Bu	0, 4	83	94
12[f]	(*S*)-**3a**	Hex	0, 4	83	94
13[f]	(*S*)-**3a**	CH_2Cy	0, 4	70	86
14	(*S*)-**3a**	CH_2OBn	0, 4	69	93
15	(*S*)-**3a**	$(CH_2)_3OBn$	0, 4	94	95
16[d,f]	(*S*)-**3a**	CH_2CO_2Me	0, 40	65	87
17[d,f]	(*S*)-**3a**	CH_2NHZ	0, 40	82	84
18[f]	(*S*)-**3a**	3-pyridylmethyl	0, 4	87	93
19	(*S*)-**3a**	*i*-Pr	rt, 24	80	97
20[f]	(*S*)-**3a**	Cy	rt, 72	89	94

[a]The reaction of an aldehyde (0.4 mmol) with **1** (0.13 mmol) in Et_2O was carried out in the presence of a catalyst (0.013 mmol). [b]The conjugate addition product was isolated as the corresponding alcohol to determine the enantioselectivity. [c]The enantiomeric excess (ee) of the product or its dibenzoate ester was determined by high-performance liquid chromatography analysis using a chiral column. [d]Use of THF as solvent. [e]Use of 3 mol % of a catalyst. [f]Use of 1.5 equiv of aldehyde.

conjugate adduct in good yield and enantioselectivity, respectively (entries 3 and 4). By lowering the temperature and using Et_2O as solvent, further improvement of enantioselectivity in the reaction using (*S*)-**3a** was achieved (entry 6). Under the optimized conditions, a variety of aldehydes underwent addition to **1** with high enantioselectivity (entries 9−20). The reactions with a lower catalyst loading (3 mol %) also gave satisfactory results (entries 7 and 10).



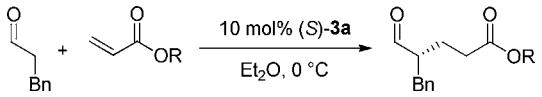
(*S*)-**3a**: Ar = Ph
(*S*)-**3b**: Ar = 3,5-$F_2C_6H_3$



(*S*)-**4a**: R = H
(*S*)-**4b**: R = TMS

While we have developed the asymmetric conjugate addition using methylenemalonate as an acrylate surrogate, the conjugate addition of aldehydes to an acrylate itself is still an attractive and challenging reaction in enamine catalysis. Thus, we then investigated conjugate addition of 3-phenylpropanal to various acrylates in Et_2O in the presence of biphenyl-based amino diol catalyst (*S*)-**3a** (10 mol %), and the results are shown in Table 2. The use of either methyl acrylate or phenyl

Table 2. Conjugate Addition of 3-Phenylpropanal to Alkyl Acrylate[a]



entry	R	time (h)	yield (%)[b]	ee (%)[c]
1	Me	24	n.d.	
2	Ph	24	n.d.	
3	$CH(CF_3)_2$ (**2**)	24	63	92
4	$CF(CF_3)_2$	72	<5	
5	$CMe(CF_3)_2$	72	38	93

[a]The reaction of 3-phenylpropanal (0.10 mmol) with an alkyl acrylate (0.50 mmol) in Et_2O was carried out in the presence of (*S*)-**3a** (0.010 mmol) at 0 °C for 24 h. [b]The conjugate addition product was isolated as the corresponding diol to determine the enantioselectivity. [c]The ee of the product was determined by high-performance liquid chromatography analysis using chiral column.

acrylate did not afford the corresponding conjugate addition product as expected (entries 1 and 2). Several fluorinated acrylates were then employed as the activated and sterically hindered acrylate. While the reaction of heptafluoroisopropyl acrylate resulted in the formation of a trace amount of the conjugate adduct (entry 4), 1,1,1,3,3,3-hexafluoroisopropyl acrylate (**2**)[13] was found to be the optimal acrylate affording the desired conjugate adduct in moderate yield with high enantioselectivity (entry 3).

We then optimized the reaction conditions as shown in Table 3. With **2**, reactions were conducted in various solvents, and we observed significant solvent effects on the reactivity and selectivity (entries 1−4). Among the solvents tested, Et_2O was found to be the optimal solvent in terms of both yield and enantioselectivity (entry 1). The yield was slightly improved by increasing the reaction temperature from 0 to 15 °C at the expense of enantioselectivity (entry 5). Fine-tuning of amino diol catalyst (*S*)-**3a** led to catalyst (*S*)-**3b**, which improved the enantioselectivity (entry 6). We have also evaluated two widely used chiral pyrrolidines, (*S*)-**4a** and (*S*)-**4b**,[12] for the ability to promote the present conjugate addition. When a pyrrolidine-based amino alcohol (*S*)-**4a** was used as a catalyst, the formation of the conjugate adduct was not detected (entry 8). (*S*)-Diphenylprolinol silyl ether (*S*)-**4b** was also less effective in terms of both reactivity and selectivity (entry 9).

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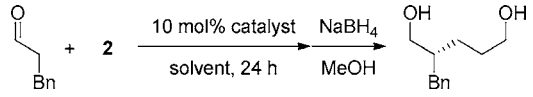
Table 3. Conjugate Addition of 3-Phenylpropanal to 2[a]

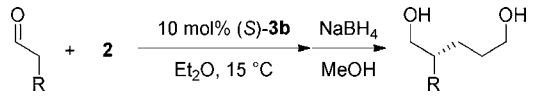


entry	catalyst	solvent	temp (°C)	yield (%)[b]	ee (%)[c]
1	(*S*)-**3a**	Et_2O	0	63	92
2	(*S*)-**3a**	THF	0	45	77
3	(*S*)-**3a**	CH_2Cl_2	0	n.d.	-
4	(*S*)-**3a**	toluene	0	n.d.	-
5	(*S*)-**3a**	Et_2O	15	73	90
6	(*S*)-**3b**	Et_2O	15	73	97
7[d]	(*S*)-**3b**	Et_2O	15	86	97
8	(*S*)-**4a**	Et_2O	15	n.d.	-
9	(*S*)-**4b**	Et_2O	15	11	−71

[a]The reaction of 3-phenylpropanal (0.10 mmol) with **2** (0.50 mmol) in a solvent was carried out in the presence of a catalyst (0.010 mmol) for 24 h. [b]The conjugate addition product was isolated as the corresponding diol to determine the enantioselectivity. [c]The ee of the product was determined by high-performance liquid chromatography analysis using chiral column. [d]Use of 10 equiv of **2**.

In the presence of 10 mol % of (*S*)-**3b**, the direct asymmetric conjugate addition of several other aldehydes to **2** was examined, and the results are shown in Table 4. In general,

Table 4. Conjugate Addition of Aldehydes to 2[a]



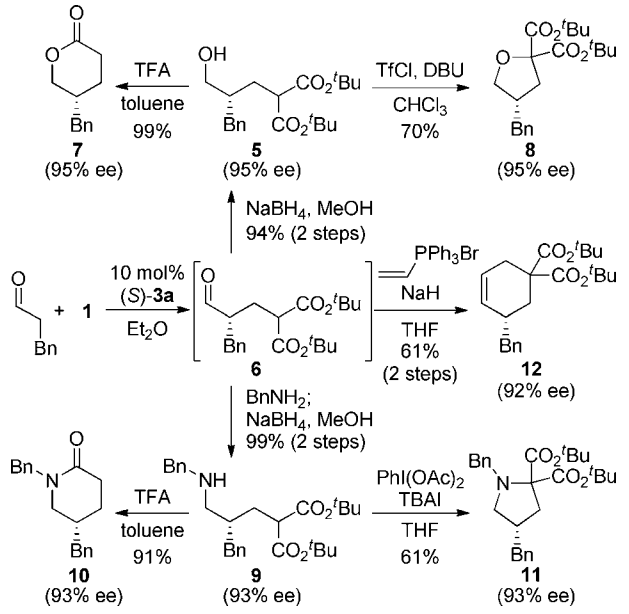
entry	R	time (h)	yield (%)[b]	ee (%)[c]
1	Me	72	80	96
2	Bu	24	70	96
3	Bn	24	86	97
4	CH_2Cy	24	70	92
5	CH_2OBn	24	60	88
6	$(CH_2)_3OBn$	24	76	94
7[d]	*i*-Pr	72	46	94
8	Cy	72	57	95

[a]Unless otherwise specified, the reaction of an aldehyde (0.050 mmol) with **2** (0.5 mmol) in Et_2O was carried out in the presence of (*S*)-**3b** (5.0 μmol) at 15 °C for 24 h. [b]The conjugate addition product was isolated as the corresponding diol to determine the enantioselectivity. [c]The ee of the product was determined by high-performance liquid chromatography analysis using a chiral column after transformation to the corresponding diol or its dibenzoate ester. [d]Use of (*S*)-**3a** instead of (*S*)-**3b**.

these direct asymmetric conjugate additions gave the corresponding adducts with excellent enantioselectivity, while sterically hindered aldehydes gave somewhat lower yield even with longer reaction time (entries 7 and 8).

The conjugate adduct **6** obtained from **1** was a versatile intermediate in organic synthesis and readily converted to important chiral building blocks (Scheme 4).[5g] When one-pot conjugate addition−reduction product **5** was treated with trifluoroacetic acid (TFA) at 80 °C, δ-lactone **7** was obtained in quantitative yield with complete retention of stereochemistry. Treatment of **5** with trifluoromethanesulfonyl chloride and 1,8-diazabicyclo[5.4.0]undec-7-ene formed cyclic ether **8** without loss of optical purity.[14] The conjugate addition product **6** could also be converted in situ to amine **9** by reductive amination.

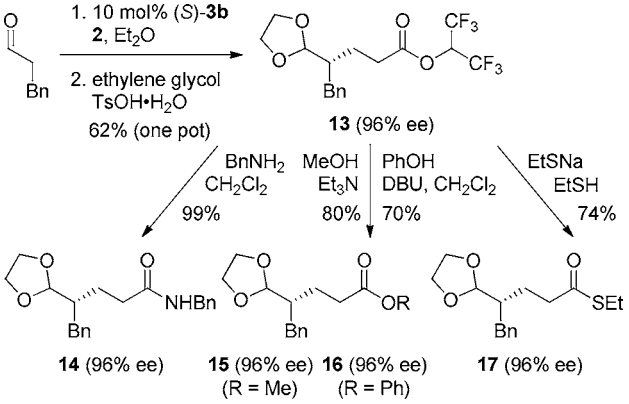
Scheme 4. Transformations of the Conjugate Adduct 6



Amine **9** was transformed to δ-lactam **10** in good yield using TFA. In the presence of (diacetoxyiodo)benzene and tetrabutylammonium iodide, amine **9** was directly cyclized to pyrrolidine **11**.[15] Moreover, cyclohexene **12** was obtained in one-pot from the reaction of **6** with NaH and triphenyl(vinyl)-phosphonium bromide.[9]

The conjugate adduct obtained from **2** has a highly reactive 1,1,1,3,3,3-hexafluoroisopropyl ester moiety and was also readily converted to important chiral building blocks (Scheme 5). When one-pot conjugate addition−protection product **13**

Scheme 5. Transformations of the Conjugate Adduct



was treated with benzylamine, the corresponding amide **14** was obtained in quantitative yield with complete retention of stereochemistry. Treatment of **13** with alcohols such as methanol and phenol in the presence of a base gave the corresponding esters **15** and **16**, respectively. Thioester **17** was also obtained from the reaction between **13** and sodium benzylthiolate without loss of optical purity. Moreover, the conjugate addition product was readily converted to δ-lactone **7** (Scheme 6).

By use of ^1H NMR, we monitored the rate of product formation and discovered that the reaction catalyzed by (*S*)-**3a** was much faster than that observed in the reaction using more

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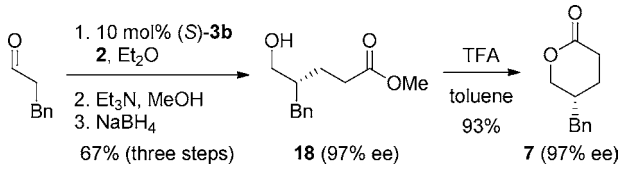
Scheme 6. Synthesis of δ-Lactone 7



nucleophilic catalyst (*S*)-**4b** (Figure 1). In the case of catalyst (*S*)-**4b**, the reaction proceeded gradually over time. This result

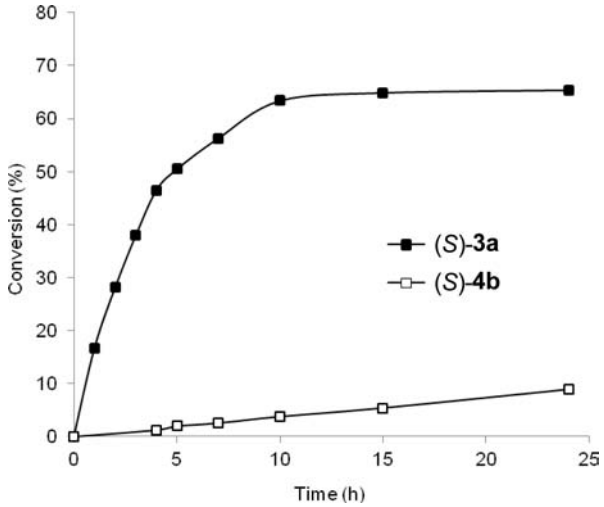


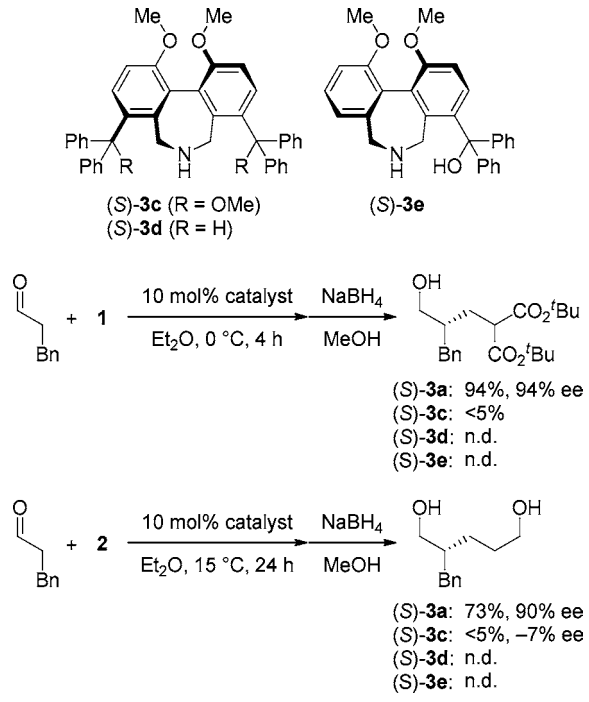
Figure 1. Product formation over time. The reaction of 3-phenylpropanal with **2** in THF-d_8 was performed in the presence of 10 mol % of (*S*)-**3a** or (*S*)-**4b** at room temperature. See the Supporting Information for details.

suggested the catalyst deactivation by conjugate addition to **2** was suppressed somewhat by the bulky substituent. Higher reactivity obtained by less nucleophilic (*S*)-**3a** may at least in part be due to the hydroxyl group of the catalyst, which can activate **2** through hydrogen bonding, in agreement with our initial hypothesis.

To elucidate the role of hydroxydiarylmethyl groups of (*S*)-**3a** and (*S*)-**3b**, we prepared *O*-methyl-protected catalyst (*S*)-**3c**, des-hydroxyl catalyst (*S*)-**3d**, and catalyst (*S*)-**3e** having a monohydroxydiphenylmethyl group. With (*S*)-**3c** or (*S*)-**3d**, both conjugate addition reactions of 3-phenylpropanal to **1** and **2** resulted in only a trace amount of the corresponding products or no product (Scheme 7). The marked effect of hydroxyl groups on the yield is apparent by comparison with (*S*)-**3a**, which affords the products in good yield with high enantioselectivity, indicating that the hydroxyl group on the catalyst is necessary to accelerate the conjugate addition. Moreover, (*S*)-**3e** was found to promote neither the conjugate addition to **1** nor **2**. These results suggested that sterically hindered hydroxydiphenylmethyl groups might create the cavity around the amine moiety, which can discriminate aldehydes from the bulky electrophiles, suppressing the undesired side reaction between the catalyst and electrophiles.

The absolute configuration of the products obtained in the present conjugate addition was determined by converting to the known compounds and comparison of the optical rotation with the value in the literature (see Supporting Information).[5g,16] On the basis of the observed stereochemistry and the experimental findings that the hydroxyl group of the catalyst

Scheme 7. Effects of Diphenylhydroxymethyl Groups on (*S*)-3a



promotes the conjugated addition, a plausible transition state model can be proposed as shown in Figure 2.[5g] The activated and oriented **1** or **2** by hydroxyl group on the catalyst approaches the *Re* face of the enamine.

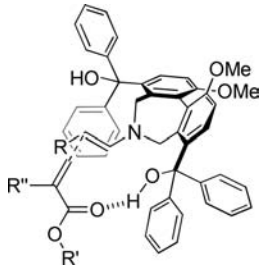


Figure 2. A plausible transition-state model for the direct asymmetric conjugate addition catalyzed by (*S*)-**3a**.

DFT calculations at the B3LYP/6-31G* level were also done to address the observed stereoselectivities.[17] The most favorable transition state is in accord with the above-mentioned transition state model for the conjugate addition reaction to **2** catalyzed by (*S*)-**3a** (Figure 3).[18]

CONCLUSIONS

In summary, we have developed a direct asymmetric conjugate addition of aldehydes to highly reactive modified acrylates such as dialkyl methylenemalonate and polyfluoroalkyl acrylate catalyzed by the novel axially chiral amino diols (*S*)-**3a** and (*S*)-**3b**. The present study represents the first example of conjugate addition to the simple and useful alkyl acrylate, which is a particularly challenging class of substrates in enamine catalysis. The conjugate addition product obtained is a versatile intermediate and could be readily converted to synthetically useful and important chiral building blocks.

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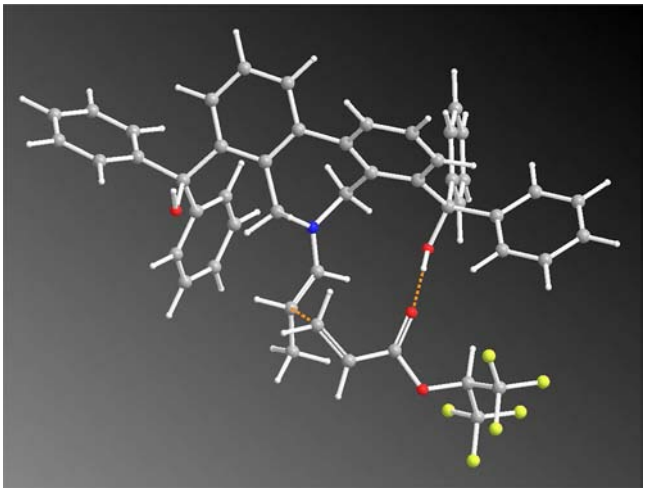

Figure 3. B3LYP/6-31G* optimized transition-state structure of the reaction.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedure and spectral data for all new compounds; computational details. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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