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An enantioselective nucleophilic addition of α,β-unsaturated trifluoromethylketones catalyzed by L-proline derivatives

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Abstract

An unexpected enantioselective 1,2-aldol reaction of acetone with α,β-unsaturated trifluoromethylketone catalyzed by L-proline derivative was described. The absolute configuration of the resulting chiral product was assigned based on a single crystal X-ray diffraction analysis. Structure–reactivity study of this organocatalytic system was briefly discussed. A reaction mechanism was tentatively postulated.
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Keywords: Aldol reaction; CF_3-enone; Acetone; Organocatalysis; L-Proline derivatives

1. Introduction

It is well-documented that α,β-unsaturated ketones are excellent Michael acceptors that provide important intermediates with various nucleophiles via 1,4-addition reaction. On the other hand, aldol reaction is another type of transformation for such molecules that based on 1,2-nucleophilic addition.[1] However, upon the introduction of trifluoromethyl group into such system, the characteristic reactions of α,β-unsaturated ketones might be alternated. This is illustrated by the recent report from Nenajdenko's group that the reaction of CF_3-enones with ethyl nitroacetate was significantly different from that of their non-CF_3 counterparts.[2]

In one of our ongoing projects, we are interested in the design and synthesis of biologically active small molecules,[3] trifluoromethylated heterocycles in particular.[4] Based on the reaction of the anions of alkylphosphonate with *N*-phenyltrifluoroacetimidoyl chloride[5] followed by subsequent reaction with aldehyde, a new and convenient one-pot synthesis of 1,2-unsaturated trifluoromethylketones was reported.[6] Our initial interest was focused on the feasibility to realize classic 1,4-Michael addition of CF_3-enones with various nucleophiles in the presence of bases. To our surprise, our experimental results demonstrated that only inseparable mixtures were resulted. However, when this particular CF_3-enone was allowed to react with acetone, 1,2-aldol addition product was isolated using L-proline as catalyst. Very recently, an effective synthesis of 2-trifluoromethylfurane derivative based on a AgOTf-catalyzed intramolecular cycloaddition was described by us.[7] Herein we would like to report an enantioselective reaction of this unique CF_3-enone with acetone catalyzed by L-proline derivatives.[8]

2. Results and discussion

As reported by Barbas III group, direct asymmetric catalytic aldol reaction was performed using 4-nitrobenzaldehyde, acetone and a catalytic amount of L-proline.[9] Because of the fact that both CF_3 and NO_2 are stronger electron-withdrawing groups, it is interesting to examine the chemical behaviour of **1** towards acetone under organocatalytic conditions. Taking **1c**, for example, to our surprise, only aldol product rather than Michael adduct was obtained. The reaction took only 15 min with 78% chemical yield and 52% ee value (Scheme 1).

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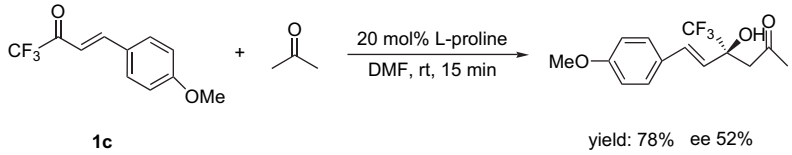


Scheme 1. Reaction of **1c** with acetone catalyzed by L-proline.

2.1. Optimization of the reaction conditions for direct asymmetric aldol reaction

In order to investigate the possibility of increasing the chemical yield as well as the ee value of the reaction, optimization of the reaction conditions was carried out. It should be noted that we only focused on the inference of different substituents on the phenyl ring concerning this unique reaction. Consequently, various factors including nature of phenyl substituents, reaction temperatures, the structure of L-proline derivatives and solvent effect on this asymmetric aldol addition were studied. Our experimental data in Table 1 indicate that this reaction is remarkably controlled by the electronic effect of phenyl substituents of the substrates. Substrates with electron-donating groups usually gave higher chemical yields and better enantioselectivity than those bearing electron-withdrawing groups (Table 1, entries 1–3 vs entries 7 and 8). Moreover, as expected, the reaction was more preferable at low temperature (0 °C) than at room temperature.

2.2. Catalytic effect of L-proline derivatives

By using substrate **1c** and acetone as the model reaction system, some commercially available L-proline derivatives (Fig. 1, **A**–**F**) were studied as the catalysts for the aldol reaction. The results are summarized in Table 2.

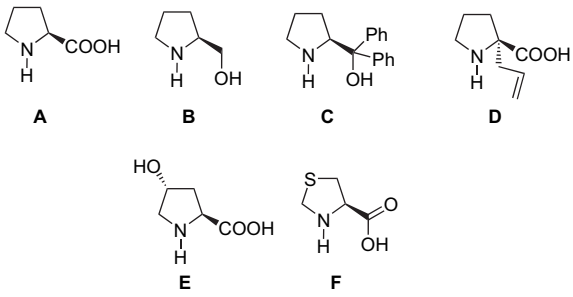
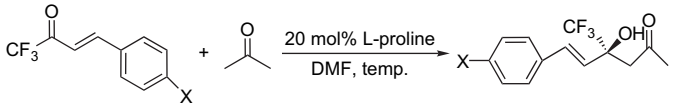


Figure 1. Catalysts' screening for the crossed aldol reaction.

Table 1
Influence of phenyl substituents and reaction temperature on the aldol reaction



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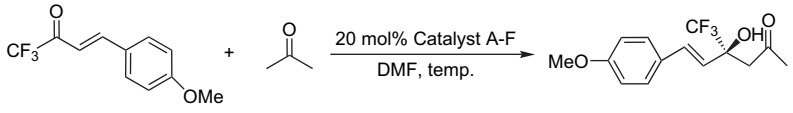
Entry	1	X	Yield (%)		ee[c] (%)		$[\alpha]_D^{25}$[d]	
			rt[a]	0 °C[b]	rt	0 °C	rt	0 °C
1	**a**	H	78	93	45	71	−30.0	−50.9
2	**b**	CH_3	69	88	49	74	−40.5	−58.3
3	**c**	OCH_3	78	88	49 (52)[e]	68 (75)[e]	−32.0	−55.6
4	**d**	$N(CH_3)_2$	70[f]	64[g]	32[h]	81[h]	−28.9[i]	−111.7[j]
5	**e**	F	60	86	44	72	−40.3	−46.1
6	**f**	Cl	66	89	52	69	−34.7	−44.4
7	**g**	CN	52[a]	73	18	55	−19.8	−40.2
8	**h**	*p*-NO_2	48[a]	57	24	52	−13.4	−41.8
9	**i**	*m*-NO_2	52[a]	50	15	57	−13.2	−40.2

[a] Unless specified, the reaction time was 15 min.
[b] Unless specified, the reaction time was 6 h.
[c] The ee value was determined by ^{19}F NMR in the presence of quinine.
[d] Unless noted, the optical rotation values were determined under the condition of 25 °C and c=1.
[e] The values in the bracket refer to the ee values determined by HPLC.
[f] The reaction time was 24 h.
[g] The reaction time was 72 h.
[h] ee value was determined by HPLC.
[i] c=0.08.
[j] c=0.10.

Table 2
Catalytic effect of L-proline derivatives using **1c** as model substrate



1c **2c**

Entry	Catalyst	Time	Yield[a] (%)	$[\alpha]_D^{25}$[b,c]
1	**A**	15 min	78	−32 (52)[d]
2	**B**	48 h	Trace	—
3	**C**	48 h	Trace	—
4	**D**	7 days	91	−39
5	**E**	2 days	>99	−47
6	**F**	2 days	80	−45

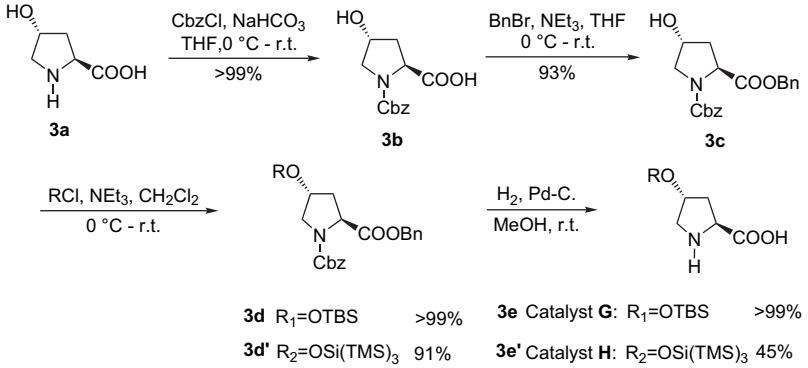
[a] Isolated yield and the reaction solvent was DMF.
[b] The optical value of the product obtained by the reaction catalyzed by L-proline (catalyst **A**) was considered as the standard data while the ee value of other products obtained can be evaluated by comparing their optical value with it.
[c] It should be pointed out that during the period of screening of the appropriate catalyst for further modification, we compared the optical values to approximately estimate the enantioselectivity of the product, using the value obtained by L-proline catalyzed one as standard.
[d] The number in the bracket is the ee value determined by HPLC.

As shown in Table 2, the presence of COOH group in L-proline is quite necessary, since the replacement of COOH by OH group would result in a complete loss of its catalytic activity (Table 2, entries 2 and 3). Good yield was obtained when catalyst **D** was applied, but it needed longer time. To our delight, when **E** and **F** were used, relatively high ee values were obtained (Table 2, entries 5 and 6). However, the reaction time was still too long (2 days), which is unfavourable to the control of the temperature. Eventually we chose catalyst **F** as the precursor for further study with the consideration that it is relatively easy to realize its structural modification. As shown in Scheme 2, we synthesized catalyst **G** according to the literature.[11] In consideration of the possible steric effect that may be confronted, more bulky tris(trimethylsilyl)silyloxy group was introduced onto the position 4 of the L-proline ring to give the potentially effective catalyst **H**.

Our experimental results demonstrate that **G** is a good catalyst that gave 81% chemical yield and 79% ee value. Since the reaction mixture was a homogeneous solution in DMF or CH_2Cl_2 at −20 °C, stirring or agitation is not necessary. Consequently, this situation makes it more convenient to carry out the reaction at low temperature. We assumed that the remarkable catalytic activity of **G** is associated with the presence of a bulky TBS group in the molecule. Therefore, it is reasonable to expect that catalyst **H** with more bulky $(TMS)_3Si$ group would lead to a more exciting result. To our delight, our postulation was proved by our experiment, as shown in Table 3, catalyst **H** was indeed more powerful, as it gave better results in DMF or CH_2Cl_2 (Table 3, entries 3, 4 and 6). As shown in Table 3, we also found that as solvent, CH_2Cl_2 is superior to DMF especially for the substrate bearing *p*-fluorophenyl group (Table 3, entry 6 vs entry 5).

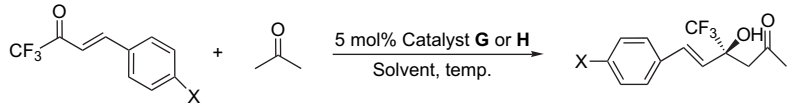
Further studies were conducted under optimized conditions (−20 °C, 5 mol % catalyst in CH_2Cl_2 or DMF) to establish the scope of this reaction. The results are summarized in Table 4.

As shown in Table 4, no significant substituent effect was observed in this reaction under the optimized condition. All substrates reacted quite well with acetone affording good chemical yields as well as high ee values. Data in Table 4 also indicate that substrates with electron-withdrawing substituents (Table 4, entries 8–10) gave better results in CH_2Cl_2 than those substrates bearing electron-donating substituents (Table 4, entries 1–3), which led to satisfactory results only in DMF or in a mixture of CH_2Cl_2 and DMF. Additionally,



Scheme 2. The synthesis of catalysts **G** and **F**.

Table 3
Catalysts' screening and reaction condition optimization



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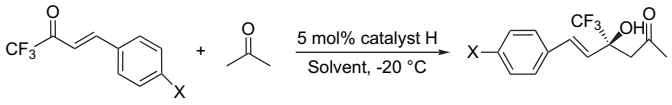
Entry	X	Catalyst	Solvent	Temp.	Time	Yield[a] (%)	$[\alpha]_D^{25}$
1	OCH_3	**G**	DMF	rt	15 min	81	−40
2	OCH_3	**G**	DMF	−20 °C	3 days	81	−51
3	OCH_3	**H**	DMF	−20 °C	3 days	88	−56 (87)[b]
4	OCH_3	**H**	CH_2Cl_2	−20 °C	3 days	92	−50 (74)[b]
5	F	**H**	DMF	−20 °C	Too slow	—	—
6	F	**H**	CH_2Cl_2	−20 °C	3 days	94	−46 (87)[b]

[a] Isolated yield.
[b] The value in the brackets was ee value determined by HPLC.

Table 4
Influence of phenyl substituents of **1** on its reaction with acetone using **H** as catalyst under the optimized condition



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Entry	1	X	Product	Time[a] (days)	Yield[b] (%)	ee[c] (%)
1	**a**	H	(*S*)-**2a**	6 (3[d])	>99 (92[d])	76 (83[d])
2	**b**	CH_3	**2b**	6 (3[d])	>99 (91[d])	80 (85[d])
3	**c**	OCH_3	**2c**	7 (3[e])	94 (92[e])	74 (87[e])
4	**d**	$N(CH_3)_2$	**2d**	3	49	91
5	**e**	F	**2e**	3	94	87
6	**f**	Cl	**2f**	3 (7[e])	96 (81[e])	80 (81[e])
7	**g**	CN	**2g**	3	97	80
8	**h**	*p*-NO_2	**2h**	3	92	79
9	**i**	*m*-NO_2	**2i**	3	89	82
10	**j**	Br	**2j**	3	90	91

[a] The reactions were monitored by TLC.
[b] Isolated yield. Unless specified, all reactions were carried out in CH_2Cl_2 and at −20 °C without the need of stirring for the time indicated.
[c] Determined by HPLC.
[d] The solvent was CH_2Cl_2/DMF (1:3).
[e] The solvent was DMF.

when the phenyl substituent is $-N(CH_3)_2$, the substrate failed to react with acetone in CH_2Cl_2 but reacted smoothly in CH_2Cl_2/DMF (1:3) to afford product with 91% ee value, though the chemical yield was relatively poor (Table 4, entry 4).

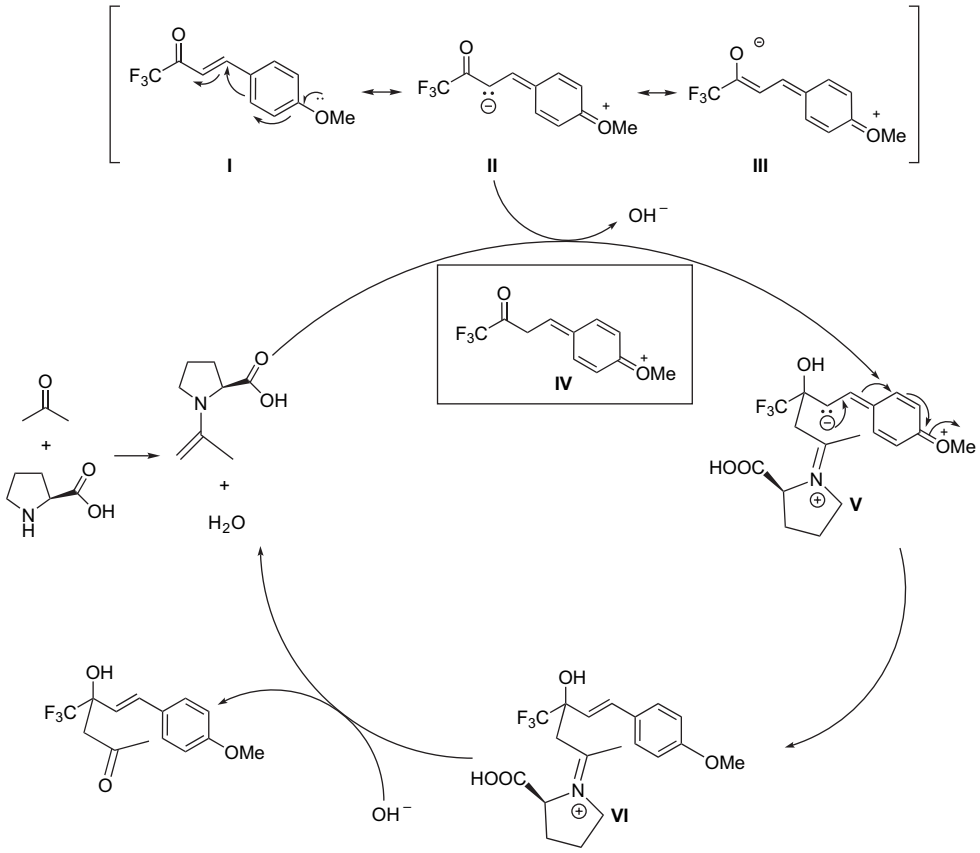
2.3. A tentative reaction mechanism

It is quite interesting to rationalize why the reaction of α,β-unsaturated trifluoromethylketone with acetone in the presence of L-proline derivatives undergoes aldol reaction rather than Michael addition. We assumed that there may be a key intermediate in the catalytic cycle (Scheme 3), consisting of resonance equilibrium forms of the CF_3-enone in which the conjugated form—intermediate **II**, exists in the solvent. Then this intermediate reacts with L-proline to afford the key intermediate **IV** in which the double bond is not in conjugation with the carbonyl group. Such intermediate allows the reaction to go through the usual aldol addition pathway to afford the intermediate **V**, which finally leads to the unexpected 1,2-addition product.

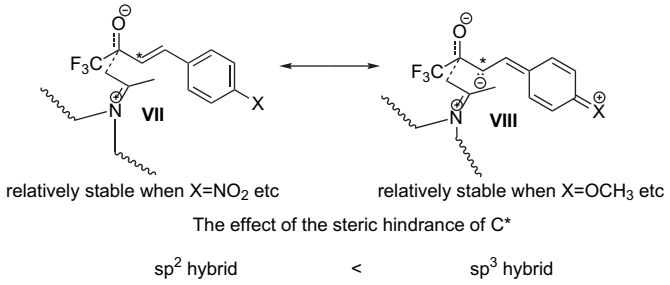
Our proposed mechanism is supported by experimental results. At room temperature, the substrates with electron-donating substituents (Table 4, entry 1) gave relatively better chemical yield and ee value than those bearing electron-withdrawing group (Table 1, entries 7–9). Obviously, intermediate **II** is more stable when X is OCH_3. However, when the reaction temperature was cooled down to −20 °C, whatever the electronic effects of the substituents are, intermediate **II** is stable enough, leading to similar results (Table 4).

As to the solvent effect, another hypothesis is postulated, which is demonstrated in Scheme 4. Intermediate **VII**, which is thought to be more stable for NO_2-substituted substrate, carries more centralized electric charge, and as a result leads to a better result in the relatively low polar solvent such as CH_2Cl_2. In contrast, due to its excellent electron-donating character, substrate bearing OCH_3 has a more decentralized electric charge (intermediate **VIII**), leading to the requirement of polar solvents such as DMF to afford good results.

To our delight, the above hypothesis gives a good explanation to the reason why the electron-rich-substituted substrates such as entry 1 afford relatively better yield and ee value than those electron-poor ones (such as entry 8) when the reactions were carried out at room temperature (Table 1). Obviously, intermediate **II** is more stable when X is OCH_3. Therefore, at room temperature, those electron-rich substrates reacted more rapidly (Table 1, entry 1, 2, etc.). However, when the temperature was reduced to −20 °C, intermediate **II** is stable enough, leading to relatively similar reaction rates for all substrates. As to the enantioselectivity of the reaction between different substrates at room temperature, Scheme 4 provides a reasonable answer: when reaction occurs at room temperature, electron-poor substrates tend to form intermediate **VII** while electron-rich ones prefer intermediate **VIII**. As shown in Scheme 4, the hybrid of C* determines its steric hindrance. Therefore, because of



Scheme 3. A proposed tentative reaction mechanism of aldol addition of acetone to CF_3-enone catalyzed by L-proline using entry **1c** as model.



Scheme 4. Proposed intermediates for the explanation of solvent effect.

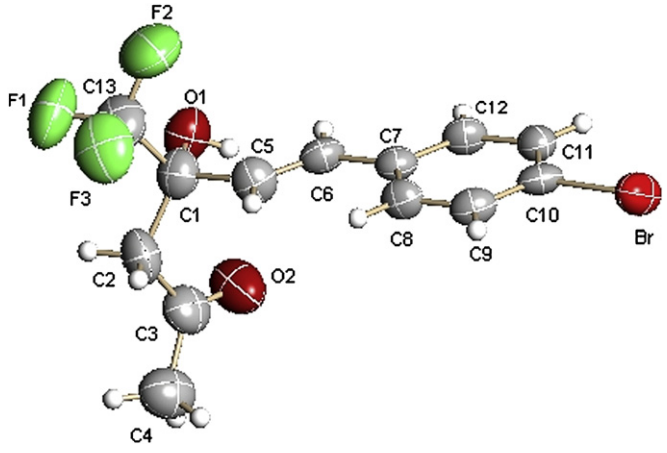
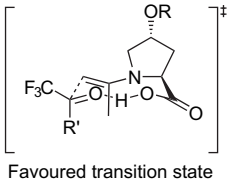


Figure 2. The absolute configuration of compound **2j** (CCDC number: 669266).

the fact that the sp^2 hybrid bears more steric hindrance than the sp^3 one, the ee value difference shown in Table 1 is easily understood.

To further clarify the reaction transition state, the absolute configuration of compound **2j** was confirmed by a single crystal X-ray diffraction analysis (Fig. 2).

According to the absolute configuration, we can assume that the *S*-product may be created by the following transition, as shown in Scheme 5. Therefore, with the increasing steric hindrance of group R, from TBS to $(TMS)_3Si$, the enantioselectivity of the reaction can be improved correspondingly.



Scheme 5. The postulated transition state for the unexpected reaction.

3. Conclusion

In summary, we have described an unexpected aldol reaction involving the reaction of α,β-unsaturated trifluoromethylketones with acetone in the presence of L-proline derivatives in good chemical yields and ee values. Various effects on the chemical yield and ee value of the reaction, including the

influence of phenyl substituents, the reaction temperature and the structure of L-proline derivatives as catalysts, were examined. The absolute configuration of the optically active product was determined by an X-ray crystallographic analysis, on the basis of which a tentative reaction mechanism was proposed. Moreover, the newly synthesized L-proline derivative, namely (4*R*)-4-tris(trimethylsilyloxy)-L-proline, demonstrated excellent catalytic activity in these reactions. We are sure that the resulting optical tertiary alcohols can be useful in organic synthesis.

4. Experimental section

4.1. General

Reactions were performed under N_2 or Ar atmosphere. All reagents were purified by standard methods.[10] Column chromatography was performed with silica gel (300–400 mesh). All yields given refer to as isolated yields. IR spectra were obtained on a Shimadzu IR-440 spectrometer. ^{1}H NMR (300 MHz) and ^{19}F NMR (282 MHz) were recorded on 300 MHz spectrometer with $CDCl_3$ as solvent and tetramethylsilane (TMS) as internal standard. Chemical shifts (δ) are reported in units (ppm) by assigning TMS resonance in the ^{1}H spectrum as 0.00 ppm. ^{19}F NMR adopted trifluoroacetic acid as external standard, downfield shifts being designated as negative. ^{13}C NMR (50 MHz) were recorded on the same instrument. Mass spectra were obtained using EI ionization at 70 eV. All reactions were monitored with the aid of TLC. The materials **1a**–**1j** are synthesized according to the method developed by our group.[6]

4.2. The synthesis of catalyst ***H***

4.2.1. *trans*-1-Benzyloxycarbonyl-4-hydroxy-L-proline (***3b***)

To a 25 mL round-bottomed flask was added 400 mg (3.04 mmol) *trans*-4-hydroxy-L-proline (**3a**), after which 4.6 mL THF was infused by syringe. The solution was stirred until it becomes homogeneity, and then 8 mL saturated $NaHCO_3$ solution was added to it. The mixture was brought to 0 °C in ice bath, after which 0.86 mL CbzCl (6 mmol) was added dropwise to the solution. The mixture was allowed to warm up to room temperature and stirred overnight. The solution was acidified to pH=1 by 1 N HCl and extracted by 20 mL×3 EtOAc, and the organic layer was dried over anhydrous Na_2SO_4 overnight. The solvent was evaporated under reduced pressure and the residue was subjected to flash chromatography on silica gel to afford 735 mg white amorphous solid, yield 91%.

$[\alpha]_D^{24}$ −79.4 (*c* 1.0, $CHCl_3$) (lit.[12] $[\alpha]_D^{24}$ −75.5 (*c* 1.0, $CHCl_3$)). ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ 7.33–7.26 (m, 5H, Ph), 5.29 (s, 1H, OCH_2Ph), 5.04 (br, 1H, OH), 4.51–4.46 (m, 2H, *CH*OH and *CH*COOH), 3.61–3.57 (m, 2H, CH_2NCbz), 2.31–2.04 (m, 1H, CH_2). ^{13}C NMR (50 MHz, $CDCl_3$, 25 °C): δ 175.8, 155.5, 136.0, 128.5, 128.1, 127.7, 69.5, 67.6, 57.8, 54.6, 37.8.

4.2.2. *trans*-1-Benzyloxycarbonyl-4-hydroxy-L-proline benzyl ester (***3c***)

To a 25 mL round-bottomed flask was added 700 mg (2.64 mmol) *trans*-1-benzyloxycarbonyl-4-hydroxy-L-proline (**3b**), after which 3 mL THF was infused by syringe. The solution was stirred until it becomes homogeneity, then 0.36 mL BnBr (0.513 g, 3 mmol) was added to it. The mixture was brought to 0 °C in ice bath, then 0.42 mL NEt_3 (3 mmol) was added dropwise to the solution. The mixture was allowed to warm up to room temperature and stirred for 18 h. The solvent was evaporated under reduced pressure and another 20 mL CH_2Cl_2 was added to resolve the residue, the mixture was then washed subsequently by 20 mL 1 N HCl, 20 mL H_2O, 20 mL 5% Na_2CO_3 and 20 mL H_2O. After dried over anhydrous Na_2SO_4, the solvent was evaporated under reduced pressure and the residue was subjected to flash chromatography on silica gel to afford 813 mg light yellow liquid, yield 87%.

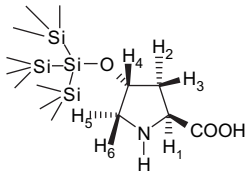
$[\alpha]_D^{27}$ −50.3 (*c* 1.0, $CHCl_3$) (lit.[11b] $[\alpha]_D^{25}$ −58.0 (*c* 1.4, $CHCl_3$)). ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ 7.31–7.18 (m, 10H, Ph×2), 5.20–5.00 (m, 2H, OCH_2Ph), 4.99 (d, 2H, *J*=6.5 Hz, OCH_2Ph), 4.54–4.38 (m, 2H, *CH*OH and N*CH*COOBn), 3.63–3.50 (m, 2H, NCH_2), 3.10 (br, 1H, OH), 2.27–1.98 (m, 2H, CH_2). ^{13}C NMR (50 MHz, $CDCl_3$, 25 °C): δ 172.4, 154.3, 136.2, 135.4, 128.4, 128.3, 128.2, 128.0, 127.9, 127.7, 69.8, 67.0, 66.8, 57.8, 54.8, 38.6.

4.2.3. *trans*-1-Benzyloxycarbonyl-4-tris(trimethylsilyloxy)-L-proline benzyl ester (***3d′***)

To a 25 mL round-bottomed flask was added 219 mg (0.617 mmol) *trans*-1-benzyloxycarbonyl-4-hydroxy-L-proline benzyl ester (**3c**), after which a solution of 1.5 mL CH_2Cl_2 and 1.5 mL DMF was infused by syringe. The solution was stirred until it becomes homogeneous, then 175 mg $(TMS)_3SiCl$ (0.617 mmol) was added to it. The mixture was chilled to 0 °C in ice bath, after which 0.085 mL NEt_3 (0.62 mmol) was added dropwise to the solution followed by the addition of 7.5 mg DMAP (0.12 mmol). The mixture was allowed to warm up to room temperature and stirred overnight. The solution was diluted with 20 mL EtOAc and the solution was washed by 30 mL distilled water and dried over anhydrous Na_2SO_4 overnight. The solvent was evaporated under reduced pressure and the residue was subjected to flash chromatography on silica gel to afford 351 mg light yellow liquid, yield 89%.

$[\alpha]_D^{27}$ −33.0 (*c* 1.0, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ 7.34–7.19 (m, 10H, Ph×2), 5.20–5.00 (m, 4H, OCH_2Ph×2), 4.50–4.10 (m, 3H, *CH*OH and N*CH*COOBn), 3.63–3.47 (m, 2H, NCH_2), 2.16–1.99 (m, 2H, CH_2), 0.16 (s, 27H, Si(Si(CH_3)$_3$)). ^{13}C NMR (50 MHz, $CDCl_3$, 25 °C): δ 172.5, 154.2, 136.6, 135.5, 128.5, 128.4, 128.3, 128.2, 127.9, 127.8, 74.1, 67.1, 66.8, 58.1, 54.9, 38.5. IR (film, cm^{-1}): 2949, 1755, 1708, 1417, 1163. EIMS (*m*/*z*): 602.3 (MH^+), 624.3 ($M+Na^+$), 640.3 ($M+K^+$). Anal. Calcd for $C_{29}H_{47}NO_5Si_4$: C, 57.86; H, 7.87; N, 2.33. Found: C, 57.81; H, 7.88; N, 2.18.

4.2.4. (4R)-4-Tris(trimethylsilyloxy)-L-proline (*H*)



To a 25 mL round-bottomed flask was added 315 mg (0.524 mmol) *trans*-1-benzyloxycarbonyl-4-tris(trimethylsilyloxy)-L-proline benzyl ester (**3d′**), and it was dissolved in 6 mL anhydrous EtOH, after which 40 mg Pd–C (10%, w/w) was added to the solution. The mixture was stirred under an atmosphere of H_2 for 24 h. Then the reaction solution was filtered and the filtrate was concentrated under reduced pressure. The obtained residue was then subjected to flash chromatography on silica gel to afford 88 mg white solid, yield 45%.

$[\alpha]_D^{27}$ −22.1 (*c* 1.0, CH_3OH). ^1H NMR (300 MHz, $CDCl_3$, 25 °C): δ 7.69 (br, 2H, NH and COOH), 4.13 (m, 1H, H_4), 4.03 (m, 1H, H_1), 3.57 (m, 1H, H_5), 2.94 (m, 1H, H_6), 2.09 (m, 1H, H_2), 2.00 (m, 1H, H_3). ^{13}C NMR (50 MHz, $CDCl_3$, 25 °C): δ 174.1, 60.6, 53.5, 39.2, 28.9, 0.4. IR (film, cm^{-1}): 2951, 1246. ESI-MS (*m*/*z*): 378.3 (MH^+). HRMS-ESI: calcd for $C_{14}H_{36}NO_3Si_4$ ($M+H^+$): 378.1767. Found: 378.1731.

4.3. General procedure for the preparation of (S)-4-trifluoromethyl-4-hydroxyl-6-aromatic-hex-5-ene-2-one

A flame dried 25 mL round-bottomed flask with a magnetic stir bar was charged with 0.3 mmol α,β-unsaturated ketones (**1a–1j**). The flask was purged with nitrogen, and then a solution of catalyst **H** (5.7 mg, 0.015 mmol, 5 mol %) in 4 mL CH_2Cl_2 was added. The reaction mixture was then subjected to −20 °C by means of ice–salt bath, after which 0.4 mL acetone was added dropwise by syringe. The reaction was run at −20 °C and monitored by TLC until completion. Another 10 mL CH_2Cl_2 was added and the mixture was washed with water and brine, and then was dried over anhydrous Na_2SO_4 overnight. The solvent was removed under reduced pressure and the residue was subjected to flash chromatography on silica gel (petroleum/EtOAc=10:1) to afford the desired product.

4.3.1. (S)-4-Trifluoromethyl-4-hydroxyl-6-phenyl-hex-5-ene-2-one (*2a*)

Light yellow liquid 71 mg, yield: 92%, ee%=83%, $[\alpha]_D^{24}$ −57.1 (*c* 1.0, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$, 25 °C): δ 7.41–7.28 (m, 5H), 6.94 (d, 1H, $^3J_{H,\ H}$=15.6 Hz), 6.13 (d, 2H, $^3J_{H,\ H}$=15.6 Hz), 5.35 (s, 1H, OH), 3.05 (d, 1H, $^3J_{H,\ H}$=16.8 Hz, CH_2CO), 2.88 (d, 1H, $^3J_{H,\ H}$=16.8 Hz, CH_2CO), 2.25 (s, 3H, CH_3CO). ^{19}F NMR (282 MHz, $CDCl_3$, 25 °C): δ −81.0 (s, 3F, CF_3). ^{13}C NMR (50 MHz, $CDCl_3$, 25 °C): δ 208.8, 135.5, 133.8, 128.7, 128.5, 126.9, 126.0 (C*), 124.2, 123.2 (C*), 75.2 (q), 44.6, 32.1. IR (film, cm^{-1}): 3381, 1706, 1531, 1418, 1354, 1249, 1172, 1062, 974. EIMS (*m*/*z*, %): 258 (M^+, 8), 131 (10). Anal. Calcd for $C_{13}H_{13}O_2F_3$: C, 60.46; H, 5.07. Found: C, 60.23; H, 5.04. HPLC analysis: DAICEL Chiralpak AD-H, hexane/2-propanol 90:10, λ=254 nm, flow rate=0.7 mL min^{-1}, retention time=9.26 min (minor) and 9.99 min (major).

4.3.2. (S)-4-Trifluoromethyl-4-hydroxyl-6-(p-methyl)phenyl-hex-5-ene-2-one (*2b*)

White solid 72 mg, yield: 91%. Mp: 67–69 °C, ee%=85%, $[\alpha]_D^{24}$ −66.0 (*c* 1.0, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$, 25 °C): δ 7.21 (d, 2H, $^3J_{H,\ H}$=8.4 Hz), 7.06 (d, 2H, $^3J_{H,\ H}$=8.4 Hz), 6.82 (d, 1H, $^3J_{H,\ H}$=15.6 Hz), 6.00 (d, 1H, $^3J_{H,\ H}$=15.6 Hz), 5.26 (s, 1H, OH), 2.94 (d, 1H, $^3J_{H,\ H}$=16.5 Hz, CH_2CO), 2.79 (d, 1H, $^3J_{H,\ H}$=16.5 Hz, CH_2CO), 2.26 (s, 3H, ArCH_3), 2.16 (s, 3H, CH_3CO). ^{19}F NMR (282 MHz, $CDCl_3$, 25 °C): δ −81.0 (s, 3F, CF_3). ^{13}C NMR (50 MHz, $CDCl_3$, 25 °C): δ 208.8, 138.5, 133.6, 132.7, 129.3, 126.8, 125.7 (C*), 123.5 (C*), 123.1, 75.2 (q), 44.6, 32.0, 21.2. IR (film, cm^{-1}): 3456, 1716, 1492, 1367, 1246, 1192, 1089, 1012, 995. EIMS (*m*/*z*, %): 272 (M^+, 7), 43 (100). Anal. Calcd for $C_{14}H_{15}O_2F_3$: C, 61.76; H, 5.55. Found: C, 62.02; H, 5.67. HPLC analysis: DAICEL Chiralpak AD-H, hexane/2-propanol 90:10, λ=254 nm, flow rate=0.7 mL min^{-1}, retention time=9.34 min (minor) and 12.0 min (major).

4.3.3. (S)-4-Trifluoromethyl-4-hydroxyl-6-(p-methoxyphenyl)-hex-5-ene-2-one (*2c*)

Light yellow liquid 79 mg, yield: 92%, ee%=87%, $[\alpha]_D^{24}$ −56.5 (*c* 1.0, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$, 25 °C): δ 7.33 (dd, 2H, $^3J_{H,\ H1}$=6.6 Hz, $^3J_{H,\ H2}$=1.5 Hz), 6.89–6.84 (m, 3H), 5.99 (d, 1H, $^3J_{H,\ H}$=15.6 Hz), 5.32 (s, 1H, OH), 3.79 (s, 3H, OCH_3), 3.00 (d, 1H, $^3J_{H,\ H}$=16.5 Hz, CH_2CO), 2.86 (d, 1H, $^3J_{H,\ H}$=16.5 Hz, CH_2CO), 2.23 (s, 3H, CH_3CO). ^{19}F NMR (282 MHz, $CDCl_3$, 25 °C): δ −81.0 (s, 3F, CF_3). ^{13}C NMR (50 MHz, $CDCl_3$, 25 °C): δ 208.8, 159.9, 133.1, 128.2, 128.1, 126.0 (C*), 123.2 (C*), 114.0, 75.6 (q), 55.2, 44.7, 32.0. IR (film, cm^{-1}): 3404, 3039, 2982, 2841, 1709, 1656, 1608, 1579, 1466, 1421, 1338, 1252, 1109, 1033, 977. EIMS (*m*/*z*, %): 288 (M^+, 16), 161 (100). Anal. Calcd for $C_{14}H_{15}O_3F_3$: C, 58.33; H, 5.24. Found: C, 58.38; H, 5.27. HPLC analysis: DAICEL Chiralpak AD-H, hexane/2-propanol 90:10, λ=214 nm, flow rate=0.8 mL min^{-1}, retention time=10.1 min (minor) and 12.6 min (major).

4.3.4. (S)-4-Trifluoromethyl-4-hydroxyl-6-(p-dimethylaminophenyl)-hex-5-ene-2-one (*2d*)

Yellow solid 44 mg, yield: 49%. Mp: 78–80 °C, ee%=91%, $[\alpha]_D^{25}$ −71.9 (*c* 1.0, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$, 25 °C): δ 7.28 (d, 2H, $^3J_{H,\ H}$=8.7 Hz), 6.80 (d, 1H, $^3J_{H,\ H}$=15.9 Hz), 6.66 (d, 2H, $^3J_{H,\ H}$=8.7 Hz), 5.91 (d, 1H, $^3J_{H,\ H}$=15.9 Hz), 5.24 (s, 1H, OH), 3.02–2.90 (m, 8H, CH_2CO and N(CH_3)$_2$), 2.23 (s, 3H, CH_3CO). ^{19}F NMR (282 MHz, $CDCl_3$, 25 °C): δ −81.1 (s, 3F, CF_3). ^{13}C NMR (50 MHz, $CDCl_3$, 25 °C): δ 208.9, 150.6, 133.5, 128.0, 126.1 (C*), 123.3, 122.4 (C*), 119.4, 112.3, 75.1 (q), 44.8, 40.4, 32.1. IR (film, cm^{-1}): 3426, 2813, 1706, 1614, 1527, 1365, 1253, 1185, 1065, 978. EIMS (*m*/*z*, %): 301 (M^+, 27), 174 (100). Anal. Calcd for $C_{15}H_{18}NO_2F_3$: C, 59.79; H, 6.02; N, 4.65. Found: C, 59.88; H, 5.95; N, 4.53.

HPLC analysis: DAICEL Chiralpak AD-H, hexane/2-propanol 90:10, λ=214 nm, flow rate=0.7 mL min^{-1}, retention time=11.1 min (minor) and 13.5 min (major).

4.3.5. (S)-4-Trifluoromethyl-4-hydroxyl-6-(p-fluorophenyl)-hex-5-ene-2-one (**2e**)

Light yellow liquid 78 mg, yield: 94%, ee%=87%, $[\alpha]_D^{22}$ −43.1 (*c* 1.00, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ 7.38 (d, 2H, $^3J_{H,\ H1}$ 8.7 Hz, J_2=5.4 Hz), 7.02 (t, 2H, $^3J_{H,\ H2}$=8.7 Hz), 6.91 (d, 1H, $^3J_{H,\ H}$=16.2 Hz), 6.05 (d, 1H, $^3J_{H,\ H}$=16.2 Hz), 5.35 (s, 1H, OH), 3.04 (d, 1H, $^3J_{H,\ H}$=17.4 Hz, CH_2CO), 2.87 (d, 1H, $^3J_{H,\ H}$=17.4 Hz, CH_2CO), 2.26 (s, 3H, CH_3CO). ^{19}F NMR (282 MHz, $CDCl_3$, 25 °C): δ −81.0 (s, 3F, CF_3), −113.0 (m, 1F). ^{13}C NMR (50 MHz, $CDCl_3$, 25 °C): δ 208.8, 164.0, 161.6, 132.7, 131.7 (d, 1C, J_{C-F}=10.5 Hz), 128.5 (d, 2C, J_{C-F}=23.7 Hz), 126.0 (C*), 124.0, 123.1 (C*), 115.6 (d, 2C, J_{C-F}=64.8 Hz), 75.1 (q), 44.6, 32.0. IR (film, cm^{-1}): 3416, 1708, 1604, 1512, 1416, 1365, 1232, 1171, 1097, 976. EIMS (*m*/*z*, %): 276 (M$^+$, 6), 43 (100). Anal. Calcd for $C_{13}H_{12}O_2F_4$: C, 56.53; H, 4.38. Found: C, 56.41; H, 4.36. HPLC analysis: DAICEL Chiralpak AD-H, hexane/2-propanol 90:10, λ=214 nm, flow rate=0.7 mL min^{-1}, retention time=9.75 min (minor) and 11.6 min (major).

4.3.6. (S)-4-Trifluoromethyl-4-hydroxyl-6-(p-chlorophenyl)-hex-5-ene-2-one (**2f**)

White solid 84 mg, yield: 96%. Mp: 69–71 °C, ee%=80%, $[\alpha]_D^{22}$ −48.8 (*c* 1.0, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ 7.23 (s, 4H), 6.82 (d, 1H, $^3J_{H,\ H}$=16.2 Hz), 6.03 (d, 1H, $^3J_{H,\ H}$=16.2 Hz), 5.30 (s, 1H, OH), 2.96 (d, 1H, $^3J_{H,\ H}$=16.5 Hz, CH_2CO), 2.79 (d, 1H, $^3J_{H,\ H}$=16.5 Hz, CH_2CO), 2.17 (s, 3H, CH_3CO). ^{19}F NMR (282 MHz, $CDCl_3$, 25 °C): δ −80.9 (s, 3F, CF_3). ^{13}C NMR (50 MHz, $CDCl_3$, 25 °C): δ 208.7, 134.2, 134.0, 132.7, 128.9, 128.1, 125.9 (C*), 124.8, 123.1 (C*), 75.2 (q), 44.5, 32.0. IR (film, cm^{-1}): 3454, 2919, 1716, 1492, 1335, 1246, 1192, 1089, 1012, 995. EIMS (*m*/*z*, %): 292 (M$^+$, 6), 43 (100). Anal. Calcd for $C_{13}H_{12}O_2F_3Cl$: C, 53.35; H, 4.13. Found: C, 53.41; H, 4.13. HPLC analysis: Nucleocel Delta S (OD), hexane/2-propanol 95:5, λ=214 nm, flow rate=0.5 mL min^{-1}, retention time=16.9 min (minor) and 19.2 min (major).

4.3.7. (S)-4-Trifluoromethyl-4-hydroxyl-6-(p-cyanophenyl)-hex-5-ene-2-one (**2g**)

Brown solid 82 mg, yield: 97%. Mp: 86–87 °C, ee%=80%, $[\alpha]_D^{29}$ −55.9 (*c* 1.0, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ 7.63 (d, 2H, $^3J_{H,\ H}$=8.1 Hz), 7.49 (d, 2H, $^3J_{H,\ H}$=8.1 Hz), 6.99 (d, 1H, $^3J_{H,\ H}$=15.9 Hz), 6.25 (d, 1H, $^3J_{H,\ H}$=15.9 Hz), 5.46 (s, 1H, OH), 3.09 (d, 1H, $^3J_{H,\ H}$=16.8 Hz, CH_2CO), 2.88 (d, 1H, $^3J_{H,\ H}$=16.8 Hz, CH_2CO), 2.28 (s, 3H, CH_3CO). ^{19}F NMR (282 MHz, $CDCl_3$, 25 °C): δ −80.7 (s, 3F, CF_3). ^{13}C NMR (50 MHz, $CDCl_3$, 25 °C): δ 208.6, 139.9, 132.5, 132.4, 128.1, 127.4, 125.8 (C*), 122.9 (C*), 118.6, 111.8, 75.2 (q), 44.4, 32.0. IR (film, cm^{-1}): 3375, 2225, 1700, 1606, 1507, 1436, 1340, 1256, 1133, 1097, 985. EIMS (*m*/*z*, %): 283 (M$^+$, 1), 43 (100). Anal. Calcd for $C_{14}H_{12}NO_2F_3$: C, 59.37; H, 4.27; N, 4.94. Found: C, 59.44; H, 4.14; N, 4.78. HPLC analysis: DAICEL Chiralpak AD-H, hexane/2-propanol 80:20, λ=214 nm, flow rate=0.8 mL min^{-1}, retention time=9.13 min (minor) and 10.6 min (major).

4.3.8. (S)-4-Trifluoromethyl-4-hydroxyl-6-(p-nitrophenyl)-hex-5-ene-2-one (**2h**)

Brown solid 84 mg, yield: 92%. Mp: 101–102 °C, ee%=79%, $[\alpha]_D^{25}$ −55.3 (*c* 1.0, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ 8.19 (d, 2H, $^3J_{H,\ H}$=8.1 Hz), 7.54 (d, 2H, $^3J_{H,\ H}$=8.1 Hz), 7.05 (d, 1H, $^3J_{H,\ H}$=15.6 Hz), 6.31 (d, 1H, $^3J_{H,\ H}$=15.6 Hz), 5.49 (s, 1H, OH), 3.11 (d, 1H, $^3J_{H,\ H}$=17.1 Hz, CH_2CO), 2.90 (d, 1H, $^3J_{H,\ H}$=17.1 Hz, CH_2CO), 2.29 (s, 3H, CH_3CO). ^{19}F NMR (282 MHz, $CDCl_3$, 25 °C): δ −80.6 (s, 3F, CF_3). ^{13}C NMR (50 MHz, $CDCl_3$, 25 °C): δ 208.7, 147.5, 141.8, 131.9, 129.0, 127.6, 125.8 (C*), 124.0, 122.9 (C*), 75.3 (q), 44.3, 31.9. IR (film, cm^{-1}): 3418, 2851, 1706, 1597, 1517, 1346, 1252, 1192, 1110, 981. EIMS (*m*/*z*, %): 303 (M$^+$, 1), 43 (100). Anal. Calcd for $C_{13}H_{12}NO_4F_3$: C, 51.49; H, 3.99; N, 4.62. Found: C, 51.53; H, 4.09; N, 4.56. HPLC analysis: DAICEL Chiralpak AD-H, hexane/2-propanol 80:20, λ=214 nm, flow rate=0.8 mL min^{-1}, retention time=9.93 min (minor) and 12.8 min (major).

4.3.9. (S)-4-Trifluoromethyl-4-hydroxyl-6-(m-nitrophenyl)-hex-5-ene-2-one (**2i**)

Brownish yellow solid 81 mg, yield: 89%. Mp: 83–84 °C, ee%=82%, $[\alpha]_D^{24}$ −54.5 (*c* 1.0, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ 8.26 (s, 1H), 8.12 (dt, 1H, $^3J_{H,\ H1}$=8.1 Hz, $^3J_{H,\ H2}$=0.9 Hz), 7.70 (d, 1H, $^3J_{H,\ H}$=7.8 Hz), 7.52 (d, 1H, $^3J_{H,\ H}$=8.7 Hz), 7.04 (d, 1H, $^3J_{H,\ H}$=15.9 Hz), 6.30 (d, 1H, $^3J_{H,\ H}$=15.9 Hz), 5.48 (s, 1H, OH), 3.11 (d, 1H, $^3J_{H,\ H}$=17.1 Hz, CH_2CO), 2.93 (d, 1H, $^3J_{H,\ H}$=17.1 Hz, CH_2CO), 2.30 (s, 3H, CH_3CO). ^{19}F NMR (282 MHz, $CDCl_3$, 25 °C): δ −80.8 (s, 3F, CF_3). ^{13}C NMR (50 MHz, $CDCl_3$, 25 °C): δ 208.8, 148.6, 137.2, 133.0, 131.8, 129.7, 128.6 (C*), 127.6, 125.8 (C*), 122.9, 121.2, 75.3 (q), 44.3, 31.9. IR (film, cm^{-1}): 3441, 3072, 1714, 1527, 1413, 1355, 1282, 1164, 1099, 973. EIMS (*m*/*z*, %): 303 (M$^+$, 1), 43 (100). Anal. Calcd for $C_{13}H_{12}NO_4F_3$: C, 51.49; H, 3.99; N, 4.62. Found: C, 51.68; H, 4.03; N, 4.47. HPLC analysis: DAICEL Chiralpak AD-H, hexane/2-propanol 90:10, λ=254 nm, flow rate=0.7 mL min^{-1}, retention time=48.3 min (minor) and 60.5 min (major).

4.3.10. (S)-4-Trifluoromethyl-4-hydroxyl-6-(p-bromophenyl)-hex-5-ene-2-one (**2j**)

White solid 84 mg, yield: 90%. Mp: 76–77 °C, ee%=91%, $[\alpha]_D^{22}$ −63.9 (*c* 1.0, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ 7.39 (d, 2H, $^3J_{H,\ H}$=8.4 Hz), 7.19 (d, 2H, $^3J_{H,\ H}$=8.4 Hz), 6.82 (d, 1H, $^3J_{H,\ H}$=16.2 Hz), 6.05 (d, 1H, $^3J_{H,\ H}$=16.2 Hz), 5.28 (s, 1H, OH), 2.97 (d, 1H, $^3J_{H,\ H}$=16.8 Hz, CH_2CO), 2.79 (d, 1H, $^3J_{H,\ H}$=16.8 Hz, CH_2CO), 2.19 (s, 3H, CH_3CO). ^{19}F NMR (282 MHz, $CDCl_3$, 25 °C): δ −81.5 (s, 3F, CF_3). ^{13}C NMR (50 MHz, $CDCl_3$, 25 °C): δ 208.7, 134.4, 132.8, 131.8, 128.4, 125.9, 125.0 (C*), 123.0, 122.4 (C*), 75.2 (q), 44.5, 32.0. IR (film, cm^{-1}): 3450, 1716, 1490, 1244, 1195, 1131, 813. EIMS (*m*/*z*, %): 337 (M$^+$, 2), 43 (100). Anal.

Calcd for $C_{13}H_{12}O_2F_3Br$: C, 46.31; H, 3.59. Found: C, 46.26; H, 3.73. HPLC analysis: DAICEL Chiralpak AD-H, hexane/2-propanol 95:5, λ=214 nm, flow rate=0.8 mL min^{-1}, retention time=10.2 min (minor) and 11.2 min (major).

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8. It is necessary to point out that, during the preparation of this manuscript, a similar communication was published by Liu group (Wang, X. J.; Zhao, Y.; Liu, J. T. *Org. Lett.* **2007**, *9*, 1343–1345). Indeed, good results were also obtained in that communication with a different catalyst. However, neither reaction mechanism nor the absolute configuration of the resulting optical products was reported.
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