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PAPER

Phosphine-catalyzed [3 + 2] cycloaddition of allenoates with trifluoromethylketones: synthesis of dihydrofurans and tetrahydrofurans†

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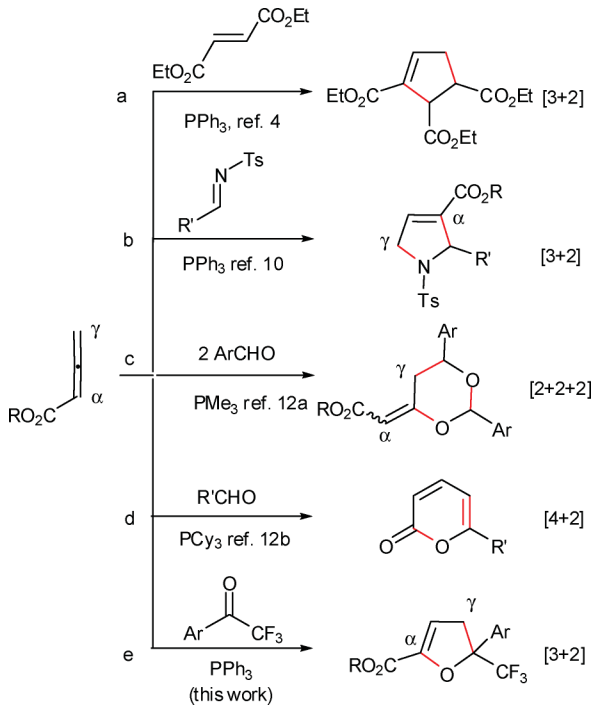
The triphenylphosphine-catalyzed formal [3 + 2] cycloaddition of allenoates and trifluoromethylketones was realized to give the corresponding dihydrofurans in good yields with excellent γ-regioselectivities. Hydrogenation of the dihydrofurans gave 2,4,4-trisubstituted tetrahydrofurans in good yields with exclusive *cis*-selectivities.

Introduction

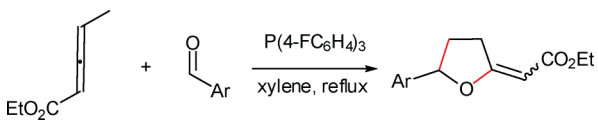
Due to the wide presence of dihydrofuran and tetrahydrofuran in a number of natural and unnatural bioactive compounds,[1] many efforts have been made for the development of their construction.[2,3] Catalytic cycloaddition reactions, in which at least two bonds are formed in one pot, feature the advantages of easily available starting materials and high efficiency.

In 1995, Lu *et al.* reported their pioneering [3 + 2] cycloaddition of allenoates with electron-deficient olefins for the synthesis of cyclopentenes (Scheme 1, reaction a).[4] Since then, many efforts have been made to develop this reaction[5–8] and its applications in the synthesis of natural products and biologically active compounds.[9] The reaction was soon successfully expanded to *N*-tosylimines to furnish pyrroline efficiently (reaction b).[7j,10,11] However, in contrast with olefins and *N*-tosylimines, when aldehydes were employed in the reaction, no corresponding [3 + 2] annulation but interesting alternative reactions were resulted.[12] In 2005, Kwon and co-workers reported the [2 + 2 + 2] annulation of allenoate with two molecules of aldehyde (reaction c).[12a] Based on the rational stereochemical analysis of the zwitterionic intermediate generated by the nucleophilic addition of a tertiary phosphine to an allenoate, the same group further realized [4 + 2] annulation of allenoates with aldehydes (reaction d).[12b] In addition, the reactions of α- and γ-substituted allenoates with aldehydes mediated by phosphine were also developed by Kwon's and He's groups.[13] It should be noted that He and co-workers also reported a novel phosphine-catalyzed [3 + 2] cycloaddition reaction of γ-methyl allenoates with aldehydes, in which the γ-methyl rather than the α-carbon takes part in the cycloaddition reaction (Scheme 2).[14]

Recently, we reported a [4 + 2] annulation of ethyl α-benzylallenoates with trifluoromethyl ketones to form the corresponding dihydropyrans.[15] The employment of trifluoromethyl ketones[16,17] was the key point for the success of this transformation. Based on this discovery, we expected that the corresponding [3 + 2] cycloaddition reaction may also be feasible if trifluoromethyl ketones were utilized (reaction e). Herein, we report our initial result of the synthesis of 5-trifluoromethyl-4,5-dihydrofurans *via*



Scheme 1 Phosphine-catalyzed cycloaddition reactions of allenoates.



Scheme 2 [3 + 2] annulation of γ-methyl allenoates with aldehydes by He *et al.*

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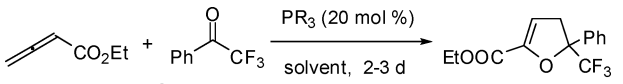
Table 1 Optimization of reaction conditions



1a **2a** (2.0 equiv.) **3aa**

Entry	PR_3	Solvent	Temp.	Yield (%)[a]
1	PPh_3	CH_2Cl_2	rt	69
2	PPh_3	Toluene	rt	61
3	PPh_3	THF	rt	57
4	PPh_3	CH_3CN	rt	49
5	PPh_3	EtOAc	rt	59
6	PPh_3	MeOH	rt	0
7	PPh_3	n-Hexane	rt	13
8	PBu^n_3	CH_2Cl_2	rt	60
9	PMe_3	CH_2Cl_2	rt	35
10	PCy_3	CH_2Cl_2	rt	31
11	PPh_3	CH_2Cl_2	reflux	55
12	PPh_3	CH_2Cl_2	0 °C	72
13	PPh_3	CH_2Cl_2	−20 °C	25

[a] Isolated yield.

phosphine-catalyzed [3 + 2] cycloaddition reactions of allenoates with trifluoromethyl ketones.

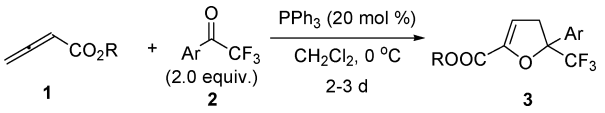
Results and discussion

The model reaction of ethyl allenoate **1a** and trifluoromethyl ketone **2a** was investigated (Table 1). We are happy to find that the expected [3 + 2] cycloadduct **3aa** could be isolated in 69% yield when the reaction was catalyzed by PPh_3 in CH_2Cl_2 at room temperature (entry 1). It is worthwhile to note that only the γ-addition cycloadduct was observed for the reaction, which is opposite to the reported [3 + 2] cycloadditon of allenoate with imines *via* α-addition (Scheme 1, reaction b).[10] The reaction also worked in toluene, THF, acetonitrile or ethyl acetate albeit in somewhat low yield (entries 2–5). Reaction in methanol or n-hexane gave no or very low yield of cycloadduct **3a** (entries 6 and 7). Trialkylphosphines, such as tributyl-, trimethyl- and tricyclohexylphosphine could also catalyze the reaction but resulted in decreased yield (entries 8–10). The reaction worked in varied temperature from −20 °C to reflux in CH_2Cl_2 and the best yield was obtained at 0 °C (entries 11–13).

With the optimized reaction conditions in hand, the reaction scope was then briefly investigated (Table 2). Aryltrifluoromethyl ketones with an electron-withdrawing substituent (Ar = 4-ClC_6H_4) worked better than those with electron-donating substituents (Ar = 4-Me, 4-$MeOC_6H_4$) (entries 2–4). Ketone **2e** with a *m*-methylphenyl group worked to give the corresponding cycloadduct in 74% yield (entry 5). Ketone **2f** with a 2-thienyl group gave the γ-addition cycloadduct **3af** plus trace of α-addition cycloadduct (entry 6). For ketones **2a**, **2c** and **2e**, when cyclohexyl allenoate **1b** was used, the yields were higher than the ethyl allenoate **1a** (entries 7–9). Unfortunately, other activated carbonyl compounds, such as methyl 2-oxo-2-phenylacetate and isatin derivatives gave only trace or very low yields of the [3 + 2] cycloadduct under the current reaction conditions (not showed in the table).

The structure of the cycloadduct **3ba** was unambiguously established by the X-ray analysis of its crystal (Fig. 1).[18]

Table 2 Synthesis of dihydrofurans through PPh_3-catalyzed annulation of allenoates and ketones

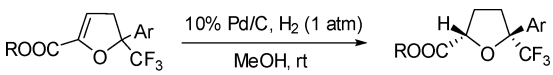


1 **2** **3**

Entry	**1** (R)	**2** (Ar)	**3**	Yield (%)[a]
1	**1a** (Et)	**2a** (Ph)	**3aa**	72
2	**1a** (Et)	**2b** (4-MeC_6H_4)	**3ab**	79
3	**1a** (Et)	**2c** (4-$MeOC_6H_4$)	**3ac**	49
4	**1a** (Et)	**2d** (4-ClC_6H_4)	**3ad**	99
5	**1a** (Et)	**2e** (3-MeC_6H_4)	**3ae**	74
6	**1a** (Et)	**2f** (2-thienyl)	**3af**	52[b]
7	**1b** (Cy)	**2a** (Ph)	**3ba**	85
8	**1b** (Cy)	**2c** (4-$MeOC_6H_4$)	**3bc**	61
9	**1b** (Cy)	**2f** (2-thienyl)	**3bf**	54

[a] Isolated yield. [b] Yield of a mixture of γ-addition product **3af** and trace of α-addition product (γ : α = 10 : 1). No α-addition product was observed for other entries.

Table 3 Synthesis of tetrahydrofurans



3 **4** (*cis*-only)

Entry	**3** (Ar, R)	**4**	Yield (%)[a]
1	Ph, Et	**4aa**[b]	74
2	4-MeC_6H_4, Et	**4ab**	72
3	4-$MeOC_6H_4$, Et	**4ac**	73
4[c]	4-ClC_6H_4, Et	**4ad**	64
5	2-Thienyl, cyclohexyl	**4bf**	80

[a] Isolated yield of *cis*-isomer, and no *trans*-**4** was detected by the NMR spectrum of its reaction mixture. [b] The relative configuration of tetrahydrofuran **4aa** was determined by its NOE spectrum. [c] The reaction was carried out in EtOH instead of MeOH to avoid the formation of the methyl ester *via* transesterification.

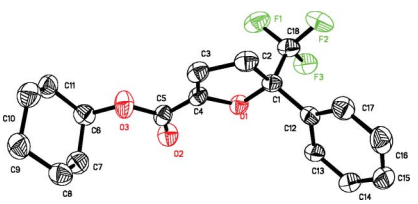
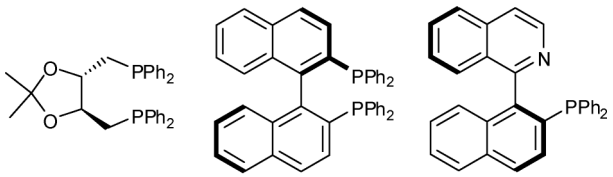


Fig. 1 X-Ray structure of cycloadduct **3ba**.

The highly functionalized dihydrofurans could be further transformed to other useful compounds. A series of tetrahydrofurans **4** could be obtained *via* the Pd/C-catalyzed hydrogenation of the dihydrofurans **3** with exclusive *cis*-selectivity (Table 3).[19,20]

Several chiral organophosphines were tested as catalysts for the [3 + 2] cycloaddition of allenoate **1a** and ketone **2a** (Scheme 3). However, only low yields and enantioselectivities were obtained under the current reaction conditions.

A possible catalytic cycle of the phosphine-catalyzed annulation is depicted in Scheme 4.[5] The nucleophilic addition of triphenylphosphine to allenoate **1** gives an allylic zwitterion **A**. The

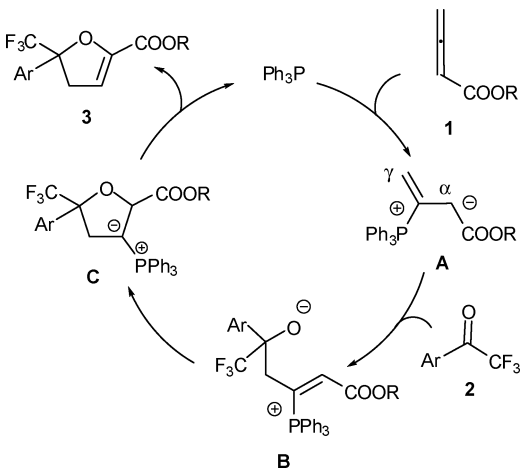


5 (+)-DIOP
29%, 6% ee

6 (*R*)-BINAP
33%, 33% ee

7 (*S*)-Quinap
14%, 11% ee

Scheme 3 Yield and ee of **3aa** for the reaction of **1a** and **2a** catalyzed by chiral phosphines (20 mol%).



Scheme 4 Possible catalytic cycle.

γ-addition of the zwitterion **A** to ketone **2** leads to zwitterion **B**. Compared to the reported α-addition of zwitterion **A** to imines,[10] more sterically demanding substrates (keteones *vs.* aldoimines) may favor the switch of selectivity to less hindered γ-addition in our cases. It should be noted that γ-selectivity is also observed and has been rationalized by computation for the [2 + 2 + 2] cycloaddition of allenoate with aldehydes by Kwon *et al.*[5a,12a] Intramolecular Michael addition affords cycloadduct **C**. Proton shift(s) followed by fragmentation furnishes the dihydrofuran and regenerates the catalyst.

Conclusions

In conclusion, the phosphine-catalyzed formal [3 + 2] cycloaddition of allenoates and carbonyl compounds was found to be feasible when trifluoromethylketones were used as the substrates. The resulting highly functionalized dihydrofurans could be easily hydrogenated to give the corresponding tetrahydrofurans with exclusive *cis*-selectivities. Further investigations of catalyzed annulation reactions of allenoates and ketones are underway in our laboratory.

Experimental

General

All reactions utilizing air or moisture sensitive reagents were performed in oven-dried glassware with magnetic stirring under nitrogen atmosphere. Column chromatography was performed with silica gel 200–300 mesh. All ^{1}H NMR (300 MHz) and ^{13}C NMR (75 MHz) spectra were recorded on a Bruker-DMX 300 spectrometer in $CDCl_3$, with tetramethylsilane as an internal standard and reported in parts per million (ppm, δ). Infrared spectra were recorded on a JASCO FT/IR-480 spectrophotometer and reported as wavenumber (cm^{-1}).

General procedure for the Ph_3P-catalyzed annulation of allenoates with ketones

To a stirred solution of allenoate **1** (0.5 mmol, 1.0 equiv.) and trifluomethylarylketone **2** (1.0 mmol, 2.0 equiv.) in CH_2Cl_2 (5 mL) was added Ph_3P (0.1 mmol, 0.2 equiv.). The solution was stirred at 0 °C until the full consumption of the allenoate. The reaction mixture was concentrated under reduced pressure, and the residue was purified by column chromatography on silica gel (petroleum ether/EtOAc as the eluent, typically 50 : 1–20 : 1) to furnish the corresponding annulation product **3**.

Ethyl 5-phenyl-5-(trifluoromethyl)-4,5-dihydrofuran-2-carboxylate (3aa). Reaction time: 48 h; Yield: 103 mg, 72%; colorless oil; R_f 0.5 (petroleum ether/ethyl acetate = 20 : 1); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.59–7.56 (m, 2H), 7.44–7.37 (m, 3H), 5.95 (t, J = 3.0 Hz, 1H), 4.30 (q, J = 7.2 Hz, 2H), 3.56 (dd, J_1 = 18 Hz, J_2 = 3.0 Hz, 1H), 3.19 (dd, J_1 = 18 Hz, J_2 = 3.0 Hz, 1H), 1.34 (t, J = 7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 159.3, 147.6, 137.0, 129.3, 128.6, 126.3, 124.5 (q, J = 281 Hz), 109.9, 88.2 (q, J = 30 Hz), 61.5, 39.8, 14.2; IR (KBr): ν 2360, 2341, 1734, 1593, 1419, 1260, 1180, 1123, 1017, 668, 411 cm^{-1}; HRMS (EI) calcd for $C_{14}H_{13}F_3O_3$ $[M]^+$ 286.0817, found 286.0820.

Ethyl 5-*p*-tolyl-5-(trifluoromethyl)-4,5-dihydrofuran-2-carboxylate (3ab). Reaction time: 72 h; Yield: 119 mg, 79%; colorless oil; R_f 0.5 (petroleum ether/ethyl acetate = 20 : 1); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.45 (d, J = 8.1 Hz, 2H), 7.21 (d, J = 8.1 Hz, 2H), 5.94 (t, J = 3.0 Hz, 1H), 4.29 (m, 2H), 3.53 (dd, J_1 = 18 Hz, J_2 = 3.0 Hz, 1H), 3.17(dd, J_1 = 18 Hz, J_2 = 3.0 Hz, 1H), 2.36 (s, 3H), 1.33 (t, J = 7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 159.3, 147.6, 139.2, 134.1, 129.3, 126.3, 124.5 (q, J = 282 Hz), 109.9, 88.2 (q, J = 30 Hz), 61.5, 39.8, 21.2, 14.3; IR (KBr): ν 2360, 1733, 1608, 1374, 1310, 1235, 1169, 1125, 1017, 815 cm^{-1}; HRMS (EI) calcd for $C_{15}H_{15}F_3O_3$ $[M]^+$ 300.0973, found 300.0978.

Ethyl 5-(4-methoxyphenyl)-5-(trifluoromethyl)-4,5-dihydrofuran-2-carboxylate (3ac). Reaction time: 72 h; Yield: 155 mg, 49% (1.0 mmol substrate was used); colorless oil; R_f 0.25 (petroleum ether/ethyl acetate = 20 : 1); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.48 (d, J = 8.7 Hz, 2H), 6.92 (d, J = 8.7 Hz, 2H), 5.94 (t, J = 3.0 Hz, 1H), 4.29 (m, 2H), 3.80 (s, 3H), 3.52 (dd, J_1 = 18 Hz, J_2 = 3.0 Hz, 1H), 3.16 (dd, J_1 = 18 Hz, J_2 = 3.0 Hz, 1H), 1.33 (t, J = 7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 160.3, 159.3, 147.5, 132.8 (q, J = 1.5 Hz), 128.8, 127.7, 124.5 (q, J = 282 Hz), 113.9, 109.9, 88.0 (q, J = 30 Hz), 61.4, 55.3, 39.7, 14.2; IR (KBr): ν 3434, 2359, 1737, 1612, 1514, 1453, 1257, 1179, 1123, 1016, 421 cm^{-1}; HRMS (EI) calcd for $C_{15}H_{15}F_3O_4$ $[M]^+$ 316.0922, found 316.0927.

Ethyl 5-(4-chlorophenyl)-5-(trifluoromethyl)-4,5-dihydrofuran-2-carboxylate (3ad). Reaction time: 72 h; Yield: 160 mg, 99%; colorless oil; R_f 0.5 (petroleum ether/ethyl acetate = 20 : 1); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.51 (d, J = 8.7 Hz, 2H), 7.38 (d, J = 8.7 Hz, 2H), 5.95 (t, J = 3.0 Hz, 1H), 4.30 (q, J = 7.2 Hz, 2H), 3.56 (dd, J_1 = 18 Hz, J_2 = 3.0 Hz, 1H), 3.14 (dd, J_1 = 18 Hz,

J_2 = 3.0 Hz, 1H), 1.34 (t, J = 7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 159.1, 147.5, 135.5 (q, J = 6.0 Hz), 131.5 (q, J = 2.3 Hz), 128.9, 127.9, 124.3 (q, J = 282 Hz), 109.8, 87.8 (q, J = 30 Hz), 61.6, 39.8, 14.2; IR (KBr): ν 3400, 2361, 1595, 1424, 1384, 1179, 1122, 470 cm^{-1}; HRMS (EI) calcd for $C_{14}H_{12}ClF_3O_3$ [M]$^+$ 320.0427, found 320.0430.

Ethyl 5-*m*-tolyl-5-(trifluoromethyl)-4,5-dihydrofuran-2-carboxylate (3ae). Reaction time: 72 h; Yield: 111 mg, 74%; colorless oil; R_f 0.5 (petroleum ether/ethyl acetate = 20 : 1); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.39–7.34 (m, 2H), 7.31–7.26 (m, 1H), 7.19–7.17 (m, 1H), 5.94 (t, J = 3.0 Hz, 1H), 4.30 (m, 2H), 3.54 (dd, J_1 = 18 Hz, J_2 = 3.0 Hz, 1H), 3.18 (dd, J_1 = 18 Hz, J_2 = 3.0 Hz, 1H), 2.37 (s, 3H), 1.33 (t, J = 7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 159.3, 147.6, 138.3, 136.9, 130.0, 128.5, 126.9, 124.5 (q, J = 282 Hz), 123.4, 109.9, 88.2 (q, J = 30 Hz), 61.5, 39.8, 21.5, 14.2; IR (KBr): ν 2359, 1737, 1649, 1448, 1373, 1311, 1265, 1234, 1168, 1125, 1015, 788, 738, 531 cm^{-1}; HRMS (EI) calcd for $C_{15}H_{15}F_3O_3$ [M]$^+$ 300.0973, found 300.0977.

Ethyl 5-(thiophen-2-yl)-5-(trifluoromethyl)-4,5-dihydrofuran-2-carboxylate (3af). Reaction time: 72 h; Yield: 45 mg, 52% (0.3 mmol substrate was used); colorless oil; R_f 0.4 (petroleum ether/ethyl acetate = 20 : 1); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.37 (dd, J_1 = 5.1 Hz, J_2 = 1.2 Hz, 1H), 7.23 (d, J = 3.6 Hz, 1H), 7.04 (dd, J_1 = 5.1 Hz, J_2 = 3.6 Hz, 1H), 5.96 (t, J = 3.0 Hz, 1H), 4.30 (qd,, J_1 = 7.2 Hz, J_2 = 1.2 Hz, 2H), 3.55 (dd, J_1 = 18 Hz, J_2 = 3.0 Hz, 1H), 3.26–3.19 (m, 1H), 1.33 (t, J = 7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 159.1, 147.6, 139.9, 127.4, 126.8, 126.4, 123.9 (q, J = 281 Hz), 109.7, 87.0 (q, J = 30 Hz), 61.6, 40.9, 14.3; IR (KBr): ν 3362, 2363, 1734, 1645, 1595, 1432, 1373, 1316, 1240, 1171, 1013, 711 cm^{-1}; HRMS (EI) calcd for $C_{12}H_{11}F_3O_3S$ [M]$^+$ 292.0381, found 292.0385.

Cyclohexyl 5-phenyl-5-(trifluoromethyl)-4,5-dihydrofuran-2-carboxylate (3ba). Reaction time: 48 h; Yield: 158 mg, 93% (room temperature); white solid, m.p. 38–39 °C; R_f 0.5 (petroleum ether/ethyl acetate = 20 : 1); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.48–7.46 (m, 2H), 7.31–7.24 (m, 3H), 5.80 (t, J = 3.0 Hz, 1H), 4.81 (m, 1H), 3.44 (dd, J_1 = 5.1 Hz, J_2 = 1.2 Hz, 1H), 3.05 (dd, J_1 = 5.1 Hz, J_2 = 1.2 Hz, 1H), 1.75–1.74 (m, 2H), 1.64–1.61 (m, 2H), 1.43–1.14 (m, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 158.5, 147.8, 137.0, 129.1, 128.4, 126.3, 124.4 (q, J = 281 Hz), 109.3, 88.0 (q, J = 30 Hz), 73.8, 39.7, 31.4, 25.3, 23.5; IR (KBr): ν 3443, 2938, 2861, 1730, 1648, 1450, 1309, 1233, 1170, 1131, 1059, 1012, 980, 739, 707, 650 cm^{-1}; HRMS (EI) calcd for $C_{18}H_{19}F_3O_3$ [M]$^+$ 340.1286, found 340.1291.

Cyclohexyl 5-(4-methoxyphenyl)-5-(trifluoromethyl)-4,5-dihydrofuran-2-carboxylate (3bc). Reaction time: 72 h; Yield: 112 mg, 61%; white solid, m.p. 34–35 °C; R_f 0.4 (petroleum ether/ethyl acetate = 20 : 1); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.49 (d, J = 8.7 Hz, 1H), 6.92 (d, J = 8.7 Hz, 1H), 5.90 (t, J = 3.0 Hz, 1H), 4.92 (m, 1H), 3.80 (s, 3H), 3.52 (dd, J_1 = 5.1 Hz, J_2 = 1.2 Hz, 1H), 3.15 (dd, J_1 = 5.1 Hz, J_2 = 1.2 Hz, 1H), 1.89–1.87 (m, 2H), 1.77–1.73 (m, 2H), 1.43–1.26(m, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 160.3, 158.7, 147.8, 128.9, 127.7, 124.5 (q, J = 281 Hz), 113.9, 109.4, 87.9 (q, J = 30 Hz), 73.9, 55.4, 39.7, 31.5, 25.4, 23.7; IR (KBr): ν 2939, 2860, 1730, 1646, 1613, 1514, 1451, 1378, 1303, 1250, 1233, 1177, 1065, 997, 951, 865, 737 cm^{-1}; HRMS (EI) calcd for $C_{19}H_{21}F_3O_4$ [M]$^+$ 370.1392, found 370.1397.

Cyclohexyl 5-(thiophen-2-yl)-5-(trifluoromethyl)-4,5-dihydrofuran-2-carboxylate (3bf). Reaction time: 72 h; Yield: 93 mg, 54%; white solid, m.p. 37–38 °C; R_f 0.5 (petroleum ether/ethyl acetate = 20 : 1); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.36 (dd, J_1 = 5.1 Hz, J_2 = 0.9 Hz, 1H), 7.23 (d, J = 3.6 Hz, 1H), 7.04 (dd, J_1 = 5.1 Hz, J_2 = 3.6 Hz, 1H), 5.92 (t, J = 3.0 Hz, 1H), 4.92 (m, 1H), 3.55 (dd, J_1 = 5.1 Hz, J_2 = 1.2 Hz, 1H), 3.20 (dd, J_1 = 5.1 Hz, J_2 = 1.2 Hz, 1H), 1.89–1.86 (m, 2H), 1.78–1.73 (m, 2H), 1.58–1.26 (m, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 158.5, 147.9, 140.0, 127.3, 126.8, 126.4, 123.9 (q, J = 281 Hz), 109.3, 86.9 (q, J = 30 Hz), 74.1, 40.9, 31.5, 25.4, 23.7; IR (KBr): ν 3442, 2938, 2860, 1731, 1646, 1450, 1377, 1314, 1239, 1171, 1126, 1004, 974, 912, 862, 711 cm^{-1}; HRMS (EI) calcd for $C_{16}H_{17}F_3O_3S$ [M]$^+$ 346.085, found 346.0856.

General procedure for the hydrogenation of dihydrofurans

An oven-dried 50 mL Schlenk tube equipped with a stirrer bar was charged with 10% Pd/C (10% weight). This tube was closed with a septum, evacuated, and back-filled with hydrogen. To this mixture was added a methanol (6 mL, except for the reaction of **3ad**, which was carried out in ethanol) solution of the dihydrofurans **3**. The mixture was stirred for 24 h at RT. The mixture was diluted with ethyl acetate and passed through a short Celite pad. The solvent was removed under reduced pressure and the residue was purified by chromatography on silica gel (petroleum ether/EtOAc = 50 : 1) to give the desired product as a colorless oil.

Ethyl 5-phenyl-5-(trifluoromethyl)-tetrahydrofuran-2-carboxylate (4aa). Colorless oil; R_f 0.4 (petroleum ether/ethyl acetate = 20 : 1); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.55–7.53 (m, 2H), 7.40–7.34 (m, 3H), 4.67–4.62 (m, 1H), 4.32–4.20 (m, 2H), 2.78–2.68 (m, 1H), 2.42–2.26 (m, 2H), 2.21–2.12 (m, 1H), 1.31 (t, J = 7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 170.9, 137.5, 128.7, 128.3, 126.6 (q, J = 0.75 Hz), 124.9 (q, J = 282 Hz), 87.1 (q, J = 29 Hz), 78.5, 61.3, 33.7, 29.3, 14.1; IR (KBr): ν 3336, 1757, 1595, 1450, 1299, 1176, 1095, 1031, 764, 702 cm^{-1}; HRMS (EI) calcd for $C_{14}H_{15}F_3O_3$ [M]$^+$ 288.0973, found 288.0977.

Ethyl 5-*p*-tolyl-5-(trifluoromethyl)-tetrahydrofuran-2-carboxylate (4ab). Colorless oil; R_f 0.4 (petroleum ether/ethyl acetate = 20 : 1); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.42 (d, J = 8.1 Hz, 2H), 7.18 (d, J = 8.1 Hz, 2H), 4.63 (t, J = 6.4 Hz, 1H), 4.34–4.17 (m, 2H), 2.75–2.65 (m, 1H), 2.41–2.27 (m, 2H), 2.35 (s, 3H), 2.20–2.14 (m, 1H), 1.31 (t, J = 7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 171.1, 138.7, 134.6, 129.1, 126.6, 125.0 (q, J = 282 Hz), 87.2 (q, J = 29 Hz), 78.5, 61.4, 33.7, 29.4, 21.1, 14.2; IR (KBr): ν 2917, 1758, 1593, 1449, 1298, 1161, 1094, 1033, 814 cm^{-1}; HRMS (EI) calcd for $C_{15}H_{17}F_3O_3$ [M]$^+$ 302.113, found 302.1133.

Ethyl 5-(4-methoxyphenyl)-5-(trifluoromethyl)-tetrahydrofuran-2-carboxylate (4ac). Colorless oil; R_f 0.4 (petroleum ether/ethyl acetate = 20 : 1); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.45 (d, J = 8.7 Hz, 2H), 6.89 (d, J = 8.7 Hz, 2H), 4.63 (t, J = 6.5 Hz, 3H), 4.34–4.16 (m, 2H), 3.79 (s, 3H), 2.74–2.64 (m, 1H), 2.41–2.27 (m, 2H), 2.25–2.11 (m, 1H), 1.31 (t, J = 7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 171.1, 159.9, 129.4, 128.0, 125.0 (q, J = 282 Hz), 113.7, 86.9 (q, J = 29 Hz), 78.5, 61.3, 55.3, 33.6, 29.4, 14.1; IR (KBr): ν 2985, 1758, 1596, 1492, 1375, 1297, 1178, 1092, 1031, 914, 826, 517 cm^{-1}; HRMS (EI) calcd for $C_{15}H_{17}F_3O_4$ [M]$^+$ 318.1079, found 318.1084.

Ethyl 5-(4-chlorophenyl)-5-(trifluoromethyl)-tetrahydrofuran-2-carboxylate (4ad). Colorless oil; R_f 0.4 (petroleum ether/ethyl acetate = 20 : 1); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.56–7.46 (m, 2H), 7.39–7.33 (m, 2H), 4.67–4.62 (m, 1H), 4.33–4.20 (m, 2H), 2.78–2.69 (m, 1H), 2.39–2.15 (m, 3H), 1.32 (t, J = 7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 170.9, 136.2, 135.0, 128.7, 128.2, 124.8 (q, J = 282 Hz), 86.9 (q, J = 29 Hz), 78.7, 61.5, 33.8, 29.4, 14.2; IR (KBr): ν 2983, 1757, 1612, 1584, 1513, 1464, 1375, 1302, 1252, 1174, 1094, 913, 832, 740 cm^{-1}; HRMS (EI) calcd for $C_{14}H_{14}ClF_3O_3$ $[M]^+$ 322.0584, found 322.0587.

Cyclohexyl 5-(thiophen-2-yl)-5-(trifluoromethyl)-tetrahydrofuran-2-carboxylate (4af). Colorless oil; R_f 0.4 (petroleum ether/ethyl acetate = 20 : 1); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.32 (dd, J_1 = 5.1 Hz, J_2 = 0.8 Hz, 1H), 7.10 (d, J = 3.6 Hz, 1H), 7.02 (dd, J_1 = 5.1 Hz, J_2 = 3.6 Hz, 1H), 4.90–4.81 (m, 1H), 4.75–4.72 (m, 1H), 2.73–2.63 (m, 1H), 2.44–2.26 (m, 3H), 1.89–1.84 (m, 2H), 1.76–1.73 (m, 2H), 1.55–1.26 (m, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 170.5, 141.6, 127.4, 126.4, 125.9 (q, J = 0.75 Hz), 124.4 (q, J = 282 Hz), 86.3 (q, J = 31 Hz), 79.2, 74.0, 34.9, 31.5 (q, J = 4.5 Hz), 29.5, 25.4, 23.7 (q, J = 2.3 Hz); IR (KBr): ν 2938, 2859, 1732, 1594, 1455, 1177, 1082, 1014, 707 cm^{-1}; HRMS (EI) calcd for $C_{16}H_{19}F_3O_3S$ $[M]^+$ 348.1007, found 348.1011.

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