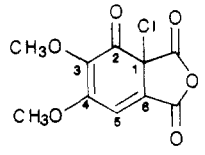
68%, respectively. These results demonstrate also that the use of high pressure is a very valuable tool for synthetic organic chemistry.

Experimental Section

General Aspects. Melting points were taken on a Yanagimoto micro hotstage apparatus and are uncorrected. Infrared spectra on KBr pellets of solids were measured on a JASCO IR-G spectrophotometer. ^1H NMR and ^{13}C NMR spectra of $CDCl_3$ solutions with Me_4Si as an internal standard were recorded on a Hitachi R-40 (90 MHz) spectrometer and a JEOL FX-90Q spectrometer, respectively. High pressure experiments were performed in Teflon-brand capsules, reported in our previous paper.[7] Mass spectra were obtained at the Rockefeller University mass spectrometric lab, by using chemical ionization.

Materials. Dichloromaleic anhydride and furan were purchased from Aldrich and purified by sublimation or distillation. Dichloromaleic anhydride melts at 122 °C. 3,4-Dimethoxyfuran and diphenyl- and methylphenylcyclopropenone[8] were prepared according to the literature.

Reaction of Dimethoxyfuran (2) with Dichloromaleic Anhydride (3). A solution of **2** (0.19 g, 1.5 mmol) and **3** (0.25 g, 1.5 mmol) in THF was compressed in a high pressure vessel for 27 h at room temperature. After evaporation of solvent, the residue was chromatographed on silica gel using hexane/ethyl acetate (95/5 and then 50/50 by v/v) as eluent. The yellow fractions gave the crude product **5** (0.26 g, 67%). Recrystallization from dichloromethane gave an analytically pure sample: mp 131–132 °C; IR (KBr) 1765, 1815, 1855 (C=O), 2925, 3120 (CH_3O) cm^{-1}; ^1H NMR (90 MHz) 3.81 (s, 3 H, 4.04 (s, 3 H), 7.35 (s, 1 H); ^{13}C NMR (90 MHz) 58.7 (q, CH_3O), 60.7 (q, CH_3O), 125.2 (s, C-1), 128.7 (s, C-6), 130.0 (d, C-5), 145.1 (s, C-3,4), 159.2 (s, C=O), 160.4 (s, C=O). Anal. Calcd. for $C_{10}H_7O_6Cl$: C, 46.44; H, 2.73; Cl, 13.71. Found: C, 46.39, H, 2.67, Cl, 13.87.



(7) Matsumoto, K.; Sera, A.; Uchida, T. *Synthesis* **1985**, 1.
(8) Breslow, R.; Haynie, R.; Mirra, J. *J. Am. Chem. Soc.* **1959**, *81*, 247.

Reaction of 2 with Diphenylcyclopropenone (6). A mixture of **1** (0.11 g, 0.86 mmol) and **6** (0.16 g, 0.78 mmol) in toluene (5 mL) was refluxed for 44 h. After evaporation of the solvent, the residue was chromtographed in Florisil successively using hexane–benzene, benzene, and benzene–methyl acetate as the eluents. The product **8** was recrystallized from hexane: yield, 0.058 g (24%); mp 155–156 °C; IR (KBr) 2950, 3000 (OCH_3), 3400 (OH) cm^{-1}; ^1H NMR 3.59, 3.87 (s, 3 H × 2, OCH_3), 4.82 (br s, 1 H, OH), 6.87 (s, 1 H, H-4), 7.26–7.63 (m, 10 H, C_6H_5 × 2); ^{13}C NMR 56.6, 60.7 (q, OCH_3), 114.4 (d, C-4), 123–147 (complex, other aromatic carbons). Anal. Calcd for $C_{20}H_{18}O_3$: C, 78.40; H, 5.93. Found: C, 78.38; H, 5.96.

Reaction of 2 with Methylphenylcyclopropenone (9). A mixture of **9** (0.29 g, 2 mmol) and **2** (0.26 g, 2 mmol) in toluene (5 mL) was refluxed for 46 h and worked up as described above, producing 2,3-dimethoxy-5-methyl-6-phenylphenol (**10**) (40 mg, 9%) and the dimer **11** (0.11 g, 10%). **10**: oil; IR (neat) 2940 (OCH_3), 3580 (OH) cm^{-1}; ^1H NMR 2.22 (s, 3 H, CH_3), 3.77 and 3.80 (each s, 3 H × 2, OCH_3 × 2), 4.90 (s, 1 H, OH), 6.60 (s, 1 H, 3-H), 7.25–7.45 (m, 5 H, C_6H_5), ^{13}C NMR 9.2 (q, CH_3), 56.4, 60.42 (each q, OCH_3), 111.3 (d, C-4), 119.3 (s, C-5), 122.5 (s, C-6), 127.7, 129.1, 129.2 (each d, CH= of Ph), 137.5 (s, C of 1'Ph), 144.9, 146.6, 147.8 (each s, C-1,2,3). Anal. Calcd for $C_{15}H_{16}O_3$: C, 73.75; H, 6.60. Found: C, 73.69; H, 6.61 **11**: mp 178–179 °C; (lit.[6] mp 169 °C); IR (KBR) 1725 (C=O) cm^{-1}; ^1H NMR 2.04 m and 2.25 (each s, 3 H × 2, CH_3), 7.05–7.36 (m, 10 H, C_6H_5 × 2); ^{13}C NMR 9.8 and 10.0 (each q, CH_3 × 2), 73.3 (s, 4a-C), 117–158 (complex, aromatic and olefinic carbons). Anal. Calcd for $C_{20}H_{16}O_2$: C, 83.31; H, 5.59. Found: C, 83.28; H, 5.43.

High Pressure Reaction of 6 (and 9) with 2. A solution of **6** (or **9**) (2 mmol) and **2** (2 mmol) in dichloromethane (8 mL) was reacted at 8 kabr and 55 °C for 48 h. After cooling and release of pressure, the mixture was worked up as described above and **8** and **10** were isolated in 51% and 69% yield, respectively.

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Registry No. **2**, 58928-51-1; **3**, 1122-17-4; **5**, 103752-32-5; **6**, 886-38-4; **8**, 103752-33-6; **9**, 26307-30-2; **10**, 103752-34-7; **11**, 56764-01-3.

Communications

Endo-Selective Insertion by Norcaranylidene Carbenoid into the α-C–H Bond of Alkoxides: Evidence of a Hydride Abstraction–Recombination Mechanism

Summary: A hydride abstraction–recombination mechanism in the insertion of the α-C–H bond of alkoxides by norcaranylidene carbenoid is proposed on the basis of the preferential endo stereoselectivity at the carbenic carbon of the insertion products.

Sir: While studies on the stereochemistry of the C–H insertion by carbenes have provided valuable information on the mechanism of the reaction,[1] the major concern has been focused on the stereochemistry of substrates, i.e., whether the insertion proceeds with retention or racemization of configuration. On the other hand, the stereochemistry on the carbenic carbon has received little attention.[2] Herein, we wish to report evidence of the hydride abstraction–recombination mechanism[3] in the insertion by norcaranylidene carbenoid[4] into the α-C–H bond of alkoxides. Our major concern in the present study is the stereochemistry of the carbenic carbon associated with the endo and exo selectivity of the insertion products.

(1) (a) Kirmse, W. *Carbene Chemistry*, 2nd ed.; Academic: New York, 1971; Chapter 7. (b) Gasper, P. P.; Hammond, G. S. *Carbenes*; Moss, R. A., Jones, M., Jr., Eds.; Wiley: New York, 1975; Vol II, Chapter 6.

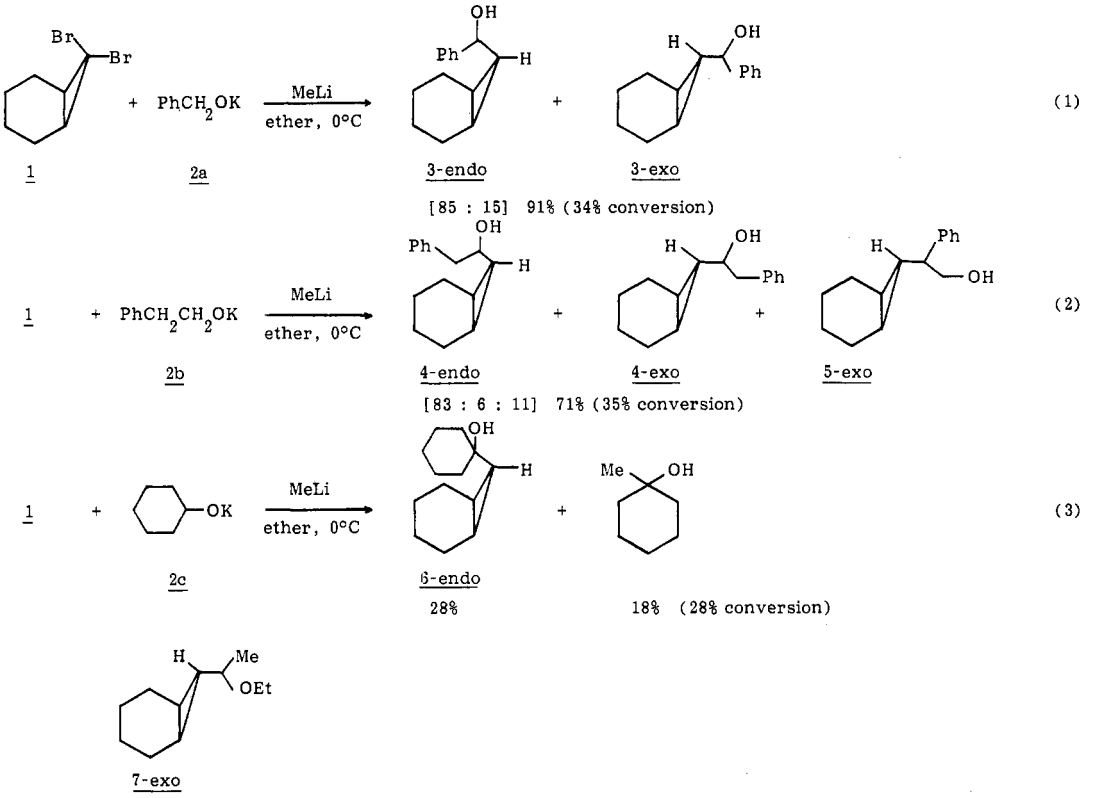
(2) (a) Newman, M. S.; Patrick, T. B. *J. Am. Chem. Soc.* **1970**, *92*, 4312. Note that a part of the work was retracted (Newman, M. S.; Patrick, T. B. *Ibid.* **1972**, *94*, 1793). (b) Stang, P. J.; Mangum, M. G.; Fox, D. P.; Haak, P. *Ibid.* **1974**, *96*, 4562.

(3) Harada, T.; Nozaki, Y.; Yamaura, Y.; Oku, A. *J. Am. Chem. Soc.* **1985**, *107*, 2189.

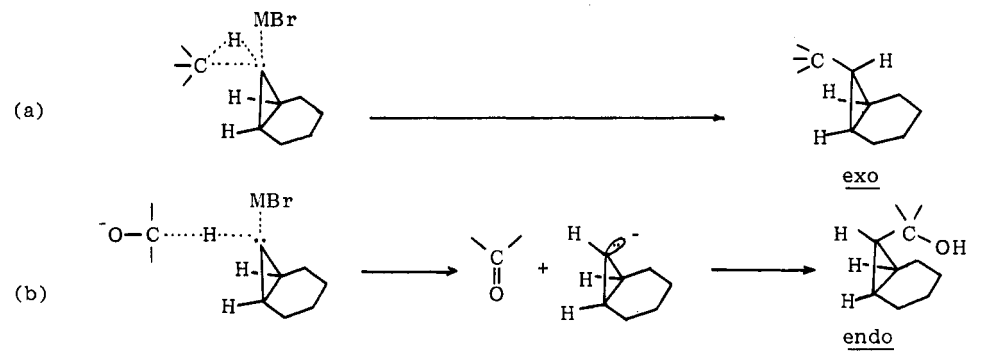
(4) For intramolecular insertion, see, (a) Paquette, L. A.; Chamot, E.; Browne, A. R. *J. Am. Chem. Soc.* **1980**, *102*, 637. (b) Paquette, L. A.; Browne, A. R.; Chamot, E.; Blount, J. F. *Ibid.* **1980**, *102*, 643 and their previous reports. (c) Review: Taylor, K. G. *Tetrahedron* **1982**, *38*, 2751 and references cited therein.

0022-3263/86/1951-3730$01.50/0

Chart I



Scheme I



Norcaranylidene carbenoid underwent insertion into the α-C–H bond of alkoxides with somewhat lower regioselectivity as compared with those of other carbenes studied previously,[5] but the reaction proceeded with a characteristic endo selectivity. Thus, when 7,7-dibromonorcarane (1) (2.0 equiv) was treated with MeLi (ether solution, 2.1 equiv) in ether at 0 °C in the presence of potassium benzyl oxide (**2a**), the corresponding stereoisomers of the α-C–H insertion products, *endo*-**3** and *exo*-**3**, were obtained in the ratio of 85:15 in 91% yield (based on the 33% conversion of **2a**) (eq 1, Chart I). Under similar reaction conditions, potassium 2-phenethyl oxide (**2b**) gave the corresponding α-C–H insertion products **4** with endo selectivity (endo:exo = 93:7) together with a minor amount of β (i.e., benzylic position) insertion product *exo*-**5** (endo isomer was not formed) (eq 2, Chart I). In the reaction of potassium cyclohexyl oxide (**2c**), an exclusive formation of *endo*-**6** was observed (eq 3, Chart I). In these reactions, a concomitant insertion reaction to ether always took place to give *exo*-**7** exclusively.[6]

The endo or exo stereochemistry of the insertion products[7] was determined by the comparison of the ^{1}H NMR vicinal coupling constants between protons attached to the cyclopropane rings[8] (*endo*-**4**, 10.0 Hz; *exo*-**4**, 5.0 Hz; *exo*-**5**, 4.8 Hz; *endo*-**6**, 9.4 Hz; *exo*-**7**, 4.8 Hz). Authentic exo isomers of **3**–**5** were also independently prepared for comparison. Thus, *exo*-**3** was prepared starting from benzaldehyde as follows:[9] (1) 7-bromo-7-lithionorcarane/THF, –90 °C; (2) *t*-BuOK/THF; (3) LAH/THF. Similarly, *exo*-**4** was prepared from phenylacetaldehyde, and *exo*-**5** was prepared by the Wittig reaction of *exo*-7-benzoylnorcarane, which was obtained in the second step of the above-men-

(5) (a) Harada, T.; Oku, A. *J. Am. Chem. Soc.* **1981**, *103*, 5965. (b) Harada, T.; Akiba, E.; Oku, A. *Ibid.* **1983**, *105*, 2771. (c) Harada, T.; Nozaki, Y.; Oku, A. *Tetrahedron Lett.* **1983**, *24*, 5665. (d) Cohen, T.; Ritter, R. H.; Ouellette, D. *J. Am. Chem. Soc.* **1982**, *104*, 7142. (e) Nilsen, N. O.; Skattebøl, L.; Sydnes, L. K. *Acta Chem. Scand., Ser. B.* **1982**, *36*, 587.

(6) Moore, W. R.; Ward, H. R.; Merritt, R. F. *J. Am. Chem. Soc.* **1961**, *83*, 2019.

(7) All insertion products showed satisfactory spectral (^{1}H NMR, IR, and mass) data.

(8) Jackman, J. M.; Sternhell, S. *Application of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry*, 2nd ed.; Pergamon: 1969; Chapter 4-2.

(9) Hiyama, T.; Takehara, S.; Kitatani, K.; Nozaki, H.; *Tetrahedron Lett.* **1974**, 3295.

tioned preparation of *exo*-**3**, followed by hydroboration.

As the exo selectivity is expected in the concerted insertion that will take place on the sterically less hindered exo face of norcaranylidene carbenoid (Scheme I, a),[10] the present stereochemical outcome clearly indicates that the endo-selective insertion into the α-C–H bond of alkoxides proceeds by a mechanism different from that for the exo-selective concerted insertion.[11] In the previous report,[3] we demonstrated a novel stepwise mechanism, hydride abstraction–recombination mechanism, in the insertion by alkylidenemethylene carbenoid into the α-C–H bond of alkoxides. The present characteristic endo selectivity is reasonably explained in terms of the hydride abstraction from the α position of alkoxides by norcaranylidene carbenoid on its exo face, followed by the recombination of the resulting *endo*-norcaranyl anion with the carbonyl compound (Scheme I, b).[12] The mechanism is further supported in the reaction of **2c** (eq 3) by the formation of 1-methylcyclohexanol, a product from the intermediate carbonyl compound trapped by MeLi.

We noted in a separate study that the hydride abstraction by carbenoids predominates when the concerted insertion is sterically retarded.[3] The minor products *exo*-**3** and *exo*-**4** formed in the reactions of primary alkoxides **2a** and **2b** are produced supposedly through a concerted mechanism, but this mechanism is completely suppressed in the reaction of sterically demanding secondary alkoxide **2c** where an exclusive endo selectivity was attained.

The present study as well as our latest report[3] shows that the hydride abstraction is a common reaction of carbenoids. A highly electrophilic character of carbenoids exhibited in the hydride abstraction supports the current view that carbenoids are electron deficient at carbon.[13-15]

Registry No. 1, 2415-79-4; **2a**, 22379-62-0; **2b**, 2245-69-4; **2c**, 54637-77-3; **3**, 100971-67-3; **4**, 103499-75-8; **5**, 103499-76-9; **6**, 103499-77-0; **7**, 6537-04-8; PhCHO, 100-52-7; $PhCH_2CHO$, 122-78-1; 1-methylcyclohexanol, 590-67-0; 7-bromo-7-lithionorcarane, 57640-05-8; 7-benzoylnorcarane, 31152-14-4; norcaranylidene carbenoid, 91781-43-0.

Supplementary Material Available: A general reaction procedure and ^1H NMR (200 MHz), IR, and mass spectral data of the insertion products (3 pages). Ordering information is given on any current masthead page.

(10) For the theoretical study on the transition-state geometry of the C–H insertion reaction, see: Jug, K.; Mishra, P. C. *Int. J. Quantum Chem.* **1983**, *23*, 887 and references cited therein.

(11) A radical chain/electron-transfer mechanism similar to that proposed for an aryl halide–methoxide system (Bunnett, J. F.; Wasmer, C. C. *J. Am. Chem. Soc.* **1967**, *89*, 6721) seems unlikely in the present reaction: the involvement of norcaranylidene radical anion (or its adduct with a carbonyl compound) in the chain cannot explain the characteristic endo selectivity.

(12) For the conformational stability of cyclopropyllithium, see: (a) Applequist, D. E.; Peterson, A. H. *J. Am. Chem. Soc.* **1961**, *83*, 862. (b) Walborsky, H. M.; Impastato, F. J.; Young, A. E. *Ibid.* **1964**, *86*, 328.

(13) Draisamy, M.; Walborsky, H. M. *J. Am. Chem. Soc.* **1984**, *106*, 5035.

(14) (a) Seebach, D.; Siegel, H.; Gabriel, J.; Hassig, R. *Helv. Chim. Acta* **1980**, *63*, 2046. (b) Seebach, D.; Hassig, R.; Gabriel, J. *Ibid.* **1983**, *66*, 308.

(15) Mareda, J.; Rondon, N. G.; Houk, K. N.; Clark, T.; Schleyer, P. v. R. *J. Am. Chem. Soc.* **1983**, *105*, 6997 and references cited therein.

Akira Oku,* Yasunari Yamaura, Toshiro Harada

Department of Chemistry
Kyoto Institute of Technology
Matsugasaki, Sakyo-ku
Kyoto 606, Japan

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((9-Fluorenylmethyl)oxy)carbonyl (Fmoc) Amino Acid Chlorides. Synthesis, Characterization, and Application to the Rapid Synthesis of Short Peptide Segments

Summary: Fmoc amino acid chlorides are described as stable, easily synthesized coupling agents and shown to be useful in a novel method of rapid, repetitive peptide synthesis.

Sir: Although protected amino acid chlorides have been known as coupling agents since the earliest days of peptide synthesis, they have never been widely used except in special circumstances.[1] Protecting groups stable enough to survive conversion to an acid chloride are generally difficult to deblock. We point out that with the development of the Fmoc amino-protecting group,[6] there is no longer a need to avoid the use of acid chlorides. Under appropriate conditions coupling occurs without loss of chirality at the carboxylic acid site. A convenient method of coupling involves a two-phase system with a mild inorganic base in the aqueous layer to minimize contact with the acid chloride. Coupling is completed within a few minutes. Simple coupling reactions in homogeneous solution are also possible.

Table I lists the Fmoc amino acid chlorides synthesized to date. Following reaction with thionyl chloride, recrystallization from CH_2Cl_2–hexane gives analytically pure samples of the acid chlorides which can be stored indefinitely in a dry atmosphere. Prior to use samples may, if desired, by analyzed for any residual acid content via a simple HPLC technique: addition to dry methanol followed by immediate injection onto a C_{18} column reveals the ratio of acid chloride (as methyl ester) and free acid.

These new acid chlorides have been used in a novel technique for the rapid solution synthesis of short peptide segments. Traditional solution methods are often tediously slow. Improvements have long been sought and several

(1) A recent authoritative review[2] on coupling methods pronounced the use of amino acid chlorides in peptide coupling as obsolete. In our view, far from being obsolete, amino acid chlorides are now among the most convenient reagents for peptide bond formation following the stepwise strategy considering ease of access, low cost, shelf stability, and speed of reaction with amino acid and peptide esters. Fmoc amino acid chlorides were previously used for the preparation of polymeric active esters, or, prepared in situ, in order to synthesize otherwise difficultly obtainable amides. [Cohen, B. J. Ph.D. Dissertation, Weizmann Institute of Science, Rehovot, Israel, 1979; Pass, S.; Amit, B.; Patchornik, A. *J. Am. Chem. Soc.* **1981**, *103*, 7674.]. The fear of racemization attending the use of ordinary protected amino acid chlorides[3-5] is not borne out. Kunz and Bechtolsheimer[3] have also recommended resurrection of the use of acid chlorides in peptide coupling, especially in the case of hindered substrates. For the [[2-(triphenylphosphonio)ethyl]oxy]carbonyl system, special interactions involving the phosphonium cation were invoked to account for the observed lack of racemization. Our work and that of others[4,5] shows that no special structural elements are needed to avoid racemization.

(2) Jones, J. H. In *The Peptides*; Gross, E., Meienhofer, J., Eds.; Academic Press: New York, 1979, Vol. 1, p 65.

(3) (a) Bechtolsheimer, H.-H.; Kunz, H. *Angew. Chem., Int. Ed. Engl* **1982**, *21*, 630. (b) Kunz, H.; Bechtolsheimer, H.-H. *Liebigs Ann. Chem.* **1982**, 2068.

(4) For additional examples of the use of chiral protected amino acid chlorides, see: (a) Cupps, T. L.; Boutin, R. H.; Rapoport, H. *J. Org. Chem.* **1985**, *50*, 3976. (b) Nordlander, J. E.; Njoroge, F. G.; Payne, M. J.; Warman, D. *J. Org. Chem.*, **1985**, *50*, 3481. (c) Nordlander, J. E.; Payne, M. J.; Njoroge, F. G.; Balk, M. A.; Laikos, G. D.; Vishwanath, V. M. *J. Org. Chem.* **1984**, *49*, 4107.

(5) Under very mild conditions even *tert*-butoxycarbonyl and benzyloxycarbonyl systems have been used successfully. See: (a) Losse, G.; Wehrstedt, K.-D. *Z. Chem.* **1981**, *21*, 148. (b) Matsuda, F.; Itoh, S.; Hattori, N.; Yanagiya, M.; Matsumoto, T. *Tetrahedron* **1985**, *41*, 3625.

(6) Carpino, L. A.; Han, G. Y. *J. Am. Chem. Soc.* **1970**, *92*, 5748; *J. Org. Chem.* **1972**, *37*, 3404.

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