Morita–Baylis–Hillman Reaction on Water without Organic Solvent, Assisted by a 'Catalytic' Amount of Amphiphilic Imidazole Derivatives

Keisuke Asano, Seijiro Matsubara*

Department of Material Chemistry, Kyoto University, Kyoutodaigaku-katsura, Nishikyo, Kyoto 615-8510, Japan
Fax +81(75)3832459; E-mail: matsubar@orgrxn.mbox.media.kyoto-u.ac.jp

Received 24 April 2009; revised 25 May 2009

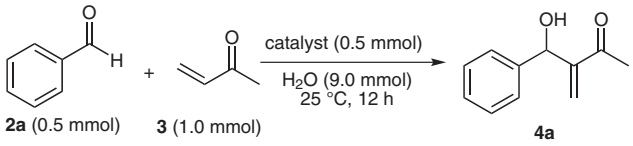
Abstract: A Morita–Baylis–Hillman (MBH) reaction using water as a solvent without any organic solvent can be performed by using an amphiphilic *N*-alkylimidazole. This reaction is accelerated by the addition of water and is the first example of a 'catalytic' MBH reaction without organic solvent in the presence of water.

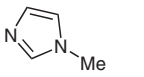
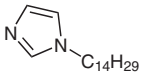
Key words: Morita–Baylis–Hillman reaction, organocatalyst, water, imidazole, amphiphilic catalyst

The use of water as a solvent for organic reactions has been important since the pioneering work by Breslow.[1] Some practical reasons, such as cost, safety, and environmental concerns, can be mentioned specially. Moreover, water as a solvent often benefits the organic reaction itself dynamically.[2] The high polarity of water may stabilize an ionic intermediate.[3] In addition, the hydrophobicity of an organic compound will give rise to cohesion of substrates, which often enhances the reaction rate.[4] The use of water as a solvent has been expanded even to the areas of organometallic chemistry, which include air- and water-sensitive species.[5] As the chemistry of organocatalytic reactions has been developed in recent years, the arguments about the contribution of water to these reactions have been rekindled.[6,7] In the reaction with an organocatalyst, an ionic intermediate is inevitable, so the use of water may be effective.[6,7,8b]

The Morita–Baylis–Hillman (MBH) reaction is a useful method of C–C bond formation using an organocatalyst.[8–10] The reaction is, however, notoriously slow and there have been many attempts to accelerate the reaction, some of which have used water.[7h–l,8b,9,10] The reaction is initialized by an amine or phosphine (Scheme 1)[9,10] and the formation of a betaine intermediate **1** is a crucial step. In order to stabilize such an ionic intermediate, one can use water as a solvent. However, the addition of water may depress the nucleophilicity of the amine. Actually, the reported methods that show rate enhancements for MBH reactions in the presence of water used excess nucleophilic mediator and organic solvents were also often used as a co-solvent.[7h–l,8b] To solve this contradiction, we designed an imidazole[11] carrying a hydrophobic group,[6,7j,9] because aggregation of the amphiphilic compounds in water will form a hydrophobic phase, which may work as protection for the nucleophilic catalyst from deactivation by water.

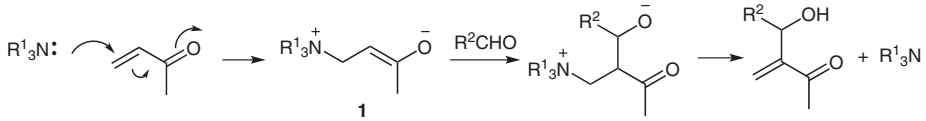
We examined the reaction between benzaldehyde (**2a**) and methyl vinyl ketone (**3**) using a stoichiometric amount of an imidazole derivative and water as the solvent (Scheme 2). Although *N*-methylimidazole **5a** afforded only a trace amount of the product **4a**, *N*-tetradecylimidazole **5b** gave **4a** in 37% yield. This suggests that the introduction of a tetradecyl group to an imidazole will make the reaction using water possible.



Catalyst		Yield (%) of **4a**
	(**5a**)	<1
	(**5b**)	37

Scheme 2 MBH reaction between benzaldehyde and methyl vinyl ketone using a stoichiometric amount of imidazole derivatives in the presence of water

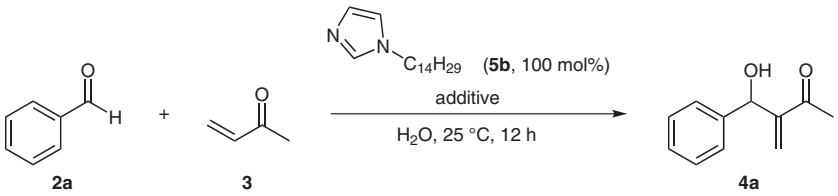
To improve the yield, we examined the addition of a catalytic amount of Brønsted acid. As shown in Table 1, Brønsted acids whose pK_a values are around 9 were effective in promoting this reaction (Table 1, entries 4–6, 8–10). The added acid should activate methyl vinyl ketone without deactivation of the imidazole derivative. Among



Scheme 1 Schematic Morita–Baylis–Hillman reaction catalyzed by an amine

SYNTHESIS 2009, No. 19, pp 3219–3226
Advanced online publication: 21.08.2009
DOI: 10.1055/s-0029-1216944; Art ID: F08809SS

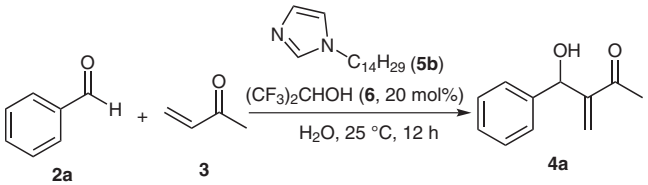
Table 1 MBH Reaction between Benzaldehyde (**2a**) and Methyl Vinyl Ketone (**3**) in the Presence of a Brønsted Acid[a]



Entry	Additive (mol%)	pK_a in H_2O	Yield[b] (%)
1	TFA (20)	–0.25	39
2	Cl_3CCO_2H (20)	0.65	49
3	BzOH (20)	4.2	37
4	4-$O_2NC_6H_4OH$ (20)	7.1	51
5	$(CF_3)_2CHOH$ (**6**) (20)	9.3	54
6	PhOH (20)	10	52
7	CF_3CH_2OH (20)	12	46
8	$(CF_3)_2CHOH$ (**6**) (40)	9.3	61
9	$(CF_3)_2CHOH$ (**6**) (60)	9.3	64
10	$(CF_3)_2CHOH$ (**6**) (100)	9.3	63

[a] Benzaldehyde (**2a**, 0.5 mmol), methyl vinyl ketone (**3**, 1.0 mmol), *N*-tetradecylimidazole **5b** (0.5 mmol), H_2O (9.0 mmol).
[b] Isolated yield.

Table 2 MBH Reaction Between Benzaldehyde (**2a**) and Methyl Vinyl Ketone (**3**) Using a Catalytic Amount of *N*-Tetradecylimidazole **5b**[a]



Entry	Catalyst loading (mol%)	Yield[b] (%)
1	100	54
2	50	53
3	40	55
4	30	57
5	20	65
6	10	41

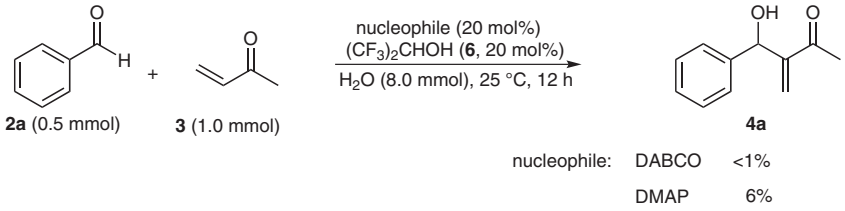
[a] Benzaldehyde (**2a**, 0.5 mmol), methyl vinyl ketone (**3**, 1.0 mmol), 1,1,1,3,3,3-hexafluoropropan-2-ol (**6**, 0.1 mmol), H_2O (9.0 mmol).
[b] Isolated yield.

them, 1,1,1,3,3,3-hexafluoropropan-2-ol (**6**) gave the best results (Table 1, entry 5). The amount of acid was also optimized and the results revealed that 20 mol% was sufficient for the reaction (Table 1, entries 5, 8–10).

We also tried to decrease the stoichiometric amount of the imidazole derivative to a catalytic amount (Table 2). The use of 20 mol% of *N*-alkylimidazole **5b** was shown to give a reasonable yield of the product (Table 2, entry 5).

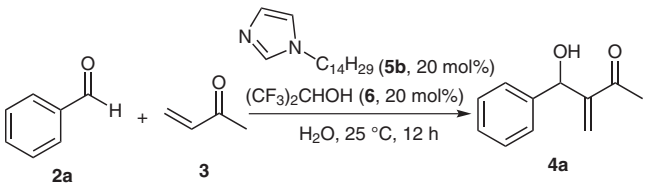
The amount of water was optimized under catalytic conditions using 20 mol% of *N*-alkylimidazole **5b** (Table 3). It is noteworthy that without water the yield decreased to 37%, while the reaction using 2.5 mmol of water afforded **4a** in 67% yield (Table 3, entries 1 and 2). The amount of water did not have a reasonable influence on the yield, and in any case, water worked for the acceleration of the reaction (Table 3, entries 2–10). Although a stoichiometric amount of nucleophile was required for acceleration by water in reported MBH reactions,[7h–l,8b] we could construct a 'catalytic MBH reaction' in the presence of water by using *N*-tetradecylimidazole **5b**. This can be attributed to its aggregation in water. The aggregation makes a hydrophobic space by the tetradecyl groups, in which nucleophilic species are protected from deactivation by water, such as protonation. In addition, the aggregation may also help the reaction by placing organic substrates in close proximity. 1,4-Diazabicyclo[2.2.2]octane and 4-(dimethylamino)pyridine, which have been regarded as efficient for MBH reactions, were also examined under our conditions; neither of them were effective catalysts (Scheme 3). Nucleophiles should be endowed with amphiphilicity for MBH reactions using water.

Then we examined the effect created by modification of the hydrophobic groups in the catalyst (Table 4). The lengths of carbon chains were arranged from C1 to C16 (Table 4, **5a–f**, entries 1–6). Imidazoles with alkyl groups more than C10 showed acceptable yields. No reasonable



Scheme 3 MBH reaction between benzaldehyde (**2a**) and methyl vinyl ketone (**3**) using DABCO and DMAP in the presence of water

Table 3 Optimization of the Amount of Water for MBH Reaction Between Benzaldehyde (**2a**) and Methyl Vinyl Ketone (**3**) Catalyzed by *N*-Tetradecylimidazole **5b**[a]



Entry	H_2O (mmol)	Yield[b] (%)
1	0	37
2	2.5	67
3	5.0	64
4	7.5	61
5	8.0	65
6	8.5	62
7	9.0	63
8	9.5	62
9	10	61
10	56 (1 mL)	61

[a] Benzaldehyde (**2a**, 0.5 mmol), methyl vinyl ketone (**3**, 1.0 mmol), *N*-tetradecylimidazole **5b** (0.1 mmol), 1,1,1,3,3,3-hexafluoropropan-2-ol (**6**, 0.1 mmol).
[b] Isolated yield.

differences concerning the yield were observed among these cases (Table 4, entries 2–6). We also introduced fluorine atoms on the carbon chain,[12] and it resulted in only a slight increase in the yield (Table 4, **5g** and **5h**, entries 7 and 8). We also tried an unsaturated carbon chain, but the introduction of a (*Z*)-olefinic group in the middle of the chain did not create any remarkable effect (Table 4, **5i**, entry 9).

In these reactions, vigorous stirring was not necessary, although many reported reactions using water as a solvent required it for the formation of emulsions or fine oil drops.[6d,13] As shown in Scheme 4, the reactions of benzaldehyde (**2a**, 0.5 mmol) and methyl vinyl ketone (**3**, 1.0 mmol) in the presence of *N*-hexadecylimidazole **5f** (0.1 mmol), 1,1,1,3,3,3-hexafluoropropan-2-ol (**6**, 0.1 mmol), and water (8.0 mmol) were examined both with and without stirring. The nonstirred reaction in a wider vial (i.d. 20 mm) gave the same yield of **4a** as the vigorous stirred reaction. However, if the nonstirred reaction was performed in a narrower vial (i.d. 5 mm), the yield of **4a** decreased to 50%.

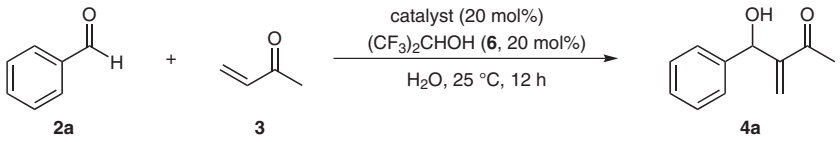
These results showed that stirring was not necessary to carry out the reaction under our conditions if there was sufficient surface area where the water and organic phase were contiguous. It seems to be important that the reaction proceeded in the range of the organic phase that is close to the surface of the water. In other words, this reaction can be classified as one of the reactions on water.[14] We could utilize the potential of water to promote an organic reaction by forming a hydrophobic field for the reaction near the boundary between water and organic compounds, not by forming emulsions.

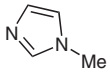
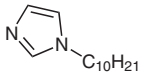
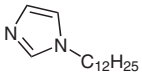
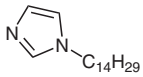
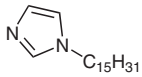
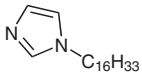
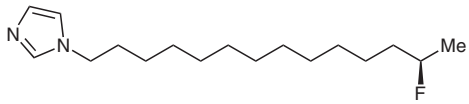
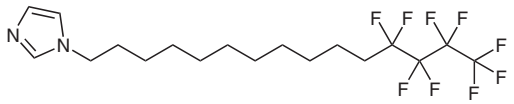
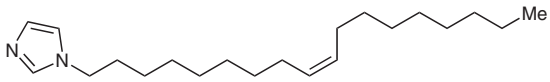
Under the optimized conditions, we examined MBH reactions of methyl vinyl ketone (**3**) with various aldehydes **2** (Table 5). The use of aryl aldehydes **2c–e** carrying electron-withdrawing groups did not effect the yield (Table 5, entries 2–4). Although the yields were not excellent, we can show the possibility of MBH reactions that are catalyzed by imidazole derivatives carrying a hydrophobic group; such reactions are also accelerated by water.

In conclusion, we have shown that some Morita–Baylis–Hillman reactions in the presence of water are initiated by a 'catalytic' amounts of *N*-alkylimidazoles; in this reaction, the addition of water accelerated the reaction. The 'catalytic' reaction promoted by water was realized by the amphiphilic imidazole derivatives carrying hydrophobic groups. The amphiphilic catalyst forms a hydrophobic field for an organic reaction near the boundary between the water and the organic compounds by self-assembly. These results show that such a reaction field constructed by an amphiphilic organocatalyst near the surface of water may be widely effective for the acceleration of organocatalytic reactions.

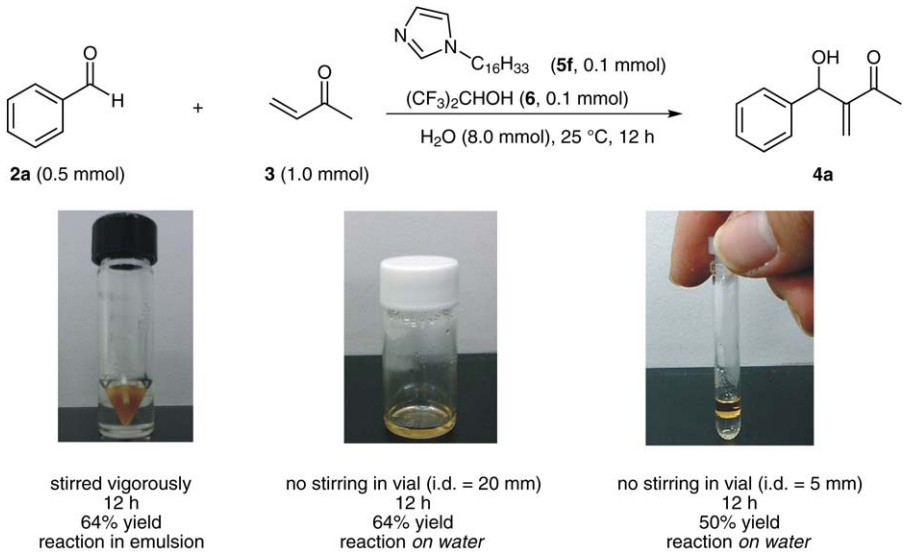
NMR spectra were taken on a Varian Unity Inova 500 (^{1}H, 500 MHz; ^{13}C, 125.7 MHz) spectrometer using TMS (^{1}H, $\delta = 0$) and $CDCl_3$ (^{13}C, $\delta = 77.0$) as internal standards. ^{19}F NMR spectra were measured on a Varian Mercury 200 (^{19}F, 188 MHz) spectrometer with hexafluorobenzene as an internal standard ($\delta = 0$). GC-MS analyses and HRMS spectra were obtained with a Jeol JMS-700 spectrometer by electron ionization at 70 eV. IR spectra were determined on a Shimadzu FTIR-8200PC spectrophotometer. Melting points were determined using a Yanako MP-500D. Optical rotations were measured on a Jasco DIP-360.

Table 4 MBH Reaction between Benzaldehyde (**2a**) and Methyl Vinyl Ketone (**3**) Catalyzed by Imidazole Derivatives **5** Having Various Hydrophobic Groups[a]



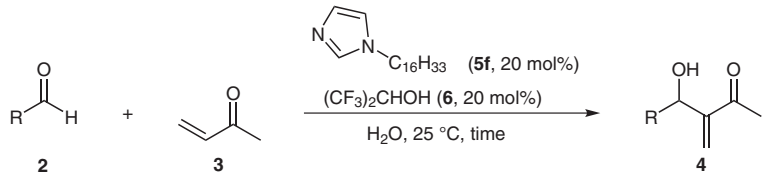
Entry	Catalyst		Yield[b] (%)
1	**5a**		16
2	**5c**		63
3	**5d**		61
4	**5b**		65
5	**5e**		64
6	**5f**		64
7	**5g**		65
8	**5h**		66
9	**5i**		62

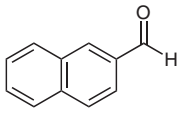
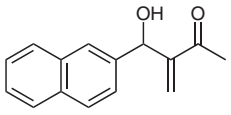
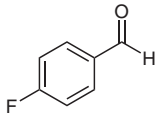
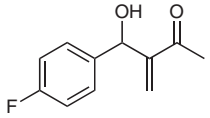
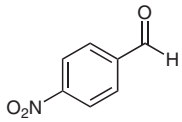
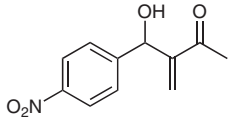
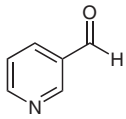
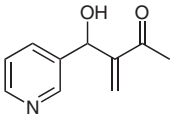
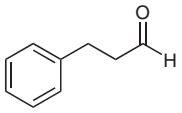
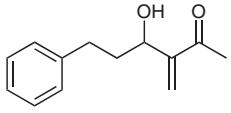
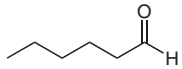
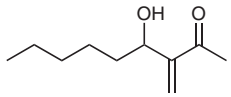
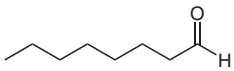
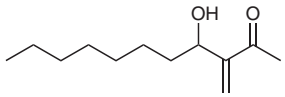
[a] Benzaldehyde (**2a**, 0.5 mmol), methyl vinyl ketone (**3**, 1.0 mmol), 1,1,1,3,3,3-hexafluoropropan-2-ol (**6**, 0.1 mmol), catalyst **5** (0.1 mmol), H_2O (8.0 mmol).
[b] Isolated yields.



Scheme 4 MBH reaction between benzaldehyde (**2a**) and methyl vinyl ketone (**3**) with/without stirring.

Table 5 MBH Reaction between Various Aldehydes **2** and Methyl Vinyl Ketone (**3**) Catalyzed by *N*-Hexadecylimidazole **5f** on Water without Organic Solvent[a]



Entry	Substrate **2**	Product **4**	Time (h)	Yield[b] (%)
1	 **2b**	 **4b**	12	37
2	 **2c**	 **4c**	12	67
3	 **2d**	 **4d**	12	64
4	 **2e**	 **4e**	12	61
5	 **2f**	 **4f**	12	65
6	 **2g**	 **4g**	24	62
7	 **2h**	 **4h**	24	63

[a] Aldehyde (**2**, 0.5 mmol), methyl vinyl ketone (**3**, 1.0 mmol), *N*-hexadecylimidazole **5f** (0.1 mmol), 1,1,1,3,3,3-hexafluoropropan-2-ol (**6**, 0.1 mmol), H_2O (8.0 mmol).
[b] Isolated yields.

Flash column chromatography was carried out using Kanto Chemical silica gel (spherical, 40–50 μm). Unless otherwise noted, commercially available reagents were used without purification.

N-Alkylimidazoles 5a–i

1-Methyl-1*H*-imidazole (**5a**) was commercially available and used without any purification.

N-Alkylimidazoles 5b–f;[15] General Procedure

A mixture of imidazole (0.75 g, 11 mmol) and alkyl bromide (11 mmol) in toluene (20 mL) in the presence of TEAI (0.57 g, 2.2 mmol) and NaOH (1.3 g, 33 mmol) was refluxed for 10 h. The resulting mixture was cooled to r.t., H_2O was added, and the mixture was extracted with EtOAc. The combined organic layers were washed with brine, dried (Na_2SO_4), and concentrated in vacuo. Purification by flash column chromatography (silica gel, EtOAc) gave the corresponding *N*-alkylimidazoles in 64–78% yield. The NMR results (^1H, ^{13}C) are as below.

1-Decyl-1*H*-imidazole (5c)

CAS [33529-02-1]. Yellow oil; yield: 64%.

^1H NMR ($CDCl_3$): δ = 7.45 (s, 1 H), 7.05 (t, *J* = 1.0 Hz, 1 H), 6.90 (t, *J* = 1.0 Hz, 1 H), 3.92 (t, *J* = 7.5 Hz, 2 H), 1.76 (tt, *J* = 7.0, 7.0 Hz, 2 H), 1.34–1.20 (m, 14 H), 0.87 (t, *J* = 7.0 Hz, 3 H).

^{13}C NMR ($CDCl_3$): δ = 137.1, 129.4, 118.7, 47.0, 31.8, 31.1, 29.5, 29.4, 29.2, 29.0, 26.5, 22.6, 14.1.

1-Dodecyl-1*H*-imidazole (5d)
CAS [4303-67-7]. Orange oil; yield: 66%.

^{1}H NMR ($CDCl_3$): δ = 7.45 (s, 1 H), 7.04 (t, *J* = 1.0 Hz, 1 H), 6.89 (t, *J* = 1.0 Hz, 1 H), 3.91 (t, *J* = 7.0 Hz, 2 H), 1.76 (tt, *J* = 7.0, 7.0 Hz, 2 H), 1.32–1.20 (m, 18 H), 0.87 (t, *J* = 7.0 Hz, 3 H).

^{13}C NMR ($CDCl_3$): δ = 137.0, 129.3, 118.7, 47.0, 31.9, 31.1, 29.6, 29.5, 29.4, 29.3, 29.0, 26.5, 22.6, 14.1.

1-Tetradecyl-1*H*-imidazole (5b)
CAS [54004-47-6]. Pale yellow solid; yield: 68%.

^{1}H NMR ($CDCl_3$): δ = 7.45 (s, 1 H), 7.05 (t, *J* = 1.0 Hz, 1 H), 6.90 (t, *J* = 1.0 Hz, 1 H), 3.91 (t, *J* = 7.5 Hz, 2 H), 1.76 (tt, *J* = 7.0, 7.0 Hz, 2 H), 1.34–1.20 (m, 22 H), 0.88 (t, *J* = 7.0 Hz, 3 H).

^{13}C NMR ($CDCl_3$): δ = 137.1, 129.4, 118.7, 47.0, 31.9, 31.1, 29.7, 29.62, 29.58, 29.50, 29.4, 29.3, 29.1, 26.5, 22.7, 14.1.

1-Pentadecyl-1*H*-imidazole (5e)
CAS [130482-55-2]. Pale yellow solid; yield: 70%.

^{1}H NMR ($CDCl_3$): δ = 7.45 (s, 1 H), 7.05 (t, *J* = 1.0 Hz, 1 H), 6.90 (t, *J* = 1.0 Hz, 1 H), 3.91 (t, *J* = 7.0 Hz, 2 H), 1.76 (tt, *J* = 7.0, 7.0 Hz, 2 H), 1.34–1.20 (m, 24 H), 0.87 (t, *J* = 7.0 Hz, 3 H).

^{13}C NMR ($CDCl_3$): δ = 137.1, 129.4, 118.7, 47.0, 31.9, 31.1, 29.66, 29.65, 29.63, 29.62, 29.58, 29.50, 29.4, 29.3, 29.1, 26.5, 22.7, 14.1.

1-Hexadecyl-1*H*-imidazole (5f)
CAS [58175-55-6]. White solid; yield: 78%.

^{1}H NMR ($CDCl_3$): δ = 7.45 (s, 1 H), 7.05 (t, *J* = 1.0 Hz, 1 H), 6.90 (t, *J* = 1.0 Hz, 1 H), 3.92 (t, *J* = 7.5 Hz, 2 H), 1.76 (tt, *J* = 7.0, 7.0 Hz, 2 H), 1.34–1.20 (m, 26 H), 0.87 (t, *J* = 7.0 Hz, 3 H).

^{13}C NMR ($CDCl_3$): δ = 137.1, 129.4, 118.7, 47.0, 31.9, 31.1, 29.67, 29.66, 29.65, 29.64, 29.62, 29.58, 29.50, 29.4, 29.3, 29.1, 26.5, 22.7, 14.1.

(*R*)-1-(13-Fluorotetradecyl)-1*H*-imidazole (5g)[16]
NaH (60%, 0.066 g, 1.65 mmol) was washed with hexane and THF (2 mL) was added. To the soln, a soln of imidazole (0.10 g, 1.5 mmol) in THF (2 mL) was added slowly at 0 °C. The mixture was stirred at r.t. for 45 min, then a soln of (*R*)-1-bromo-13-fluorotetradecane (0.44 g, 1.5 mmol) in THF (1 mL) was added slowly to the mixture, and it was stirred for 7 d. The mixture was filtered and the filtrate was concentrated in vacuo. Purification by flash column chromatography (silica gel, EtOAc) gave **5g** (0.30 g, 72%) as a white solid; mp 32.6–32.8 °C.

$[\alpha]_D^{28}$ –6.7 (*c* 4.46, $CHCl_3$).

IR (KBr) 2930, 2849, 2359, 1512, 1471, 1385, 1283, 1231, 1132, 1107, 1082, 1057, 1036, 1007, 907, 837, 816, 750, 731, 665, 623 cm^{-1}.

^{1}H NMR ($CDCl_3$): δ = 7.45 (s, 1 H), 7.05 (t, *J* = 1.0 Hz, 1 H), 6.90 (t, *J* = 1.0 Hz, 1 H), 4.64 (m, 1 H), 3.92 (t, *J* = 7.5 Hz, 2 H), 1.76 (m, 2 H), 1.65 (m, 1 H), 1.56–1.38 (m, 2 H), 1.33 (t, *J* = 6.0 Hz, 3 H), 1.36–1.22 (m, 17 H).

^{13}C NMR ($CDCl_3$): δ = 137.1, 129.4, 118.7, 91.1 (d, *J* = 164 Hz), 47.0, 36.9 (d, *J* = 21 Hz), 31.1, 29.52, 29.48, 29.47, 29.42, 29.40, 29.1, 26.5, 25.1, 25.0, 21.0 (d, *J* = 23 Hz).

^{19}F NMR ($CDCl_3$): δ = –10.3.

HRMS: *m*/*z* $[M]^+$ calcd for $C_{17}H_{31}FN_2$: 282.2471; found: 282.2472.

1-(12,12,13,13,14,14,15,15,15-Nonafluoropentadecyl)-1*H*-imidazole (5h)[16]
NaH (60%, 0.15 g, 3.7 mmol) was washed with hexane and THF (3 mL) was added. To the soln, a soln of imidazole (0.23 g, 3.4 mmol) in THF (3 mL) was added slowly at 0 °C. The mixture was stirred at r.t. for 15 min. Then a soln of 1-bromo-12,12,13,13,14,14,15,15,15-nonafluoropentadecane (1.5 g, 3.3 mmol) in THF (4 mL) was added slowly to the mixture, and it was stirred for 7 d. The mixture was filtered and the filtrate was concentrated in vacuo. Purification by flash column chromatography (silica gel, EtOAc) gave **5h** (1.1 g, 79%) as a colorless oil.

IR (neat): 2930, 2857, 1508, 1468, 1356, 1233, 1132, 1076, 1032, 907, 880, 847, 812, 733, 719, 664, 625, 592, 532 cm^{-1}.

^{1}H NMR ($CDCl_3$): δ = 7.46 (s, 1 H), 7.05 (t, *J* = 1.0 Hz, 1 H), 6.90 (t, *J* = 1.0 Hz, 1 H), 3.92 (t, *J* = 7.5 Hz, 2 H), 2.04 (m, 2 H), 1.76 (tt, *J* = 7.0, 7.0 Hz, 2 H), 1.59 (m, 2 H), 1.39–1.24 (m, 14 H).

^{19}F NMR ($CDCl_3$): δ = 80.2 (3 F), 46.9 (2 F), 37.0 (2 F), 35.5 (2 F).

HRMS: *m*/*z* $[M]^+$ calcd for $C_{18}H_{25}F_9N_2$: 440.1874; found: 440.1874.

(*Z*)-1-(Octadec-9-enyl)-1*H*-imidazole (5i)[15]
A mixture of imidazole (0.34 g, 5.0 mmol) and (*Z*)-1-bromooctadec-9-ene (1.7 g, 5.0 mmol) in toluene (10 mL) in the presence of TEAI (0.26 g, 1.0 mmol) and NaOH (0.60 g, 15 mmol) was refluxed for 18.5 h. The resulting mixture was cooled to r.t., H_2O was added, and the mixture was extracted with EtOAc. The combined organic layers were washed with brine, dried (Na_2SO_4), and concentrated in vacuo. Purification by flash column chromatography (silica gel, EtOAc) gave **5i** (1.2 g, 75%) as a yellow oil.

CAS [90343-81-0].

^{1}H NMR ($CDCl_3$): δ = 7.45 (s, 1 H), 7.05 (t, *J* = 1.0 Hz, 1 H), 6.90 (t, *J* = 1.0 Hz, 1 H), 5.34 (m, 2 H), 3.91 (t, *J* = 7.0 Hz, 2 H), 2.00 (dt, *J* = 6.0, 7.0 Hz, 4 H), 1.76 (tt, *J* = 7.0, 7.0 Hz, 2 H), 1.36–1.22 (m, 22 H), 0.88 (t, *J* = 7.5 Hz, 3 H).

^{13}C NMR ($CDCl_3$): δ = 137.1, 130.0, 129.7, 129.4, 118.7, 47.0, 31.9, 31.1, 29.73, 29.66, 29.5, 29.4, 29.3, 29.1, 29.03, 29.01, 27.2, 27.1, 26.5, 22.7, 14.1.

MBH Reaction between Aldehydes and Methyl Vinyl Ketone; General Procedure
To a 5-mL vial were added sequentially aldehyde **2** (0.5 mmol), methyl vinyl ketone (**3**, 1.0 mmol), imidazole derivative **5** (0.1 mmol), 1,1,1,3,3,3-hexafluoropropan-2-ol (**6**, 0.1 mmol), and H_2O (8.0 mmol). The mixture was stirred in an oil bath kept at 25 °C for 12 h. The mixture was diluted with Et_2O, dried (anhyd Na_2SO_4), and concentrated in vacuo. Purification by flash column chromatography (silica gel, hexane–EtOAc) gave the corresponding products.

4-Hydroxy-3-methylene-4-phenylbutan-2-one (4a)
CAS [73255-39-7]. Colorless oil.

^{1}H NMR ($CDCl_3$): δ = 7.37–7.25 (m, 5 H), 6.20 (s, 1 H), 5.98 (d, *J* = 1.0 Hz, 1 H), 5.62 (d, *J* = 5.0 Hz, 1 H), 3.13 (d, *J* = 5.0 Hz, 1 H), 2.34 (s, 3 H).

^{13}C NMR ($CDCl_3$): δ = 200.4, 149.9, 141.4, 128.4, 127.7, 126.7, 126.5, 72.9, 26.5.

4-Hydroxy-3-methylene-4-(2-naphthyl)butan-2-one (4b)
CAS [849900-45-4]. Colorless oil.

^{1}H NMR ($CDCl_3$): δ = 7.86–7.79 (m, 4 H), 7.50–7.40 (m, 3 H), 6.23 (s, 1 H), 6.01 (d, *J* = 1.5 Hz, 1 H), 5.80 (d, *J* = 5.0 Hz, 1 H), 3.25 (dd, *J* = 5.0, 1.0 Hz, 1 H), 2.36 (s, 3 H).

^{13}C NMR ($CDCl_3$): δ = 200.4, 149.8, 138.8, 133.2, 132.9, 128.12, 128.07, 127.6, 127.0, 126.1, 126.0, 125.4, 124.5, 72.9, 26.5.

4-(4-Fluorophenyl)-4-hydroxy-3-methylenebutan-2-one (4c)
CAS [888966-21-0]. Colorless oil.

^{1}H NMR ($CDCl_3$): δ = 7.37–7.33 (m, 2 H), 7.06–7.01 (m, 2 H), 6.22 (d, *J* = 0.5 Hz, 1 H), 5.99 (d, *J* = 1.5 Hz, 1 H), 5.61 (d, *J* = 5.0 Hz, 1 H), 3.10 (d, *J* = 5.0 Hz, 1 H), 2.36 (s, 3 H).

^{13}C NMR ($CDCl_3$): δ = 200.3, 162.2 (d, *J* = 246 Hz), 149.8, 137.2, 128.2 (d, *J* = 7.7 Hz), 126.8, 115.2 (d, *J* = 21 Hz), 72.3, 26.5.

^{19}F NMR ($CDCl_3$): δ = 46.6.

4-Hydroxy-3-methylene-4-(4-nitrophenyl)butan-2-one (4d)
CAS [203111-49-3]. Colorless oil.

^{1}H NMR ($CDCl_3$): δ = 8.20 (dt, *J* = 9.0, 2.0 Hz, 2 H), 7.55 (ddt, *J* = 9.0, 0.5, 2.0 Hz, 2 H), 6.27 (s, 1 H), 6.03 (d, *J* = 1.5 Hz, 1 H), 5.68 (d, *J* = 5.5 Hz, 1 H), 3.29 (d, *J* = 5.5 Hz, 1 H), 2.36 (s, 3 H).

^{13}C NMR ($CDCl_3$): δ = 200.1, 148.93, 148.86, 147.3, 127.8, 127.2, 123.6, 72.3, 26.4.

4-Hydroxy-3-methylene-4-(3-pyridyl)butan-2-one (4e)
CAS [223393-88-2]. White solid.

^{1}H NMR ($CDCl_3$): δ = 8.54 (d, *J* = 2.0 Hz, 1 H), 8.47 (dd, *J* = 5.0, 1.5 Hz, 1 H), 7.72 (ddd, *J* = 8.0, 1.5, 0.5 Hz, 1 H), 7.26 (ddd, *J* = 8.0, 5.0, 0.5 Hz, 1 H), 6.25 (d, *J* = 0.5 Hz, 1 H), 6.08 (d, *J* = 1.5 Hz, 1 H), 5.64 (s, 1 H), 3.79 (br, 1 H), 2.35 (s, 3 H).

^{13}C NMR ($CDCl_3$): δ = 200.0, 149.3, 148.8, 148.3, 137.3, 134.3, 127.1, 123.3, 70.7, 26.4.

4-Hydroxy-3-methylene-6-phenylhexan-2-one (4f)
CAS [108762-30-7]. Colorless oil.

^{1}H NMR ($CDCl_3$): δ = 7.30–7.26 (m, 2 H), 7.22–7.16 (m, 3 H), 6.11 (s, 1 H), 6.01 (d, *J* = 1.0 Hz, 1 H), 4.45 (ddd, *J* = 6.5, 6.5, 6.5 Hz, 1 H), 2.82 (m, 1 H), 2.74 (d, *J* = 6.5 Hz, 1 H), 2.68 (m, 1 H), 2.35 (s, 3 H), 1.93 (m, 2 H).

^{13}C NMR ($CDCl_3$): δ = 200.9, 150.0, 141.7, 128.5, 128.4, 125.9, 125.8, 71.0, 37.7, 32.1, 26.5.

4-Hydroxy-3-methylenenonan-2-one (4g)
CAS [108762-27-2]. Colorless oil.

^{1}H NMR ($CDCl_3$): δ = 6.10 (s, 1 H), 5.99 (d, *J* = 1.0 Hz, 1 H), 4.40 (ddd, *J* = 6.5, 6.5, 6.5 Hz, 1 H), 2.63 (d, *J* = 6.5 Hz, 1 H), 2.36 (s, 3 H), 1.59 (m, 2 H), 1.42 (m, 1 H), 1.34–1.23 (m, 5 H), 0.88 (t, *J* = 7.0 Hz, 3 H).

^{13}C NMR ($CDCl_3$): δ = 200.8, 150.3, 125.6, 71.6, 36.2, 31.6, 26.5, 25.6, 22.6, 14.0.

4-Hydroxy-3-methyleneundecan-2-one (4h)
CAS [108762-27-2]. Colorless oil.

^{1}H NMR ($CDCl_3$): δ = 6.10 (s, 1 H), 5.99 (d, *J* = 0.5 Hz, 1 H), 4.40 (ddd, *J* = 6.5, 6.5, 6.5 Hz, 1 H), 2.63 (d, *J* = 6.5 Hz, 1 H), 2.36 (s, 3 H), 1.59 (tt, *J* = 7.0, 7.0 Hz, 2 H), 1.42 (m, 1 H), 1.35–1.20 (m, 9 H), 0.87 (t, *J* = 7.0 Hz, 3 H).

^{13}C NMR ($CDCl_3$): δ = 200.8, 150.3, 125.6, 71.6, 36.3, 31.8, 29.4, 29.2, 26.5, 25.9, 22.6, 14.1.

Acknowledgment

This work was supported financially by the Japanese Ministry of Education, Culture, Sports, Science and Technology.

References

(1) (a) Rideout, D. C.; Breslow, R. *J. Am. Chem. Soc.* **1980**, *102*, 7816. (b) Breslow, R. *Acc. Chem. Res.* **1991**, *24*, 159.
(2) (a) Lubineau, A. *Chem. Ind.* **1996**, 123. (b) Lindström, U. M. *Chem. Rev.* **2002**, *102*, 2751. (c) Lubineau, A.; Augé, J.; Queneau, Y. *Synthesis* **1994**, 741. (d) Li, C.-J. *Chem. Rev.* **2005**, *105*, 3095.
(3) (a) Dong, V. M.; Fiedler, D.; Carl, B.; Bergman, R. G.; Raymond, K. N. *J. Am. Chem. Soc.* **2006**, *128*, 14464. (b) Vaitheeswaran, S.; Thirumalai, D. *J. Am. Chem. Soc.* **2006**, *128*, 13490.
(4) (a) Larsen, S. D.; Grieco, P. A. *J. Am. Chem. Soc.* **1985**, *107*, 1768. (b) Loncaric, C.; Manabe, K.; Kobayashi, S. *Chem. Commun.* **2003**, 574. (c) Ponaras, A. A. *J. Org. Chem.* **1983**, *48*, 3866. (d) Coates, R. M.; Roger, B. D.; Hobbs, S. J.; Peck, D. R.; Curran, D. P. *J. Am. Chem. Soc.* **1987**, *109*, 1160. (e) Gajewski, J. J.; Jurayj, J.; Kimbrough, D. R.; Gande, M. E.; Ganem, B.; Carpenter, B. K. *J. Am. Chem. Soc.* **1987**, *109*, 1170. (f) Inoue, Y.; Araki, K.; Shiraishi, S. *Bull. Chem. Soc. Jpn.* **1991**, *64*, 3079.
(5) (a) Runge, M. B.; Mwangi, M. T.; Miller, A. L. II.; Perring, M.; Bowden, N. B. *Angew. Chem. Int. Ed.* **2008**, *47*, 935. (b) Cornils, B.; Herrmann, W. A. In *Aqueous-Phase Organometallic Chemistry*; Wiley-VCH: Weinheim, **1998**. (c) Li, C.-J.; Chan, T.-H. In *Organic Reactions in Aqueous Media*; John Wiley: New York, **1997**.
(6) (a) Asano, K.; Matsubara, S. *Org. Lett.* **2009**, *11*, 1757. (b) Manabe, K.; Sun, X.-M.; Kobayashi, S. *J. Am. Chem. Soc.* **2001**, *123*, 10101. (c) Hayashi, Y.; Aratake, S.; Okano, T.; Takahashi, J.; Sumiya, T.; Shoji, M. *Angew. Chem. Int. Ed.* **2006**, *45*, 5527. (d) Mase, N.; Nakai, Y.; Ohara, N.; Yoda, H.; Takabe, K.; Tanaka, F.; Barbas, C. F. III *J. Am. Chem. Soc.* **2006**, *128*, 734. (e) Luo, S.; Mi, X.; Liu, S.; Xu, H.; Cheng, J.-P. *Chem. Commun.* **2006**, 3687.
(7) (a) Pellissier, H. *Tetrahedron* **2007**, *63*, 9267. (b) Mukherjee, S.; Yang, J. W.; Hoffmann, S.; List, B. *Chem. Rev.* **2007**, *107*, 5471. (c) Pan, C.; Wang, Z. *Coord. Chem. Rev.* **2008**, *252*, 736. (d) Kočovský, P.; Malkov, A. V. *Pure Appl. Chem.* **2008**, *80*, 953. (e) Gruttadauria, M.; Giacalone, F.; Lo Meo, P.; Marculescu, A. M.; Riela, S.; Noto, R. *Eur. J. Org. Chem.* **2008**, 1589. (f) Brogan, A. P.; Dickerson, T. J.; Janda, K. D. *Angew. Chem. Int. Ed.* **2006**, *45*, 8100. (g) Hayashi, Y. *Angew. Chem. Int. Ed.* **2006**, *45*, 8103. (h) Luo, S.; Zhang, B.; He, J.; Janczuk, A.; Wang, P. G.; Cheng, J.-P. *Tetrahedron Lett.* **2002**, *43*, 7369. (i) Gatri, R.; Gaïed, M. M. E. *Tetrahedron Lett.* **2002**, *43*, 7835. (j) Caumul, P.; Hailes, H. C. *Tetrahedron Lett.* **2005**, *46*, 8125. (k) Davies, H. J.; Ruda, A. M.; Tomkinson, N. C. O. *Tetrahedron Lett.* **2007**, *48*, 1461. (l) Hayashi, Y.; Okado, K.; Ashimine, I.; Shoji, M. *Tetrahedron Lett.* **2002**, *43*, 8683.
(8) (a) Aggarwal, V. K.; Mereu, A.; Tarver, G. J.; McCague, R. *J. Org. Chem.* **1998**, *63*, 7183. (b) Aggarwal, V. K.; Dean, D. K.; Mereu, A.; Williams, R. *J. Org. Chem.* **2002**, *67*, 510.
(9) Asano, K.; Matsubara, S. *Synlett* **2009**, 35.
(10) (a) Basavaiah, D.; Rao, K. V.; Reddy, R. J. *Chem. Soc. Rev.* **2007**, *36*, 1581. (b) Ciganek, E. *Org. React.* **1997**, *51*, 201. (c) Langer, P. *Angew. Chem. Int. Ed.* **2000**, *39*, 3049. (d) Cabrera, S.; Alemán, J.; Bolze, P.; Bertelsen, S.; Jørgensen, K. A. *Angew. Chem. Int. Ed.* **2008**, *47*, 121. (e) Lin, Y.-S.; Liu, C.-W.; Tsai, T. Y. R. *Tetrahedron Lett.* **2005**, *46*, 1859. (f) Tang, H.; Zhao, G.; Zhou, Z.; Gao, P.; He, L.; Tang, C. *Eur. J. Org. Chem.* **2008**, 126.

(11) (a) Enders, D.; Balensiefer, T. *Acc. Chem. Res.* **2004**, *37*, 534. (b) Nair, V.; Bindu, S.; Sreekumar, V. *Angew. Chem. Int. Ed.* **2004**, *43*, 5130. (c) Suzuki, Y. *J. Org. Synth. Chem. Jpn.* **2008**, *66*, 377. (d) Enders, D.; Niemeier, O.; Henseler, A. *Chem. Rev.* **2007**, *107*, 5606.
(12) (a) Kurihara, K.; Kunitake, T. *J. Am. Chem. Soc.* **1992**, *114*, 10927. (b) Matsubara, S.; Matsuda, H.; Hamatani, T.; Schlosser, M. *Tetrahedron* **1988**, *44*, 2855.
(13) (a) Zhong, L.; Gao, Q.; Gao, J. B.; Xiao, J.; Li, C. *J. Catal.* **2007**, *250*, 360. (b) Li, J.; Zhang, Y.; Han, D.; Jia, G.; Gao, J.; Zhong, L.; Li, C. *Green Chem.* **2008**, *10*, 608.
(14) Narayan, S.; Muldoon, J.; Finn, M. G.; Fokin, V. V.; Kolb, H. C.; Sharpless, K. B. *Angew. Chem. Int. Ed.* **2005**, *44*, 3275.
(15) Khabnadideh, S.; Rezaei, Z.; Khalafi-Nezhad, A.; Bahrinajafi, R.; Mohamadi, R.; Farrokhroz, A. A. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 2863.
(16) Vitz, J.; Mac, D. H.; Legoupy, S. *Green Chem.* **2007**, *9*, 431.