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Selective synthesis of unsymmetrical ethers from different alcohols catalyzed by sodium bisulfite

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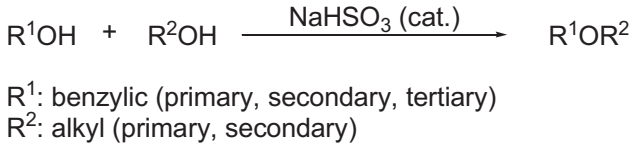
ABSTRACT

An efficient method for the preparation of unsymmetrical ethers from alcohols catalyzed by sodium bisulfite is reported. The procedure enables the direct dehydration of primary, secondary, and tertiary benzylic alcohols with aliphatic alcohols in the absence of solvent to selectively produce unsymmetrical ethers in high yields with low catalyst loading. No symmetrical ethers are generated in the reactions. The etherification of a chiral secondary benzyl alcohol with butanol exclusively yields racemic ethers, suggesting that the reaction involves a carbocation intermediate mechanism.

1. Introduction

Ether bond formation is of great importance in organic synthesis. The classical synthetic methods for ethers include Williamson ether synthesis,[1] dehydration coupling of alcohols,[2] as well as reductive etherification of carbonyl compounds.[3] Williamson ether synthesis is the most widely used protocol for the preparation of both symmetrical and unsymmetrical ethers. However, it requires the conversion of a hydroxyl group into a good leaving group, such as halogen or tosyl, and the reaction needs to be carried out in the presence of a strong base, which does not allow for substrates bearing basic-intolerant groups.[4] The method is also less effective for secondary and tertiary halides (tosylates) due to the competition of elimination reactions. In addition, the usage of halides, together with the production of waste salts, is environmentally less desirable.

The direct preparation of ethers from alcohols is more environmentally friendly. In this context, symmetrical ethers can be readily generated by acid-catalyzed condensation of alcohols.[5] However, traditionally, unsymmetrical ethers can be prepared only from the reaction of a tertiary alcohol with a primary or secondary alcohol. Because the reactions involve the formation of carbocation intermediates from the tertiary alcohols, they always suffer from the competition of the elimination reactions, which are in many cases, even more favorable. In the past decades, a variety of transition metal[6] or Lewis acid[7] catalyzed cross-coupling reactions of different alcohols have been reported. In 2002, Kobayashi et al. described that Brønsted acid (dodecylbenenesulfonic acid) catalyzed the reactions of benzyl alochols with dodecanol to afford the corresponding benzyl dodecyl ethers.[8] In this paper, we describe that the cross-coupling reactions of two different alcohols can be catalyzed by sodium bisulfite to selectively afford unsymmetrical ethers (Scheme 1).



Scheme 1. $NaHSO_3$-catalyzed formation of unsymmetrical ethers from discrete alcohols.

2. Results and discussion

2.1. Optimization of the reaction condition

In the initial study, we investigated the straightforward etherification of *p*-methoxybenzyl alcohol **1a** with *n*-BuOH **2a** under the

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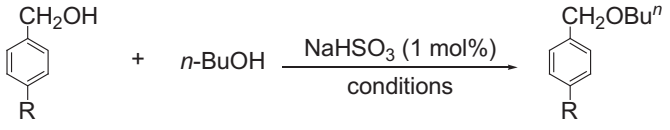
catalysis of 1 mol % of $NaHSO_3$ (Table 1). No formation of the unsymmetrical ether was detected when the reaction was performed in CH_2Cl_2, toluene, THF or CH_3CN, and the starting materials were recovered completely (entries 1–4). In $MeNO_2$, the reaction could give rise to 4-methoxybenzyl ether **3a** in 46% yield after refluxing for 14 h (entry 5). However, in the absence of additional solvent, the reaction could produce **3a** in 82% isolated yield after heating at 100 °C for 1 h (entry 6). No etherification occurred at lower temperature (60 °C) and the starting materials were recovered (entry 7). In the case of benzyl alcohol or *para*-nitrobenzyl alcohol, the corresponding ethers could not be obtained even the reaction time was prolonged to 6 (entry 8) or 16 h (entry 9).

Table 1
Optimization on the $NaHSO_3$-catalyzed etherification of benzylic alcohol **1** with *n*-BuOH[a]



1 **2a** **3**

Entry	R	Solvent	Time (h)	Temp (°C)	Yield[b] (%)
1	OMe	CH_2Cl_2	1	Reflux	NR[c]
2	OMe	$PhCH_3$	1	Reflux	NR[c]
3	OMe	THF	1	Reflux	NR[c]
4	OMe	CH_3CN	1	Reflux	NR[c]
5	OMe	CH_3NO_2	14	Reflux	46
6	OMe	—	1	100	82
7	OMe	—	1	60	NR[c]
8	H	—	6	110	NR[c]
9	NO_2	—	16	110	NR[c]

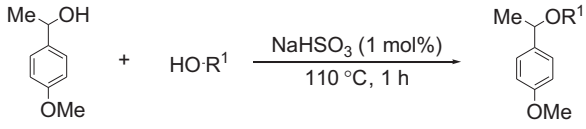
[a] Unless otherwise noted, the reactions were performed with *p*-methoxybenzyl alcohol (2.0 mmol), *n*-BuOH (8.0 mmol), and $NaHSO_3$ (1 mol %) in 5 mL of solvent.
[b] Isolated yield.
[c] No reaction.

2.2. Substrate adaptability

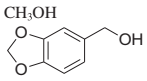
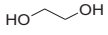
Under the optimized reaction conditions, we tested the reaction of **1a** with aliphatic primary, secondary, and tertiary alcohols **2a**–**g** in the absence of solvent (Table 2). In the case of primary and secondary alcohols, the $NaHSO_3$ catalyst was effective in promoting the reactions (entries 1–5). Notably, allyl alcohol **2f** also successfully reacted with **1a** to give desired ether **3f** (entry 6). 2-Butyl-4-methoxybenzyl ether **3g** has a fruity pear odor and is a potential fragrance compound.[7n] The unsymmetrical ether **3g** could be obtained in 70% yield after longer reaction time (entry 7). A scale-up reaction of 1.1 g **1a** with **2g** also gave **3g** in up to 72% isolated yield, which is comparable to that of small amount etherification. In the case of aliphatic alcohols with steric hindrance, such as *t*-BuOH, no unsymmetrical ether was obtained and the starting material remained.

We then explored the synthesis of unsymmetrical ethers from secondary benzyl alcohol **1b** and the results are summarized in Table 3. In the case of linear primary alcohols, unsymmetrical

Table 3
$NaHSO_3$-catalyzed etherification of 1-(4-methoxyphenyl)ethanol **1b**[a]

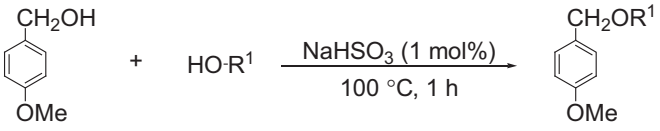


1b **2a–l** **4a–l**

Entry	Alcohol **2**		Ratio (**1b**:**2**)	Temp (°C)	Time (h)	Product	Yield[b] (%)
1	$CH_3(CH_2)_3OH$	**2a**	1:4	110	1	**4a**	80
2	$CH_3(CH_2)_6OH$	**2b**	1:4	110	1	**4b**	85
3	$CH_3(CH_2)_{11}OH$	**2c**	1:1	110	1	**4c**	77
4	$CH_3(CH_2)_{17}OH$	**2d**	1:1	110	1	**4d**	85
5	$(CH_3)_2CH(CH_2)_2OH$	**2e**	1:4	110	1	**4e**	83
6	$CH_2{=}CHCH_2OH$	**2f**	1:10	90	14	**4f**	81
7	$CH_3CH(OH)CH_2CH_3$	**2g**	1:10	110	24	**4g**	75
8	$(CH_3)_2CHOH$	**2h**	1:10	90	14	**4h**	53
9	$(CH_3)_3COH$	**2i**	1:10	90	14	**4i**	NR[c]
10	CH_3OH	**2j**	1:10	60	14	**4j**	87
11[d]		**2k**	1:1	110	1	**4k**	87
12		**2l**	1:10	90	24	**4l**	72

[a] Unless otherwise noted, the reactions were performed with 1-(4-methoxyphenyl) ethanol (2.0 mmol), alcohol **2** (8.0 mmol), and $NaHSO_3$ (1 mol %) at 110 °C for 1 h.
[b] Isolated yields.
[c] No reaction.
[d] $NaHSO_3$ (0.3 mol %) was applied.

Table 2
$NaHSO_3$-catalyzed etherification of *p*-methoxybenzyl alcohol **1a**[a]



1a **2a–g** **3a–g**

Entry	Alcohol **2**		Ratio (**1a**:**2**)	Time (h)	Product	Yield[b] (%)
1	$CH_3(CH_2)_3OH$	**2a**	1:4	1	**3a**	82
2	$CH_3(CH_2)_6OH$	**2b**	1:4	1	**3b**	84
3	$CH_3(CH_2)_{11}OH$	**2c**	1:4	1	**3c**	86
4	$CH_3(CH_2)_{17}OH$	**2d**	1:1	3	**3d**	86
5	$(CH_3)_2CH(CH_2)_2OH$	**2e**	1:4	1	**3e**	82
6	$CH_2{=}CHCH_2OH$	**2f**	1:10	1	**3f**	87
7[c]	$CH_3CH(OH)CH_2CH_3$	**2g**	1:4	12	**3g**	70

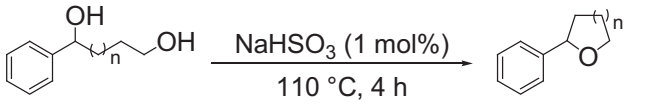
[a] Unless otherwise noted, the reactions were performed with *p*-methoxybenzyl alcohol (2.0 mmol), alcohol **2** (8.0 mmol), and $NaHSO_3$ (1 mol %) at 100 °C for 1 h.
[b] Isolated yields.
[c] The reaction was carried out at 110 °C.

ethers **4** were always the main product without any contamination of the symmetrical ether derived from **1b**. For example, **1b** reacted with *n*-heptanol **2b** to afford **4b** in up to 85% isolated yield (entry 2). For alcohols that are volatile, such as **2f** and **2j**, a larger excess of amount was loaded (entries 6 and 10). Again, the reaction was applicable to secondary alcohols, such as *s*-BuOH **2g** and isopropanol **2h** (entries 7 and 8). However, the reaction of **2h** required a large excess due to its steric hindrance and low boiling point. For *t*-BuOH **2i**, neither unsymmetrical nor symmetric ether was detected even though the reaction time was prolonged to 24 h and the starting materials were recovered (entry 9), probably due to its much higher hindrance.

The reactions of primary alcohols **2k** and **2l**, which bear an additional functional group, also afforded the corresponding ethers in good to high yields (Table 3, entries 11 and 12). It is worthwhile to notice the fact that etherification of **1b** with **2k** proceeded smoothly even with 0.3 mol % catalyst loading when the two alcohols were in 1:1 ratio (entry 11). In addition, no symmetrical ethers derived from either of the alcohols were detected. The formation of **4l** required an excess amount of **2l** (entry 12). When the ratio of **1b** to **2l** was 1:1 or 2:1, the reaction gave complicated results.

Substituent effects on the aromatic ring of the secondary benzyl alcohol were also investigated (Table 4). It was found that the electron donating substituent, such as methyl or methoxy group was indispensable. The *meta*-substituted precursor could also form the desired ether in good yield, albeit needing longer reaction times (entry 2). Higher temperature was required for the reaction of *para*-methyl substituted **1d** with **2b** (entry 3). It is noteworthy that tertiary alcohol **1e** could also react with **2a** to produce **4p** in 48% yield (entry 5). In the case of 1-phenylethanol, no unsymmetrical ethers were detected.

Intramolecular coupling reactions of diols **5a** and **5b** were also investigated (Scheme 2), which afforded the corresponding ether in 72% and 18% yields, respectively. For the latter reaction, dehydration product 5-phenylpent-4-en-1-ol was found to be the major product.



5a: n = 1
5b: n = 2

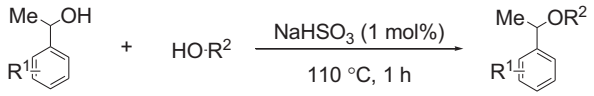
6a: n = 1, 72 %
6b: n = 2, 18 %

Scheme 2. Intramolecular coupling reaction of diols.

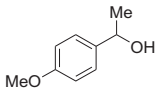
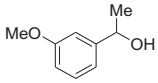
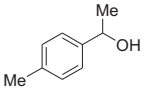
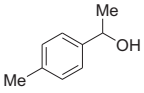
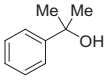
2.3. Mechanism studies

To get insight into the mechanism of this $NaHSO_3$-catalyzed reaction, we further performed the reactions of two chiral substrates. It was found that the reaction of **1a** with (*S*)-2-butanol **2g** afforded chirality retained ether (*S*)-**3g** (Scheme 3), the chirality of which was established by comparing its specific rotation with that of the model compound prepared using the Williamson method from (*S*)-**3g** and 1-(chloromethyl)-4-methoxybenzene.[9] Contrary to this observation, the reaction of chiral benzyl alcohol (*R*)-**1b** with *n*-BuOH **2a** afforded **4a** as a racemic ether (Scheme 4). These results

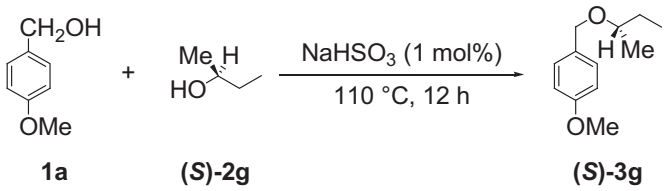
Table 4
$NaHSO_3$-catalyzed etherification of aliphatic alcohols **2** with benzylic alcohol **1** bearing different substituents[a]



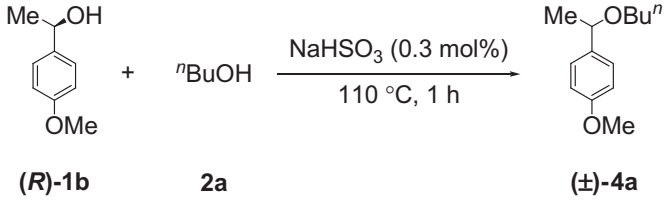
1 **2** **4**

Entry	Alcohol **1**		Alcohol **2**	Temp (°C)	Time (h)	Product	Yield (%)[b]
1		**1b**	$CH_3(CH_2)_3OH$ **2a**	110	1	**4a**	80
2		**1c**	$CH_3(CH_2)_3OH$ **2a**	110	8	**4m**	78
3		**1d**	$CH_3(CH_2)_6OH$ **2b**	130	1	**4n**	71
4		**1d**	$CH_3CH(OH)CH_2CH_3$ **2g**	110	24	**4o**	75
5		**1e**	$CH_3(CH_2)_3OH$ **2a**	110	1	**4p**	48

[a] Unless otherwise noted, the reactions were performed with alcohol **1** (2.0 mmol), alcohol **2** (8.0 mmol), and $NaHSO_3$ (1 mol %) at 110 °C for 1 h.
[b] Isolated yields.



Scheme 3. The formation of chiral ether (*S*)-**3g** from the reaction of **1a** with (*S*)-**2g**.



Scheme 4. Racemized etherification of chiral benzyl alcohol (*R*)-**1b** with achiral alkyl alcohol.

suggested that the reactions involved a benzyl cation intermediate, which reacted with the aliphatic alcohols to yield the unsymmetrical ethers.

3. Conclusion

We demonstrate that $NaHSO_3$ can efficiently catalyze the reactions of primary, secondary, and tertiary benzyl alcohols with primary and secondary alcohols to selectively produce unsymmetrical ethers. The reactions take place smoothly without the use of any solvent and both intermolecular and intramolecular reactions can give rise to the expected ethers in good to high yields. The new method avoids the use of transition metal and thus should be particularly useful for the preparation of unsymmetrical ethers for biological and pharmaceutical purposes.

4. Experimental section

4.1. General remarks

All commercially available reagents for reactions were of analytical grade and were used as received. Benzyl alcohols **1b**,[10] **1c**,[11] and **1d**[11] were prepared by reduction of 4-methoxyacetophenone, 3-methoxyacetophenone, and 4-methylacetophenone, respectively. 1-Phenylbutane-1,4-diol **5a** and 1-phenylpentane-1,5-diol **5b** were obtained as described in the literature.[12] Analytical thin-layer chromatography (TLC) was performed using silica gel 60 F_{254} precoated glass. Flash column chromatography was performed on silica gel 60 (230–400 mesh ASTM) using petroleum ether and ethyl acetate as eluting solvents. All reaction temperatures were those of oil bath melting points (mp) were determined with a Reichert Thermovar Kofler microscope and the values were uncorrected. Optical rotations were measured with an AUTO POL IV automatic polarimeter. ^1H and ^{13}C NMR spectra were recorded on JEOL ECA-400 Fourier Transform spectrometer. High resolution ESI mass spectra were obtained on a Bruker micro TOF II instrument.

4.2. Typical experimental procedure for the syntheses of 3a–g

A mixture of *p*-methoxybenzyl alcohol **1a** (0.28 g, 2.0 mmol), *n*-BuOH **2a** (0.59 g, 8.0 mmol), and $NaHSO_3$ (2.1 mg, 0.02 mmol) was stirred at 100 °C in oil bath for 1 h. After the reaction finished, the residue was purified by flash column chromatography on silica gel to give the corresponding ether **3a** in 82% isolated yield.

*4.2.1. 1-(Butoxymethyl)-4-methoxybenzene (**3a**).*[7n] Colorless oil, 82% yield. ^1H NMR (400 MHz, $CDCl_3$) δ 7.26 (d, J=7.8 Hz, 2H), 6.87 (d, J=7.8 Hz, 2H), 4.43 (s, 2H), 3.79 (s, 3H), 3.44 (t, J=6.1 Hz, 2H), 1.60–1.58 (m, 2H), 1.41–1.36 (m, 2H), 0.91 (t, J=7.0 Hz, 3H).

*4.2.2. 1-(Heptyloxymethyl)-4-methoxybenzene (**3b**).* Colorless oil, 84% yield. ^1H NMR (400 MHz, $CDCl_3$) δ 7.26 (d, J=8.6 Hz, 2H), 6.87 (d, J=8.6 Hz, 2H), 4.43 (s, 2H), 3.80 (s, 3H), 3.43 (t, J=6.7 Hz, 2H), 1.61–1.58 (m, 2H), 1.32–1.27 (m, 8H), 0.88 (t, J=6.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.2, 130.9, 129.1, 113.6, 72.6, 70.3, 55.3, 31.9, 29.9, 29.3, 26.3, 22.7, 14.2; HR-MS (ESI): m/z=259.1662, calcd for $C_{15}H_{24}O_2Na$ $[M+Na]^+$: 259.1674.

*4.2.3. 1-(Dodecyloxymethyl)-4-methoxybenzene (**3c**).* Colorless oil, 86% yield. ^1H NMR (400 MHz, $CDCl_3$) δ 7.26 (d, J=7.6 Hz, 2H), 6.87 (d, J=8.3 Hz, 2H), 4.43 (s, 2H), 3.80 (s, 3H), 3.43 (t, J=6.4 Hz, 2H), 1.61–1.58 (m, 2H), 1.34–1.25 (m, 18H), 0.88 (t, J=6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.2, 130.9, 129.3, 113.8, 72.6, 70.4, 55.4, 32.1, 29.9, 29.7, 29.6, 29.5, 26.3, 22.8, 14.2; HR-MS (ESI): m/z=329.2441, calcd for $C_{20}H_{34}O_2Na$ $[M+Na]^+$: 329.2457.

*4.2.4. 1-Methoxy-4-(octadecyloxymethyl)benzene (**3d**).* White solid, mp 46.2–46.4 °C, 86% yield. ^1H NMR (400 MHz, $CDCl_3$) δ 7.25 (d, J=8.4 Hz, 2H), 6.87 (d, J=8.4 Hz, 2H), 4.43 (s, 2H), 3.80 (s, 3H), 3.43 (t, J=6.5 Hz, 2H), 1.59–1.55 (m, 2H), 1.33–1.25 (m, 30H), 0.88 (t, J=5.9 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.2, 131.0, 129.4, 113.9, 72.6, 70.4, 55.3, 31.9, 29.9, 29.8, 29.6, 29.5, 26.4, 22.8, 14.2; HR-MS (ESI) m/z=413.3373, calcd for $C_{26}H_{46}O_2Na$ $[M+Na]^+$: 413.3396.

*4.2.5. 1-(Isopentyloxymethyl)-4-methoxybenzene (**3e**).*[7g] Colorless oil, 82% yield. ^1H NMR (400 MHz, $CDCl_3$) δ 7.25 (d, J=8.5 Hz, 2H), 6.87 (d, J=8.5 Hz, 2H), 4.42 (s, 2H), 3.79 (s, 3H), 3.46 (t, J=6.8 Hz, 2H), 1.75–1.70 (m, 1H), 1.52–1.47 (m, 2H), 0.88 (d, J=6.6 Hz, 6H).

*4.2.6. 1-(Allyloxymethyl)-4-methoxybenzene (**3f**).*[7g] Colorless oil, 87% yield. ^1H NMR (400 MHz, $CDCl_3$) δ 7.27 (d, J=7.7 Hz, 2H), 6.88 (d, J=7.3 Hz, 2H), 6.00–5.90 (m, 1H), 5.29 (d, J=17.2 Hz, 1H), 5.19 (d, J=10.3 Hz, 1H), 4.46 (s, 2H), 4.00 (d, J=5.3 Hz, 2H), 3.80 (s, 3H).

*4.2.7. 1-(sec-Butoxymethyl)-4-methoxybenzene (**3g**).*[7n] Colorless oil, 70% yield. ^1H NMR (400 MHz, $CDCl_3$) δ 7.27 (d, J=8.7 Hz, 2H), 6.87 (d, J=7.9 Hz, 2H), 4.45 (AB, J_{AB}=11.4 Hz, 2H), 3.80 (s, 3H), 3.45–3.40 (m, 1H), 1.63–1.44 (m, 2H), 1.17 (d, J=6.0 Hz, 3H), 0.91 (t, J=7.4 Hz, 3H).

4.3. Typical experimental procedure for 4a–p

A mixture of 1-(4-methoxyphenyl)ethanol **1b** (0.30 g, 2.0 mmol), *n*-BuOH **2a** (0.59 g, 8.0 mmol), and $NaHSO_3$ (2.1 mg, 0.02 mmol) was stirred at 110 °C in oil bath for 1 h. After the reaction finished, the residue was purified by flash column chromatography on silica gel to give the corresponding ether **4a** in 80% isolated yield.

*4.3.1. 1-(1-Butoxyethyl)-4-methoxybenzene (**4a**).*[7n] Colorless oil, 80% yield. ^1H NMR (400 MHz, $CDCl_3$) δ 7.23 (d, J=8.2 Hz, 2H), 6.88 (d, J=8.2 Hz, 2H), 4.33 (q, J=6.3 Hz, 1H), 3.81 (s, 3H), 3.26 (t, J=6.5 Hz, 2H), 1.58–1.50 (m, 2H), 1.41 (d, J=6.3 Hz, 3H), 1.37–1.30 (m, 2H), 0.88 (t, J=7.3 Hz, 3H).

*4.3.2. 1-(1-Heptyloxyethyl)-4-methoxybenzene (**4b**).* Colorless oil, 85% yield. ^1H NMR (400 MHz, $CDCl_3$) δ 7.23 (d, J=7.6 Hz, 2H), 6.88 (d, J=7.4 Hz, 2H), 4.33 (q, J=6.5 Hz, 1H), 3.81 (s, 3H), 3.25 (t, J=6.4 Hz, 2H), 1.54–1.52 (m, 2H), 1.41 (d, J=5.9 Hz, 3H), 1.32–1.25 (m, 8H), 0.87 (t, J=6.5 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.0, 136.5,

127.2, 113.8, 77.5, 68.7, 55.3, 32.0, 30.1, 29.3, 26.3, 24.3, 22.7, 14.2; HR-MS (ESI) m/z=273.1815, calcd for $C_{16}H_{26}O_2Na$ $[M+Na]^+$: 273.1830.

*4.3.3. 1-(1-Dodecyloxyethyl)-4-methoxybenzene (**4c**).* Colorless oil, 77% yield. ^1H NMR (400 MHz, $CDCl_3$) δ 7.23 (d, J=7.6 Hz, 2H), 6.87 (d, J=7.6 Hz, 2H), 4.33 (q, J=6.4 Hz, 1H), 3.80 (s, 3H), 3.25 (t, J=6.4 Hz, 2H), 1.54–1.52 (m, 2H), 1.41 (d, J=6.0 Hz, 3H), 1.29–1.24 (m, 18H), 0.88 (t, J=6.7 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.0, 136.5, 127.4, 113.8, 77.5, 68.7, 55.4, 32.1, 30.1, 29.7, 29.6, 29.5, 26.3, 24.3, 22.8, 14.3; HR-MS (ESI) m/z=343.2608, calcd for $C_{21}H_{36}O_2Na$ $[M+Na]^+$: 343.2613.

*4.3.4. 1-Methoxy-4-(1-(octadecyloxy)ethyl)benzene (**4d**).* Colorless oil, 85% yield. ^1H NMR (400 MHz, $CDCl_3$) δ 7.23 (d, J=8.3 Hz, 2H), 6.88 (d, J=8.4 Hz, 2H), 4.33 (q, J=6.3 Hz, 1H), 3.80 (s, 3H), 3.25 (t, J=6.6 Hz, 2H), 1.54–1.50 (m, 2H), 1.41 (d, J=6.3 Hz, 3H), 1.30–1.25 (m, 30H), 0.88 (t, J=7.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.0, 136.5, 127.4, 113.8, 77.5, 68.7, 55.4, 32.1, 30.1, 29.9, 29.8, 29.6, 29.5, 26.4, 24.3, 22.8, 14.3; HR-MS (ESI) m/z=427.3553, calcd for $C_{27}H_{48}O_2Na$ $[M+Na]^+$: 427.3552.

*4.3.5. 1-(1-Isopentyloxyethyl)-4-methoxybenzene (**4e**).*[5a] Colorless oil, 83% yield. ^1H NMR (400 MHz, $CDCl_3$) δ 7.23 (d, J=7.7 Hz, 2H), 6.87 (d, J=7.6 Hz, 2H), 4.33 (q, J=6.6 Hz, 1H), 3.81 (s, 3H), 3.27 (t, J=6.6 Hz, 2H), 1.69–1.62 (m, 1H), 1.45 (d, J=7.2 Hz, 3H), 1.46–1.25 (m, 2H), 0.86 (d, J=6.5 Hz, 3H), 0.83 (d, J=6.5 Hz, 3H).

*4.3.6. 1-(1-Allyloxyethyl)-4-methoxybenzene (**4f**).*[13] Colorless oil, 81% yield. ^1H NMR (400 MHz, $CDCl_3$) δ 7.24 (d, J=8.0 Hz, 2H), 6.88 (d, J=7.5 Hz, 2H), 5.93–5.86 (m, 1H), 5.23 (d, J=17.2 Hz, 1H), 5.14 (d, J=10.2 Hz, 1H), 4.42 (q, J=6.3 Hz, 1H), 3.86 (d, J=8.2 Hz, 2H), 3.80 (s, 3H), 1.44 (d, J=6.2 Hz, 3H).

*4.3.7. 1-(1-sec-Butoxyethyl)-4-methoxybenzene (**4g**).*[7n] Colorless oil, 75% yield. ^1H NMR (400 MHz, $CDCl_3$) δ 7.24 (d, J=7.6 Hz, 2H), 6.87 (d, J=7.9 Hz, 2H), 4.51–4.44 (m, 1H), 3.80 (s, 3H), 3.33–3.29 (m, 0.5× 1H), 3.22–3.17 (m, 0.5× 1H), 1.55–1.33 (m, 2H), 1.39 (d, J=6.3 Hz, 3H), 1.11 (d, J=5.4 Hz, 0.5× 3H), 1.02 (d, J=5.4 Hz, 0.5× 3H), 0.89 (t, J=7.2 Hz, 0.5× 3H), 0.80 (t, J=7.2 Hz, 0.5× 3H).

*4.3.8. 1-(1-Isopropoxyethyl)-4-methoxybenzene (**4h**).*[14] Colorless oil, 53% yield. ^1H NMR (400 MHz, $CDCl_3$) δ 7.28 (d, J=8.4 Hz, 2H), 6.91 (d, J=8.0 Hz, 2H), 4.52 (q, J=6.3 Hz, 1H), 3.84 (s, 3H), 3.53–3.47 (m, 1H), 1.42 (d, J=6.3 Hz, 3H), 1.17 (d, J=5.8 Hz, 3H), 1.11 (d, J=6.0 Hz, 3H).

*4.3.9. 1-Methoxy-4-(1-methoxyethyl)benzene (**4j**).*[13] Colorless oil, 87% yield. ^1H NMR (400 MHz, $CDCl_3$) δ 7.23 (d, J=7.6 Hz, 2H), 6.88 (d, J=7.5 Hz, 2H), 4.25 (q, J=5.9 Hz, 1H), 3.81 (s, 3H), 3.19 (s, 3H), 1.42 (d, J=5.8 Hz, 3H).

*4.3.10. 5-((1-(4-Methoxyphenyl)ethoxy)methyl)benzo[d][1,3]dioxole (**4k**).* Colorless oil, 87% yield. ^1H NMR (400 MHz, $CDCl_3$) δ 7.26 (d, J=8.6 Hz, 2H), 6.90 (d, J=8.1 Hz, 2H), 6.82 (s, 1H), 6.75 (d, J=7.8 Hz, 1H), 6.72 (d, J=7.8 Hz, 1H), 5.93 (s, 2H), 4.42 (q, J=6.4 Hz, 1H), 4.23 (AB, J_{AB}=11.4 Hz, 2H), 3.82 (s, 3H), 1.44 (d, J=6.7 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.1, 147.7, 147.0, 135.7, 132.6, 127.6, 121.3, 113.9, 108.6, 108.1, 100.9, 76.5, 69.9, 55.3, 24.2; HR-MS (ESI) m/z=309.1110, calcd for $C_{17}H_{18}O_4Na$ $[M+Na]^+$: 309.1103.

*4.3.11. 2-(1-(4-Methoxyphenyl)ethoxy)ethanol (**4l**).* Colorless oil, 72% yield. ^1H NMR (400 MHz, $CDCl_3$) δ 7.23 (d, J=7.6 Hz, 2H), 6.88 (d, J=7.4 Hz, 2H), 4.40 (q, J=6.2 Hz, 1H), 3.81 (s, 3H), 3.68 (d, J=1.8 Hz, 2H), 3.40 (d, J=1.8 Hz, 2H), 2.04–1.99 (m, 1H), 1.45 (d, J=6.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.1, 135.4, 127.5, 113.9, 78.0, 69.6, 62.0, 55.3, 23.9; HR-MS (ESI) m/z=219.0999, calcd for $C_{11}H_{16}O_3Na$ $[M+Na]^+$: 219.0997.

*4.3.12. 1-(1-Butoxyethyl)-3-methoxybenzene (**4m**).* Colorless oil, 78% yield. ^1H NMR (400 MHz, $CDCl_3$) δ 7.23 (s, 1H), 6.88–6.79 (m, 3H), 4.36 (q, J=6.1 Hz, 1H), 3.82 (s, 3H), 3.30 (t, J=6.8 Hz, 2H), 1.56 (br s, 2H), 1.42 (d, J=6.0 Hz, 3H), 1.37–1.34 (m, 2H), 0.89 (t, J=6.9 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.9, 146.3, 129.4, 118.6, 112.8, 111.5, 77.9, 68.6, 55.2, 32.3, 24.3, 19.5, 14.0; HR-MS (ESI) m/z=231.1335, calcd for $C_{13}H_{20}O_2Na$ $[M+Na]^+$: 231.1361.

*4.3.13. 1-(1-Heptyloxyethyl)-4-methylbenzene (**4n**).* Colorless oil, 71% yield. ^1H NMR (400 MHz, $CDCl_3$) δ 7.25–7.14 (m, 4H), 4.34 (q, J=6.2 Hz, 1H), 3.26 (t, J=6.4 Hz, 2H), 2.34 (s, 3H), 1.55–1.53 (m, 2H), 1.41 (d, J=6.3 Hz, 3H), 1.30–1.24 (m, 8H), 0.87 (t, J=5.5 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 141.4, 136.9, 129.1, 126.2, 77.8, 68.8, 32.0, 30.1, 29.3, 26.3, 24.4, 22.7, 21.2, 14.2; HR-MS (ESI) m/z=257.1873, calcd for $C_{16}H_{26}ONa$ $[M+Na]^+$: 257.1881.

*4.3.14. 1-(1-sec-Butoxyethyl)-4-methylbenzene (**4o**).* Colorless oil, 75% yield. ^1H NMR (400 MHz, $CDCl_3$) δ 7.24–7.12 (m, 4H), 4.51 (q, J=6.5 Hz, 0.5× 1H), 4.48 (d, J=6.5 Hz, 0.5× 1H), 3.35–3.29 (m, 0.5× 1H), 3.23–3.16 (m, 0.5× 1H), 2.34 (s, 3H), 1.55–1.38 (m, 2H), 1.40 (d, J=6.5 Hz, 0.5× 3H), 1.39 (d, J=6.5 Hz, 0.5× 3H), 1.11 (d, J=6.0 Hz, 0.5× 3H), 1.03 (d, J=6.3 Hz, 0.5× 3H), 0.89 (t, J=7.4 Hz, 0.5× 3H), 0.80 (t, J=7.4 Hz, 0.5× 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 142.1, 141.7, 136.9, 136.8, 129.0, 126.4, 126.2, 75.2, 74.3, 74.0, 73.3, 30.4, 28.5, 24.9, 24.8, 24.6, 21.2, 20.4, 18.9, 10.3, 9.5; HR-MS (ESI) m/z=215.1405, calcd for $C_{13}H_{20}ONa$ $[M+Na]^+$: 215.1412.

*4.3.15. 1-(2-Butoxypropan-2-yl)benzene (**4p**).*[2b] Colorless oil, 48% yield. ^1H NMR (400 MHz, $CDCl_3$) δ 7.42–7.21 (m, 5H), 3.14 (t, J=6.7 Hz, 2H), 1.53 (s, 6H), 1.50–1.48 (m, 2H), 1.35–1.28 (m, 2H), 0.87 (t, J=7.3 Hz, 3H).

4.4. Characterization for 6a and 6b

*4.4.1. 2-Phenyl-tetrahydrofuran (**6a**).*[12] Colorless oil, 72% yield. ^1H NMR (400 MHz, $CDCl_3$) δ 7.34–7.21 (m, 5H), 4.89 (t, J=7.2 Hz, 1H), 4.13–4.08 (m, 1H), 3.91–3.97 (m, 1H), 2.35–2.29 (m, 1H), 2.05–1.96 (m, 2H), 1.85–1.76 (m, 1H).

*4.4.2. 2-Phenyl-tetrahydro-2H-pyran (**6b**).*[12] Colorless oil, 18% yield. ^1H NMR (400 MHz, $CDCl_3$) δ 7.35–7.32 (m, 5H), 4.32 (d, J=8.9 Hz, 1H), 4.14 (d, J=9.7 Hz, 1H), 3.60 (t, J=11.2 Hz, 1H), 1.93–1.82 (m, 1H), 1.69–1.65 (m, 1H), 1.62–1.58 (m, 4H).

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Supplementary data

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