JOC The Journal of Organic Chemistry

Article

pubs.acs.org/joc

Cinchona Alkaloid Squaramide-Catalyzed Asymmetric Michael Addition of α-Aryl Isocyanoacetates to β-Trifluoromethylated Enones and Its Applications in the Synthesis of Chiral β-Trifluoromethylated Pyrrolines

Mei-Xin Zhao,*[,†,‡] Hui-Kai Zhu,[†] Tong-Lei Dai,[†] and Min Shi[†,§]

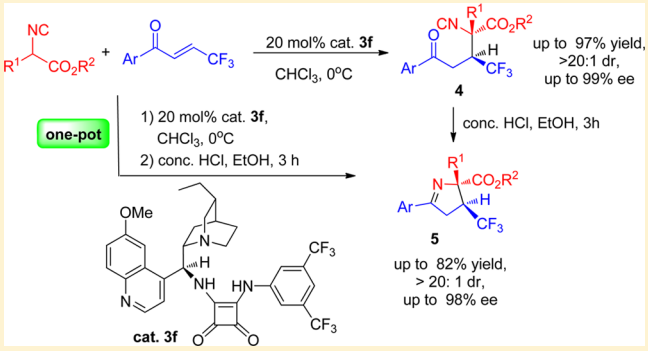
[†]Key Laboratory for Advanced Materials and Institute of Fine Chemicals, East China University of Science and Technology, 130 Mei Long Road, Shanghai 200237, China

[‡]CAS Key Laboratory of Molecular Recognition and Function, Institute of Chemistry, Chinese Academy of Sciences, Beijing 100190, China

[§]State Key Laboratory of Organometallic Chemistry, Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, 354 Fenglin Road, Shanghai 200032, China

Supporting Information

ABSTRACT: Cinchona alkaloid squaramide can effectively catalyze the asymmetric Michael addition of α-aryl isocyanoacetates to β-trifluoromethylated enones, affording the corresponding adducts with an adjacent chiral tertiary carbon center bearing a CF_3 group and a quaternary carbon center in moderate to good yields along with excellent stereoselectivities. The adduct can be easily transformed into biologically attractive chiral β-trifluoromethylated pyrroline carboxylate in high yield via an isocyano group hydrolysis/cyclization/dehydration cascade reaction by treating with acid. The one-pot enantioselective Michael addition/isocyano group hydrolysis/cyclization/dehydration sequential protocol has also been investigated.



INTRODUCTION

Trifluoromethylated heterocycles constitute a major family of pharmaceuticals and agrochemicals due to the high lipophilicity brought by the CF_3 moiety, which make them promising modern targets in the fields of medicinal and agricultural chemistry.[1] Among them, trifluoromethylated 3,4-dihydro-2*H*-pyrroles, such as β-trifluoromethylated pyrrolines, are an important class of trifluoromethylated heterocycles with remarkable biological activities (Figure 1) and have been well-documented in the literature;[2] however, optically active pyrrolines with a chiral tertiary carbon center bearing a CF_3 group in the β-position are very rare.[3a,b] Recently, Shibata et al. described convenient methods for the synthesis of chiral β-trifluoromethyl-substituted pyrroline derivatives by conjugated additions of adamantyl glycine imine[3a] or nitromethane[3b] to β-trifluoromethylated enones, conjugate cyanation[3c] or conjugated addition of nitromethane[3d] to β-aryl-β-trifluoromethyl-disubstituted enones, followed by deprotection or a reduction/cyclization/dehydration sequence (Scheme 1, eqs 1−3). The products accessed by these approaches feature a tertiary C2 carbon atom containing a carboxylic acid functional group or methylene and a tertiary or quaternary trifluoromethyl-substituted C3 carbon atom. To the best of our knowledge, the enantioselective synthesis of chiral β-trifluoromethylated pyrroline carboxylates bearing an adjacent chiral quaternary carbon center at C2 and a tertiary carbon center at C3 containing a trifluoromethyl group had not been reported.

α-Isocyanoacetates are well-known irreplaceable building blocks for the synthesis of numerous enantioenriched five-membered heterocycles[4] by Lewis-acid- and organomolecule-catalyzed enantioselective [3 + 2] cycloadditions with carbonyl compounds,[5] imines,[6] azodicarboxylates,[7] and polarized carbon−carbon double bonds, such as nitroolefins[8] and α,β-unsaturated carbonyl compounds.[9] Furthermore, α-isocyanoacetates have also been found to be a glycine template for the synthesis of α,α-disubstituted α-amino acid derivatives by the enantioselective allylation[10] or Michael addition with a polarized C═C double bond.[11] Because β-trifluoromethylated enones are potential building blocks for the construction of a stereogenic C−CF_3 center,[3,12] the reaction of isocyanoacetates with α,β-unsaturated carbonyl compounds can be stopped at the Michael adduct stage under the appropriate reaction conditions, and the isocyano group is easily hydrolyzed into the

Received: August 7, 2015
Published: November 2, 2015

DOI: 10.1021/acs.joc.5b01829
J. Org. Chem. 2015, 80, 11330−11338

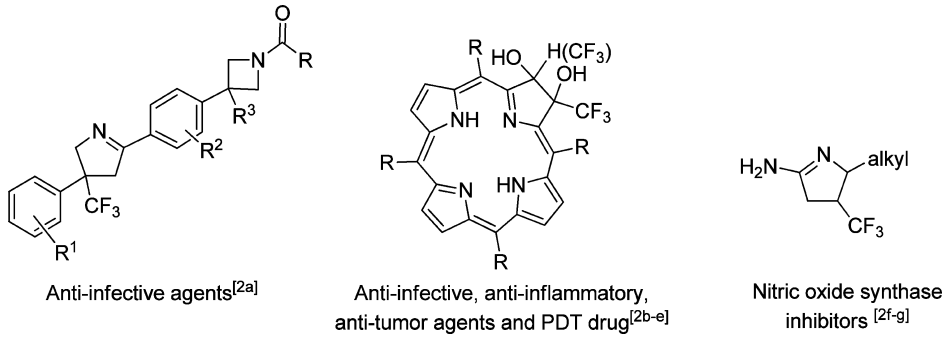
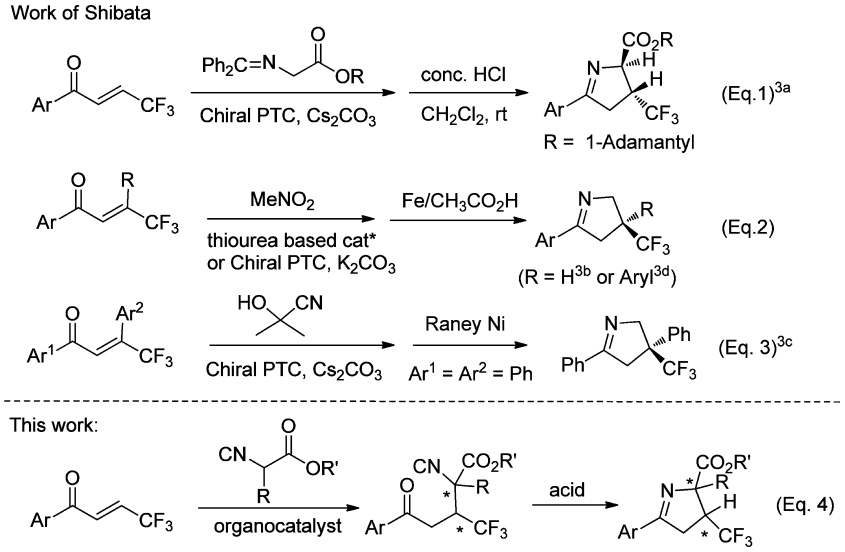


Figure 1. Examples of biologically active β-trifluoromethylated pyrrolines.

Scheme 1. Enantioselective Synthesis of β-Trifluoromethylated Pyrrolines



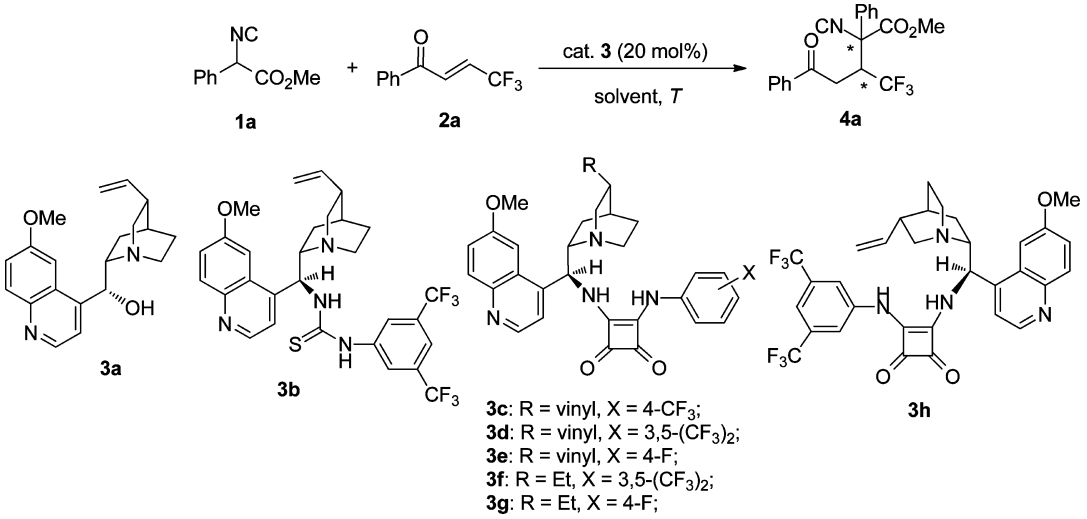
free amine under acidic conditions. We envisioned that the β-trifluoromethylated pyrroline carboxylates bearing an adjacent chiral quaternary carbon center at C2 and a tertiary carbon center at C3 containing a trifluoromethyl group can be readily synthesized by the organocatalyzed Michael addition of α-substituted α-isocyanoacetates with β-trifluoromethylated enones, followed by an isocyano group hydrolysis/cyclization/dehydration sequence (Scheme 1, eq 4). As part of our ongoing interest in the enantioselective reactions of α-aryl isocyanoacetates with unsaturated compounds for the synthesis of polysubstituted chiral heterocycles,[5h,6i,7c,9d,11b] we describe herein the highly diastereo- and enantioselective synthesis of β-trifluoromethylated pyrrolines with two contiguous asymmetric quaternary–tertiary carbon atoms by an asymmetric conjugate addition of α-aryl isocyanoacetates to β-trifluoromethylated enones under the catalysis of a cinchona alkaloid-derived squaramide, followed by an isocyano group hydrolysis/cyclization/dehydration sequence in moderate to good yields and excellent diastereoselectivities and enantioselectivities.

RESULTS AND DISCUSSION

We initially examined quinine and several cinchona alkaloid-derived bifunctional thiourea or squaramides **3** as potential catalysts for the reaction of α-phenyl isocyanoacetate **1a** with β-trifluoromethylated enone **2a** in the CH_2Cl_2 at room temperature (Table 1). It was found that quinine **3a** and quinine-derived thiourea **3b** are not suitable catalysts for this reaction, affording the corresponding adducts **4a** in moderate to good yields along with low diastereo- and enantioselectivities (Table 1, entries 1 and 2). When quinine- or dihydroquinine-derived squaramides **3c–g** were used as the catalysts, to our delight, moderate yields, good diastereoselectivities, and excellent enantioselectivities were observed (Table 1, entries 3–7). Quinidine-derived squaramide **3h**, a pseudoenantiomer of **3d**, also effectively catalyzed this reaction but gave **4a** with opposite absolute configuration in much lower enantioselectivity (Table 1, entry 8 vs 4). Since squaramides **3c–g** provided products with similar yields and enantioselectivities, they were investigated further to identify the optimal catalyst by conducting the reactions at low temperature. It was demonstrated that slightly higher diastereo- and enantioselectivities were observed for the reaction carried out at 0 °C, but the yields varied. Squaramides **3d** and **3f** bearing a bis(trifluoromethyl)phenyl group on the squaramide moiety gave high yields along with excellent stereoselectivities. However, replacing a bis(trifluoromethyl)phenyl group with 4-trifluoromethylphenyl and 4-fluorophenyl groups gave the desired product **4a** in very low yields, probably due to the weak acidity of the N–H of squaramide group of **3c**, **3e**, and **3g** (Table 1, entries 9–13). Comparison of the catalytic ability of catalysts **3f** and **3d** indicated that **3f** was superior to **3d** and was the optimal catalyst for this reaction (Table 1, entry 10 vs 12). Upon screening the various solvents, we found that chloroform produced better results than any other less polar solvents, such

DOI: 10.1021/acs.joc.5b01829
J. Org. Chem. 2015, 80, 11330–11338

Table 1. Optimization of Reaction Conditions for the Asymmetric Michael Addition Reaction of α-Phenyl Isocyanoacetate 1a to β-Trifluoromethylated Enone 2a[a]



entry	cat. 3	solvent	T (°C)	t (day)	yield (%)	dr[b]	ee (%)[c]
1	**3a**	CH_2Cl_2	25	2	86	1.3:1	8
2	**3b**	CH_2Cl_2	25	5	46	2.7:1	46
3	**3c**	CH_2Cl_2	25	5	51	>15:1	96
4	**3d**	CH_2Cl_2	25	4.5	48	>15:1	91
5	**3e**	CH_2Cl_2	25	5	39	>15:1	92
6	**3f**	CH_2Cl_2	25	4	59	>15:1	92
7	**3g**	CH_2Cl_2	25	5	62	>15:1	91
8	**3h**	CH_2Cl_2	25	4	52	>15:1	−83
9	**3c**	CH_2Cl_2	0	7	21	>20:1	98
10	**3d**	CH_2Cl_2	0	7	75	>20:1	96
11	**3e**	CH_2Cl_2	0	7	26	>20:1	95
12	**3f**	CH_2Cl_2	0	7	78	>20:1	96
13	**3g**	CH_2Cl_2	0	7	30	>20:1	95
14	**3f**	$CHCl_3$	0	7	86	>20:1	96
15	**3f**	DCE	0	7	60	>20:1	96
16	**3f**	toluene	0	7	14	1:1.3	70
17	**3f**	THF	0	7	68	1:3	87
18	**3f**	CH_3CN	0	7	52	1.4:1	63
19[d]	**3f**	$CHCl_3$	0	7	53	>20:1	96
20[e]	**3f**	$CHCl_3$	0	7	82	>20:1	96
21[f]	**3f**	$CHCl_3$	0	7	68	>20:1	96

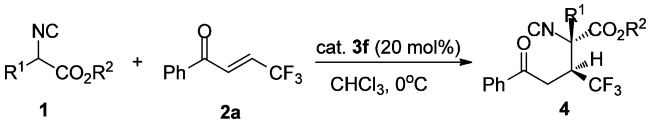
[a]Unless otherwise noted, all reactions were carried out with isocyanoacetate **1a** (0.15 mmol), enone **2a** (0.30 mmol), and catalyst **3** (0.03 mmol) in 1.0 mL of solvent. [b]Determined by ^{1}H NMR analysis for the pure product. [c]Enantiomeric excesses were determined by chiral HPLC analysis. [d]2.0 mL of $CHCl_3$ was used. [e]0.5 mL of $CHCl_3$ was used. [f]10 mol % of cat. **3f** was added.

as dichloroethane, toluene, and THF, or polar solvents, with 86% yield and excellent stereoselectivity (>20:1 dr, 96% ee) (Table 1, entries 14−18). No further improvement on enantioselectivity was observed under higher or lower reaction concentration, and the yield was dropped to 68% when reducing the catalyst loading to 10 mol % (Table 1, entries 19−21). Thus, the best result was obtained when carrying out the reaction with 1.0 equiv of isocyanoacetate **1a** and 2.0 equiv of trifluoromethylated enone **2a** in chloroform (0.15 M for **1a**) at 0 °C in the presence of 20 mol % of **3f** as catalyst (Table 1, entry 14, 86% yield, >20:1 dr, 96% ee).

With these optimized reaction conditions, we first investigated the substrate scope of isocyanoacetates by varying the aryl and ester substituents (Table 2). It was found that isocyanoacetates, whether bearing an electron-withdrawing or an electron-donating group on the *para* and *meta* position of the phenyl ring, are tolerated, affording the corresponding adducts **4a−h** in moderate to good yields (45−91% yields) along with excellent enantioselectivities (95−97% ee) (Table 2, entries 1−8). However, those without a substituent or bearing an electron-withdrawing group yielded, in general, the desired Michael adducts in yields higher than those having an electron-donating group (Table 2, entries 1−4 and 7 vs 5, 6, and 8). The presence of a substituent on the *ortho* position was deleterious to the reaction, as only a trace Michael adduct was detected when isocyanoacetate **1i** was used, presumably owing to steric hindrance (Table 2, entry 9). Variation on the ester moiety was then examined. The benzyl or *tert*-butyl isocyanoacetates **1j,k** participated in this reaction efficiently, providing the corresponding adducts **4j,k** in good to excellent yields and excellent stereoselectivities (Table 2, entries 10 and 11). Moreover, a limitation was observed with less reactive α-alkyl-substituted

DOI: 10.1021/acs.joc.5b01829
J. Org. Chem. 2015, 80, 11330−11338

Table 2. Scope of Isocyanoacetates 1[a]



1 2a 4

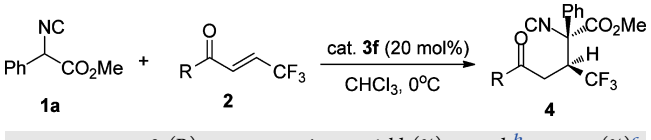
entry	1 (R^1/R^2)	4	yield (%)	dr[b]	ee (%)[c]
1	**1a** (Ph/Me)	**4a**	86	>20:1	96
2	**1b** (4-FC_6H_4/Me)	**4b**	90	>20:1	96
3	**1c** (4-ClC_6H_4/Me)	**4c**	83	>20:1	96
4	**1d** (4-BrC_6H_4/Me)	**4d**	86	>20:1	96
5	**1e** (4-MeC_6H_4/Me)	**4e**	51	>20:1	96
6	**1f** (4-$MeOC_6H_4$/Me)	**4f**	45	>20:1	97
7	**1g** (3-FC_6H_4/Me)	**4g**	91	>20:1	95
8	**1h** (3-MeC_6H_4/Me)	**4h**	61	>20:1	97
9	**1i** (2-MeC_6H_4/Me)	**4i**	trace	nd	nd
10	**1j** (Ph/Bn)	**4j**	82	>20:1	98
11	**1k** (Ph/*t*-Bu)	**4k**	97	>20:1	99
12	**1l** (Bn/Me)	**4l**	nr	nd	nd

[a]All reactions were carried out with isocyanoacetates **1** (0.15 mmol), enone **2a** (0.30 mmol), and catalyst **3f** (0.03 mmol) in 1.0 mL of $CHCl_3$ for 7 days. [b]Determined by ^{1}H NMR analysis for the pure product. [c]Enantiomeric excesses were determined by chiral HPLC analysis.

isocyanoacetates. For example, using α-benzyl-substituted isocyanoacetate **1l** as the reactant, no reaction occurred under the standard conditions (Table 2, entry 12).

To broaden the substrate scope, various β-trifluoromethylated enones **2** with an aromatic, heteroaromatic, or alkyl group bound to the carbonyl group were next evaluated (Table 3).

Table 3. Scope of β-Trifluoromethylated Enones 2[a]



1a 2 4

entry	2 (R)	4	yield (%)	dr[b]	ee (%)[c]
1	**2b** (4-ClC_6H_4)	**4m**	85	>20:1	97
2	**2c** (4-$NO_2C_6H_4$)	**4n**	87	>20:1	89
3	**2d** (4-MeC_6H_4)	**4o**	77	>20:1	96
4	**2e** (4-$MeOC_6H_4$)	**4p**	50	>20:1	97
5	**2f** (3-BrC_6H_4)	**4q**	80	>20:1	97
6	**2g** (3-MeC_6H_4)	**4r**	72	>20:1	97
7	**2h** (2-MeC_6H_4)	**4s**	54	18:1	92
8	**2i** (2-furyl)	**4t**	71	>20:1	79
9	**2j** (2-thienyl)	**4u**	74	>20:1	86
10	**2k** ($PhCH_2CH_2$)	**4v**	nr	nd	nd

[a]All reactions were carried out with isocyanoacetate **1a** (0.15 mmol), enones **2** (0.30 mmol), and catalyst **3f** (0.03 mmol) in 1.0 mL of $CHCl_3$ for 7 days. [b]Determined by ^{1}H NMR analysis for the pure product. [c]Enantiomeric excesses were determined by chiral HPLC analysis.

Generally, all of the aryl-substituted β-trifluoromethylated enones **2** can effectively react with isocyanoacetate **1a** to afford the corresponding Michael adducts in moderate to good yields and high diastereo- and enantioselectivities (>20:1 dr, 89–97% ee) (Table 3). The yields and enantioselectivities varied depending on the substituent's electronic and steric property. β-Trifluoromethylated enones, bearing an electron-withdrawing or weak electron-donating group on the *para* or *meta* position of the aromatic ring, led to yields higher than that bearing a strong electron-donating group (Table 3, entries 1–3 and 5–6 vs 4). Much lower enantioselectivity was obtained for enone **2c**, which had a strong electron-withdrawing group on the *para* position of the aromatic ring (Table 3, entry 2). In the case of *ortho*-substituted β-trifluoromethylated enone **2h**, both yield and stereoselectivity of the corresponding Michael adduct dropped (54% yield, 18:1 dr and 92% ee), indicating the existence of steric effect of the *ortho* substituent on the reactivity (Table 3, entry 7). Additionally, heteroaryl-substituted β-trifluoromethylated enones **2i** and **2j** can also serve as the substrates, affording the corresponding Michael adducts in good yields and excellent diastereoselectivities, albeit with somewhat lower enantioselectivities (Table 3, entries 8 and 9). A diminished reactivity was observed for alkyl-substituted β-trifluoromethylated enone **2k**, and no reaction occurred under the standard conditions (Table 3, entry 10).

The relative and absolute configurations of the adjacent stereocenters in major diastereomer of adducts **4** were unambiguously confirmed to be (2*R*,3*S*) by X-ray crystallographic analysis of adduct **4q**.[13] The other adducts were deduced by an analogue. On the basis of this result and commonly accepted mechanism for the squaramide catalyst, a plausible dual-activation transition-state model is proposed (Figure 2). The isocyanoacetate **1a** was enolized by a tertiary

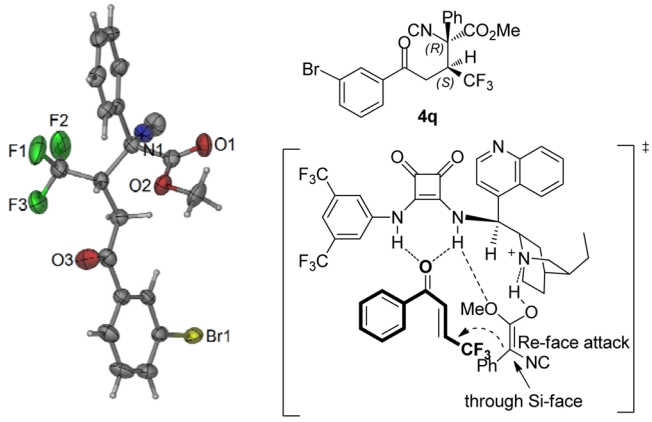


Figure 2. ORTEP plot of the X-ray crystal structure of **4q** (displacement ellipsoids are drawn at the 50% probability level) and proposed transition state.

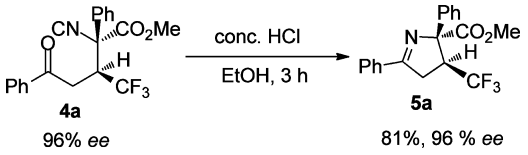
amine and resulted in a hydrogen-bonding interaction between the OH group and the tertiary amine. The squaramide motif directed the enone **2a** and isocyanoacetate **1a** through a H-bonding interaction between the N–H moiety and carbonyl or methoxy group, which forced the enolic isocyanoacetate through its *Si* face to approach the enone from the *Re* face, affording the corresponding adduct **4a** with (2*R*,3*S*) configuration.

Considering that β-trifluoromethyl-substituted pyrrolines **5** are potential drug candidates, the transformation of adduct **4a** to **5a** was investigated. When adduct **4a** was treated with concentrated HCl in EtOH, β-trifluoromethylated pyrroline **5a** was obtained in good yield and without the influence of enantioselectivity via an isocyano group hydrolysis/cyclization/dehydration sequential protocol (Scheme 2).

To further improve the synthetic efficiency of β-trifluoromethylated pyrrolines **5**, we tried combining the Michael addition and the subsequent isocyano group hydrolysis/

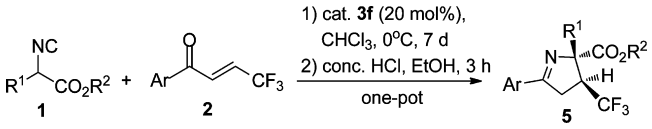
DOI: 10.1021/acs.joc.5b01829
J. Org. Chem. 2015, 80, 11330–11338

Scheme 2. Synthesis of β-Trifluoromethylated Pyrroline 5a from 4a



cyclization/dehydration cascade reaction in a one-pot sequential protocol. To our delight, β-trifluoromethyl-substituted pyrrolines **5**, whether bearing an electron-donating or an electron-withdrawing group on the aromatic ring of isocyanoacetates or enones, were obtained in good yields and excellent diastereo- and enantioselectivities by this novel sequence (Table 4). These results demonstrated that the novel one-pot

Table 4. One-Pot Synthesis of β-Trifluoromethylated Pyrrolines[a]



entry	1	2	5 (R^1/R^2/Ar)	yield (%)	dr[b]	ee (%)[c]
1	**1a**	**2a**	**5a** (Ph/Me/Ph)	68	>20:1	96
2	**1b**	**2a**	**5b** (4-FC_6H_4/Me/Ph)	62	>20:1	96
3	**1e**	**2a**	**5c** (4-MeC_6H_4/Me/Ph)	54	>20:1	94
4	**1k**	**2a**	**5d** (Ph/*t*-Bu/Ph)	82	>20:1	98
5	**1a**	**2b**	**5e** (Ph/Me/4-ClC_6H_4)	77	>20:1	97

[a]All reactions were carried out with isocyanoacetates **1** (0.15 mmol), enones **2** (0.30 mmol), and catalyst **3f** (0.03 mmol) in 1.0 mL of $CHCl_3$. [b]Determined by ^1H NMR analysis for the pure product. [c]Enantiomeric excesses were determined by chiral HPLC analysis.

enantioselective Michael addition/isocyano group hydrolysis/cyclization/dehydration cascade reaction between isocyanoacetates and β-trifluoromethylated enones is a promising approach for the convenient synthesis of optically active β-trifluoromethylated pyrrolines **5**.

CONCLUSION

In conclusion, we have developed the first example of cinchona alkaloid-derived squaramide-catalyzed enantioselective Michael addition of α-aryl isocyanoacetates to β-trifluoromethyl α,β-unsaturated ketones. A wide variety of α-aryl isocyanoacetates and β-trifluoromethylated enones, with different electronic and steric properties, were tolerated in this catalytic enantioselective Michael addition, leading to the corresponding adducts with an adjacent chiral tertiary carbon center attached to a trifluoromethyl group and quaternary carbon center in moderate to good yields with excellent diastereoselectivities (>20:1 dr) and enantioselectivities (up to 99% ee). Additionally, biologically attractive chiral β-trifluoromethylated pyrroline carboxylates **5** were readily synthesized by a one-pot enantioselective Michael addition/isocyano group hydrolysis/cyclization/dehydration sequential protocol. The use of easy prepared substrates and catalysts and a simple experimental procedure constitutes additional advantages of this method. Investigations aimed at developing more effective enantioselective addition reactions of isocyanoacetates with other electrophiles are currently ongoing in our laboratory.

EXPERIMENTAL SECTION

General Procedure for Squaramide Catalyst 3f Catalyzing the Enantioselective Michael Addition Reaction of Isocyanoacetates 1 with β-Trifluoromethylated Enones 2. To the solution of isocyanoacetates **1** (0.15 mmol) and β-trifluoromethylated enones **2** (0.30 mmol) in $CHCl_3$ (1.0 mL) was added **3f** (19.0 mg, 0.03 mmol). The resulting mixture was stirred at 0 °C for 7 days until the reaction completed (monitored by TLC). After concentration, the residue was directly subjected to flash column chromatography on silica gel (petroleum ether/ethyl acetate = 25:1) to furnish the corresponding Michael adducts **4**.

*(2R,3S)-Methyl 2-Isocyano-5-oxo-2,5-diphenyl-3-(trifluoromethyl)pentanoate (**4a**):* Colorless oil; yield 48.6 mg (86%); $[\alpha]_D^{25}$ +96.5 (*c* 1.00, CH_2Cl_2) (96% ee); the ee was determined by HPLC analysis with a Chiralcel OD-H column (95/5 hexane/*i*-PrOH; 0.5 mL/min; λ = 254 nm; t_{major} = 18.31 min; t_{minor} = 14.07 min); >20:1 dr; ^1H NMR ($CDCl_3$, 400 MHz) δ 3.07 (d, *J* = 18.4 Hz, 1H), 3.75 (dd, *J* = 18.0, 7.6 Hz, 1H), 3.74 (s, 3H), 4.66 (qd, *J* = 7.6, 2.0 Hz, 1H), 7.43−7.48 (m, 3H), 7.52 (t, *J* = 7.6 Hz, 2H), 7.62 (d, *J* = 7.6 Hz, 1H), 7.67 (d, *J* = 7.6 Hz, 2H), 8.03 (d, *J* = 8.0 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 36.2 (q, *J* = 2.3 Hz), 45.2 (q, *J* = 25.5 Hz), 54.6, 71.3 (m), 125.26 (q, *J* = 280.7 Hz), 125.30, 128.2, 128.8, 129.0, 129.7, 131.5, 133.9, 135.6, 164.8, 166.4, 193.4; ^{19}F NMR (376 MHz, $CDCl_3$) δ −64.2; IR (film) ν 2137, 1750, 1694, 1450, 1259, 1217, 1136 cm^{-1}; HRMS (ESI-TOF) *m*/*z* $[M + H]^+$ calcd for $C_{20}H_{17}F_3NO_3$ 376.1161; found 376.1164.

*(2R,3S)-Methyl 2-(4-Fluorophenyl)-2-isocyano-5-oxo-5-phenyl-3-(trifluoromethyl)pentanoate (**4b**):* Colorless oil; yield 53.1 mg (90%); $[\alpha]_D^{25}$ +69.6 (*c* 1.00, CH_2Cl_2) (96% ee); the ee was determined by HPLC analysis with a Chiralcel OD-H column (98/2 hexane/*i*-PrOH; 0.5 mL/min; λ = 254 nm; t_{major} = 28.80 min, t_{minor} = 21.76 min); >20:1 dr; ^1H NMR ($CDCl_3$, 400 MHz) δ 3.05 (dt, *J* = 18.4, 1.6 Hz, 1H), 3.74 (dd, *J* = 18.0, 8.0 Hz, 1H), 3.75 (s, 3H), 4.62 (qd, *J* = 8.0, 1.2 Hz, 1H), 7.15 (t, *J* = 8.4 Hz, 2H), 7.52 (t, *J* = 7.6 Hz, 2H), 7.62−7.67 (m, 3H), 8.02 (d, *J* = 7.2 Hz, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 36.1 (q, *J* = 1.5 Hz), 45.2 (q, *J* = 25.4 Hz), 54.8, 70.8 (m), 116.1 (d, *J* = 22.5 Hz), 125.2 (q, *J* = 280.4 Hz), 127.3 (d, *J* = 2.5 Hz), 127.5 (d, *J* = 7.8 Hz), 128.2, 128.9, 134.0, 135.5, 163.3 (d, *J* = 249.0 Hz), 165.2, 166.3, 193.3; ^{19}F NMR ($CDCl_3$, 376 MHz) δ −111.5, −64.1; IR (film) ν 2139, 1751, 1694, 1510, 1259, 1166, 1136 cm^{-1}; HRMS (ESI-TOF) *m*/*z* $[M + H]^+$ calcd for $C_{20}H_{16}F_4NO_3$ 394.1066; found 394.1066.

*(2R,3S)-Methyl 2-(4-Chlorophenyl)-2-isocyano-5-oxo-5-phenyl-3-(trifluoromethyl)pentanoate (**4c**):* White solid; yield 51.4 mg (83%); mp 87.2−88.0 °C; $[\alpha]_D^{25}$ +114.9 (*c* 1.00, CH_2Cl_2) (96% ee); the ee was determined by HPLC analysis with a Chiralcel OD-H column (98/2 hexane/*i*-PrOH; 0.5 mL/min; λ = 254 nm; t_{major} = 29.67 min, t_{minor} = 21.46 min); >20:1 dr; ^1H NMR ($CDCl_3$, 400 MHz) δ 3.05 (dt, *J* = 18.4, 1.6 Hz, 1H), 3.74 (dd, *J* = 18.4, 7.6 Hz, 1H), 3.75 (s, 3H), 4.62 (qd, *J* = 8.0, 2.0 Hz, 1H), 7.44 (dt, *J* = 8.8, 2.0 Hz, 2H), 7.52 (t, *J* = 8.0 Hz, 2H), 7.61 (d, *J* = 8.8 Hz, 2H), 7.64 (t, *J* = 7.2 Hz, 1H), 8.02 (dd, *J* = 8.8, 1.6 Hz, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 36.1 (q, *J* = 1.5 Hz), 45.1 (q, *J* = 25.8 Hz), 54.8, 70.9 (m), 125.2 (q, *J* = 280.9 Hz), 126.9, 128.2, 128.9, 129.2, 130.1, 134.0, 135.5, 136.0, 165.3, 166.1, 193.2; ^{19}F NMR ($CDCl_3$, 376 MHz) δ −64.1; IR (film) ν 2138, 1751, 1694, 1493, 1261, 1217, 1170, 1134 cm^{-1}; HRMS (ESI-TOF) *m*/*z* $[M + H]^+$ calcd for $C_{20}H_{16}ClF_3NO_3$ 410.0771; found 410.0764.

*(2R,3S)-Methyl 2-(4-Bromophenyl)-2-isocyano-5-oxo-5-phenyl-3-(trifluoromethyl)pentanoate (**4d**):* White solid; yield 68.0 mg (86%); mp 109.8−110.6 °C; $[\alpha]_D^{25}$ +74.3 (*c* 1.00, CH_2Cl_2) (96% ee); the ee was determined by HPLC analysis with a Chiralcel OD-H column (98/2 hexane/*i*-PrOH; 0.5 mL/min; λ = 254 nm; t_{major} = 31.08 min, t_{minor} = 22.38 min); >20:1 dr; ^1H NMR ($CDCl_3$, 400 MHz) δ 3.07 (d, *J* = 18.4 Hz, 1H), 3.738 (s, 3H), 3.740 (dd, *J* = 18.4, 8.0 Hz, 1H), 4.62 (qd, *J* = 8.0, 1.2 Hz, 1H), 7.50−7.65 (m, 7H), 8.02 (d, *J* = 7.6 Hz, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 36.0 (q, *J* = 1.5 Hz), 45.0 (q, *J* = 25.8 Hz), 54.8, 70.9 (m), 124.1, 125.1 (q, *J* = 280.9 Hz), 127.1, 128.2, 128.8, 130.6, 132.2, 133.9, 135.4, 165.4, 166.0, 193.2; ^{19}F NMR ($CDCl_3$, 376 MHz) δ −64.1; IR (film) ν 2138, 1753, 1693, 1262, 1218, 1169, 1137 cm^{-1}; HRMS (ESI-TOF) *m*/*z* $[M + H]^+$ calcd for $C_{20}H_{16}BrF_3NO_3$ 454.0266; found 454.0270.

DOI: 10.1021/acs.joc.5b01829
J. Org. Chem. 2015, 80, 11330−11338

*(2R,3S)-Methyl 2-Isocyano-5-oxo-5-phenyl-2-(p-tolyl)-3-(trifluoromethyl)pentanoate (**4e**):* White solid; yield 30.0 mg (51%); mp 98.7−99.2 °C; $[\alpha]_D^{25}$ +86.5 (*c* 1.00, CH_2Cl_2) (96% ee); the ee was determined by HPLC analysis with a Chiralcel OD-H column (99/1 hexane/*i*-PrOH; 0.8 mL/min; λ = 254 nm; t_{major} = 21.42 min, t_{minor} = 14.67 min); >20:1 dr; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.38 (s, 3H), 3.05 (d, *J* = 18.4 Hz, 1H), 3.73 (s, 3H), 3.74 (dd, *J* = 18.4, 8.0 Hz, 1H), 4.63 (qd, *J* = 8.0, 1.6 Hz, 1H), 7.25 (d, *J* = 8.4 Hz, 2H), 7.52 (t, 4H, *J* = 8.0 Hz, 4H), 7.63 (t, *J* = 7.2 Hz, 1H), 8.02 (d, *J* = 7.6 Hz, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 21.0, 36.2 (q, *J* = 1.5 Hz), 45.1 (q, *J* = 25.5 Hz), 54.6, 71.2 (m), 125.2, 125.3 (q, *J* = 280.0 Hz), 128.2, 128.6, 128.8, 129.7, 133.9, 135.6, 139.8, 164.5, 166.6, 193.5; ^{19}F NMR ($CDCl_3$, 376 MHz) δ −64.1; IR (film) ν 2139, 1750, 1695, 1260, 1167, 1129 cm^{-1}; HRMS (ESI-TOF) *m*/*z* [M + H]$^+$ calcd for $C_{21}H_{19}F_3NO_3$ 390.1317; found 390.1317.

*(2R,3S)-Methyl 2-Isocyano-2-(4-methoxyphenyl)-5-oxo-5-phenyl-3-(trifluoromethyl)pentanoate (**4f**):* Colorless oil; yield 49.5 mg (45%); $[\alpha]_D^{25}$ +60.2 (*c* 1.00, CH_2Cl_2) (97% ee); the ee was determined by HPLC analysis with a Chiralcel OD-H column (98/2 hexane/*i*-PrOH; 0.5 mL/min; λ = 254 nm; t_{major} = 37.10 min, t_{minor} = 28.36 min); >20:1 dr; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 3.03 (dt, *J* = 18.4, 1.6 Hz, 1H), 3.735 (dd, *J* = 18.4, 8.0 Hz, 1H), 3.737 (s, 3H), 3.83 (s, 3H), 4.60 (qd, *J* = 8.0, 1.6 Hz, 1H), 6.95 (d, *J* = 8.8 Hz, 2H), 7.51 (t, *J* = 8.0 Hz, 2H), 7.56 (d, *J* = 9.2 Hz, 2H), 7.63 (t, *J* = 7.2 Hz, 1H), 8.02 (d, *J* = 7.2 Hz, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 36.1 (q, *J* = 1.5 Hz), 45.1 (q, *J* = 25.9 Hz), 54.6, 55.3, 70.9 (m), 114.2, 123.3, 125.3 (q, *J* = 280.5 Hz), 126.7, 128.2, 128.8, 133.9, 135.6, 160.4, 164.3, 166.6, 193.5; ^{19}F NMR ($CDCl_3$, 376 MHz) δ −64.2; IR (film) ν 2143, 1751, 1693, 1513, 1258, 1181, 1168 cm^{-1}; HRMS (ESI-TOF) *m*/*z* [M + H]$^+$ calcd for $C_{21}H_{19}F_3NO_4$ 406.1266; found 406.1267.

*(2R,3S)-Methyl 2-(3-Fluorophenyl)-2-isocyano-5-oxo-5-phenyl-3-(trifluoromethyl)pentanoate (**4g**):* White solid; yield 53.9 mg (91%); mp 75.6−76.2 °C; $[\alpha]_D^{25}$ +94.1 (*c* 1.00, CH_2Cl_2) (95% ee); the ee was determined by HPLC analysis with a Chiralcel OD-H column (99/1 hexane/*i*-PrOH; 0.5 mL/min; λ = 254 nm; t_{major} = 34.96 min, t_{minor} = 24.46 min); >20:1 dr; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 3.06 (dt, *J* = 18.4, 1.6 Hz, 1H), 3.74 (dd, *J* = 18.4, 7.6 Hz 1H), 3.76 (s, 3H), 4.63 (qd, *J* = 8.0, 1.6 Hz, 1H), 7.12−7.16 (m, 1H), 7.40−7.48 (m, 3H), 7.52 (t, *J* = 7.6 Hz, 2H), 7.64 (t, *J* = 7.6 Hz, 1H), 8.02 (d, *J* = 7.6 Hz, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 36.1 (q, *J* = 1.5 Hz), 45.2 (q, *J* = 26.2 Hz), 54.8, 70.9 (m), 113.1 (d, *J* = 24.8 Hz), 116.8 (d, *J* = 21.2 Hz), 121.1 (d, *J* = 2.9 Hz), 125.0 (q, *J* = 280.1 Hz), 128.2, 128.9, 130.7 (d, *J* = 8.0 Hz), 133.96, 133.99 (d, *J* = 7.5 Hz), 135.5, 162.8 (d, *J* = 246.5 Hz), 165.4, 166.0, 193.2; ^{19}F NMR ($CDCl_3$, 376 MHz) δ −110.6, −64.3; IR (film) ν 2139, 1752, 1695, 1596, 1449, 1264, 1170, 1135 cm^{-1}; HRMS (ESI-TOF) *m*/*z* [M + H]$^+$ calcd for $C_{20}H_{16}F_4NO_3$ 394.1066; found 394.1061.

*(2R,3S)-Methyl 2-Isocyano-5-oxo-5-phenyl-2-(m-tolyl)-3-(trifluoromethyl)pentanoate (**4h**):* Colorless oil; yield 35.8 mg (61%); $[\alpha]_D^{25}$ +112.7 (*c* 1.00, CH_2Cl_2) (97% ee); the ee was determined by HPLC analysis with a Chiralcel OD-H column (98/2 hexane/*i*-PrOH; 0.5 mL/min; λ = 254 nm; t_{minor} = 16.14 min, t_{major} = 21.23 min); >20:1 dr; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.41 (s, 3H), 3.07 (d, *J* = 18.4 Hz, 1H), 3.74 (s, 3H), 3.75 (dd, *J* = 18.4, 8.0 Hz, 1H), 4.64 (quint, *J* = 7.6 Hz, 1H), 7.24 (t, *J* = 7.6 Hz, 1H), 7.34 (t, *J* = 7.6 Hz, 1H), 7.45 (s, 2H), 7.52 (t, *J* = 7.2 Hz, 2H), 7.63 (t, *J* = 7.2 Hz, 1H), 8.03 (d, *J* = 7.6 Hz, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 21.5, 36.2 (q, *J* = 1.5 Hz), 45.1 (q, *J* = 25.6 Hz), 54.6, 71.3 (m), 122.4, 125.3 (q, *J* = 280.8 Hz), 125.7, 128.2, 128.82, 128.84, 130.4, 131.4, 133.8, 135.6, 138.9, 164.5, 166.5, 193.5; ^{19}F NMR ($CDCl_3$, 376 MHz) δ −64.2; IR (film) ν 2138, 1750, 1695, 1450, 1255, 1224, 1168, 1135 cm^{-1}; HRMS (ESI-TOF) *m*/*z* [M + H]$^+$ calcd for $C_{21}H_{19}F_3NO_3$ 390.1317; found 390.1317.

*(2R,3S)-Benzyl 2-Isocyano-5-oxo-2,5-diphenyl-3-(trifluoromethyl)pentanoate (**4j**):* Colorless oil; yield 55.1 mg (82%); $[\alpha]_D^{25}$ +61.6 (*c* 1.00, CH_2Cl_2) (98% ee); the ee was determined by HPLC analysis with a Chiralcel OD-H column (98/2 hexane/*i*-PrOH; 0.5 mL/min; λ = 254 nm; t_{major} = 32.39 min, t_{minor} = 25.60 min); >20:1 dr; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.95 (dt, *J* = 18.4, 1.6 Hz, 1H), 3.69 (dd, *J* = 18.4, 8.0 Hz, 1H), 4.67 (qd, *J* = 8.0, 1.6 Hz, 1H), 5.15 (s, 2H), 7.16−7.20 (m, 5H), 7.41−7.43 (m, 3H), 7.50 (t, *J* = 7.6 Hz, 2H), 7.61−7.66 (m, 3H), 7.94 (d, *J* = 7.6 Hz, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 36.1 (q, *J* = 2.1 Hz), 44.9 (q, *J* = 26.0 Hz), 69.4, 71.5 (m), 125.2 (q, *J* = 282.1 Hz), 125.3, 128.17, 128.18, 128.5, 128.6, 128.7, 128.9, 129.1, 129.6, 131.3, 133.8, 135.5, 164.8, 165.6, 193.2; ^{19}F NMR ($CDCl_3$, 376 MHz) δ −64.2; IR (film) ν 2138, 1751, 1694, 1451, 1373, 1266, 1221, 1168, 1136 cm^{-1}; HRMS (ESI-TOF) *m*/*z* [M + H]$^+$ calcd for $C_{26}H_{21}F_3NO_3$ 452.1474; found 452.1470.

*(2R,3S)-tert-Butyl 2-Isocyano-5-oxo-2,5-diphenyl-3-(trifluoromethyl)pentanoate (**4k**):* White solid; yield 58.7 mg (97%); mp 66.7−67.1 °C; $[\alpha]_D^{25}$ +76.4 (*c* 1.00, CH_2Cl_2) (99% ee); the ee was determined by HPLC analysis with a Chiralpak AD-H column (99/1 hexane/*i*-PrOH; 0.5 mL/min; λ = 254 nm; t_{minor} = 38.45 min, t_{major} = 25.72 min); >20:1 dr; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.34 (s, 9H), 3.07 (dt, *J* = 18.4, 1.6 Hz, 1H), 3.74 (dd, *J* = 18.4, 7.6 Hz, 1H), 4.63 (qd, *J* = 8.0, 1.6 Hz, 1H), 7.39−7.47 (m, 3H), 7.52 (t, *J* = 8.0 Hz, 2H), 7.61−7.69 (m, 3H), 8.03 (d, *J* = 8.4 Hz, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 27.2, 36.1 (q, *J* = 1.5 Hz), 44.6 (q, *J* = 25.9 Hz), 72.1 (m), 85.8, 125.2, 125.4 (q, *J* = 280.6 Hz), 128.1, 128.8, 128.9, 129.4, 132.0, 133.8, 135.6, 164.0, 164.2, 193.6; ^{19}F NMR ($CDCl_3$, 376 MHz) δ −64.4; IR (film) ν 2138, 1751, 1695, 1450, 1372, 1266, 1217, 1167, 1136 cm^{-1}; HRMS (ESI-TOF) *m*/*z* [M + H]$^+$ calcd for $C_{23}H_{23}F_3NO_3$ 418.1630; found 418.1619.

*(2R,3S)-Methyl 5-(4-Chlorophenyl)-2-isocyano-5-oxo-2-phenyl-3-(trifluoromethyl)pentanoate (**4m**):* White solid; yield 52.0 mg (85%); mp 104.5−105.1 °C; $[\alpha]_D^{25}$ +107.2 (*c* 1.00, CH_2Cl_2) (97% ee); the ee was determined by HPLC analysis with a Chiralcel OD-H column (98/2 hexane/*i*-PrOH; 0.5 mL/min; λ = 254 nm; t_{major} = 56.15 min, t_{minor} = 23.48 min); >20:1 dr; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 3.05 (d, *J* = 18.4 Hz, 1H), 3.72 (dd, *J* = 18.4, 7.6 Hz, 1H), 3.74 (s, 3H), 4.63 (quint, *J* = 7.6 Hz, 1H), 7.41−7.49 (m, 5H), 7.65 (d, *J* = 7.6 Hz, 2H), 7.96 (d, *J* = 8.4 Hz, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 36.2 (q, *J* = 1.4 Hz), 45.1 (q, *J* = 25.8 Hz), 54.7, 71.2 (m), 125.17 (q, *J* = 281.6 Hz), 125.22, 129.0, 129.1, 129.6, 129.7, 131.4, 133.8, 140.4, 164.8, 166.4, 192.3; ^{19}F NMR ($CDCl_3$, 376 MHz) δ −64.2; IR (film) ν 2138, 1750, 1697, 1591, 1259, 1169, 1137, 1094 cm^{-1}; HRMS (ESI-TOF) *m*/*z* [M + H]$^+$ calcd for $C_{20}H_{16}ClF_3NO_3$ 410.0771; found 410.0774.

*(2R,3S)-Methyl 2-Isocyano-5-(4-nitrophenyl)-5-oxo-2-phenyl-3-(trifluoromethyl)pentanoate (**4n**):* Colorless oil; yield 54.6 mg (87%); $[\alpha]_D^{25}$ +60.6 (*c* 1.00, CH_2Cl_2) (89% ee); the ee was determined by HPLC analysis with a Chiralcel OD-H column (80/20 hexane/*i*-PrOH; 0.8 mL/min; λ = 254 nm; t_{major} = 55.65 min, t_{minor} = 20.26 min); >20:1 dr; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 3.11 (dt, *J* = 18.0, 1.6 Hz, 1H), 3.76 (s, 3H), 3.77 (dd, *J* = 18.4, 8.0 Hz, 1H), 4.59 (qd, *J* = 8.0, 1.6 Hz, 1H), 7.42−7.50 (m, 3H), 7.63 (dd, *J* = 8.0, 1.6 Hz, 2H), 8.18 (d, *J* = 8.8 Hz, 2H), 8.36 (d, *J* = 8.8 Hz, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 36.8 (q, *J* = 1.5 Hz), 45.3 (q, *J* = 25.8 Hz), 54.8, 71.1 (m), 124.1, 125.1 (q, *J* = 280.7 Hz), 125.2, 129.1, 129.3, 129.8, 131.3, 140.0, 150.7, 165.1, 166.5, 192.3; ^{19}F NMR ($CDCl_3$, 376 MHz) δ −64.2; IR (film) ν 2137, 1749, 1702, 1529, 1347, 1258, 1169, 1137 cm^{-1}; HRMS (ESI-TOF) *m*/*z* [M − H]$^+$ calcd for $C_{20}H_{14}F_3N_2O_5$ 419.0855; found 419.0860.

*(2R,3S)-Methyl 2-Isocyano-5-oxo-2-phenyl-5-(p-tolyl)-3-(trifluoromethyl)pentanoate (**4o**):* White solid; yield 45.1 mg (77%); mp 111.4−111.9 °C; $[\alpha]_D^{25}$ +99.1 (*c* 1.00, CH_2Cl_2) (96% ee); the ee was determined by HPLC analysis with a Chiralcel OD-H column (98/2 hexane/*i*-PrOH; 0.5 mL/min; λ = 254 nm; t_{major} = 27.27 min, t_{minor} = 18.46 min); >20:1 dr; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.44 (s, 3H), 3.04 (dt, *J* = 18.0, 1.6 Hz, 1H), 3.72 (dd, *J* = 18.4, 7.6 Hz, 1H), 3.73 (s, 3H), 4.65 (qd, *J* = 18.4, 7.6 Hz, 1H), 7.31 (d, *J* = 8.0 Hz, 2H), 7.41−7.48 (m, 3H), 7.68 (d, *J* = 8.4 Hz, 2H), 7.92 (d, *J* = 8.0 Hz, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 21.7, 36.0 (q, *J* = 1.5 Hz), 45.1 (q, *J* = 25.8 Hz), 54.6, 71.4 (m), 125.26 (q, *J* = 280.9 Hz), 125.30, 128.3, 129.0, 129.5, 129.6, 131.5, 133.1, 144.9, 164.6, 166.4, 192.9; ^{19}F NMR ($CDCl_3$, 376 MHz) δ −64.1; IR (film) ν 2138, 1751, 1689, 1607, 1451, 1254, 1168, 1136 cm^{-1}; HRMS (ESI-TOF) *m*/*z* [M + Na]$^+$ calcd for $C_{21}H_{18}F_3NNaO_3$ 412.1136; found 412.1141.

*(2R,3S)-Methyl 2-Isocyano-5-(4-methoxyphenyl)-5-oxo-2-phenyl-3-(trifluoromethyl)pentanoate (**4p**):* Colorless oil; yield 30.4 mg (50%); $[\alpha]_D^{25}$ +79.9 (*c* 1.00, CH_2Cl_2) (97% ee); the ee was

DOI: 10.1021/acs.joc.5b01829
J. Org. Chem. 2015, 80, 11330−11338

determined by HPLC analysis with a Chiralcel OD-H column (95/5 hexane/*i*-PrOH; 0.5 mL/min; λ = 254 nm; t_{major} = 33.48 min, t_{minor} = 24.00 min); >20:1 dr; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 3.01 (dt, J = 18.8, 1.6 Hz, 1H), 3.69 (dd, J = 18.0, 8.0 Hz, 1H), 3.73 (s, 3H), 3.89 (s, 3H), 4.65 (qd, J = 7.6, 1.6 Hz, 1H), 6.98 (d, J = 8.8 Hz, 2H), 7.40−7.48 (m, 3H), 7.66 (d, J = 6.8 Hz, 2H), 8.00 (d, J = 9.2 Hz, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 35.7 (q, J = 1.5 Hz), 45.2 (q, J = 26.0 Hz), 54.6, 55.5, 71.4 (m), 114.0, 125.3 (q, J = 280.9 Hz), 125.4, 128.6, 129.0, 129.6, 130.6, 131.6, 164.1, 164.7, 166.4, 191.8; ^{19}F NMR ($CDCl_3$, 376 MHz) δ −64.2; IR (film) ν 2138, 1750, 1683, 1601, 1451, 1260, 1171, 1135 cm^{-1}; HRMS (ESI-TOF) m/z [M + Na]$^+$ calcd for $C_{21}H_{18}F_3NNaO_4$ 428.1086; found 428.1078.

*(2R,3S)-Methyl 5-(3-Bromophenyl)-2-isocyano-5-oxo-2-phenyl-3-(trifluoromethyl)pentanoate (**4q**):* White solid; yield 54.2 mg (80%); mp 114.3−114.9 °C; $[\alpha]_D^{25}$ +47.1 (c 1.00, CH_2Cl_2) (97% ee); the ee was determined by HPLC analysis with a Chiralpak AS-H column (95/5 hexane/*i*-PrOH; 0.8 mL/min; λ = 254 nm; t_{major} = 14.63 min, t_{minor} = 16.60 min); >20:1 dr; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 3.04 (dt, J = 18.4, 1.6 Hz, 1H), 3.70 (dd, J = 18.4, 8.0 Hz, 1H), 3.76 (s, 3H), 4.61 (qd, J = 8.0, 1.6 Hz, 1H), 7.38−7.49 (m, 4H), 7.75 (d, J = 8.0 Hz, 2H), 7.75 (d, J = 8.0 Hz, 1H), 7.94 (d J = 7.6 Hz, 1H), 8.13 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 36.3 (q, J = 2.2 Hz), 45.1 (q, J = 26.2 Hz), 54.7, 71.2 (m), 123.2, 125.2 (q, J = 280.7 Hz), 125.3, 126.7, 129.1, 129.7, 130.4, 131.2, 131.4, 136.7, 137.3, 164.9, 166.4, 192.2; ^{19}F NMR ($CDCl_3$, 376 MHz) δ −64.2; IR (film) ν 2138, 1749, 1699, 1451, 1254, 1169, 1137 cm^{-1}; HRMS (ESI-TOF) m/z [M + Na]$^+$ calcd for $C_{20}H_{15}BrF_3NNaO_3$ 476.0085; found 476.0090.

*(2R,3S)-Methyl 2-Isocyano-5-oxo-2-phenyl-5-(m-tolyl)-3-(trifluoromethyl)pentanoate (**4r**):* Colorless oil; yield 41.8 mg (72%); $[\alpha]_D^{25}$ +101.0 (c 1.00, CH_2Cl_2) (97% ee); the ee was determined by HPLC analysis with a Chiralcel OD-H column (98/2 hexane/*i*-PrOH; 0.5 mL/min; λ = 254 nm; t_{major} = 22.16 min, t_{minor} = 17.50 min); >20:1 dr; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.45 (s, 3H), 3.03 (dt, J = 18.0, 1.2 Hz, 1H), 3.73 (dd, J = 18.0, 8.0 Hz, 1H), 3.74 (s, 3H), 4.66 (qd, J = 8.0, 2.0 Hz, 1H), 7.50−7.38 (m, 5H), 7.67 (dd, J = 8.4, 1.6 Hz, 2H), 7.81−7.83 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 21.3, 36.3 (q, J = 2.1 Hz), 45.1 (q, J = 26.3 Hz), 54.6, 71.4 (m), 125.25 (q, J = 275.4 Hz), 125.32, 125.4, 128.7, 129.0, 129.2, 129.7, 131.6, 134.6, 135.6, 138.7, 164.7, 166.4, 193.5; ^{19}F NMR ($CDCl_3$, 376 MHz) δ −64.2; IR (film) ν 2138, 1750, 1692, 1451, 1268, 1166, 1136 cm^{-1}; HRMS (ESI-TOF) m/z [M + Na]$^+$ calcd for $C_{21}H_{18}F_3NNaO_3$ 412.1136; found 412.1140.

*(2R,3S)-Methyl 2-Isocyano-5-oxo-2-phenyl-5-(o-tolyl)-3-(trifluoromethyl)pentanoate (**4s**):* Colorless oil; yield 31.7 mg (54%); $[\alpha]_D^{25}$ +43.6 (c 1.00, CH_2Cl_2) (92% ee); the ee was determined by HPLC analysis with a Chiralcel OD-H column (98/2 hexane/*i*-PrOH; 0.5 mL/min; λ = 254 nm; t_{major} = 20.27 min, t_{minor} = 15.73 min); 18:1 dr; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.25 (s, 3H), 2.63 (ddt, J = 18.4, 2.4, 0.8 Hz, 1H), 3.24 (dd, J = 18.4, 6.8 Hz, 1H), 3.76 (s, 3H), 4.65 (qd, J = 7.6, 2.8 Hz, 1H), 7.11 (d, J = 7.6 Hz, 2H), 7.19 (dd, J = 6.8, 1.2 Hz, 1H), 7.25−7.35 (m, 4H), 7.61 (dt, J = 6.8, 1.6 Hz, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 21.0, 36.6 (q, J = 1.5 Hz), 45.0 (q, J = 26.3 Hz), 54.4, 70.0 (m), 125.6 (q, J = 281.3 Hz), 125.7, 125.9, 128.1, 129.3, 129.9, 131.6, 131.96, 131.98, 136.1, 138.4, 165.5, 166.4, 197.4; ^{19}F NMR ($CDCl_3$, 376 MHz) δ −65.9; IR (film) ν 2147, 1752, 1693, 1453, 1436, 1254, 1168, 1136 cm^{-1}; HRMS (ESI-TOF) m/z [M + Na]$^+$ calcd for $C_{21}H_{18}F_3NNaO_3$ 412.1136; found 412.1133.

*(2R,3S)-Methyl 5-(Furan-2-yl)-2-isocyano-5-oxo-2-phenyl-3-(trifluoromethyl)pentanoate (**4t**):* Colorless oil; yield 39.1 mg (71%); $[\alpha]_D^{25}$ +68.8 (c 1.00, CH_2Cl_2) (79% ee); the ee was determined by HPLC analysis with a Chiralcel OD-H column (95/5 hexane/*i*-PrOH; 0.5 mL/min; λ = 254 nm; t_{major} = 27.96 min, t_{minor} = 22.30 min); >20:1 dr; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.97 (dt, J = 18.0, 1.6 Hz, 1H), 3.62 (dd, J = 18.4, 8.0 Hz, 1H), 3.74 (s, 3H), 4.53 (qd, J = 8.0, 2.0 Hz 1H), 6.59 (dd, J = 3.6, 1.6 Hz, 1H), 7.31 (d, J = 3.6 Hz, 1H), 7.41−7.47 (m, 3H), 7.63−7.65 (m, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 35.9 (q, J = 1.6 Hz), 44.7 (q, J = 25.9 Hz), 54.6, 71.2 (m), 112.7, 117.9, 125.1 (q, J = 280.6 Hz), 125.3, 129.0, 129.6, 131.4, 147.0, 151.5, 164.9, 166.3, 182.6; ^{19}F NMR ($CDCl_3$, 376 MHz) δ −64.3; IR (film) ν 2137, 17512, 1678, 1570, 1468, 1369, 1265, 1082 cm^{-1}; HRMS (EI-TOF) m/z [M]$^+$ calcd for $C_{18}H_{14}F_3NO_4$ 365.0875; found 365.0876.

*(2R,3S)-Methyl 2-Isocyano-5-oxo-2-phenyl-5-(thiophen-2-yl)-3-(trifluoromethyl)pentanoate (**4u**):* Colorless oil; yield 44.7 mg (74%); $[\alpha]_D^{25}$ + 74.0 (c 1.00, CH_2Cl_2) (86% ee); the ee was determined by HPLC analysis with a Chiralcel OD-H column (95/5 hexane/*i*-PrOH; 0.5 mL/min; λ = 254 nm; t_{major} = 30.82 min, t_{minor} = 22.34 min); >20:1 dr; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 3.05 (dt, J = 18.4, 1.6 Hz, 1H), 3.65 (dd, J = 18.4, 8.0 Hz, 1H), 3.75 (s, 3H), 4.57 (qd, J = 8.0, 2.0 Hz, 1H), 7.18 (dd, J = 4.8, 4.0 Hz, 1H), 7.40−7.48 (m, 3H), 7.64−7.66 (m, 2H), 7.72 (dd, J = 4.8, 1.2 Hz, 1H), 7.83 (dd, J = 4.0, 1.2 Hz, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 36.7 (q, J = 1.5 Hz), 45.2 (q, J = 25.9 Hz), 54.6, 71.2 (m), 125.2 (q, J = 280.7 Hz), 125.3, 128.3, 129.0, 129.7, 131.4, 132.5, 134.8, 142.5, 164.9, 166.3, 186.3; ^{19}F NMR ($CDCl_3$, 376 MHz) δ −64.1; IR (film) ν 2137, 1747, 1672, 1414, 1369, 1254, 1171, 1136 cm^{-1}; HRMS (EI-TOF) m/z [M]$^+$ calcd for $C_{18}H_{14}F_3NO_3S$ 381.0646; found 381.0646.

Procedure for the Synthesis of 5a from 4a. To the solution of adduct **4a** (56.3 mg, 0.15 mmol) in EtOH (2.0 mL) was added concentrated HCl (0.5 mL), and the resulting solution was stirred at room temperature for 3 h until the reaction completed (monitored by TLC). After concentration, the residue was made alkaline with NH_4OH (pH >7), and the resulting mixture was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layers were washed with brine, dried over Na_2SO_4, filtered, concentrated, and purified by silica gel chromatography (petroleum ether/ethyl acetate = 15:1, v/v) to give the β-trifluoromethylated pyrroline **5a**.

*(2R,3S)-Methyl 2,5-Diphenyl-3-(trifluoromethyl)-3,4-dihydro-2H-pyrrole-2-carboxylate (**5a**):* White solid; yield 42.2 mg (81%); mp 89.7−90.4 °C; $[\alpha]_D^{25}$ +174.6 (c 1.00, CH_2Cl_2) (96% ee); the ee was determined by HPLC analysis with a Chiralcel OD-H column (98/2 hexane/*i*-PrOH; 0.5 mL/min; λ = 254 nm; t_{major} = 15.39 min, t_{minor} = 20.42 min); >20:1 dr; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 3.36 (dd, J = 17.6, 6.0 Hz, 1H), 3.49 (dd, J = 17.6, 9.6 Hz, 1H), 3.79 (s, 3H), 4.29 (qd, J = 9.6, 3.6 Hz, 1H), 7.28−7.38 (m, 5H), 7.47−7.57 (m, 3H), 8.01 (d, J = 8.4 Hz, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 37.2 (q, J = 1.8 Hz), 48.0 (q, J = 26.5 Hz), 53.5, 86.5 (m), 125.9 (q, J = 277.0 Hz), 127.0, 128.1, 128.21, 128.22, 128.7, 131.9, 132.6, 135.9, 172.3, 173.4; ^{19}F NMR ($CDCl_3$, 376 MHz) δ −65.5; IR (film) ν 1732, 1620, 1449, 1350, 1245, 1178, 1148, 1116 cm^{-1}; HRMS (ESI-TOF) m/z [M + H]$^+$ calcd for $C_{19}H_{17}F_3NO_2$ 348.1211; found 348.1220.

One-pot Synthesis of β-Trifluoromethylated Pyrrolines 5 by Asymmetric Michael Addition Reaction of Isocyanoacetates 1 with β-Trifluoromethylated Enones 2 and Subsequent Isocyano Group Hydrolysis/Cyclization/Dehydration Cascade Reaction. To the solution of isocyanoacetates **1** (0.15 mmol) and β-trifluoromethylated enones **2** (0.30 mmol) in $CHCl_3$ (1.0 mL) was added **3f** (19.0 mg, 0.03 mmol). The resulting mixture was stirred at 0 °C for 7 days until the reaction completed (monitored by TLC). After concentration, the residue was dissolved in EtOH (2.0 mL) and treated with concentrated HCl (0.5 mL) at room temperature for 3 h. After concentration, the residue was made alkaline with NH_4OH (pH >7), and the resulting mixture was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layers were washed with brine, dried over Na_2SO_4, filtered, concentrated, and purified by silica gel chromatography (petroleum ether/ethyl acetate = 15:1, v/v) to give the β-trifluoromethylated pyrrolines **5**.

*(2R,3S)-Methyl 2,5-Diphenyl-3-(trifluoromethyl)-3,4-dihydro-2H-pyrrole-2-carboxylate (**5a**):* Yield 35.5 mg (68%).

*(2R,3S)-Methyl 2-(4-Fluorophenyl)-5-phenyl-3-(trifluoromethyl)-3,4-dihydro-2H-pyrrole-2-carboxylate (**5b**):* Colorless oil; yield 34.0 mg (62%); $[\alpha]_D^{25}$ +159.3 (c 1.00, CH_2Cl_2) (96% ee); the ee was determined by HPLC analysis with a Chiralcel OD-H column (95/5 hexane/*i*-PrOH; 0.5 mL/min; λ = 254 nm; t_{major} = 11.51 min, t_{minor} = 16.98 min); >20:1 dr; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 3.36 (dd, J = 17.6, 5.6 Hz, 1H), 3.49 (dd, J = 17.6, 9.2 Hz, 1H), 3.78 (s, 3H), 4.29 (qd, J = 9.6, 4.0 Hz, 1H), 7.04 (t, J = 8.8 Hz, 2H), 7.29 (dd, J = 8.8, 5.6 Hz, 2H), 7.49 (t, J = 7.6 Hz, 2H), 7.55 (t, J = 7.6 Hz, 1H), 8.00 (dt, J = 8.4, 1.2 Hz, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 37.3 (q, J = 1.5 Hz), 48.0 (q, J = 26.3 Hz), 53.5, 86.0 (m), 115.1 (d, J = 21.5 Hz), 125.9 (q, J = 276.7 Hz), 128.2, 128.8, 128.9 (d, J = 8.5 Hz), 131.8 (d, J = 3.1

DOI: 10.1021/acs.joc.5b01829
J. Org. Chem. 2015, 80, 11330−11338

Hz), 132.0, 132.5, 162.6 (d, J = 245.7 Hz), 172.1, 173.6; ^{19}F NMR ($CDCl_3$, 376 MHz) δ −113.9, −65.6; IR (film) ν 1734, 1621, 1510, 1450, 1350, 1245, 1117 cm^{-1}; HRMS (ESI-TOF) m/z [M + H]$^+$ calcd for $C_{19}H_{16}F_4NO_2$ 366.1117; found 366.1114.

*(2R,3S)-Methyl 5-Phenyl-2-(p-tolyl)-3-(trifluoromethyl)-3,4-dihydro-2H-pyrrole-2-carboxylate (**5c**):* Colorless oil; yield 29.4 mg (54%); $[\alpha]_D^{25}$ +156.0 (c 1.00, CH_2Cl_2) (94% ee); the ee was determined by HPLC analysis with a Chiralcel OD-H column (95/5 hexane/*i*-PrOH; 0.5 mL/min; λ = 254 nm; t_{major} = 11.38 min, t_{minor} = 14.38 min); >20:1 dr; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.35 (s, 3H), 3.34 (dd, J = 17.6, 6.8 Hz, 1H), 3.47 (dd, J = 17.6, 9.2 Hz, 1H), 3.78 (s, 3H), 4.27 (qd, J = 9.6, 3.2 Hz, 1H), 7.12−7.18 (m, 4H), 7.46−7.55 (m, 3H), 8.01 (dt, J = 7.2, 1.2 Hz, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 21.1, 37.1 (q, J = 2.2 Hz), 48.0 (q, J = 26.4 Hz), 53.4, 86.4 (m), 126.0 (q, J = 276.0 Hz), 126.8, 128.2, 128.7, 128.8, 131.8, 132.7, 132.9, 137.9, 172.5, 173.2; ^{19}F NMR ($CDCl_3$, 376 MHz) δ −65.5; IR (film) ν 1732, 1621, 1514, 1350, 1278, 1245, 1179, 1115 cm^{-1}; HRMS (ESI-TOF) m/z [M + H]$^+$ calcd for $C_{20}H_{19}F_3NO_2$ 362.1368; found 362.1363.

*(2R,3S)-tert-Butyl 2,5-Diphenyl-3-(trifluoromethyl)-3,4-dihydro-2H-pyrrole-2-carboxylate (**5d**):* White solid; yield 47.9 mg (82%); mp 101.2−102.0 °C; $[\alpha]_D^{25}$ +132.6 (c 1.00, CH_2Cl_2) (98% ee); the ee was determined by HPLC analysis with a Chiralcel OD-H column (98/2 hexane/*i*-PrOH; 0.5 mL/min; λ = 254 nm; t_{major} = 8.94 min, t_{minor} = 12.26 min); >20:1 dr; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.46 (s, 9H), 3.34 (dd, J = 17.6, 6.4 Hz, 1H), 3.44 (dd, J = 17.6, 9.2 Hz, 1H), 4.23 (qd, J = 9.6, 3.2 Hz, 1H), 7.28−7.34 (m, 5H), 7.47−7.55 (m, 3H), 7.99−8.02 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 27.8, 37.2 (q, J = 2.1 Hz), 48.0 (q, J = 26.2 Hz), 82.9, 87.0 (m), 126.1 (q, J = 277.1 Hz), 127.2, 127.78, 127.82, 128.2, 128.6, 131.6, 133.0, 136.4, 170.7, 172.8; ^{19}F NMR ($CDCl_3$, 376 MHz) δ −65.4; IR (film) ν 1721, 1622, 1449, 1369, 1259, 1157, 1116 cm^{-1}; HRMS (ESI-TOF) m/z [M + H]$^+$ calcd for $C_{22}H_{23}F_3NO_2$ 390.1681; found 390.1673.

*(2R,3S)-Methyl 5-(4-Chlorophenyl)-2-phenyl-3-(trifluoromethyl)-3,4-dihydro-2H-pyrrole-2-carboxylate (**5e**):* White solid; yield 44.0 mg (77%); mp 113.4−114.5 °C; $[\alpha]_D^{25}$ +156.6 (c 1.00, CH_2Cl_2) (96% ee); the ee was determined by HPLC analysis with a Chiralcel OD-H column (98/2 hexane/*i*-PrOH; 0.5 mL/min; λ = 254 nm; t_{major} = 15.85 min, t_{minor} = 17.87 min); >20:1 dr; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 3.32 (dd, J = 17.6, 6.4 Hz, 1H), 3.45 (dd, J = 17.6, 9.2 Hz, 1H), 3.79 (s, 3H), 4.30 (qd, J = 9.6, 3.6 Hz, 1H), 7.27 (d, J = 7.2 Hz, 2H), 7.33−7.38 (m, 3H), 7.47 (d, J = 8.4 Hz, 2H), 7.94 (d, J = 8.8 Hz, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 37.1 (q, J = 2.1 Hz), 48.1 (q, J = 26.3 Hz), 53.5, 86.6 (m), 125.8 (q, J = 277.2 Hz), 126.9, 128.1, 128.3, 129.0, 129.5, 131.0, 135.7, 138.1, 172.1, 172.4; ^{19}F NMR ($CDCl_3$, 376 MHz) δ −65.6; IR (film) ν 1733, 1619, 1493, 1436, 1345, 1278, 1247, 1178, 1118, 1092 cm^{-1}; HRMS (ESI-TOF) m/z [M + H]$^+$ calcd for $C_{19}H_{16}ClF_3NO_2$ 382.0822; found 382.0820.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.5b01829.

Copies of NMR spectra and HPLC analysis spectra of compounds **4** and **5** (PDF)

X-ray structural data of compound **4q** (CIF)

■ AUTHOR INFORMATION

Corresponding Author

*Fax: +86-21-34201699. E-mail: mxzhao@ecust.edu.cn.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We are grateful for financial support from the National Natural Science Foundation of China (21072056, 21272067).

■ REFERENCES

(1) (a) *Fluorinated Heterocyclic Compounds: Synthesis, Chemistry, and Applications*; Petrov, V. A., Ed.; Wiley: Hoboken, NJ, 2009. (b) Muzalevskiy, V. M.; Shastin, A. V.; Balenkova, E. S.; Haufe, G.; Nenajdenko, V. G. *Synthesis* **2009**, *2009*, 3905. (c) Erian, A. W. *J. Heterocycl. Chem.* **2001**, *38*, 793. (d) Lin, P.; Jiang, J. *Tetrahedron* **2000**, *56*, 3635. (e) Silvester, M. J. *Adv. Heterocycl. Chem.* **1994**, *59*, 1. (f) Welch, J. T. *Tetrahedron* **1987**, *43*, 3123.

(2) For selected examples, see: (a) Vaillancourt, V.; Sheehan, S. M. K. PCT Int. Appl. WO 2013169622, 2013. (b) Aicher, D.; Wiehe, A.; Stark, C. B. W.; Albrecht, V.; Gräfe, S. U.S. Patent Appl. US 20130041307, 2013. (c) Aicher, D.; Wiehe, A.; Stark, C. B. W.; Albrecht, V.; Gräfe, S. PCT Int. Appl. WO 2012012809, 2012. (d) Aicher, D.; Albrecht, V.; Gitter, B.; Stark, C. B. W.; Wiehe, A. PCT Int. Appl. WO 2013015774, 2013. (e) Aicher, D.; Gräfe, S.; Stark, C. B.W.; Wiehe, A. *Bioorg. Med. Chem. Lett.* **2011**, *21*, 5808. (f) Hagen, T. J.; Bergmanis, A. A.; Kramer, S. W.; Fok, K. F.; Schmelzer, A. E.; Pitzele, B. S.; Swenton, L.; Jerome, G. M.; Kornmeier, C. M.; Moore, W. M.; Branson, L. F.; Connor, J. R.; Manning, P. T.; Currie, M. G.; Hallinan, E. A. *J. Med. Chem.* **1998**, *41*, 3675. (g) Hansen, D. W., Jr.; Hallinan, E. A.; Hagen, T. J.; Kramer, S. W.; Metz, S.; Peterson, K. B.; Spangler, D. P.; Toth, M. V.; Fok, K. F.; Bergmanis, A. A.; Webber, R. K.; Trivedi, M.; Tjoeng, F. S.; Pitzele, B. S. U.S. Patent Appl. US 6011028, 2000. (h) Shaitanova, E. N.; Gerus, I. I.; Kukhar, V. P. *Tetrahedron Lett.* **2008**, *49*, 1184. (i) Marrec, O.; Christophe, C.; Billard, T.; Langlois, B.; Vors, J.-P.; Pazenok, S. *Adv. Synth. Catal.* **2010**, *352*, 2825.

(3) (a) Kawai, H.; Sugita, Y.; Tokunaga, E.; Sato, H.; Shiro, M.; Shibata, N. *Chem. Commun.* **2012**, *48*, 3632. (b) Kawai, H.; Kitayama, T.; Tokunaga, E.; Matsumoto, T.; Sato, H.; Shiro, M.; Shibata, N. *Chem. Commun.* **2012**, *48*, 4067. (c) Kawai, H.; Okusu, S.; Tokunaga, E.; Sato, H.; Shiro, M.; Shibata, N. *Angew. Chem., Int. Ed.* **2012**, *51*, 4959. (d) Kawai, H.; Yuan, Z.; Kitayama, T.; Tokunaga, E.; Shibata, N. *Angew. Chem., Int. Ed.* **2013**, *52*, 5575.

(4) For a recent review on isocyanoacetates, see: Gulevich, A. V.; Zhdanko, A. G.; Orru, R. V. A.; Nenajdenko, V. G. *Chem. Rev.* **2010**, *110*, 5235.

(5) For selected examples, see: (a) Ito, Y.; Sawamura, M.; Hayashi, T. *J. Am. Chem. Soc.* **1986**, *108*, 6405. (b) Ito, Y.; Sawamura, M.; Hayashi, T. *Tetrahedron Lett.* **1987**, *28*, 6215. (c) Hayashi, T.; Sawamura, M.; Ito, Y. *Tetrahedron* **1992**, *48*, 1999. (d) Hayashi, T.; Uozumi, Y.; Yamazaki, A.; Sawamura, M.; Hamashima, H.; Ito, Y. *Tetrahedron Lett.* **1991**, *32*, 2799. (e) Xue, M.-X.; Guo, C.; Gong, L.-Z. *Synlett* **2009**, *2009*, 2191. (f) Sladojevich, F.; Trabocchi, A.; Guarna, A.; Dixon, D. J. *J. Am. Chem. Soc.* **2011**, *133*, 1710. (g) Kim, H. Y.; Oh, K. *Org. Lett.* **2011**, *13*, 1306. (h) Zhao, M.-X.; Zhou, H.; Tang, W.-H.; Qu, W.-S.; Shi, M. *Adv. Synth. Catal.* **2013**, *355*, 1277.

(6) (a) Zhou, X.-T.; Lin, Y.-R.; Dai, L.-X.; Sun, J.; Xia, L.-J.; Tang, M.-H. *J. Org. Chem.* **1999**, *64*, 1331. (b) Zhou, X.-T.; Lin, Y.-R.; Dai, L.-X. *Tetrahedron: Asymmetry* **1999**, *10*, 855. (c) Aydin, J.; Rydeń, A.; Szabó, K. J. *Tetrahedron: Asymmetry* **2008**, *19*, 1867. (d) Zhang, Z.-W.; Lu, G.; Chen, M.-M.; Lin, N.; Li, Y.-B.; Hayashi, T.; Chan, A. S. C. *Tetrahedron: Asymmetry* **2010**, *21*, 1715. (e) Nakamura, S.; Maeno, Y.; Ohara, M.; Yamamura, A.; Funahashi, Y.; Shibata, N. *Org. Lett.* **2012**, *14*, 2960. (f) Ortín, I.; Dixon, D. J. *Angew. Chem., Int. Ed.* **2014**, *53*, 3462. (g) Shao, P.-L.; Liao, J.-Y.; Ho, Y. A.; Zhao, Y. *Angew. Chem., Int. Ed.* **2014**, *53*, 5435. (h) Hayashi, M.; Iwanaga, M.; Shiomi, N.; Nakane, D.; Masuda, H.; Nakamura, S. *Angew. Chem., Int. Ed.* **2014**, *53*, 8411. (i) Zhao, M.-X.; Bi, H.-L.; Jiang, R.-H.; Xu, X.-W.; Shi, M. *Org. Lett.* **2014**, *16*, 4566.

(7) (a) Monge, D.; Jensen, K. L.; Marín, I.; Jørgensen, K. A. *Org. Lett.* **2011**, *13*, 328. (b) Wang, M.; Liu, X.; He, P.; Lin, L.; Feng, X. *Chem. Commun.* **2013**, *49*, 2572. (c) Zhao, M.-X.; Bi, H.-L.; Zhou, H.; Yang, H.; Shi, M. *J. Org. Chem.* **2013**, *78*, 9377.

(8) Guo, C.; Xue, M.-X.; Zhu, M.-K.; Gong, L.-Z. *Angew. Chem., Int. Ed.* **2008**, *47*, 3414.

(9) (a) Arróniz, C.; Gil-González, A.; Semak, V.; Escolano, C.; Bosch, J.; Amat, M. *Eur. J. Org. Chem.* **2011**, *2011*, 3755. (b) Song, J.; Guo, C.; Chen, P.-H.; Yu, J.; Luo, S.-W.; Gong, L.-Z. *Chem. - Eur. J.* **2011**, *17*,

7786. (c) Padilla, S.; Adrio, J.; Carretero, J. C. *J. Org. Chem.* **2012**, *77*, 4161. (d) Zhao, M.-X.; Wei, D.-K.; Ji, F.-H.; Zhao, X.-L.; Shi, M. *Chem. - Asian J.* **2012**, *7*, 2777. (e) Wang, L.-L.; Bai, J.-F.; Peng, L.; Qi, L.-W.; Jia, L.-N.; Guo, Y.-L.; Luo, X.-Y.; Xu, X.; Wang, L.-X. *Chem. Commun.* **2012**, *48*, 5175.

(10) Ito, Y.; Sawamura, M.; Matsuoka, M.; Matsumoto, Y.; Hayashi, T. *Tetrahedron Lett.* **1987**, *28*, 4849.

(11) (a) Bai, J.-F.; Wang, L.-L.; Peng, L.; Guo, Y.-L.; Jia, L.-N.; Tian, F.; He, G.-Y.; Xu, X.-Y.; Wang, L.-X. *J. Org. Chem.* **2012**, *77*, 2947. (b) Zhao, M.-X.; Ji, F.-H.; Wei, D.-K.; Shi, M. *Tetrahedron* **2013**, *69*, 10763. (c) Buyck, T.; Wang, Q.; Zhu, J. *Angew. Chem., Int. Ed.* **2013**, *52*, 12714.

(12) (a) Konno, T.; Tanaka, T.; Miyabe, T.; Morigaki, A.; Ishihara, T. *Tetrahedron Lett.* **2008**, *49*, 2106. (b) Matoba, K.; Kawai, H.; Furukawa, T.; Kusuda, A.; Tokunaga, E.; Nakamura, S.; Shiro, M.; Shibata, N. *Angew. Chem., Int. Ed.* **2010**, *49*, 5762. (c) Blay, G.; Fernández, I.; Muñoz, M. C.; Pedro, J. R.; Vila, C. *Chem. - Eur. J.* **2010**, *16*, 9117. (d) Wang, W.; Lian, X.; Chen, D.; Liu, X.; Lin, L.; Feng, X. *Chem. Commun.* **2011**, *47*, 7821. (e) Su, Y.; Ling, J.-B.; Zhang, S.; Xu, P.-F. *J. Org. Chem.* **2013**, *78*, 11053. (f) Kawai, H.; Okusu, S.; Yuan, Z.; Tokunaga, E.; Yamano, A.; Shiro, M.; Shibata, N. *Angew. Chem., Int. Ed.* **2013**, *52*, 2221. (g) Wu, S.; Pan, D.; Cao, C.; Wang, Q.; Chen, F.-X. *Adv. Synth. Catal.* **2013**, *355*, 1917. (h) Kwiatkowski, P.; Cholewiak, A.; Kasztelan, A. *Org. Lett.* **2014**, *16*, 5930. (i) Chen, W.; Jing, Z.; Chin, K. F.; Qiao, B.; Zhao, Y.; Yan, L.; Tan, C.-H.; Jiang, Z. *Adv. Synth. Catal.* **2014**, *356*, 1292.

(13) CCDC 1405897 (for **4q**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

DOI: 10.1021/acs.joc.5b01829
J. Org. Chem. 2015, 80, 11330−11338