Pergamon

Tetrahedron 56 (2000) 7199–7203

TETRAHEDRON

Trifluoromethanesulfonic Acid Catalyzed Novel Friedel–Crafts Acylation of Aromatics with Methyl Benzoate[1]

Je Pil Hwang,[†] G. K. Surya Prakash* and George A. Olah*

Donald P. and Katherine B. Loker Hydrocarbon Research Institute and Department of Chemistry, University of Southern California, Los Angeles, CA 90089-1661, USA

Dedicated to Professor Rolf Huisgen on the occasion of his 80th birthday

Received 22 June 2000; accepted 17 July 2000

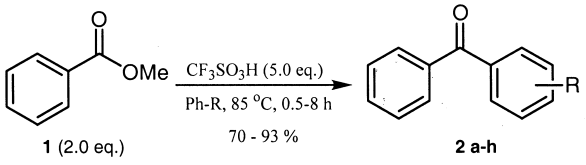
Abstract—Methyl benzoate, protolytically activated by superacidic trifluoromethanesulfonic acid, reacts with aromatic compounds to give benzophenone derivatives in good to excellent yields (70–93%). Even highly deactivated nitrobenzene as well as benzotrifluoride underwent smooth benzoylation under the reaction conditions to respective *meta*-substituted benzophenones.

Introduction

Friedel–Crafts reactions[2] are widely used in organic synthesis for carbon–carbon bond formation. Friedel–Crafts acylation is a very important method for the preparation of aromatic ketones. Aromatic ketones have been prepared by the reaction of carboxylic acids with aromatic hydrocarbons catalyzed by a wide variety of catalysts (generally used in excess of molar amounts) such as methanesulfonic acid,[3] zeolite,[4] palladium catalyst,[5] trimethylsilyl polyphosphate,[6] Nafion-H[7] and $SiCl_4$–Silver salts.[8] Aromatic acylations have also been achieved with carboxylic acid anhydrides and acid chlorides with various active Lewis acid catalysts (with more than one molar equivalent basis).[9] Recently, we have focused our attention on superelectrophilic activation of electrophiles using frequently trifluoromethanesulfonic acid as the superacid.[10,11] We wish to report now that methyl benzoate is activated in trifluoromethanesulfonic acid to a highly reactive benzoylating reagent that reacts with aromatic compounds to give benzophenone derivatives in good to excellent yields. Although the Friedel–Crafts preparation of benzophenone derivatives is well known,[12,13] direct acylation of aromatic compounds using benzoic acid esters was not well explored.

Results and Discussion

Methyl benzoate and the corresponding aromatic compound were mixed with trifluormethanesulfonic acid and the resulting mixture was heated to 85°C (see Table 1 for reaction time). Two and a half molar amount of trifluoromethanesulfonic acid compared to methylbenzoate was necessary to achieve suitable reaction which involves superelectrophilic activation. A number of substituted aromatics including benzene gave the respective benzophenones as major isolable products (Eq. (1)). In no case was there further electrophilic reaction of benzophenones with the aromatics observed. The yield of benzophenones obtained ranged from 70 to 93%. Even highly deactivated nitrobenzene and benzotrifluoride showed good reactivity and gave the corresponding *meta*-substituted benzophenones in high yield. The results are summarized in Table 1.



(1)

A possible mechanism of acylation involving activated dicationic intermediates such as **VII** or **VIII** are shown in Scheme 1. It is also possible that diprotonated ester intermediates **V** or **VI** may also directly react with the aromatic substrate to give the product. Possible formation of such activated intermediates in strong acids have been earlier explored.[11,14–16] Benzoic acid itself does not react with benzene under similar reaction conditions. After three days of reflux, only a trace of benzophenone (**2a**) was obtained indicating that a carboxylic acid is much less reactive than its methyl ester under the reaction conditions.

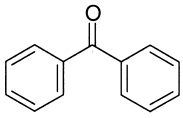
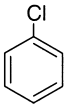
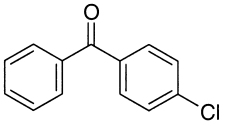
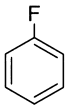
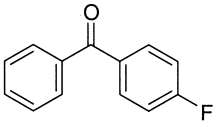
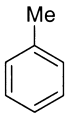
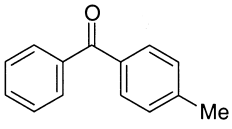
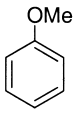
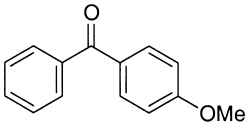
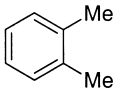
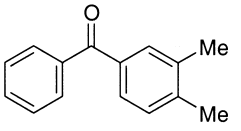
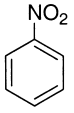
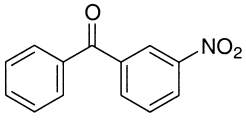
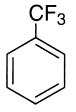
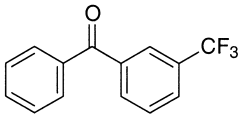
Keywords: methyl benzoate; benzoylation; trifluoromethanesulfonic acid; benzo-phenones; superelectrophilic activation.

* Corresponding authors. Tel.: +1-213-740-5976; fax: +1-213-740-5087; e-mail: olah@methyl.usc.edu

† Post-doctoral fellow.

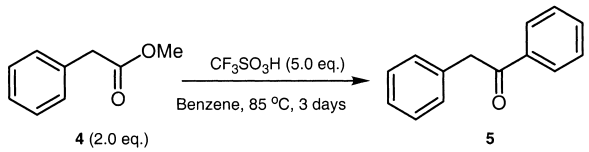
0040–4020/00/$ - see front matter
PII: S0040-4020(00)00633-5

Table 1. Acylation of artomatics with methyl benzonate using trifluoromethanesulfonic acid

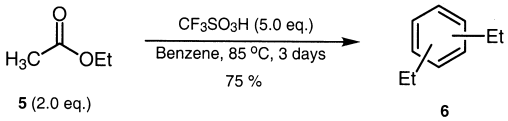
Ar-H	Reaction Time		Product	Yield (%)[a]
	8.0 hr	**2a**		75
	1.0 hr	**2b**		78
	1.0 hr	**2c**		85
	0.5 hr	**2d**		70
	2.0 hr	**2e**		93
	2.0 hr	**2f**		76
	8.0 hr	**2g**		82
	2.0 hr	**2h**		84

[a] Isolated yields.

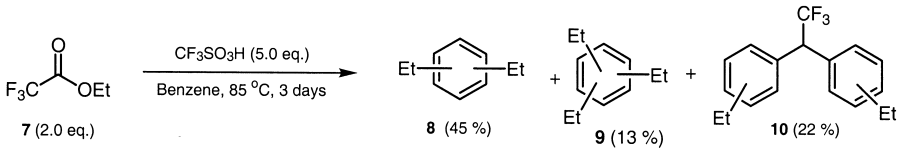
Aliphatic esters, under the reaction conditions, are less reactive than benzoic acid esters. For example, methyl phenyl acetate (**4**) reacted with benzene only under prolonged reflux for three days in the presence of trifluoromethanesulfonic acid to give deoxybenzoin (**5**) as the major product (Eq. (2)) in 54% yield. Ethyl acetate with benzene under similar reaction conditions gave exclusively ethylated products (Eq. (3)). Ethyl trifluoroacetate, on the other hand, gave besides ethylated products also acylation products that underwent further arylation to give **10** (Eq. (4)).



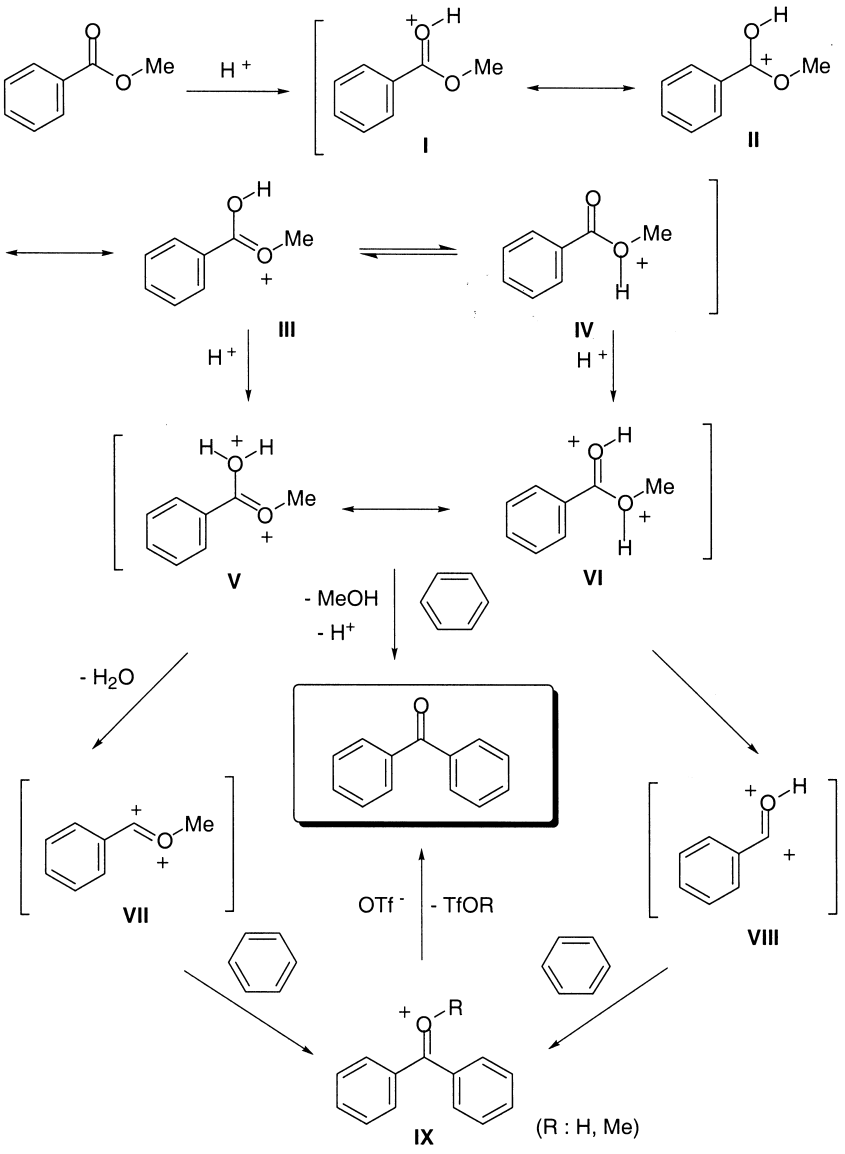
(2)



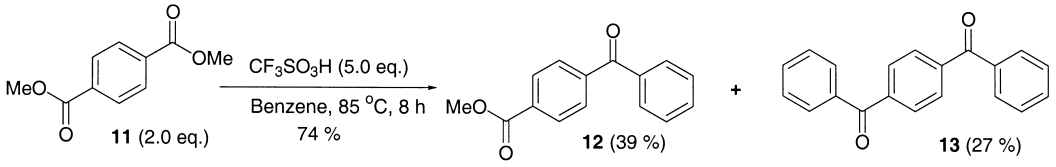
(3)



(4)

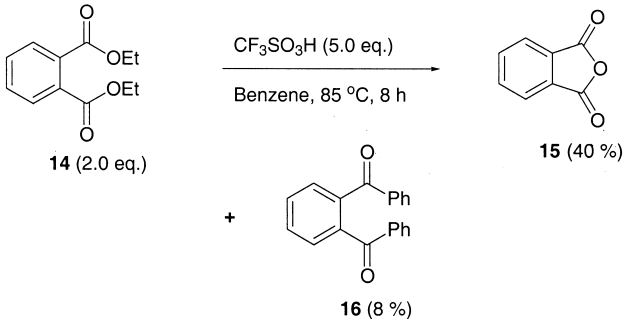


Scheme 1.



(5)

Diesters such as 1,4-dimethyl terephthalate (**11**) under similar reaction conditions with benzene (reflux for 8 h) gave a mixture of 4-benzoyl methyl benzoate (**12**) and 1,4-dibenzoyl benzene (**13**) as major products (Eq. (5)). In the case of 1,2-diethyl phthalate (**14**), however, phthalic anhydride (**15**) was the major product along with some 1,2-dibenzoyl benzene (**16**) (Eq. (6)).



(6)

In summary, we have shown that methylbenzoate can be activated in trifluormethanesulfonic acid to a superelectrophilic benzoylating agent that reacts with both activated and

deactivated aromatics to give their respective benzophenones in preparatively useful yields.

Experimental

General

Methyl benzoate, benzene, fluorobenzene and trifluorotoluene were obtained from Aldrich Chemical Co. and used as received. Chlorobenzene, toluene, anisole, nitrobenzene and *o*-xylene were obtained from Fluka and Mallinckrodt Chemical Co. and were also used without further purification. Trifluoromethanesulfonic acid was obtained from 3M Co. and distilled under a dry nitrogen atmosphere before use (bp:162°C). Column chromatography was carried out on silica gel, Merck grade 60 (230–400 mesh). Melting points were determined on a Mel-Temp II (Laboratory devices) apparatus with a microscope attachment. ^{1}H, ^{13}C NMR spectra were measured in $CDCl_3$ solutions on a Varian Unity-300 spectrometer and the chemical shifts are referenced to TMS. MS spectra were taken on a HP 5890 GC-HP 5971 mass spectrometer system. Exact mass measurements were made at the UC Riverside Mass Spectroscopic facilities. *Caution: Trifluoromethanesulfonic acid is a corrosive and hygroscopic liquid that should be handled under a dry atmosphere.*

Preparation of benzophenone (2a) from methyl benzoate and benzene under trifluormethanesulfonic acid catalysis (typical procedure)

Trifluromethanesulfonic acid (5.0 mmol; 750 mg) was added slowly to a solution of methyl benzoate (2.0 mmol; 272 mg) in dry benzene (5 mL) at room temperature under a dry nitrogen atmosphere. The heterogeneous solution was stirred vigorously for 8 h under reflux, gradually the reaction mixture turned deep brown in color. Progress of the reaction was monitored by thin layer chromatography (silica) using hexane/ethyl acetate (20:1) as eluent. After the completion of the reaction, the reaction mixture was neutralized with ice-water (20 mL) containing saturated $NaHCO_3$ solution and extracted carefully with 3×25 mL of ethyl acetate. The organic layer was separated, washed with brine solution, dried over anhydrous $MgSO_4$, and concentrated under reduced pressure. After removal of the organics a low melting solid remained. The solid was further purified by column chromatography (hexane/ethyl acetate, 20:1) to obtain 254.8 mg of benzophenone (75% yield) as a white solid.

Benzophenone (2a). 75%; Mp 49°C; ^{1}H NMR: δ 7.77–7.74 (d, 4H, J=7 Hz), 7.55–7.50 (t, 2H, J=7 Hz), 7.45–7.40 (t, 2H, J=7 Hz); ^{13}C NMR: δ 196.61 (CO), 137.49, 132.33, 128.19; MS (%) 182 (M, 58), 105 (100), 77 (57), *m*/*e* calcd for $C_{13}H_{10}O$ (M) 182.22, found 182.00.

***p*-Chlorobenzophenone (2b).** 78%; Mp 75°C; ^{1}H NMR: δ 7.77–7.71 (m, 4H), 7.64–7.57 (t, 1H, J=7 Hz), 7.53–7.44 (q, 5H, J=6.8 Hz); ^{13}C NMR: δ 195.18 (CO), 135.76, 134.10, 132.73, 129.53, 128.34, 126.89, 125.51, 125.28; MS (%) 216 (M, 100), 181 (23), 139 (74), 105 (64), 77 (74), *m*/*e* calcd for $C_{13}H_{10}OCl$ (M) 216.68, found 216.00.

***p*-Fluorobenzophenone (2c).** 85%; Mp 48°C; ^{1}H NMR: δ 7.85–7.80 (m, 3H), 7.76 (s, 2H), 7.74–7.73 (t, 1H, J=7 Hz), 7.48–7.44 (t, 2H, J=7 Hz), 7.16–7.10 (t, 2H, J=9 Hz); ^{13}C NMR: δ 195.26 (CO), 167.04, 163.67, 137.47, 132.71, 132.59, 132.45, 129.86, 128.34, 115.58, 115.29; MS (%) 200 (M, 100), 181 (0.7), 170 (10), 123 (61), 105 (33), 95 (47), 77 (39), *m*/*e* calcd for $C_{13}H_{10}OF$ (M) 200.22, found 200.05.

***p*-Methylbenzophenone (2d).** 70%; Mp 57°C; ^{1}H NMR: δ 7.79–7.76 (d, 2H, J=7 Hz), 7.73–7.70 (d, 2H, J=8 Hz), 7.59–7.54 (t, 1H, J=6 Hz), 7.48–7.43 (t, 2H, J=7 Hz), 7.29–7.26 (d, 2H, J=8 Hz), 2.42 (s, 3H); ^{13}C NMR: δ 196.35 (CO), 134.14, 137.86, 134.79, 132.08, 130.22, 129.85, 128.90, 128.13, 21.63 (Me); MS (%) 196 (M, 63), 181 (12), 119 (100), 105 (27), 77 (23), *m*/*e* calcd for $C_{14}H_{12}O$ (M) 196.25, found 196.00.

***p*-Methoxybenzophenone (2e).** 93%; Mp 62°C; ^{1}H NMR: δ 7.82–7.79 (d, 2H, J=9 Hz), 7.74–7.71 (d, 2H, J=8 Hz), 7.60–7.53 (t, 1H, J=7 Hz), 7.46–7.41(t, 2H, J=7 Hz), 6.95–6.92 (d, 2H, J=9 Hz), 3.87 (s, 3H); ^{13}C NMR: δ 197.17 (CO), 163.18, 138.24, 132.55, 131.86, 130.10, 129.70, 128.16, 113.52, 55.48 (OMe); MS (%) 212 (M, 20), 181 (7), 135 (100), 105 (11), 92 (25), 77 (55), *m*/*e* calcd for $C_{14}H_{12}O_2$ (M) 212.25, found 212.05.

3,4-Dimethylbenzophenone (2f). 76%; Mp 46°C; ^{1}H NMR: δ 7.80–7.75 (d, 2H, J=7 Hz), 7.60 (s, 1H), 7.56–7.49 (q, 2H, J=7 Hz), 7.48–7.40 (t, 2H, J=8 Hz), 7.22–7.18 (t, 2H, J=7 Hz), 2.33 (s, 3H), 2.30 (s, 3H); ^{13}C NMR: δ 196.54 (CO), 141.87, 137.98, 136.64, 135.21, 131.99, 131.09, 129.84, 129.35, 128.09, 127.95, 19.98 (Me), 19.73 (Me); MS (%) 210 (M, 97), 195 (31), 165 (16), 133 (100), 105 (33), 95 (47), 77 (71), *m*/*e* calcd for $C_{15}H_{14}O$ (M) 210.29, found 210.15.

***m*-Nitrobenzophenone (2g).** 82%; Mp 93°C; ^{1}H NMR: δ 8.61–8.60 (s, 1H), 8.45–8.44 (d, 1H, J=8 Hz), 8.14–8.11 (d, 1H, J=7 Hz), 7.80–7.77 (d, 2H, J=7 Hz), 7.72–7.62 (m, 2H), 7.54–7.49 (t, 2H, J=7 Hz), 7.16 (s, 1H); ^{13}C NMR: δ 199.72 (CO), 139.02, 136.21, 135.44, 133.36, 130.00, 129.63, 128.72, 126.72, 124.70; MS (%) 227 (M, 30), 150 (12), 105 (100), 77 (40), *m*/*e* calcd for $C_{13}H_9NO_3$ (M) 227.23, found 227.10.

***m*-Trifluoromethylbenzophenone (2h).** 84%; Mp 53°C; ^{1}H NMR: δ 8.12–8.10 (d, 1H, J=7 Hz), 7.63–7.58 (t, 2H, J=8 Hz), 7.49–7.44 (t, 2H, J=7 Hz), 7.16 (s, 1H); ^{13}C NMR: δ 195.14 (CO), 138.24, 136.71, 133.11, 132.99, 131.60, 131.17, 130.73, 130.30, 130.00, 129.08, 128.93, 128.83, 128.79, 128.54, 126.66, 125.49, 121.88, 118.27; MS (%) 250 (M, 98), 231 (15), 173 (43), 145 (41), 105 (100), 77 (37), *m*/*e* calcd for $C_{14}H_{12}O_2$ (M) 250.23, found 249.90.

Deoxybenzoin (5). 53%; Mp 55°C; ^{1}H NMR: δ 8.14–8.10 (d, 1H, J=7 Hz), 8.04–7.95 (d, 3H, J=7 Hz), 7.64–7.41 (m, 1H), 7.36–7.22 (m, 4H), 4.24 (s, 2H); ^{13}C NMR: δ 196.49 (CO), 136.51 134.47, 133.70, 133.13, 130.14, 129.72, 129.41, 128.62, 128.56, 128.45, 126.84, 45.46 (–CH_2–); MS (%) 196 (M, 2), 105 (100), 91 (7), 77 (36), *m*/*e* calcd for $C_{14}H_{12}O$ (M) 196.25, found 196.10.

Phthalic anhydride (15). 40%; Mp 132°C; ^{1}H NMR: δ 8.04–7.96 (m, 4H), 7.76–7.71 (m, 1H), 7.56–7.53 (m, 1H); ^{13}C NMR: δ 168.58 (–CO–O), 163.20 (–CO–O), 136.52, 131.18, 129.21, 125.78; MS (%) 148 (M, 16), 104 (100), 76 (73), *m*/*e* calcd for $C_8H_4O_3$ (M) 148.12, found 147.95.

Acknowledgements

Support of this work by the National Science Foundation and Korea Science and Engineering Foundation is gratefully acknowledged.

References

1. *Chemistry in Superacids*, Part 54, For Part 53 see, Rasul, G.; Prakash, G. K. S.; Olah, G. A. *J. Am. Chem. Soc.* Submitted for publication.
2. (a) Olah, G. A. *Friedel–Crafts and Related Reactions*; Vol. I–IV; Wiley-Interscience: New York, 1965. (b) Olah, G. A. *Friedel–Crafts Chemistry*; Wiley-Interscience: New York, 1973.
3. Premasagar, V.; Palaniswamy, V. A.; Eisenbraun, E. J. *J. Org. Chem.* **1981**, *46*, 2974.
4. Chiche, B.; Finiels, A.; Ganthier, C.; Geneste, P.; Graille, J.; Pioch, D. *J. Org. Chem.* **1986**, *51*, 2128.
5. (a) Kikukawa, K.; Kono, K.; Wada, F.; Matsuda, T. *Chem. Lett.* **1982**, 35. (b) Ishiyama, T.; Kizaki, H.; Miyaura, N.; Suzuki, A. *Tetrahedron Lett.* **1993**, *34*, 7595. (c) Cho, C. S.; Yoshimori, Y.; Uemura, S. *Bull. Chem. Soc. Jpn* **1995**, *68*, 950.
6. Bermon, E. M.; Showwalter, H. D. H. *J. Org. Chem.* **1989**, *54*, 5642.
7. Yamato, T.; Hideshima, C.; Prakash, G. K. S.; Olah, G. A. *J. Org. Chem.* **1991**, *36*, 3955.
8. Suzuki, K.; Kitagawa, H.; Mukaiyama, T. *Bull. Chem. Soc. Jpn* **1993**, *66*, 3729.
9. (a) Benkeser, R. A.; Krysiak, H. *J. Am. Chem. Soc.* **1954**, *76*, 599. (b) Olah, G. A.; Kobayashi, S. *J. Am. Chem. Soc.* **1971**, *93*, 6964. (c) Pearson, D. E.; Buehler, C. A. *Synthesis* **1972**, 533. (d) Elfenberger, F.; Steegmuller, D. *Chem. Ber.* **1988**, *121*, 117. (e) Mukaiyama, T.; Ohno, T.; Nishimura, T.; Suda, S.; Kobayashi, S. *Chem. Lett.* **1991**, 1059. (f) Mukaiyama, T.; Suzuki, K.; Han, T. S.; Kobayashi, S. *Chem. Lett.* **1992**, 435. (g) Tagaki, K.; Shimiishi, Y.; Shimiishi, K. *Chem. Lett.* **1994**, 2055. (h) Evans, P. A.; Nelson, J. D.; Stunley, A. L. *J. Org. Chem.* **1995**, *60*, 2298. (i) Kim, S.-H.; Hanson, M. V.; Rieke, R. D. *Tetrahedron Lett.* **1996**, *37*, 2197. (j) Desmurs, J. R.; Labrouille, M.; Roux, C. L.; Gaspard, H.; Laporterie, A.; Dubac, J. *Tetrahedron Lett.* **1997**, *38*, 8871.
10. (a) Olah, G. A.; Rasul, G.; York, C.; Prakash, G. K. S. *J. Am. Chem. Soc.* **1995**, *117*, 11211. (b) Olah, G. A.; Klumpp, D. A.; Neyer, G.; Wang, Q. *Synthesis* **1996**, 321. (c) Klumpp, D. A.; Beak, D. N.; Prakash, G. K. S.; Olah, G. A. *J. Org. Chem.* **1997**, *62*, 6666. (d) Hwang, J. P.; Prakash, G. K. S.; Olah, G. A. *Abstract Paper* 216th National Meeting of American Chemical Society, Boston, MA, August 1998, Abstract ORGN 595.
11. Olah, G. A. *Angew. Chem. Int. Ed. Engl.* **1993**, *32*, 767.
12. (a) Olah, G. A.; Malhotra, R.; Narang, S. C.; Olah, J. A. *Synthesis* **1978**, 672. (b) Ayyangar, N. R.; Lahoti, R. J.; Srinivasan, K. V.; Daniel, T. *Synthesis* **1991**, 322. (c) Paul, V.; Sudalai, A.; Daniel, T.; Srinivasan, K. V. *Tetrahedron Lett.* **1994**, *35*, 2602. (d) Furstner, A.; Bruner H. *Tetrahedron Lett.* **1996**, *37*, 7009. (e) Satoh, T.; Itaya, T.; Miura, M.; Nomura, M. *Chem. Lett.* **1996**, 823. (f) Khadikar, B. M.; Borkar, S. D. *Tetrahedron Lett.* **1997**, *38*, 1641. (g) Patil, M. L.; Jnaneshwara., Sabde, D. P.; Dongare, M. K.; Sudalai, A.; Deshpande, V. H. *Tetrahedron Lett.* **1996**, *37*, 2137.
13. Ravindranathan, T.; Chavan, S. P.; Awachat, M. M.; Kelkar, S. V. *Tetrahedron Lett.* **1995**, *36*, 2277.
14. (a) Ohwada, T.; Yamagata, N.; Shudo, K. *J. Am. Chem. Soc.* **1991**, *113*, 1364. (b) Saito, S.; Sato, Y; Ohwada, T.; Shudo, K. *J. Am. Chem. Soc.* **1994**, *116*, 2312. (c) Saito, S.; Ohwada, T.; Shudo, K. *J. Am. Chem. Soc.* **1995**, *117*, 11081. (d) Saito, S.; Ohwada, T.; Shudo, K. *J. Org. Chem.* **1996**, *61*, 8089.
15. White, A. M.; Olah, G. A. *J. Am. Chem. Soc.* **1969**, *91*, 2943.
16. (a) Olah, G. A.; Westerman, P. W. *J. Org. Chem.* **1973**, *38*, 1986. (b) Olah, G. A.; Hartz, N.; Rasul, G.; Burrichter, A.; Prakash, G. K. S. *J. Am. Chem. Soc.* **1995**, *117*, 6421.