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Titanocene(III) Chloride Mediated Stereoselective Synthesis of Trisubstituted Tetrahydrofurans and a Spirolactone by Tandem Radical Reactions

Shirshendu Mukherjee,[a] Rajdip Roy,[a] and Subhas Chandra Roy*[a]

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The titanocene(III) chloride (Cp_2TiCl) mediated stereoselective synthesis of highly substituted tetrahydrofurans has been achieved by a reaction that proceeds through a tandem radical cyclization reaction between a Baylis–Hillman adduct and an activated bromo/iodo compound. The reaction of an epoxide with the Baylis–Hillman adduct furnished a spirolactone through a radical cyclization followed by an in situ lactonization. Cp_2TiCl was prepared in situ from commercially available Cp_2TiCl_2 and zinc dust in tetrahydrofuran.

Introduction

Carbon–carbon bond formation and functional group transformations are the most important reactions for designing molecular frameworks in organic chemistry.[1] Amongst the large number of carbon–carbon bond-forming reactions, the Baylis–Hillman reaction[2] is considered a useful carbon–carbon bond-forming protocol, and attention for it has increased because of its two important features – atom economy and the generation of functional groups in close proximity to provide valuable intermediates for synthetic organic chemists. Radical-mediated reactions have also become an important synthetic tool for the development of efficient carbon–carbon bond-forming reactions because of the mild reaction conditions, high levels of regio- and stereoselectivity, and significant functional group tolerance.[3] An intramolecular radical cyclization reaction is a well-known and useful tool to construct carbocyclic and heterocyclic rings.[4] When carbon–carbon bond formation is achieved through an intermolecular tandem radical cyclization, it obviously becomes an important synthetic approach to synthesize many useful intermediates for natural product synthesis. The mild and efficient bis(cyclopentadienyl)titanium(III) chloride (Cp_2TiCl) mediated radical reactions have been in the spotlight in recent years to utilize radical technology for the development of significant protocols for the syntheses of natural products and related useful compounds.[5]

Substituted tetrahydrofurans are widely found in various types of bioactive natural products. Because of their widespread occurrence in nature and broad range of biological activities, trisubstituted tetrahydrofurans[6] have attracted much attention by organic chemists over the years. In addition, some tetrahydrofurans are precursors to α-methylene-γ-butyrolactones, an important structural unit that is mainly present in sesquiterpenes and other cytotoxic and antitumor agents.[7] Spirolactones also contain an important fragment that is found in a wide range of natural products and related biologically active compounds.[8] As a result, the syntheses of substituted tetrahydrofurans[6] and spirolactones[9] have for years received much attention, and, still, it is a challenge to organic chemists to develop a viable method. We report, herein, a mild and efficient method for the syntheses of trisubstituted tetrahydrofurans and a spirolactone in satisfactory yields. The reaction proceeds through a tandem radical reaction by employing a Baylis–Hillman adduct[10] and either an activated bromo/iodo compounds or epoxide along with Cp_2TiCl as a radical generator[5a].

Results and Discussion

Tandem radical reactions between methyl 2-[aryl(prop-2-ynyloxy)methyl]acrylates and activated bromo/iodo compounds with Ti^{III} species as the radical initiator provided methyl 4-methylene-3-arylethyl-2-aryltetrahydrofuran-3-carboxylates as the sole product. Not only esters but also several 2-[aryl(prop-2-ynyloxy)methyl]acrylonitriles underwent similar radical reactions under these conditions (see Scheme 1).

Initially, the reaction was performed with methyl 2-[phenyl(prop-2-ynyloxy)methyl]acrylate (**1a**) and benzyl bromide in tetrahydrofuran (THF, 26 mL per mmol) in the presence of Cp_2TiCl in dry deoxygenated THF to afford **2a** in an unsatisfactory yield. When the reaction was performed in a concentrated solution in THF (0.067 M), however, the yield of **2a** increased considerably. Thus, a series of activated ester and cyano compounds **1** were subjected to the titanocene(III) chloride mediated reaction with various bromo/iodo compounds to furnish **2**, and the results are

[a] Department of Organic Chemistry, Indian Association for the Cultivation of Science,
Jadavpur, Kolkata 700032, India
E-mail: ocscr@iacs.res.in
http://www.iacs.res.in

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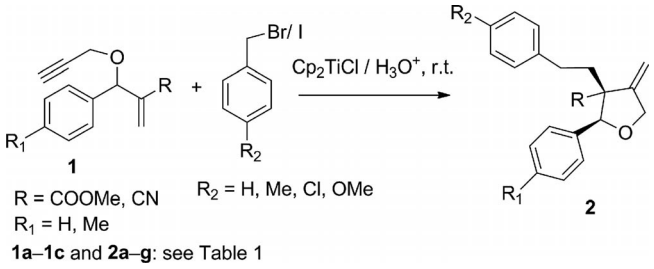


Scheme 1. Titanocene(III) chloride mediated synthesis of tetrahydrofurans.

summarized in Table 1. It is noteworthy that no other isomer was produced or any unreacted starting material was recovered in all the transformations.

The reaction was initiated by an intermolecular addition of the radical species that is generated from the activated bromide or iodide to the activated double bond of the carboxylate or carbonitrile (i.e., **1**) followed by an intramolecular radical cyclization that involves the triple bond of the propargyl group to give **2**. It was shown that electron-donating groups on the benzene ring of the bromo compound (see Table 1, Entry 8) provided the optimum yield to give **2h**. Both a substituted bromo compound (see Table 1, Entries 2 and 7) and a chloro-substituted bromo compound (see Table 1, Entries 3 and 6) were employed, but there were no significant differences in the yields of these reactions. Activated iodo compounds also underwent a similar reaction with good yield of the product (see Table 1, Entries 9–12). However, when a strong electron-withdrawing group (i.e., NO_2) was present on the aromatic ring (see Table 1, Entry 13), the reaction did not proceed, and only the starting compound was isolated. We also observed no significant difference between the yields of reactions that used 2-[aryl(prop-2-ynyloxy)methyl]acrylonitriles and those resulting from the corresponding acrylate esters. The structural connectivity and the relative stereochemistry of all the products **2a**–**2h** were determined by spectral and analytical studies and finally confirmed by a single-crystal X-ray diffraction study of 3-(4-chlorophenylethyl)-4-methylene-2-*p*-tolyltetrahydrofuran-3-carbonitrile (**2f**, see Figure 1).

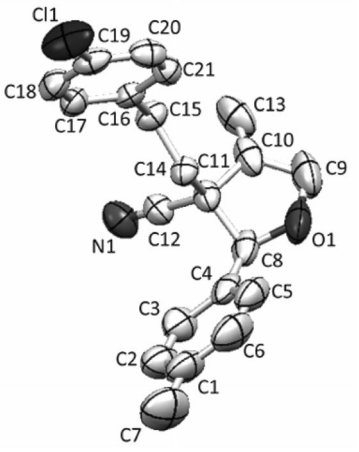
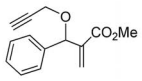
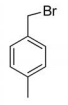
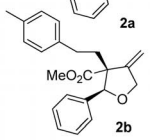
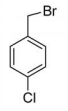
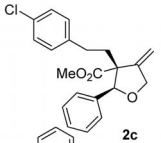
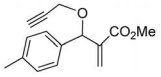
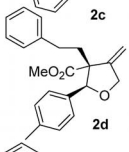
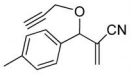
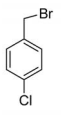
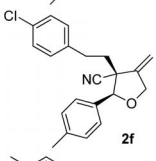
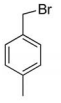
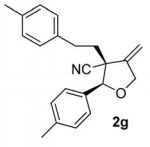
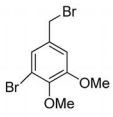
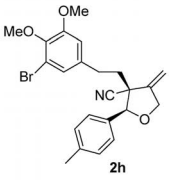
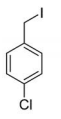
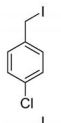
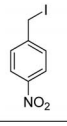


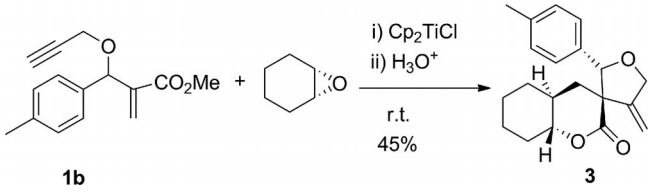
Figure 1. X-ray crystal structure of **2f**.

Table 1. Titanocene(III) mediated synthesis of tetrahydrofurans.

Entry	Substrate	Halide	Product	Yield (%)[a]
1	 **1a**		 **2a**	58
2	**1a**		 **2b**	66
3	**1a**		 **2c**	58
4	 **1b**		 **2d**	60
5	 **1c**		 **2e**	66
6	**1c**		 **2f**	56
7	**1c**		 **2g**	55
8	**1c**		 **2h**	68
9	**1a**		**2a**	60
10	**1a**		**2c**	58
11	**1b**		**2d**	63
12	**1c**		**2f**	58
13	**1a**		no reaction	

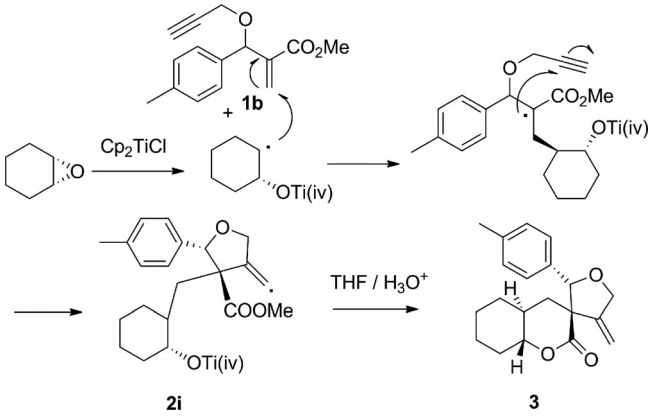
[a] Isolated yield after column chromatography.

In continuation of the synthesis of trisubstituted tetrahydrofurans, we have also developed a method for the synthesis of a spirolactone, the reaction of which proceeds through a tandem radical cyclization and in situ lactonization in one pot with Cp_2TiCl as the radical initiator (see Scheme 2). Thus, the treatment of the ester **1b** with cyclohexene epoxide in the presence of Cp_2TiCl in THF at room temperature afforded only spirolactone **3** in moderate yield after column chromatography. There was no trace amount of any other isomer or the starting material. The moderate yield of compound **3** is probably a result of the formation of some polymeric material, which could not be isolated or characterized.



Scheme 2. Synthesis of spirolactone **3**.

The probable mechanism for the formation of spirolactone **3** is shown in Scheme 3. The reason for the high diastereoselectivity in the radical cyclization steps is not clear at this stage.



Scheme 3. Probable mechanism for the formation of spirolactone **3**.

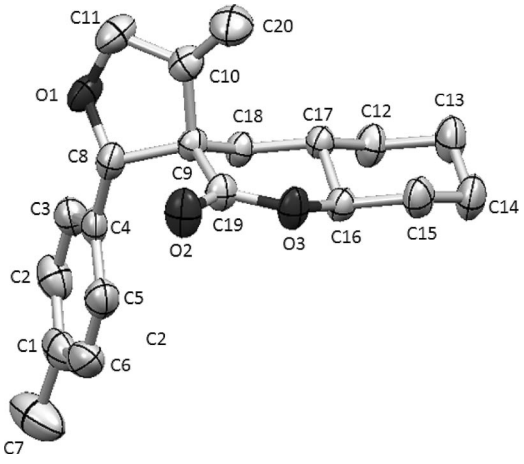


Figure 2. X-ray structure of **3**.

On the basis of the stereochemistry of **2f**, which was already established by X-ray studies, the stereochemistry of other derivatives of tetrahydrofuran could be easily predicted. The stereochemistry of spirolactone **3** was determined by spectral and analytical studies and finally confirmed by a single-crystal X-ray diffraction study (see Figure 2).

Conclusions

In summary, we have developed an efficient method for the stereoselective synthesis of trisubstituted tetrahydrofurans and a spirolactone. These reactions proceed through a tandem radical cyclization by using Cp_2TiCl as the radical initiator to give the products in satisfactory yields.

Experimental Section

General Methods: Melting points were measured in open capillary tubes. The ^1H and ^{13}C NMR spectroscopic data were recorded with a Bruker DPX 300 spectrometer by using $CDCl_3$ with tetramethylsilane as the internal standard. IR spectra were recorded with a Shimadzu FT IR-8300. Column chromatography was performed on silica gel (60–120 mesh), and preparative TLC was performed with precoated silica 60 F254 plates (0.2 mm). High resolution mass spectrometry was carried out with a Qtof Micro YA263 instrument. Diethyl ether and tetrahydrofuran were freshly distilled from sodium. Methylene chloride was freshly distilled from calcium hydride. Light petroleum with a boiling range of 60–80 °C was used for chromatography.

Typical Procedure for the Synthesis of (2*S*,3*R*)-Methyl 4-Methylene-3-phenethyl-2-phenyltetrahydrofuran-3-carboxylate (2a): A solution of Cp_2TiCl_2 (270 mg, 1.09 mmol) in dry deoxygenated THF (5 mL) was stirred with activated Zn dust (161 mg, 2.47 mmol) for 1 h under argon. [The activated zinc dust was prepared by washing commercially available Zn dust (20 g) with of 4 N HCl (60 mL) and then with water until the washings were neutral. The Zn was then washed with dry acetone and dried in vacuo.] The resulting green solution, without the zinc dust, was transferred through a cannula into a dropping funnel. The solution was then was added dropwise over a period of 8 h to a stirred solution of benzyl bromide (84 mg, 0.5 mmol) and methyl 2-[phenyl(prop-2-ynyloxy)methyl]acrylate (**1a**, 75 mg, 0.33 mmol) in dry deoxygenated THF (2.5 mL) under argon. The reaction mixture was stirred for an additional 4 h and then quenched with saturated aqueous sodium dihydrogen phosphate solution (2 mL). The solvent was removed under reduced pressure, and the residue was extracted with diethyl ether (3 × 25 mL). The combined ether layers were washed with brine (2 × 10 mL) and dried with anhydrous Na_2SO_4. After removal of the solvent, the crude residue was purified by chromatography on a silica gel column (0.5% ethyl acetate in light petroleum, R_f = 0.24) to furnish methyl 4-methylene-3-phenethyl-2-phenyltetrahydrofuran-3-carboxylate (**2a**, 62 mg, 58%) as a colorless oil. IR (neat): $\tilde{\nu}$ = 1731, 1514, 1454, 1234 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 1.69–1.82 (m, 2 H), 2.14–2.2 (m, 1 H), 2.38–2.44 (m, 1 H), 3.84 (s, 3 H), 4.57 (d, J = 13.5 Hz, 1 H), 4.71 (d, J = 13.0 Hz, 1 H), 5.19 (t, J = 2.5 Hz, 2 H), 5.59 (s, 1 H), 6.85 (d, J = 7.5 Hz, 2 H),

7.09 (t, J = 7.0 Hz, 2 H), 7.16 (t, J = 7.5 Hz, 2 H), 7.29–7.4 (m, 4 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 29.9, 31.1, 35.2, 52.5, 60.7, 71.0, 86.2, 107.2, 125.8, 126.7, 127.9, 128.2, 128.3, 128.4, 128.5, 129.3, 137.6, 142.4, 150.8, 173.6 ppm. HRMS (ESI): calcd. for $C_{21}H_{22}O_3Na$ [M + Na]$^+$ 345.1467; found 345.1468.

Methyl (2*S*,3*R*)-3-(4-Methylphenethyl)-4-methylene-2-phenyltetrahydrofuran-3-carboxylate (2b): Colorless oil (78 mg, 66% yield). IR (neat): $\tilde{\nu}$ = 3010, 1732, 1650, 1514, 1455, 1434, 1234, 1087 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.67–1.79 (m, 2 H), 2.09–2.16 (m, 1 H), 2.26 (s, 3 H), 2.33–2.37 (m, 1 H), 3.84 (s, 3 H), 4.56 (d, J = 13.5 Hz, 1 H), 4.69 (d, J = 13.0 Hz, 1 H), 5.16–5.19 (m, 2 H), 5.59 (s, 1 H), 6.75 (d, J = 8.0 Hz, 2 H), 6.98 (d, J = 7.5 Hz, 2 H), 7.28–7.39 (m, 5 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 21.1, 29.9, 30.6, 35.3, 52.6, 60.7, 71.0, 76.7, 86.2, 107.3, 126.7, 127.9, 128.2, 128.3, 128.8, 128.9, 129.1, 135.3, 137.6, 139.3, 150.8, 173.6 ppm. HRMS (ESI): calcd. for $C_{22}H_{24}O_3Na$ [M + Na]$^+$ 359.1623; found 359.1620.

Methyl (2*S*,3*R*)-3-(4-Chlorophenethyl)-4-methylene-2-phenyltetrahydrofuran-3-carboxylate (2c): Colorless oil (70 mg, 58% yield). IR (neat): $\tilde{\nu}$ = 3010, 1732, 1655, 1514, 1455, 1234, 1087 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.63–1.78 (m, 2 H), 2.1–2.16 (m, 1 H), 2.34–2.41 (m, 1 H), 3.84 (s, 3 H), 4.56 (d, J = 13.5 Hz, 1 H), 4.68 (d, J = 13.5 Hz, 1 H), 5.17 (t, J = 2.0 Hz, 1 H), 5.19 (s, 1 H), 5.58 (s, 1 H), 6.76 (d, J = 8.5 Hz, 2 H), 7.13 (d, J = 7.0 Hz, 2 H), 7.29–7.38 (m, 5 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 30.4, 35.1, 52.6, 60.5, 71.0, 86.1, 107.2, 126.5, 128.0, 128.3, 128.4, 129.7, 137.4, 140 8, 150.7, 173.4 ppm. HRMS (ESI): calcd. for $C_{21}H_{22}ClO_3$ [M + H]$^+$ 357.125; found 357.1172.

Methyl (2*S*,3*R*)-4-Methylene-3-phenethyl-2-*p*-tolyltetrahydrofuran-3-carboxylate (2d): Colorless oil (72 mg, 60% yield). IR (neat): $\tilde{\nu}$ = 3010, 1732, 1650, 1514, 1455, 1087 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.68–1.80 (m, 2 H), 2.18–2.24 (m, 1 H), 2.36 (s, 3 H), 2.39–2.45 (m, 1 H), 3.83 (s, 3 H), 4.56 (d, J = 13.0 Hz, 1 H), 4.68 (d, J = 13.0 Hz, 1 H), 5.18 (d, J = 10.5 Hz, 2 H), 5.54 (s, 1 H), 6.88 (d, J = 7.0 Hz, 2 H), 7.08–7.18 (m, 5 H), 7.24 (m, 2 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 21.3, 29.8, 31.1, 34.9, 52.5, 60.6, 70.9, 86.2, 107.2, 125.7, 126.5, 128.3, 128.4, 129.0, 134.4, 137.5, 142.5, 150.7, 173.6 ppm. HRMS (ESI): calcd. for $C_{22}H_{24}O_3Na$ [M + Na]$^+$ 359.1623; found 359.1625.

(2*S*,3*S*)-4-Methylene-3-phenethyl-2-*p*-tolyltetrahydrofuran-3-carbonitrile (2e): Crystalline solid (72 mg, 66% yield); m.p. 60–65 °C. IR (neat): $\tilde{\nu}$ = 3012, 1731, 1718, 1650, 1515, 1406, 1261, 1062 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.47–1.53 (m, 1 H), 1.59–1.64 (m, 1 H), 2.34 (s, 3 H), 2.43–2.49 (m, 1 H), 2.63–2.69 (m, 1 H), 4.59 (d, J = 13.5 Hz, 1 H), 4.71 (d, J = 13.5 Hz, 1 H), 5.18 (s, 1 H), 5.36 (s, 1 H), 5.52 (d, J = 2.5 Hz, 1 H), 6.99 (d, J = 7.5 Hz, 2 H), 7.14–7.23 (m, 5 H), 7.36 (d, J = 8.0 Hz, 2 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 21.3, 29.8, 30.8, 33.1, 50.8, 69.9, 86.2, 110.0, 120.4, 126.2, 128.4, 128.6, 129.3, 131.7, 138.5, 140.6, 147.2 ppm. HRMS (ESI): calcd. for $C_{21}H_{21}NONa$ [M + Na]$^+$ 326.1521; found 326.1523.

(2*S*,3*S*)-3-(4-Chlorophenethyl)-4-methylene-2-*p*-tolyltetrahydrofuran-3-carbonitrile (2f): Crystalline solid (101 mg, 56% yield); m.p. 90–95 °C. IR (neat): $\tilde{\nu}$ = 3012, 1731, 1718, 1650, 1515, 1406, 1261, 1062, 1024 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.42–1.54 (m, 2 H), 2.36 (s, 3 H), 2.41–2.46 (m, 1 H), 2.59–2.67 (m, 1 H), 4.58 (d, J = 13.6 Hz, 1 H), 4.71 (d, J = 13.5 Hz, 1 H), 5.18 (s, 1 H), 5.36 (s, 1 H), 5.50 (dd, J = 3.6 Hz, J = 2.0 Hz, 1 H), 6.91 (d, J = 8.4 Hz, 2 H), 7.16–7.20 (m, 4 H), 7.35 (d, J = 8.4 Hz, 2 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.3, 29.8, 30.2, 33.1, 50.6, 69.9, 86.2, 110.1, 120.2, 126. 2, 128.7, 129.4, 129.8, 131.6, 132.1, 138.6, 139.0, 147.1 ppm. HRMS (ESI): calcd. for $C_{21}H_{20}NOClNa$ [M + Na]$^+$ 360.1131; found 360.1131.

(2*S*,3*S*)-3-(4-Methylphenethyl)-4-methylene-2-*p*-tolyltetrahydrofuran-3-carbonitrile (2g): Crystalline solid (66 mg, 55% yield); m.p. 50–55 °C. IR (neat): $\tilde{\nu}$ = 3010, 1731, 1718, 1650, 1515, 1406, 1261, 1062, 1024 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.44–1.52 (m, 2 H), 2.27 (s, 3 H), 2.34 (s, 3 H), 2.38–2.46 (m, 1 H), 2.58–2.66 (m, 1 H), 4.59 (d, J = 14.0 Hz, 1 H), 4.71 (d, J = 14.0 Hz, 1 H), 5.18 (d, J = 4.4 Hz, 1 H), 5.35 (s, 1 H), 5.50 (t, J = 2.4 Hz, 1 H), 6.86 (d, J = 7.2 Hz, 2 H), 7.02 (d, J = 8.0 Hz, 2 H), 7.17 (d, J = 8.0 Hz, 2 H), 7.34 (d, J = 8.0 Hz, 2 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 21.0, 21.3, 22.8, 29.8, 30.4, 33.2, 50.8, 69.9, 75.2, 86.2, 111.3, 118.8, 120.4, 126.2, 128.3, 128.9, 129.1, 129.2, 129.3, 129.9, 135.8, 137.5, 138.5, 147.8 ppm. HRMS (ESI): calcd. for $C_{22}H_{23}NONa$ [M + Na]$^+$ 340.1677; found 340.1677.

(2*S*,3*S*)-3-(3-Bromo-4,5-dimethoxyphenethyl)-4-methylene-2-*p*-tolyltetrahydrofuran-3-carbonitrile (2h): Crystalline solid (114 mg, 68% yield); m.p. 65–70 °C. IR (neat): $\tilde{\nu}$ = 3010, 1731, 1644, 1515, 1406, 1261, 1023 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.33–1.39 (m, 1 H), 1.64–1.70 (m, 1 H), 2.34 (s, 3 H), 2.42–2.49 (m, 1 H), 2.76–2.82 (m, 1 H), 3.77 (s, 3 H), 3.80 (s, 3 H), 4.59 (d, J = 13.5 Hz, 1 H), 4.76 (d, J = 13.5 Hz, 1 H), 5.19 (s, 1 H), 5.38 (s, 1 H), 5.53 (s, 1 H), 6.45 (s, 1 H), 6.91 (s, 1 H), 7.18 (d, J = 8.0 Hz, 2 H), 7.36 (d, J = 8.0 Hz, 2 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 14.2, 21.3, 22.8, 29.5, 29.8, 31.3, 32.1, 50.6, 56.2, 56.3, 70.1, 86.1, 110.2, 113.3, 114.0, 115.8, 120.4, 126.3, 129.6, 131.8, 138.5, 146.8, 148.3, 148.6 ppm. HRMS (ESI): calcd. for $C_{23}H_{24}BrNO_3Na$ [M + Na]$^+$ 464.0837; found 464.0837.

Synthesis of Spirolactone 3: A solution of Cp_2TiCl_2 (137 mg, 0.55 mmol) in dry deoxygenated THF (6 mL) was stirred with activated Zn dust (82 mg, 1.26 mmol) for 1 h under argon. [The activated zinc dust was prepared by washing commercially available Zn dust (20 g) with of 4 N HCl (60 mL) an then with water until the washings were neutral, The Zn dust was then washed with dry acetone and dried in vacuo.] The resulting green solution, without the zinc dust, was transferred through a cannula into a dropping funnel. The solution was then added dropwise over a period of 8 h to a stirred solution of cyclohexene oxide (61 mg, 0.62 mmol) and the ester methyl 2-[(prop-2-ynyloxy)(*p*-tolyl)methyl]acrylate (**1b**, 75 mg, 0.30 mmol) in dry deoxygenated THF (2.5 mL) under argon. The reaction mixture was stirred for an additional 4 h and then carefully quenched with 20% aqueous H_2SO_4 (2 mL). The solvent was removed under reduced pressure, and the residue was extracted with diethyl ether (3 × 25 mL). The combined ether layers were washed with brine (2 × 10 mL) and dried with anhydrous Na_2SO_4. After removal of the solvent, the crude residue was purified by chromatography on a silica gel column (0.3% ethyl acetate in light petroleum, R_f = 0.25) to furnish spirolactone **3** (42 mg, 45% yield) as a crystalline solid; m.p. 110–115 °C. IR (neat): $\tilde{\nu}$ = 2927, 1720, 1514, 1456, 1330, 1226, 1062 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.87–0.90 (m, 1 H), 1.09–1.17 (m, 1 H), 1.21–1.26 (m, 2 H), 1.43 (dd, J = 2.8, 13.4 Hz, 2 H), 1.62–1.66 (m, 2 H), 1.79 (d, J = 10.8 Hz, 2 H), 2.06 (dd, J = 12.4, 3.2 Hz, 1 H), 2.34 (s, 3 H), 3.57 (dt, J = 21.8 Hz, J = 4.0 Hz, 1 H), 4.61 (d, J = 13.2 Hz, 1 H), 4.68 (d, J = 13.2 Hz, 1 H), 5.07 (d, J = 6.8 Hz, 2 H), 5.69 (s, 1 H), 7.14 (d, J = 8.0 Hz, 2 H), 7.21 (d, J = 8.0 Hz, 2 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.3, 24.2, 25.2, 30.5, 32.2, 32.4, 34.7, 58.7, 70.1, 84.6, 86.6, 106.6, 126.2, 129.1, 134.0, 137.6, 154.3, 172.0 ppm. HRMS (ESI): calcd. for $C_{20}H_{24}O_3Na$ [M + Na]$^+$ 335.1623; found 335.1625.

Typical Procedure for the Synthesis of Methyl 2-[Phenyl(prop-2-ynyloxy)methyl]acrylate (1a): Methyl 2-[hydroxy(phenyl)methyl]-

acrylate (415 mg, 2.15 mmol) was treated with lithium bis(trimethylsilyl)amide (1.0 M in THF, 2 equiv.) and hexamethylphosphoramide (0.76 mL, 4.3 mmol) in dry THF (2 mL) at –40 °C for 30 min. Propargyl bromide (0.30 mL, 4.3 mmol) was then added, and the resulting mixture was stirred at room temperature for 2.5 h. Upon completion (monitored by TLC), the reaction was quenched with distilled water (2 mL). Most of the solvent was removed under reduced pressure, and the residue was extracted with diethyl ether (3 × 25 mL). The combined organic layers were washed with water (2 × 10 mL) and saturated brine (2 × 5 mL) and then dried with anhydrous Na_2SO_4. The solvent was removed under reduced pressure, and the crude residue was purified by chromatography on a silica gel column (2% ethyl acetate in light petroleum, R_f = 0.24) to afford methyl 2-[phenyl(prop-2-ynyloxy)methyl]acrylate (**1a**, 380 mg, 77%) as a colorless oil. IR (neat): $\tilde{\nu}$ = 3303, 2160, 1722, 1406, 1255 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 2.44 (d, J = 2.0 Hz, 1 H), 3.69 (s, 3 H), 4.03 (dd, J = 15.5 Hz, J = 2.0 Hz, 1 H), 4.15 (dd, J = 16.0 Hz, J = 2.0 Hz, 1 H), 5.50 (s, 1 H), 6.00 (s, 1 H), 6.37 (s, 1 H), 7.28–7.37 (m, 5 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 51.9, 56.0, 74.8, 77.8, 79.6, 125.5, 128.0, 128.3, 128.5, 138.6, 140.7, 166.2 ppm. HRMS (ESI): calcd. for $C_{14}H_{14}O_3Na$ [M + Na]$^+$ 253.0841; found 253.0840.

Methyl 2-[(Prop-2-ynyloxy)(*p*-tolyl)methyl]acrylate (1b): Colorless oil (412 mg, 67% yield). IR (neat): $\tilde{\nu}$ = 3303, 2160, 1722, 1406, 1255 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 2.25 (s, 3 H), 2.36 (d, J = 2.5 Hz, 1 H), 3.62 (s, 3 H), 3.92 (dd, J = 15.7 Hz, J = 2.5 Hz, 1 H), 4.06 (dd, J = 15.7 Hz, J = 2.0 Hz, 1 H), 5.39 (s, 1 H), 5.92 (s, 1 H), 6.27 (s, 1 H), 7.0 (d, J = 8.0 Hz, 2 H), 7.18 (d, J = 7.5 Hz, 2 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 21.2, 51.9, 55.8, 74.6, 79.6, 125.2, 127.9, 129.2, 135.6, 138.0, 140.8, 166.2 ppm. HRMS (ESI): calcd. for $C_{15}H_{16}O_3Na$ [M + Na]$^+$ 267.0997; found 267.0996.

2-[(Prop-2-ynyloxy)(*p*-tolyl)methyl]acrylonitrile (1c): Colorless oil (411 mg, 68% yield). IR (neat): $\tilde{\nu}$ = 3303, 2227, 2160, 1722, 1514, 1406, 1255 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 2.36 (s, 3 H), 2.47 (t, J = 2 Hz, 1 H), 4.07 (dd, J = 16.0 Hz, J = 2.0 Hz, 1 H), 4.22 (dd, J = 15.7 Hz, J = 2.5 Hz, 1 H), 5.16 (s, 1 H), 6.05 (d, J = 6.5 Hz, 2 H), 7.20 (d, J = 8.0 Hz, 2 H), 7.26 (d, J = 7.5 Hz, 2 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 21.3, 55.8, 75.8, 78.7, 79.1, 116.9, 124.7, 127.4, 129.7, 130.8, 133.4, 139.2 ppm. HRMS (ESI): calcd. for $C_{14}H_{13}NONa$ [M + Na]$^+$ 234.0895; found 234.0890.

Supporting Information (see footnote on the first page of this article): ^1H and ^{13}C NMR spectra of compounds **1a**–**1c**, **2a**–**2h**, and **3** as well as X-ray crystallographic data of compounds **2f** and **3**.

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