

1-*tert*-Butoxy-2-*tert*-butoxycarbonyl-1,2-dihydroisoquinoline: A Novel and Chemoselective *tert*-Butoxycarbonylation Reagent

Hidekazu Ouchi, Yukako Saito, Yutaka Yamamoto, and Hiroki Takahata*

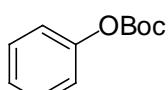
Faculty of Pharmaceutical Sciences, Tohoku Pharmaceutical University
Sendai, 981-8558, Japan.

Supporting Information

General Information. Melting points were determined on a Mel-Temp melting point apparatus using an open capillary tube. All melting and boiling points are uncorrected. Infrared (IR) spectra were recorded on a Perkin-Elmer 1600 series FT-IR spectrometer. Mass spectra (MS) were recorded on a JEOL JMN-DX 303/JMA-DA 5000 spectrometer. Microanalyses were performed on a Perkin-Elmer CHN 2400 Elemental Analyzer. Optical rotations were measured with a JASCO DIP-360 digital polarimeter. Proton nuclear magnetic resonance (¹H NMR) spectra were recorded on a JEOL JNM-EX 270 (270 MHz) or a JEOL JNM-PMX 60si (60 MHz) spectrometer, using tetramethylsilane as an internal standard. The following abbreviations are used: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad. Column chromatography was carried out on Merck Silica gel 60 (230-400 mesh for flash chromatography).

1-*tert*-Butoxy-2-*tert*-butoxycarbonyl-1,2-dihydroisoquinoline is abbreviated as BBDI.

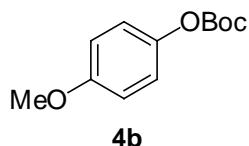
***tert*-Butoxycarbonylation of Phenols by BBDI.**



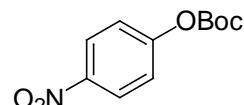
4a

***tert*-Butyl Phenyl Carbonate (4a).** A mixture of BBDI (1.52 g, 5 mmol) and phenol (**3a**, 0.47 g, 5 mmol) in benzene (10 mL) was heated under reflux for 1 hr. The reaction mixture

was washed with 5 % HCl solution (10 mL) and brine (10 mL), dried (MgSO_4), and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel to give **4a** (0.96 g, 99 %) as a colorless liquid; bp 88–90 °C (1 mmHg) [lit.¹ bp 74–78 °C (0.5 mmHg)]. IR (neat) cm^{-1} : 1758. ^1H NMR (60 MHz, CDCl_3) δ 1.53 (s, 9H), 6.97–7.50 (m, 5H). MS (EI) m/z 194 (M^+).

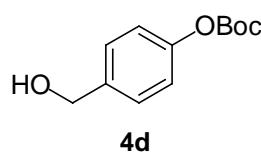


tert-Butyl 4-Methoxyphenyl Carbonate (4b). This compound was prepared from BBDI (1.52 g, 5 mmol) and 4-methoxyphenol (**3b**, 0.62 g, 5 mmol) by the same procedure as described for **4a** to give **4b** (1.03 g, 92 %) as colorless plates; mp 66–67 °C (hexane). IR (KBr) cm^{-1} : 1752. ^1H NMR (60 MHz, CDCl_3) δ 1.57 (s, 9H), 3.78 (s, 3H), 6.70–7.20 (m, 4H). MS (EI) m/z 224 (M^+). *Anal.* Calcd for $\text{C}_{12}\text{H}_{16}\text{O}_4$: C, 64.27%; H, 7.19%. Found: C, 64.21%; H, 7.24%.



4c

tert-Butyl 4-Nitrophenyl Carbonate (4c). A mixture of BBDI (1.52 g, 5 mmol) and 4-nitrophenol (**3c**, 0.695 g, 5 mmol) in benzene (10 mL) was stirred at room temperature for 3 hr. The reaction mixture was worked up by the same procedure as described above for **4a** to give **4c** (1.15 g, 96 %) as a white powder; mp 78–79 °C (hexane) [lit.² mp 78.5–79.5 °C]. IR (KBr) cm^{-1} : 1346, 1757. ^1H NMR (60 MHz, CDCl_3) δ 1.58 (s, 9H), 7.38 (d, J = 9 Hz, 2H), 8.30 (d, J = 9 Hz, 2H). MS (EI) m/z 240 (M^++1).



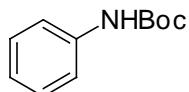
tert-Butyl 4-(Hydroxymethyl)phenyl Carbonate (4d). A mixture of BBDI (1.0 g, 3.3

¹ Carpino, L. A.; Carpino, B. A.; Giza, C. A.; Murray, R. W.; Santilli, A. A.; Terry, P. H. *Org. Syn., Coll. Vol. V* **1973**, 168–171.

² Anderson, J. W.; McGregor, A. C. *J. Am. Chem. Soc.* **1957**, 79, 6180–6183.

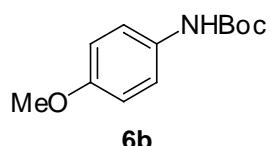
mmol) and 4-(hydroxymethyl)phenol (**3d**, 0.372 g, 3 mmol) in benzene (10 mL) was heated under reflux for 3 hr. The reaction mixture was worked up by the same procedure as described above for **4a** to give **4d**³ (0.612 g, 91 %) as a white powder; mp 39–40 °C (pentane). IR (KBr) cm^{-1} : 1762, 3270. ^1H NMR (270 MHz, CDCl_3) δ 1.56 (s, 9H), 1.87 (br s, 1H), 4.66 (s, 2H), 7.36 (d, J = 8.6 Hz, 2H), 7.15 (d, J = 8.6 Hz, 2H). MS (EI) m/z 224 (M^+).

General Procedure for the *tert*-Butoxycarbonylation of Anilines by BBDI. A solution of BBDI (6 mmol) in DME (10 mL) was added to a stirred suspension of aniline hydrochloride (5 mmol) in DME (10 mL), with stirring at room temperature for 16 hr. After removing DME under reduced pressure, the residue was dissolved in AcOEt, washed with 5 % HCl solution (10 mL) and brine (10 mL), dried (MgSO_4), and concentrated *in vacuo*. The residue was purified by flash column chromatography on silica gel.



6a

***tert*-Butyl N-Phenylcarbamate (6a).** Yield 0.93 g (97 %); colorless needles; mp 137–138 °C (Et_2O –hexane) [lit.⁴ mp 135–136 °C]. IR (KBr) cm^{-1} : 1687, 3313. ^1H NMR (270 MHz, CDCl_3) δ 1.52 (s, 9H), 6.49 (br s, 1H), 6.99–7.06 (m, 1H), 7.25–7.37 (m, 4H). MS (EI) m/z 193 (M^+).



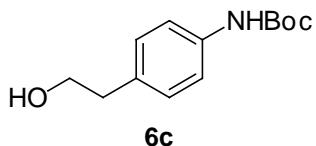
6b

***tert*-Butyl N-(4-Methoxyphenyl)carbamate (6b).** Yield 1.09 g (98 %); colorless needles; mp 96–97 °C (hexane) [lit.⁵ 91.5–92.5 °C]. IR (KBr) cm^{-1} : 1695, 3366. ^1H NMR (270 MHz, CDCl_3) δ 1.51 (s, 9H), 3.78 (s, 3H), 6.34 (br s, 1H), 6.83 (d, J = 9.1 Hz, 2H), 7.26 (d, J = 9.1 Hz, 2H). MS (EI) m/z 223 (M^+).

³ Ito, H.; Ichimura, K. *Macromol. Chem. Phys.* **2000**, *201*, 132–138.

⁴ Bailey, W. J.; Griffith, J. R. *J. Org. Chem.* **1978**, *43*, 2690–2692.

⁵ Cho, I. –S.; Gong, L.; Muchowski, J. M. *J. Org. Chem.* **1991**, *56*, 7288–7291.



tert-Butyl N-[4-(2-Hydroxyethyl)phenyl]carbamate (6c). Yield 1.15 g (97 %); a white powder; mp 109–110 °C (hexane). IR (KBr) cm^{-1} : 1699, 3364, 3413. ^1H NMR (270 MHz, CDCl_3) δ 1.40 (t, J = 5.8 Hz, 1H), 1.51 (s, 9H), 2.82 (t, J = 6.5 Hz, 2H), 6.82 (dd, J = 6.4, 12.3 Hz, 2H), 6.45 (br s, 1H), 7.15 (d, J = 8.4 Hz, 2H), 7.30 (d, J = 8.6 Hz, 2H). MS (EI) m/z 237 (M^+). *Anal.* Calcd for $\text{C}_{13}\text{H}_{19}\text{NO}_3$: C, 65.80%; H, 8.07%; N, 5.90%. Found : C, 66.01%; H, 8.03%; N, 5.88%.

General Procedure for the *N*-tert-Butoxycarbonylation of Amino Acid Esters by BBDI.

Method A: A solution of BBDI (15 mmol) in DME (20 mL) was added to a stirred suspension of amino acid ester hydrochloride (5 mmol) in DME (10 mL), with stirring at room temperature for overnight. After removing DME under reduced pressure, the residue was dissolved in AcOEt, washed with 5 % HCl solution (10 mL x 2) and brine (10 mL), dried (MgSO_4), and concentrated *in vacuo*. The residue was purified by flash column chromatography on silica gel. Method B: A stirred mixture of BBDI (15 mmol) and amino acid alkyl ester hydrochloride (5 mmol) in Et_2O (30 mL) was refluxed for overnight. The reaction mixture was washed with 5 % HCl solution (10 mL x 2) and brine (10 mL), dried over MgSO_4 and then evaporated. The residue was purified by flash column chromatography on silica gel.

Boc–Met–OMe: a colorless liquid, $[\alpha]_D^{26} -34.0^\circ$ (c 2.6, MeOH) [lit.⁶ $[\alpha]_D^{\text{amb}} -34.0^\circ$ (c 1.0, MeOH)]. IR (neat) cm^{-1} : 1715, 1745, 3359. ^1H NMR (270 MHz, CDCl_3) δ 1.45 (s, 9H), 1.84–1.99 (m, 1H), 2.08–2.18 (m, 1H), 2.10 (s, 3H), 2.54 (t, J = 7.6 Hz, 2H), 3.76 (s, 3H), 4.34–4.46 (br, 1H), 5.08–5.20 (br, 1H). MS (EI) m/z 263 (M^+).

Boc–Ala–OEt: a colorless liquid, $[\alpha]_D^{26} -39.8^\circ$ (c 2.5, MeOH) [lit.⁷ $[\alpha]_D -42.5^\circ$ (c 1.0, MeOH)]. IR(neat) cm^{-1} : 1715, 1738, 3367. ^1H NMR (270 MHz, CDCl_3) δ 1.28 (t, J = 7.2 Hz, 3H), 1.38 (d, J = 7.3 Hz, 3H), 1.45 (s, 9H), 4.20 (q, J = 7.1 Hz, 2H), 4.23–4.36 (m, 1H), 5.06–5.18 (br, 1H). MS (EI) m/z 217 (M^+).

⁶ Dhaon, M. K.; Olsen, R. K.; Ramasamy, K. *J. Org. Chem.* **1982**, *47*, 1962–1965.

⁷ Cantacuzène, D.; Pascal, F.; Guerreiro, C. *Tetrahedron* **1987**, *43*, 1823–1826.

Boc–Leu–OEt: a colorless liquid, $[\alpha]_D^{25} -34.6^\circ$ (*c* 2.3, MeOH) [lit.⁷ $[\alpha]_D -37.0^\circ$ (*c* 1.0, MeOH)]. IR (neat) cm^{-1} : 1716, 1740, 3365. ^1H NMR (270 MHz, CDCl_3) δ 0.95 (d, *J* = 6.4 Hz, 6H), 1.28 (t, *J* = 7.1 Hz, 3H), 1.44 (s, 9H), 1.48–1.78 (m, 3H), 4.18 (q, *J* = 7.2 Hz, 2H), 4.24–4.33 (m, 1H), 4.83–4.88 (br, 1H). MS (EI) *m/z* 260 ($\text{M}^+ + 1$).

Boc–Val–OMe: a colorless liquid, $[\alpha]_D^{25} -21.9^\circ$ (*c* 2.2, MeOH) [lit.⁶ $[\alpha]_D^{\text{amb}} -22.7^\circ$ (*c* 2.0, MeOH)]. IR (neat) cm^{-1} : 1715, 1746, 3369. ^1H NMR (270 MHz, CDCl_3) δ 0.93 (dd, *J* = 17.7, 6.9 Hz, 6H), 1.45 (s, 9H), 2.06–2.16 (m, 1H), 3.74 (s, 3H), 4.20–4.25 (dd, *J* = 9.0, 4.8 Hz, 1H), 5.03 (br d, *J* = 8.1 Hz, 1H). MS (EI) *m/z* 231 (M^+).

Boc–Phe–OMe: a colorless liquid, $[\alpha]_D^{25} -6.0^\circ$ (*c* 2.5, MeOH) [lit.⁸ $[\alpha]_D^{20} -3.0^\circ$ (*c* 2.0, MeOH)]. IR (neat) cm^{-1} : 1716, 1746, 3368. ^1H NMR (270 MHz, CDCl_3) δ 1.41 (s, 9H), 2.97–3.16 (m, 2H), 3.69 (s, 3H), 4.52–4.65 (m, 1H), 5.03 (br d, *J* = 7.6 Hz, 1H), 7.18–7.34 (m, 5H). MS (EI) *m/z* 279 (M^+).

Boc–Pro–OMe: a colorless liquid, $[\alpha]_D^{18} -63.3^\circ$ (*c* 2.1, MeOH) [lit.⁹ $[\alpha]_D^{25} -52.47^\circ$ (*c* 0.99, CH_2Cl_2)]. IR (neat) cm^{-1} : 1702, 1752. ^1H NMR (270 MHz, CDCl_3) δ 1.41 and 1.46 (2 x s, 9H), 1.85–2.03 (m, 3H), 2.14–2.30 (m, 1H), 3.36–3.60 (m, 2H), 3.72 (s, 3H), 4.20–4.35 (m, 1H). MS (EI) *m/z* 229 (M^+).

Boc–Glu(OEt)–OEt: colorless needles, mp 46–47 °C (pentane), $[\alpha]_D^{26} -38.1^\circ$ (*c* 2.5, MeOH) [lit.¹⁰ mp 46–47 °C, $[\alpha]_D -16.4^\circ$ (*c* 1.0, Acetone)]. IR (KBr) cm^{-1} : 1682, 1694, 1732, 3352. ^1H NMR (270 MHz, CDCl_3) δ 1.26 (t, *J* = 7.1 Hz, 3H), 1.29 (t, *J* = 7.1 Hz, 3H), 1.44 (s, 9H), 1.88–2.01 (m, 1H), 2.12–2.24 (m, 1H), 2.30–2.44 (m, 2H), 4.14 (q, *J* = 7.1 Hz, 2H), 4.20 (q, *J* = 7.1 Hz, 2H), 4.23–4.37 (m, 1H), 5.12 (br d, *J* = 7.6 Hz, 1H). MS (EI) *m/z* 304 ($\text{M}^+ + 1$).

Boc–Ser–OMe: a colorless liquid, $[\alpha]_D^{25} +7.2^\circ$ (*c* 2.5, MeOH) [lit.¹¹ $[\alpha]_D^{20} +9.0^\circ$ (*c* 1.0, CHCl_3)]. IR (neat) cm^{-1} : 1717, 1747, 3399. ^1H NMR (60 MHz, CDCl_3): 1.45 (s, 9H), 2.55–2.80 (br, 1H), 3.76 (s, 3H), 3.70–4.03 (m, 2H), 4.15–4.50 (m, 1H). MS (EI) *m/z* 220

⁸ Bajgrowicz, J. A.; Hallaoui, A. E.; Jacquier, R.; Pigiere, C.; Viallefont, P. *Tetrahedron* **1985**, *41*, 1833–1843.

⁹ Keith, J.; King, -C. W. *Tetrahedron* **1991**, *47*, 7179–7184.

¹⁰ Santiago, C.; Paloma, L. -S.; Marta, F.; María, I. B.; Ana, M.; María, I. R. -F. *Tetrahedron* **1997**, *53*, 11745–11752.

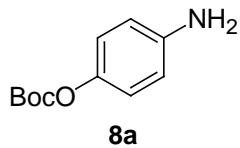
¹¹ Torrini, I.; Zecchini, P. Z.; Agrosi, F.; Paradisi, M. P. *J. Heterocycl. Chem.* **1986**, *23*, 1459–1463.

(M⁺+1).

Boc–Cys–OMe: a colorless liquid, $[\alpha]_D^{25} +27.2^\circ$ (*c* 2.0, MeOH) [lit.¹² $[\alpha]_D^{21} +28.5^\circ$ (*c* 318 mM, CHCl_3)]. IR (neat) cm^{-1} : 1712, 1747, 3368. $^1\text{H-NMR}$ (60 MHz, CDCl_3) δ 1.45 (s, 9H), 1.55 (s, 1H), 2.93 (d, *J* = 4 Hz, 1H), 3.08 (d, *J* = 4 Hz, 1H), 3.76 (s, 3H), 4.45–4.80 (m, 1H), 5.25–5.60 (br, 1H). MS (EI) *m/z* 235 (M⁺).

Boc–Tyr–OMe: colorless prisms, mp 102–104 °C (Et_2O –hexane), $[\alpha]_D^{21} +8.8^\circ$ (*c* 1.7, MeOH) [lit.¹³ mp 101–103 °C, $[\alpha]_D^{25} +10.6^\circ$ (*c* 2, EtOH)]. IR(KBr) cm^{-1} : 1690, 1716, 1761, 3389. ^1H NMR (270 MHz, CDCl_3) δ 1.42 (s, 9H), 2.91–3.07 (m, 2H), 3.71 (s, 3H), 4.47–4.60 (m, 1H), 5.04 (br d, *J* = 8.1 Hz, 1H), 6.35 (s, 1H), 6.73 (d, *J* = 8.1 Hz, 2H), 6.95 (d, *J* = 8.6 Hz, 2H). MS (EI) *m/z* 295 (M⁺).

Boc–Tyr(OBoc)–OMe: colorless needles, mp 90–91 °C (hexane), $[\alpha]_D^{20} -0.6^\circ$ (*c* 2.3, MeOH). IR (KBr) cm^{-1} : 1716, 1758, 3455. $^1\text{H-NMR}$ (270 MHz, CDCl_3) δ 1.42 (s, 9H), 1.55 (s, 9H), 3.02–3.14 (m, 2H), 3.71 (s, 3H), 4.51–4.62 (m, 1H), 4.98 (br d, *J* = 8.1 Hz, 1H), 7.60–7.16 (m, 4H). MS (EI) *m/z* 395 (M⁺). *Anal.* Calcd for $\text{C}_{20}\text{H}_{29}\text{NO}_7$: C, 60.74%; H, 7.39%; N, 3.54%. Found: C, 60.64%; H, 7.24%; N, 3.63%.



***tert*-Butyl 4-Aminophenyl Carbonate (8a).**

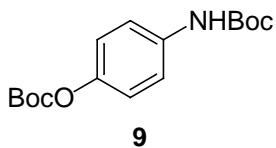
A mixture of BBDI (3.03 g, 10 mmol) and 4-aminophenol (**7a**, 0.55 g, 5 mmol) in benzene (15 mL) was heated under reflux for 8 hr. The reaction mixture was concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel to give **8a** (0.98 g, 94 %) as colorless needles, **9** (0.08 g, 5 %) as a brown powder.

8a: mp 113–114 °C (Et_2O –hexane) [lit.¹⁴ mp 113.5–114.5 °C]. IR (KBr) cm^{-1} : 1744, 3384, 3475. $^1\text{H-NMR}$ (270 MHz, CDCl_3) δ 1.54 (s, 9H), 3.58 (br s, 2H), 6.64 (d, *J* = 8.8 Hz, 2H), 6.94 (d, *J* = 8.9 Hz, 2H). MS (EI) *m/z* 209 (M⁺).

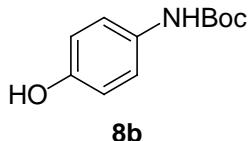
¹² Threadgill, M. D.; Gledhill, A. P. *J. Org. Chem.* **1989**, *54*, 2940–2949.

¹³ Kolodziejczyk, A. M.; Manning, M. *J. Org. Chem.* **1981**, *46*, 1944–1946.

¹⁴ Houlihan, F.; Bouchard, F.; Fréchet, J. M. J.; Willson, C. G. *Can. J. Chem.* **1985**, *63*, 153–162.



9: mp 137–138 °C (hexane) [lit.¹⁴ mp 135–137 °C]. IR (KBr) cm^{-1} : 1704, 1754. ^1H NMR (60 MHz, CDCl_3) δ 1.50 (s, 9H), 1.55 (s, 9H), 3.67 (br s, 1H), 7.06 (d, J = 9 Hz, 2H), 7.38 (d, J = 9 Hz, 2H). MS (EI) m/z 309 (M^+).

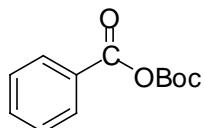


***tert*-Butyl N-(4-Hydroxyphenyl)carbamate (8b).**

A solution of BBDI (3.03 g, 10 mmol) in DME (15 mL) was added to a stirred suspension of 4-aminophenol hydrochloride (**7b**, 0.73 g, 5 mmol) in DME (10 mL), with stirring at room temperature for 16 hr. After removing DME under reduced pressure, the residue was dissolved in AcOEt, washed with 5 % HCl solution (10 mL x 2) and brine (10 mL), dried (MgSO_4), and concentrated *in vacuo*. The residue was purified by flash column chromatography on silica gel to give **8b** (0.97 g, 93 %) as colorless needles, **9** (0.08 g, 5 %) as a brown powder.

8b: mp 142–143 °C (Et_2O –hexane) [lit.¹⁵ mp 144–145 °C]. IR (KBr) cm^{-1} : 1698, 3362. ^1H NMR (270 MHz, CDCl_3) δ 1.51 (s, 9H), 5.32 (s, 1H), 6.34 (br s, 1H), 6.73 (d, J = 8.9 Hz, 2H), 7.16 (d, J = 8.8 Hz, 2H). MS (EI) m/z 209 (M^+).

General Procedure for the *tert*-Butoxycarbonylation of Benzoic Acids by BBDI. To a solution of BBDI (5 mmol) in benzene (15 mL) was added benzoic acid (5 mmol) at room temperature, and the resulting mixture was stirred at room temperature for 10 min. The reaction mixture was washed with 5% HCl solution (10 mL), dried, and concentrated *in vacuo*. The residue was purified by flash column chromatography on silica gel

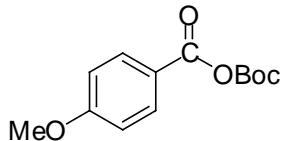


11a

Benzoic *tert*-Butylcarboxylic Anhydride (11a). Yield 0.95 g (86 %); a colorless liquid. IR

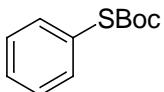
¹⁵ Vigroux, A.; Bergon, M.; Zedde, C. *J. Med. Chem.* **1995**, 38, 3983–3994.

(neat) cm^{-1} : 1742, 1800. ^1H NMR (60 MHz, CDCl_3) δ 1.60 (s, 9H), 7.25–7.70 (m, 3H), 8.00–8.23 (m, 2H). MS (EI) m/z 222 (M^+). *Anal.* Calcd for $\text{C}_{12}\text{H}_{14}\text{O}_4$: C, 64.85%; H, 6.35%. Found : C, 64.71%; H, 6.39%.



11b

4-Methoxybenzoic *tert*-Butylcarboxylic Anhydride (11b). Yield 1.10 g (87 %); a colorless liquid. IR (neat) cm^{-1} : 1736, 1795. ^1H NMR (270 MHz, CDCl_3) δ 1.58 (s, 9H), 3.87 (s, 3H), 6.94 (d, J = 8.9 Hz, 2H), 8.01 (d, J = 9.1 Hz, 2H). MS (EI) m/z 252 (M^+). *Anal.* Calcd for $\text{C}_{13}\text{H}_{16}\text{O}_5$: C, 61.90%; H, 6.39%. Found : C, 61.71%; H, 6.40%.



13

O-*tert*-Butyl S-Phenyl Thioarcarbonate (13). A mixture of BBDI (1.0 g, 3.3 mmol) and thiophenol (**12**, 0.33 g, 3 mmol) in benzene (10 mL) was heated under reflux for 5 hr. The reaction mixture was washed with 5 % HCl solution (5 mL x 2) and brine (5 mL), dried (MgSO_4), and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel to give **13**¹⁴ (0.56 g, 89 %) as a colorless liquid. IR (neat) cm^{-1} : 1728, 1698. ^1H NMR (270 MHz, CDCl_3) δ 1.51 (s, 9H), 7.36–7.42 (m, 3H), 7.51–7.56 (m, 2H). MS (EI) m/z 210 (M^+).