

Successive Carbon–Carbon Bond Formation by Sequential Generation of Radical and Anionic Species with Manganese and Catalytic Amounts of $PbCl_2$ and Me_3SiCl

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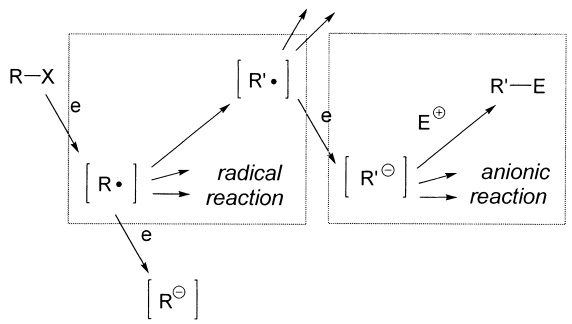
(Received July 24, 2002)

Three-component coupling reactions of iodoalkanes, α,β-unsaturated nitriles (or esters), and carbonyl compounds are achieved in good to excellent yields with a moderate reducing system derived from manganese metal and a catalytic amount of $PbCl_2$ and Me_3SiCl. Although the role of $PbCl_2$ is unclear, addition of a catalytic amount of the salt is essential for reducing the iodoalkane. The reaction proceeds with primary, secondary, and tertiary iodoalkanes. Both acrylonitrile and acrylic esters can be employed as activated olefins, while the reaction with an alkyl vinyl ketone gives a complex mixture. Ketones and aldehydes can be used as the third component and the diastereoselectivity of the anionic addition is approximately 1:1–2:1 ratio. By using the heterogenerative process, i.e., successive 1,4-addition by radical and anionic internal addition, cyclopropanation of electron-deficient olefins is achieved with chloroiodomethane, manganese, $PbCl_2$, Me_3SiCl, and DMAP.

Effectiveness is important for organic synthesis. The more bonds that can be formed in a single step, the fewer the steps that will be required in a synthetic scheme. Such expressions as domino, tandem, and cascade are used for the sequential reactions in one-pot, and Wender classified the reactions into two categories: homogenerative and heterogenerative processes.[1] Because intermolecular sequential reactions cannot use the advantage of an entropy factor, which intramolecular reactions have, it is difficult to perform intermolecular carbon–carbon bond formation in a pair-selective manner using homogenerative processes. In contrast, a heterogenerative process in which two (or more) reactive species participate can discriminate the corresponding reaction-partners more easily, and is usually employed for intermolecular cases. Carbanion and radical chemistry represent integral parts of organic synthesis, and the reactivities of the two intermediates are sometimes complementary. Therefore, sequential utilization of the two offers untapped potential for building more complex molecules effectively (Scheme 1).[2,3]

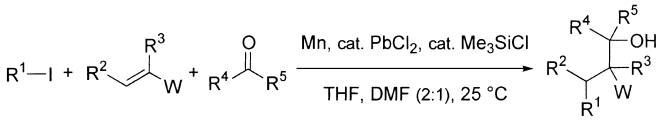


Scheme 1. Sequential utilization of a radical and anionic species.

Alkyl radicals are usually prepared either by chain methods, homolytic cleavage of covalent bonds, or by nonchain methods based on redox reactions. One of the latter accesses radicals by reduction of alkyl halides (R–X) with reducing agents; however, the method is not so popular because further reduction of the initial radicals (R•) leading to alkyl anions (R^-) normally proceeds faster than the first radical formation under the reduction conditions.[3] Although intramolecular radical cyclization before anionic reactions has been observed in several cases,[3a,4] there are few examples of the intermolecular version due to the above restriction.[5,6] Two requirements exist for a suitable reducing agent to connect the two reactions: (1) The initial radical (R•) is not easily reduced to R^- and has sufficient lifetime to undergo an intermolecular reaction. (2) The final radical (R′•) is easily subjected by one-electron reduction to R'^-. Therefore, the desired reductant should be weak enough to be able to discriminate between the two radicals R• and R′•. With these considerations in mind, a novel manganese-lead reducing agent was utilized, and the above concept was realized as a three-component coupling reaction and cyclopropanation of electron deficient olefins.

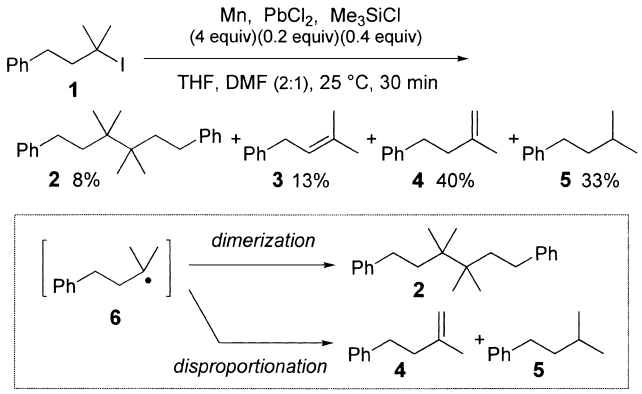
Although manganese metal (Mn(II)/Mn(0), $E^0 = -1.185$) has stronger reduction potential than zinc (Zn(II)/Zn(0), $E^0 = -0.762$), its powder[7] is less reactive toward organic compounds than zinc powder due to a tight layer of manganese oxide on its surface. Recently, it was found that such metal oxide is effectively removed by treatment with Me_3SiCl;[8,9] and moreover, the manganese metal is especially activated by addition of a catalytic amount of $PbCl_2$.[8] We employed this activated manganese in the following experiments.

Table 1. Three-Component Coupling of Iodoalkanes, Electron-Deficient Olefins and Carbonyl Compounds[a)]

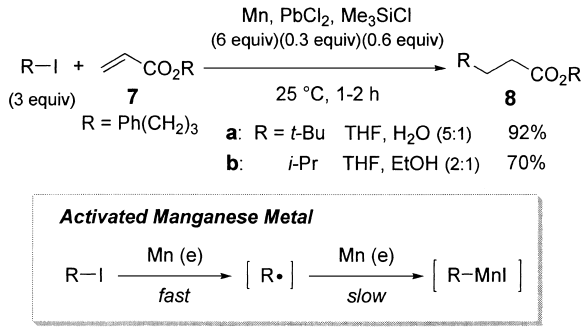


Run	R^1	R^2	R^3	W	R^4	R^5	Time/h	Yield[b)]/%	d.r.[c)]
1	*i*-Pr	H	H	CN	–$(CH_2)_5$–		0.5	86	—
2					Ph	H	0.5	96	57/43
3					Et	H	1	85[d,e)]	68/32
4		H	H	CO_2Me	–$(CH_2)_5$–		0.5	83	—
5					Ph	H	0.5	81	41/59[f)]
6					Et	H	1	77[d,e)]	51/49[f)]
7		Me	H	CN	Ph	H	6	68[e)]	—[g)]
8		H	Me	CN	Ph	H	0.5	67	52/48
9	*n*-Pr	H	H	CN	Ph	H	6	67[e)]	55/45
10		H	H	CO_2Me	–$(CH_2)_5$–		4	61[e)]	—
11	*t*-Bu	H	H	CN	Ph	H	0.5	86	59/41

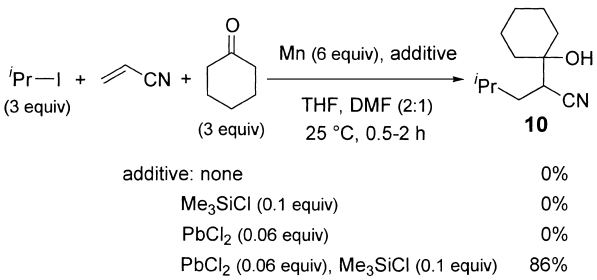
a) Reaction was conducted on a 2.0 mmol scale. An iodoalkane (3.0 mol), a carbonyl compound (3.0 mol), Mn (6.0 mol), $PbCl_2$ (0.06 mol), and Me_3SiCl (0.10 mol) were used per mol of an activated olefin. b) Isolated yields. c) Diastereomer ratios were determined by isolation, GLPC or NMR. d) An aldehyde (1.2 mol) was used per mol of an electron-deficient olefin. e) $PbCl_2$ (0.3 mol) was used per mol of an olefin. f) *anti*/*syn* ratio. g) A mixture of four isomers of undetermined structures.



Scheme 2.



Scheme 3.



Scheme 4.

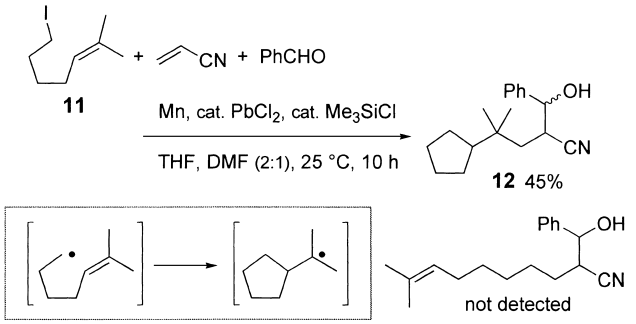
Results and Discussion

Three-Component Coupling Reactions of Iodoalkanes, Electron-Deficient Olefins, and Carbonyl Compounds.[10] Treatment of the tertiary iodoalkane **1** with the activated manganese metal in a mixed solvent of THF and DMF afforded four compounds **2**-**5** (Scheme 2). The result suggests the formation of an alkyl radical by reduction of the iodide with the manganese system, as the dimer **2** could be produced by homocoupling of the radical **6**, and **4** and **5** could be produced by disproportionation of **6**.

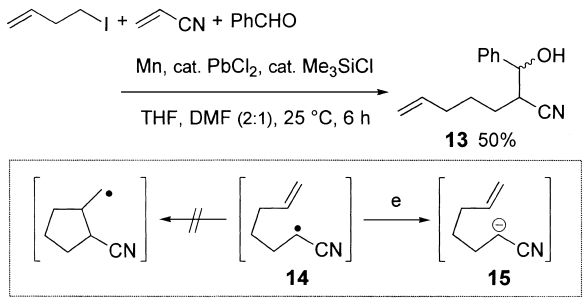
In order to examine the nature of the manganese-generated alkyl radicals, intermolecular 1,4-addition of the radicals to α,β-unsaturated ester **7** under protic conditions was conducted, and it was found that 1,4-adducts **8** were obtained in excellent yields (Scheme 3).[11] It is likely, therefore, that the second one-electron reduction leading to an alkylmanganese compound is slower than the first reduction with this manganese system.

When the reaction was conducted in an aprotic solvent, the produced anionic species could be trapped with a carbonyl compound under mild conditions (Scheme 4).[12] Although the role of $PbCl_2$ is unclear, addition of a catalytic amount of the salt was essential for reducing the iodoalkane. Addition of Et_2AlCl or anhydrous hydrochloric acid in place of Me_3SiCl was also effective in promoting the reaction.

The results of three-component coupling of iodoalkanes, activated olefins, and carbonyl compounds are shown in Table 1. Three mol of iodoalkanes and of carbonyl compounds were



Scheme 5.



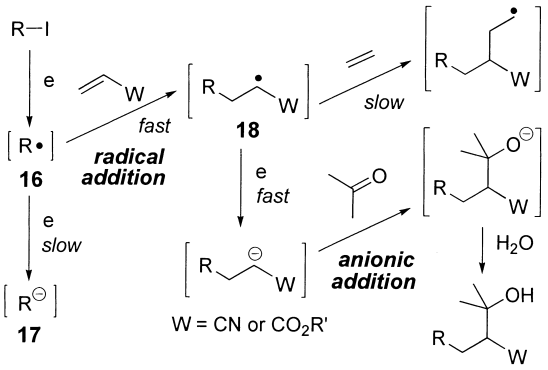
Scheme 6.

used per mole of olefins. The reaction proceeded with primary, secondary, and tertiary iodoalkanes. In the case of primary iodide, the amount of $PbCl_2$ was increased from 1 to 5 mol% of manganese to accelerate the reduction of the iodide (Table 1, runs 9 and 10). Both acrylonitrile and acrylic esters could be employed as activated olefins, while the reaction with an alkyl vinyl ketone gave a complex mixture. A substituent at the β-position of the electron-deficient olefin decreased the reactivity of the olefin, and the reaction also required 5 mol% of $PbCl_2$ (run 7). Ketones and aldehydes could be used as the third component, and the diastereoselectivity of the anionic addition was approximately 1:1–2:1 ratio.

When 7-iodo-2-methyl-2-heptene (**11**) was used as an iodoalkane, intramolecular radical cyclization occurred before intermolecular addition to acrylonitrile (Scheme 5). No three-component coupling product without the cyclization, however, was detected.

Hydroxynitrile **13** was obtained in 50% yield in the case of 4-iodo-1-butene (Scheme 6), although no coupling product was obtained from further cyclization. The result suggests that the second one-electron reduction of radical **14** to a nitrile anion **15** proceeds very quickly.

Consequently, the three-component coupling is realized by a subtle balance of the reaction rates (Scheme 7). The reduction rate of an alkyl radical **16** to an alkyl anion **17** is slower than 1,4-addition of the radical to an electron-deficient olefin. However, one-electron transfer to the resulting radical **18** having an electron-withdrawing group proceeds faster than addition to a different unsaturated bond. Sequential generation and utilization of a radical and anionic species, therefore, are the essential factors in the coupling reaction of iodoalkanes, α,β-unsaturated nitriles (or esters), and ketones (or aldehydes), and the protocol itself can provide a new access to similar coupling



Scheme 7. A Possible mechanism for the three-component coupling.

products that are difficult to obtain with organocuprates in one-pot reactions due to their complex nature.[13]

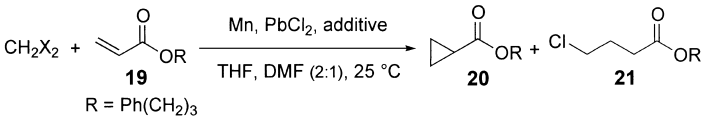
In 1978, Shono and Nishiguchi reported a similar three-component coupling of iodoalkanes, α,β-unsaturated nitriles (or esters), and carbonyl compounds using zinc metal.[14] Although the mechanism of the zinc-mediated coupling reaction has not yet been clarified, the reaction could also be a similar heterogenerative process of a radical and anionic species.

Cyclopropanation of Electron-Deficient Olefins. Simmons-Smith reaction, the carbenoid approach, is usually employed for cyclopropanation of olefinic double bonds;[15,16] however, the reaction with electron-deficient olefins proceeds slowly and sometimes results in recovery of the olefins.[15b–d] The other pathway to cyclopropanation of electron-deficient olefins is a sequential 1,4-addition-substitution reaction.[17,18] We describe here a manganese-mediated cyclopropanation via the latter approach, where an alkyl radical plays the key role for the first 1,4-addition step.[19]

One-electron reduction of iodoalkanes with the activated manganese metal proceeds smoothly to give the corresponding alkyl radicals, which add to α,β-unsaturated esters in a 1,4-fashion.[10] Successive one-electron reduction affords ester enolates, which add to carbonyl compounds to give aldol-type adducts.[6] Thus, we examined intramolecular trapping of the formed enolates with alkyl halides at the γ-position of the esters, which will provide cyclopropyl compounds.

As a methylene radical-cation synthon, *gem*-dihalomethanes were used. Treatment of 3-phenylpropyl acrylate (**19**) with diiodomethane, manganese, $PbCl_2$, and Me_3SiCl in THF produced the desired cyclopropanecarboxylic ester **20** in 3% yield after being stirred for 24 h; The acrylate **19** was recovered in 88% yield (Table 2, run 1). Reactions with dibromo- and dichloromethane did not proceed, either, and in each case, **19** was recovered in almost quantitative yields (runs 2 and 3). Addition of LiI to the reaction with dibromomethane resulted in formation of **20** in 7% yield (run 4), which suggests that one of the halogen should be an easily-reduced iodine atom. Therefore, the ester **19** was treated with a combination of chloroiodomethane and the activated manganese, and cyclopropanecarboxylic ester **20** was produced in 62% yield, along with 4-chlorobutanoate **21**, the 1,4-adduct in 16% yield (run 5). The yield of the ester **20** was improved by addition of 0.15 equiv. of 4-(dimethylamino)pyridine (DMAP) as an activator of

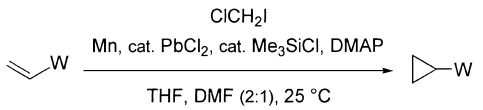
Table 2. Cyclopropanation of 3-Phenylpropyl Acrylate with Dihalomethane and Activated Manganese[a)]



Run	CH_2X_2	Me_3SiCl/equiv	Additive, equiv	Time/h	Yield/%[b)]		Recov./%[b)]
					20	**21**	**19**
1	CH_2I_2	0.15		24	3	0	88
2	CH_2Cl_2	0.15		24	0	0	95
3	CH_2Br_2	0.15		24	0	0	92
4		0.15	LiI, 3.0	24	7	0	66
5	CH_2ClI	0.15		0.3	62	16	0
6		0.15	DMAP, 0.15	0.3	74	12	0
7		3.0		0.5	70	20	0
8		3.0	DMAP, 3.0	0.5	4	66	0

a) Reactions were conducted on a 1.0 mmol scale. Dihalomethane (3.0 mol), Mn (8.5 mol), and $PbCl_2$ (0.085 mol) were employed per mol of the acrylate. b) Isolated yields.

Table 3. Cyclopropanation of Electron-Deficient Olefins with Chloroiodomethane and Activated Manganese[a)]

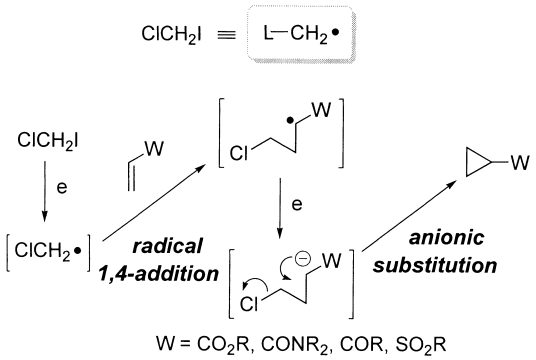


Run	W	Time/h	Yield/%[b)]
1	Ph, **22**	0.3	61, 62[c)]
2	O, Ph, **19**	0.3	74, 81[c)]
3	O, Ph	72	33[d)]
4	N, Me, Ph, **23**	0.5	63, 67[c)]
5	SO_2Ph	0.5	59
6	Ph	24	0[e)]

a) Reactions were conducted on a 1.0 mmol scale. Chloroiodo-methane (3.0 mol), Mn (8.5 mol), $PbCl_2$ (0.085 mol), Me_3SiCl (0.15 mol) and DMAP (0.15 mol) were employed per mol of an olefin. b) Isolated yields. c) The amounts of Mn and $PbCl_2$ were increased to 18 and 0.18 mmol, respectively. d) *anti*/*syn* = 13/1. e) Recovery: 97%.

Me_3SiCl (run 6).[20] Addition of 3 equiv of both Me_3SiCl and DMAP, however, resulted in formation of **21** (run 8), probably due to smooth trapping of the formed enolate as a ketene silyl acetal before workup.

The cyclopropanation with chloroiodomethane and activated manganese also proceeded with an α,β-unsaturated ketone and an amide (Table 3, runs 1 and 4).[16] The yield of **20** was improved to 81% when the amount of manganese metal was increased to 18 equiv of the ester **19**; however, only slight improvements were observed in the case of the ketone **22** and amide **23**. It is worth noting that the protocol could also be applied to a vinyl sulfone with which the Simmons-Smith reaction does not work well (run 5).[15c] The substituent at the β-position of α,β-unsaturated ester retarded the reaction considerably, as is usually observed in 1,4-addition mediated by an alkyl radical (run 3). In contrast to the Simmons-Smith reaction, 2-methyl-5-phenyl-2-pentene, the trisubstituted olefin, was recovered almost quantitatively (run 6).



Scheme 8. A Possible mechanism for cyclopropanation.

A possible mechanism for the cyclopropanation is shown in Scheme 8: 1) One-electron reduction of chloroiodomethane to a chloromethyl radical by activated manganese metal with $PbCl_2$ and Me_3SiCl; 2) 1,4-Addition of the radical to an electron-deficient olefin; 3) One-electron reduction of the resulting radical having an electron-withdrawing group; 4) Anionic intramolecular substitution leading to a cyclopropane compound. Because of the mild reducing power of the activated manganese metal, further reduction of chloromethyl radical to its anion proceeds slower than 1,4-addition of the radical to an electron-deficient olefin.[10,21] In contrast, the second one-electron reduction proceeds smoothly due to the electron-withdrawing group. Therefore, the cyclopropanation is also realized via successive generation and utilization of a radical and anionic species.

In summary, the mild reductant system, manganese metal and a catalytic amount of $PbCl_2$ and Me_3SiCl, can discriminate

between iodoalkanes, alkyl radicals, and radicals at the α position of esters. In the presence of the manganese reductant, the alkyl radical is so long-lived that it can undergo intermolecular addition to an α,β-unsaturated ester. Rapid one-electron reduction of the formed radical at the α position of the ester results in a manganese enolate, which adds to a carbonyl compound to afford a three-component coupling product. When chloroiodomethane is used as the iodoalkane, an intramolecular reaction of the manganese enolate with a halogen at the 4 position occurs to give a cyclopropyl compound.

Experimental

General. Unless otherwise noted, materials were obtained from commercial suppliers and were used without further purification. Manganese powder was purchased from either Rare Metallic Co. (99% purity, –80 mesh) or Kojundo Chemical Laboratory (99.9% purity, –50 mesh). $PbCl_2$ (99.999% purity) was purchased from Rare Metallic Co., Japan. Tetrahydrofuran (THF) was distilled from sodium/benzophenone just before use. *N*,*N*-Dimethylformamide (DMF) was distilled from calcium hydride under reduced pressure with nitrogen bubbling. Distillations of small amounts of products were performed with a Büchi Kugelrohr, and boiling points are indicated by an air bath temperature without correction. FT-IR spectra were obtained on a Bio-Rad FTS-7 or a Nicolet Protégé 460 spectrometer. ^{1}H and ^{13}C NMR spectra were determined with a Varian Gemini-200 or a JEOL JNM-LA400 instrument. Chemical shifts are expressed in ppm downfield from internal tetramethylsilane using the δ scale. Low and high resolution of EI mass spectra were obtained with a capillary GC interfaced JEOL JMS-SX102A. Column chromatography was done with silica gel (230–400 mesh).

General Procedure for Three-Component Addition Reactions. To a mixture of manganese powder (0.66 g, 12 mmol) and $PbCl_2$ (34 mg, 0.12 mmol) in THF (8 mL) was added Me_3SiCl (26 μL, 0.20 mmol) at 25 °C, and the mixture was stirred at 25 °C for 30 min. A solution of an electron-deficient olefin (2.0 mmol) and a carbonyl compound (6.0 mmol) in DMF (2 mL) was added to the suspension, and then a solution of an iodoalkane (6.0 mmol) in DMF (2 mL) was added slowly to the mixture at 25 °C, producing an exothermic reaction (ca. 40 °C). After being stirred at 25 °C for an appropriate time as described in Table 1, the reaction was quenched by addition of a few drops of water. The mixture was filtered with Celite using ether (50 mL) as an eluent. Organic extracts were washed with water and dried over $MgSO_4$ and then concentrated. Purification of the crude product by column chromatography on silica gel gave the desired coupling product.

2-(1-Hydroxycyclohexyl)-4-methylpentanenitrile (10).[14] Mp 55–56 °C; bp 92 °C (bath temp, 0.10 Torr); IR (nujol) 3457, 2955, 2245, 1444, 1163, 1140, 985, 908, 845 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.92 (d, J = 6.5 Hz, 3H), 1.00 (d, J = 6.6 Hz, 3H), 1.15–1.93 (m, 14H), 2.59 (dd, J = 12.0, 4.4 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 20.8, 21.2, 21.3, 23.4, 25.2, 26.3, 34.5, 34.7, 42.5, 71.5, 120.7.

2-(1-Hydroxy-1-phenylmethyl)-4-methylpentanenitrile.[14] Two diastereomers were produced in a ratio of **A/B** = 57/43 and could not be separated by column chromatography on silica gel. Bp 112 °C (bath temp, 0.08 Torr); IR (neat) 3450, 3064, 3032, 2958, 2872, 2243, 1456, 1389, 1043, 762, 702 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.86–0.97 (m, 6H), 1.10–2.00 (m, 3H), 2.34 (d, J = 3.3 Hz, 1H(**A**)), 2.42 (d, J = 3.7 Hz, 1H(**B**)), 2.89 (dt, J = 11.2, 5.2 Hz, 1H(**B**)), 3.02 (dt, J = 11.1, 4.8 Hz, 1H(**A**)), 4.7–4.85 (m, 1H), 7.3–7.5 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 21.0, 22.9 (**A**), 23.0 (**B**), 25.9, 36.4, 36.5, 37.5 (**B**), 38.4 (**A**), 39.0 (**B**), 73.5 (**A**), 73.7 (**B**), 120.1, 126.0 (**B**), 126.3 (**A**), 128.3, 128.4, 140.0 (**A**), 140.6 (**B**).

3-Hydroxy-2-isobutylpentanenitrile.[14] Two diastereomers were produced in a ratio of **A/B** = 68/32 and could not be separated by column chromatography on silica gel. bp 70 °C (bath temp, 0.5 Torr); IR (neat) 3447, 2962, 2937, 2875, 2241, 1467, 1370, 1114, 1061, 980 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.90–1.10 (m, 9H), 1.25–1.50 (m, 1H), 1.50–1.95 (m, 5H), 2.60–2.82 (m, 1H), 3.49–3.66 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 9.94, 21.1 (**B**), 21.4 (**A**), 22.9 (**A**), 23.2 (**B**), 26.0 (**A**), 26.2 (**B**), 27.0 (**B**), 28.5 (**A**), 36.6 (**B**), 36.9 (**A**), 37.1 (**B**), 37.7 (**A**), 72.9 (**A**), 73.1 (**B**), 120.2 (**A**), 120.7 (**B**).

Methyl 2-(1-Hydroxycyclohexyl)-4-methylpentanoate. Bp 67 °C (bath temp, 0.08 Torr); IR (neat) 3500, 2935, 2868, 1717, 1438, 1367, 1197, 1169, 982, 665 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.86 (d, J = 1.9 Hz, 3H), 0.91 (d, J = 2.1 Hz, 3H), 1.18–1.82 (m, 14H), 2.51 (dd, J = 11.8, 3.1 Hz, 1H), 3.69 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 21.3, 21.6, 21.8, 23.6, 25.6, 26.5, 34.3, 35.5, 37.1, 51.2, 52.6, 71.6, 176.8. Anal. Calcd for $C_{13}H_{24}O_3$: C, 68.38; H, 10.59%. Found: C, 68.09; H, 10.88%.

***anti*-Methyl 2-(1-Hydroxy-1-phenylmethyl)-4-methylpentanoate.** Mp 69–71 °C (hexane); IR (nujol) 3470, 2953, 2854, 1737, 1453, 1378, 1158, 1046, 767, 704, 665 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.80 (d, J = 2.7 Hz, 3H), 0.83 (d, J = 2.8 Hz, 3H), 1.03 (ddd, J = 13.5, 8.9, 4.3 Hz, 1H), 1.35–1.75 (m, 2H), 2.73 (d, J = 5.6 Hz, 1H), 2.79–2.94 (m, 1H), 3.69 (s, 3H), 4.75 (dd, J = 7.8, 2.2 Hz, 1H), 7.20–7.40 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 21.4, 23.2, 26.0, 38.5, 51.2, 75.9, 126.4, 127.9, 128.5, 142.1, 176.0. Anal. Calcd for $C_{14}H_{20}O_3$: C, 71.16; H, 8.53%. Found: C, 71.00; H, 8.76%.

***syn*-Methyl 2-(1-Hydroxy-1-phenylmethyl)-4-methylpentanoate.** Bp 72 °C (bath temp, 0.08 Torr); IR (neat) 3455, 2956, 2871, 1734, 1437, 1367, 1247, 1195, 1167, 1044, 771, 701 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.79 (d, J = 6.1 Hz, 3H), 0.85 (d, J = 6.3 Hz, 3H), 1.25–1.50 (m, 2H), 1.55–1.80 (m, 1H), 2.75–2.86 (m, 2H), 3.59 (s, 3H), 4.93 (dd, J = 5.4, 2.7 Hz, 1H), 7.20–7.38 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 21.3, 23.4, 26.3, 36.1, 51.3, 51.5, 74.5, 126.0, 127.6, 128.2, 141.5, 175.5. Anal. Calcd for $C_{14}H_{20}O_3$: C, 71.16; H, 8.53%. Found: C, 71.13; H, 8.48%.

***anti*-Methyl 3-Hydroxy-2-isobutylpentanoate.** Bp 48 °C (bath temp, 0.12 Torr); IR (neat) 3430, 2959, 2874, 1737, 1466, 1439, 1369, 1197, 1169, 1108, 981, 666 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.85–0.94 (m, 6H), 0.96 (t, J = 7.8 Hz, 3H), 1.25–1.80 (m, 5H), 2.33 (d, J = 4.6 Hz, 1H), 2.56 (dt, J = 10.9, 3.8 Hz, 1H), 3.62–3.77 (m, 4H); ^{13}C NMR ($CDCl_3$) δ 10.2, 21.6, 23.4, 26.4, 27.1, 35.9, 48.7, 51.6, 73.8, 176.2. Anal. Calcd for $C_{10}H_{20}O_3$: C, 63.80; H, 10.71%. Found: C, 63.51; H, 10.98%.

***syn*-Methyl 3-Hydroxy-2-isobutylpentanoate.** Bp 46 °C (bath temp, 0.13 Torr); IR (neat) 3450, 2958, 2873, 1710, 1471, 1438, 1369, 1197, 1169, 1124, 976 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.87 (d, J = 4.5 Hz, 3H), 0.91 (d, J = 4.6 Hz, 3H), 0.96 (t, J = 7.3 Hz, 3H), 1.22–1.77 (m, 5H), 2.44 (d, J = 8.1 Hz, 1H), 2.55 (dt, J = 9.8, 5.0 Hz, 1H), 3.44–3.62 (m, 1H), 3.69 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 10.0, 21.9, 23.0, 26.2, 28.6, 38.7, 48.5, 51.5, 74.1, 176.3. Anal. Calcd for $C_{10}H_{20}O_3$: C, 63.80; H, 10.71%. Found: C, 63.55; H, 10.95%.

2-(1-Hydroxy-1-phenylmethyl)-3,4-dimethylpentanenitrile.[14] Four diastereomers were produced with undefined structures; they could not be separated by column chromatography on silica gel. bp 114 °C (bath temp, 0.08 Torr); IR (neat) 3448, 2965, 2877, 2243, 1458, 1388, 1267, 1053, 738, 701, 665 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.75–1.30 (m, 9H), 1.55–2.20 (m, 3H), 2.95–

3.10, 4.75–5.03 (m, 1H), 7.20–7.55 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 11.2, 11.8, 12.8, 13.3, 15.2, 15.6, 18.8, 19.5, 20.2, 20.3, 21.4, 21.5, 29.2, 29.6, 31.1, 31.7, 36.5, 36.8, 37.2, 37.7, 43.9, 44.1, 45.4, 46.7, 70.7, 71.7, 72.3, 73.1, 118.8, 119.3, 119.6, 125.6, 126.2, 126.5, 126.8, 126.9, 128.3, 128.4, 128.6, 128.7, 128.8, 139.8, 140.3, 140.9, 141.3.

2-(1-Hydroxy-1-phenylmethyl)-2,4-dimethylpentanenitrile.[14] Two diastereomers were produced in a ratio of 52/48; they could not be separated by column chromatography. bp 117 °C (bath temp, 0.07 Torr); IR (neat) 3458, 2959, 2873, 2238, 1458, 1389, 1267, 1172, 1167, 1056, 768, 703 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.92–1.14 (m, 6H), 1.15–1.55 (m, 1H), 1.19 and 1.40 (s, 3H), 1.75–2.00 (m, 2H), 2.30 and 2.38 (d, J = 3.4 Hz, 1H), 4.56 and 4.59 (d, J = 3.5 Hz, 1H), 7.30–7.50 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 20.2, 20.5, 23.2, 23.3, 24.3, 24.5, 24.9, 25.0, 42.0, 42.4, 43.4, 44.2, 78.0, 78.7, 123.3, 123.4, 127.5, 128.1, 128.5, 128.5, 138.9, 139.0.

2-(1-Hydroxy-1-phenylmethyl)hexanenitrile. Two diastereomers were produced in a ratio of 55/45; they could not be separated by column chromatography. bp 75 °C (bath temp, 0.07 Torr); IR (neat) 3446, 2958, 2931, 2871, 2250, 1663, 1456, 1388, 1098, 1057, 762, 703 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.80–1.96 (m, 3H), 1.20–1.70 (m, 6H), 2.20 and 2.31 (d, J = 3.4 Hz, 1H), 2.75–3.00 (m, 1H), 4.74–4.88 (m, 1H), 7.30–7.50 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 13.6, 13.7, 22.0, 22.1, 27.5, 28.5, 29.1, 29.1, 40.3, 40.9, 73.4, 73.7, 120.1. 120.2, 126.1, 126.4, 128.4, 128.5, 128.5, 128.6, 140.0, 140.4. Anal. Calcd for $C_{13}H_{17}NO$: C, 76.81; H, 8.43; N, 6.89%. Found: C, 76.92; H, 8.59; N, 6.85%.

Methyl 2-(1-Hydroxycyclohexyl)hexanoate. Bp 72 °C (bath temp, 0.07 Torr); IR (neat) 3510, 2934, 2861, 1710, 1435, 1356, 1195, 1170, 982, 926, 852, 665 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.88 (t, J = 7.0 Hz, 3H), 1.10–1.85 (m, 16H), 2.41 (dd, J = 10.9, 4.2 Hz, 1H), 2.72 (s, 1H), 3.71 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 13.6, 21.4, 21.6, 22.4, 25.5, 25.9, 29.9, 34.3, 36.8, 51.0, 54.7, 71.3, 176.5. Anal. Calcd for $C_{13}H_{24}O_3$: C, 68.38; H, 10.59%. Found: C, 68.09; H, 10.92%.

2-(1-Hydroxy-1-phenylmethyl)-4,4-dimethylpentanenitrile. Two diastereomers were produced in a ratio of **A/B** = 59/41; they could not be separated by column chromatography. mp 68–70 °C (ether–hexane); IR (nujol) 3381, 2951, 2853, 2244, 1453, 1378, 1289, 1232, 1084, 1066, 1041, 767, 713 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.92 and 0.94 (s, 9H), 1.21–1.78 (m, 2H), 2.27 (d, J = 3.6 Hz, 1H(**A**)), 2.36 (d, J = 3.6 Hz, 1H(**B**)), 2.82 (ddd, J = 10.5, 6.1, 2.3 Hz, 1H(**B**)), 2.92 (ddd, J = 9.1, 5.1, 4.0 Hz, 1H(**A**)), 4.76 (dd, J = 5.9, 3.5 Hz, 1H(**B**)), 4.81 (dd, J = 5.8, 3.6 Hz, 1H(**A**)), 7.30–7.47 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 29.0, 29.1, 30.3, 30.3, 35.5 (**A**), 36.2 (**B**), 41.1 (**A**), 42.3 (**B**), 74.2 (**A**), 74.7 (**B**), 121.5 (**B**), 121.7 (**A**), 126.3, 126.4, 128.4, 128.5, 139.7 (**A**), 140.1 (**B**). Anal. Calcd for $C_{14}H_{19}NO$: C, 77.34; H, 8.81; N, 6.45%. Found: C, 77.63; H, 8.92; N, 6.47%.

4-Cyclopentyl-2-(1-hydroxy-1-phenylmethyl)-4-methylpentanenitrile (12). Two diastereomers were produced in a ratio of 52/48; they could not be separated by column chromatography. bp 138 °C (bath temp, 0.08 Torr); IR (neat) 3442, 2956, 2868, 2242, 1453, 1390, 1369, 1058, 763, 716, 702, 666 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.81, 0.84, 0.87, and 0.88 (s, 6H), 1.00–2.00 (m, 11H), 2.20–2.38 (m, 1H), 2.78–2.98 (m, 1H), 4.67–4.84 (m, 1H), 7.30–7.48 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 23.9, 24.1, 25.6, 26.6, 26.7, 34.5, 34.6, 34.9, 35.8, 38.8, 40.3, 49.0, 49.0, 74.5, 75.2, 121.6, 121.8, 126.3, 126.4, 128.4, 128.5, 139.8, 140.2. Anal. Calcd for $C_{18}H_{25}NO$: C, 79.66; H, 9.28; N, 5.16%. Found: C, 79.37; H, 9.53; N, 4.97%.

2-(1-Hydroxy-1-phenylmethyl)-6-heptenenitrile (13). Two diastereomers were produced in a ratio of 56/44; they could not be separated by column chromatography. bp 124 °C (bath temp, 0.06 Torr); IR (neat) 3447, 3066, 2928, 2864, 2243, 1640, 1456, 1048, 995, 915, 764, 702 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.40–1.80 (m, 4H), 1.98–2.12 (m, 2H), 2.42 (d, J = 2.7 Hz, 1H(**A**)), 2.51 (d, J = 3.3 Hz, 1H(**B**)), 2.78–3.02 (m, 1H), 4.76 (dd, J = 6.1, 3.6 Hz, 1H(**B**)), 4.81 (dd, J = 6.3, 3.1 Hz, 1H(**A**)), 4.90–5.07 (m, 2H), 5.62–5.88 (m, 1H), 7.30–7.48 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 26.2, 27.4, 28.4, 32.9, 33.0, 40.3, 40.9, 73.7, 74.0, 115.3, 115.3, 120.0, 126.1, 126.4, 128.7, 128.8, 137.5, 137.6, 140.0, 140.3; EI MS *m/z* (%) 215 (M^+, 8), 198 (4), 167 (4), 147 (25), 108 (95), 107 (95), 105 (80), 79 (100), 77 (98). HRMS (EI) *m/z* calcd for (M^+) $C_{14}H_{17}NO$: 215.1310, found 215.1320.

Typical Procedure for 3-Phenylpropyl Cyclopropanecarboxylate (20). To a suspension of manganese powder (0.47 g, 8.5 mmol),[6] $PbCl_2$ (24 mg, 0.085 mmol),[6] and DMAP (18 mg, 0.15 mmol) in THF (6 mL) was added Me_3SiCl (0.019 mL, 0.15 mmol), and the mixture was stirred at 25 °C for 30 min. A solution of 3-phenylpropyl acrylate (0.19 g, 1.0 mmol) in DMF (1.5 mL) and a solution of chloroiodomethane (0.53 g, 3.0 mmol) in DMF (1.5 mL) were successively added to the mixture. After being stirred at 25 °C for 15 min, the resulting mixture was poured into an NH_4Cl solution (10 mL) and the mixture was extracted with ether (3 × 10 mL). The organic extracts were washed with brine, dried over anhydrous $MgSO_4$ and concentrated. Purification by column chromatography on silica gel (ethyl acetate–hexane, 1:30–1:50) afforded cycropropanecarboxylic ester **20** in 74% yield (0.15 g) and 1,4-adduct **21** in 12% yield (29 mg).

3-Phenylpropyl Cyclopropanecarboxylate (20): Bp 80 °C (bath temp, 0.11 Torr); IR (neat) 3026, 2955, 2928, 2857, 1727, 1497, 1454, 1403, 1372, 1267, 1200, 1175, 1077, 1030, 745, 700 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.84–0.88 (m, 2H), 0.97–1.02 (m, 2H), 1.58–1.65 (m, 1H), 1.93–2.00 (m, 2H), 2.70 (t, J = 7.3 Hz, 2H), 4.10 (t, J = 6.6 Hz, 2H), 7.12–7.35 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 8.3, 12.9, 30.3, 32.2, 63.8, 126.0, 128.4, 128.4, 141.3, 174.9. Anal. Calcd for $C_{13}H_{16}O_2$: C, 76.44; H, 7.90%. Found: C, 76.30; H, 8.06%.

3-Phenylpropyl 4-Chlorobutanoate (21). Bp 95 °C (bath temp, 0.47 Torr); IR (neat) 3027, 2958, 2862, 1735, 1497, 1454, 1315, 1299, 1242, 1209, 1176, 1147, 1019, 747, 700 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.94–2.01 (m, 2H), 2.05–2.13 (m, 2H), 2.50 (t, J = 7.2 Hz, 2H), 2.70 (t, J = 7.8 Hz, 2H), 3.61 (t, J = 6.3 Hz, 2H), 4.12 (t, J = 6.6 Hz, 2H), 7.16–7.32 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 27.7, 30.2, 31.2, 32.2, 44.1, 64.0, 126.0, 128.4, 141.1, 172.7. Anal. Calcd for $C_{13}H_{17}ClO_2$: C, 64.86; H, 7.12%. Found: C, 64.58; H, 7.06%.

1-Cyclopropyl-3-phenyl-1-propanone.[22] Bp 80 °C (bath temp, 0.20 Torr); IR (neat) 3027, 3008, 2950, 2929, 1698, 1497, 1453, 1388, 1100, 1086, 1073, 1032, 1012, 750, 700, 666 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.83–0.89 (m, 2H), 1.00–1.04 (m, 2H), 1.88–1.95 (m, 1H), 2.86–2.95 (m, 4H), 7.15–7.33 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 10.7, 20.5, 29.9, 45.0, 126.0, 128.3, 128.4, 141.2, 210.0.

3-Phenylpropyl 2-Methylcyclopropanecarboxylate. Bp 85 °C (bath temp, 0.40 Torr); IR (neat) 3027, 2957, 2870, 1725, 1497, 1454, 1411, 1376, 1323, 1265, 1182, 1167, 1077, 1032, 746, 700, 666 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.71–0.76 (m, 1H), 1.18 (d, J = 6.0 Hz, 3H), 1.20–1.25 (m, 1H), 1.38–1.49 (m, 2H), 1.99–2.06 (m, 2H), 2.76 (t, J = 7.8 Hz, 2H), 4.14 (t, J = 6.6 Hz, 2H), 7.24–7.40 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 16.7, 17.2, 17.9, 21.3, 30.3, 32.2, 63.7, 126.0, 128.4, 128.4, 141.3, 174.5. Anal. Calcd

for $C_{14}H_{18}O_2$: C, 77.03; H, 8.31%. Found: C, 76.79; H, 8.40%.

***N*-Benzyl-*N*-methylcyclopropanecarboxamide.** Bp 125 °C (bath temp, 0.17 Torr); IR (neat) 3479, 3029, 2927, 2636, 1495, 1453, 1417, 1357, 1281, 1219, 1207, 1120, 1088, 1030, 881, 733, 700 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.72–0.82 (m, 2H), 1.01–1.07 (m, 2H), 1.70–1.82 (m, 1H), 2.97 and 3.08 (s, 3H), 4.61 and 4.72 (s, 2H), 7.22–7.39 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 7.6 and 7.7, 11.2 and 11.3, 34.4 and 34.8, 51.2, 53.3, 126.4, 127.2 and 127.5, 128.0, 128.5 and 128.8, 137.1 and 137.6, 173.6 and 173.9. Anal. Calcd for $C_{12}H_{15}NO$: C, 76.16; H, 7.99%. Found: C, 75.91; H, 8.11%.

Cyclopropyl Phenyl Sulfone.[23] Bp 130 °C (bath temp, 0.5 Torr); IR (neat) 3058, 1447, 1317, 1291, 1149, 1090, 886, 763, 732, 691 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.00–1.06 (m, 2H), 1.33–1.38 (m, 2H), 2.43–2.50 (m, 1H), 7.54–7.58 (m, 2H), 7.62–7.66 (m, 1H), 7.88–7.92 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 6.0, 32.9, 127.5, 129.2, 133.3, 140.7.

Financial support from the Novartis Foundation (Japan) for the Promotion of Science and from the Ministry of Education, Science and Culture is gratefully acknowledged.

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