o-Benzoylbenzoic Acid Synthesis by Condensation of (o-Lithioaryl)oxazolines with Acid Chlorides. Preparation of a Potential Intermediate for Anthracycline Synthesis

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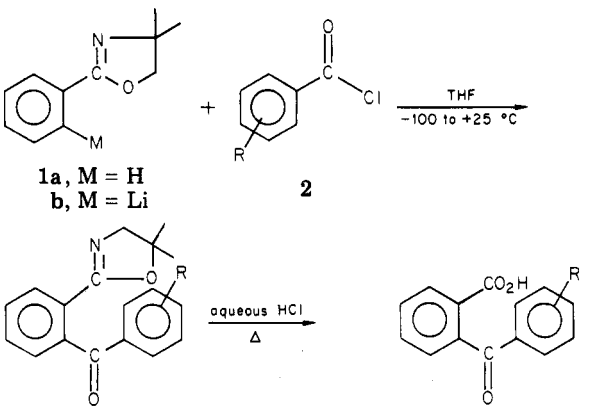
It is possible to prepare o-benzoylbenzoic acids in good yields by the addition of aroyl chlorides to lithium o-lithiobenzoates at −100 °C.[1] This preference for ketone rather than tertiary alcohol formation is not characteristic of all aryllithium reagents, even at −100 °C, and has been observed rarely.[2] The aryllithium reagents which we have found to react with aroyl chlorides to form ketones preferentially (lithium o-lithiobenzoate, o-lithiobenzonitrile, and N,o-dilithio-N-methylbenzamide) have in common an electron-attracting group ortho to the lithium atom. By analogy, the readily available[3,4] 4,4-dimethyl-2-(o-lithiophenyl)-Δ^2-oxazoline (**1b**) should likewise react with aroyl chlorides at −100 °C to give ketones as the major product.

The addition of aroyl chlorides (**2**) to **1b** yielded phenyloxazolines (**3**) which were not purified but subjected to acidic hydrolysis to yield the expected o-benzoylbenzoic acids (**4**). In all but one case simple recrystallization was sufficient to provide the pure compounds **4a–f** in good overall yields as summarized in Scheme I. No evidence of tertiary alcohol byproducts was observed. For example, chromatographic purification of the crude carboxylic acid product from condensation of **1b** with p-toluoyl chloride followed by hydrolysis gave only **4b**, benzoic acid, and p-toluic acid, accounting for 100% of the starting materials.

It seemed likely that reaction of an appropriate (lithiophenyl)oxazoline and acid chloride would afford a benzoylbenzoic acid of potential utility in the synthesis of anthracycline antitumor agents. Several related routes to these interesting and much-sought compounds were reported[5–9] during and after the course of this work, while the utility of anthraquinones as anthracycline and rhodomycin precursors has been amply demonstrated.[10–12] The previously unknown (m-methoxyphenyl)oxazoline **5** was synthesized in high yield by techniques analogous to those of Meyers and co-workers.[13] Metalation of **5** occurred in the 2-position, ortho to both the directing groups as expected[14] and as demonstrated by carbonation of the reaction mixture to afford 3-methoxyphthalic acid (Scheme II). Further, condensation of **6** with simple aroyl chlorides proceeded smoothly to afford, after hydrolysis, previously unknown keto acids **9** in 56% and 57% yields, respectively (Scheme II).

Scheme I



1a, M = H
b, M = Li

2

3

4a, R = H (58% yield)
b, R = p-CH_3 (60% yield)
c, R = p-Cl (58% yield)
d, R = p-OCH_3 (78% yield)
e, R = m-OCH_3 (61% yield)
f, R = o-OCH_3 (57% yield)

Condensation of aryllithium **6** with key functionalized acid chloride **10**[15,16] afforded a mixture of desired ketone **11** and starting materials. Vigorous acidic hydrolysis of this crude product by the technique used for more simple oxazolines led to inseparable mixtures due to partial cleavage of the benzyl protective groups. In contrast, gentle removal of the oxazoline moiety[17] involving initial quaternization of the oxazoline nitrogen with methyl iodide, followed by mild alkaline hydrolysis, gave pure benzoylbenzoic acid **12** in 41% overall yield for the three steps. The benzyl protective groups were cleanly removed by atmospheric pressure catalytic hydrogenolysis leading to hydroquinone **13**, which has been cyclized in high yield to islandicin methyl ether **14**.[18] Thus the synthesis of a highly functionalized diaryl ketone via clean low-temperature condensation of an aryllithium reagent and an aroyl chloride has made possible the brief and efficient preparation of potential anthracycline precursor **14**.

Experimental Section

General low-temperature lithiation techniques have been described elsewhere.[19] Reaction temperatures of −45 °C were achieved by using liquid N_2 in an ethanol–water mixture, while temperatures of −100 °C were achieved by using a liquid N_2–ether mixture. Infrared spectra were obtained by using Perkin-Elmer Model 137, 237, and 297 grating spectrometers. ^1H NMR spectra were obtained on a JEOL JNM-MH-100 instrument and ^{13}C spectra on a JEOL FX-60 15-MHz Fourier transform instrument with a $CDCl_3$ or $(CD_3)_2SO$ lock. Melting points were observed on a Mel-Temp heating block apparatus or a Thomas-Hoover melting point apparatus and are uncorrected.

The term "concentrated" refers to removal of solvents on a rotary evaporator. The term "dried" refers to drying of organic residues by using anhydrous magnesium sulfate. Elemental analyses were performed by MHW Laboratories, Phoenix, AZ.

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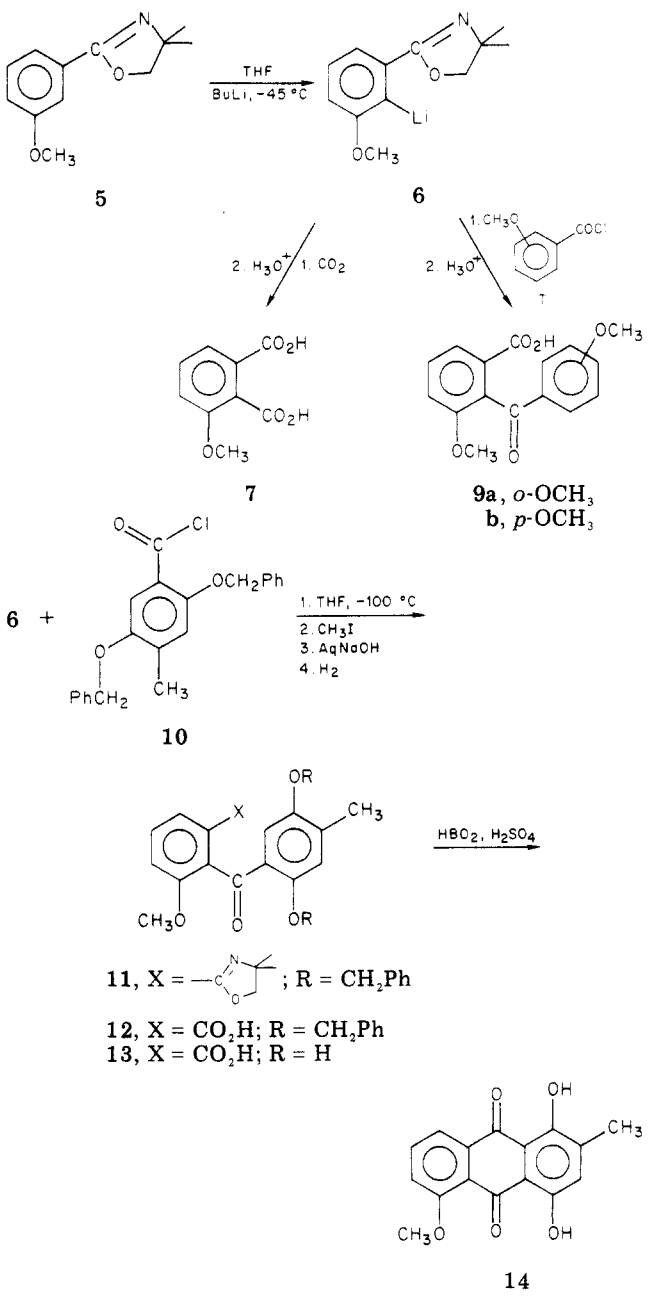
Scheme II



General Procedure. The phenyloxazolines (15–25 mmol) were metalated at −45 °C in THF (4 mL/mmol of oxazoline) by the precedure of Meyers.[4] The resulting aryllithium reagent was cooled to −100 °C and treated with 1 equiv of acid chloride in THF (1 mL/mmol of acid chloride) at −90 to −100 °C. After an appropriate reaction period at −100 °C (1–4 h), the mixture was allowed to warm to room temperature and then was worked up by quenching in water, stirring vigorously for 2 h at room temperature to ensure complete hydrolysis of the acid chloride, and extraction with CH_2Cl_2. The organics were washed with water and aqueous $NaHCO_3$, dried, filtered, and concentrated to afford the crude oxazolines, which were examined spectroscopically and then hydrolyzed overnight at reflux with 5% aqueous HCl. The dark, heterogeneous reaction mixture was quenched by being poured into ice, the layers were separated, and the aqueous layer was extracted with $CHCl_3$. Extraction of the organic layers with saturated aqueous $NaHCO_3$, acidification of the bicarbonate extracts, chloroform extraction, and drying and concentration of the chloroform extracts gave the crude benzoic acids **4a–f** and **9a,b**, which were purified by recrystallization, trituration, or column chromatography.

2-Benzoylbenzoic Acid (4a). Hydrolysis of the crude mixture of **1a** and **3a** gave **4a** [^{1}H NMR ($CDCl_3$) δ 1.00 (s, 6, CH_3), 3.44 (s, 2, CH_2), 7.00–7.80 (m, Ar H, 9)], which was recrystallized once from $CHCl_3$–ligroin in 58% yield; mp 124.5–125.5 °C. One further recrystallization gave **4a** whose melting point was not depressed by admixture with an authentic sample.

2-(4-Methylbenzoyl)benzoic Acid (4b). Hydrolysis of the crude mixture of **1a** and **3b** [^{1}H NMR ($CDCl_3$) δ 1.06 (s, 6, $C(CH_3)_2$), 2.37 (s, 3, $ArCH_3$), 3.64 (s, 2, CH_2), 7.05–8.13 (m, 8, Ar H)] gave **4b**. The product was purified by chromatography on silica gel (hexane–ethyl acetate), followed by recrystallization from toluene–ligroin to afford **4b** as small white prisms: 60% yield; mp 138–139.5 °C (lit.[20] mp 139–140 °C); ^{1}H NMR ($CDCl_3$) δ 2.44 (s, 3, $ArCH_3$), 7.24–7.87 (m, 7, Ar H), 8.08–8.25 (m, 1, *o*-HOOCAr**H**), 9.28 (br s, 1, COOH); ^{13}C NMR ($CDCl_3$) δ 21.7, 127.9, 128.1, 129.4, 129.9, 131.1, 133.4, 134.8, 143.1, 144.3, 171.3, 197.3.

Anal. Calcd for $C_{15}H_{12}O_3$: C, 74.99; H, 5.03. Found: C, 75.28; H, 4.95.

2-(4-Chlorobenzoyl)benzoic Acid (4c). Compound **4c** was obtained by hydrolysis of the crude mixture of **1a** and **3c** [^{1}H NMR ($CDCl_3$) δ 1.04 (s, 6, $C(CH_3)_2$), 3.60 (s, 2, CH_2), 7.16–7.95 (m, 8, Ar H)] followed by one recrystallization from benzene–ligroin to give **4c** as white needles: 57% yield; mp 140–147 °C; ^{1}H NMR ($CDCl_3$) δ 7.36–7.91 (m, 7, Ar H), 8.08–8.28 (m, 1, *o*-HOOCAr**H**); ^{13}C NMR ($CDCl_3$) δ 127.7, 127.9, 129.1, 130.0, 130.9, 131.2, 133.7, 135.7, 139.8, 142.5, 171.1, 195.8. Another recrystallization from benzene gave analytically pure **4c** as white prisms, mp 148–149 °C (lit.[21] mp 147–148 °C).

Anal. Calcd for $C_{14}H_9ClO_3$: C, 64.51; H, 3.48; Cl, 13.60. Found: C, 64.36; H, 3.27; Cl, 13.72.

2-(4-Methoxybenzoyl)benzoic Acid (4d). Compound **4d** was obtained by hydroylsis of the crude mixture of **1a** and **3d** followed by one recrystallization from $CHCl_3$–ligroin: 78% yield; mp 139–145 °C; ^{1}H NMR ($CDCl_3$) δ 3.86 (s, 3, OCH_3), 6.87–7.03 (d, J = 9 Hz, 2, *o*-CH_3OAr**H**), 7.31–7.87 (m, 5, Ar H), 8.03–8.23 (m, 1, *o*-HOOCAr**H**), 11.37 (br s, 1, COOH); ^{13}C NMR ($CDCl_3$) δ 55.5, 113.9, 127.9, 128.1, 129.6, 130.3, 131.1, 132.1, 133.3, 143.1, 163.9, 171.3, 196.2. One further recrystallization from $CHCl_3$–ligroin gave analytically pure **4d** as large, clear, colorless prisms, mp 142.5–144 °C (lit.[22] mp 144.4–146.6 °C).

Anal. Calcd for $C_{15}H_{12}O_4$: C, 70.31; H, 4.72. Found: C, 70.28; H, 4.64.

2-(3-Methoxybenzoyl)benzoic Acid (4e). Compound **4e** was obtained by hydrolysis of the crude mixture of **1a** and **3e** [^{1}H NMR ($CDCl_3$) δ 1.07 (s, 6, $C(CH_3)_2$), 3.70 (s, 2, CH_2), 3.89 (s, 3, OCH_3), 7.09–8.15 (m, 8, Ar H)] followed by recrystallization from $CHCl_3$–ligroin: 61% yield; mp and mmp (with authentic **4e**) 153.5–156 °C (lit.[22] mp 154.5–155.4 °C; ^{1}H NMR ($CDCl_3$) δ 3.87 (s, 3, OCH_3), 7.05–7.83 (m, 7, Ar H), 8.08–8.27 (m, 1, *o*-HOOCAr**H**), 13.10 (br s, 1, COOH); ^{13}C NMR ($CDCl_3$) δ 55.5, 113.3, 120.0, 122.8, 127.9, 128.1, 129.6, 129.8, 131.0, 138.6, 143.0, 147.3, 160.0, 171.1.

2-(2-Methoxybenzoyl)benzoic Acid (4f). Hydrolysis of the crude mixture of **1a** and **3f** [^{1}H NMR ($CDCl_3$) δ 1.10 (s, 6, $C(CH_3)_2$), 3.62 and 3.64 (s, 5, CH_2 and OCH_3), 6.84–8.00 (m, 8, Ar H)] followed by trituration of the crude product with acetone and filtration gave **4f** in 57% yield as white prisms: mp 142.5–143.5 °C; ^{1}H NMR ($CDCl_3$/$(CD_3)_2SO$) δ 3.60 (s, 3, OCH_3),6.88–8.08 (m, 8, Ar H), 9.12 (br s, 1, COOH); ^{13}C NMR ($CDCl_3$)/$(CD_3)_2SO$) δ 55.6, 112.6, 120.4, 121.9, 126.9, 127.1, 129.2, 130.1, 131.4, 131.6, 134.1, 144.7, 159.1, 168.2, 195.8. One recrystallization from chloroform gave an analytical sample, mp 144–146 °C (lit.[23] mp 144–145 °C).

Anal. Calcd for $C_{15}H_{12}O_4$: C, 70.31; H, 4.72. Found: C, 70.24; H, 4.52.

4,4-Dimethyl-2-(3-methoxyphenyl)-Δ^2-oxazoline (5). This compound was synthesized by a procedure closely analogous to that used by Meyers[4] for **1a** from *m*-anisic acid: 74% yield; bp 79.0–80.5 °C (0.005 mm); ^{1}H NMR ($CDCl_3$) δ 1.42 (s, 6, $C(CH_3)_2$), 3.85 (s, 3, OCH_3), 4.11 (s, 2, CH_2), 6.94–7.64 (m, 4, Ar H); IR (neat) 1640 cm^{-1} (C=N).

Anal. Calcd for $C_{12}H_{15}O_2N$: C, 70.22; H, 7.37; N, 6.82. Found: C, 70.12; H, 7.43; N, 6.71.

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2-(2-Methoxybenzoyl)-3-methoxybenzoic Acid (9a). Compound **9a** was obtained by hydrolysis of the crude reaction mixture containing **5** and the desired product oxazoline, followed by a single recrystallization from chloroform–methanol, as white prisms: 56% yield; mp 171.5–173.5 °C; ^{1}H NMR ($(CD_3)_2SO$) δ 3.48 (s, 3, OCH_3), 3.68 (s, 3, *m*-HOOCArOCH_3), 6.95–7.88 (m, 8, Ar H and COOH); ^{13}C NMR ($(CD_3)_2SO$) δ 55.7, 56.0, 113.0, 115.4, 120.3, 121.9, 127.1, 129.1, 129.8, 131.0, 134.2, 156.1, 159.6, 167.3, 193.2. One further recrystallization (chloroform–methanol) gave analytically pure **9a** as large, clear prisms, mp 172–173.5 °C.

Anal. Calcd for $C_{16}H_{14}O_5$: C, 67.13; H, 4.93. Found: C, 67.36; H, 4.81.

2-(4-Methoxybenzoyl)-3-methoxybenzoic Acid (9b). Hydrolysis of the crude reaction mixture containing **5** and the desired oxazoline, followed by one recrystallization from chloroform, afforded **9b** as white prisms: 57% yield; mp 169.5–171.5 °C; ^{1}H NMR ($CDCl_3$/$(CD_3)_2SO$) δ 3.68 (s, 3, OCH_3), 3.79 (s, 3, OCH_3), 6.70–7.80 (m, 7. Ar H), 9.00 (br s, 1, COOH); ^{13}C NMR ($(CD_3)_2SO$) δ 55.4, 56.0, 113.8, 115.8, 122.0, 130.1, 130.2, 130.5, 130.7, 156.3, 162.9, 166.5, 193.4. A small sample was recrystallized once more from chloroform–cyclohexane to provide an analytical sample of **9b** as white prisms, mp 171.5–173 °C.

Anal. Calcd for $C_{16}H_{14}O_5$: C, 67.13; H, 4.93. Found: C, 66.89; H, 4.88.

2-[2,5-Bis(benzyloxy)-4-methylbenzoyl]-3-methoxybenzoic Acid (12). (*m*-Methoxyphenyl)oxazoline **5** (1.68 g, 8.18 mmol) was metalated at −45 °C with butyllithium for 5 h in accordance with the general procedure. Acid chloride **10**[15,16] (3.00 g, 8.18 mmol) was added to the aryllithium reagent at −100 °C as in the general procedure, and then the solution was stirred for 0.5 h at −100 °C. The solution was then warmed to 25 °C over 2 h and stirred overnight at ambient temperature. The orange solution was poured into 50 mL of saturated aqueous NaCl, the resulting mixture was stirred vigorously for 60 min, the layers were separated, and the aqueous layer was extracted with chloroform (3 × 75 mL). The organics were combined, washed with saturated aqueous $NaHCO_3$ (2 × 70 mL) and saturated aqueous NaCl (2 × 70 mL), dried, filtered, and concentrated to afford 5.16 g of heavy orange oil which was methylated by adding methyl iodide (20 mL) and stirring overnight. The reaction mixture was concentrated, THF (30 mL) and 1 N NaOH (20 mL) were added to the residue, and hydrolysis[17] was completed by vigorous stirring for 7 days at ambient temperature. Ether (40 mL) was added to the reaction mixture, the layers were separated, and the aqueous layer was extracted with ether (2 × 50 mL) and chloroform (2 × 50 mL). The combined organic extracts were washed with saturated aqueous $NaHCO_3$ (2 × 50 mL) to remove *m*-methoxybenzoic acid from the bicarbonate-insoluble **12**, with water (10 mL), and with saturated aqueous NaCl (50 mL). The organic extract was dried, filtered, and concentrated to 4.17 g of heavy orange oil. Recrystallization from benzene afforded 1.62 g of **12** (3.36 mmol, 41%) as a white powder: mp 178–181.5 °C; ^{1}H NMR ($CDCl_3$) δ 2.28 (s, 3, $ArCH_3$), 3.63 (s, 3, OCH_3), 4.77 (s, 2, benzylic CH_2 meta to ketone), 5.01 (s, 2, benzylic CH_2 ortho to ketone), 6.50 (br s, 1, COOH), 6.80–7.55 (m, 13, Ar H); ^{13}C NMR ($CDCl_3$) δ 17.0, 56.0, 70.5, 71.2, 112.7, 115.8, 116.2, 121.7, 124.8, 127.4, 127.7, 128.3, 128.4, 129.1, 134.1, 135.9, 136.1, 137.4, 151.1, 153.0, 155.7, 170.5. One further recrystallization from benzene afforded an analytical sample of **12** as a white powder, mp 183.5–185 °C.

Anal. Calcd for $C_{30}H_{26}O_6$: C, 74.67; H, 5.43. Found: C, 74.65; H, 5.42.

2-(2,5-Dihydroxy-4-methylbenzoyl)-3-methoxybenzoic Acid (13). Dibenzyl ether **12** (100 mg, 0.207 mmol) was dissolved in 50 mL of ethyl acetate and placed in a round-bottomed flask with 300 mg of 10% Pd/C and a magnetic stirring bar. The stirred mixture was hydrogenated under 1 atm of H_2 at 20 °C for 5 h, filtered, and concentrated; the residue was recrystallized from methanol–water to give **13** as yellow needles: 50 mg (0.165 mmol, 80%); mp 232–234 °C dec (lit.[18] mp 228–231 °C decomp); ^{1}H NMR ($C(CD_3)_2CO$) δ 2.21 (s, 3, $ArCH_3$), 3.73 (s, 3, OCH_3), 4.70 (br s, 3, OH), 6.48 (s, 1, *o*-CH_3Ar**H**), 6.68 (s, 1, *m*-CH_3Ar**H**), 7.08–7.75 (m, 3, Ar H); ^{13}C NMR ($CDCl_3$/$(CD_3)_2SO$) δ 15.1, 54.5, 114.1, 117.5, 120.9, 128.3, 128.7, 134.1, 145.7, 154.2, 155.2, 164.4.

Registry No. **1a**, 19312-06-2; **3a**, 80764-39-2; **3b**, 80764-40-5; **3c**, 80764-41-6; **3d**, 80764-42-7; **3e**, 80764-43-8; **3f**, 80764-44-9; **4a**, 85-52-9; **4b**, 85-55-2; **4c**, 85-56-3; **4d**, 1151-15-1; **4e**, 2159-36-6; **4f**, 1151-04-8; **5**, 73453-77-7; **9a**, 80764-46-1; **9b**, 80764-47-2; **10**, 40931-17-7; **12**, 80764-48-3; **13**, 80764-49-4; *m*-anisic acid, 586-38-9; benzoyl chloride, 98-88-4; *p*-methylbenzoyl chloride, 874-60-2; *p*-chlorobenzyl chloride, 122-01-0; *p*-methybenzoyl chloride, 100-07-2; *m*-methoxybenzoyl chloride, 1711-05-3; *o*-methoxybenzoyl chloride, 21615-34-9.

Biphasic Sonochemistry. Convenient Generation of Dichlorocarbene[1]

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We herein report an unusually simple procedure for the generation of dichlorocarbene. Our method is based on the action of ultrasound derived from a common laboratory cleaner on stirred $NaOH/CHCl_3$ two-phase systems.[2] Dichlorocarbene formed in this manner adds readily to alkenes, affording excellent yields of corresponding dichlorocyclopropanes.

Effective reaction between sodium hydroxide and chloroform to produce dichlorocarbene normally requires the use of a phase-transfer catalyst.[3-5] We have now discovered that such catalysts are unnecessary in solid/liquid systems, provided that efficient stirring and ultrasonic irradiation are employed. Immersion of a mixture of powdered sodium hydroxide and chloroform solution of styrene (2 mmol) into a bath cleaner, followed by ultrasonic irradiation and mechanical stirring, afforded at 95% isolated yield of 1,1-dichloro-2-phenylcyclopropane after 1.5 h. Similar isolated yields of dichlorocyclopropanes have been obtained for a variety of substituted alkenes and are presented in Table I. In general, reaction times and yields compare favorably with analogous phase-transfer procedures reported in the literature.[3-5] While small-scale preparations gave excellent and reproducible results, larger reactions (>5 mmol of alkene) gave poor conversions; we assume that this is due to the limited power of the bath cleaner used. Competition experiments carried out with cyclohexene as a reference standard further reveal that the selectivity of this carbene is very similar to that produced from $KOC(CH_3)_3/CHCl_3$ systems (Table II).[6]

The major advantage of this new dichlorocarbene generation procedure lies in its simplicity and the avoidance of phase-transfer catalysts. It should find broad use, especially for small-scale preparations of dichlorocyclopropanes.

Experimental Section

General Methods. Unless stated otherwise, all reagents and chemicals were obtained commercially and were used without further purification. Reagent grade chloroform (Aldrich) used in all experiments contained 0.75% ethanol. All ^{1}H NMR and IR spectra were recorded with Varian A-60 and Beckman Acculab

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(2) For recent applications of ultrasound in heterogeneous organic reactions, see Raucher, S.; Klein, P. *J. Org. Chem.* **1981** *46*, 3558 and references cited therein.

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