The Use of Bromotrichloromethane in Chlorination Reactions

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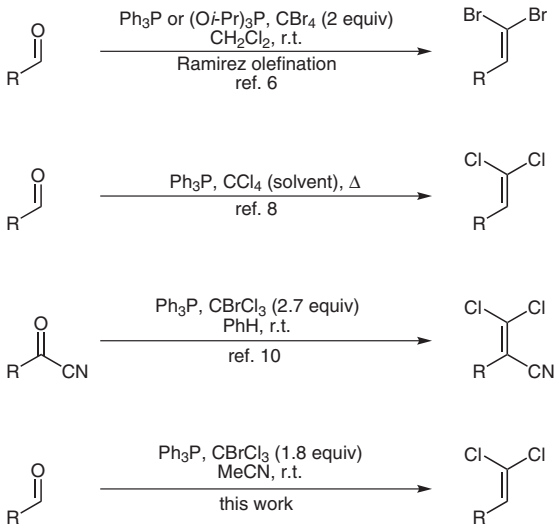
Abstract: Carbon tetrachloride is no longer used as a common solvent due to its toxicity and harmful environmental impact. The synthesis of *gem*-dichloroalkenes from aldehydes by using triphenylphosphine typically requires carbon tetrachloride as a solvent. We report that stoichiometric bromotrichloromethane in acetonitrile can be used in place of solvent quantities of carbon tetrachloride in this transformation. Similarly, bromotrichloromethane in dichloromethane can be used for the room-temperature Appel reaction of benzyl alcohols to form benzyl chlorides, which is commonly carried out in refluxing carbon tetrachloride.

Key words: olefination, aldehydes, halogenation, Appel reaction, benzyl halides

The *gem*-dihaloalkene group is well known as an intermediate in the synthesis of terminal alkynes from aldehydes via the Corey–Fuchs reaction.[1] A recent surge in the literature has seen *gem*-dihaloalkenes used in metal-catalyzed cross-coupling reactions towards the synthesis of trisubstituted alkenes,[2] internal alkynes,[3] heterocycles,[4] and other transformations.[5] *gem*-Dibromoalkenes are most common due to their ease of synthesis from aldehydes via the Ramirez olefination and recent modifications (Scheme 1).[6] While numerous methods have been developed for the synthesis of *gem*-dichloroalkenes, none benefit from the generality, ease, and excellent yields of the Ramirez olefination. Yet *gem*-dichloroalkenes are known to undergo many of the same reactions as *gem*-dibromoalkenes in similar or improved yields.[7] Moreover, the use of chlorinated substrates provides an advantage in terms of molecular weight over the corresponding brominated substrates. Herein, we report a reliable, operationally simple, high-yielding synthesis of *gem*-dichloroalkenes by using triphenylphosphine and bromotrichloromethane in a single step from the corresponding aldehydes. Moreover, we have found that this substrate combination can be used to effect high-yielding Appel reactions of benzylic alcohols, thus avoiding the use of large quantities of carbon tetrachloride.

The classical method for synthesizing *gem*-dichloroalkenes is by refluxing an aldehyde and triphenylphosphine in carbon tetrachloride (Scheme 1).[8] Since carbon tetrachloride has been identified as a toxic, environmentally harmful substance, its use as a solvent has become restricted. Moreover, carbon tetrachloride and triphenylphosphine produce significant amounts of reactive dichlorotriphenylphosphorus as a stoichiometric byproduct, which can lead to side reactions at elevated temperatures. The problems with this reaction are perhaps best illustrated by observing the wealth of literature dedicated to finding improved methods for making *gem*-dichloroalkenes from aldehydes.[9] These alternative routes often involve multiple steps, cryogenic temperatures, use of a large excess of carbon tetrachloride, and/or generation of stoichiometric metal waste. We recently became interested in the synthesis of *gem*-dichloroalkenes for use in cross-coupling reactions, and sought to improve their method of synthesis. Our attention was drawn to a report by Soulen and co-workers, describing the use of triphenylphosphine and bromotrichloromethane in benzene for the synthesis of *gem*-dichloroalkenes from acyl nitriles in an operationally simple and efficient procedure.[10] Since bromotrichloromethane and carbon tetrachloride are comparable in price,[11] the total difference in cost between using a slight excess of bromotrichloromethane and using carbon tetrachloride as a solvent or co-solvent becomes significant. Surprisingly, no general evaluation of this set of conditions was used on simple aldehydes in the literature.



Scheme 1 Methods for the synthesis of *gem*-dichloroalkenes

We initiated our studies with the transformation of aldehyde **1a** to *gem*-dichloroalkene **2a**, which had recently been prepared in 66% yield by using carbon tetrachloride as a solvent (Scheme 2).[4d] We experimented with Soulen's original conditions and found that using 1.8

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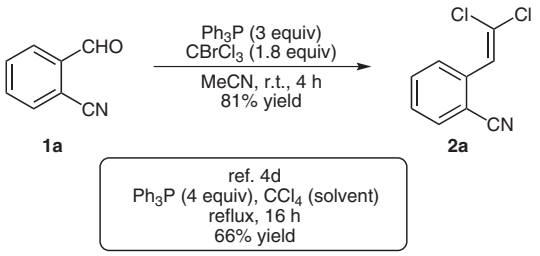
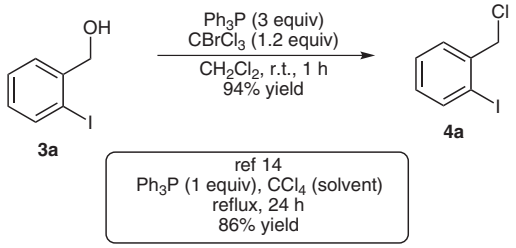
equivalents of bromotrichloromethane and three equivalents of triphenylphosphine in acetonitrile at room temperature gave **2a** in 82% yield in just four hours. The use of acetonitrile as a solvent was crucial, as other solvents such as 1,2-dimethoxyethane and dichloromethane gave large quantities of byproducts.



Scheme 2 Improved synthesis of *gem*-dichloroalkenes

By using these conditions, a range of *gem*-dichloroalkenes could be synthesized in good yields (Table 1). Electron-poor and electron-neutral benzaldehydes worked well. Tetrasubstituted alkene **2g** could be prepared, albeit with lower conversion. Aliphatic alkene **2h** and electron-rich alkene **2i** could be prepared, however these were isolated along with 10% of an inseparable impurity.[12]

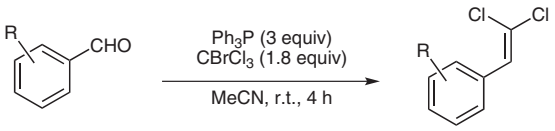
The remarkable improvement observed when using bromotrichloromethane in place of carbon tetrachloride for olefination chemistry led us to explore whether similar conditions could affect the substitution of alcohols for chlorides (Appel reaction).[13] Similar to the above discussed dichloroolefination reaction, the classical Appel reaction involves refluxing an alcohol and triphenylphosphine in carbon tetrachloride as a solvent or co-solvent. For example, 2-iodobenzyl chloride (**4a**) can be prepared from the reaction of corresponding alcohol **3a** with triphenylphosphine in refluxing carbon tetrachloride (Scheme 3).[14]



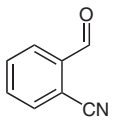
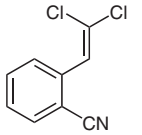
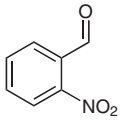
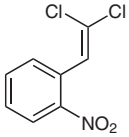
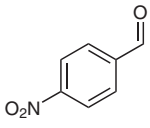
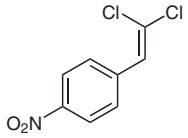
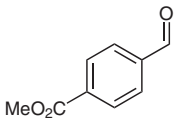
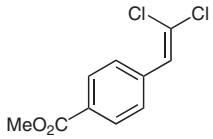
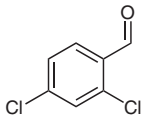
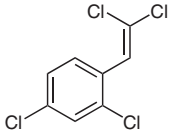
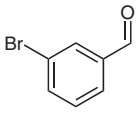
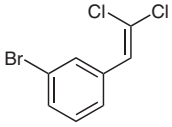
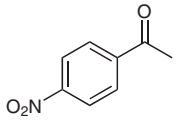
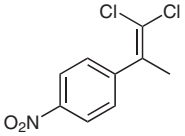
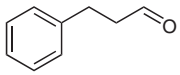
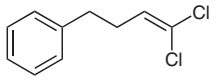
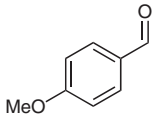
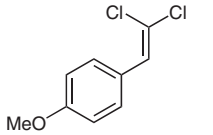
Scheme 3 Improved synthesis of benzyl chlorides

We found that by using just 1.2 equivalents of bromotrichloromethane and three equivalents of triphenylphosphine in dichloromethane, the same transformation could be carried out at room temperature in 94% yield (Scheme 3). The choice of solvent and order of addition of reagents were found to be crucial. In the optimized procedure, the bromotrichloromethane and triphenylphosphine are first premixed in dichloromethane for 40 minutes before addition of the alcohol, which is almost immediately consumed. Removal of triphenylphosphine oxide by column chromatography provides the benzyl chloride in excellent yield. These conditions could be applied to the synthesis of a diverse range of electron-rich and electron-poor benzyl chlorides (Table 2). The reaction could be run

Table 1 Reaction Scope of the Dichloroolefination with Bromotrichloromethane



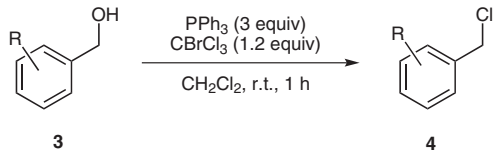
1 2

Entry	Substrate		Product		Yield (%)[a]
1	**1a**		**2a**		82
2	**1b**		**2b**		81
3	**1c**		**2c**		93
4	**1d**		**2d**		86
5	**1e**		**2e**		83
6	**1f**		**2f**		84
7	**1g**		**2g**		65
8	**1h**		**2h**		78[b]
9	**1i**		**2i**		89[b]

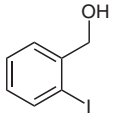
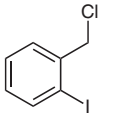
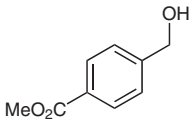
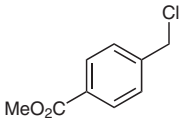
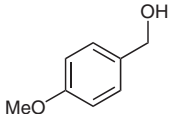
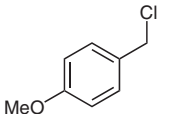
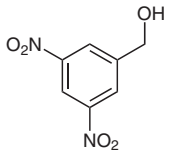
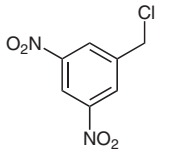
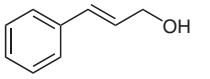
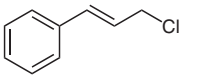
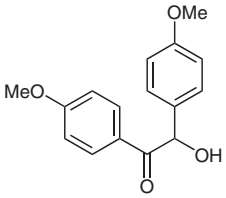
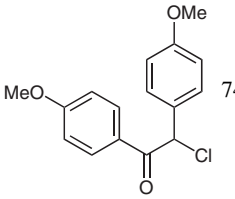
[a] Isolated yield.
[b] Approximately 90% purity by ^{1}H NMR analysis.

on gram scale without loss of yield (Table 2, entry 2). Unfortunately, this optimized procedure appeared to be efficient only on benzylic alcohols, with simple aliphatic alcohols giving mixtures of chlorination and bromination products. While this limits the scope, it still serves to highlight how bromotrichloromethane can be used in place of a large excess of carbon tetrachloride to significantly reduce the cost and environmental impact of simple, well-known reactions.

Table 2 Reaction Scope of the Benzylic Appel Reaction with Bromotrichloromethane



3 4

Entry		Product	Yield (%)[a]
1	**3a** 	**4a** 	94
2	**3b** 	**4b** 	98[b]
3	**3c** 	**4c** 	84
4	**3d** 	**4d** 	96
5	**3e** 	**4e** 	80
6	**3f** 	**4f** 	74

[a] Isolated yield.
[b] On a scale of 5 mmol.

In conclusion, we have shown that the combination of bromotrichloromethane and triphenylphosphine can be used to convert aldehydes into *gem*-dichloroalkenes, and benzyl alcohols into benzyl chlorides. These procedures provide a significant improvement over the classical methods which require expensive and toxic carbon tetrachloride to be used as a solvent or co-solvent.

Flash chromatography was performed by using Ultra Pure 230–400 mesh silica gel purchased from Silicycle. Melting points were taken on a Fisher-Johns melting point apparatus. IR spectra were obtained by using a Shimadzu FTIR-8400S FT-IR spectrometer; samples were prepared on NaCl plates. ^{1}H, ^{13}C, ^{19}F, and ^{31}P NMR spectra were obtained by using either a Bruker Avance III 400 MHz or Varian Mercury 400 MHz spectrometer. CH_2Cl_2 was purified by using an MBraun Solvent Purification System. $CBrCl_3$ (97%) was purchased from Alfa Aesar and used as received. Ph_3P (99%) was purchased from Strem Chemicals and used as received. All aldehydes and alcohols were purchased from commercial sources and used as received.

gem-Dichloroalkenes 2 from Aldehydes 1; General Procedure A

Aldehyde **1** (1 equiv), MeCN (0.1 M), and Ph_3P (3 equiv) were added to a flask equipped with a magnetic stir bar. The mixture was stirred for 5 min, after which $CBrCl_3$ (1.8 equiv) was added in one portion. The reaction mixture was stirred under an air atmosphere at r.t. for 4 h, by which time the aldehyde and Ph_3P had been consumed, as shown by TLC. The mixture was diluted with a Et_2O–pentane mixture (3:1) until solid Ph_3PO began to precipitate. The heterogeneous mixture was then filtered through a pad of silica gel, which was rinsed with a Et_2O–pentane mixture (3:1). Rotary evaporation provided clean **2** after most reactions, as indicated by ^{1}H NMR spectroscopy. The products were purified additionally by flash chromatography.

Benzyl Chlorides 4 from Alcohols 3; General Procedure B

Ph_3P (3 equiv) and CH_2Cl_2 (2 mL per 3.0 mmol Ph_3P) were added to a flask equipped with a magnetic stir bar. $CBrCl_3$ (1.2 equiv) was added, the flask was closed with a septum, and the mixture was stirred under air at r.t. for 40 min, during which the colorless soln turned deep brown. A soln of the requisite alcohol **3** (1.0 equiv) in CH_2Cl_2 (3 mL per 1.0 mmol alcohol) was added dropwise, and the mixture was stirred at r.t. until the starting material had been consumed (as indicated by TLC; approximately 10 min). The mixture was diluted with a Et_2O–pentane mixture (3:1) until solid Ph_3PO began to precipitate. The heterogeneous mixture was then filtered through a pad of silica gel, which was rinsed with a Et_2O–pentane mixture (3:1). Rotary evaporation provided clean **4** after most reactions, as indicated by ^{1}H NMR spectroscopy. The products were purified additionally by flash chromatography.

2-(2,2-Dichlorovinyl)benzonitrile (2a)

General procedure A was followed (0.156 mmol scale). The product was purified by flash column chromatography (silica gel, EtOAc–pentane, 5:95); this provided **2a** as a white solid. Characterization data match those previously reported.[3]

Yield: 24.4 mg (82%); mp 59–60 °C (Lit.[3] 62–64 °C).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.89 (d, *J* = 8.0 Hz, 1 H), 7.70 (d, *J* = 7.8 Hz, 1 H), 7.64 (t, *J* = 7.7 Hz, 1 H), 7.44 (t, *J* = 7.7 Hz, 1 H), 7.15 (s, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 136.6, 133.0, 132.7, 129.0, 128.7, 126.2, 124.8, 117.2, 112.4.

1-(2,2-Dichlorovinyl)-2-nitrobenzene (2b)

General procedure A was followed (0.5 mmol scale). The product was purified by flash column chromatography (silica gel, EtOAc–pentane, 5:95); this provided **2b** as an off-white solid. Characterization data match those previously reported.[1]

Yield: 88 mg (81%); mp 48–49 °C (Lit.[1] 49–50 °C).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.11 (d, *J* = 8.3 Hz, 1 H), 7.53–7.70 (m, 2 H), 7.53 (t, *J* = 8.4 Hz, 1 H), 7.24 (s, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 147.2, 133.4, 131.6, 129.3, 128.9, 125.3, 124.8, 124.2.

1-(2,2-Dichlorovinyl)-4-nitrobenzene (2c)
General procedure A was followed (0.5 mmol scale). The product was purified by flash column chromatography (silica gel, EtOAc–pentane, 5:95); this provided **2c** as a white solid. Characterization data match those previously reported.[2]

Yield: 101 mg (93%); mp 88–89 °C (Lit.[2] 88.5–89.5 °C).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.23 (d, *J* = 8.8 Hz, 2 H), 7.70 (d, *J* = 8.7 Hz, 2 H), 6.94 (s, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 147.2, 139.6, 129.4, 126.8, 125.3, 123.8.

Methyl 4-(2,2-Dichlorovinyl)benzoate (2d)
General procedure A was followed (0.5 mmol scale). The product was purified by flash column chromatography (silica gel, EtOAc–pentane, 5:95); this provided **2d** as an off-white solid. Characterization data match those previously reported.[4]

Yield: 99.5 mg (86%); mp 62–63 °C (Lit.[4] 57–58 °C).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.02 (d, *J* = 8.4 Hz, 2 H), 7.59 (d, *J* = 8.3 Hz, 2 H), 6.88 (s, 1 H), 3.92 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 166.5, 137.7, 129.8, 129.7, 128.6, 127.8, 123.3, 52.3.

2,4-Dichloro-1-(2,2-dichlorovinyl)benzene (2e)
General procedure A was followed (0.5 mmol scale). The product was purified by flash column chromatography (silica gel, EtOAc–pentane, 3:97); this provided **2e** as a white solid. Characterization data match those previously reported.[5]

Yield: 100.4 mg (83%); mp 47–48 °C (Lit.[5] 49–50 °C).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.63 (d, *J* = 8.5 Hz, 1 H), 7.41 (d, *J* = 2.0 Hz, 1 H), 7.27 (dd, *J* = 8.6, 2.0 Hz, 1 H), 6.97 (s, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 134.8, 134.2, 130.7, 130.4, 129.4, 127.0, 124.7, 124.2.

1-Bromo-3-(2,2-dichlorovinyl)benzene (2f)
General procedure A was followed (0.5 mmol scale). The product was purified by flash column chromatography (silica gel, EtOAc–pentane, 3:97); this provided **2f** as a colorless oil. Characterization data match those previously reported.[5]

Yield: 106.0 mg (84%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.67 (s, 1 H), 7.43 (m, *J* = 7.9 Hz, 2 H), 7.22 (d, *J* = 7.8 Hz, 1 H), 6.77 (s, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 135.3, 131.4, 131.3, 129.9, 127.2, 127.1, 122.6, 122.5.

1,1-Dichloro-2-(4-nitrophenyl)prop-1-ene (2g)
General procedure A was followed (0.5 mmol scale). The product was purified by flash column chromatography (silica gel, EtOAc–pentane, 5:95); this provided **2g** as a clear oil. Characterization data match those previously reported.[6]

Yield: 76 mg (65%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.24 (d, *J* = 8.9 Hz, 2 H), 7.46 (d, *J* = 8.9 Hz, 2 H), 2.24 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 147.2, 146.6, 133.9, 129.0, 123.8, 119.2, 22.3.

1,1-Dichloro-4-phenylbut-1-ene (2h)
General procedure A was followed (0.5 mmol scale). The product was purified by flash column chromatography (silica gel, Et_2O–pentane, 5:95); this provided **2h** as a clear oil with 5–10% inseparable impurities. Characterization data match those previously reported.[7]

Yield: 78.2 mg (78%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.15–7.32 (m, 5 H), 5.86 (t, *J* = 7.3 Hz, 1 H), 2.71 (t, *J* = 7.4 Hz, 2 H), 2.48 (t, *J* = 7.3 Hz, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 140.6, 128.9, 128.5, 128.4, 126.2, 120.6, 34.2, 31.3.

1-(2,2-Dichlorovinyl)-4-methoxybenzene (2i)
General procedure A was followed (0.5 mmol scale). The product was purified by flash column chromatography (silica gel, Et_2O–pentane, 5:95); this provided **2i** as a clear oil with 5–10% inseparable impurities. Characterization data match those previously reported.[4]

Yield: 90.0 mg (89%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.49 (d, *J* = 8.6 Hz, 2 H), 6.88 (d, *J* = 8.7 Hz, 2 H), 6.77 (s, 1 H), 3.81 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 159.6, 130.1, 128.0, 126.0, 118.8, 113.9, 55.3.

1-(Chloromethyl)-2-iodobenzene (4a)
General procedure B was followed (1 mmol scale). The product was purified by flash column chromatography (silica gel, pentane); this provided **4a** as a colorless oil. Characterization data matched those of commercially available material.

Yield: 238 mg (94%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.86 (d, *J* = 7.9 Hz, 1 H), 7.48 (d, *J* = 7.7 Hz, 1 H), 7.37 (t, *J* = 7.6 Hz, 1 H), 7.01 (t, *J* = 7.7 Hz, 1 H), 4.67 (s, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 139.9 (2C), 130.2, 130.1, 128.8, 99.5, 51.1.

Methyl 4-(Chloromethyl)benzoate (4b)
General procedure B was followed (5 mmol scale). The product was purified by flash column chromatography (silica gel, Et_2O–pentane, 5:95); this provided **4b** as a white solid. Characterization data matched those of commercially available material.

Yield: 910 mg (98%); mp 38–39 °C (Lit.[15] 39–40 °C).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.04 (d, *J* = 8.3 Hz, 2 H), 7.47 (d, *J* = 8.3 Hz, 2 H), 4.62 (s, 2 H), 3.92 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 166.5, 142.2, 130.1, 130.0, 128.5, 52.2, 45.4.

1-(Chloromethyl)-4-methoxybenzene (4c)
General procedure B was followed (1 mmol scale). The product was purified by flash column chromatography (silica gel, Et_2O–pentane, 5:95); this provided **4c** as a colorless oil. Characterization data matched those of commercially available material.

Yield: 131 mg (84%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.31 (d, *J* = 8.7 Hz, 2 H), 6.88 (d, *J* = 8.7 Hz, 2 H), 4.57 (s, 2 H), 3.81 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 159.7, 130.1, 129.7, 114.2, 55.3, 46.3.

1-(Chloromethyl)-3,5-dinitrobenzene (4d)
General procedure B was followed (1 mmol scale). The product was purified by flash column chromatography (silica gel, Et_2O–pentane, 15:85); this provided **4d** as a white solid. Characterization data matched those of commercially available material.

Yield: 208 mg (96%); mp 79–80 °C (Lit.[16] 79–79.5 °C).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.03 (t, *J* = 2.0 Hz, 1 H), 8.62 (d, *J* = 2.0 Hz, 2 H), 4.76 (s, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 148.7, 141.6, 128.6, 118.7, 43.5.

(*E*)-(3-Chloroprop-1-en-1-yl)benzene (4e)
General procedure B was followed (1 mmol scale). The product was purified by flash column chromatography (silica gel, pentane); this provided **4e** as a colorless oil. Characterization data matched those of commercially available material.

Yield: 122 mg (80%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.23–7.41 (m, 5 H), 6.65 (d, *J* = 15.6 Hz, 1 H), 6.26–6.36 (m, 1 H), 4.24 (d, *J* = 8.3 Hz, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 135.9, 134.2, 128.7, 128.3, 126.8, 125.0, 45.5.

2-Chloro-1,2-bis(4-methoxyphenyl)ethanone (4f)
General procedure B was followed (1 mmol scale). The product was purified by recrystallization from Et_2O–pentane; this provided **4f** as a white solid. Characterization data perfectly match the previously reported ^{1}H and ^{13}C NMR data.[8] However, the authors reported the substrate to be a colorless oil.[8] We find this surprising, since the corresponding diphenylethanone has been reported to be a solid that melts at 64–65 °C.[17]

Yield: 215 mg (74%); mp 70–71 °C (Lit.[8] oil).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.94 (d, *J* = 9.0 Hz, 2 H), 7.40 (d, *J* = 8.7 Hz, 2 H), 6.85–6.92 (m, 4 H), 6.29 (s, 1 H), 3.84 (s, 3 H), 3.79 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 190.0, 163.9, 160.2, 131.5, 130.5, 129.9, 128.3, 127.2, 114.6, 114.0, 62.1, 55.6, 55.4.

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

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