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Tetrahedron 62 (2006) 11760–11765
Tetrahedron

Transition metal-catalyzed formation of CF_3-substituted α,β-unsaturated alkene and the synthesis of α-trifluoromethyl substituted β-amino ester

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Received 12 July 2006; revised 11 September 2006; accepted 12 September 2006

Abstract—A new transition metal-catalyzed formation of CF_3-substituted α,β-unsaturated alkenes through the ylide intermediate from the reaction between methyl 3,3,3-trifluoro-2-diazopropionate **1** and aryl aldehydes has been developed. Further transformation of the alkene affords the α-trifluoromethyl substituted β-amino ester, a valuable intermediate in the synthesis of fluorine-containing amino acids with potential biological application.
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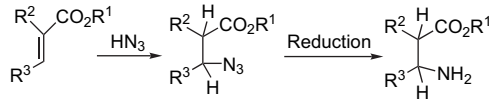
1. Introduction

It is well documented that the replacement of hydrogen with fluorine in organic molecules can make a profound and unexpected influence on the physical and biological properties of organic compounds.[1] Much attention has been directed toward the fluoro substitution during the last decade.[2] What is more, due to the unique physical and biological properties impacted by the CF_3 group, trifluoromethylation is an ongoing area of research. Thus, the preparation of trifluoromethyl containing molecules has been of great interest not only to biochemists and medicinal chemists, but also to the synthetic organic fluorine chemists.[3]

Amino acids are the basic units of proteins. More than 200 different amino acids are found in living organisms.[4] Hence, synthesis of novel amino acids has always been one of the research focuses of organic chemists. Among them, fluorine-containing amino acids have attracted considerable attention and enjoyed widespread bioorganic applications.[5] The strong carbon–fluorine bond is particularly resistant to metabolic transformations, and the electronegativity of fluorine can have a significant effect on the basicity or acidity of neighboring groups and on the electron distribution, and can change the overall reactivity and stability of the molecules.[6]

Fluorinated amino acids also play an important role in the field of biological tracers, mechanistic probes, enzyme inhibitors, and medical applications including control of blood pressure, treatment of allergies, and inhibition of tumor growth.[7] Additionally, fluorinated β-amino acids are now recognized as potentially exciting building blocks for the synthesis of β-peptides, antibiotics, and enzyme inhibitors.[8]

Usually, β-amino acid can be synthesized from the α,β-unsaturated carboxylic ester. Michael addition of hydrazoic acid (HN_3) produces the azide compound, which can be easily converted to the corresponding β-amino ester using well established chemistry (Scheme 1).[9] In this paper, in order to avoid the explosive hydrazoic acid, we chose the readily available and relatively stable sodium azide as the direct azide source. Advantages of the protocol include high-yielding reaction and mild reaction condition.



Scheme 1.

In our previous work, we have developed several methods to synthesize fluorinated alkene from fluorinated diazo compounds and aldehydes through the ylide intermediate.[10a] Therefore, we wondered whether methyl 3,3,3-trifluoro-2-diazopropionate **1** could react with aldehydes to give the

Keywords: Catalysis; CF_3-substituted; Ylide; α,β-Unsaturated alkenes; β-Amino ester.
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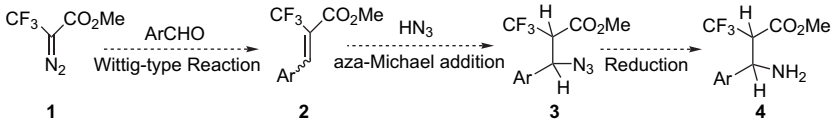
doi:10.1016/j.tet.2006.09.041



Scheme 2.

corresponding CF_3-containing α,β-unsaturated alkenes **2** through the ylide intermediate, which could be easily transformed into the corresponding trifluoromethyl containing β-amino esters (Scheme 2).

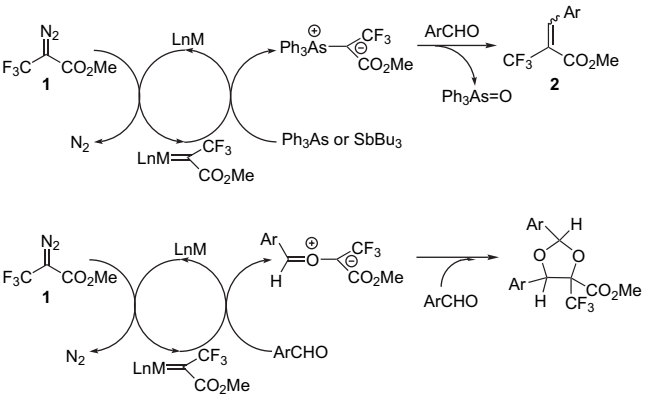
Herein, we wish to report a successful synthesis of trifluoromethylated β-amino esters from diazo compound **1**.

2. Results and discussion

Initially, arsonium ylide intermediate was used to prepare alkene **2**. 4-Nitrobenzaldehyde was used as the substrate, 1 mol % $Rh_2(OAc)_4$ was used as the catalyst, and refluxing THF as the solvent. The expected alkene **2b** was isolated in only 9% yield. In the meantime, trace amount of 1,3-dioxolane **5** (3%) was isolated (Table 1, entry1). It should come from the 1,3-dipolar addition of the carbonyl ylide intermediate and the aldehyde (Scheme 3).[3a]

The proposed reaction mechanism is depicted in Scheme 4. Due to the electron-withdrawing properties of the flanking trifluoromethyl and methoxyl carbonyl groups, the ylide intermediate could be too stable to react with the aldehyde to give alkene **2**. To improve the yield, more severe reaction conditions were employed. Increasing the reaction temperature to 80 °C (refluxing in benzene), improved the yields of alkene **2b** and 1,3-dioxolane **5** to 19 and 14%, respectively (Table 1, entry 2). Further increasing the reaction temperature to 110 °C (refluxing in toluene), improved the yield of **2b** to 36%. But the yield of **5** fell to 7% (Table 1, entry 3).

As indicated in Table 1, the reaction yields, through arsonium ylide intermediate, are unsatisfied even using refluxing toluene. It is known that antimony ylide is more reactive than the arsonium ylide. We envisioned that antimony ylide could give better reaction results. When $SbBu_3$ was used instead of Ph_3As, under the same reaction conditions, however, no alkene product was detected (Table 1, entries 4 and 5). It may be explained that the rhodium catalyst was poisoned by the strong reductive $SbBu_3$. When cuprous bromide (CuBr) was used as the catalyst, alkene **2c** was isolated in moderate yield in refluxing benzene (Table 1, entry 6). The yield of product **2c** was not improved at higher temperature (refluxing in toluene) (Table 1, entry 7). Inorganic or organic copper catalyst such as CuBr, $Cu(acac)_2$, and $Cu(hfacac)_2$

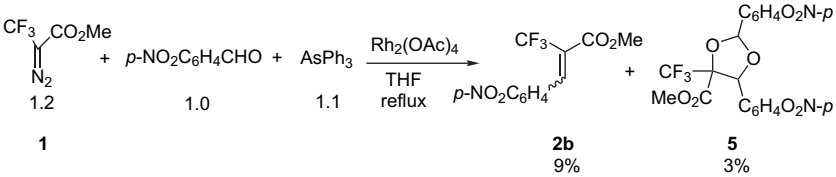


Scheme 4.

Table 1. The optimization of reaction condition

Entry	ArCHO (Ar=)	Lewis base	Catalyst	Solvent	Product yield (%)[a]	
					2	**5**
1	*p*-$NO_2C_6H_4$-	Ph_3As	$Rh_2(OAc)_4$	THF	9 (**2b**)	3
2	*p*-$NO_2C_6H_4$-	Ph_3As	$Rh_2(OAc)_4$	Benzene	19 (**2b**)	14
3	*p*-$NO_2C_6H_4$-	Ph_3As	$Rh_2(OAc)_4$	Toluene	36 (**2b**)	7
4	*p*-BrC_6H_4-	$SbBu_3$	$Rh_2(OAc)_4$	Benzene	—	—
5	*p*-BrC_6H_4-	$SbBu_3$	$Rh_2(OAc)_4$	Toluene	—	—
6	*p*-BrC_6H_4-	$SbBu_3$	CuBr	Benzene	55 (**2c**)	—
7	*p*-BrC_6H_4-	$SbBu_3$	CuBr	Toluene	59 (**2c**)	—
8	*p*-BrC_6H_4-	$SbBu_3$	$Cu(acac)_2$	Benzene	57 (**2c**)	—
9	*p*-BrC_6H_4-	$SbBu_3$	$Cu(hfacac)_2$	Toluene	54 (**2c**)	—

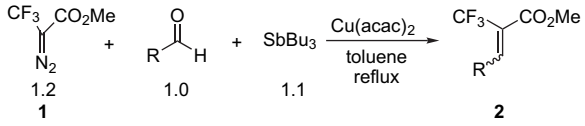
[a] Isolated yields based on aldehyde.



Scheme 3.

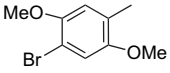
gave the corresponding alkenes in similar yields (Table 1, entries 6–9).

Then under the optimized reaction conditions (Table 1, entry 8), (Scheme 5), a series of aromatic aldehydes were used to prepare various alkene **2**. The results are summarized in Table 2.



Scheme 5.

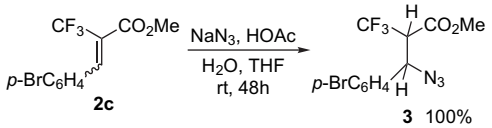
Table 2. Reaction results of **1** with aryl aldehydes and $SbBu_3$[a]

Entry	ArCHO (Ar=)	Product	Yield (%)[b]
1	Ph-	**2a**	46
2	*p*-$NO_2C_6H_4$-	**2b**[c]	36
3	*p*-BrC_6H_4-	**2c**	57
4	*o*-ClC_6H_4-	**2d**	69
5	*p*-$CH_3OC_6H_4$-	**2e**	62
6		**2f**	62
7	*trans*-PhCH=CH-	**2g**	85
8		**2h**	77

[a] $Cu(acac)_2$ (10 mol %), diazo compound:aldehyde:$SbBu_3$=1.2:1.0:1.1 are used for all reactions.
[b] Isolated yields based on aldehyde.
[c] $Rh_2(OAc)_4$ and Ph_3As system was used.

It shows that all of the aromatic aldehydes employed afford the corresponding alkene **2** in satisfying yields.

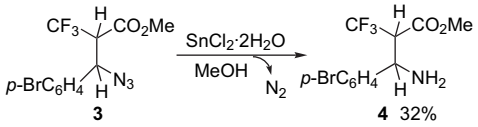
With the α,β-unsaturated alkenes in hand, we then explored its reaction with the hydrazoic acid (HN_3) to produce the azide compound. It is necessary to generate the HN_3 in situ, because it is explosive and poisonous. Based on the literature,[12] methyl 3-(4-bromophenyl)-2-(trifluoromethyl)-acrylate **2c** was chosen as the substrate. In aqueous THF, **2c** reacted with the hydrazoic acid, which was generated in situ from NaN_3 and HOAc, for 48 h at room temperature to give the corresponding azide **3** in quantitative yield. The product was essentially pure after general work-up and could be used directly in the next step (Scheme 6).



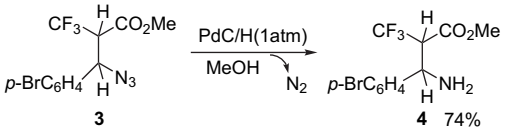
Scheme 6.

It is well known that azide can be easily reduced to give the corresponding amine product.[11] Initially, $SnCl_2 \cdot 2H_2O$ was used to reduce the azide **3** to give only 32% of the desired α-trifluoromethyl substituted β-amino ester **4** (Scheme 7).

Pd–C/H_2 is the most popular catalytic system for the reduction of the azide. Furthermore, it is an atom economical and environmental benign reaction. The reaction results showed that the azide can be easily transformed into the desired amino ester **4** in 74% yield using Pd–C/H_2 (1 atm) (Scheme 8).



Scheme 7.



Scheme 8.

The structure of **4** was further confirmed by the X-ray crystal diffraction (Fig. 1).

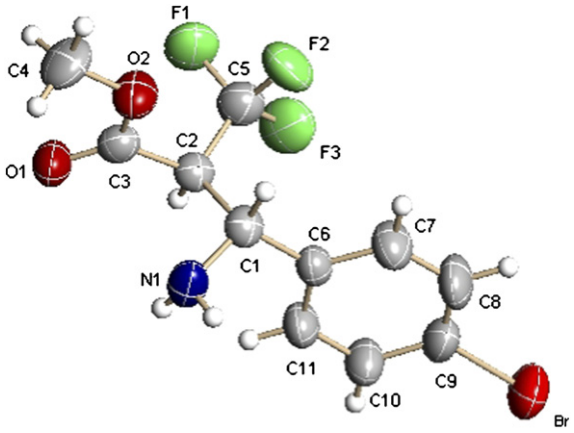


Figure 1. Crystal structure of **4**.

3. Conclusion

In summary, we successfully synthesize a series of CF_3-substituted α,β-unsaturated alkenes from the transition metal-catalyzed reaction between methyl 3,3,3-trifluoro-2-diazopropionate **1** and aryl aldehydes. CF_3-Substituted α,β-unsaturated alkenes can be further transferred into β-amino ester through a two-step procedure. This paper provides a good choice for the synthesis of CF_3-substituted β-amino acid.

4. Experimental

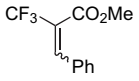
4.1. General

Melting points were measured in a SGW® X-4 micro-melting point apparatus and were uncorrected. ^1H and ^{19}F NMR spectra were recorded on a Bruker AM-300 spectrometer with Me_4Si and $CFCl_3$ (with upfield negative) as the internal and external standards, respectively. IR spectra were obtained with a Nicolet AV-360 spectrophotometer. Low-resolution mass spectra or high-resolution mass spectra (HRMS) were obtained on a Finnigan GC–MS 4021 or a Finnigan MAR-8430 instrument using the electron impact ionization technique (70 eV), respectively. The X-ray structural analysis was performed with a Rigaku/AFC 7R Diffractometer. Elemental analyses were performed by this institute.

4.2. General method for the reaction of methyl 3,3,3-trifluoro-2-diazopropionate 1 with aldehydes

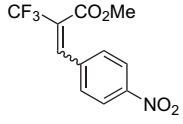
A mixture of **2** (1 mmol), $AsPh_3$ or $SbBu_3$ (1.5 mmol), and $Rh_2(OAc)_4$ (5 mg, 1 mol %) or $Cu(acac)_2$ (78.6 mg, 20 mmol %) in anhydrous toluene (1.5 ml) in a schrock tube was heated to reflux and a solution of **1a** (252 mg, 1.5 mmol) in toluene (2 ml) was added dropwise. The resulting mixture was stirred for 15 h under N_2 atmosphere. Upon completion of the reaction (monitored by TLC), the reaction mixture was cooled to room temperature and the crude product was filtered. The residue was purified by column chromatography on silica gel using ethyl ester–hexane as eluent to give **3a** (106 mg, 46%).

4.2.1. Methyl 3-phenyl-2-(trifluoromethyl)acrylate (3a).



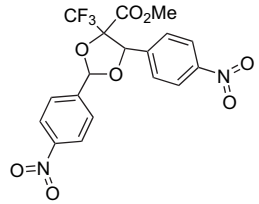
Colorless liquid, *Z*/*E*=1:3.6. IR (KBr), cm^{-1}: 2956, 2929, 1958, 1736, 1638, 1578, 1496, 1450, 1438, 1391, 1280, 1167, 1136, 1043. ^1H NMR ($CDCl_3$, 300 MHz): δ 8.10 (1H, s), 7.42–7.37 (5H, m, Ar), 3.90 (3H, s, *Z*), 3.78 (3H, s, *E*) ppm. ^{19}F NMR ($CDCl_3$, 282 MHz): δ −58.0 (CF_3, s, *Z*), −63.8 (CF_3, s, *E*) ppm. ^{13}C NMR ($CDCl_3$, 75.44 MHz): δ 163.8, 140.4 (t, J_{CF}=5.8 Hz), 132.2, 130.4, 130.2, 129.3, 128.8, 128.3, 52.3 ppm. MS (70 eV, EI): 230 (M^+, 54), 229 (M^+−1, 52), 211 (M^+−F, 1.6), 199 (57), 151 (40), 109 (100), 77 (25), 69 (8.0). HRMS for $C_{11}H_9O_2F_3$ calcd: 230.0555. Found: 230.0556.

4.2.2. Methyl 3-(4-nitrophenyl)-2-(trifluoromethyl)acrylate (3b).



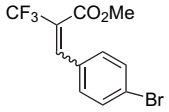
Colorless solid with mp: 54–56 °C. IR (KBr), cm^{-1}: 2998, 2964, 1941, 1733, 1655, 1602, 1523, 1443, 1384, 1354, 1312, 1237, 1217, 1164, 1143, 1019. ^1H NMR ($CDCl_3$, 300 MHz): δ 8.26 (d, 2H, *J*=9.0 Hz), 7.54 (d, 2H, *J*=9.0 Hz), 3.79 (s, 3H) ppm. ^{19}F NMR ($CDCl_3$, 282 MHz): δ −64.7 (s, *E*) ppm. MS (70 eV, EI): 275 (M^+, 90), 274 (70), 258 (58), 244 (100), 243 (52), 228 (27), 206 (M^+−F, 13), 198 (67), 169 (55). Anal. Calcd for $C_{11}H_8F_3O_4N$: C, 48.01; H, 2.93; N, 5.09%. Found: C, 48.26; H, 3.06; N, 5.00%.

4.2.3. Methyl 2,5-bis(4-nitrophenyl)-4-(trifluoromethyl)-1,3-dioxolane-4-carboxylate (5).



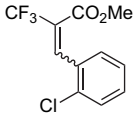
Colorless solid with mp: 171–173 °C. IR (KBr), cm^{-1}: 3089, 2958, 1752, 1608, 1521, 1351, 1302, 1200, 1117. ^1H NMR ($CDCl_3$, 300 MHz): δ 8.33 (2H, d, *J*=9.0 Hz), 8.28 (2H, d, *J*=9.0 Hz), 7.78 (2H, d, *J*=9.0 Hz), 7.60 (2H, d, *J*=9.0 Hz), 6.87 (1H, s), 5.65 (1H, s), 3.43 (3H, s) ppm. ^{19}F NMR ($CDCl_3$, 282 MHz): δ −73.8 (CF_3, s) ppm. MS (70 eV, EI): 443 ($[M+1]^+$, 1), 291 (13), 275 (42), 258 (16), 166 (100), 150 (19), 89 (30), 59 (30). Anal. Calcd for $C_{18}H_{13}F_3O_8N_2$: C, 48.88; H, 2.96; N, 6.33%. Found: C, 49.01; H, 3.01; N, 6.23%.

4.2.4. Methyl 3-(4-bromophenyl)-2-(trifluoromethyl)-acrylate (3c).



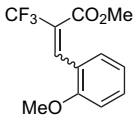
Colorless solid with mp: 43–45 °C, *Z*/*E*=1:3.3. IR (KBr), cm^{-1}: 2996, 2959, 1917, 1724, 1649, 1490, 1440, 1384, 1312, 1278, 1133, 1021. ^1H NMR ($CDCl_3$, 300 MHz): δ 7.56–7.51 (2H, m), 7.27–7.24 (2H, m), 379 (3H, s) ppm. ^{19}F NMR ($CDCl_3$, 282 MHz): δ −58.5 (CF_3, s, Z), −64.4 (CF_3, s, E) ppm. MS (70 eV, EI): 310 (M^+, 100), 308 (95), 291 (M^+−F, 2.7), 279 (63), 277 (67), 250 (40), 248 (40), 198 (48), 189 (25), 187 (23), 170 (50), 169 (49), 151 (37), 101 (29), 75 (47), 69 (39). Anal. Calcd for $C_{11}H_8BrF_3O_2$: C, 42.75; H, 2.61%. Found: C, 42.86; H, 2.65%.

4.2.5. Methyl 3-(2-chlorophenyl)-2-(trifluoromethyl)-acrylate (3d).



Colorless liquid, *Z*/*E*=1:5.3. IR (KBr), cm^{-1}: 2957, 1739, 1647, 1471, 1439, 1387, 1290, 1269, 1171, 1141, 1045. ^1H NMR ($CDCl_3$, 300 MHz): δ 8.18 (1H, s), 7.44–7.25 (4H, m, Ar), 3.91 (3H, s, *Z*), 3.70 (3H, s, *E*) ppm. ^{19}F NMR ($CDCl_3$, 282 MHz): δ −58.5 (CF_3, s, *Z*), −64.1 (CF_3, s, *E*) ppm. ^{13}C NMR ($CDCl_3$, 75.44 MHz): δ 163.0, 145.5 (t, J_{CF}=3.0 Hz), 133.3, 131.8, 131.0, 130.9, 129.3, 129.2, 126.5, 126.4, 53.0 ppm. MS (70 eV, EI): 264 (M^+, 1.4), 245 (M^+−F, 1.0), 233 (12), 230 (13), 229 (100), 195 (14), 161 (17), 101 (12), 75 (20), 69 (6.6). HRMS for $C_{11}H_8O_2F_2Cl$ calcd: 245.0181. Found 245.0182 (M^+−F).

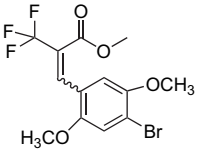
4.2.6. Methyl 3-(2-methyloxyphenyl)-2-(trifluoromethyl)-acrylate (3e).



Colorless liquid, *Z*/*E*=1:1.4. IR (KBr), cm^{-1}: 2957, 2843, 1732, 1634, 1514, 1463, 1439, 1393, 1264, 1175, 1129, 1032. ^1H NMR ($CDCl_3$, 300 MHz): δ 8.00 (1H, s, *Z*), 7.40 (2H, m, Ar), 6.93–6.88 (2H, m, Ar), 3.87 (3H, s, *Z*), 3.84 (3H, s) 3.82 (3H, s, *E*) ppm. ^{19}F NMR ($CDCl_3$, 282 MHz): δ −58.0 (CF_3, s, *Z*), −63.3 (CF_3, s, *E*) ppm. ^{13}C NMR ($CDCl_3$, 75.44 MHz): δ 164.2, 148.3 (t, J_{CF}=2.8 Hz, *Z*),

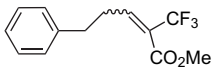
140.1 (t, J_{CF}=5.6 Hz, *E*), 132.3, 131.6, 124.6, 124.5, 114.1, 113.9, 55.3, 52.3 ppm. MS (70 eV, EI): 260 (M^+, 100), 241 (M^+−F, 3.9), 229 (55), 200 (52), 139 (83), 75 (8.5), 69 (7.9). HRMS for $C_{12}H_{11}O_3F_3$ calcd: 260.0660. Found: 260.0660.

4.2.7. Methyl 3-(2,5-dimethyloxy-4-bromophenyl)-2-(trifluoromethyl)acrylate (3f).



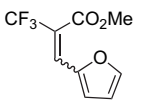
Colorless solid with mp: 127–129 °C, *Z*/*E*=3.2:1. IR (KBr), cm^{-1}: 2969, 2857, 1732, 1632, 1603, 1488, 1465, 1441, 1432, 1394, 1296, 1258, 1214, 1179, 1127, 1054, 1040, 1025. ^1H NMR ($CDCl_3$, 300 MHz): δ 8.12 (1H, s), 7.12 (1H, s, Ar), 6086 (1H, s, Ar), 3.90 (3H, s, *Z*), 3.85 (3H, s), 3.83 (3H, s, *E*) ppm. ^{19}F NMR ($CDCl_3$, 282 MHz): δ −58.6 (CF_3, s, *Z*), −63.7 (CF_3, s, *E*) ppm. MS (70 eV, EI): 370 (M^++1, 56), 369 (M^+, 9.3), 368 (55), 339 (54), 337 (61), 246 (23), 231 (44), 69 (14), 59 (100). Anal. Calcd for $C_{13}H_{12}BrF_3O_4$: C, 42.30; H, 3.28%. Found: C, 42.41; H, 3.36%.

4.2.8. Methyl 3-phenylvinyl-2-(trifluoromethyl)acrylate (3g).



Colorless liquid, *Z*/*E*=1:1.8. IR (KBr), cm^{-1}: 3027, 2956, 1724, 1624, 1595, 1438, 1384, 1293, 1245, 1129. ^1H NMR ($CDCl_3$, 300 MHz): δ 7.96 (1H, dd, *J*=15, 11 Hz), 7.57–7.54 (2H, m, Ar), 7.40–7.37 (3H, m, Ar), 7.31 (1H, d, *J*=11 Hz), 7.08 (1H, d, *J*=15 Hz), 3.86 (3H, s, *Z*), 3.89 (3H, s, *E*) ppm. ^{19}F NMR ($CDCl_3$, 282 MHz): δ −57.9 (CF_3, s, *Z*), −63.0 (CF_3, s, *E*) ppm. ^{13}C NMR ($CDCl_3$, 75.44 MHz): δ 163.1, 146.0 (t, J_{CF}=5.3 Hz), 147.2, 135.5, 130.4, 129.0, 128.1, 124.6, 123.0, 121.0, 52.1 ppm. MS (70 eV, EI): 256 (M^+, 38), 237 (M^+−F, 2.9), 177 (100), 128 (52), 102 (32), 77 (47), 69 (23), 51 (49). HRMS for $C_{13}H_{11}O_2F_3$ calcd: 256.0711. Found: 256.0711.

4.2.9. Methyl 3-furan-2-(trifluoromethyl)acrylate (3h).

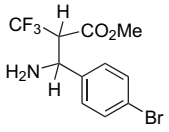


Colorless liquid, *Z*/*E*=1:4.5. IR (KBr), cm^{-1}: 2959, 2928, 2856, 1731, 1633, 1468, 1438, 1377, 1285, 1224, 1134, 1044, 1025. ^1H NMR ($CDCl_3$, 300 MHz): δ 7.81 (1H, s, *Z*), 7.58 (1H, s, *E*), 7.67 (1H, d, *J*=1 Hz, *Z*), 7.30 (1H, d, *J*=3 Hz, *E*), 7.08 (1H, d, *J*=3 Hz, *Z*), 7.24 (1H, d, *J*=1 Hz, *E*), 6.59 (1H, dd, *J*=1, 3 Hz, *Z*), 6.56 (1H, dd, *J*=1, 3 Hz, *E*), 3.92 (3H, s, *Z*), 3.88 (3H, s, *E*) ppm. ^{19}F NMR ($CDCl_3$, 282 MHz): δ −59.5 (CF_3, s, *Z*), −63.0 (CF_3, s, *E*) ppm. ^{13}C NMR ($CDCl_3$, 75.44 MHz): δ 163.3, 152.2, 146.3, 128.0 (t, J_{CF}=3.0 Hz), 119.6, 119.5, 113.0, 112.9, 52.4 ppm. MS (70 eV, EI): 220 (M^+, 34), 201 (M^+−F, 3.9), 189 (48), 160 (18), 113 (32), 99 (100), 83 (23), 69 (9.1), 68 (2.9), 63 (52), 59 (43). HRMS for $C_9H_7O_3F_3$ calcd: 220.0347. Found: 220.0351.

4.3. General method for the synthesis of α-trifluoromethyl substituted β-amino ester (4)

In a 25 ml flask containing alkene **2c** (352 mg, 1 mmol) was added 5 ml of THF and cooled in an ice-water bath, then a solution of NaN_3 (260 mg, 4 mmol) in H_2O (1 ml) was added. The temperature of the mixture is adjusted to 0 °C, and a solution of HOAc (240 mg, 4 mmol) was added dropwise with vigorous stirring over 20–30 min. The yellow reaction mixture was allowed to stir for 48 h at room temperature. After the reaction was completed (monitored by TLC), the reaction mixture was diluted with CH_2Cl_2, which was washed with saturated $NaHCO_3$ and water, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure using a rotary evaporator. The yield was almost quantitative. The product was essentially pure after general work-up and could be used directly in the next step. A mixture of the crude azide and 10% palladium-on-carbon (20 mg) in absolute ethanol (6 ml) was stirred at 25 °C under 1 atm of hydrogen for 24 h. The catalyst was filtered and washed with CH_2Cl_2. The filtrates were concentrated under reduced pressure using a rotary evaporator, and the crude reaction product was purified by column chromatography on silica gel using ethyl acetate–hexane as eluent to give **4** (243 mg, 74%).

4.3.1. Methyl 2-(amino(4-bromophenyl)methyl)-3,3,3-trifluoropropanoate (4).



Colorless solid with mp: 72–74 °C. IR (KBr), cm^{-1}: 2957, 2930, 1908, 1751, 1641, 1489, 1438, 1409, 1354, 1163, 1119, 1074, 1012. ^1H NMR (300 MHz, $CDCl_3$): δ 7.48–7.43 (2H, m), 7.23–7.19 (2H, m), 4.51–4.47 (1H, m), 3.76 (3H, s), 3.44 (1H, s), 1.73 (2H, s) ppm. ^{19}F NMR ($CDCl_3$, 282 MHz): δ −65.1 (d, *J*=7.9 Hz), −64.32 (d, *J*=8.4 Hz) ppm. EIMS (*m*/*z*, %): 327/325 (M+2/M^+, 3/3), 186 (98), 184 (100), 159 (9), 157 (9), 77 (27), 59 (16). Anal. Calcd for $C_{11}H_{11}F_3BrO_2N$: C, 40.51; H, 3.40; N, 4.30%. Found: C, 40.69; H, 3.52; N, 4.19%.

4.3.1.1. X-ray data of 4. $C_{11}H_{11}BrF_3NO_2$: MW=326.12, CCDC no. 614315, monoclinic, space group: *C*2/*c*, *a*=21.606(3) Å, *b*=5.4235(7) Å, *c*=24.378(3) Å; α=90.00°, β=2599.4(6)°, γ=90.00°; *V*=2599.4(6) $Å^3$, *Z*=8, Dc=1.667 g/cm^3, *F*(000)=1296. Radiation, Mo Kα (λ=0.71073 Å). Crystal dimension, 0.467×0.89×0.329 mm.

Intensity data were collected at 293(2) K with a Bruker P4 four-circle diffractometer with graphite monochromator and Mo Kα radiation (λ=0.71073 Å). A total of 2815 independent reflection was measured in the range $1.84<\theta<27.00°$.

The structure was solved by directed methods and expanded using Fourier techniques. The nonhydrogen atoms were refined anisotropically; hydrogen atoms were included but not refined. The final cycle of full matrix least-square refinement was based on F^2. The final R and wR value were 0.0457 and 0.0889, respectively. All calculations were performed using the SHELX-97 program.

Acknowledgements

The authors thank the National Natural Science Foundation of China (NNSFC) (Nos. 20472106 and 20532040) for financial support.

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