CATALYTIC AND STOICHIOMETRIC LEWIS ACID PARTICIPATION IN ALDEHYDE ENE CYCLISATIONS

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Dedicated to Professor Otakar Červinka on the occasion of his 75th birthday, in appreciation of his contributions to organic stereochemistry.

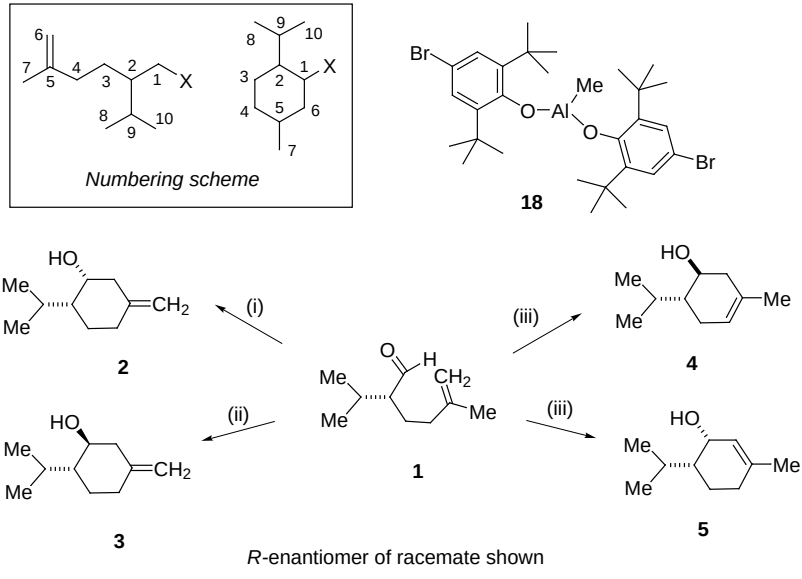
Racemic 2-isopropyl-2-methylhex-5-enal has been synthesised in order to probe ene cyclisations leading to menthol analogues. The objective was first to discover catalytic conditions for preferential cyclisation to the menthol rather than the neomenthol series and then to develop (dynamic) kinetic resolution procedures which afforded a single enantiomer of product. It was found that catalytic quantities of both Me_2AlCl and a bulky methylaluminium bis(phenoxide) reagent gave products attributed to a Meerwein–Pondorff–Verley reaction. In this the aldehyde is reduced to a primary alcohol and the ene product oxidised to the corresponding α,β-unsaturated ketone. By contrast, a related bulky chloroaluminium reagent catalysed the ene cyclisation cleanly, but preferentially to the undesired neomenthyl stereoisomer.

Key words: Ene reactions; Aldehydes; Aluminium catalysts; Lewis acids; Terpenoids; Stereoselective cyclisations.

One of the most successful methods for the catalytic asymmetric synthesis of C–C bonds is the carbonyl ene reaction of alkenes[1] in which Mikami's contribution has been at the forefront[2]. In the main, successful examples involve an activated carbonyl compound such as a glyoxylate ester[3], fluoral[4] or formaldehyde[5]. The glyoxylate ester ene reaction has been applied with success by other authors[6], and transition-state models have been proposed[7]. Yamamoto's outstanding contributions to the development of intramolecular cases do not include a prescription for catalytic asymmetric synthesis[8], and there are rather few successful contributions to this problem[9]. In a related reaction where an enantiomerically pure reactant cyclises under the influence of an enantiomerically pure catalyst, only modest

matching is observed[10]. The limitations encourage the search for new ene cyclisation catalysts[11].

The incentive for our work was the potential ease of access to menthol and its stereoisomeric relatives through an intramolecular ene reaction, already demonstrated by Yamamoto and co-workers. The aim was to provide a basis for an asymmetric synthesis through detailed analysis of the reactivity and stereoselectivity of ene cyclisation of a single reactant. In the first part of this work, we described a broad mechanistic framework for defining the stereochemical course of Type II ene cyclisations of compound **1**, and how variations in mechanism with change of Lewis acid provide routes to different products and also to distinct stereoisomers[12]. The formation of the various products **2**–**5** may be rationalised according to a common mechanistic framework (Scheme 1). A further paper will provide information on the synthesis and cyclisation of enantiomerically pure aldehyde **1** (ref.[13]). Here we describe an evaluation of different aluminium compounds as Lewis acids and progress from stoichiometric promotion of the ene reaction towards catalysis.



(i) Me_2AlCl; (ii) MABR **18**; (iii) $Sc(OTf)_3$ or $Cp_2Ti(OTf)_2$

SCHEME 1

EXPERIMENTAL

General

Boiling point values recorded for short-path distillations were obtained using a Büchi GKR-51 Kugelrohr oven. The value quoted is the uncorrected pot temperature. Elemental microanalyses were performed by Mrs V. Lamburn in the Dyson Perrins Laboratory using a Carlo Erba 1106 elemental analyser. Infrared spectra (wavenumbers in cm^{-1}) were recorded on a Perkin–Elmer 1750 Fourier Transform spectrometer. Samples were prepared as thin films on sodium chloride plates or as potassium bromide disks. Abbreviations used in the description of spectra are: w weak, m medium, s strong, br broad, def. deformation. ^1H NMR spectra were recorded on a Varian Gemini 200 (200 MHz), Bruker WH 300 (300 MHz) or Bruker AM 500 (500 MHz) spectrometer. Chemical shifts (δ_H) are quoted in ppm and are referenced to the residual solvent of chloroform (7.27 ppm), coupling constants *J* are given in Hz. ^{13}C NMR spectra were recorded on a Varian Gemini 200 (50.3 MHz) or Bruker AM 500 (125.6 Hz) spectrometer using DEPT editing on the former. Quaternary carbons were assigned from a broad-band-decoupled analysis used in conjunction with the DEPT program. Chemical shifts (δ_C) are quoted in ppm and are internally referenced to the solvent ($CDCl_3$, δ_C 77.0). Mass spectra were recorded on a Trio-1 GCMS (Hewlett–Packard GC) spectrometer by chemical ionisation with ammonia gas. Solvents were purchased from Rhône–Poulenc, Fisons, Rathburns or the Aldrich Chemical Company, and were dried prior to use by distillation from standard drying agents according to the procedures of Perrin *et al.*[14]. Commercial samples of butyllithium were titrated against freshly recrystallised diphenylacetic acid immediately before use[15]. NMR solvents were stored under argon in the presence of activated 4Å molecular sieves and distilled where necessary from standard drying agents immediately before use. All other reagents were purified according to the procedures described by Perrin *et al.* or used as obtained from commercial sources.

3-Methylbut-3-en-1-yl Tosylate (**8**)

3-Methylbut-3-en-1-yl tosylate was prepared using a modified synthesis of Maitlin *et al.*[16]. Tosyl chloride (42.0 g, 220 mmol) was added in portions to a stirred solution of 3-methylbut-3-en-1-ol (20.0 ml, 200 mmol) in pyridine (200 ml) at 0 °C . The mixture was allowed to stand for 16 h at 0 °C and then diluted with water (200 ml). The organics were extracted with diethyl ether (3 × 300 ml), washed with ice-cold 1 M HCl (3 × 500 ml), water (200 ml) and brine. The organic layer was dried ($MgSO_4$), filtered and the solvent evaporated to afford the title compound as a thermally sensitive pale yellow oil (40.3 g, 85%). IR (thin film): 3 078 w (sp^2 CH), 2 971 m (sp^3 CH), 2 955 m (sp^3 CH), 2 925 m (sp^3 CH), 1 653 (C=C), 1 599 m (Ar C=C), 1 496 m (Ar C=C), 1 450 m (CH def.), 1 359 s (SO_2–O–), 1 176 s (SO_2–O–). ^1H NMR (200 MHz, $CDCl_3$): 7.81 (2 H, d, *J* = 8.4, 2′-H); 7.36 (2 H, d, *J* = 8.4, 3′-H); 4.80 (1 H, br s, 4-H); 4.69 (1 H, br s, 4-H); 4.14 (2 H, t, *J* = 6.8, 1-H); 2.47 (3 H, s, 5′-H); 2.36 (2 H, br t, *J* = 6.8, 2-H); 1.67 (3 H, s, 5-H). ^{13}C NMR (50.3 MHz, $CDCl_3$): 145.0 (C3), 140.3 (C1′), 133.2 (C4′), 130.0 (C2′), 128.1 (C3′), 113.2 (C4), 68.5 (C1), 36.6 (C2), 22.2 (C5′), 21.5 (C5). MS (CI^+, NH_3), *m/z* (rel.%): 258 ($M + 18^+$, 100), 241 ($M + 1^+$, 13), 136 (5), 108 (5), 68 (3).

4-Bromo-2-methylbut-1-ene (**9**)

3-Methylbut-3-en-1-yl tosylate (24.0 g, 100 mmol) was added dropwise *via* a double ended needle to a solution of vacuum dried LiBr (17.4 g, 200 mmol) in dry DMF (50 ml) under argon at room temperature. The solution was stirred for 24 h, water (200 ml) was added and then extracted with pentane (3 × 100 ml). The organics were washed with water (3 × 100 ml), dried ($MgSO_4$), filtered and the solvent evaporated to give a pale yellow oil. Short-path distillation under reduced pressure yielded the title compound as a sweet-smelling colourless oil (11.4 g, 76%), b.p. 100 °C (0.1 mm Hg). IR (thin film): 3 079 m (sp^2 CH), 2 971 s (sp^3 CH), 2 938 s (sp^3 CH), 1 651 m (C=C), 1 450 s (CH def.). ^{1}H NMR (200 MHz, $CDCl_3$): 4.87 (1 H, br s, 4-H); 4.79 (1 H, br s, 4-H); 3.49 (2 H, t, *J* = 7.4, 1-H); 2.63 (2 H, br t, *J* = 7.4, 2-H); 1.76 (3 H, s, 5-H). ^{13}C NMR (50.3 MHz, $CDCl_3$): 142.6 (C3), 112.8 (C4), 40.8 (C1), 30.7 (C2), 21.8 (C5). MS (EI^+), *m/z* (rel.%): 150 (M^+, 10), 148 (M^+, 9), 137 (6), 109 (11), 69 ($C_5H_9^+$, 100), 58 (70).

4-Iodo-2-methylbut-1-ene (**10**)

3-Methylbut-3-en-1-yl tosylate (38.4 g, 160 mmol) was added dropwise to a solution of sodium iodide (48.0 g, 320 mmol) in acetone (400 ml) at reflux. A pale yellow precipitate was formed immediately. The mixture was refluxed for a further 2 h and then cooled to room temperature. The inorganics were solubilised by the addition of water (500 ml) and the organics extracted with pentane (2 × 250 ml). The combined extracts were washed with brine, dried (anhydrous $MgSO_4$), filtered and evaporated to give a bright red oil. Short-path distillation under reduced pressure yielded the title compound as a colourless oil (22.5 g, 72%), b.p. 45 °C (0.01 mm Hg). IR (thin film): 3 077 s (sp^2 CH), 2 969 s (sp^3 CH), 2 936 s (sp^3 CH), 2 915 s (sp^3 CH), 1 651 s (C=C), 1 446 s (CH def.). ^{1}H NMR (200 MHz, $CDCl_3$): 4.88 (1 H, br s, 4-H); 4.77 (1 H, br s, 4-H); 3.28 (2 H, t, *J* = 7.4, 1-H); 2.60 (2 H, br t, *J* = 7.4, 2-H); 1.75 (3 H, s, 5-H). ^{13}C NMR (50.3 MHz, $CDCl_3$): 144.1 (C3), 112.5 (C4), 41.8 (C2), 21.6 (C5), 3.4 (C1). MS (EI^+), *m/z* (rel.%): 196 (M^+, 3), 127 (55), 69 ($C_5H_9^+$, 100).

N-(3-Methylbutylidene)cyclohexylamine (**6**)

3-Methylbutanal (17.2 g, 200 mmol) was added dropwise to cyclohexylamine (19.8 g, 200 mmol) with stirring at 0 °C. The mixture immediately turned milky. Sodium hydroxide pellets (8.8 g, 220 mmol) were added, the homogeneous liquid filtered and distilled to yield the title compound as a colourless liquid (21.2 g, 63%), b.p. 212–213 °C. For $C_{11}H_{21}N$ (167.3) calculated: 78.98% C, 12.65% H, 8.37% N; found: 78.96% C, 12.46% H, 8.58% N. IR (thin film): 2 956 s (sp^3 CH), 2 929 s (sp^3 CH), 2 855 s (sp^3 CH), 2 577 s (sp^3 CH), 1 667 m (C=N). ^{1}H NMR (500 MHz, $CDCl_3$): 7.63 (1 H, t, *J* = 5.4, 1-H); 2.89 (1 H, tt, *J* = 10.7, 4.2, 1′-H); 2.10 (2 H, dd, *J* = 7.0, 5.4, 2-H); 1.86 (1 H, tqq, *J* = 7.0, 6.8, 6.8, 3-H); 1.76 (2 H, br dt, *J* = 13.2, 3.3, 3′$_{eq}$-H); 1.63 (3 H, m, 2′$_{eq}$-H, 4′$_{eq}$-H); 1.47 (2 H, dq, *J* = 12.1, 3.1, 2′$_{ax}$-H); 1.29 (2 H, tq, *J* = 12.7, 3.3, 3′$_{ax}$-H); 1.18 (1 H, tq, *J* = 12.4, 3.2, 4′$_{ax}$-H); 0.93 (6 H, d, *J* = 6.8, 4-H, 5-H). ^{13}C NMR (50.3 MHz, $CDCl_3$): 162.4 (C1), 69.8 (C1′), 44.5 (C2), 34.3 (C2′), 26.3 (C3), 25.5 (C3′), 24.7 (C4′), 22.2 (C4, C5). MS (CI^+, NH_3), *m/z* (rel.%): 168 ($M + 1^+$, 100), 152 (5), 125 (10), 110 (5).

(±)-*N*-(2-Isopropyl-5-methylhex-5-enylidene)cyclohexylamine (**11**)

Method A: Butyllithium (2.3 ml, 1.6 mol l^{-1} in hexanes) was added to a stirred solution of diisopropylamine (0.51 ml, 3.6 mmol) in dry THF (5 ml) under argon at –78 °C. The pale straw yellow solution was stirred for 1 h at –78 °C and then added *via* a double ended needle to a stirred solution of *N*-(3-methylbutylidene)cyclohexylamine (**6**) (0.55 g, 3.3 mmol) in THF (10 ml) under argon at –20 °C. The bright yellow solution was stirred at –20 °C for 1 h. A solution of 4-bromo-2-methylbut-1-ene (**9**) (0.54 g, 3.6 mmol) in dry THF (5 ml) was added whereupon the bright yellow colour was discharged. The mixture was allowed to warm to room temperature over a period of 2 h, and then quenched with water (2 ml). THF was removed under reduced pressure, and the residue partitioned between pentane (20 ml) and water (20 ml). The water layer was extracted with pentane (2 × 20 ml), the combined organics dried ($MgSO_4$), filtered and the solvent evaporated to give a dark yellow oil. ^{1}H NMR analysis of the crude mixture showed 25% conversion to the title compound (**11**).

Method B: Alkylation of *N*-(3-methylbutylidene)cyclohexylamine (**6**) with 4-iodo-2-methylbut-1-ene in place of bromide. The following quantities of reagents were used: Butyllithium (118 ml, 1.6 mol l^{-1} in hexanes); diisopropylamine (31 ml, 222 mmol) in THF (120 ml); *N*-(3-methylbutylidene)cyclohexylamine (**6**) (28.6 g, 171 mmol) in THF (100 ml); 4-iodo-2-methylbut-1-ene (**10**) (47 g, 256 mmol) in THF (30 ml). Fractional distillation under reduced pressure afforded the title compound (**11**) as a colourless liquid (25.0 g, 62%) b.p. 90-92 °C (0.01 mm Hg). For $C_{16}H_{29}N$ (235.4) calculated: 81.63% C, 12.42% H, 5.95% N; found: 81.27% C, 12.99%H, 5.76% N. IR (thin film): 3 074 m (sp^2 CH), 2 927 s (sp^3 CH), 2 856 s (sp^3 CH), 1 666 s (C=N), 1 650 m (C=C), 1 450 s (CH def.). ^{1}H NMR (500 MHz, $CDCl_3$): 7.42 (1 H, d, *J* = 7.5, 1-H); 4.68 (1 H, br s, 6-H); 4.66 (1 H, br s, 6-H); 2.92 (1 H , tt, *J* = 10.6, 4.2, 1′-H); 1.95 (3 H, m, 2-H, 4α-H, 4β-H); 1.75 (2 H, br dt, *J* = 13.2, 3.3, $3'_{eq}$-H); 1.74 (1 H, dqq, *J* = 7.0, 6.9, 6.9, 9-H); 1.69 (3 H, br s, 7-H); 1.64 (4 H, m, $2'_{eq}$-H, $4'_{eq}$-H, 3β-H); 1.52 (3 H, m, $2'_{ax}$-H, 3α-H); 1.30 (2 H, tq, *J* = 12.7, 3.3, $3'_{ax}$-H); 1.24 (1 H, tq, *J* = 12.4, 3.2, $4'_{ax}$-H); 0.93 (3 H, d, *J* = 6.9, 8-H); 0.90 (3 H, d, *J* = 6.9, 10-H). ^{13}C NMR (50.3 MHz, $CDCl_3$): 165.3 (C1), 145.7 (C5), 110.0 (C6), 70.0 (C1′), 50.6 (C2), 35.2 (C4), 34.4 (C2′), 30.3 (C9), 27.5 (C3), 25.4 (C3′), 24.6 (C4′), 22.2 (C7), 19.5 (C8), 20.1 (C10). MS (CI^+, NH_3), *m/z* (rel.%): 236 ($M + 1^+$, 100), 167 (13).

(±)-2-Isopropyl-2-methylhex-5-enal (**1**)

(±)-2-Isopropyl-2-methylhex-5-enal was prepared using the general procedure of House *et al.*[19]. A two-phase mixture of (±)-*N*-(2-isopropyl-5-methylhex-5-enylidene)cyclohexylamine (**11**) (3.82 g, 16 mmol) in hexane (16 ml) and acetic acid (2.9 g, 48 mmol) in water (48 ml) was stirred vigorously at room temperature for 2 h. The water layer was saturated with solid sodium chloride and the organics extracted with diethyl ether (3 × 50 ml). The combined organics were washed with saturated aqueous sodium hydrogencarbonate (3 × 100 ml), brine and water. The organic layer was dried (anhydrous $MgSO_4$), filtered and the solvent evaporated. Purification by flash chromatography on silica gel (3% ethyl acetate in pentane) gave the title compound as a colourless liquid (1.82 g, 74%). For $C_{10}H_{18}O$ (154.3) calculated: 77.87% C, 11.76% H; found: 77.60% C, 12.06% H. IR (thin film): 3 075 m (sp^2 CH), 2 963 s (sp^3 CH), 2 921 s (sp^3 CH), 2 837 s (sp^3 CH), 2 707 m (O=C–H), 1 724 s (C=O), 1 650 m (C=C), 1 456 s (CH def.). ^{1}H NMR (500 MHz, $CDCl_3$): 9.66 (1 H, d, *J* = 3.2, 1-H); 4.74 (1 H, br s, 6-H); 4.69 (1 H, br s, 6-H); 2.10 (1 H, dddd, *J* = 9.4, 6.2, 3.6, 3.2, 2-H); 2.03 (1 H, dqq, *J* = 6.8, 6.8, 6.2, 9-H); 2.02 (1 H, br ddd, *J* = 14.8, 10.1, 5.5, 4β-H); 1.95 (1 H, br ddd *J* = 14.8,

9.4, 6.6, 4α-H); 1.81 (1 H, dddd, *J* = 13.6, 9.4, 9.4, 5.5, 3β-H); 1.72 (3 H, br s, 7-H); 1.61 (1 H, dddd, *J* = 13.6, 10.1, 6.6, 3.6, 3α-H); 0.99 (3 H, d, *J* = 6.8, 8-H); 0.98 (3 H, d, *J* = 6.8, 10-H). ^{13}C NMR (50.3 MHz, $CDCl_3$): 206.1 (C1), 145.3 (C5), 110.7 (C6), 57.5 (C2), 35.5 (C4), 28.2 (C9), 23.6 (C3), 22.2 (C7), 20.1 (C8), 19.5 (C10). MS (CI^+, NH_3), *m/z* (rel.%): 172 ($M + 18^+$, 23), 155 ($M + 1^+$, 10), 137 (100), 121 (15), 111 (23), 93 (18), 81 (33), 69 (31).

(±)-2-Isopropyl-5-methylhex-5-en-1-ol (**12**)

Sodium borohydride (27 mg, 0.6 mmol) was added in one portion to a solution of (±)-2-isopropyl-2-methylhex-5-enal (**1**) (77 mg, 0.5 mmol) in ethanol (10 ml). Water (10 ml) was added after 10 min followed by careful addition of dilute 1 M HCl (10 ml). The organics were extracted with diethyl ether (3 × 10 ml), the extracts combined, dried (anhydrous $MgSO_4$), filtered and the solvent evaporated to give the title compound as a colourless oil (78 mg, 100%). IR (thin film): 3 600–3 100 br s (OH), 3 074 w (sp^2 CH), 2 959 s (sp^3 CH), 2 943 s (sp^3 CH), 2 874 s (sp^3 CH), 1 650 m (C=C), 1 454 m (sp^3 CH def.), 1 387 m, 1 370 m, 1 037 m, 886 m. ^{1}H NMR (500 MHz, $CDCl_3$): 4.72 (1 H, br s, 6-H); 4.70 (1 H, br s, 6-H); 3.61 (2 H, m, H-1), 2.09 (1 H, ddd, *J* = 14.7, 10.9, 5.9, 4α-H); 2.03 (1 H, ddd, *J* = 14.7, 9.3, 6.1, 4β-H); 1.83 (1 H, dqq, *J* = 6.9, 6.9, 4.7, 9-H); 1.74 (3 H, br s, 7-H); 1.50 (1 H, dddd, *J* = 13.8, 10.9, 6.1, 5.0, 4α-H); 1.40 (1 H, dddd, *J* = 3.8, 9.3, 7.8, 5.9, 4β-H); 1.34 (1 H, ddddd, *J* = 7.8, 5.0, 5.0, 5.0, 4.7, 2-H); 0.92 (3 H, d, *J* = 6.9, 8-H); 0.91 (3 H, d, *J* = 6.9, 10-H). ^{13}C NMR (50.3 MHz, $CDCl_3$): 146.5 (C5), 110.0 (C6), 63.4 (C1), 46.0 (C2), 35.8 (C4), 27.7 (C9), 25.6 (C3), 22.3 (C7), 19.6 (C8), 19.0 (C10). MS (CI^+, NH_3), *m/z* (rel.%): 174 ($M + 18^+$, 7), 157 ($M + 1^+$, 100), 138 (13), 123 (47), 109 (10), 95 (83), 82 (94), 69 (67), 55 (38).

Effect of a Substoichiometric Amount of Dimethylaluminium Chloride on (±)-2-Isopropyl-2-methylhex-5-enal (**1**)

A solution of dimethylaluminium chloride in hexane (0.2 ml, 1 mol l^{-1}, 20 mole %) was added to a stirred solution of (±)-2-isopropyl-2-methylhex-5-enal (**1**) (154 mg, 1 mmol) in dichloromethane (2 ml) at room temperature under argon. The colourless solution was stirred for 16 h and then quenched with 1 M sulfuric acid (2 ml). The organics were extracted with dichloromethane (3 × 10 ml), combined, dried (anhydrous $MgSO_4$), filtered and the solvent evaporated to give a pale yellow oil (148 mg). The crude material was analysed by ^{1}H NMR and was found to consist of a 1 : 2 : 2 mixture of unreacted aldehyde **1**, identical with previously prepared material, (±)-2-isopropyl-5-methylhex-5-en-1-ol (**12**) and (±)-6-isopropyl-3-methylcyclohex-2-en-1-one (**13**) (piperitone)[17]. ^{1}H NMR (300 MHz, $CDCl_3$): 5.83 (1 H, s, 6-H); 2.2–1.2 (6 H, m, 2-H, 3-H, 4-H, 8-H); 1.90 (3 H, s, 7-H); 0.95 (3 H, d, *J* = 6.7, 9-H); 0.93 (3 H, d, *J* = 6.7, 10-H).

Effect of the Alkoxides **14a** and **14c** Generated Directly from Two Equivalents of (1*R**,2*R**)-(**2**) and (1*S**,2*R**)-(2-Isopropyl-5-methylidene)cyclohexan-1-ol (**3**) on (±)-2-Isopropyl-2-methylhex-5-enal (**1**)

A solution of dimethylaluminium in hexane (0.2 ml, 1 mol l^{-1}, 0.2 mmol) was added separately to stirred solutions of (1*R**,2*R**)- and (1*S**,2*R**)-(2-isopropyl-5-methylidene)-cyclohexan-1-ol (**2**) and (**3**) (62 mg, 0.4 mmol) in dichloromethane (2 ml) at room temperature under argon. Vigorous effervescence occurred and after 1 h (±)-2-isopropyl-2-methylhex-5-enal (**1**) (154 mg, 1.0 mmol) was added to the colourless solutions. After 16 h

the mixtures were quenched with 1 M sulfuric acid (5 ml) and the organics were extracted with dichloromethane (3 × 10 ml). The combined organics were dried (anhydrous $MgSO_4$), filtered and the solvent evaporated to give yellow oils (203 and 211 mg respectively). The crude materials were analysed by ^{1}H NMR. Both systems showed the same product distribution: a 3 : 2 : 2 ratio of unreacted aldehyde **1**, (±)-2-isopropyl-5-methylhex-5-en-1-ol (**12**) and (±)-6-isopropyl-3-methylcyclohex-2-en-1-one (**13**).

Effect of a Substoichiometric Amount of MABR (**18**)
on (±)-2-Isopropyl-2-methylhex-5-enal (**1**)

A solution of trimethylaluminium in toluene (0.1 ml, 2 mol l^{-1}, 0.2 mmol) was added dropwise to a solution of 4-bromo-2,6-di-*tert*-butylphenol (114 mg, 0.4 mmol) in dichloromethane (2 ml) with vigorous effervescence at 0 °C under argon. After 1 h the red solution was cooled to −78 °C and added dropwise to a solution of (±)-2-isopropyl-2-methylhex-5-enal (**1**) (154 mg, 1 mmol) in dichloromethane (2 ml). The solution was stirred for 1 h and then allowed to warm to room temperature. After 5 days the mixture was quenched with 1 M sulfuric acid (5 ml), the organics were extracted with dichloromethane (3 × 10 ml), dried (anhydrous $MgSO_4$), filtered and the solvent evaporated to give a dark brown residue. ^{1}H NMR analysis showed that no aldehyde **1** remained and a 1 : 1 mixture of (±)-2-isopropyl-5-methylhex-5-en-1-ol (**12**) and (±)-6-isopropyl-3-methylcyclohex-2-en-1-one (**13**) was obtained.

Effect of Chloroaluminium Bis(4-bromo-2,6-di-*tert*-butylphenoxide) (**21**) (CABR)
on (±)-2-Isopropyl-2-methylhex-5-enal (**1**)

Method A: A solution of dimethylaluminium chloride in hexanes (1.0 ml, 1 mol l^{-1}, 1.0 mmol) was added dropwise to a solution of 4-bromo-2,6-di-*tert*-butylphenol (627 mg, 2.2 mmol) in dichloromethane (2 ml) at room temperature under argon. Effervescence occurred and after 1 h (±)-2-isopropyl-2-methylhex-5-enal (**1**) (77 mg, 0.5 mmol) was added to the deep red solution at 0 °C. The mixture was stirred for 0.5 h and then worked-up in the usual manner. The crude material was analysed by ^{1}H NMR.

Method B: As for method *A* but with a catalytic amount (20 mole %) of CABR. The following amount of materials were used: Dimethylaluminium chloride (0.2 ml, 1 mol l^{-1}, 0.2 mmol), 4-bromo-2,6-di-*tert*-butylphenol (125 mg, 0.44 mmol) and (±)-2-isopropyl-2-methylhex-5-enal (**1**) (77 mg, 0.5 mmol).

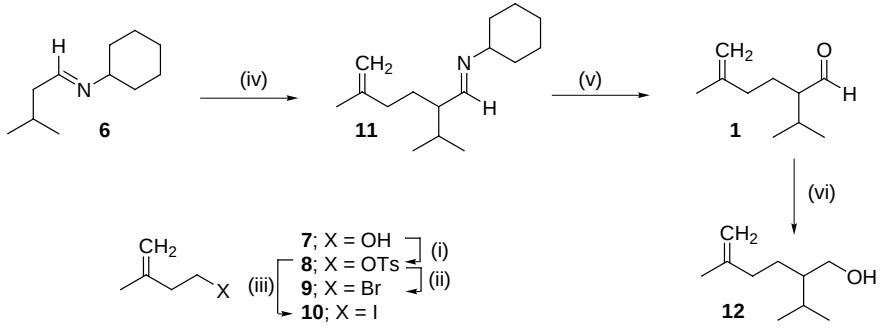
RESULTS AND DISCUSSION

Synthesis of (±)-2-Isopropyl-2-methylhex-5-enal (1)

(±)-2-Isopropyl-2-methylhex-5-enal (**1**) was synthesised *via* alkylation of *N*-(3-methylbutylidene)cyclohexylamine (**6**), itself prepared by condensation of neat 3-methylbutenal and cyclohexylamine in the presence of sodium hydroxide. Previous work had shown 4-bromo-2-methylbut-1-ene (**9**) to be an effective electrophile for alkylation of the dianion of isovaleric acid[18]. Bromide **9** was readily prepared from 3-methylbut-3-en-1-ol (**7**) *via*

tosylate **8**. Attempted alkylation of imine **6** with bromide **7** in THF using lithium diisopropylamide (LDA) at –20 °C gave approximately 25% of the desired product as judged by ^{1}H NMR. The remainder of the material was recovered imine **6**. Changing the solvent to 1,2-dimethoxyethane or employing *N*,*N*′-propyleneurea as a co-solvent gave no improvement in yield. Deuterium quench experiments (methanol-d_4) showed that essentially complete deprotonation of imine **6** had occurred at –40 °C. Moreover, alkylation with 1-bromobutane, a saturated electrophile, in THF at –20 °C gave 83% of alkylated adduct. These experiments show that alkylation and elimination are competing processes, with elimination of hydrogen bromide made more facile by the presence of a homoallylic double bond.

As an alternative alkylating agent, 4-iodo-2-methylbut-1-ene (**10**), also prepared from 3-methylbut-3-en-1-ol (**7**), was employed. Alkylation of imine **6** with 1.3 equivalents of LDA and 1.5 equivalents of iodide **10** in THF resulted in 75% conversion to (±)-*N*-(2-isopropyl-5-methyl hex-5-enylidene)cyclohexylamine (**11**) as a mixture of *Z* and *E* geometrical isomers. Imine **11** was purified by fractional distillation under reduced pressure (b.p. 90–92 °C) and the thermodynamically favoured *E* isomer was obtained exclusively as a colourless liquid. The aldehyde functionality was unmasked by vigorous stirring of imine **11** in a hexane–aqueous acetic acid mixture[19] for 2 h to give (±)-2-isopropyl-2-methylhex-5-enal (**1**) as an analytically pure oil after chromatography. Alcohol **12** was obtained as a colourless oil on $NaBH_4$ reduction (Scheme 2).



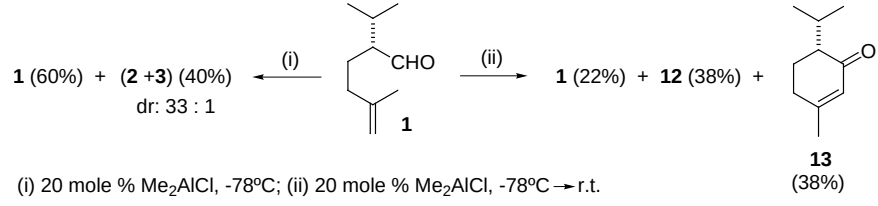
(i) TsCl, Py, 85%; (ii) LiBr, DMF, 76%; (iii) NaI, acetone, reflux, 72%; (iv) LDA, THF, **9** or **10**, 62%; (v) AcOH, H_2O, hexane, 74%; (vi) $NaBH_4$, EtOH, 100%

SCHEME 2

Lewis Acid Catalysed Cyclisations

Many of the successful applications of Lewis acid promotion to ene reaction chemistry involve aluminium complexes. The generation of strong acids in some Lewis chloro-acid-mediated ene reactions (*e.g.* BCl_3, $TiCl_4$) creates side reactions which are circumvented by the stoichiometric use of alkylaluminiums. They act not only as Lewis acids but as Brønsted bases[20]. Alcohol–alkylaluminium complexes formed in carbonyl ene reactions decompose rapidly and irreversibly to generate alkanes (methane in the case of dimethylaluminium chloride) and non-basic aluminium alkoxides that are stable until work-up.

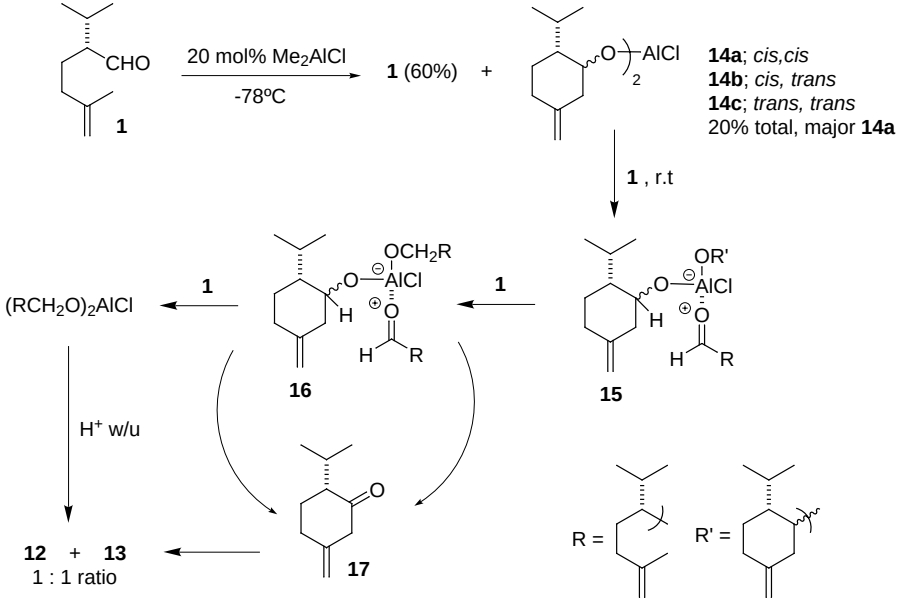
The same feature that allows alkylaluminium reagents to be used so successfully in ene reactions limits their use to stoichiometric amounts, however. When (±)-**1** was treated with 20 mole % of dimethylaluminium chloride at –78 °C, the reaction proceeded to approximately 40% completion. Analysis of the crude reaction mixture by ^{1}H NMR after acidic work-up showed that the *cis* and *trans* cycloadducts **2** and **3** were formed in the same diastereomeric ratio (33 : 1) as when a stoichiometric amount of Lewis acid was used. If the mixture was allowed to warm from –78 °C to room temperature for 24 h a 1 : 1 mixture of (±)-**12** (38%) and (±)-6-isopropyl-3-methylcyclohex-2-en-1-one (**13**) (38%) was obtained along with a substantial quantity of unreacted (±)-**1** (22%) and a trace of *cis* cycloadduct **2** (2%) (Scheme 3). Here and elsewhere, dilute sulfuric acid was used as the proton source in the work-up procedures described here, resulting in water-soluble aluminium complexes, an improvement on the oft-described use of dilute hydrochloric acid.



SCHEME 3

Alcohol **12** and α,β-unsaturated ketone **13** result from a Meerwein–Pondorff–Verley (MPV) type reaction[21] whereby the metal centre in the aluminium bis(alkoxides) **14a**–**14c** generated from the ene cyclisation are sufficiently deactivated by the resonance stabilisation conferred from the oxygen atoms to prevent further ene cyclisation at –78 °C. At elevated tem-

peratures aldehyde **1** is instead preferentially reduced to alcohol **12** with concomitant oxidation of the bound alkoxides *via* tetrahedral aluminium complexes **15** and **16**. None of the expected β,γ-unsaturated ketone **17** was observed and the double bond presumably shifts into conjugation with the ketone under the reaction conditions (Scheme 4).



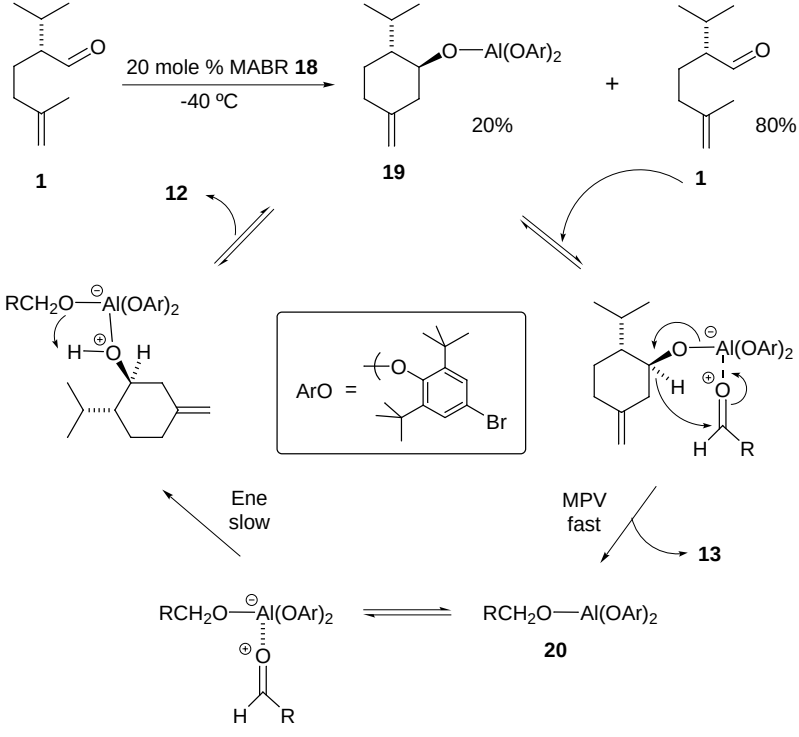
SCHEME 4

The relative ratios of the products indicate that little or no ene cyclisation occurs once the chloroaluminium bis(alkoxide) species **14a**–**14c** have been formed and that the cyclohexenol adducts **2** and **3** act as MPV reductants. MPV type processes are reversible and do not usually proceed to completion without selective removal of one of the products or by the use of a large excess of reductant (or both). In this case, the driving force where the MPV equilibrium essentially lies completely to one side is the formation of an α,β-unsaturated ketone **13** and a primary alcohol **12** from secondary alcohols **2** or **3** and aldehyde **1** respectively.

Confirmation that the aluminium alkoxide **14a** was behaving as an *in situ* MPV reductant was demonstrated by its direct formation from two equivalents of *cis*-cyclohexenol **2** and dimethylaluminium chloride (with concomitant methane generation) and allowing it to react with 5 equiva-

lents of (±)-aldehyde **1** at room temperature for 16 h. A similar experiment was performed with the aluminium alkoxide **14c** generated from *trans*-cycloadduct **3**. In both cases a 1 : 1 mixture of alcohol **12** (29%) and α,β-unsaturated ketone **13** (29%) was produced along with the corresponding amount of unreduced aldehyde **1** (42%). Only traces of unreacted cyclohexenols **2** and **3** were observed in the ^{1}H NMR spectra.

When aldehyde **1** was treated with a catalytic quantity (20 mole %) of methylaluminium bis(4-bromo-2,6-di-*tert*-butylphenoxide) (**18**) (MABR) an analogous MPV process occurred and the usual 1 : 1 mixture of alcohol **12** and α,β-unsaturated ketone **13** was obtained (Scheme 5). After five days no aldehyde **1** remained in the reaction mixture indicating that the alkoxyaluminium diphenoxide **19** so produced acts as a fast MPV reductant for unreacted aldehyde **1** generating alkoxide **20** which in turn is capable of catalysing the ene cyclisation in a rate limiting sequence. The electron-withdrawing nature of the two 4-bromo-2,6-di-*tert*-butylphenoxide ligands

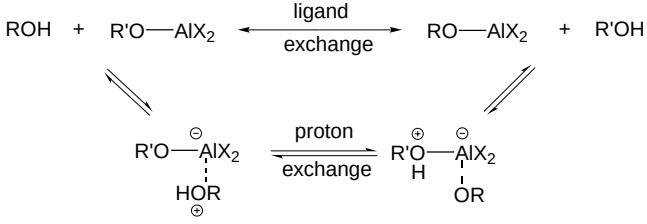


SCHEME 5

in alkoxide **20** is apparently sufficient to allow further, albeit slow, ene cyclisation.

Hence MPV type reactions occur when an aluminium reagent cannot catalyse the ene cyclisation of (±)-**1** without the intervention of alkoxide intermediates. This permits a useful probe for the catalytic effectiveness of aluminium complexes. If an aluminium based Lewis acid maintains its structural integrity, then MPV-type products will not be observed and the Lewis acid can be assumed to be a true catalyst.

Lacking α-hydrogen atoms, 4-bromo-2,6-di-*tert*-butylphenoxide is effectively a spectator ligand in the proposed MPV processes occurring when aldehyde **1** is treated with a catalytic amount of MABR **18**. The various aromatic and aliphatic alcohols in solution compete for the aluminium binding sites *via* fast proton exchange and dissociation of the protonated species from the metal centre (Scheme 6).



SCHEME 6

The relative pK_a values of phenols (≈10) and aliphatic alcohols (≈17) should ensure that the two aromatic ligands in MABR remain bound to the aluminium metal centre throughout the reaction regardless of the chemistry occurring at the other co-ordination sites. This would enable phenols to act as ligands on aluminium for catalytic turnover of the ene cyclisation provided that alkoxide intermediates like **19** are prevented from forming. If the methyl group in MABR was exchanged for a group that does not act as a Brønsted base (*e.g.*, chloride) then a catalytic reagent could be envisaged. Thus dimethylaluminium chloride was treated with 2 equivalents of 4-bromo-2,6-di-*tert*-butylphenol at room temperature in an attempt to generate a catalytic version of MABR. The resulting Lewis acid chloroaluminium bis(4-bromo-2,6-di-*tert*-butylphenoxide) (**21**) (CABR) was treated with 5 equivalents of (±)-**1** in dichloromethane at 0 °C.

The CABR reagent **21** was found to act as a catalyst: aldehyde **1** was rapidly (<0.5 h) converted into cycloadducts **2** and **3** with only trace amounts of MPV products (<5%) and small amounts of unidentified side products

(<5%). However, the diastereomeric ratio of cycloadducts **2** and **3** resulting from the catalytic use of CABR was found to be different from that of MABR (at a stoichiometric level) and the *cis*-cycloadduct **2** was produced as the major diastereomer in 70% de. This was unexpected and several control experiments were performed in an attempt to provide a rationale (Table I). The experiments performed with MABR at catalytic and stoichiometric levels are included in the table for comparative purposes.

It was found that the use of CABR at a stoichiometric level resulted in the same diastereoselectivity as at a catalytic level. When the catalytic (entry 6, Table I) and stoichiometric (entry 7, Table I) reactions with CABR were performed at –40 °C (see the literature conditions for MABR, entry 1, Table I), the reaction rates were slower (as expected) but little effect on the diastereoselectivities was observed. Indeed it was found that MABR could be used with little loss in diastereoselectivity in stoichiometric amounts at 0 °C and the reaction was complete within 0.5 h (entry 3, Table I).

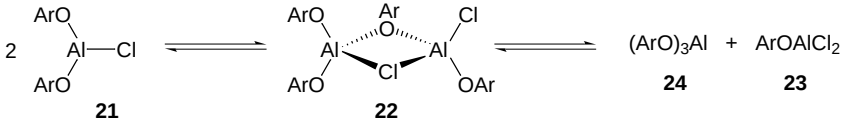
These experiments do not provide any clear insight into the dramatic loss of *trans*-cycloadduct **3** diastereoselectivity when CABR mediates the ene cyclisation of aldehyde **1** rather than MABR. The lack of significant quantities of MPV products suggests that alcoholysis of the aluminium–chlorine bond is not a major process. However, it seems unlikely that the catalyti-

TABLE I
Diastereomeric ratios (**2** : **3**) of products of cyclisation of aldehyde **1** depending on the Lewis acid used

Entry	Lewis acid	Mole %	*T*, °C[a]	Reaction time, h	**2** : **3**[b]
1	**18**	200	–40	2	5:95
2	**18**	20	–40–0	96	MPV
3	**18**	200	0	<0.5	7:93
4	**21**	20	0	<0.5	81:19[c]
5	**21**	200	0	<0.5	82:18[c]
6	**21**	20	–40	6[d]	77:23[c]
7	**21**	200	–40	1	79:21[c]

[a] All experiments performed in dichloromethane with 0.5 mmol aldehyde **1.** [b] As judged by integration of the ^{1}H NMR resonances at δ_H 4.12 and 3.51 ppm for the cycloadducts **2** and **3** respectively in the ^{1}H NMR spectrum of the crude reaction mixture. [c] Traces of MPV-type products were observed. [d] Approximately 85% complete after this time.

cally active species has a related structure to that of MABR. On this basis it is tentatively suggested that a disproportionation process *via* a dimeric species of the type **22** occurs to some extent generating the relatively powerful but much less bulky Lewis acid dichloroaluminium 4-bromo-2,6-di-*tert*-butylphenoxide (**23**) that is responsible for catalysis. The other product of this disproportionation reaction, aluminium tris(4-bromo-2,6-di-*tert*-butylphenoxide) (**24**) would not be expected to act readily as a catalyst both on steric and electronic grounds (Scheme 7).



ArO = 4-bromo-2,6-di-*tert*-butylphenoxide

SCHEME 7

SUMMARY AND CONCLUSIONS

The application of ene cyclisation chemistry to unsaturated aldehydes, following Yamamoto's work, is successful at the stoichiometric level when aluminium-based Lewis acids are employed. In earlier work we had employed deuterium labelled reactants in order to define the stereochemical course of cyclisation, and proposed a general model to account for results described in the literature. Here the attempts made to move from stoichiometric chemistry to catalysis are described; these proved to be successful, with one important proviso. Part of the value of the Yamamoto procedure is that the product can be formed with either relative configuration at the two adjacent stereogenic centres. This is a consequence of the fact that the six-membered ring transition-state for cyclisation can be chair-like, with a small Lewis acid giving **2** or boat-like with a bulky one (MABR) giving **3**. In turn this provides a sensitive test for the nature of the catalyst, which is revealing here. Although significant turnover is observed in several cases, it is associated with low steric demands in the catalyst. This is even true in the case where CABR is the ligand, and indicates that the true catalyst is part-dissociated. This will clearly provide a limitation in attempts to develop aluminium-based Lewis acids for asymmetric catalysis of the ene reaction.

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REFERENCES AND NOTES

1. Many aldol-type reactions of vinyl ethers and ketene acetals may follow an ene-pathway. In excluding these from the discussion we follow the inclinations of the original authors with regard to classification see, *e.g.* Berrisford D. J., Bolm C.: *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 1717.
2. a) Mikami K., Shimizu M.: *Chem. Rev.* **1992**, *92*, 1021; b) Mikami K., Terada M., Narisawa S., Nakai T.: *Synlett* **1992**, 255; c) Mikami K.: *Pure Appl. Chem.* **1996**, *68*, 639; and earlier papers.
3. a) Mikami K., Motoyama Y., Terada M.: *Inorg. Chim. Acta* **1994**, *222*, 71; b) Terada M., Matsukawa S., Mikami K.: *J. Chem. Soc., Chem. Commun.* **1993**, 327; c) Terada M., Mikami K.: *J. Chem. Soc., Chem. Commun.* **1994**, 833; d) Terada M., Mikami K.: *J. Chem. Soc., Chem. Commun.* **1995**, 2391; e) Mikami K., Terada M., Narisawa S., Nakai T.: *Org. Synth.* **1993**, *71*, 14; f) Terada M., Sayo N., Mikami K.: *Synlett* **1995**, 411; g) Mikami K., Matsukawa S.: *Tetrahedron Lett.* **1994**, *35*, 3133; h) Kitamoto D., Imma H., Nakai T.: *Tetrahedron Lett.* **1995**, *36*, 1861; i) Mikami K., Yoshida A., Matsumoto Y.: *Tetrahedron Lett.* **1996**, *37*, 8515.
4. a) Mikami K., Yajima T., Terada M., Uchimaru T.: *Tetrahedron Lett.* **1993**, *34*, 7591; b) Mikami K., Yajima T., Siree N., Terada M., Suzuki Y., Kobayashi I.: *Synlett* **1996**, 837; c) Mikami K., Yajima T., Takasaki T., Matsukawa S., Terada M., Uchimaru T., Maruta M.: *Tetrahedron* **1996**, *52*, 85; d) Mikami K., Yajima T., Siree N., Terada M., Suzuki Y., Takanishi Y., Takezoe H.: *Synlett* **1999**, 1895.
5. Mikami K., Yoshida A.: *Synlett* **1995**, 29.
6. a) Evans D. A., Johnson J. S., Burgey C. S., Campos K. R.: *Tetrahedron Lett.* **1999**, *40*, 2879; b) Evans D. A., Burgey C. S., Paras N. A., Vojkovsky T., Tregay S. W.: *J. Am. Chem. Soc.* **1998**, *120*, 5824; c) Johannsen M., Joergensen K. A.: *J. Org. Chem.* **1995**, *60*, 5757.
7. Corey E. J., Barnes-Seeman D., Lee T. W., Goodman S. N.: *Tetrahedron Lett.* **1997**, *38*, 6513.
8. a) Maruoka K., Ooi T., Yamamoto H.: *J. Am. Chem. Soc.* **1990**, *112*, 9011; b) Ooi T., Maruoka K., Yamamoto Y.: *Tetrahedron* **1994**, *50*, 6505; see also c) Marshall J. A., Andersen M. W.: *J. Org. Chem.* **1992**, *57*, 5851.
9. Mikami K., Terada M., Sawa E., Nakai T.: *Tetrahedron Lett.* **1991**, *32*, 6571.
10. Mikami K., Koizumi Y., Osawa A., Terada M., Takayama H., Nakagawa K., Okano T.: *Synlett* **1999**, 1899.
11. Kočovský P., Ahmed G., Srogl J., Malkov A. V., Steele J.: *J. Org. Chem.* **1999**, *64*, 2765.
12. Braddock D. C., Hii K. K., Brown J. M.: *Angew. Chem., Int. Ed. Engl.* **1998**, *37*, 1720.
13. Braddock D. C., Brown J. M.: *J. Chem. Soc., Perkin Trans. 1*, submitted, April 2000.
14. Perrin D. D., Armarego W. L. F., Perrin D. R.: *Purification of Laboratory Chemicals*. Pergamon, Oxford 1988.
15. Kofron W. G., Backlawski L. M.: *J. Org. Chem.* **1976**, *41*, 1879.
16. Maitlin A. R., Wolff S., Agosta W. C.: *J. Am. Chem. Soc.* **1986**, *108*, 3393.
17. a) Burbott A. J., Hennessey J. P., Jr., Johnson W. C., Jr., Loomis W. D.: *Phytochemistry* **1983**, *22*, 2227; b) Le Maux P., Massonneau V., Simonneaux G.: *Tetrahedron* **1988**, *44*, 1409.

18. Creger P. L.: *J. Am. Chem. Soc.* **1970**, *92*, 1397.
19. House H. E., Liang W. C., Weeks P. D.: *J. Org. Chem.* **1974**, *39*, 3102.
20. Snider B. B.: *Acc. Chem. Res.* **1980**, *13*, 426; and references therein.
21. Wilds A. L.: *Org. React.* **1974**, *2*, 178.