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A Mild, Convenient, and Inexpensive Procedure for Conversion of Vinyl Halides to α-Haloketones

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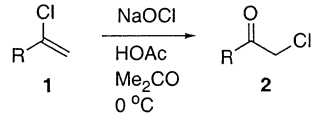
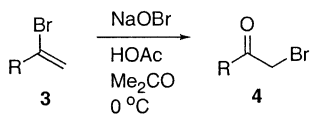
Abstract: Treatment of a vinyl chloride with commercially available aqueous sodium hypochlorite solution in a 2:5 mixture of acetic acid/acetone at 0 °C for about 1 h cleanly leads to the corresponding α-chloroketone. Similarly, if a vinyl bromide is exposed to sodium hypobromite (freshly prepared from bromine and sodium hydroxide) at 0 °C in 2:5 acetic acid/acetone as solvent, an α-bromoketone is produced. This methodology has been applied to a number of vinyl chlorides and vinyl bromides, and the transformations generally proceed in high yields. The mild reaction conditions are compatible with a variety of functional groups including amides, esters, and imines.

As part of a natural product total synthesis currently underway in these laboratories, we have been interested in developing an annulation strategy which would involve the initial formation of an α-haloketone from the corresponding vinyl halide. This type of transformation has previously been effected using NCS, NBS, or NIS in aqueous acetonitrile with a catalytic amount of HX at room temperature, but this potentially useful methodology has not been widely utilized.[1] We have recently developed a very mild, convenient, and general alternative to the *N*-halosuccinimide procedure, and this paper describes the details of our work.

We have found that treatment of a vinyl chloride **1** with commercially available aqueous sodium hypochlorite solution in a 2:5 mixture of acetic acid/acetone at 0 °C for about 1 h cleanly leads to the corresponding α-chloroketone **2** (eq 1). It was also observed that if the acetic acid is omitted, no reaction occurs.

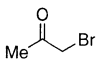
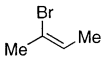
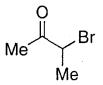
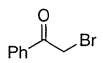
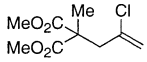
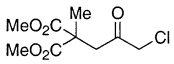
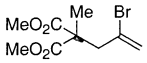
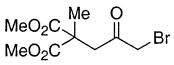
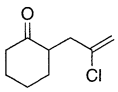
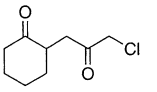
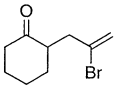
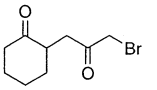
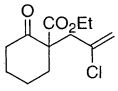
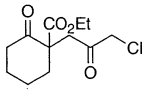
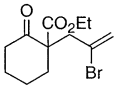
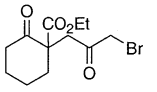
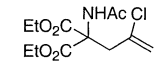
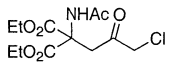
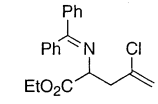
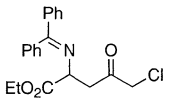


(1)



(2)

TABLE 1. Conversion of Vinyl Halides to α-Haloketones with Sodium Hypohalite in Acetone/Acetic Acid

entry	vinyl halide	α-haloketone	isolated yield (%)
a			72
b			83
c			88
d			99
e			82
f			87
g			66
h			95
i			81
j			80
k			99
l			52

Similarly, if a vinyl bromide **3** is exposed to sodium hypobromite (freshly prepared from bromine and sodium hydroxide[2]) again at 0 °C in 2:5 acetic acid/acetone as solvent, an α-bromoketone **4** is produced (eq 2).[3] We have applied this methodology to a number of vinyl chlorides and vinyl bromides as shown in Table 1. As can be seen, the transformations generally proceed in high yields, and the mild reaction conditions are compatible with a variety of functional groups including amides, esters, and imines.

(1) (a) Hsiao, C.-N.; Leanna, M. R.; Bhagavatula, L.; DeLara, E.; Zydowski, T. M.; Horrom, B. W.; Morton, H. E. *Synth. Commun.* **1990**, *20*, 3507. (b) Morton, H. E.; Leanna, M. R. *Tetrahedron Lett.* **1993**, *34*, 4481. (c) Leanna, M. R.; Morton, H. E. *Tetrahedron Lett.* **1993**, *34*, 4485. (d) Duncan, R.; Drueckhammer, D. G. *Tetrahedron Lett.* **1993**, *34*, 1733.

(2) Allen, C. F. H.; Wolf, C. N. *Organic Syntheses*; Wiley: New York, 1963; Collect. Vol. IV, p 45.

(3) A single example of the conversion of a vinyl bromide to an α-bromoketone using $Br_2/NaHCO_3$ has been reported.[1c]

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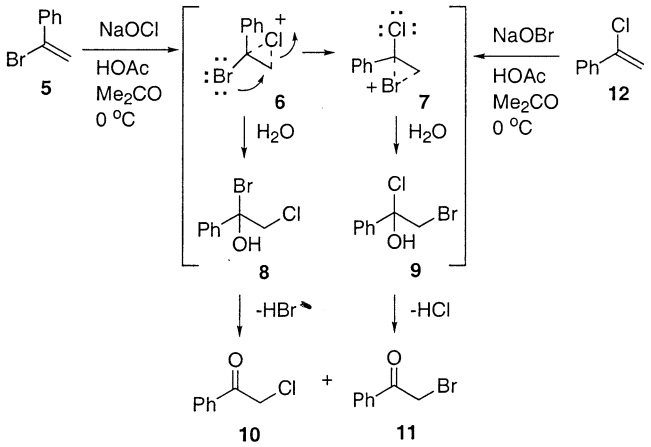
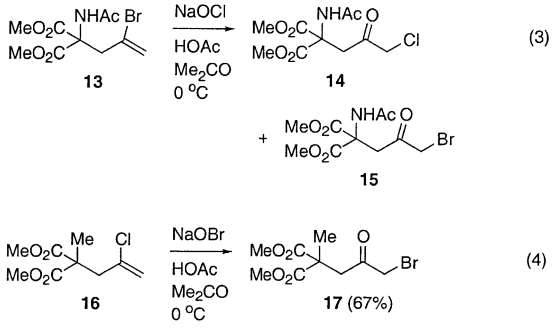
SCHEME 1



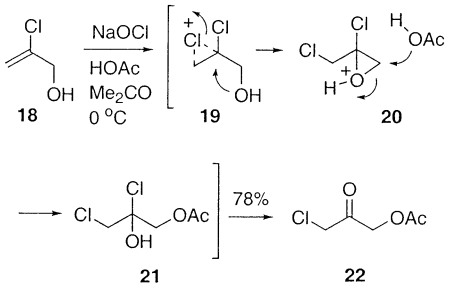
Interestingly, the reaction of α-bromostyrene (**5**) with sodium hypochlorite under our standard conditions affords a 1:1 mixture of α-chloroacetophenone (**10**) and α-bromoacetophenone (**11**) (Scheme 1). That the conversion of the expected chloride **10** to the bromide **11** is not simply a Finkelstein process can be demonstrated by the fact that α-chloroacetophenone is not converted to the bromoacetophenone with excess NaBr under the conditions of the hypochlorite reaction. One mechanistic rationale for this result is that the initially formed chloronium ion **6**, formed from vinyl bromide **5** and hypochlorous acid, partially rearranges to the isomeric bromonium ion **7** prior to hydrolysis to halohydrins **8** and **9**, respectively.[4,5] On the other hand, treatment of α-chlorostyrene (**12**) with sodium hypobromite in acetic acid/acetone by the usual procedure leads exclusively to α-bromoacetophenone (**11**). This experiment would seem to indicate that the corresponding rearrangement of bromonium ion **7** to the chloronium species **6** is either relatively slow or does not occur.

This halogen scrambling with vinyl bromides seems to be a problem with other substrates as well. Thus, treatment of vinyl bromide **13** with hypochlorite gave a 3:1 mixture of α-chloroketone **14** and α-bromoketone **15** (eq 3).[4] However, the fact that a bromonium ion like **7** does not rearrange rapidly to the corresponding chloronium ion **6** allows one to prepare an α-bromoketone starting from the vinyl chloride. For example, exposure of vinyl chloride **16** to sodium hypobromite under our standard conditions provides only the α-bromoketone **17** (eq 4).

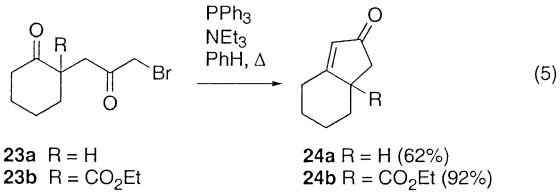


Surprisingly, vinyl chloride substrate **18**, when exposed to our usual conditions with sodium hypochlorite, afforded α-chloroketone acetate **22** as the only isolable product in 78% yield (Scheme 2).[6] We believe this reaction occurs via an initial chloronium ion **19**, which rearranges to epoxide **20**. Opening of intermediate **20** with acetic acid then leads to chlorohydrin **21**, which subsequently can lose HCl to afford the observed product **22**.

SCHEME 2



Finally, this methodology also lends itself to a simple Wichterle-like annulation strategy. For instance, the α-bromoketones **23a** and **23b**, generated by the procedure described in this paper (see Table 1), can be efficiently cyclized to the known enones **24a**[7a] and **24b**,[7b] respectively, in a simple one-pot procedure involving treatment with triphenylphosphine in refluxing benzene containing triethylamine (eq 5).[8]



In summary, we have developed a new method for conversion of vinyl chlorides and bromides to the corresponding α-haloketones utilizing inexpensive reagents. The yields of haloketones using this methodology are similar to those reported for the halosuccinimide procedure.[1] The mild reaction conditions, which are compatible with many functional groups, should make this underutilized reaction more attractive to synthetic chemists.

Experimental Section

Except for the compounds below, the substrates and products in Table 1 have previously been synthesized[1] or are commercially available.

(4) It should be noted that similar experimental observations have previously been described by Morton and Leanna using the *N*-halosuccinimide methodology, but no explanation was offered for the halogen scrambling.[1b]

(5) For convenience, the halonium ions in Scheme 1 are shown as symmetrical. However, the actual mechanism might involve unsymmetrical halonium ions or even unbridged carbocations. See: Ruasse, M.-F. *Prog. Phys. Org. Chem.* **1993**, *28*, 207. Lenoir, D.; Chiappe, C. *Chem. Eur. J.* **2003**, *9*, 1030.

(6) Compound **22** has previously been prepared by a different method: Pero, R. W.; Babiarz, P.; Fondy, T. P. *J. Med. Chem.* **1975**, *20*, 644.

(7) (a) Lopez, A.; Moreno-Manas, M.; Pleixats, R.; Roglans, A.; Ezquerra, J.; Pedregal, C. *Tetrahedron* **1996**, *52*, 8365. (b) Corey, E. J.; Ghosh, A. K. *Tetrahedron Lett.* **1987**, *28*, 175.

(8) Trost, B. M.; Curran, D. P. *J. Am. Chem. Soc.* **1980**, *102*, 5699. Chorlton, A. P.; Morris, G. A.; Sutherland, J. K. *J. Chem. Soc., Perkin Trans 1* **1991**, 1205.

2-(2-Bromoallyl)-2-methylmalonic Acid Dimethyl Ester (Table 1, Entry f). To a solution of dimethyl methylmalonate (1.00 g, 6.84 mmol) in THF (20 mL), cooled to 0 °C was added potassium *tert*-butoxide (921 mg, 8.2 mmol), and the solution was stirred for 15 min. 2,3-Dibromopropene (1.00 mL, 8.20 mmol, 1.93 g/mL, 85% v/v) was added, and the solution was stirred overnight at rt. The mixture was poured into water and dichloromethane. The aqueous layer was extracted twice with dichloromethane, and the combined organic layers were dried with $MgSO_4$ and concentrated. The crude product was purified by flash chromatography on silica gel (hexanes/ether, 9/1) to afford the vinyl bromide as an oil (1.2 g 80%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.46 (s, 1H), 5.38 (br m, 1H), 3.53 (s, 6H), 2.95 (s, 2H), 1.29 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.4, 127.0, 121.6, 52.8, 52.6, 45.8, 19.1; IR (neat) 1736, 1625 cm^{-1}; LRMS (APCI$^+$) *m*/*z* (relative intensity) 267 (100), 265 (98, MH$^+$), 234 (56), 242 (56), 207 (52), 205 (53).

2-(Benzhydrylideneamino)-4-chloropent-4-enoic Acid Ethyl Ester (Table 1, Entry l). To a solution of 2,3-dichloropropene (830 mL, 9.0 mmol) in acetone (10 mL) was added sodium iodide (1.6 g, 10.8 mmol), and the mixture was stirred at rt for 4 h. The solution was filtered through Celite and concentrated, and the crude iodide was used directly in the next step.

To a solution of glycine ethyl ester benzophenone imine (1.00 g, 6.84 mmol)[8] in THF (25 mL) cooled to 0 °C was added potassium *tert*-butoxide (921 mg, 8.20 mmol), and the solution was stirred at rt for 15 min. The 2-chloro-3-iodopropene prepared as decribed above was added, and the solution was stirred at rt overnight. The mixture was poured into water and ether. The aqueous layer was extracted twice with ether, and the combined organic layers were dried with $MgSO_4$ and concentrated. The crude product was purified by flash chromatography on silica gel (hexanes/ether, 9/1) to afford the vinyl chloride as an oil (1.6 g, 63%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.10−7.60 (m, 10H), 5.15 (s, 1H), 5.09 (s, 1H), 4.30 (dd, J = 8.00, 3.00 Hz, 1H), 4.08 (m, 2H), 2.91 (m, 2H) 1.15 (t, J = 5.1 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.7, 171.0, 139.5, 138.5, 137.5, 135.8, 130.3, 129.8, 128.8, 128.6, 128.2, 128.1, 127.9, 127.1, 115.2, 62.7, 61.1, 43.3, 14.1; IR (neat) 1737, 1625 cm^{-1}; LRMS (APCI$^+$) *m*/*z* (relative intensity) 344 (41), 342 (100, MH$^+$).

1-(2-Chloroallyl)-2-oxocyclohexanecarboxylic Acid Ethyl Ester (Table 1, Entry i). To a solution of ethyl cyclohexanone carboxylate (1.48 g, 9.25 mmol) in THF (20 mL) cooled to 0 °C was added potassium *tert*-butoxide (1.24 g, 11.1 mmol) and the solution was stirred for 15 min. 2-Chloro-3-iodopropene prepared as described above (11.1 mmol) was added, and the solution was stirred at rt overnight. The mixture was poured into water and dichloromethane. The aqueous layer was extracted twice with dichloromethane and the combined organic layers were dried over $MgSO_4$ and concentrated. The crude product was purified by flash chromatography on silica gel (hexanes/ether, 9/1) to afford the vinyl chloride as an oil (1.30 g, 58%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.11 (s, 1H), 5.03 (s, 1H), 4.05 (q, J = 7.1 Hz, 2H), 2.93 (d, J = 14.8 Hz, 1H), 2.54−2.61 (m, 2H), 2.26−2.37 (m, 2H), 1.94 (m, 1H), 1.60−1.80 (m, 2H), 1.30−1.60 (m, 2H), 1.12 (t, J = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 205.7, 170.0, 137.3, 116.5, 61.3, 59.7, 43.5, 40.6, 35.1, 27.3, 22.1, 13.7; IR (neat) 1716, 1631 cm^{-1}; LRMS (APCI$^+$) *m*/*z* (relative intensity) 247 (35), 245 (98, MH$^+$), 209 (100).

2-Acetylamino-2-(2-chloroallyl)malonic Acid Diethyl Ester (Table 1, Entry k). To a solution of diethyl acetamidomalonate (2.00 g, 10.31 mmol) in THF (25 mL) cooled to 0 °C was added potassium *tert*-butoxide (1.15 mg, 10.31 mmol), and the solution was stirred for 15 min. 2-Chloro-3-iodopropene (10.31 mmol), prepared as described above, was added, and the solution was stirred at rt overnight. The mixture was poured into water and dichloromethane. The aqueous layer was extracted twice with dichloromethane, and the combined organic layers were dried with $MgSO_4$ and concentrated. The crude product was purified by flash chromatography on silica gel (hexanes/ethyl acetate, 2/1) to afford the vinyl chloride as an oil (1.80 g, 67%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.86 (s, 1H), 5.06 (s, 1H), 4.96 (s, 1H), 4.03 (q, J = 6.5 Hz, 4H), 3.24 (s, 2H), 1.82 (s, 3H), 1.05 (t, J = 7.2 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169,6, 167.3, 136.6, 117.8, 65.3, 63.0, 41.7, 22.9, 14.1; IR (neat) 1743, 1633 cm^{-1}; LRMS (APCI$^+$) *m*/*z* (relative intensity) 294 (39), 292 (100, MH$^+$), 252 (14), 250 (42).

Typical Procedure for Conversion of a Vinyl Chloride to an α-Chloroketone. 2-Acetylamino-2-(3-chloro-2-oxopropyl)malonic Acid Diethyl Ester (Table 1, Entry k). To a solution of the vinyl chloride (530 mg, 2.40 mmol) in acetone (10 mL) and acetic acid (4 mL), cooled to 0 °C, was added sodium hypochlorite (1.15 mL, 2.40 mmol, 1.21 g/mL, 13% v/v) dropwise. The solution was stirred for 1 h at 0 °C until the reaction was complete as monitored by TLC. The solution was poured into saturated sodium bicarbonate (50 mL) and diluted with dichloromethane. The aqueous layer was extracted twice with dichloromethane, and the combined organic layers were dried with $MgSO_4$ and concentrated in vacuo. The crude product was purified by flash chromatography on silica gel (hexanes/ethyl acetate, 1/1) to afford the α-chloroketone as a white solid: mp 70−72 °C (188 mg, 99%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.05 (s, 1H), 4.14 (q, J = 7.1 Hz, 4H), 4.03 (s, 2H), 3.75 (s, 2H), 1.93 (s, 3H), 1.15 (t, J = 7.2 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 199.3, 169.6, 166.5, 63.5, 62.9, 47.9, 43.0, 22.7, 13.7; IR (neat) 1743, 1664 cm^{-1}; LRMS (APCI$^+$) *m*/*z* (relative intensity) 310 (27), 308 (100, MH$^+$), 266 (21), 102 (58).

2-(Benzhydrylideneamino)-5-chloro-4-oxopentanoic Acid Ethyl Ester (Table 1, Entry l). Purified by flash chromatography on silica gel (hexanes/ethyl acetate/triethylamine, 80/18/2) to afford the α-chloroketone as an oil (52%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.21−7.51 (m, 10H), 4.52 (dd, J = 6.4, 8.0 Hz, 1H), 4.05 (m, 4H), 3.25 (dd, J = 6.4, 18.8 Hz, 1H), 3.04 (dd, J = 8.1, 18.8 Hz, 1H), 1.20 (t, J = 7.9 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 199.7, 172.1, 170.7, 139.2, 135.9, 130.5, 130.5, 128.7, 128.4, 128.0, 127.8, 61.4, 61.3, 48.7, 43.0, 14.0; IR (neat) 1732, 1712 cm^{-1}; LRMS (APCI$^+$) *m*/*z* (relative intensity) 360 (35), 358 (100, MH$^+$).

2-(3-Chloro-2-oxopropyl)cyclohexanone (Table 1, Entry g). The crude product was purified by flash chromatography on silica gel (hexanes/ether, 1/1) to afford the α-chloroketone as a yellow oil (66%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.14 (s, 2H) 2.86 (m, 2H), 1.92−2.41 (m, 6H), 1.27−1.90 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 210.9, 200.9, 48.6, 46.9, 41.3, 39.3, 33.5, 27.4, 24.8; IR (neat) 1735, 1706 cm^{-1}; LRMS (APCI$^+$) *m*/*z* (relative intensity) 191 (34), 189 (100, MH$^+$).

1-(3-Chloro-2-oxopropyl)-2-oxocyclohexanecarboxylic Acid Ethyl Ester (Table 1, Entry i). The crude product was purified by flash chromatography to afford the α-chloroketone as a yellow oil (81%): ^{1}H NMR (360 MHz, $CDCl_3$) δ 4.14−4.21 (m, 4H), 2.76−2.88 (m, 3H), 2.37 (m, 2H), 2.00 (m, 1H), 1.57−1.73 (m, 4H), 1.23 (t, J = 7.0 Hz, 3H); ^{13}C NMR (90 MHz, $CDCl_3$) d 207.2, 199.4, 171.3, 61.6, 60.0, 48.4, 44.0, 40.2, 37.1, 26.8, 21.7, 13.8; IR (neat) 1731, 1710 cm^{-1}; LRMS (APCI$^+$) *m*/*z* (relative intensity) 263 (2), 261 (5, MH$^+$), 245 (37), 244 (15), 243 (100), 135 (38), 102 (24).

Typical Procedure for Conversion of a Vinyl Bromide to an α-Bromoketone. 2-(3-Bromo-2-oxopropyl)-2-methylmalonic Acid Dimethyl Ester (Table 1, Entry f). To a solution of sodium hydroxide (2.0 g, 50.0 mmol) in water (25 mL) at 0 °C was slowly added bromine (0.85 mL, 16.6 mmol).[2] The solution was stirred for 15 min and used immediately. To a solution of the vinyl bromide (300 mg, 1.13 mmol) in acetone (10 mL) and acetic acid (4 mL) cooled to 0 °C was added dropwise the sodium hypobromite solution (1.70 mL, 1.13 mmol, 0.664 M). The solution was stirred for 1 h at 0 °C as the progress of the reaction was monitored by TLC. The solution was poured into saturated sodium bicarbonate solution and diluted with dichloromethane. The aqueous layer was extracted twice with dichloromethane and the combined organic layers were dried with $MgSO_4$ and concentrated. The crude product was purified by flash chromatography on silica gel (hexanes/ether, 7/3) to afford the known α-bromoketone[1] as an oil (290 mg, 87%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.88 (s, 2H), 3.65 (s, 6H), 3.19 (s, 2H), 1.46 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 198.5, 171.3, 52.7, 51.6, 45.0, 34.0, 20.3; IR (neat) 1734 cm^{-1}; LRMS (APCI$^+$) *m*/*z*

(relative intensity) 283 (100), 281 (98, MH^+), 251 (16), 249 (17), 223 (23), 221 (23), 203 (40).

1-(3-Bromo-2-oxopropyl)-2-oxocyclohexanecarboxylic Acid Ethyl Ester (Table 1, Entry j). The crude product was purified by flash chromatography on silica gel (hexanes/ether, 1/1) to afford the α-bromoketone as a yellow oil (80%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.11 (m, 2H), 3.95 (dd, J = 13.0, 32.7 Hz, 2H), 2.82 (dd, J = 16.6, 23.4 Hz, 2H), 2.66−2.74 (m, 1H), 2.26−2.34 (m, 2H), 1.91 (m, 1H), 1.51−1.65 (m, 4H), 1.15 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 207.1, 198.6, 171.1, 61.3, 59.9, 44.0, 40.0, 36.7, 35.0, 26.6, 21.5, 13.7; IR (neat) 1711 (br) cm^{-1}; LRMS (APCI$^+$) m/z (relative intensity) 307 (17), 305 (18, MH^+), 289 (100), 287 (98), 209 (100).

1,4,5,6,7,7a-Hexahydroinden-2-one (24a). To a solution of α-bromoketone **23a** (361 mg, 1.55 mmol) in benzene (50 mL) were added triphenylphosphine (409 mg, 1.55 mmol) and triethylamine (324 μL, 2.33 mmol), and the mixture was refluxed for 24 h. The mixture was concentrated, and the residue was purified by flash chromatography on silica gel (hexanes/ether, 1/1) to afford known[7a] enone **24a** as an oil (131 mg, 62%). Known eneone **24b**[7b] was prepared by the same procedure from α-bromoketone **23b** (92%).

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Supporting Information Available: Copies of proton and carbon NMR spectra of new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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