Isoprene as Lithiation Mediator: Synthesis of 2-Substituted 1-Alkylimidazole Derivatives

Regina Martínez, Rosario Torregrosa, Isidro M. Pastor,* Miguel Yus*

Departamento de Química Orgánica, Facultad de Ciencias and Instituto de Síntesis Orgánica (ISO), Universidad de Alicante, Apdo. 99, 03080 Alicante, Spain
Fax +34(96)5903549; E-mail: ipastor@ua.es; E-mail: yus@ua.es

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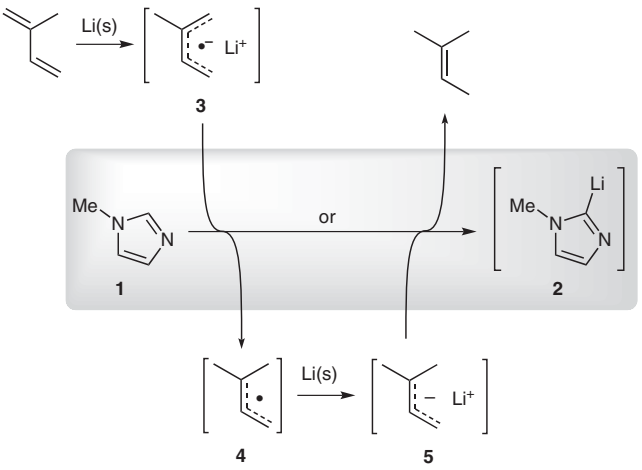
Abstract: The lithiation of different imidazoles bearing a primary (i.e., butyl, pentyl, dodecyl) or secondary (i.e., cyclohexyl, 1-methylheptyl) alkyl substituent on the nitrogen has been successfully achieved by means of an isoprene-mediated protocol. The subsequent reaction of the 2-lithioimidazole intermediates with different electrophiles leads to the formation of interesting 1,2-disubstituted imidazoles.

Key words: imidazole derivatives, isoprene-mediated lithiation, lithium metal, nucleophilic addition, deprotonation

The synthesis of heterocyclic compounds, which constitute the largest and most varied family of organic compounds, is a broad field of interest, probably due to the remarkable bioactivity of such compounds. Indeed, the significant aptitude of heterocyclic moieties to serve both as biomimetics and reactive pharmacophores has largely contributed to their unique value in the synthesis of numerous drugs.[1] In fact, more than 67% of the compounds listed in the Comprehensive Medicinal Chemistry (CMC) database contain heterocyclic rings.[2] Among them, azoles represent a broad group of heterocyclic systems which have been extensively considered in bioactive products.[3]

Lithium metal in combination with a substoichiometric amount of an arene, as electron carrier, has become a very versatile methodology in the preparation of organolithium intermediates.[4] A significant variety of functionalized organolithium reagents have been prepared by means of this protocol.[5] Additionally, arene-promoted lithiation has been employed in the preparation of polylithiated synthons[6] and in the generation of active nanoparticles by activation of transition metals.[7] In our laboratory, mechanistic studies on the arene-catalyzed lithiation process have been undertaken, providing interesting information regarding this well-established methodology.[8]

During the last few years, we have been working on the preparation of 2-functionalized imidazoles from the corresponding 2-lithioimidazole derivatives. Lithium metal is able to form 2-lithio-*N*-methylimidazole (2-Li-NMI, **2**) starting from the corresponding *N*-methylimidazole (NMI, **1**), but the use of a diene (i.e., isoprene) as a promoting agent during the lithiation step turned out to be an interesting improvement.[9] Furthermore, the remaining isoprene or its derivatives after the lithiation process can be easily removed. Regarding the role of isoprene, it seems to act as a base, after being reduced by Li(s), giving the 1,1-dimethylallyl anion radical **3**, on the basis of density functional theory calculations. Radical **4** can be further reduced by the excess lithium to give the anion **5** which can proceed once more as a base (Scheme 1).[9] Thus, isoprene-mediated lithiation of different imidazole derivatives, such as 1-methyl-,[10] 1-phenyl-,[11] and 1-(diethoxymethyl)-1*H*-imidazole,[12] has been reported by us. In sharp contrast, the functionalization of other 1-alkylimidazoles, via the corresponding 2-lithio derivatives, has been less studied.[13] In this paper, we report the application of the isoprene-mediated lithiation process for the preparation of imidazole derivatives bearing a primary or secondary alkyl substituent on the nitrogen.[14]



Scheme 1 Proposed mechanism for the isoprene-mediated lithiation of NMI employing lithium metal

The 1-alkylimidazole derivatives **6**–**11** were easily prepared either by substitution of the corresponding alkyl halide with imidazole, or by ring formation starting from the corresponding alkylamines.[3] Thus, imidazole was reacted with 1-bromopentane under phase-transfer conditions, giving the corresponding 1-pentyl-1*H*-imidazole (**6**) in good isolated yield (Scheme 2).[15] On the other hand, an equimolecular mixture of formaldehyde, glyoxal, ammonia and the corresponding amine (i.e., butan-1-amine, dodecan-1-amine, cyclohexanamine or octan-2-amine) was heated at 75 °C for three hours, yielding the expected imidazoles **7**–**10** (Scheme 3). This methodology was not suc-

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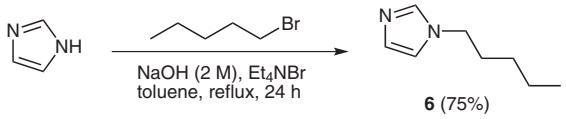
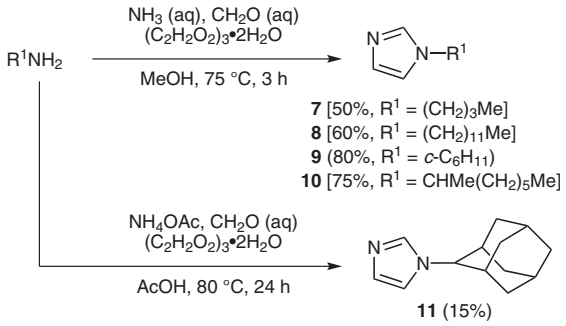
cessful when employing tertiary amines, such as *tert*-butylamine or adamantylamine. Alternatively, the use of ammonium acetate as ammonia source and performing the reaction in acetic acid allowed the preparation of 1-adamantyl-1*H*-imidazole (**11**), but not the *tert*-butylimidazole derivative (Scheme 3).



Scheme 2 Synthesis of 1-pentyl-1*H*-imidazole (**6**) from 1-bromopentane

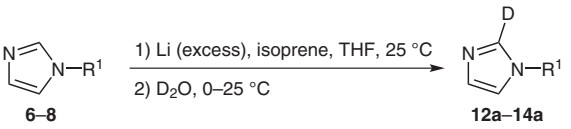


Scheme 3 Synthesis of 1-alkylimidazole derivatives **7**–**11** from the corresponding alkylamines by ring formation

First of all, we conducted a study of the amount of isoprene needed for the formation of the corresponding 2-lithioimidazole derivatives with the primary alkyl substituents (i.e., butyl, pentyl and dodecyl), which were afterwards quenched with deuterium oxide to determine the deuterium incorporation. 1-Pentyl-1*H*-imidazole (**6**) produced a high incorporation of deuterium (>95%) when one equivalent of isoprene was used, giving the corresponding imidazole **12a** (Table 1, entry 1). In contrast, a higher amount of isoprene was required in order to perform the lithiation of 1-butyl-1*H*-imidazole (**7**) or 1-dodecyl-1*H*-imidazole (**8**). Indeed, the use of one equivalent of isoprene only produced 10 mol% of deuterium incorporation in product **13a**, up to two equivalents being needed in order to obtain good results (Table 1, entries 2–4). Formation of 2-deutero-1-docecyl-1*H*-imidazole (**14a**) was only possible at room temperature when 300 mol% of isoprene was employed during the lithiation process, but with low deuterium incorporation (Table 1, entry 7). The deuterium incorporation was increased to 95% by warming the reaction mixture to 45 °C during the lithiation step (Table 1, entry 8).

Different 2-substituted imidazole derivatives were prepared employing the amount of isoprene stated for the lithiation–deuteration reactions. Thus, 2-lithio-1-pentyl-1*H*-imidazole, which was generated by reaction of **6** with an excess of lithium powder and one equivalent of isoprene at 25 °C during one hour, subsequently underwent nucleophilic addition to different carbonyl compounds, yielding the corresponding 2-(hydroxyalkyl)-1-pentyl-

Table 1 Lithiation–Deuteration Reaction of Imidazoles **6**–**8**[a]



Entry	R^1	Isoprene (mol%)	Product	D Incorporation[b] (%)
1	**6**: $(CH_2)_4Me$	100	**12a**	>95
2	**7**: $(CH_2)_3Me$	100	**13a**	10
3	**7**: $(CH_2)_3Me$	150	**13a**	25
4	**7**: $(CH_2)_3Me$	200	**13a**	>95
5	**8**: $(CH_2)_{11}Me$	100	**14a**	<5
6	**8**: $(CH_2)_{11}Me$	200	**14a**	<5
7	**8**: $(CH_2)_{11}Me$	300	**14a**	20
8	**8**: $(CH_2)_{11}Me$	300	**14a**	>95[c]

[a] The reactions were carried out using the imidazole derivative **6**–**8** (1 mmol), lithium powder (3 mmol) and isoprene in THF (5 mL).
[b] Determined by ^1H NMR spectroscopy.
[c] The lithiation step was performed at 45 °C instead of 25 °C.

1*H*-imidazoles **12b**–**g** (Figure 1; Table 2, entries 1–6). The corresponding 1-butyl-2-lithio-1*H*-imidazole was prepared employing a higher amount of isoprene (200 mol%) and increasing the temperature during the lithiation step to 45 °C, being afterwards reacted with different

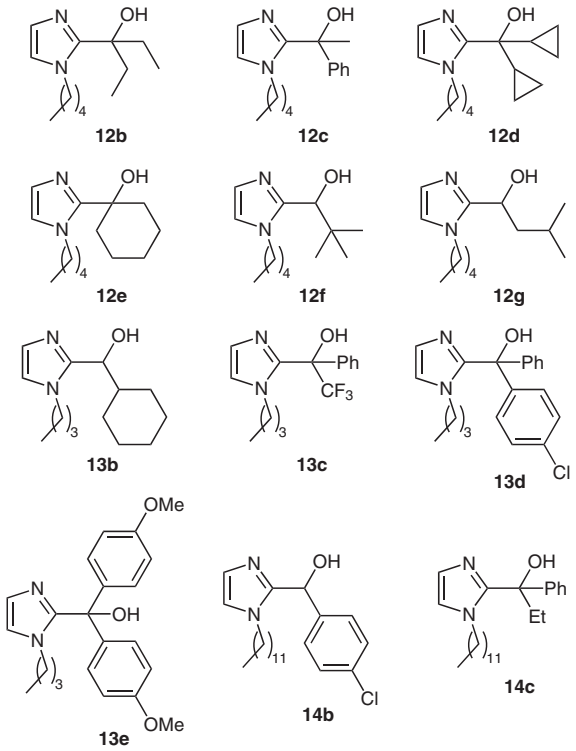
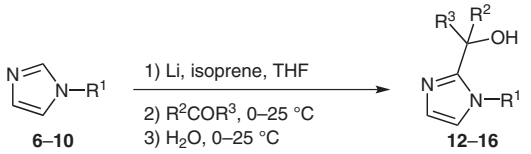


Figure 1 Imidazole derivatives **12**–**14** prepared from 1-alkylimidazoles **6**–**8**

carbonyl compounds to generate derivatives **13b**–**e** (Figure 1; Table 2, entries 7–10). Finally, the imidazole derivative **8** was also successfully lithiated at 45 °C, albeit an excess (300 mol%) of isoprene was needed. The corresponding imidazol-2-ylcarbinol derivatives **14b**,**c** (Figure 1; Table 2, entries 11 and 12) were isolated after reacting the 2-lithio intermediate with electrophiles. In general, the products were obtained with moderate to good yields, except in the case of enolizable carbonyl compounds probably due to the basic character of the reactive species. Derivatives with a similar motif of aryl(azolyl)carbinol are reported to be effective in the treatment of different diseases, syndromes and disorders.[16]

Imidazole derivatives bearing a secondary alkyl substituent on the nitrogen reacted smoothly with lithium in the presence of isoprene as mediator. Indeed, 1-cyclohexyl-1*H*-imidazole (**9**) were treated with lithium in the presence of a substoichiometric amount of isoprene (20 mol%) at room temperature during 90 minutes, producing the corresponding 1-cyclohexyl-2-lithio-1*H*-imidazole which afterwards underwent nucleophilic addition to pentan-3-one to provide the imidazole derivative **15a** in 80% isolated yield.[17] Moreover, **15a** was obtained, with comparable yield, in a shorter reaction time by employing an excess of isoprene during the lithiation step (Figure 2; Table 2, entry 13). Similarly, the 1-cyclohexyl-2-lithio-1*H*-imidazole intermediate was successfully employed in the preparation of the functionalized imidazoles **15b** and **15c** (Figure 2; Table 2, entries 14 and 15). 1-(1-Methylheptyl)-1*H*-imidazole (**10**) was, as well, treated with the mixture lithium/isoprene (300 mol%:200 mol%) at room temperature producing the expected organolithium inter-

Table 2 Lithiation of 1-Alkylimidazole Derivatives and Subsequent Reaction with Electrophiles



6–10 **12–16**

Entry	Starting imidazole	Conditions[a]	R^2	R^3	Product[b]	Yield[c] (%)
1	**6**	A	Et	Et	**12b**	61
2	**6**	A	Ph	Me	**12c**	28
3	**6**	A	*c*-Pr	*c*-Pr	**12d**	74
4	**6**	A	$-(CH_2)_5-$		**12e**	30
5	**6**	A	*t*-Bu	H	**12f**	54
6	**6**	A	*i*-Bu	H	**12g**	21
7	**7**	B	Cy	H	**13b**	55
8	**7**	B	Ph	CF_3	**13c**	56
9	**7**	B	4-ClC_6H_4	Ph	**13d**	86
10	**7**	B	4-$MeOC_6H_4$	4-$MeOC_6H_4$	**13e**	64
11	**8**	C	4-ClC_6H_4	H	**14b**	73
12	**8**	C	Ph	Et	**14c**	19
13	**9**	D	Et	Et	**15a**	82
14	**9**	D	Ph	Me	**15b**	53
15	**9**	D	*t*-Bu	H	**15c**	65
16	**10**	D	Et	Et	**16a**	65
17	**10**	D	Ph	Me	**16b**	92[d]
18	**10**	D	*t*-Bu	H	**16c**	94[e]

[a] The lithiation reactions were conducted, during 1 h, under the following conditions: (A) lithium powder (300 mol%), isoprene (100 mol%), 25 °C; (B) lithium powder (300 mol%), isoprene (200 mol%), 45 °C; (C) lithium powder (300 mol%), isoprene (300 mol%), 45 °C; (D) lithium powder (300 mol%), isoprene (200 mol%), 25 °C.
[b] All products were >95% pure (by GLC and/or 300-MHz ^{1}H NMR spectroscopy).
[c] Isolated yield after column chromatography (silica gel, hexane–EtOAc), based on the starting imidazole **6**–**10**.
[d] Obtained as a mixture of diastereoisomers (50% de, by ^{1}H NMR spectroscopy).
[e] Obtained as a mixture of diastereoisomers (9% de, by ^{1}H NMR spectroscopy).

mediate which was subsequently reacted with various carbonyl compounds giving, after quenching with water, the corresponding products **16** (Figure 2; Table 2, entries 16–18). In this case, the reaction with a prochiral electrophile (i.e., acetophenone or pivalaldehyde) occurred with some diastereoselectivity. Thus, compounds **16b** and **16c** were obtained with 50% and 9% de, respectively.

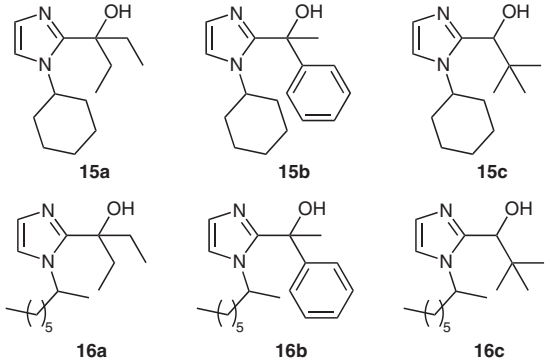


Figure 2 Imidazole derivatives **15** and **16** prepared from 1-alkylimidazoles **9** and **10**

In conclusion, we have shown that the isoprene-mediated lithiation methodology is effective in the preparation of 2-lithioimidazole intermediates having a primary or a secondary substituent on the nitrogen. Lithiation of imidazoles with a primary alkyl substituent depends on the chain length: 1-dodecyl-1*H*-imidazole needs higher amounts of isoprene and increased temperature than 1-butyl- or 1-pentyl-1*H*-imidazole, although 1-butyl-1*H*-imidazole also gave better results at 45 °C. Lithiation of imidazoles bearing a secondary alkyl substituent (i.e., cyclohexyl or 1-methylheptyl) on the nitrogen takes place under mild reaction conditions, similarly to a short, primary alkyl substituent. 1-Adamantyl-1*H*-imidazole does not form the corresponding organolithium intermediate under the studied reaction conditions. Additionally, the nucleophilic addition of the generated lithiated imidazole derivatives to different electrophiles allows the preparation of a variety of imidazol-2-ylcarbinol derivatives which are an interesting class of compounds with potential pharmacological properties.

All lithiation reactions were carried out under argon atmosphere in oven-dried glassware. All commercially available reagents (Acros, Aldrich, Fluka) were used without further purification, except in the case of liquid electrophiles which were freshly distilled before use. Lithium powder was commercially available (Medalchemy S.L.). THF was dried in a Sharlab PS-400-3MD solvent purification system using an alumina column. Infrared analysis was performed with a Nicolet Impact 400D FTIR or a Jasco 4100LE (Pike MIRacle ATR) spectrophotometer, and wavenumbers are given in cm^{-1}. NMR spectroscopic data were recorded with Bruker Avance 300 and 400 spectrometers (300 and 400 MHz for ^1H NMR, 75 and 100 MHz for ^{13}C NMR) using $CDCl_3$ as the solvent and TMS as the internal standard. Chemical shifts are given in parts per million (δ), and coupling constants (*J*) are given in hertz. Mass spectra (EI) were obtained at 70 eV with an Agilent 5973 spectrometer, and fragment ions are given as *m*/*z* with relative intensities (%) in parenthesis; where indicated, the samples were inserted in the modality of direct insertion probe (DIP) and, where indicated, mass spectra were obtained with an Agilent 1100 Series HPLC system with electrospray ionization (ESI). High-resolution mass spectrometry (HRMS) analyses were carried out with a Finningan MAT 95S spectrometer. The purity of volatile compounds and the chromatographic analyses (GLC) were determined with an Agilent 6890N instrument equipped with a flame ionization detector and a 30-m capillary column (diameter: 0.25 mm, film thickness: 0.25 μm), using nitrogen (2 mL/min) as the carrier gas [$T_{injector}$ = 275 °C, T_{column} = 80 °C (3 min) then 80–270 °C (15 °C/min)]; retention times (t_R) are given in minutes under these conditions. Analytical TLC was performed on Merck aluminum sheets with silica gel 60 F254. Silica gel 60 (40–60 microns) was employed for flash chromatography.

Synthesis of 1-Alkyl-1*H*-imidazoles 6–11

1-Pentyl-1*H*-imidazole (6)[15]

A soln of 1*H*-imidazole (1.36 g, 20 mmol) in toluene (8 mL) was placed in a 50-mL round-bottom flask, then a soln of NaOH (1.60 g, 40 mmol) and Et_4NBr (1.05 g, 5 mmol) in H_2O (10 mL) was added. The resulting mixture was heated to reflux, which was followed by the dropwise addition of 1-bromopentane (2.48 mL, 20 mmol). The reaction mixture was stirred under reflux for 24 h. After the reaction mixture was cooled, it was extracted with EtOAc (3 × 10 mL). The resulting organic phase was dried (anhyd $MgSO_4$), and the solvent was evaporated under reduced pressure. The crude material was purified by column chromatography (silica gel, EtOAc), giving the imidazole **6**; yield: 2.1 g (75%).

Pale brown oil; GLC: t_R = 9.9 min; R_f = 0.21 (EtOAc).

IR (film): 3110 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 0.88 (t, *J* = 7.1 Hz, 3 H, CH_3), 1.26–1.34, 1.77 (2 m, 4 H, 2 H, $CH_3CH_2CH_2CH_2$), 3.91 (t, *J* = 7.2 Hz, 2 H, NCH_2), 6.89, 7.04, 7.45 (3 s, 3 × 1 H, imidazole).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 13.8, 22.1, 28.6, 30.7, 47.0, 118.7, 129.2, 137.0.

MS (EI): *m*/*z* (%) = 138 (48) [M^+], 137 (10), 123 (12), 111 (97), 96 (32), 95 (13), 83 (13), 82 (100), 81 (76), 70 (18), 68 (23), 55 (38), 54 (21).

HRMS: *m*/*z* [M^+] calcd for $C_8H_{14}N_2$: 138.1157; found: 138.1167.

1-Butyl-1*H*-imidazole (7);[15] Typical Procedure

A soln of butan-1-amine (0.99 mL, 10 mmol) and 25% aq NH_3 (0.75 mL, 10 mmol) in MeOH (4 mL) and a soln of glyoxal (trimer dihydrate; 0.70 g, 10 mmol of glyoxal) and 36% aq formaldehyde (0.77 mL, 10 mmol) in a mixture of MeOH (4 mL) and H_2O (4 mL) were slowly and simultaneously added to a round-bottom flask with MeOH (7 mL) heated to 50 °C. After the addition was finished, the reaction mixture was heated to 75 °C for 3 h. The reaction mixture was cooled, Et_2O and H_2O were added in equal portions until two phases were observed, and the aqueous layer was extracted with Et_2O (3 × 10 mL). The combination of all the organic phases was dried (anhyd $MgSO_4$), and the solvent was evaporated under reduced pressure. The crude material was purified by column chromatography (silica gel, mixtures of hexane and EtOAc), giving the imidazole **7**; yield: 0.62 g (50%).

Yellow oil; GLC: t_R = 8.9 min; R_f = 0.19 (EtOAc).

IR (film): 3105 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 0.94 (t, *J* = 7.4 Hz, 3 H, CH_3), 1.33, 1.76 (2 m, 2 H, 2 H, $CH_3CH_2CH_2$), 3.93 (t, *J* = 7.1 Hz, 2 H, NCH_2), 6.90, 7.04, 7.45 (3 s, 3 × 1 H, imidazole).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 13.5, 19.7, 33.0, 46.7, 118.7, 129.3, 137.0.

MS (EI): *m*/*z* (%) = 124 (48) [M^+], 97 (85), 82 (100), 69 (22), 68 (35), 55 (71), 54 (37).

HRMS: *m*/*z* [M$^+$] calcd for $C_7H_{12}N_2$: 124.1000; found: 124.1007.

1-Dodecyl-1*H*-imidazole (8)[15]
Following the same procedure, although employing dodecan-1-amine (2.32 mL, 10 mmol), the imidazole **8** was isolated; yield: 1.42 g (60%).

Yellow oil; GLC: t_R = 15.7 min; R_f = 0.36 (EtOAc).

IR (film): 3105 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.88 (t, *J* = 6.7 Hz, 3 H, CH_3), 1.25–1.30 (m, 18 H, 9 × CH_2), 1.77 (m, 2 H, NCH_2CH_2), 3.92 (t, *J* = 7.1 Hz, 2 H, NCH_2), 6.90, 7.05, 7.46 (3 s, 3 × 1 H, imidazole).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.0, 22.6, 26.5, 29.0, 29.2, 29.3, 29.4, 29.5, 31.0, 31.8, 47.0, 118.7, 129.2, 137.0.

MS (EI): *m*/*z* (%) = 236 (32) [M$^+$], 235 (46), 221 (13), 207 (33), 179 (31), 165 (26), 151 (28), 137 (132), 123 (44), 110 (21), 109 (33), 96 (50), 95 (40), 83 (17), 82 (100), 81 (45), 69 (49), 68 (20), 55 (42), 54 (19).

HRMS: *m*/*z* [M$^+$] calcd for $C_{15}H_{28}N_2$: 236.2252; found: 236.2242.

1-Cyclohexyl-1*H*-imidazole (9)[18]
Following the same procedure, although employing cyclohexanamine (1.14 mL, 10 mmol), the imidazole **9** was isolated; yield: 1.20 g (80%).

Yellow oil; GLC: t_R = 11.8 min; R_f = 0.15 (EtOAc).

IR (film): 3110 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.21–1.32, 1.42–1.50, 1.59–1.74, 1.75–1.80, 1.89–1.95, 2.11–2.15 (6 m, 1 H, 2 H, 2 H, 1 H, 2 H, 2 H, 5 × CH_2), 3.93 [m, 1 H, NC*H*(CH_2)CH_2], 6.97, 7.06, 7.55 (3 s, 3 × 1 H, imidazole).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 25.2, 25.4, 34.4, 56.7, 116.9, 128.9, 135.3.

MS (EI): *m*/*z* (%) = 151 (11) [M$^+$ + 1], 150 (100) [M$^+$], 123 (95), 122 (14), 107 (13), 95 (13), 83 (19), 81 (15), 69 (96), 68 (33), 67 (30), 55 (62), 54 (13), 53 (13).

1-(1-Methylheptyl)-1*H*-imidazole (10)[19]
Following the same procedure, although employing octan-2-amine (1.68 mL, 10 mmol), the imidazole **10** was isolated; yield: 1.35 g (75%).

Yellow oil; GLC: t_R = 9.9 min; R_f = 0.55 (EtOAc).

IR (film): 3105 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.84 (t, *J* = 6.8 Hz, 3 H, CH_2CH_3), 1.10–1.26 (m, 8 H, 4 × CH_2), 1.44 (d, *J* = 6.8 Hz, 3 H, $NCHCH_3$), 1.70 (m, 2 H, $NCHCH_2$), 4.10 (m, 1 H, NC*H*CH_3), 6.90, 7.00, 7.47 (3 s, 3 × 1 H, imidazole).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.0, 22.2, 22.5, 26.0, 28.8, 31.6, 37.8, 53.7, 116.4, 129.2, 135.8.

MS (EI): *m*/*z* (%) = 180 (24) [M$^+$], 165 (36), 153 (47), 138 (13), 137 (30), 124 (11), 111 (11), 110 (24), 109 (14), 97 (15), 96 (100), 95 (71), 81 (16), 69 (62), 68 (30), 57 (12), 55 (13).

1-Adamantyl-1*H*-imidazole (11)
To a 50-mL round-bottom flask was added adamantylamine (3.075 g, 20 mmol), NH_4OAc (1.54 g, 20 mmol), H_2O (2 mL) and AcOH (10 mL), and the mixture was heated to 80 °C. Then, a soln of 36% aq formaldehyde (1.53 mL, 20 mmol) and 40% aq glyoxal (2.30 mL, 20 mmol) in AcOH (5 mL) was added slowly, and the reaction mixture was stirred for 24 h. The reaction mixture was cooled and was slowly added to a soln of $NaHCO_3$ (14.7 g) in H_2O (150 mL). The resulting mixture was extracted with CH_2Cl_2 (3 × 15 mL), then the extracts were dried (anhyd $MgSO_4$), and the solvent was evaporated under reduced pressure. The obtained yellow solid was purified by recrystallization (CH_2Cl_2–hexane) to give the imidazole **11**; yield: 0.61 g (15%).

Yellow solid; mp 105–106 °C (EtOAc); GLC: t_R = 15.7 min; R_f = 0.16 (EtOAc).

IR (KBr): 3112 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.77, 2.10, 2.20 (3 m, 6 H, 6 H, 3 H, adamantyl), 7.07 (m, 2 H, imidazole), 7.65 (s, 1 H, imidazole).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 29.4, 35.9, 43.2, 55.0, 115.3, 128.6, 133.5.

MS (EI): *m*/*z* (%) = 202 (23) [M$^+$], 136 (11), 135 (100), 107 (11), 93 (23), 91 (10), 79 (26), 77 (11).

HRMS: *m*/*z* [M$^+$] calcd for $C_{13}H_{18}N_2$: 202.1692; found: 202.1460.

Isoprene-Mediated Lithiation; General Procedure
To a 25-mL Schlenk flask were added lithium powder (0.042 g, 6 mmol) and isoprene (2–6 mmol, see Table 2) in THF (5 mL). The corresponding 1-alkyl-1*H*-imidazole (2 mmol) was added to the suspension, and the mixture was stirred for 1 h at 25 or 45 °C (see Table 2). The flask was placed in an ice–water bath and the electrophile (2.2 mmol) was added dropwise; the stirring was continued for 45 min while allowing the mixture to reach r.t. (for deuteration experiments, D_2O was added instead of electrophile). The reaction was quenched, at 0 °C, with H_2O (10 mL), the mixture was extracted with EtOAc (3 × 10 mL), and the resulting organic phase was dried (anhyd $MgSO_4$). The solvent was evaporated under reduced pressure, and the resulting crude material was purified by column chromatography (silica gel, mixtures of hexane and EtOAc). Yields are given in Table 2; physical, spectroscopic and analytical data, as well as literature references for known compounds, follow.

2-Deutero-1-pentyl-1*H*-imidazole (12a)
^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.90 (t, *J* = 7.0 Hz, 3 H, CH_3), 1.22–1.39, 1.78 (2 m, 4 H, 2 H, $CH_3CH_2CH_2CH_2$), 3.92 (t, *J* = 7.2 Hz, 2 H, NCH_2), 6.90 (d, *J* = 1.2 Hz, 1 H, imidazole), 7.05 (d, *J* = 1.2 Hz, 1 H, imidazole).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 13.9, 22.1, 28.7, 30.7, 47.0, 118.7, 129.3, 137.0 (t, *J* = 16.0 Hz).

MS (EI): *m*/*z* (%) = 139 (43) [M$^+$], 138 (13), 124 (11), 112 (84), 97 (26), 96 (18), 84 (12), 83 (93), 82 (100), 81 (23), 70 (17), 69 (31), 68 (10), 55 (71), 54 (11).

3-(1-Pentyl-1*H*-imidazol-2-yl)pentan-3-ol (12b)
Pale yellow oil; yield: 0.274 g (61%); GLC: t_R = 12.8 min; R_f = 0.31 (EtOAc).

IR (film): 3114 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.77 [t, *J* = 7.4 Hz, 6 H, $C(OH)(CH_2CH_3)_2$], 0.92 (t, *J* = 7.4 Hz, 3 H, $CH_2CH_2CH_3$), 1.36 (m, 5 H, $CH_2CH_2CH_3$ and OH), 1.78 (m, 2 H, NCH_2CH_2), 1.89 [m, 4 H, $C(OH)(CH_2CH_3)_2$], 4.02 (m, 2 H, NCH_2), 6.89, 6.92 (2 s, 2 × 1 H, 1 H, imidazole).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 8.1, 14.0, 22.4, 29.0, 31.2, 33.4, 47.1, 76.5, 120.8, 126.0, 150.0.

MS (EI): *m*/*z* (%) = 224 (2) [M$^+$], 196 (14), 195 (100), 125 (33), 69 (17).

HRMS: *m*/*z* [M$^+$] calcd for $C_{13}H_{24}N_2O$: 224.1889; found: 224.1897.

1-(1-Pentyl-1*H*-imidazol-2-yl)-1-phenylethanol (12c)
White solid; yield: 0.145 g (28%); mp 174–176 °C (EtOAc); GLC: t_R = 14.6 min; R_f = 0.57 (EtOAc).

IR (KBr): 3113 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.76 (t, *J* = 7.1 Hz, 3 H, CH_2CH_3), 0.96–1.11, 1.37–1.42 (2 m, 5 H, 1 H, 3 × CH_2), 1.94 (s, 3 H, CH_3COH), 3.67–3.77 (m, 2 H, NCH_2), 6.88, 6.92 (2 s, 2 H, imidazole), 7.22–7.28 (m, 5 H, 5 × ArH).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 13.4, 21.2, 28.4, 29.7, 31.7, 46.4, 72.7, 120.5, 124.3, 125.2, 126.6, 127.9, 146.0, 150.8.

MS (EI): *m*/*z* (%) = 258 (4) [M$^+$], 257 (23), 243 (79), 241 (24), 240 (37), 239 (35), 213 (29), 197 (36), 183 (34), 181 (29), 173 (46), 169 (41), 138 (22), 137 (20), 120 (21), 111 (77), 105 (100), 96 (21), 95 (29), 82 (64), 81 (49), 77 (77), 69 (26), 68 (18), 55 (31), 51 (19).

HRMS: *m*/*z* [M$^+$] calcd for $C_{16}H_{22}N_2O$: 258.1732; found: 258.1718.

Dicyclopropyl(1-pentyl-1*H*-imidazol-2-yl)methanol (12d)
White solid; yield: 0.367 g (74%); mp 52–54 °C (EtOAc); R_f = 0.47 (EtOAc).

IR (KBr): 3147, 3005 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.27–0.34, 0.37–0.43, 0.46–0.53, 0.69–0.75 (4 m, 4 × 2 H, 2 × C*H*$_2$C*H*$_2$CH), 0.92 (t, *J* = 6.8 Hz, 3 H, CH_3), 1.20–1.27 (m, 2 H, 2 × CH_2CH_2CH), 1.34–1.38, 1.84 (2 m, 4 H, 2 H, $CH_3CH_2CH_2CH_2$), 4.05 (br s, 1 H, OH), 4.14 (m, 2 H, NCH_2), 6.90 (s, 2 H, imidazole).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 13.9, 19.2, 22.4, 29.0, 30.1, 31.3, 47.3, 70.6, 120.9, 125.5, 152.4.

MS (HPLC, ESI): *m*/*z* = 249 [M$^+$ + 1], 231 [M$^+$ + 1 – 18].

1-(1-Pentyl-1*H*-imidazol-2-yl)cyclohexanol (12e)
White solid; yield: 0.142 g (30%); mp 86–88 °C (EtOAc); GLC: t_R = 14.8 min; R_f = 0.22 (EtOAc).

IR (KBr): 3253 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.91 (t, *J* = 6.9 Hz, 3 H, CH_3), 1.29–1.38, 1.66–1.70, 1.73–1.84, 1.88–1.93, 1.99–2.09 (5 m, 5 H, 4 H, 3 H, 2 H, 3 H, 8 × CH_2 and OH), 4.18 (m, 2 H, NCH_2), 6.87 (d, *J* = 1.2 Hz, 1 H, imidazole), 6.90 (d, *J* = 1.2 Hz, 1 H, imidazole).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 13.9, 22.2, 22.4, 25.4, 29.0, 31.4, 37.3, 47.1, 71.7, 120.7, 126.3, 151.8.

MS (EI): *m*/*z* (%) = 336 (12) [M$^+$], 335 (12), 219 (100), 207 (32), 194 (18), 193 (86), 181 (47), 179 (20), 175 (15), 165 (29), 137 (64), 123 (39), 109 (11), 96 (14), 95 (23), 82 (26), 81 (25), 69 (35), 55 (27), 54 (11).

HRMS: *m*/*z* [M$^+$] calcd for $C_{14}H_{24}N_2O$: 236.1889; found: 236.1848.

2,2-Dimethyl-1-(1-pentyl-1*H*-imidazol-2-yl)propan-1-ol (12f)
Pale yellow solid; yield: 0.242 g (54%); mp 72–74 °C (EtOAc); GLC: t_R = 12.8 min; R_f = 0.59 (EtOAc).

IR (KBr): 3110 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.86–0.91 (t, *J* = 6.8 Hz, 3 H, CH_2CH_3), 0.96 [s, 9 H, $C(CH_3)_3$], 1.29–1.32 (m, 4 H, C*H*$_2$C*H*$_2$CH$_3$), 1.75 (m, 2 H, NCH_2CH_2), 3.67 (br s, 1 H, OH), 3.89 (m, 2 H, NCH_2), 4.36 (s, 1 H, *H*COH), 6.82, 6.95 (2 s, 1 H, 1 H, imidazole).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 13.8, 22.2, 25.9, 28.8, 30.7, 37.0, 46.3, 73.6, 118.8, 127.1, 148.5.

MS (EI): *m*/*z* (%) = 224 (3) [M$^+$], 168 (13), 167 (100), 137 (19), 97 (49).

HRMS: *m*/*z* [M$^+$] calcd for $C_{13}H_{24}N_2O$: 224.1889; found: 224.1895.

3-Methyl-1-(1-pentyl-1*H*-imidazol-2-yl)butan-1-ol (12g)
Colorless oil; yield: 0.094 g (21%); GLC: t_R = 12.8 min; R_f = 0.40 (EtOAc).

IR (film): 3176 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.90–0.95 (m, 3 H, CH_2CH_3), 0.96–0.99 [m, 6 H, $CH(CH_3)_2$], 1.33–1.37 (m, 4 H, C*H*$_2$C*H*$_2$CH$_3$), 1.70–1.90 [m, 6 H, $CH_2CH(CH_3)_2$, NCH_2CH_2 and OH], 3.93–4.00 (m, 2 H, NCH_2), 4.76–4.80 (m, 1 H, *H*COH), 6.87, 6.97 (2 s, 2 × 1 H, 1 H, imidazole).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 13.9, 22.0, 22.2, 23.2, 24.6, 28.8, 30.8, 45.6, 45.9, 64.7, 119.6, 126.9, 149.7.

MS (DIP, EI): *m*/*z* (%) = 224 (1) [M$^+$], 155 (23), 154 (11), 141 (14), 140 (100), 126 (36), 95 (35).

HRMS: *m*/*z* [M$^+$] calcd for $C_{13}H_{24}N_2O$: 224.1889; found: 224.1889.

1-Butyl-2-deutero-1*H*-imidazole (13a)
Yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.94 (t, *J* = 7.3 Hz, 3 H, CH_3), 1.33, 1.76 (2 m, 2 × 2 H, $CH_3CH_2CH_2$), 3.94 (t, *J* = 7.1 Hz, 2 H, NCH_2), 6.90 (d, *J* = 1.1 Hz, 1 H, imidazole), 7.05 (d, *J* = 1.1 Hz, 1 H, imidazole).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 13.5, 19.7, 33.0, 46.7, 118.7, 129.2, 136.4 (t, *J* = 31.4 Hz).

MS (EI): *m*/*z* (%) = 125 (58) [M$^+$], 98 (93), 83 (100), 82 (96), 81 (12), 70 (20), 69 (31), 56 (13), 55 (85), 54 (10).

(1-Butyl-1*H*-imidazol-2-yl)cyclohexylmethanol (13b)
Yellow oil; yield: 0.260 g (55%); GLC: t_R = 14.9 min; R_f = 0.20 (EtOAc).

IR (film): 3115 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.96 (t, *J* = 7.3 Hz, 3 H, CH_3), 0.99–1.41, 1.60–1.87 (2 m, 9 H, 6 H, 7 × CH_2 and OH), 2.03–2.05 (d, *J* = 8.0 Hz, 1 H, HOCHC*H*), 3.93 (t, *J* = 7.5 Hz, 2 H, NCH_2), 4.37 (d, *J* = 8.0 Hz, 1 H, HOC*H*), 6.84, 6.96 (2 s, 2 × 1 H, imidazole).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 13.7, 19.9, 25.8, 26.0, 26.3, 28.8, 29.4, 33.2, 43.7, 45.6, 71.1, 119.4, 127.0, 149.1.

MS (EI): *m*/*z* (%) = 236 (4) [M$^+$], 219 (12), 154 (59), 153 (100), 123 (35), 112 (10), 97 (75), 81 (11), 69 (15), 55 (13).

HRMS: *m*/*z* [M$^+$] calcd for $C_{14}H_{24}N_2O$: 236.1889; found: 236.1901.

1-(1-Butyl-1*H*-imidazol-2-yl)-2,2,2-trifluoro-1-phenylethanol (13c)
White solid; yield: 0.334 g (56%); mp 123–125 °C (EtOAc); R_f = 0.70 (EtOAc).

IR (KBr): 3068 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.73 (t, *J* = 7.3 Hz, 3 H, CH_3), 1.06, 1.25–1.35 (2 m, 2 × 2 H, $CH_3CH_2CH_2$), 3.55–3.67 (m, 2 H, NCH_2), 4.96 (br s, 1 H, OH), 7.00 (d, *J* = 1.1 Hz, 1 H, imidazole), 7.14 (d, *J* = 1.1 Hz, 1 H, imidazole), 7.45–7.51 (m, 5 H, 5 × ArH).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 13.4, 19.7, 32.2, 46.6, 76.2 (q, *J* = 29.8 Hz), 122.0, 124.2 (q, *J* = 286 Hz), 127.0, 127.2, 128.4, 129.1, 136.0, 143.7.

MS (DIP, EI): *m*/*z* (%) = 299 (10) [M$^+$ + 1], 298 (27) [M$^+$], 297 (10), 269 (28), 256 (11), 251 (14), 241 (12), 230 (15), 229 (90), 199 (60), 187 (10), 173 (100), 165 (17), 149 (13), 144 (10), 133 (10), 123 (11), 117 (10), 105 (51), 95 (39), 91 (18), 77 (34), 69 (10), 57 (11), 55 (10), 43 (15), 41 (14).

HRMS: *m*/*z* [M$^+$] calcd for $C_{15}H_{17}F_3N_2O$: 298.1293; found: 298.1289.

(1-Butyl-1*H*-imidazol-2-yl)(4-chlorophenyl)phenylmethanol (13d)
Yellow oil; yield: 0.585 g (86%); R_f = 0.69 (EtOAc).

IR (film): 3058 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.68 (t, *J* = 7.2 Hz, 3 H, CH_3), 0.93–1.03, 1.10–1.17 (2 m, 2 × 2 H, $CH_3CH_2CH_2$), 3.55–3.63 (m, 2 H, NCH_2), 6.90–6.92, 6.98–7.00 (2 m, 2 × 1 H, imidazole), 7.18–7.36 (m, 9 H, 9 × ArH).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 13.5, 19.8, 32.2, 47.1, 77.2, 121.1, 126.4, 127.2, 127.5, 127.8, 127.9, 128.1, 129.2, 129.3, 144.4, 150.2.

MS (DIP, EI): *m*/*z* (%) = 340 (7) [M$^+$], 307 (21), 306 (100), 305 (31), 287 (13), 249 (16), 231 (11), 229 (54), 199 (14), 173 (54), 165 (10), 105 (42), 95 (16), 77 (32).

HRMS: *m/z* [M$^+$] calcd for $C_{20}H_{21}ClN_2O$: 340.1342; found: 340.1329.

(1-Butyl-1*H*-imidazol-2-yl)[bis(4-methoxyphenyl)]methanol (13e)
White solid; yield: 0.469 g (64%); mp 107–108 °C (EtOAc); R_f = 0.55 (EtOAc).

IR (KBr): 3109 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.72 (t, *J* = 7.2 Hz, 3 H, $CH_3CH_2CH_2$), 1.03, 1.14–1.22 (2 m, 2 × 2 H, $CH_3CH_2CH_2CH_2$), 3.61 (m, 2 H, NCH_2), 3.80 (s, 6 H, 2 × OCH_3), 6.85 (m, 4 H, 4 × ArH), 6.91 (d, *J* = 1.3 Hz, 1 H, imidazole), 7.01 (d, *J* = 1.3 Hz, 1 H, imidazole), 7.15 (m, 4 H, 4 × ArH).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 13.5, 30.9, 32.4, 47.1, 55.3, 77.9, 113.3, 121.0, 126.3, 129.0, 136.9, 150.6, 159.0.

MS (DIP, EI): *m/z* (%) = 367 (20) [M$^+$ + 1], 366 (86) [M$^+$], 260 (16), 259 (100), 226 (32), 203 (29), 151 (23), 135 (65), 95 (12), 77 (13).

HRMS: *m/z* [M$^+$] calcd for $C_{22}H_{26}N_2O_3$: 366.1943; found: 366.1910.

2-Deutero-1-dodecyl-1*H*-imidazole (14a)
Yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.88 (t, *J* = 6.7 Hz, 3 H, CH_3), 1.25–1.30 (m, 18 H, 9 × CH_2), 1.77 (m, 2 H, NCH_2CH_2), 3.92 (t, *J* = 7.2 Hz, 2 H, NCH_2), 6.90 (d, *J* = 1.1 Hz, 1 H, imidazole), 7.05 (d, *J* = 1.1 Hz, 1 H, imidazole).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.0, 22.6, 26.5, 29.0, 29.2, 29.3, 29.4, 29.5, 31.0, 31.8, 47.0, 118.7, 129.2, 136.4 (t, *J* = 31.7 Hz).

MS (EI): *m/z* (%) = 237 (53) [M$^+$], 236 (42), 235 (31), 222 (19), 208 (42), 194 (41), 180 (39), 166 (35), 152 (37), 138 (37), 124 (44), 123 (30), 111 (30), 110 (15), 109 (18), 97 (59), 96 (62), 95 (19), 83 (100), 82 (73), 70 (44), 69 (34), 55 (45).

(4-Chlorophenyl)(1-dodecyl-1*H*-imidazol-2-yl)methanol (14b)
Yellow solid; yield: 0.549 g (73%); mp 31–33 °C; R_f = 0.48 (EtOAc).

IR (KBr): 3142 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.88 (t, *J* = 6.9 Hz, 3 H, CH_3), 1.09–1.32 (m, 19 H, 9 × CH_2 and OH), 1.38–1.51 (m, 2 H, NCH_2CH_2), 3.67 (m, 2 H, NCH_2), 5.84 (s, 1 H, HOC*H*), 6.83 (d, *J* = 1.2 Hz, 1 H, imidazole), 6.93 (d, *J* = 1.2 Hz, 1 H, imidazole), 7.25–7.31 (m, 4 H, 4 × ArH).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.1, 22.7, 26.5, 29.1, 29.2, 29.3, 29.4, 29.5, 29.6, 30.4, 31.9, 46.0, 68.7, 120.5, 126.8, 127.9, 128.6, 133.6, 139.7, 148.2.

MS (DIP, EI): *m/z* (%) = 379 (3) [M$^+$ + 3], 378 (15) [M$^+$ + 2], 377 (12) [M$^+$ + 1], 376 (43) [M$^+$], 345 (15), 265 (11), 251 (14), 236 (20), 235 (100), 207 (11), 97 (22), 43 (11), 41 (11).

HRMS: *m/z* [M$^+$] calcd for $C_{22}H_{33}ClN_2O$: 376.2281; found: 376.2279.

1-(1-Dodecyl-1*H*-imidazol-2-yl)-1-phenylpropan-1-ol (14c)
Yellow oil; yield: 0.141 g (19%); R_f = 0.53 (EtOAc).

IR (film): 3074 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.84–0.88 (m, 6 H, 2 × CH_3), 1.26–1.96 (m, 20 H, 10 × CH_2), 2.43 (m, 2 H, HOCCH_2), 2.90 (br s, 1 H, OH), 3.61–3.69 (m, 2 H, NCH_2), 6.85, 6.99 (2 s, 2 × 1 H, imidazole), 7.26–7.30 (m, 5 H, 5 × ArH).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 7.5, 14.1, 22.7, 26.5, 29.0, 29.3, 29.5, 29.6, 30.5, 30.9, 31.9, 35.0, 46.5, 75.7, 120.8, 125.6, 126.1, 127.0, 128.1, 143.8, 150.4.

MS (DIP, EI): *m/z* (%) = 370 (6) [M$^+$], 342 (26), 341 (100), 173 (11), 105 (7).

HRMS: *m/z* [M$^+$] calcd for $C_{24}H_{38}N_2O$: 370.2984; found: 370.2983.

3-(1-Cyclohexyl-1*H*-imidazol-2-yl)pentan-3-ol (15a)
White solid; yield: 0.387 g (82%); mp 132–134 °C (EtOAc); GLC: t_R = 11.8 min; R_f = 0.24 (EtOAc).

IR (KBr): 3113 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.78 (t, *J* = 7.4 Hz, 6 H, 2 × CH_2CH_3), 1.23–1.42, 1.58–1.68, 1.76–1.80, 1.85–2.00 (4 m, 4 H, 4 H, 1 H, 6 H, 7 × CH_2 and OH), 4.21–4.27 (m, 1 H, CH-cyclohexyl), 6.95, 6.98 (2 s, 2 × 1 H, imidazole).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 8.0, 25.2, 26.0, 33.3, 34.9, 56.2, 75.4, 117.7, 126.0, 149.4.

MS (EI): *m/z* (%) = 236 (4) [M$^+$], 207 (50), 125 (100), 69 (17).

HRMS: *m/z* [M$^+$] calcd for $C_{14}H_{24}N_2O$: 236.1889; found: 236.1892.

1-(1-Cyclohexyl-1*H*-imidazol-2-yl)-1-phenylethanol (15b)
Pale yellow solid; yield: 0.286 g (53%); mp 207–209 °C (EtOAc); GLC: t_R = 11.9 min; R_f = 0.52 (EtOAc).

IR (KBr): 3140, 3120 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.67–0.76, 0.84–0.87, 0.99–1.55, 1.71–1.75, 1.86–1.90 (5 m, 1 H, 1 H, 7 H, 1 H, 1 H, 5 × CH_2 and OH), 2.16 (s, 3 H, CH_3), 4.04–4.12 (m, 1 H, CH), 6.89, 6.92 (2 s, 1 H, 1 H, imidazole), 7.20–7.22, 7.27–7.29 (2 m, 4 H, 1 H, 5 × ArH).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 25.2, 25.6, 25.7, 31.8, 33.3, 34.2, 55.2, 72.9, 117.7, 124.7, 125.8, 126.9, 128.1, 146.1, 150.6.

MS (DIP, EI): *m/z* (%) = 271 (11) [M$^+$ + 1], 270 (55) [M$^+$], 255 (12), 188 (14), 187 (35), 174 (12), 173 (100), 171 (18), 169 (12), 145 (18), 111 (28), 105 (13), 95 (19), 77 (10), 55 (11), 44 (11).

HRMS: *m/z* [M$^+$] calcd for $C_{17}H_{22}N_2O$: 270.1732; found: 270.1738.

1-(1-Cyclohexyl-1*H*-imidazol-2-yl)-2,2-dimethylpropan-1-ol (15c)
White solid; yield: 0.307 g (65%); mp 172–174 °C (EtOAc); GLC: t_R = 11.8 min; R_f = 0.60 (EtOAc).

IR (KBr): 3114 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.01 [s, 9 H, $C(CH_3)_3$], 1.22–1.29, 1.35–1.45, 1.50–1.55, 1.65–1.69, 1.75–1.78, 1.86–1.95, 1.98–2.01 (7 m, 1 H, 2 H, 1 H, 1 H, 1 H, 1 H, 2 H, 2 H, 5 × CH_2), 4.00–4.05 (m, 1 H, CH-cyclohexyl), 4.40 (s, 1 H, *H*COH), 6.92, 7.01 (2 s, 2 × 1 H, imidazole).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 25.2, 25.8, 30.9, 33.7, 35.3, 36.8, 55.3, 73.6, 115.7, 127.3, 147.9.

MS (DIP, EI): *m/z* (%) = 236 (4) [M$^+$], 180 (11), 179 (61), 98 (12), 97 (100).

HRMS: *m/z* [M$^+$] calcd for $C_{14}H_{24}N_2O$: 236.1889; found: 236.1878.

3-[1-(1-Methylheptyl)-1*H*-imidazol-2-yl]pentan-3-ol (16a)
Yellow oil; yield: 0.346 g (65%); GLC: t_R = 14.0 min; R_f = 0.51 (EtOAc).

IR (film): 3176 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.77 [t, *J* = 7.3 Hz, 6 H, $C(OH)(CH_2CH_3)_2$], 0.86 (t, *J* = 6.7 Hz, 3 H, $CH_2CH_2CH_3$), 1.23–1.30, 1.67–1.74 (2 m, 8 H, 2 H, 5 × CH_2), 1.36 (d, *J* = 6.6 Hz, 3 H, CH_3CH), 1.84–2.03 [m, 4 H, $C(OH)(CH_2CH_3)_2$], 4.46–4.53 (m, 1 H, CH), 6.93, 6.94 (2 s, 2 × 1 H, imidazole).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 8.0, 14.0, 22.5, 22.6, 26.4, 29.0, 31.5, 33.1, 38.1, 52.6, 75.5, 116.8, 126.2, 149.6.

MS (EI): *m/z* (%) = 266 (2) [M$^+$], 238 (10), 237 (54), 125 (100), 95 (11), 69 (21).

HRMS: *m/z* [M$^+$] calcd for $C_{16}H_{30}N_2O$: 266.2358; found: 266.2333.

1-[1-(1-Methylheptyl)-1*H*-imidazol-2-yl]-1-phenylethanol (16b)
Yield: 0.552 g (92%).

Major Diastereoisomer

White solid; mp 115–117 °C (EtOAc); R_f = 0.52 (EtOAc).

IR (KBr): 3110 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 0.71 (d, J = 6.7 Hz, 3 H, CH_3CH), 0.85 (t, J = 6.9 Hz, 3 H, CH_3CH_2), 1.13–1.24, 1.45–1.54 (2 m, 8 H, 2 H, 5 × CH_2), 2.02 (s, 3 H, CH_3COH), 3.20 (br s, 1 H, OH), 4.23 (sextet, J = 6.9 Hz, 1 H, CH_3CH), 6.89, 7.01 (2 m, 2 × 1 H, imidazole), 7.20–7.31 (m, 5 H, 5 × ArH).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.0, 21.0, 21.9, 22.5, 26.0, 29.0, 31.6, 37.9, 51.8, 73.3, 117.0, 125.0, 126.5, 127.0, 128.2, 145.6, 150.7.

MS (DIP, EI): m/z (%) = 301 (12) [M^+ + 1], 300 (54) [M^+], 285 (18), 255 (26), 229 (10), 188 (15), 187 (52), 179 (15), 173 (100), 171 (22), 169 (15), 149 (16), 145 (23), 111 (40), 105 (34), 96 (15), 95 (35), 77 (23), 69 (24), 57 (13), 55 (12), 43 (40), 41 (23).

HRMS: m/z [M^+] calcd for $C_{19}H_{28}N_2O$: 300.2202; found: 300.2200.

Minor Diastereoisomer

White solid; mp 110–112 °C (EtOAc); R_f = 0.41 (EtOAc).

IR (KBr): 3115 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 0.50–0.60, 0.86–0.92, 0.95–1.05, 1.08–1.16, 1.24–1.37 (5 m, 2 H, 1 H, 2 H, 3 H, 2 H, 5 × CH_2), 0.84 (t, J = 7.2 Hz, 3 H, CH_3CH_2), 1.18 (d, J = 6.6 Hz, 3 H, CH_3CH), 2.02 (s, 3 H, CH_3COH), 3.02 (br s, 1 H, OH), 4.19 (m, 1 H, CH_3CH), 6.89, 7.00 (2 m, 2 × 1 H, imidazole), 7.20–7.35 (m, 5 H, 5 × ArH).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.0, 22.1, 22.4, 26.0, 28.8, 31.5, 32.5, 37.3, 52.1, 73.5, 117.1, 125.0, 126.5, 127.1, 128.2, 145.6, 150.5.

MS (EI): m/z (%) = 301 (11) [M^+ + 1], 300 (56) [M^+], 299 (14), 285 (18), 255 (26), 229 (10), 188 (15), 187 (52), 179 (12), 173 (100), 171 (20), 169 (15), 149 (14), 145 (24), 111 (39), 105 (34), 96 (15), 95 (34), 77 (23), 69 (23), 57 (11), 55 (11), 43 (39), 41 (22).

HRMS: m/z [M^+] calcd for $C_{19}H_{28}N_2O$: 300.2202; found: 300.2190.

2,2-Dimethyl-1-[1-(1-methylheptyl)-1*H*-imidazol-2-yl]propan-1-ol (16c)[20]

Yield: 0.500 g (94%).

Major Diastereoisomer

Colorless solid; mp 69–71 °C (EtOAc); GLC: t_R = 14.1 min; R_f = 0.26 (hexane–EtOAc, 1:1).

IR (KBr): 3701–3005 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 0.85 (t, J = 6.9 Hz, 3 H, CH_3CH_2), 0.99 [s, 9 H, $C(CH_3)_3$], 1.22 (m, 8 H, 4 × CH_2), 1.44 (d, J = 6.6 Hz, 3 H, CH_3CH), 1.64–1.66 (m, 2 H, CH_2CH), 3.08 (br s, 1 H, OH), 4.17–4.29 (m, 1 H, CH_3CH), 4.37 (s, 1 H, $HCOH$), 6.89, 7.05 (2 s, 2 × 1 H, imidazole).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.0, 21.5, 22.5, 25.7, 25.9, 28.9, 31.5, 36.9, 38.8, 51.8, 73.4, 115.0, 127.7, 148.7.

MS (EI): m/z (%) = 267 (2) [M^+ + 1], 266 (4) [M^+], 210 (13), 209 (82), 179 (15), 98 (10), 97 (100).

HRMS: m/z [M^+] calcd for $C_{16}H_{30}N_2O$: 266.2358; found: 266.2338.

Minor Diastereoisomer

Colorless solid; mp 79–81 °C (EtOAc); GLC: t_R = 14.2 min; R_f = 0.20 (hexane–EtOAc, 1:1).

IR (KBr): 3706–2999 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 0.88 (t, J = 7.0 Hz, 3 H, CH_3CH_2), 1.02 [s, 9 H, $C(CH_3)_3$], 1.27–1.35 (m, 11 H, 4 × CH_2 and CH_3CH), 1.76–1.78 (m, 2 H, CH_2CH), 2.90 (br s, 1 H, OH), 4.22–4.33 (m, 1 H, CH_3CH), 4.38 (s, 1 H, $HCOH$), 6.89, 7.03 (2 s, 2 × 1 H, imidazole).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.0, 22.5, 22.8, 25.9, 26.5, 29.1, 31.5, 36.7, 36.9, 51.8, 73.5, 115.1, 127.6, 148.2.

MS (EI): m/z (%) = 267 (1) [M^+ + 1], 266 (3) [M^+], 210 (10), 209 (64), 179 (15), 98 (10), 97 (100), 69 (10).

HRMS: m/z [M^+] calcd for $C_{16}H_{30}N_2O$: 266.2358; found: 266.2348.

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