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Benzylation of Hydroxy Groups with tertiary amine as a base

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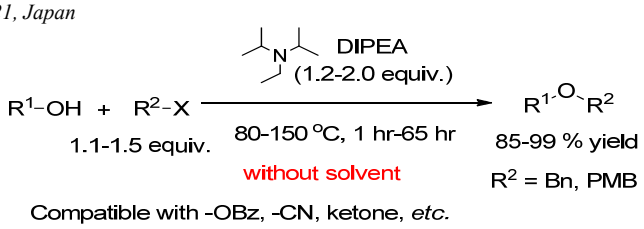

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Benzylation of Hydroxy Groups with tertiary amine as a base

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ABSTRACT

The Benzylation of hydroxyl groups in the presence of tertiary amines is described. A mixture of an alcohol and a benzyl halide afforded the corresponding benzyl ether in good to excellent yields in the presence of diisopropylethylamine. The importance of solventless conditions was observed. The reaction showed high tolerance to many functional groups including benzoate, even at a reaction temperature of 150 °C. Sodium iodide was found to be an efficient catalyst to accelerate the reaction.

1. Introduction

The benzylation of hydroxy groups is one of the most fundamental reactions in organic synthesis.[1] Since coupling reactions between alkoxides and alkyl halides was first reported more than 160 years ago by Williamson, the method has been the reliable first choice for ether synthesis.[2] However, the reaction requires strong basic condition to generate alkoxides as nucleophilic intermediates thus limiting compatible functionalities. The benzylation of hydroxyl groups by well-designed benzylating reagents allows performance of the reaction under nearly neutral conditions, conditions under which tolerance to functional groups such as nitriles and ketones have been reported.[3] However, *in situ* activation of benzyl alcohols to alkylating agents is a sophisticated method that offers little control to the stereochemistry of benzylic position of ether.[4] The acidic activation of benzyl alcohols is advantageous because of its economical benefits.[5] Reductive benzylation with benzylidene acetals has emerged as an efficient approach for selective introduction of benzyl groups into diol motifs.[6]

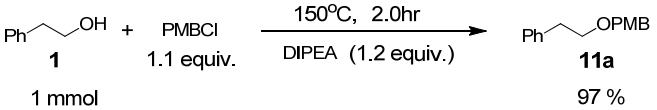
Among the various approaches available for generating ether bonds, the reactions between alcohols and alkyl halides is prime due to its simplicity and reliability. For instance, reaction in the presence of stoichiometric or excess amounts of silver salts can promote benzylation under nearly neutral conditions.[7] Lewis-acid-catalyzed reactions have also been achieved at elevated temperatures.[8] Cesium fluoride-Celite has been reported to be an efficient additive for aromatic esters and ethers under weak basic conditions.[9] The catalytic activities of phenylboronic acids and copper salts have been elucidated for the monobenzylation of 1,2-diols in the presence of carbonate.[10] Despite the above studies, the development of methods for the introduction of benzyl groups at sites with hydroxyl groups under mild conditions remains an important challenge in synthetic organic chemistry. It is surprising that benzylation reactions under weak basic conditions are not well documented in spite of the fundamental importance of these reactions and their broad potential for synthetic applications. In this communication, we present the general features of benzylation reaction under weak basic conditions.

2. Results

The reaction proceeded efficiently in the presence of *N,N'*-diisopropylethylamine (Hünig's base; DIPEA) without a solvent. High compatibility with many functional groups including esters was observed.

Investigating various weak basic reaction conditions, we found that the reaction of 2-phenylethanol (**1**) and 1.1 equivalents of *p*-methoxybenzyl chloride (PMBCl) in the presence of 1.2 equivalents of DIPEA at 80~150 °C without solvent afforded corresponding ether **11a** in good yield (Table 1, entries 7 and 8).

Table 1. Properties of the reaction between 2-phenylethanol and PMBCl in the presence of amines



entry	Base	Solvent /additive	Temp. [c]	Time	Yield of **11a**
1	DIPEA	DMF[a]	150 °C	2hrs	28[b]
2	DIPEA	1,2-DCB[a]	150 °C	2hrs	<5[c]
3	TEA	none	150 °C	2hrs	92[b]
4	DIPEA	none	80 °C	2hrs	33[b]
5	DIPEA	none	100 °C	2hrs	61[b]
6	DIPEA	none	120 °C	2hrs	87[b]

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7	DIPEA	none	150 °C	2hrs	97[d]
8	DIPEA	NaI	80 °C	65hrs	97[d]

[a] DMF and 1,2-DCB represent dimethylformamide and 1,2-dichlorobenzene respectively; the resulting concentration was 0.2M. [b] Yields were determined by HPLC. [c] Less than detection limit. [d] Isolated yield.

No benzylation of DIPEA to ammonium salt was observed under the reaction conditions even in the absence of **1.** Perhaps this was due to the shielding of the nitrogen atom of DIPEA by the two bulky isopropyl groups thereby limiting accessibility to PMBCl. Interestingly, the use of triethylamine (TEA) instead of DIPEA also afforded satisfactory yield (entry 3). This was despite the reaction between TEA and PMBCl being confirmed to produce the corresponding ammonium salt. The result suggests that the benzylation of hydroxyl group is much faster than the benzylation of TEA under the reaction conditions. The yields of **11a** increased with increasing temperature (entries 4, 5, 6 and 7) in a fixed reaction time of 2 hrs. The bath temperature of 150 °C appears to be suitable to complete the reaction in 2 hrs. Despite the relatively low boiling point of DIPEA(127 °C) and PMBCl(127 °C /24mmHg), only a small amount of refluxing occurred at the observed temperature of 145 °C in the reaction vessel. This may have been due to the molar boiling point elevation of the mixture of the three components of DIPEA, PMBCl and **1**(219 °C/24mmHg). Although the reaction rate appeared to decrease with decreasing reaction temperatures, a higher temperature was not entirely essential to promote the reaction. In fact, **11a** was obtained at a 97% yield when the reaction was run at 80 °C for 65 hrs in the presence of 10 mol% NaI (entry 4). As long as a higher temperature does not promote significant side reactions, a simpler reaction system with a shorter reaction time should be practical and useful. The addition of solvent had a large negative impact on the yield of **11a**. The reaction in standard organic solvents, such as dimethylformamide (DMF) and 1,2-dichlorobenzene (1,2-DCB) yielded poor results (entries 1 and 2). These results indicated the importance of the solventless condition. In fact, it turned out that even an excess amount of DIPEA exhibited significant negative impact on the kinetics of the reaction. The reaction of **1** and a slight excess (1.1 equiv.) of PMBCl was monitored by ^{1}H NMR for various ratios of DIPEA (1.2, 2.0, and 3.0 equiv.). The most efficient conversion of **1** was observed when the reaction was performed in the presence of a slight excess (1.2 equiv.) of DIPEA (Figure 1 A).

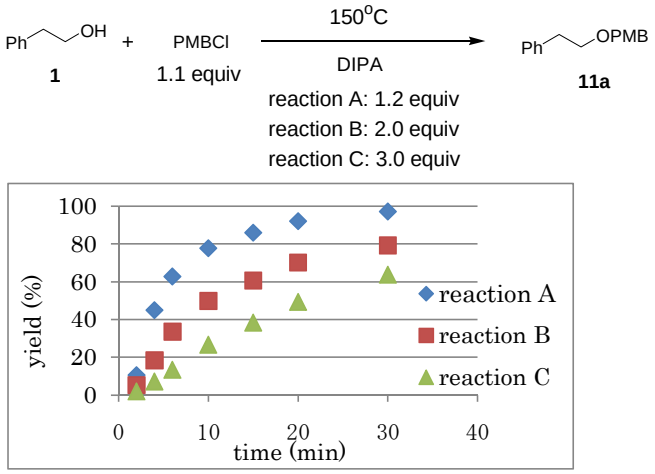
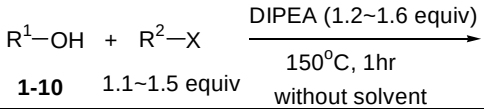


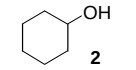
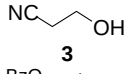
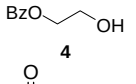
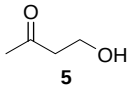
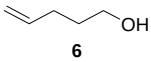
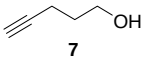
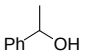
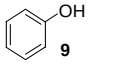
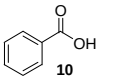
Figure 1. Formation of **11a** in the reaction of **1** and PMBCl: The yield (%) of **11a** estimated by the integral intensity of ^{1}H NMR plotted as a function of time. The reaction of **1** (1 mmol) and PMBCl (1.1 mmol) was performed in the presence of varying amounts of DIPEA: reaction A, 1.2 mmol; reaction B, 2.0 mmol; and reaction C, 3.0 mmol.

Increasing the ratio of DIPEA resulted in slower formation of **11a** (Figure 1; reactions B and C). This result implies that intimate contact between alcohols and PMBCl is important for efficient conversion. However, greater than stoichiometric amount of DIPEA was essential to complete the reaction. When half equivalent of DIPEA relative to **1** was applied, ether formation stopped at around 50%. Thus, when determining the standard reaction conditions, it would be essential to account for the loss of DIPEA to obtain reproducible conversion when using a reaction temperature higher than the boiling point of DIPEA (127 °C).

The reaction of a variety of alcohols with benzyl bromide and PMBCl was then examined. The results are summarized in Table 2.

Table 2. Benzylation in the presence of diisopropylethylamine



entry	R^1-OH	R^2-X[c]	R^1-O-R^2	Yield(%)[a]
1	**1**	BnBr	**11b**	87
2	 **2**	PMBCl	**12a**	98
3		BnBr[d]	**12b**	99
4	 **3**	PMBCl	**13a**	85
5		BnBr	**13b**	89
6[b]	 **4**	PMBCl	**14a**	91
7[b]		BnBr	**14b**	86
8	 **5**	PMBCl	**15a**	90
9		BnBr[d]	**15b**	94
10	 **6**	PMBCl	**16a**	98
11		BnBr	**16b**	94
12	 **7**	PMBCl[d]	**17a**	98
13		BnBr	**17b**	89
14	 **8**	PMBCl	**18b**	92
15	 **9**	BnBr	**19b**	95
16	 **10**	PMBCl	**20a**	98
17		BnBr	**20b**	99

[a] Isolated yields. [b] Compound **4** was prepared according to the reported method [Ref. 14a]. [c] Unless marked with [d], 1.1 equivalents of R^2-X was applied with 1.2 equivalents of DIPEA. [d] In this case, 1.5 equivalents of R^2-X was applied with 1.6 equivalents of DIPEA.

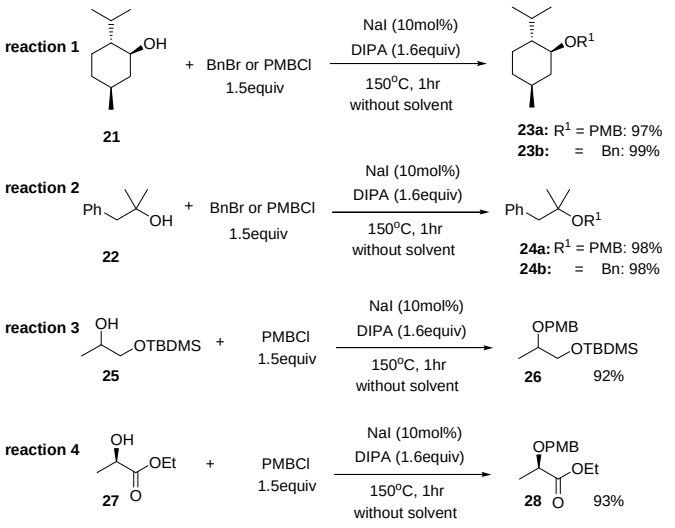
Benzyl bromide (BnBr) exhibited a tendency similar to that of PMBCl, which is presented in Table 1, although a somewhat lower reactivity of BnBr was observed in this experiment. The reaction of **1** and BnBr produced corresponding ether **11b** with a satisfactory yield (entry 1). Cyclohexanol, which is a representative secondary alcohol, also reacted with PMBCl and BnBr with good yields (entries 3 and 4). Many functionalized compounds, such as nitriles, benzoates, ketones, alkenes, and alkynes, were converted into the corresponding ethers with good

yields, and their functionalities remained intact during the reaction (entries 4 to 13).

Acid-labile alcohol **8** also produced corresponding ether **18b** with a satisfactory yield (entry 14). It is traditionally thought that such tolerance to functionalities can only be achieved when using well-designed benzylation reagents.[3] The reaction system presented here allows us to use commercially available benzyl halides without any modification. With regard to PMBCl, the compound is also conveniently accessible from 4-methoxybenzyl alcohol via acidic treatment[11] or can be purchased from commercial sources. No significant side reaction was observed at temperatures up to 150 °C. The result shows that weak basic conditions are important to achieve high tolerance to many functional groups in the benzylation reaction. The reaction was also confirmed to be applicable to phenols and carboxylic acids (entries 15, 16, and 17). Coupling between nearly stoichiometric amounts of alcohol and benzyl bromide was achieved. The solventless and weak basic conditions may allow us to scale up the reaction in a safe and economical manner. Because the reaction did not proceed at room temperature, regulation of the reaction should be easy by controlling the reaction temperature.

Sterically hindered alcohols such as menthol (**21**) and 1,1-dimethylphenylethanol (**22**) depicted relatively unsatisfactory yields under the standard reaction conditions in Table 2.[12] However, the yields of **23a**, **23b**, **24a** and **24b** were significantly improved by addition of the 10 mol% NaI (Scheme 1, reactions 1 and 2). The system was successfully applied for mono-silylated 1,2-propandiol **25** without migration of TBDMS group (Scheme 1, reaction 3). Furthermore, L-lactic acid ethyl ester **27** was efficiently reacted with PMBCl to afford **28** in 93% yield (Scheme 1, reaction 4). Somehow, the specific rotation of the compound **28** has been reported as various values.[13] Preservation of optical purity of **28** during the reaction 4 was confirmed by chiral stationary phase HPLC technique.

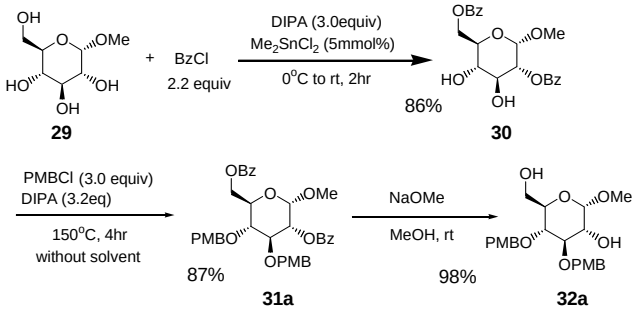
Scheme 1. Benzylation of sterically hindered alcohols in the presence of NaI



Despite the development of several efficient techniques for ether bond formation, it is still difficult to achieve selective ether bond formation to substrates bearing multiple hydroxy groups.[14] Unfortunately, the presented reaction did not show useful selectivity between primary and secondary alcohols. Recently, several region- and stereoselective ester formation reactions have been developed for substrates bearing multiple hydroxy groups.[15] Because the present system was compatible with the benzoyloxy group, selective introduction of a benzyl group after selective esterification was examined as a practical solution for regioselective benzylation.

When selectively di-benzoylated sugar **30**, which is readily accessible via the dimethyltin dichloride catalyzed reaction of methyl α-D-glucoside (**29**), was treated with 3 equivalents of PMBCl and 3.2 equivalents of DIPEA at 150 °C 4hrs, ethereal product **31a** was isolated with an 87% (Scheme 2). No proof of acyl migration was obtained during the reaction. The two benzoyl groups of **31a** were readily hydrolyzed by treatment with MeONa/MeOH at room temperature to produce **32a**. Although direct control of the benzylation reaction is still difficult, selective introduction of a benzyl group was possible by combination with a selective acylation process. So far, ether bond formation that is compatible with benzoates has only been achieved by specially designed benzylation reagents or assistance of excess amount of silver salt.[7c] The high cost of the benzylation step is one of the serious barriers for the synthesis of sugar derivatives because of the necessary repetitive protection-deprotection steps. The method presented here may provide low cost access to selectively and partially protected sugars.

Scheme 2. Protection-deprotection strategy based on the combination of benzylation and benzoylation for the selective derivatization of methyl α-D-glucoside



In conclusion, simple benzylation methods for hydroxy groups were exploited. Higher compatibility with many functional groups and high conversion were achieved under weak basic conditions. In addition, the significance of the solventless reaction conditions for obtaining substantial conversion was clearly demonstrated. Because the reaction is compatible with the benzoate group, this method should be a useful for protection de-protection strategy for many types of organic syntheses. The reaction is suitable for large-scale syntheses because it requires a less hazardous amine as a base, uses an economical solventless system, and is controllable by the temperature. Catalytic acceleration of the reaction at lower temperatures and the use of other alkylating reagents are currently under investigation in our laboratory.

3. Experimental section

NMR spectra were recorded on a Varian Gemini 300,

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500MHz and JEOL JNM-AL400 MHz for ^{1}H and ^{13}C respectively. Proton and carbon NMR were processed using the ACD/NMR Processor Academic Edition software. Data for ^{1}H NMR spectra are reported as follows: chemical shift (δ ppm) (multiplicity, coupling constant (Hz), integration). Multiplicity and qualifier abbreviations are as follows: s = singlet, d = doublet, dd = doublet of doublet, t = triplet, q = quartet and m = multiplet. IR spectra were recorded on a Nexus670NT FT-IR and are reported in frequency of absorption (cm^{-1}). High resolution mass spectra were obtained on JEOL JMS-700N for electron ionization or on JEOL JMS-T100TD for electrospray ionization. The compound **25** was prepared according to the reported method.[16] All other reagents and solvents were used as supplied without further purification.

Alcohol (1 mmol), p-methoxybenzyl chloride (1.1 mmol), and diisopropylethylamine (2 mmol) were charged in reaction vessel equipped with magnetic stirring bar under nitrogen atmosphere. The mixture was refluxed in 150 °C bath for 2 hrs. The resulting mixture typically showed two phases. Ethyl acetate (5 mL) and 10% aqueous sodium bisulphate (5 mL) were added to the mixture and the organic phase extracted by three potions of EtOAc. Combined organic layer was dried over magnesium sulfate and the solvent evaporated in vacuo. Further purification was carried out by silica gel column chromatography.

1-Methoxy-4-(phenethoxymethyl)benzene (11a): a yellow oil, ^{1}H NMR (300MHz, $CDCl_3$, TMS, r.t.) δ (ppm): 2.94(2H, t, *J*=7.2Hz), 3.67(2H, t, *J*=7.2Hz), 3.79(3H, s), 4.45(2H, s), 6.85(2H, d, *J*=8.4Hz), 7.24(7H, m); ^{13}C NMR (400MHz, $CDCL_3$, TMS, r.t.) δ (ppm): 36.25, 55.13, 70.88, 72.53, 113.75, 126.15, 128.31, 129.20, 130.51, 139.02, 159.19; IR (KBr, cm^{-1}): 1035, 1097, 1248, 1513, 1612, 2858, 3028; HRMS *calcd for* $C_{16}H_{18}O_2$ *m/z* 242.1307, found HR-EI (+) *m/z* 242.1301.

2-Benzyloxyethylbenzene (11b): a colourless oil, ^{1}H NMR (300MHz, $CDCl_3$, TMS, r.t.) δ (ppm): 2.93(2H, t, *J*=7.3Hz), 3.69(2H, t, *J*=7.2Hz), 4.53(2H, s), 7.27(10H, m); ^{13}C NMR (400MHz, $CDCL_3$, TMS, r.t.) δ (ppm): 36.21, 71.15, 72.87, 126.19, 127.63, 128.33, 128.35, 128.92, 138.33, 138.93; IR (KBr, cm^{-1}): 1104, 1274, 1453, 1496, 1719, 3028; HRMS *calcd for* $C_{15}H_{16}O$ *m/z* 212.1201, found HR-EI (+) *m/z* 212.1183.

1-Cyclohexyloxymethyl-4-methoxy-benzene (12a): a colourless oil, ^{1}H NMR (300MHz, $CDCl_3$, TMS, r.t.) δ (ppm): 1.48(10H, m), 3.32(1H, sep, *J*=3.9Hz), 3.77(3H, s), 4.46(2H, s), 6.84(H, d, *J*=9.0Hz), 7.25(2H, d, *J*=8.7); ^{13}C NMR (400MHz, $CDCL_3$, TMS, r.t.) δ (ppm): 24.05, 25.74, 32.17, 55.16, 69.22, 76.57, 113.72, 129.02, 131.43, 159.04; IR (KBr, cm^{-1}): 1248, 1513, 1613, 2856, 2932; HRMS *calcd for* $C_{14}H_{20}O_2$ *m/z* 220.1463, found HR-EI (+) *m/z* 220.1456.

Cyclohexyloxymethylbenzene (12b): a yellow oil, ^{1}H NMR (300MHz, $CDCl_3$, TMS, r.t.) δ (ppm): 1.48(10H, m), 3.35(1H, sep, *J*=3.8Hz), 4.55(3H, s), 7.34(5H, m); ^{13}C NMR (400MHz, $CDCL_3$, TMS, r.t.) δ (ppm): 23.92, 25.68, 32.04, 69.50, 76.77, 127.20, 127.39, 28.21, 139.24; IR (KBr, cm^{-1}): 697, 1096, 1452, 2856, 2932; HRMS *calcd for* $C_{13}H_{18}O$ *m/z* 190.1358, found HR-EI (+) *m/z* 190.1327.

3-(4-Methoxybenzyloxy)propanenitrile (13a): a yellow oil, ^{1}H NMR (300MHz, $CDCl_3$, TMS, r.t.) δ (ppm): 2.61(2H, t, *J*=6.3Hz), 3.65(2H, t, *J*=6.3Hz), 3.80(3H, s), 4.51(2H, s), 6.88(2H, d, *J*=8.7Hz), 7.25(2H, d, *J*=8.7Hz); ^{13}C NMR (400MHz, $CDCL_3$, TMS, r.t.) δ (ppm): 18.79, 55.23, 64.20, 72.94, 113.97, 117.84, 129.30, 129.45, 159.57; IR (KBr, cm^{-1}): 1099, 1249, 1514, 1612, 1685, 2252, 2873; HRMS *calcd for* $C_{11}H_{13}NO_2$ *m/z* 191.0946, found HR-EI (+) *m/z* 191.0925.

3-Benzyloxypropanenitrile (13b): a yellow oil, ^{1}H NMR (300MHz, $CDCl_3$, TMS, r.t.) δ (ppm): 2.62(2H, t, *J*=6.3Hz), 3.68(2H, t, *J*=6.3Hz), 4.58(2H, s), 7.34(5H, m); ^{13}C NMR (400MHz, $CDCL_3$, TMS, r.t.) δ (ppm): 18.42, 64.26, 72.79, 117.75, 127.45, 128.25, 137.14; IR (KBr, cm^{-1}): 670, 1105, 1455, 2252, 2873, 3032; HRMS *calcd for* $C_{10}H_{11}NO$ *m/z* 161.0841, found FAB (+) *m/z* 161.0848.

2-((4-methoxybenzyl)oxy)ethyl benzoate (14a): a colourless oil, ^{1}H NMR (300MHz, $CDCl_3$, TMS, r.t.) δ (ppm): 3.79(5H, m), 4.49(4H, m), 6.87(2H, m), 7.29(2H, m), 7.44(2H, m), 7.56(1H, m), 8.05(2H, m); ^{13}C NMR (400MHz, $CDCL_3$, TMS, r.t.) δ (ppm): 55.13, 64.07, 67.54, 72.69, 113.67, 113.73, 128.22, 129.24, 129.59, 129.92, 130.04, 132.87, 159.19, 166.44; IR (KBr, cm^{-1}): 1117, 1250, 1460, 1511, 1612, 1736, 2866. HRMS calcd *for* $C_{17}H_{18}O_4$ *m/z* 286.12051, found FAB (+) *m/z* 286.1203.

2-Benzyloxyethyl benzoate (14b): a colourless oil, ^{1}H NMR (300MHz, $CDCl_3$, TMS, r.t.) δ (ppm): 3.81(2H, t, *J*=9.6Hz), 4.50(2H, t, *J*=9.6Hz), 4.61(2H, s), 7.35(5H, m), 7.44(2H, m), 7.54(1H, m), 8.05(2H, d, *J*=6.9Hz); ^{13}C NMR (400MHz, $CDCL_3$, TMS, r.t.) δ (ppm): 63.98, 67.85, 72.99, 127.62, 127.66, 128.27, 128.36, 129.63, 132.91, 137.94, 166.52; IR (KBr, cm^{-1}): 1094, 1273, 1452, 1601, 1719, 2862; HRMS *calcd for* $C_{16}H_{16}O_3$ *m/z* 256.1099, found HR-EI (+) *m/z* 256.1088.

4-(4-Methoxybenzyloxy)butan-2-one (15a): a colourless oil, ^{1}H NMR (300MHz, $CDCl_3$, TMS, r.t.) δ (ppm): 2.15(3H, d, *J*=3.0Hz), 2.71(2H, t, *J*=6.6Hz), 3.7(2H, t, *J*=6.6Hz), 3.79(3H, d, *J*=0.6Hz), 4.44(2H, s), 6.85(2H, d, *J*=8.4Hz), 7.25(2H, d, *J*=8.1Hz); ^{13}C NMR (400MHz, $CDCL_3$, TMS, r.t.) δ (ppm): 30.34, 43.72, 55.22, 64.91, 72.85, 113.84, 129.38, 130.21, 159.33, 207.44; IR (KBr, cm^{-1}): 1034, 1101, 1173, 1249, 1514, 1613, 1714, 2867, 3737; HRMS *calcd for* $C_{12}H_{16}O_3$ *m/z* 208.1099, found HR-EI (+) *m/z* 208.1089.

4-(Benzyloxy)butan-2-one (15b): a yellow oil, ^{1}H NMR (300MHz, $CDCl_3$, TMS,r.t.) δ (ppm): 2.18(3H, s), 2.71(2H, t, *J*=6.6Hz), 3.73(2H, t, *J*=6.6Hz), 4.51(2H, s), 7.33(5H, m); ^{13}C NMR (400MHz, $CDCL_3$, TMS, r.t.) δ (ppm): 30.29, 43.64, 65.19, 73.13, 127.65, 128.38, 138.11, 207.20; IR (KBr, cm^{-1}): 699, 1105, 1364, 1454, 1715, 2867; HRMS *calcd for* $C_{11}H_{14}O_2$ *m/z* 178.0983, found HR-EI (+) *m/z* 178.0994.

1-Methoxy-4-(pent-4-en-1-yloxymethyl)benzene (16a): a colourless oil, ^{1}H NMR (300MHz, $CDCl_3$, TMS, r.t.) δ (ppm): 1.69(2H, Quintet, *J*=6.6Hz), 2.12(2H, m), 3.45(2H, t, *J*=6.6Hz), 3.78(3H, s), 4.42(2H, s) 4.98(2H, m), 5.79(1H, m), 6.85(2H, d, *J*=8.4Hz), 7.24(2H, t, *J*=8.4Hz); ^{13}C NMR (400MHz, $CDCL_3$, TMS, r.t.) δ (ppm): 28.83, 30.24, 55.15, 69.36, 72.46, 113.74, 114.66, 129.21, 130.73, 138.34, 159.18; IR (KBr, cm^{-1}): 1036, 1100, 1248, 1514, 2856, 2936; HRMS *calcd for* $C_{13}H_{18}O_2$ *m/z* 206.1307, found HR-EI (+) *m/z* 206.1289.

Pent-4-en-1-yloxymethyl-benzene (16b): a yellow oil, ^{1}H NMR (300MHz, $CDCl_3$, TMS, r.t.) δ (ppm): 1.71(2H, q, *J*=6.6Hz), 2.13(2H, m), 3.48(2H, t, *J*=6.6Hz), 4.50(2H, s), 4.97(2H, m), 5.81(1H, m), 7.33(5H, m); ^{13}C NMR (400MHz, $CDCL_3$, TMS, r.t.) δ (ppm): 28.77, 30.17, 69.61, 72.79, 106.58, 114.72, 114.97, 126.95, 127.64, 128.33, 129.08, 138.13, 138.26; IR (KBr, cm^{-1}): 913, 1101, 1453, 1641, 1720, 2938, 3319. HRMS *calcd for* $C_{12}H_{16}O$ *m/z* 176.1201, found HR-EI (+) *m/z* 176.1174.

1-Methoxy-4-(pent-4-yn-1-yloxymethyl)benzene (17a): a colourless oil, ^{1}H NMR (300MHz, $CDCl_3$, TMS, r.t.) δ (ppm): 1.81(2H, quin., *J*=6.9Hz), 1.94(1H, t, *J*=2.7Hz), 2.30(2H, m), 3.55(2H, t, *J*=6.0Hz), 3.81(3H, s), 4.44(2H, s), 6.86(2H, d, *J*=8.7Hz), 7.25(2H, d, *J*=8.7Hz); ^{13}C NMR (400MHz, $CDCL_3$, TMS, r.t.) δ (ppm): 15.23, 28.61, 55.25, 68.38, 72.65, 84.01, 113.83, 128.28, 130.65, 159.28; IR (KBr, cm^{-1}): 1035, 1102, 1248, 1513, 2859, 3293; HRMS *calcd for* $C_{13}H_{16}O_2$ *m/z* 204.1150, found HR-EI (+) *m/z* 204.1161.

Pent-4-yn-1-yloxymethyl-benzene (17b): a colourless oil, ^{1}H NMR (300MHz, $CDCl_3$, TMS, r.t.) δ (ppm): 1.83(2H, quint., *J*=6.3Hz), 1.935(1H, t, *J*=2.7Hz), 2.32(2H, m), 3.57(3H, t, *J*=6.0Hz), 4.52(2H, s), 7.34(5H, m); ^{13}C NMR (400MHz, $CDCL_3$, TMS, r.t.) δ (ppm): 15.21, 28.60, 68.40, 68.65, 72.98, 83.96, 127.61, 127.66, 128.42, 138.54; IR (KBr, cm^{-1}): 1028, 1105, 1365, 1454, 2861, 3295. HRMS *calcd for* $C_{12}H_{14}O$ *m/z* 174.1045, found HR-EI (+) *m/z* 174.1017.

1-methoxy-4-((1-phenylethoxy)methyl)benzene (18b): a colourless oil, ^{1}H NMR (300MHz, $CDCl_3$, TMS, r.t.) δ (ppm): 1.46(3H,d, *J*=6.3Hz), 3.79(3H, s), 4.22(1H, d, *J*=6.2Hz), 4.38(1H, d, *J*=6.2Hz), 4.48(1H, q, *J*=6.3Hz), 6.87(2H, d, *J*=8.5Hz), 7.38(7H, m); ^{13}C NMR (400MHz, $CDCL_3$, TMS, r.t.) δ (ppm): 25.19, 47.26, 55.20, 63.45, 75.66, 113.73, 126.09, 127.81, 128.70, 130.66, 131.94, 138.51, 158.89; IR (KBr, cm^{-1}): 1036, 1250, 1450, 1609, 1612, 2973; HRMS *calcd for* $C_{16}H_{18}O_2$ *m/z* 242.1307, found HR-EI (+) *m/z* 242.1301.

4-methoxybenzyl benzoate (19b): a white solid, MP: 37 – 38 °C; ^{1}H NMR (300MHz, $CDCl_3$, TMS, r.t.) δ (ppm): 3.82(3H, s), 5.30(2H, s), 6.90(2H, d, *J*=8.4Hz), 7.42(4H, m), 7.44(1H, t, *J*=3.7Hz), 8.05(2H, d, *J*=6.9Hz); ^{13}C NMR (400MHz, $CDCL_3$, TMS, r.t.) δ (ppm): 69.87, 114.89, 120.97, 127.51, 127.96, 128.60, 129.52, 137.14, 158.88. IR (KBr, cm^{-1}): 1029, 1242, 1496, 1599, 2866, 3032; HRMS *calcd for* $C_{13}H_{12}O$ *m/z* 184.0888, found HR-EI (+) *m/z* 184.0880.

4-Methoxy benzoate (20a): a colourless oil, ^{1}H NMR (300MHz, $CDCl_3$, TMS, r.t.) δ (ppm): 3.77(3H, s), 5.28(2H, s), 4.53(2H, s), 6.89(2H, d, *J*=7.4Hz), 7.37 (4H, d, *J*=7.4Hz), 7.5(1H, s), 8.05(2H, d, *J*=6.9Hz); ^{13}C NMR (400MHz, $CDCL_3$, TMS, r.t.) δ (ppm): 55.11, 66.41, 113.93, 128.16, 128.30, 129.62, 130.03, 130.27, 132.90, 159.68, 166.47; IR (KBr, cm^{-1}): 712, 1272, 1515, 1720, 2837, 2957. HRMS *calcd for* $C_{15}H_{14}O_3$ *m/z* 242.0943, found HR-EI (+) *m/z* 242.0933.

Benzyl benzoate (20b): a colourless oil, ^{1}H NMR (300MHz, $CDCl_3$, TMS, r.t.) δ (ppm): 5.3(2H, s), 7.32(8H, m), 8.05(2H, d, *J*=8Hz); ^{13}C NMR (400MHz, $CDCL_3$, TMS, r.t.) δ (ppm): 68.67, 128.27, 128.34, 128.48, 128.71, 129.81, 130.31, 133.11, 136.26, 166.49; IR (KBr, cm^{-1}): 1026, 1070, 1110, 1272, 1314, 1452, 1720, 3034, 3065. HRMS *calcd for* $C_{14}H_{12}O_2$ *m/z* 212.0806, found HR-EI (+) *m/z* 212.080.

Reaction of various types of alcohols:

Benzylation of sterically hindered alcohols such as menthol (**21**) and 1,1-dimethylphenylethanol (**22**) that were otherwise slow under the standard reaction condition were activated by a catalytic amount of NaI. Menthol (1 mmol) or 1,1-dimethylphenylethanol (1 mmol) were added to the reaction vessel containing DIPEA (1.6 mmol), then 1.5 equivalent of alkyl halide (R^2-X) and 10 mol% of NaI added. The mixture was stirred for 1 hr at 150 °C. Upon cooling, to the resulting mixture ethyl acetate (5 mL) and 10% aqueous sodium bisulphate (5 mL) were added and the organic phase extracted by three potions of EtOAc. Combined organic layer was dried over magnesium sulfate and the solvent evaporated in vacuo. Further purification was carried out by silica gel column chromatography.

1-((((1S,2R,5S)-2-isopropyl-methylcyclohexyl)oxy) methyl)-4-methoxybenzene (23a): a colourless oil, ^{1}H NMR (300MHz, $CDCl_3$, TMS, r.t.) δ (ppm): 0.7(3H, d, *J*=6.8Hz), 0.91(9H, m), 1.3(2H, m), 1.63(2H, m), 2.25(2H, m), 3.15(1H, td, *J*=10.4Hz), 3.79(3H, m), 4.31(1H, d, *J*=10.5Hz), 4.57(1H, d, *J*=10.5Hz), 6.83(2H, m), 7.29(2H, m); ^{13}C NMR (400MHz, $CDCL_3$, TMS, r.t.) δ (ppm): 15.90, 20.86, 22.22, 23.14, 25.35, 31.42, 34.47, 40.21, 48.19, 55.08, 69.93, 78.30, 113.66, 129.31, 159.07; IR (KBr, cm^{-1}): 1084, 1171, 1248, 1456, 1513, 1613, 2963. HRMS *calcd for* $C_{18}H_{28}O_2$ *m/z* 276.2089, found HR-EI (+) *m/z* 276.2078.

((((1S,2R,5S)-2-isopropyl-5-methylcyclohexyl)oxy) methyl)benzene (23b): a brown oil, ^{1}H NMR (300MHz, CDCl3, TMS, r.t.) δ (ppm): 0.71(3H, d, *J*=6.9Hz), 0.88(9H, m), 1.33(2H, m), 1.63(3H, m), 2.3(1H, m), 3.17(1H, m), 4.4(1H, d, *J*=11.3Hz), 4.66(1H, d, *J*=11.5Hz), 7.32(5H, m); ^{13}C NMR (400MHz, CDCL3, TMS, r.t.) δ (ppm): 15.96, 20.91, 22.26, 23.19, 25.42, 31.48, 34.51, 40.24, 48.26, 70.35, 78.68, 127.37, 127.83, 128.27, 139.19; IR (CM^{-1}): 1069, 1110, 1344, 1369, 1454, 2869, 2955. HRMS *calcd for* $C_{17}H_{26}O$ *m/z* 246.3877, found HR-EI (+) *m/z* 246.1975.

1-methoxy-4-(((2-methyl-1-phenylpropan-2-yl)oxy) methyl) benzene (24a): a colourless oil, ^{1}H NMR (300MHz, $CDCl_3$, TMS, r.t.) δ (ppm): 1.23(6H, s), 2.87(2H, s), 3.79(3H, s), 4.46(2H, s), 6.87(2H, m) 7.25(7H, m); ^{13}C NMR (400MHz, CDCL3, TMS, r.t.) δ (ppm): 25.16, 39.01, 49.65, 55.16, 63.41, 71.37, 75.63, 113.70, 126.05, 126.44, 127.77, 128.67, 130.44, 130.63, 131.91, 138.47, 158.85; IR (KBr, cm^{-1}): 1035, 1174, 1247, 1513, 1612, 1699, 2970; HRMS *calcd for* $C_{18}H_{22}O_2$ *m/z* 270.1620, found HR-EI (+) *m/z* 270.1621.

(2-(benzyloxy)-2-methylpropyl)benzene (24b): a colourless oil, ^{1}H NMR (300MHz, $CDCl_3$, TMS, r.t.) δ (ppm): 1.26(6H, s), 2.92(2H, s), 4.57(2H, s), 7.31(10H, m); ^{13}C NMR (400MHz, $CDCL_3$, TMS, r.t.) δ (ppm): 25.10, 47.26, 63.72, 75.68, 126.07, 127.00, 127.15, 127.78, 128.21, 130.63, 138.39, 139.84; IR (KBr, cm^{-1}): 697, 1061, 1454, 2972;

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HRMS *calcd for* $C_{17}H_{20}O$ *m/z* 240.1514, found HR-EI (+) *m/z* 240.1512.

(*R*)-ethyl 2-((4-methoxybenzyl)oxy)propanoate (26): a colourless oil, $[\alpha]^{20}_D$ -82.1 (c 1.00, $CHCl_3$). ^1H NMR (300MHz, CDCl3, TMS, r.t.) δ (ppm): 1.30(3H, t, *J*=7.14Hz), 1.41(3H, d, *J*=6.87 Hz), 3.80(3H, s), 4.03(1 H, q, *J*=6.87 Hz), 4.22(2H, q, *J*=7.14 Hz), 4.39(1H, d, *J*=11.26 Hz), 4.62(1H, d, *J*=11.26 Hz), 6.88(2H, d, *J*=8.52 Hz), 7.29(2H, m); ^{13}C NMR (400MHz, CDCL3, TMS, r.t.) δ (ppm): 13.96, 18.43, 54.99, 60.54, 71.41, 73.51, 113.65, 129.50, 159.29, 173.25. IR (KBr, cm^{-1}): 1143, 1243, 1612, 1754, 2984; HRMS *calcd for* $C_{13}H_{18}NaO_4$ *m/z* 261.1205, found HR-ESI (+Na) *m/z* 261.1103.

***tert*-butyl(2-((4-methoxybenzyl)oxy)propoxy)dimethylsilane (28):** a yellowish oil, ^1H NMR (300MHz, CDCl3, TMS, r.t.) δ (ppm): 0.05(6H, s), 0.90(9H, s), 1.15(3H, d, *J*=6.04 Hz), 3.57(3H, m), 3.80(3H s), 4.54(2H, s), 6.87(2H, d, *J*=8.79 Hz), 7.28(2H m); ^{13}C NMR (400MHz, CDCL3, TMS, r.t.) δ (ppm): 16.98, 18.23, 25.84, 55.22, 67.17, 70.86, 75.39, 113.74, 129.20, 131.22, 159.12. IR (KBr, cm^{-1}): 1103, 1249, 1513, 1612, 2857, 2955; HRMS *calcd for* $C_{17}H_{30}NaO_3Si$ *m/z* 333.1964, found HR-ESI (+Na) *m/z* 333.1862.

(2R,3S,4S,5R,6S)-5-(benzoyloxy)-3,4-dihydroxy-6-methoxytetrahydro-2H-pyran-2-yl)methyl benzoate (30): a white solid, Mp: 139-140 °C. ^1H NMR(300MHz, CDCl3, TMS, r.t.) δ (ppm): 3.35(3H, s), 3.61(1H, t, *J*=8.9Hz), 3.95(1H, d, *J*=7.1Hz), 4.19(1H, t, *J*=8.9Hz), 4.53(1H, d, *J*=12.1Hz), 4.78(1H, dd, *J*=11.9, 3.2Hz), 4.95(1H, dd, *J*=9.6, 3.0Hz), 5.05(1H, d, *J*=3.3Hz), 7.4(4H, m), 7.54(2H, q, *J*=6.8Hz), 8.08(4H, d, *J*=7.4Hz); ^{13}C-NMR (400MHz, CDCL3, TMS, r.t.) δ (ppm): 55.37, 63.60, 69.55, 70.66, 71.54, 73.69, 97.34, 128.49, 128.53, 129.53, 129.59, 129.90, 129.99, 133.43, 133.45, 166.52, 167.40; IR (KBr, cm^{-1}): 1291, 1453, 1694, 2948, 3468. HRMS *calcd for* $C_{21}H_{22}O_8$ *m/z* 402.1315, found HR-EI (+) *m/z* 402.1302.

((2R,3R,4S,5R,6S)-5-(benzoyloxy)-6-methoxy-3,4-bis((4-methoxybenzyl)oxy)tetrahydro-2H-pyran-2-yl)methyl benzoate (31a): a colourless oil, ^1H NMR (300MHz, CDCl3, TMS, r.t.) δ (ppm): 3.38(3H, s), 3.74(6H, m), 4.0(1H, m), 4.22(1H, t, *J*=9.4Hz), 4.54(3H, m), 4.8(4H, m), 5.01(1H, d, *J*=3.7Hz), 5.14(1H, dd, *J*=10.0, 3.7Hz), 6.78(4H, m), 7.17(4H, m), 7.45(4H, q, *J*=8.0Hz), 7.58(2H, m), 8.05(4H, m); ^{13}C NMR (400MHz, CDCL3, TMS, r.t.) δ (ppm): 55.17, 55.22, 63.16, 68.86, 73.96, 74.77, 75.35, 77.08, 80.01, 97.23, 113.78, 113.90, 128.39, 128.45, 129.63, 129.76, 129.82, 130.19, 133.08, 133.27, 159.23, 159.36, 165.89, 166.20; IR (KBr, cm^{-1}): 711, 1067, 1271, 1513, 1721, 2837, 2936; HRMS *calcd for* $C_{37}H_{38}NaO_{10}$ *m/z* 665.2465, found HR-ESI (+Na) *m/z* 665.2363.

(2S,3R,4R,5R,6R)-6-(hydroxymethyl)-4,5-bis((4-methoxybenzyl)oxy)tetrahydro-2H-pyran-2,3-diol (32a): a white solid, Mp: 83-84°C. ^1H NMR (300MHz, CDCl3, TMS, r.t.) δ (ppm): 3.64(17H, m), 4.59(1H, d, *J*=10.7Hz), 4.77(4H, m), 6.87(4H, d, *J*=8.2Hz), 7.27(4H, m); ^{13}C NMR (400MHz, CDCL3, TMS, r.t.) δ: 55.09, 55.18, 61.75, 71.00, 72.90, 74.52, 82.67, 99.36, 113.87, 113.90, 129.57, 129.66, 130.27, 130.80, 159.31, 159.41. IR (CM^{-1}): 1038, 1251, 1514, 1614, 2932, 3402; HRMS *calcd for* $C_{23}H_{30}NaO_8$ *m/z* 457.1838, found HR-ESI (+Na) *m/z* 457.1843.

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