DOI: 10.1002/adsc.200800039

# Highly Enantioselective Construction of a Quaternary Carbon Center of Dihydroquinazoline by Asymmetric Mannich Reaction and Chiral Recognition

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Received: January 19, 2008; Revised: March 4, 2008; Published online: May 9, 2008

Supporting information for this article is available on the WWW under http://asc.wiley-vch.de/home/.

**Abstract:** The highly enantioselective construction of a quaternary carbon center of dihydroquinazoline by an asymmetric Mannich reaction and chiral recognition are described. The key transformation was to establish the chiral trifluoromethyl quaternary carbon center by a diamine-Brønsted acid-catalyzed enantioselective and regioselective Mannich reaction of a methyl ketone and 4-trifluoromethyldihydroquinazoline. An unusual phenomenon of self-discrimination of enantiomers in hydrogen-bonded dimers was observed. A valuable intermediate was transformed into the enantiopure HIV reverse transcriptase inhibitor DPC 083 (>99.9 *ee*) simply by reduction of the carbonyl group and elimination of the hydroxy group in hexamethylphosphoric tramide (HMPA).

**Keywords:** C–C coupling; HIV therapeutics; hydrogen bonds; organocatalysis; self-discrimination

## Introduction

Chiral nitrogen-containing compounds are widely distributed in nature and include many biologically important molecules. The generation of tertiary alcohol stereocenters can be achieved easily in most cases by using the appropriate chiral auxiliary, reagent, or catalyst. However, the approach to complex compounds bearing quaternary stereocenters, such as tertiary amines and related systems, is still a challenge for synthetic organic chemists, and every enantioselective procedure for the construction of a fully substituted carbon center is of great value.[1]

In recent years, a number of dihydroquinazolines bearing a chiral trifluoromethyl group have occupied a central role in fighting AIDS. For example, DPC 961 and DPC 083 are second-generation non-nucleoside HIV reverse transcriptase inhibitors (NNRTIs) with enhanced potency in comparison with Efavirenz (Sustiva™) (Figure 1).[2] The challenge for synthesizing this class of NNRTIs is to form a tertiary carbinamine with absolute stereocontrol. Previously, tremendous efforts mainly focused on the synthesis of this class of compounds *via* formation of the chiral propargylamine, for example, the diastereoselective 1,4-addition of a magnesium acetylide to 2(3*H*)-quinazolinones containing a chiral auxiliary N-substituent,[3] 1,2-enantioselective addition of a lithium acetylide to cyclic *N*-acylketimines using lithium *Cinchona* alkaloids as the chiral moderator.[4] Our group also developed a mild and efficient method for the asymmetric synthesis of DPC 961, in which a highly enantioselec-

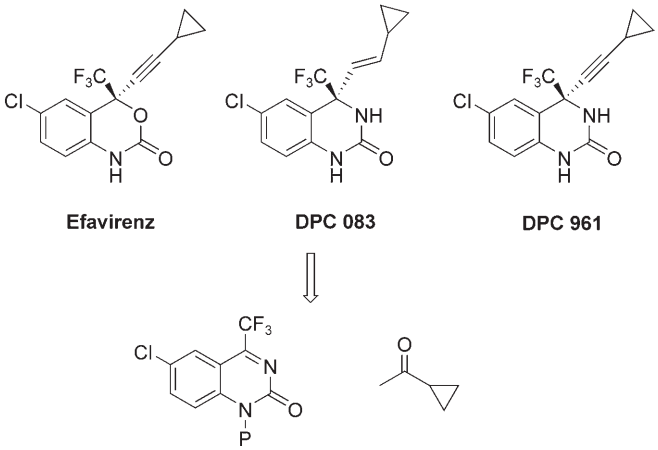



**Figure 1.** Structures of Efavirenz, DPC 961 and DPC 083 and retrosynthesis of DPC 083.

tive addition of zinc acetylide to a cyclic *N*-acylketimine in the presence of the chiral chloramphenicol ligand was employed as the key step.[5] In contrast to DPC 961, little work has been done on the synthesis of DPC 083. The only method developed for DPC 083 was reduction of DPC 961 by lithium aluminum hydride,[3] which is obviously not suitable in large-scale synthesis. Therefore, it is highly desirable to seek a practical and scalable alternative for the construction of the tertiary carbinamine stereogenic center and asymmetric synthesis of DPC 083 and its analogues to meet clinical demands. We envisioned that DPC 083 could be prepared by the reduction-dehydration sequence from a β-amino ketone intermediate, which could be regarded as a potential asymmetric Mannich adduct (Figure 1).

It is well known that the catalytic asymmetric Mannich reaction is an effective C–C bond forming process for the construction of chiral β-amino carbonyl compounds. In recent years, a tremendous amount of work and effort has been devoted to the development of efficient and versatile organocatalyzed asymmetric Mannich reactions,[6] but the structure of the electrophile has been restricted to imines derived from aldehydes. The organocatalytic enantioselective Mannich reaction of imines derived from ketones (ketimines) is very limited, although the substrates would constitute an interesting template for the synthesis of quaternary β-amino carbonyl compounds. To the best of our knowledge, the only example of an organocatalytic enantioselective Mannich reaction of ketimines and unmodified aldehydes was reported by the Jorgensen group,[7] while the asymmetric synthesis of tertiary carbinamines by the organocatalyzed Mannich reaction of unsymmetrical ketones with ketimines has generated considerable frustration. Thus, the development of an efficient protocol for an enantioselective direct Mannich reaction of a ketimine with a ketone remains challenging, especially when the Mannich adducts could be applied in the practical synthesis of pharmaceutically important compounds.

Herein, we present a novel and efficient protocol for the construction of a chiral quaternary carbon center of dihydroquinazoline (cyclic *N*-acylketimine) by a diamine-Brønsted acid-catalyzed enantioselective and regioselective Mannich reaction of a methyl ketone and 4-trifluoromethyldihydroquinazoline and self discrimination of enantiomers in the hydrogen-bonded dimers, which was applied to the preparation of the HIV reverse transcriptase inhibitor DPC 083 with excellent enantiopurity (>99.9 *ee*).

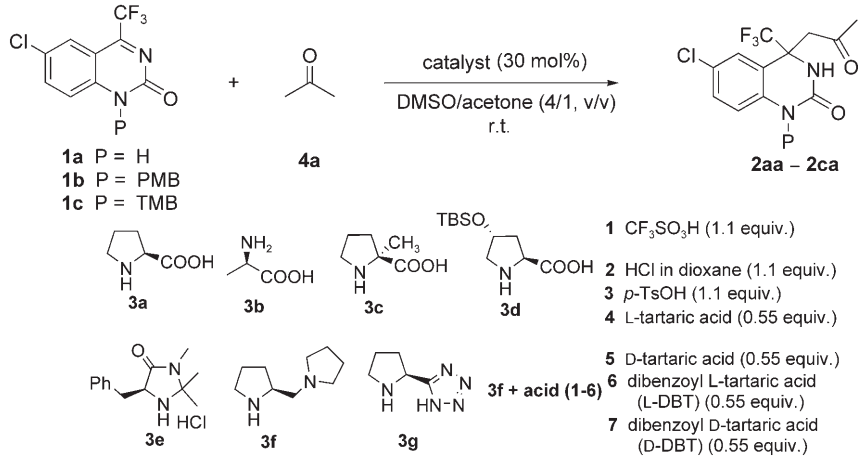
## Results and Discussion

Initially, 4-trifluoromethyldihydroquinazolines (**1a**–**1c**)[3a] and acetone were investigated as model substrates, and the direct Mannich reactions were carried out using a catalytic amount of L-proline (30 mol%) in DMSO at room temperature. It was found that the reaction proceeded rapidly and the desired products **2** (P = H, P = PMB) were afforded in quantitative yields within 2 h. However, the enantioselectivities were quite low (20–30% *ee*) (Table 1, entries 1–3). A more bulky protecting group, 2,4,6-trimethylbenzyl (TMB), seemed to prolong the reaction time to 12 h, with no beneficial effect on the enantioselectivity. A number of solvents were tested, only DMSO and DMF could give good yields. Decreasing the amount of the catalyst or lowering the temperature (<10 °C) had little effect on the enantioselectivity, however, the reaction was slowed down and this resulted in loss of the yield. All of the optimization conditions did not lead to significant improvements in enantioselectivity under the catalysis of L-proline.

Then we turned to screening other structurally diverse amine catalysts (**3b**–**3g**) (Table 1, entries 4–9). α-Methylproline (**3c**) provided moderate yield and enantioselectivity. However, the major product had an opposite absolute configuration (entry 5). The more soluble catalyst, 4-siloxyproline (**3d**),[8] gave good yield but with poor enantioselectivity (entry 6). The MacMillan chiral imidazolidinone[9] (HCl salt) (**3e**) could not catalyze the reaction at all (entry 7). The tetrazole catalyst (**3g**)[10] behaved similarly to L-proline with a rapid reaction rate and good yield, but poor enantioselectivity (entry 9). The chiral diamine (*S*)-2-(1-pyrrolidinylmethyl)pyrrolidine (**3f**), a catalyst of choice in the Mannich reaction of ketimines and unmodified aldehydes reported by the Jorgensen group,[7] also promoted the reaction and gave a better enantioselectivity (51% *ee*) (entry 8), but the yield was very low (38%). It is known that the proper design of acid-base catalysis has been shown to be effective for achieving high reactivity and selectivity in the asymmetric direct aldol reaction during the development of diamine-Brønsted acid types of catalyst.[11] Thus, we attempted to optimize the reaction through the addition of Brønsted acids. The combinations of diamine **3f** with different Brønsted acids in a ratio of 1:1.1 were employed as catalysts in the direct Mannich reactions (Table 1, entries 10–17). Indeed, Brønsted acids could accelerate the reaction dramatically and a few of the **3f**-Brønsted acid salts (1:1.1) were found to catalyze the formation of **2ba** in good yields. Interestingly, the diacid, dibenzoyl-L-tartaric acid (L-DBT, 0.55 equiv.), proved to be superior (entry 15) and the chirality of tartaric acid seemed to have no influence on the stereoselectivity of the reaction (entry 16). When switching the protecting group from PMB to more the bulky TMB, **2ca** was obtained in 92% yield with an improved enantioselectivity (71% *ee*). Using **1a** as a substrate, the activity of the diamine-Brønsted acid catalysts was quite poor (yield

**Table 1.** Direct Mannich reaction of 4-trifluoromethyldihydroquinazolines **1a**–**1c** and acetone.[a]




| Entry | Catalyst | Substrate | *t* [h] | Product | Yield [%][b] | *ee* [%][c] |
|---|---|---|---|---|---|---|
| 1 | **3a** | **1a** | 2 | **2aa** | quant. | 23 |
| 2 | **3a** | **1b** | 2 | **2ba** | quant. | 30 |
| 3 | **3a** | **1c** | 12 | **2ca** | 97 | 20 |
| 4 | **3b**[d] | **1b** | 24 | **2ba** | 80 | <2 |
| 5 | **3c** | **1b** | 72 | **2ba** | 65 | 55[e] |
| 6 | **3d** | **1b** | 48 | **2ba** | 82 | 21 |
| 7 | **3e** | **1b** | 24 | **2ba** | N.R | nd |
| 8 | **3f** | **1b** | 120 | **2ba** | 38 | 51 |
| 9 | **3g** | **1b** | 2 | **2ba** | 98 | 25 |
| 10 | **3f**+**1**[f] | **1b** | 12 | **2ba** | 91 | 18 |
| 11 | **3f**+**2**[f] | **1b** | 24 | **2ba** | 64 | 55 |
| 12 | **3f**+**3**[f] | **1b** | 48 | **2ba** | 76 | 17 |
| 13 | **3f**+**4**[f] | **1b** | 72 | **2ba** | 88 | 47 |
| 14 | **3f**+**5**[f] | **1b** | 72 | **2ba** | 89 | 49 |
| 15 | **3f**+**6**[f] | **1b** | 12 | **2ba** | 95 | 54 |
| 16 | **3f**+**7**[f] | **1b** | 12 | **2ba** | 89 | 49 |
| 17 | **3f**+**6**[f] | **1c** | 24 | **2ca** | 92 | 71 |

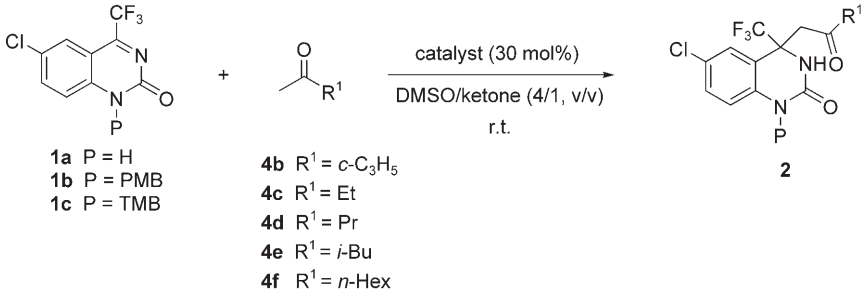
[a] All reactions were performed on 0.14 mmol scale in DMSO (1 mL) and acetone (0.25 mL) at room temperature (PMB = *p*-methoxybenzyl, TMB = 2,4,6-trimethylbenzyl).
[b] Isolated yield.
[c] Determined by chiral HPLC analysis.
[d] 50 mol% L-alanine was used.
[e] Opposite stereoselectivity was obtained.
[f] 1:1.1 mixture of diamine and Brønsted acid was used.

<50%), probably due to the influence of the active proton on the distal nitrogen of **1a**.

To expand the scope of the reaction, various ketones were tested as Mannich donors under the catalysis of **3f**-DBT. L-Proline **3a** was also tested for comparison. The results are illustrated in Table 2. It was found that the bulkiness of the ketone substituent ($R^1$) could dramatically influence the reaction outcomes. The reactions of linear alkyl methyl ketones (**4c**, **4d**, **4f**) or cyclopropyl methyl ketone (**4b**) with the dihydroquinazolines (**1a**–**1c**) proceeded smoothly and gave the desired products **2** in high yields (91–95%) (Table 2, entries 1–10, 14, 15). However, the bulky isobutyl methyl ketone gave only 51–75% yield in reactions under the catalysis of **3f**-DBT (entries 12 and 13). Isopropyl methyl ketone and the more bulky *tert*-butyl methyl ketone were found to be inert donors for this reaction. Furthermore, worthy of note is the unique regioselectivity observed in our cases. Generally, the regioselectivity in an organocatalyzed enantioselective direct Mannich reaction was affected by the structure and electronic properties of both the unsymmetrical ketone and imine. The highly regioselectivities reported so far were obtained only when an α-hydroxy ketone as a donor or an electron-deficient imine derived from α-imino glyoxylate as an acceptor were used, and the C–C bond formation occurred exclusively on the more substituted side of the ketone to afford branched β-amino carbonyl compounds. In contrast, nucleophilic addition of a non-oxygen-substi-

**Table 2.** Reaction of 4-trifluoromethyldihydroquinazolines **1a**–**1c** with unsymmetrical methyl ketones.




**1a** P = H
**1b** P = PMB
**1c** P = TMB

**4b** $R^1$ = *c*-$C_3H_5$
**4c** $R^1$ = Et
**4d** $R^1$ = Pr
**4e** $R^1$ = *i*-Bu
**4f** $R^1$ = *n*-Hex

**2**

| Entry | Ketone | Catalyst[a] | Ketimine | Product | *t* [h] | Yield [%][b] | *ee* [%][c] |
|---|---|---|---|---|---|---|---|
| 1 | **4b** | **3a** | **1a** | **2ab** | 96 | 94 | 44 |
| 2 | **4b** | **3a** | **1b** | **2bb** | 72 | 89 | 40 |
| 3 | **4b** | **3f**+DBT | **1b** | **2bb** | 72 | 94 | 57 |
| 4 | **4b** | **3f**+DBT | **1c** | **2cb** | 96 | 95 | 75 |
| 5 | **4c** | **3a** | **1a** | **2ac** | 24 | 95[d] | 30 |
| 6 | **4c** | **3a** | **1b** | **2bc** | 24 | 95 | 58 |
| 7 | **4c** | **3f**+DBT | **1b** | **2bc** | 48 | 95 | 69 |
| 8 | **4c** | **3f**+DBT | **1c** | **2cc** | 72 | 94 | 78 |
| 9 | **4d** | **3a** | **1b** | **2bd** | 72 | 96 | 47 |
| 10 | **4d** | **3f**+DBT | **1b** | **2bd** | 72 | 91 | 74 |
| 11 | **4e** | **3a** | **1b** | **2be** | 72 | 89 | 66 |
| 12 | **4e** | **3f**+DBT | **1b** | **2be** | 120 | 75 | 76 |
| 13 | **4e** | **3f**+DBT | **1c** | **2ce** | 192 | 51 | 66 |
| 14 | **4f** | **3a** | **1b** | **2bf** | 48 | 91 | 61 |
| 15 | **4f** | **3f**+DBT | **1b** | **2bf** | 72 | 92 | 78 |
| 16 | **4f** | **3f**+DBT | **1c** | **2cf** | 96 | 87 | 79 |

[a] L-DBT was used.
[b] Isolated yield.
[c] Determined by chiral-phase HPLC.
[d] Total yield of the two regioisomers (11:1), *ee* of major product is shown.

tuted unsymmetrical ketone to other imines often resulted in a mixture of regioisomers.[12] To our surprise, high regioselectivities were observed in most of our cases. The dihydroquinazoline was regiospecifically attacked by the methyl side of unsymmetrical methyl ketones to give the linear β-amino ketone as the sole product. Only in the case of ethyl methyl ketone **4c** and dihydroquinazoline **1a** were regioisomers obtained in the ratio of 11:1 (entry 5). Regarding enantioselectivity, diamine-Brønsted acid catalyst **3f**-DBT showed much higher *ee* than L-proline **3a** (entries 2/3, 6/7, 9/12, 14/15). In addition, the bulkier TMB protecting group in the dihydroquinazoline substrate gave enhanced enantioselectivities (69–79% *ee*) in most cases (entries 7, 8, 15, 16). To our delight, under the catalysis of **3f**-DBT, the Mannich donor cyclopropyl methyl ketone **4b** (entries 1–4) reacted with **1c** to afford **2cb** in 95% yield with 75% *ee*, which could be considered as a valuable intermediate to synthesize DPC 083.

Although the enantioselectivity of the reaction was not satisfactory for a practical asymmetric synthesis, an interesting phenomenon of self-discrimination of enantiomers in the hydrogen-bonded dimers provided an efficient alternative for rapid access to a series of enantiopure compounds **2**. Initially, we tried to improve the enantiopurity of this series of compounds **2** by recrystallization, however, it was found that the crystals we collected were racemates in all cases. X-ray crystallography of representative racemic crystals revealed that two enantiomers with opposite absolute configurations bind to each other through multiple hydrogen bonds in a $C_2$-symmetric heterochiral dimeric form (Figure 2).[13] On the other hand, since the solubility of heterochiral dimers were extremely poor in ethanol, the *ee* value of compounds **2** can be easily enhanced from 57–75% to >99% by a single recrystallization, and the yield was approximately equal to the enantiomeric excess (*ee*) before crystallization (Table 3). Enantiopure compounds **2** remained in the mother liquor and racemic crystals were removed by simple filtration (see Experimental Section). However, compounds **2aa**, **2ab**, **2ac** without a protecting group on the distal nitrogen (P=H) did not display self-discrimination under various conditions.

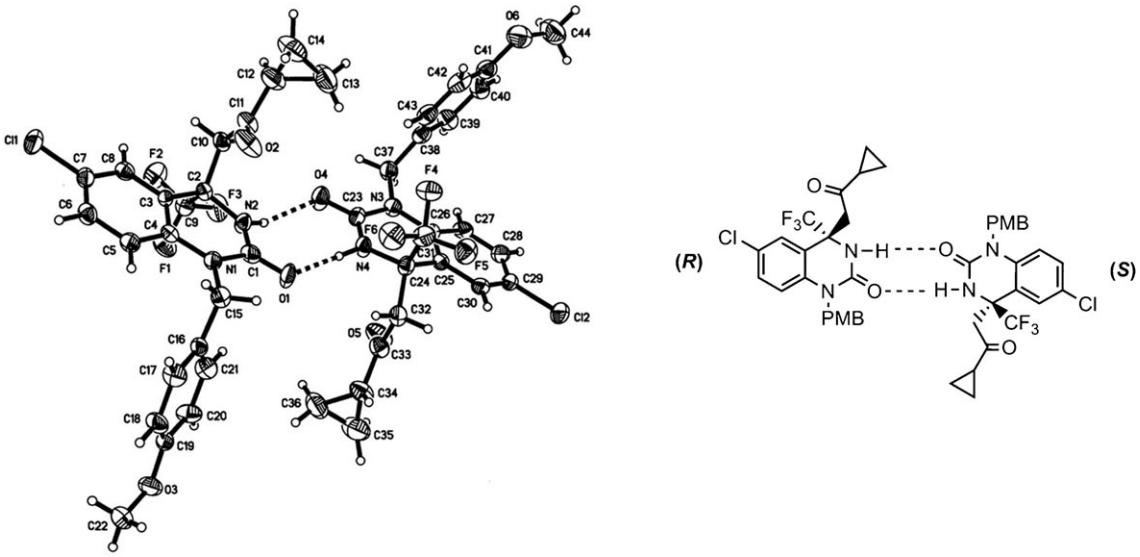
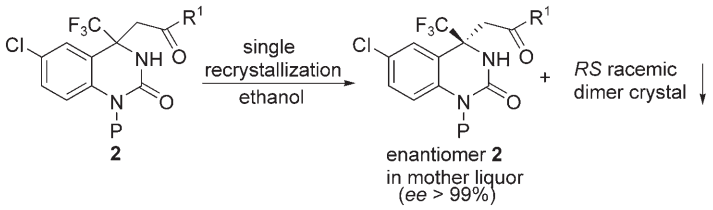



**Figure 2.** X-ray crystallography of the heterochiral hydrogen-bonded dimers (*RS*)-**2bb**.

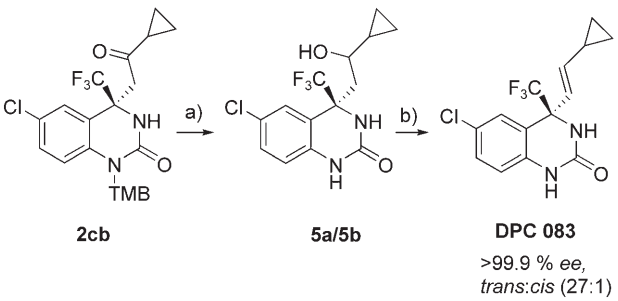
**Table 3.** A single recrystallization increases the enantiomeric purity of these series of compounds.[a]




| Entry | $R^1$ | P | Compound[b] | *ee* [%][c] before recrystallization | *ee* [%][c] after recrystallization | Yield [%][d] |
|---|---|---|---|---|---|---|
| 1 | Et | PMB | **2bc** | 58 | 99.1 | 55 |
| 2 | Et | PMB | **2bc** | 69 | 99.6 | 67 |
| 3 | Et | TMB | **2cc** | 57 | 99.7 | 53 |
| 4 | *c*-$C_3H_5$ | PMB | **2bb** | 57 | 99.3 | 53 |
| 5 | *c*-$C_3H_5$ | TMB | **2cb** | 75 | >99.9 | 67 |
| 6 | *i*-Bu | PMB | **2be** | 66 | 99.5 | 60 |
| 7 | *n*-Hex | PMB | **2bf** | 61 | >99.9 | 58 |

[a] All reactions and single recrystallizations were performed on 1–2 g scale.
[b] Compounds were purified by column chromatography (silica, $CH_2Cl_2$/EtOAc).
[c] Determined by chiral-phase HPLC analysis.
[d] Yield = the isolated pure enantiomers, all before recrystallization (In theory, the yield should be equal to the *ee* values before recrystallization).

With enantiopure **2cb** in hand, we then focused on the synthesis of DPC 083. As shown in Scheme 1, the TMB protecting group was removed under TFA/anisole conditions to afford **2ab** in quantitive yield. Reduction of the carbonyl group in **2ab** by $KBH_4$ gave two diastereoisomers **5a** and **5b** in a 98% yield with a ratio of 2:1. The isomeric mixture was directly dehydrated in HMPA[14] to give DPC 083. Recrystallization from $CHCl_3$/hexane gave enantiopure DPC 083 [>99.9% *ee*, containing 3.5% (*Z*)-isomer] with a specific rotation of $[\alpha]_D^{20}$: −22.5 (*c* 0.40 in $CH_3OH$), which was in accordance with the optical rotation data[15] of




**Scheme 1.** The synthesis of DPC 083 from enantiopure **2cb**: a) i. TFA, anisole, 70 °C, 20 min, quant.; ii. 4 equiv. $KBH_4$, MeOH, room temperature, overnight, 98%; b) HMPA, 230 °C, 7–10 min, 60%.

(*S*)-DPC 083 synthesized from (*S*)-DPC 961 by lithium aluminum hydride reduction.[2a] Therefore, the stereochemistry of the final product and the key organocatalyzed direct Mannich adduct **2cb** were assigned as the *S* configuration.

## Conclusions

In summary, a highly enantioselective construction of a quaternary carbon center of trifluoromethyldihydroquinazoline by an asymmetric Mannich reaction and chiral recognition is described. The key transformation was to establish the chiral trifluoromethyl quaternary carbon center by a diamine-Brønsted acid-catalyzed enantioselective and regioselective direct Mannich reaction of a methyl ketone and a 4-trifluoromethyldihydroquinazoline. Particularly, special regioselectivities were observed in all cases. An unusual phenomenon of self-discrimination of enantiomers in the hydrogen-bonded dimers was observed, and by taking advantage of the unique spontaneous chiral recognition of the Mannich adducts, a rapid access to enantipure DPC 083 (>99.9% *ee*) was demonstrated. Compared with the reported process, our process was carried out under extremely mild conditions, simple manipulation and short reaction steps with higher enantiopurity.

## Experimental Section

### General Procedure for the Organocatalytic Enantioselective Direct Mannich Reactions of 4-Trifluoromethyldihydroquinazolines 1a–1c and Methyl Ketones 4a-4f

*(a)* L-*Proline as the catalyst:* To a solution of 4-trifluoromethyldihydroquinazolines (**1a–1c**) (0.14 mmol) and L-proline (4.8 mg, 0.04 mmol) in dry DMSO (1 mL), was added the ketone (0.25 mL) in one portion under an argon atmosphere. The reaction mixture was stirred at room temperature until the ketimine disappeared (monitored by $^{19}F$ NMR or TLC). Water (4 mL) was added, the mixture was extracted with EtOAc (5 mL×4), the combined organic layers were washed with brine and dried over $Na_2SO_4$. Concentration under vacuum and purification by flash chromatography on silica gel (for P=PMB, TMB, $CH_2Cl_2$:EtOAc=20:1 or hexane:EtOAc=4:1 to 3:1; for P=H, hexane:EtOAc=2:1 to 1:1) provided product **2.**

*(b) 3f-DBT as the catalyst:* To a solution of L-DBT (8 mg, 0.022 mmol) in dry DMSO (1 mL), was added diamine **3f** (6.9 uL, 0.042 mmol) in one portion under argon. After the reaction mixture had been stirred for 15 min, ketone (0.25 mL) and 4-trifluoromethyldihydroquinazoline (**1b**, **1c**) (0.14 mmol) were added. The reaction mixture was stirred at room temperature until the 4-trifluoromethyldihydroquinazolines disappeared. Water (4 mL) was added, the mixture was extracted with EtOAc (5 mL x 4), the combined organic layers were washed with brine, dried over $Na_2SO_4$. Concentration under vacuum and purification by flash chromatography on silica gel (for P=PMB, TMB, $CH_2Cl_2$:EtOAc=20:1 or hexane:EtOAc=4:1 to 3:1; for P=H, hexane:EtOAc=2:1 to 1:1) provided product **2aa–2cf**.

### Typical Procedure for the Recrystallization to Increase the Enantiomeric Purity

Compound **2cb** (1.75 g, *ee*=75%) was dissolved in boiling ethanol, then the mixture was slowly concentrated within 1 h and the volume of solvent was reduced to *ca.*15 mL. (The major part of the *RS* dimer has already precipitated at this time). The mixture was cooled to room temperature and allowed to stand overnight, then further cooled to −20 °C and allowed to stand for 2 h. After quick filtration, the mother liquor was concentrated under vacuum to give **2cb** (yield: 1.18 g, 67%, *ee*=99.9%) as a white solid, and the filter cake was dried to afford (*RS*)-**2cb** (yield: 470 mg, *ee*<4%). The *ee* value was determined by HPLC using Chiralcel AD-H column, *i*-PrOH/hexane=40:60, flow rate=0.7 mL min$^{-1}$, $t_{major}$=7.39 min, $t_{minor}$=19.62 min, 254 nm.

### (*S*)-6-Chloro-4-(2-cyclopropyl-2-oxoethyl)-4-(trifluoromethyl)-3,4-dihydroquinazolin-2(1*H*)-one [(*S*)-2ab]

A mixture of (*S*)-**2cb** (100 mg, 0.216 mmol, *ee*>99.9%), TFA (2 mL) and anisole (1 mL) was heated at 70 °C for 10 min. After cooling to room temperature. Water (10 mL) was added and the mixture was extracted with EtOAc (5 mL×5). The combined organic layers were washed with 1 N NaOH, brine and dried over $Na_2SO_4$. Concentration under vacuum gave the crude product, which was purified by flash chromatography on silica gel (hexane:EtOAc=2:1) to give (*S*)-**2ab** as a white solid; yield: 71 mg (quant.); $[\alpha]_D^{20}$: + 5.29 (*c* 0.48 in acetone); *ee*>99.9%; the *ee* value was determined by HPLC using Chiralcel AD-H column, *i*-PrOH/hexane=10:90, flow rate=0.5 mL min$^{-1}$, $t_r(S)$=46.79 min, $t_r(R)$=50.39 min, 254 nm.

### (4*S*)-6-Chloro-4-(2-cyclopropyl-2-hydroxyethyl)-4-(trifluoromethyl)-3,4-dihydroquinazolin-2(1*H*)-one (5a) and (5b)

To a solution of (*S*)-**2ab** (580 mg, 1.7 mmol) in methanol (20 mL), was added $KBH_4$ (424 mg, 7.86 mmol) in portions at room temperature. After being stirred at room temperature overnight, the mixture was concentrated; the residue was partitioned between $H_2O$ and EtOAc. The organic layer was separated, washed with brine, and dried over $Na_2SO_4$. Concentration under vacuum provided the crude product, which was purified by flash chromatography on silica gel (hexane:EtOAc=2:1 to 1:1) to provided a mixture of **5a** and **5b** (570 mg, **5a**/**5b**=2/1), yield: 98%.

### (*S*,*E*)-6-Chloro-4-(2-cyclopropylvinyl)-4-(trifluoromethyl)-3,4-dihydroquinazolin-2(1*H*)-one (DPC 083)

A solution of **5a** and **5b** (480 mg, 1.44 mmol) in dry HMPA (5 mL) was heated to 225–230 °C under argon. After being kept gently boiling for 7–10 min, the solution was then quickly cooled to room temperature. The mixture was dilut-

ed with water (20 mL) and extracted with EtOAc (20 mL × 6). The combined organic layers were washed with brine and dried over $Na_2SO_4$. Concentration under vacuum provided the crude product, which was purified by flash chromatography on silica gel (hexane:EtOAc = 4:1) and recrystallization from $CHCl_3$/hexane then cyclohexane to give DPC 083 as colorless crystals; yield: 270 mg (60%); *ee* > 99.9%, (*E*, *S*)/(*Z*, *S*) = 27:1. The *ee* value was determined by HPLC using Chiralcel AD-H column, *i*-PrOH/hexane = 5:95, flow rate = 0.7 mL min$^{-1}$, $t_r(Z,S) = 23.95$ min, $t_r(E,R) = 26.54$ min, $t_r(E,S) = 30.44$ min, 254 nm; $[\alpha]_D^{20}$: −22.5 (*c* 0.40 in $CH_3OH$).

### Supporting Information

Characterization data for all compounds are available as Supporting Information.

## Acknowledgements

*Financially support of this work by the Science & Technology Commission of Shanghai Municipality, the National Natural Science Foundation of China and Chinese Academy of Sciences is gratefully acknowledged.*

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[15] The specific rotation of DPC 083 {$[\alpha]_D^{20}$: −6.81 (*c* 0.382 in $CH_3OH$)} reported in ref.[2a] is not corrected. DPC 083 (>99% *ee*) synthesized from (*S*)-DPC 961 by lithium aluminum hydride reduction gave the specific rotation of $[\alpha]_D^{20}$: −17.9 (*c* 0.40 in $CH_3OH$).

  