gem-Dibromomethyl Aromatics: Efficient Aldehyde Equivalents in the Knoevenagel–Doebner Reaction

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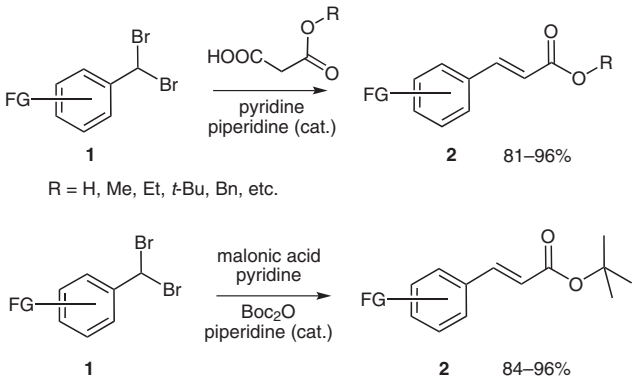
Abstract: A valuable variation of the Knoevenagel–Doebner reaction for the efficient synthesis of cinnamic esters is described. This reaction provides cinnamic esters in a single step from *gem*-dibromomethyl aromatics, which otherwise require the hydrolytic conversion of *gem*-dibromides into aldehydes, and demonstrates the use of an alternative reagent for noncommercial and expensive aldehydes. Further, the reaction of *gem*-dibromomethyl aromatics with malonic acid and di-*tert*-butyl dicarbonate for the one-pot synthesis of *tert*-butyl cinnamates is also described.

Key words: Knoevenagel–Doebner reaction, *tert*-butyl cinnamates, *gem*-dibromomethyl aromatics, di-*tert*-butyl dicarbonate, hydrolytic

Cinnamic esters compose a relatively large family of organic compounds, which are important reagents in organic synthesis both as intermediates and final products. For example, they have been incorporated into nylon monofilaments of toothbrush bristles as antimicrobial agents[1] and used to prepare compounds of biological relevance.[2] Chlorogenic acid, a natural cinnamic ester, is a major phenolic compound in coffee, that is widespread in plants, and can be isolated from the leaves and fruit.[3] This compound, long known as an antioxidant, also slows the release of glucose into the bloodstream after a meal.[4] This substance is claimed to have antiviral,[5] antibacterial,[6] and antifungal[7] effects with relatively low toxicity and side effects. For use in the food, polymer, and perfume industries and for their medical and technical applications, cinnamic esters are synthesized on a commercial scale.

The synthesis of cinnamic esters from aldehydes is regularly required and a variety of methods have been developed for this transformation.[8] In the Wittig reaction, an aldehyde reacts with a stabilized ylide to produce cinnamic esters.[9] In this reaction, triphenylphosphine oxide is a stoichiometric byproduct and it has to be removed chromatographically and disposed of. The Horner–Wadsworth–Emmons variant has the advantage of producing a water-soluble phosphate salt as the byproduct, which can be removed via aqueous extraction.[10] This variant, however, typically requires the use of a strong base such as sodium hydride and, as in the Wittig reaction, stoichiometric byproduct formation can challenge waste management. The decarboxylative Knoevenagel-type reaction of malonic acid half esters with aldehydes to give α,β-unsaturated esters is another alternative.[11] Water and carbon dioxide are produced as byproducts, hence it has a significantly improved advantage.

In a previous paper, we reported a valuable variation to the Knoevenagel–Doebner reaction by using *gem*-dibromomethyl aromatics as a substitute for aldehydes for the synthesis of cinnamic acids[12] and now wish to report the synthesis of cinnamic esters as an extension of this procedure (Scheme 1). This eventually avoids the hydrolytic cleavage of the *gem*-dibromides to aldehydes[13] for their use in the synthesis of cinnamic acid derivatives.



Scheme 1

In initial studies, we treated commercially available benzal bromide (**1a**, 1.0 equiv) with ethyl hydrogen malonate (1.2 equiv) in pyridine in the presence of a catalytic quantity (0.04 equiv) of piperidine at reflux (Table 1, entry l); this was the optimized method for the synthesis of cinnamic acid from benzal bromide.[12] The starting material was consumed in 1.5 hours as indicated by TLC analysis. After workup, ethyl cinnamate was isolated in 81% yield. Screening of various base catalysts such as triethylamine, *N*,*N*-diisopropylethylamine, 1,8-diazabicyclo[5.4.0]undec-7-ene, pyrrolidine, and morpholine was carried out. While pyrrolidine and morpholine catalyzed the reaction in quantitative yields in 2–3 hours, other bases were found to be inefficient in promoting this reaction. With a catalytic amount of piperidine, the reaction took barely an hour for completion. Further, we have screened various malon-

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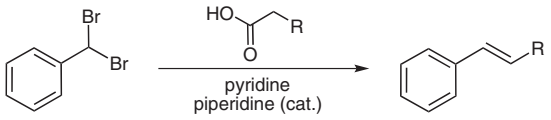
ic acid half esters with benzal bromide (**1a**) for the synthesis of corresponding cinnamates and the results are summarized in Table 1.

Table 1 Reaction of Benzal Bromide (**1a**) with Malonic Acid Half Esters



1a **2**

Entry	R	Time (h)	Yield (%)
1	CO_2Et	1.5	81
2	CO_2Me	1.5	84
3	CO_2t-Bu	0.5	93
4	CO_2Bn	1.5	82
5	CN[a]	2	76

[a] An active methylene compound.

While ethyl, methyl, and benzyl malonates provided good yield of the corresponding cinnamates, *tert*-butyl hydrogen malonate (Table 1, entry 3) provided an excellent yield in a shorter duration. It is worthy of note that cyanoacetic acid, an active methylene compound, also reacted under the above standard reaction conditions to provide cinnamonitrile in moderate yield (Table 1, entry 5).

Compounds possessing the *tert*-butyl carboxylate functionality are useful building blocks in organic synthesis, due to their ease of deprotection to the corresponding carboxylic acid in acidic medium. So we decided to take up the synthesis of *tert*-butyl cinnamates to demonstrate the scope and generality of utilizing *gem*-dibromomethyl aromatics as a substitute for aldehydes. Various *gem*-dibromomethyl aromatics **1b–i** (for which, either the corresponding aldehydes are not available or expensive) were prepared using known protocols[14] and further subjected to the modified Knoevenagel–Doebner reaction with *tert*-butyl hydrogen malonate to yield the corresponding *tert*-butyl cinnamates **2b–i** in excellent yields (Table 2). The reaction proceeded well with all substrates we tried and an aqueous extraction was sufficient to obtain the products with good purity; chromatographic purification was not required.

Takeda and co-workers have reported the use of di-*tert*-butyl dicarbonate as an esterification reagent to produce *tert*-butyl cinnamates.[15] It was of interest to explore if we could use di-*tert*-butyl dicarbonate in a one-pot reaction with *gem*-dibromomethyl aromatics for the synthesis of *tert*-butyl cinnamates in the modified Knoevenagel–Doebner reaction as shown in Scheme 1. Thus, **1a** (1.0 equiv) was treated with malonic acid (2.0 equiv) and di-*tert*-butyl dicarbonate (1.1 equiv) in anhydrous pyridine in the presence of a catalytic quantity (0.04 equiv) of piperidine at reflux (Scheme 1). As expected, the starting material was completely consumed in 25 minutes to provide *tert*-butyl cinnamate (**2a**) in 56% yield along with cinnamic acid in 30% isolated yield. After few optimization reactions, we could achieve **2a** in 88% yield by allowing the reaction to continue for two hours at reflux. When di-*tert*-butyl dicarbonate was omitted in the above reaction, cinnamic acid was isolated as the sole product in 92% yield.[12] The use of two equivalents of malonic acid was found to be optimal for the complete conversion of **1a** into **2a**.

Table 2 Reaction of *gem*-Dibromomethyl Aromatics **1a–i** with *tert*-Butyl Hydrogen Malonate

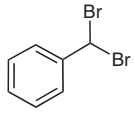
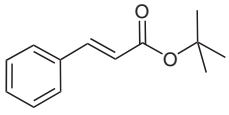
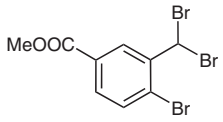
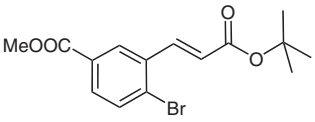
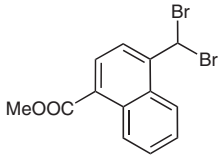
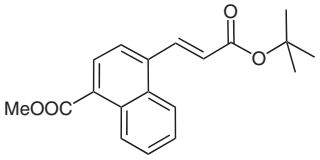
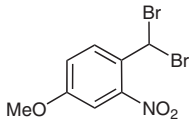
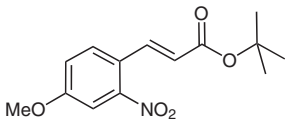
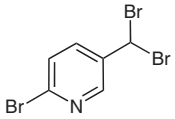
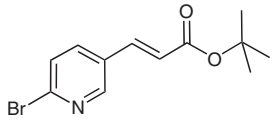
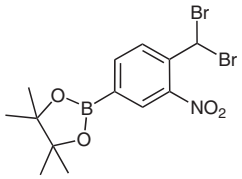
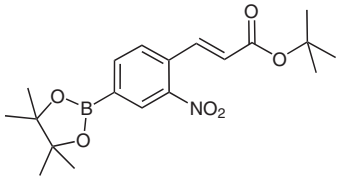
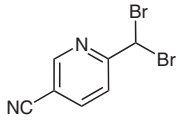
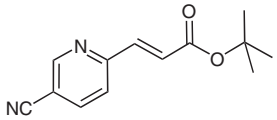
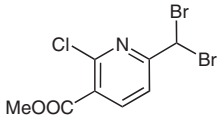
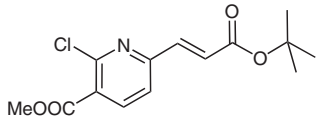
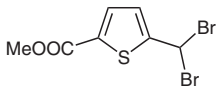
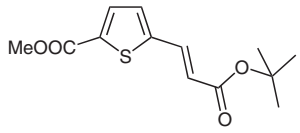
Entry	Substrate	Product	Yield[a] (%)
1	 **1a**	 **2a**	93
2	 **1b**	 **2b**	87
3	 **1c**	 **2c**	85

Table 2 Reaction of *gem*-Dibromomethyl Aromatics **1a–i** with *tert*-Butyl Hydrogen Malonate (continued)

Entry	Substrate	Product	Yield[a] (%)
4	 **1d**	 **2d**	89
5	 **1e**	 **2e**	91
6	 **1f**	 **2f**	94
7	 **1g**	 **2g**	88
8	 **1h**	 **2h**	91
9	 **1i**	 **2i**	96

[a] Isolated yields

Table 3 Reaction of *gem*-Dibromomethyl Aromatics **1a,j–r** with Malonic Acid and Di-*tert*-butyl Dicarbonate

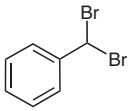
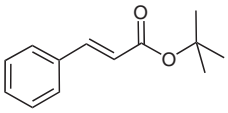
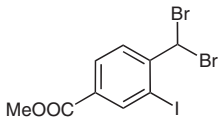
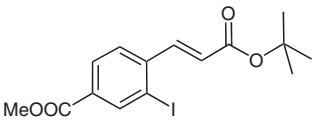
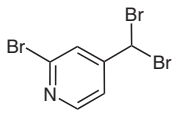
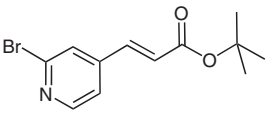
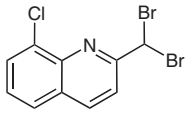
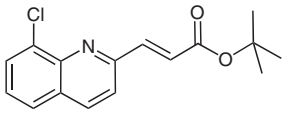
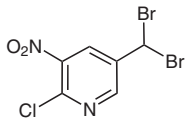
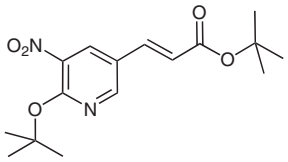
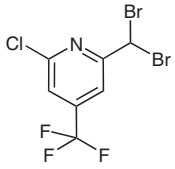
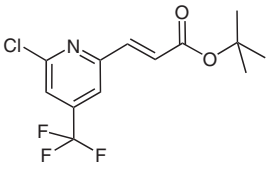
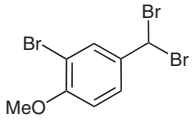
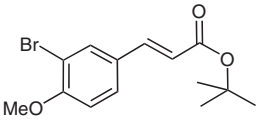
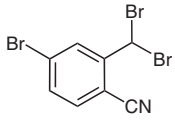
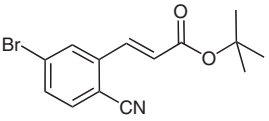
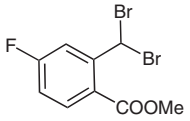
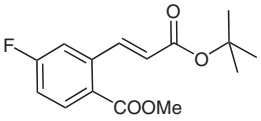
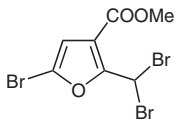
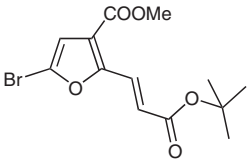
Entry	Substrate	Product	Yield[a] (%)
1	 **1a**	 **2a**	88
2	 **1j**	 **2j**	87
3	 **1k**	 **2k**	87

Table 3 Reaction of *gem*-Dibromomethyl Aromatics **1a,j–r** with Malonic Acid and Di-*tert*-butyl Dicarbonate (continued)

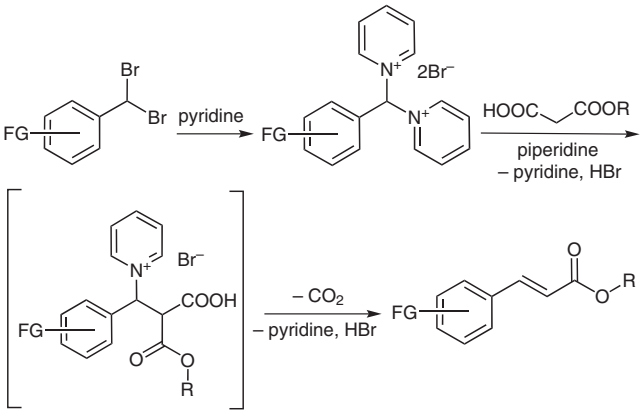
Entry	Substrate	Product	Yield[a] (%)
4	 **1l**	 **2l**	89
5	 **1m**	 **2m**	91
6	 **1n**	 **2n**	93
7	 **1o**	 **2o**	87
8	 **1p**	 **2p**	96
9	 **1q**	 **2q**	85
10	 **1r**	 **2r**	84

[a] Isolated yields.

Having obtained standard reaction conditions, we synthesized a variety of aromatic and heteroaromatic *tert*-butyl cinnamates **2j–r** in good to excellent yields (Table 3). A substrate possessing a reactive halogen on the aryl ring (Table 3, entry 5) provided the corresponding *tert*-butyl ether **2m** due to displacement of the chloro group with *tert*-butyl alcohol under basic conditions. From Tables 2 and 3, we can discern that this reaction tolerates a wide range of functional groups, such as nitro, halo, cyano, carboxylate, methoxy, trifluoromethyl, and boronate (Table 2, entry 6) to provide the corresponding cinnamates in good yields. Similarly, electron-withdrawing or electron-donating groups on the substrate did not affect the yield of α,β-unsaturated carboxylates.

The reaction is believed to proceed through nucleophilic catalysis between the bis-pyridinium cation[12] and malonic acid half ester followed by decarboxylative elimination of pyridine to produce the cinnamic esters (Scheme 2). When malonic acid is used, the decarboxylative elimination of pyridine provides cinnamic acid, which further reacts with di-*tert*-butyl dicarbonate under basic conditions to provide the corresponding *tert*-butyl cinnamate.

In conclusion, we have demonstrated a valuable variation of the Knoevenagel–Doebner reaction wherein, *gem*-dibromomethyl aromatics are employed as aldehyde equivalents for the efficient synthesis of *tert*-butyl cinnamates. As this reaction provides cinnamic esters in a single step from *gem*-dibromomethyl aromatics, which otherwise re-



Scheme 2

quire the hydrolytic conversion of *gem*-dibromides into aldehydes, and demonstrates the use of an alternative reagent for noncommercial and expensive aldehydes, we believe that this methodology would be of appreciable use to the synthetic community. Further, this reaction provides an interesting insight into the chemistry of *gem*-dibromomethyl aromatics and represents a useful way of utilizing them as aldehyde counterparts with active methylene compounds.

^{1}H NMR and ^{13}C NMR spectra were recorded on 400 MHz and 100 MHz Bruker spectrometer respectively and elemental analysis was performed on a Thermo Finnigan FLASH EA 1112 CHN analyzer. Melting points were recorded (uncorrected) on Buchi Melting Point B-545 instrument. IR spectra were recorded on a Thermo Scientific Nicolet 6700 FT-IR spectrophotometer. Reactions were carried out in an oven dried three-necked round-bottomed flask. Yields in the tables refer to isolated yields of compounds with purity >96% as determined by ^{1}H NMR and HPLC analysis.

***gem*-Dibromomethyl Aromatics 1b–r; General Procedure**

Without any critical deviation to the reported protocol,[14] all the *gem*-dibromomethyl aromatics were prepared and purified by chromatography.

Methyl 4-Bromo-3-(dibromomethyl)benzoate (1b)

White solid; yield: 73%; mp 86 °C.

IR (KBr): 1717, 1590, 1432, 1299, 1110, 638 cm^{-1}.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 3.89 (s, 3 H), 7.39 (s, 1 H), 7.80–7.85 (m, 2 H), 8.46 (s, 1 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 40.3, 52.6, 125.1, 130.0, 131.6, 134.0, 140.3, 164.8.

Anal. Calcd for $C_9H_7Br_3O_2$: C, 27.94; H, 1.82. Found: C, 27.99; H, 1.87.

Methyl 4-(Dibromomethyl)naphthalene-1-carboxylate (1c)[12]

Yield: 75%.

1-(Dibromomethyl)-4-methoxy-2-nitrobenzene (1d)[12]

Yield: 82%.

2-Bromo-5-(dibromomethyl)pyridine (1e)[14]

Yield: 77%.

4-(Dibromomethyl)-2-nitrophenylboronic Acid Pinacol Ester (1f)

White solid; yield: 78%; mp 109 °C.

IR (KBr): 1706, 1618, 1530, 1334, 1097, 662 cm^{-1}.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 1.30 (s, 12 H), 7.49 (s, 1 H), 8.05–8.09 (m, 2 H), 8.19–8.21 (t, 1 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 24.5, 36.0, 84.6, 129.3, 131.6, 137.5, 139.6, 144.2.

Anal. Calcd for $C_{13}H_{16}BBr_2NO_4$: C, 37.10; H, 3.83; N, 3.33. Found: C, 37.15; H, 3.88; N, 3.29.

6-(Dibromomethyl)pyridine-3-carbonitrile (1g)

Colorless liquid; yield: 83%.

IR(neat): 2234, 1585, 1471, 1375, 649 cm^{-1}.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 7.40 (s, 1 H), 7.84 (d, J = 8.1 Hz, 1 H), 8.40 (dd, J = 6.1, 2.1 Hz, 1 H), 9.08 (s, 1 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 41.9, 109.8, 116.3, 120.6, 141.9, 152.4, 160.9.

Anal. Calcd for $C_7H_4Br_2N_2$: C, 30.47; H, 1.46; N, 10.15. Found: C, 30.52; H, 1.53; N, 10.04.

Methyl 2-Chloro-6-(dibromomethyl)pyridine-3-carboxylate (1h)

White solid; yield: 67%; mp 78 °C.

IR (KBr): 1720, 1575, 1434, 1264, 1058, 670 cm^{-1}.

^{1}H NMR (400 MHz, CD_3OD): δ = 3.95 (s, 3 H), 6.97 (s, 1 H), 7.82 (d, J = 7.9 Hz, 1 H), 8.31 (d, J = 7.9 Hz, 1 H).

^{13}C NMR (100 MHz, CD_3OD): δ = 40.0, 55.0, 121.0, 128.7, 143.2, 149.6, 162.3, 165.6.

Anal. Calcd for $C_9H_8Br_2ClNO_2$: C, 30.24; H, 2.26; N, 3.92. Found: C, 30.30; H, 2.29; N, 3.89.

Methyl 5-(Dibromomethyl)thiophene-2-carboxylate (1i)[12]

Yield: 76%.

Methyl 4-(Dibromomethyl)-3-iodobenzoate (1j)

Colorless liquid; yield: 72%.

IR (neat): 1708, 1636, 1494, 1225, 1055, 774 cm^{-1}.

^{1}H NMR (400 MHz, CD_3OD): δ = 3.93 (s, 3 H), 7.07 (s, 1 H), 8.05–8.12 (m, 2 H), 8.39 (d, J = 1.5 Hz, 1 H).

^{13}C NMR (100 MHz, CD_3OD): δ = 45.7, 53.1, 95.1, 131.1, 133.5, 141.3, 149.1, 165.8.

Anal. Calcd for $C_9H_7Br_2IO_2$: C, 24.92; H, 1.63. Found: C, 25.01; H, 1.70.

2-Bromo-4-(dibromomethyl)pyridine (1k)[14]

Yield: 75%.

8-Chloro-2-(dibromomethyl)quinoline (1l)

White solid; yield: 69%; mp 157 °C.

IR (KBr): 1596, 1498, 1453, 1301, 1140, 989, 608 cm^{-1}.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 7.41 (s, 1 H), 7.65 (t, 1 H), 8.01–8.04 (m, 3 H), 8.61 (d, J = 8.6 Hz, 1 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 44.1, 120.7, 127.8, 128.6, 129.4, 131.2, 132.7, 139.7, 141.9, 159.2.

Anal. Calcd for $C_{10}H_6Br_2ClN$: C, 35.81; H, 1.80; N, 4.18. Found: C, 35.86; H, 1.87; N, 4.09.

2-Chloro-5-(dibromomethyl)-3-nitropyridine (1m)

Colorless liquid; yield: 66%.

IR (neat): 1591, 1557, 1532, 1345, 1061, 810 cm^{-1}.

^1H NMR (400 MHz, DMSO-d_6): δ = 7.50 (s, 1 H), 8.83 (d, *J* = 2.2 Hz, 1 H), 8.94 (d, *J* = 2.2 Hz, 1 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 35.0, 133.6, 138.7, 142.1, 143.9, 150.0.

Anal. Calcd for $C_6H_3Br_2ClN_2O_2$: C, 21.81; H, 0.92; N, 8.48. Found: C, 21.88; H, 1.01; N, 8.41.

2-Chloro-6-(dibromomethyl)-4-(trifluoromethyl)pyridine (1n)
White solid; yield: 68%; mp 90 °C.

IR (KBr): 1597, 1478, 1443, 1140, 989, 878, 648 cm^{-1}.

^1H NMR (400 MHz, DMSO-d_6): δ = 7.38 (s, 1 H), 7.99 (s, 1 H), 8.05 (s, 1 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 40.6, 117.9, 122.4, 123.0, 123.4, 140.7, 141.0, 141.4, 141.7, 152.0, 161.7.

Anal. Calcd for $C_7H_3Br_2ClF_3N$: C, 23.79; H, 0.86; N, 3.96. Found: C, 23.86; H, 0.89; N, 3.89.

2-Bromo-4-(dibromomethyl)anisole (1o)
This compound is unstable and hence the crude dibromide was used in the subsequent reaction.

^1H NMR (400 MHz, $CDCl_3$): δ = 3.93 (s, 3 H), 6.59 (s, 1 H), 6.86 (d, *J* = 8.6 Hz, 1 H), 7.49 (dd, *J* = 8.6, 2.4 Hz, 1 H), 8.08 (s, 1 H).

4-Bromo-2-(dibromomethyl)benzonitrile (1p)
White solid; yield: 77%; mp 120 °C.

IR (KBr): 2226, 1578, 1482, 1145, 826, 646, 552 cm^{-1}.

^1H NMR (400 MHz, DMSO-d_6): δ = 7.39 (s, 1 H), 7.82 (dd, *J* = 8.2, 1.9 Hz, 1 H), 7.92 (d, *J* = 8.2 Hz, 1 H), 8.03 (s, 1 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 36.7, 109.6, 115.9, 127.6, 130.9, 134.1, 137.0, 145.4.

Anal. Calcd for $C_8H_4Br_3N$: C, 27.16; H, 1.14; N, 3.96. Found: C, 27.20; H, 1.14; N, 3.89.

Methyl 2-(Dibromomethyl)-4-fluorobenzoate (1q)
White solid; yield: 73%; mp 54 °C.

IR (KBr): 1712, 1605, 1581, 1431, 1116, 703 cm^{-1}.

^1H NMR (400 MHz, DMSO-d_6): δ = 3.87 (s, 3 H), 7.36–7.41 (m, 1 H), 7.83–7.86 (m, 2 H), 7.89–7.92 (m, 1 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 37.1, 52.7, 117.2, 117.4, 117.5, 117.7, 121.8, 121.8, 132.9, 133.0, 145.0, 145.1, 162.9, 165.2, 165.4.

Anal. Calcd for $C_9H_7Br_2FO_2$: C, 33.16; H, 2.16. Found: C, 33.20; H, 2.22.

Methyl 5-Bromo-2-(dibromomethyl)furan-3-carboxylate (1r)[12]
Yield: 70%.

***tert*-Butyl Cinnamate (2a); Typical Procedure for 2a–i Using *tert*-Butyl Hydrogen Malonate**
To a mixture of **1a** (10 g, 0.04 mol) and *tert*-butyl hydrogen malonate (7.68 g, 0.048 mol) in pyridine (40 mL) was added piperidine (0.14 mL, 0.0016 mol) and the mixture was refluxed for 1.5 h under N_2 (completion confirmed by TLC). The brown mixture was cooled and poured onto ice-water. The aqueous phase was extracted with Et_2O (2 × 50 mL). The combined organic phases were washed with H_2O (1 × 100 mL), 10% aq $NaHCO_3$ (1 × 50 mL), and brine (1 × 50 mL) and dried (Na_2SO_4). The solvent was removed under vacuum to afford **2a**[16] (7.6 g, 93%) as a colorless liquid.

***tert*-Butyl Cinnamate (2a); Typical Procedure for 2a,j–r Using Malonic Acid and Di-*tert*-Butyl Dicarbonate**
To a mixture of **1a** (5 g, 0.02 mol) and malonic acid (4.16 g, 0.04 mol) in pyridine (25 mL) was added Boc_2O (4.8 g, 0.022 mol) followed by piperidine (0.07 mL, 0.0008 mol) and the mixture was refluxed for 2 h (completion confirmed by TLC). The brown mixture was cooled and poured onto ice-water. The aqueous phase was extracted with Et_2O (2 × 50 mL). The combined organic phases were washed with H_2O (1 × 100 mL) and brine (1 × 50 mL) and dried (Na_2SO_4). The solvent was removed under vacuum and the crude product was passed through a small plug of silica using hexane to afford **2a** (3.6 g, 88%) as colorless liquid.

Methyl 4-Bromo-3-(3-*tert*-butoxy-3-oxoprop-1-enyl)benzoate (2b)
White solid; yield: 87%; mp 92 °C.

IR (KBr): 1723, 1638, 1435, 1143, 755 cm^{-1}.

^1H NMR (400 MHz, DMSO-d_6): δ = 1.48 (s, 9 H), 3.86 (s, 3 H), 6.60 (d, *J* = 15.8 Hz, 1 H), 7.78 (d, *J* = 15.8 Hz, 1 H), 7.83–7.88 (m, 2 H), 8.28 (d, *J* = 1.9 Hz, 1 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 28.2, 52.9, 81.0, 124.7, 129.1, 129.9, 130.2, 132.0, 134.2, 134.6, 140.6, 165.2, 165.9.

Anal. Calcd for $C_{15}H_{17}BrO_4$: C, 52.80; H, 5.02. Found: C, 52.87; H, 5.10.

Methyl 4-(3-*tert*-Butoxy-3-oxoprop-1-enyl)naphthalene-1-carboxylate (2c)
White solid; yield: 85%; mp 110 °C.

IR (KBr): 1696, 1635, 1438, 1260, 1127, 766 cm^{-1}.

^1H NMR (400 MHz, DMSO-d_6): δ = 1.52 (s, 9 H), 3.94 (s, 3 H), 6.64 (d, *J* = 15.6 Hz, 1 H), 7.68–7.74 (m, 2 H), 7.99 (d, *J* = 7.6 Hz, 1 H), 8.08 (d, *J* = 7.6 Hz, 1 H), 8.25–8.27 (m, 1 H), 8.35 (d, *J* = 15.7 Hz, 1 H), 8.74 (d, *J* = 1.3 Hz, 1 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 27.8, 52.4, 80.4, 123.8, 124.1, 124.8, 125.7, 127.3, 127.9, 128.3, 129.1, 130.5, 130.9, 135.8, 139.2, 165.0, 167.0.

Anal. Calcd for $C_{19}H_{20}O_4$: C, 73.06; H, 6.45. Found: C, 73.11; H, 6.50.

***tert*-Butyl 3-(4-Methoxy-2-nitrophenyl)prop-2-enoate (2d)**
Colorless liquid; yield: 89%.

IR (neat): 1706, 1614, 1528, 1248, 1144, 756 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 1.52 (s, 9 H), 3.88 (s, 3 H), 6.23 (d, *J* = 15.8 Hz, 1 H), 7.14 (dd, *J* = 8.7, 2.6 Hz, 1 H), 7.47 (d, *J* = 2.68 Hz, 1 H), 7.57 (d, *J* = 8.7 Hz, 1 H), 7.92 (d, *J* = 15.8 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 28.1, 56.0, 80.8, 109.3, 119.8, 122.6, 123.4, 129.9, 138.1, 149.2, 160.6, 165.3.

Anal. Calcd for $C_{14}H_{17}NO_5$: C, 60.21; H, 6.14; N, 5.02. Found: C, 60.27; H, 6.20; N, 4.93.

***tert*-Butyl 3-(6-Bromopyridin-3-yl)prop-2-enoate (2e)**
White solid; yield: 91%; mp 117 °C.

IR (KBr): 1696, 1638, 1457, 1368, 1145, 980, 825 cm^{-1}.

^1H NMR (400 MHz, DMSO-d_6): δ = 1.47 (s, 9 H), 6.71 (d, *J* = 15.8 Hz, 1 H), 7.55 (d, *J* = 15.8 Hz, 1 H), 7.69 (d, *J* = 8.3 Hz, 1 H), 8.12 (dd, *J* = 8.4, 2.3 Hz, 1 H), 8.67 (d, *J* = 2.1 Hz, 1 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 28.2, 80.8, 123.2, 128.6, 130.2, 138.2, 139.3, 142.9, 150.9, 165.4.

Anal. Calcd for $C_{12}H_{14}BrNO_2$: C, 50.72; H, 4.97; N, 4.93. Found: C, 50.80; H, 5.01; N, 4.86.

***tert*-Butyl 3-[2-Nitro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]prop-2-enoate (2f)**
Colorless liquid; yield: 94%.

IR (neat): 1712, 1531, 1343, 1343, 1145, 755 cm^{-1}.

^1H NMR (400 MHz, DMSO-d_6): δ = 1.31 (s, 12 H), 1.47 (s, 9 H), 6.53 (d, *J* = 15.8 Hz, 1 H), 7.84 (d, *J* = 15.8 Hz, 1 H), 7.91–7.95 (m, 2 H), 8.30 (s, 1 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 24.5, 27.7, 80.6, 84.5, 125.0, 129.1, 129.7, 131.9, 138.4, 138.9, 147.8, 164.6.

Anal. Calcd for $C_9H_{26}BNO_6$: C, 60.82; H, 6.98; N, 3.73. Found: C, 60.89; H, 7.04; N, 3.68.

***tert*-Butyl 3-(5-Cyanopyridin-2-yl)prop-2-enoate (2g)**
White solid; yield: 88%; mp 127 °C.

IR (KBr): 2230, 1690, 1589, 1325, 1196, 857 cm^{-1}.

^1H NMR (400 MHz, DMSO-d_6): δ = 1.48 (s, 9 H), 6.90 (d, *J* = 15.8 Hz, 1 H), 7.58 (d, *J* = 15.8 Hz, 1 H), 7.95 (d, *J* = 8.2 Hz, 1 H), 8.38 (dd, *J* = 8.1, 2.1 Hz, 1 H), 9.03 (s, 1 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 28.1, 81.2, 109.5, 117.4, 124.5, 127.0, 141.4, 141.6, 153.0, 155.9, 165.1.

Anal. Calcd for $C_{13}H_{14}N_2O_2$: C, 67.81; H, 6.13; N, 12.17. Found: C, 67.88; H, 6.19; N, 12.10.

Methyl 6-(3-*tert*-Butoxy-3-oxoprop-1-enyl)-2-chloropyridine-3-carboxylate (2h)
White solid; yield: 91%; mp 63 °C.

IR (KBr): 1731, 1699, 1579, 1366, 1057, 785 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 1.52 (s, 9 H), 3.96 (s, 3 H), 6.93 (d, *J* = 15.8 Hz, 1 H), 7.38 (d, *J* = 7.8 Hz, 1 H), 7.49 (d, *J* = 15.8 Hz, 1 H), 8.17 (d, *J* = 7.8 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 28.0, 52.8, 81.2, 121.7, 126.2, 128.0, 139.3, 141.1, 150.1, 155.8, 164.6, 165.2.

Anal. Calcd for $C_{14}H_{16}ClNO_4$:C, 56.48; H, 5.42; N, 4.70. Found: C, 56.52; H, 5.44; N, 4.65.

Methyl 5-(3-*tert*-Butoxy-3-oxoprop-1-enyl)thiophene-2-carboxylate (2i)
White solid; yield: 96%; mp 50 °C.

IR (KBr): 1698, 1627, 1477, 1283, 1136, 829 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 1.51 (s, 9 H), 3.88 (s, 3 H), 6.27 (d, *J* = 15.8 Hz, 1 H), 7.18 (d, *J* = 4.0 Hz, 1 H), 7.60 (d, *J* = 15.8 Hz, 1 H), 7.68 (d, *J* = 4.0 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 28.1, 52.3, 81.0, 121.9, 129.9, 133.8, 134.5, 135.0, 145.6, 162.1, 165.4.

Anal. Calcd for $C_{13}H_{16}O_4S$: C, 58.19; H, 6.01. Found: C, 58.23; H, 6.08.

Methyl 4-(3-*tert*-Butoxy-3-oxoprop-1-enyl)-3-iodobenzoate (2j)
White solid; yield: 87%; mp 80 °C.

IR (KBr): 1720, 1698, 1319, 1251, 972, 763 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 1.55 (s, 9 H), 3.92 (s, 3 H), 6.32 (d, *J* = 15.8 Hz, 1 H), 7.59 (d, *J* = 7.8 Hz, 1 H), 7.81 (d, *J* = 15.8 Hz, 1 H), 7.98 (dd, *J* = 7.8, 1.6 Hz, 1 H), 8.53 (d, *J* = 1.5 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 28.1, 52.5, 81.4, 100.2, 125.0, 126.9, 129.3, 134.4, 140.9, 142.1, 145.5, 165.0, 165.1.

Anal. Calcd for $C_{15}H_{17}IO_4$: C, 46.41; H, 4.41. Found: C, 46.46; H, 4.43.

***tert*-Butyl 3-(2-Bromopyridin-4-yl)prop-2-enoate (2k)**
White solid; yield: 87%; mp 68 °C.

IR (KBr): 1698, 1581, 1459, 1364, 1291, 1156, 707 cm^{-1}.

^1H NMR (400 MHz, DMSO-d_6): δ = 1.46 (s, 9 H), 6.86 (d, *J* = 15.8 Hz, 1 H), 7.49 (d, *J* = 15.8 Hz, 1 H), 7.74 (dd, *J* = 5.1, 1.2 Hz, 1 H), 7.98 (s, 1 H), 8.40 (d, *J* = 5.1 Hz, 1 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 27.6, 80.7, 121.5, 126.0, 126.4, 139.3, 142.2, 144.8, 150.8, 164.6.

Anal. Calcd for $C_{12}H_{14}BrNO_2$: C, 50.72; H, 4.97; N, 4.93. Found: C, 50.81; H, 5.01; N, 4.85.

***tert*-Butyl 3-(8-Chloroquinolin-2-yl)prop-2-enoate (2l)**
White solid; yield: 89%; mp 100 °C.

IR (KBr): 1698, 1594, 1251, 1150, 971, 830, 750 cm^{-1}.

^1H NMR (400 MHz, DMSO-d_6): δ = 1.51 (s, 9 H), 7.03 (d, *J* = 15.8 Hz, 1 H), 7.59 (t, 1 H), 7.71 (d, *J* = 15.8 Hz, 1 H), 7.95–7.97 (m, 2 H), 8.03 (d, *J* = 8.5 Hz, 1 H), 8.48 (d, *J* = 8.5 Hz, 1 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 27.7, 80.6, 121.7, 125.9, 127.3, 127.4, 129.1, 130.1, 132.4, 137.7, 142.6, 143.2, 153.5, 164.9.

Anal. Calcd for $C_{16}H_{16}ClNO_2$: C, 66.32; H, 5.57; N, 4.83. Found: C, 66.36; H, 5.62; N, 4.76.

***tert*-Butyl 3-(6-*tert*-Butoxy-5-nitropyridin-3-yl)prop-2-enoate (2m)**
Colorless liquid; yield: 91%.

IR (neat): 1708, 1606, 1532, 1463, 1365, 778 cm^{-1}.

^1H NMR (400 MHz, DMSO-d_6): δ = 1.46 (s, 9 H), 1.58 (s, 9 H), 6.65 (d, *J* = 15.7 Hz, 1 H), 7.57 (d, *J* = 15.7 Hz, 1 H), 8.72 (m, 2 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 28.2, 28.5, 80.6, 84.5, 121.9, 124.2, 132.9, 136.2, 138.6, 151.2, 155.4, 165.6.

Anal. Calcd for $C_{16}H_{22}N_2O_5$: C, 59.62; H, 6.88; N, 8.69. Found: C, 59.66; H, 6.91; N, 8.56.

***tert*-Butyl 3-[6-Chloro-4-(trifluoromethyl)pyridin-2-yl]prop-2-enoate (2n)**
White solid; yield: 93%; mp 72 °C.

IR (KBr): 1701, 1557, 1333, 1304, 1132, 699 cm^{-1}.

^1H NMR (400 MHz, DMSO-d_6): δ = 1.48 (s, 9 H), 6.89 (d, *J* = 15.8 Hz, 1 H), 7.60 (d, *J* = 15.8 Hz, 1 H), 8.01 (s, 1 H), 8.22 (s, 1 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 28.1, 81.2, 119.7, 119.8, 121.0, 121.6, 123.8, 126.9, 140.1, 140.9, 141.3, 151.8, 155.3, 164.9.

Anal. Calcd for $C_{13}H_{13}ClF_3NO_2$: C, 50.75; H, 4.26; N, 4.55. Found: C, 50.81; H, 4.31; N, 4.49.

***tert*-Butyl 3-(3-Bromo-4-methoxyphenyl)prop-2-enoate (2o)**
Colorless liquid; yield: 87%.

IR (neat): 1701, 1557, 1367, 1333, 1134, 707 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 1.53 (s, 9 H), 3.92 (s, 3 H), 6.25 (d, *J* = 15.7 Hz, 1 H), 6.88 (d, *J* = 8.4 Hz, 1 H), 7.49–7.40 (m, 2 H), 7.73 (s, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 28.1, 56.3, 80.4, 111.7, 112.1, 119.1, 128.7, 132.4, 141.6, 157.1, 166.2.

Anal. Calcd for $C_{14}H_{17}BrO_3$: C, 53.69; H, 5.47. Found: C, 53.72; H, 5.52.

***tert*-Butyl 3-(5-Bromo-2-cyanophenyl)prop-2-enoate (2p)**
White solid; yield: 96%; mp 124 °C.

IR (KBr): 2226, 1701, 1626, 1478, 1299, 1167, 819 cm^{-1}.

^1H NMR (400 MHz, DMSO-d_6): δ = 1.48 (s, 9 H), 6.91 (d, *J* = 15.8 Hz, 1 H), 7.63 (d, *J* = 15.8 Hz, 1 H), 7.79–7.86 (m, 2 H), 8.38 (s, 1 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 27.7, 80.8, 110.7, 116.7, 126.0, 127.9, 130.2, 133.4, 134.9, 136.8, 138.4, 164.6.

Anal. Calcd for $C_{14}H_{14}BrNO_2$: C, 54.56; H, 4.58; N, 4.55. Found: C, 54.60; H, 4.62; N, 4.50.

Methyl 2-(3-*tert*-Butoxy-3-oxoprop-1-enyl)-4-fluorobenzoate (2q)

Colorless liquid; yield: 85%.

IR (neat): 1711, 1579, 1489, 1252, 1149, 757 cm^{-1}.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 1.47 (s, 9 H), 3.84 (s, 3 H), 6.51 (d, *J* = 15.8 Hz, 1 H), 7.32–7.37 (m, 1 H), 7.72–7.75 (m, 1 H), 7.92–7.95 (m, 1 H), 8.19 (d, *J* = 15.8 Hz, 1 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 27.7, 52.4, 80.2, 114.5, 116.5, 116.7, 123.7, 126.0 (d), 133.2 (d), 138.1 (d), 140.3 (d), 162.8, 165.0, 165.3, 165.8.

Anal. Calcd for $C_{15}H_{17}FO_4$: C, 64.28; H, 6.11. Found: C, 64.33; H, 6.20.

Methyl 5-Bromo-2-(3-*tert*-butoxy-3-oxoprop-1-enyl)furan-3-carboxylate (2r)

Colorless liquid; yield: 84%.

IR (neat): 1719, 1552, 1432, 1380, 1252, 618 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.52 (s, 9 H), 3.88 (s, 3 H), 6.49 (d, *J* = 15.8 Hz, 1 H), 6.73 (s, 1 H), 7.87 (d, *J* = 15.8 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 28.1, 52.1, 81.0, 114.2, 120.5, 123.4, 124.9, 127.5, 155.2, 161.9, 165.4.

Anal. Calcd for $C_{13}H_{15}BrO_5$: C, 47.15; H, 4.57. Found: C, 47.22; H, 4.63.

Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synthesis.

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References

(1) Weinrich, K. P.; Heggs, R. P.; Northrup, V. M.; Ponce, E. M.; Balducci, J. J.; Weinstein, S.; Barcelon, S. A.; Rieger, M. WO 9,413,870, **1994**.
(2) (a) Song, J.; Hesse, M. *Tetrahedron* **1993**, *49*, 6797. (b) Marquardt, U.; Schmid, D.; Jung, G. *Synlett* **2000**, 1131. (c) Callow, R. K.; Johnston, N. C. *Bee World* **1960**, *41*, 152.
(3) Clifford, M. N.; Johnston, K. L.; Knigh, S.; Kuhnert, N. *J. Agric. Food. Chem.* **2003**, *51*, 2900.
(4) Johnston, K. L.; Clifford, M. N.; Morgan, L. M. *Am. J. Clin. Nutr.* **2003**, *79*, 728.
(5) Jassim, S. A. A.; Naji, M. A. *J. Appl. Microbiol.* **2003**, *95*, 412.
(6) De Sotillo, D. R.; Hadley, M.; Wolf-Hall, C. *J. Food Sci.* **1998**, *63*, 907.
(7) Bowels, B. L.; Miller, A. J. *J. Food Sci.* **1994**, *59*, 905.
(8) For selected examples, see: (a) Maryanoff, B. E.; Reitz, A. B. *Chem. Rev.* **1989**, *89*, 863. (b) Hatsuda, M.; Kuroda, T.; Seki, M. *Synth. Commun.* **2003**, *33*, 427. (c) Kisanga, P.; 'Sa, B. D.; Verkade, J. *Tetrahedron* **2001**, *57*, 8047. (d) Herrmann, W. A.; Wang, M. *Angew. Chem., Int. Ed. Engl.* **1991**, *30*, 1641; *Angew. Chem.* **1991**, *103*, 1709. (e) Ledford, B. E.; Carreira, E. M. *Tetrahedron Lett.* **1997**, *38*, 8125. (f) Barma, D. K.; Kundu, A.; Bandyopadhyay, A.; Sangras, B.; Briot, A.; Mioskowski, R.; Falck, J. R. *Tetrahedron Lett.* **2004**, *45*, 5917. (g) Taguchi, H.; Shimoji, K.; Yamamoto, H.; Nozaki, H. *Bull. Chem. Soc. Jpn.* **1974**, *47*, 2529. (h) Matui, S.; Tanaka, K.; Kaji, A. *Synthesis* **1983**, 127. (i) Huang, Y.; Shen, Y.; Chen, C. *Tetrahedron Lett.* **1986**, *27*, 2903. (j) Olah, G. A.; Wu, A. H.; Farooq, O.; Prakash, G. K. *Synthesis* **1988**, 537.
(9) For a two step process for recycling Ph_3PO, see p. 7 in: Hermeling, D.; Bassler, P.; Hammes, P.; Hugo, R.; Lechtken, P.; Siegel, H. EP 0638580, **1995**.
(10) (a) Horner, L.; Hoffmann, H. M. R.; Wippel, H. G. *Chem. Ber.* **1958**, *91*, 61. (b) Wadsworth, W. S. Jr.; Emmons, W. D. *Org. Synth. Coll. Vol. V*; John Wiley & Sons: London, **1973**, 547. (c) Nagaoka, H.; Kishi, Y. *Tetrahedron* **1981**, *37*, 3873. (d) Ando, K. *J. Org. Chem.* **1997**, *62*, 1934.
(11) (a) Galat, A. *J. Am. Chem. Soc.* **1946**, *68*, 376. (b) Martin, C. J.; Schepartz, A. I.; Daubert, B. F. *J. Am. Chem. Soc.* **1948**, *70*, 2601. (c) Klein, J.; Bergmann, E. D. *J. Am. Chem. Soc.* **1957**, *79*, 3452.
(12) Augustine, J. K.; Naik, Y. A.; Mandal, A. B.; Chowdappa, N.; Praveen, V. B. *J. Org. Chem.* **2007**, *72*, 9854.
(13) For selected examples, see: (a) Larock, R. C. *Comprehensive Organic Transformations*, 2nd Ed.; John Wiley & Sons: Chichester, **1999**, 1224. (b) Chung, S. J.; Kim, D. H. *Tetrahedron* **1995**, *51*, 12549. (c) Sander, W.; Exner, M. *J. Chem. Soc., Perkin Trans. 2* **1999**, 2285. (d) Tabushi, I.; Sasaki, T. *Tetrahedron Lett.* **1982**, *23*, 1913. (e) Dann, O.; Char, H.; Griessmeier, H. *Liebigs Ann. Chem.* **1982**, 1836. (f) Li, W.; Li, J.; DeVincentis, D.; Mansour, T. S. *Tetrahedron Lett.* **2004**, *45*, 1071. (g) Coleman, G. H.; Honeywell, G. E. *Org. Synth. Coll. Vol. II*; John Wiley & Sons: London, **1943**, 98–91. (h) Bankston, D. *Synthesis* **2004**, 282. (i) Gillespie, J. S.; Acharya, S. P.; Shamblee, D. A.; Davis, R. E. *Tetrahedron* **1975**, *31*, 3. (j) Zondervan, C.; Beuken, E.; Kooijman, H.; Spek, A. L.; Feringa, B. L. *Tetrahedron Lett.* **1997**, *38*, 3111. (k) Helms, A.; Heiler, D.; McLendon, G. *J. Am. Chem. Soc.* **1992**, *114*, 6227. (l) Waehaelae, K.; Ojanperae, I.; Haeyri, L.; Hase, T. A. *Synth. Commun.* **1987**, *17*, 137. (m) Man, Y.-M.; Thomas, C. W.; Wong, H. N. C. *J. Org. Chem.* **1990**, *55*, 3214. (n) Jung, M. E.; Hogan, K. T. *Tetrahedron Lett.* **1988**, *29*, 6199.
(14) Mandal, A. B.; Augustine, J. K.; Quattropani, A.; Bombrun, A. *Tetrahedron Lett.* **2005**, *46*, 6033.
(15) Takeda, K.; Akiyama, A.; Nakamura, H.; Takizawa, S.; Mizuno, Y.; Takayanagi, H.; Harigaya, Y. *Synthesis* **1994**, 1063.
(16) Srinivas, K. V. N. S.; Mahender, I.; Das, B. *Synthesis* **2003**, 2479.