The Use of Tin (IV) Chloride to Selectively Cleave Benzyl Esters over Benzyl Ethers and Benzyl Amines

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ABSTRACT: Benzyl esters are cleaved upon reaction with $SnCl_4$, resulting in isolation of the corresponding carboxylic acid. Importantly, benzyl ethers, amines and amides do not undergo debenzylation under these conditions, nor do a variety of other common protecting groups for alcohols, thereby rendering $SnCl_4$ selective amongst Lewis acids. The scope, tolerance and limitations of the strategy are demonstrated through the analysis of several multi-functional substrates, including those bearing Cbz groups.

Keywords

Benzyl ester, deprotection, protecting group, chemoselective debenzylation.

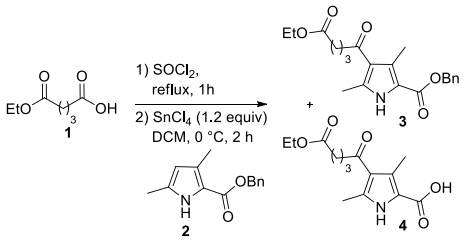
Introduction

The use of protecting groups is essential to much of modern organic chemistry, despite admirable examples of natural product syntheses that lean to the contrary.[1] The benzyl protecting group is of particular interest courtesy of the fact that it may be easily removed using hydrogenolysis, by virtue of properties inherent to the benzylic position.[2,3] Although there is a plethora of reported conditions under which debenzylation may be achieved,[2,3] palladium-catalyzed hydrogenolysis is the most commonly adopted tactic. As such, benzyl-protected ethers, amines and acids may be deprotected in a manner that is or-

thogonal to methods employed for alkyl-protected functional groups. However, hydrogenolysis falls short of being the ideal deprotection strategy. For most substrates and routine sets of conditions, the reaction set-up for hydrogenolysis may also effect the hydrogenation of unsaturated bonds. Furthermore, benzyl ethers, amines and esters are often hydrogenolyzed concurrently. Additionally, safety considerations are essential when manipulating hydrogen gas and hydrogenolysis apparatus. We herein report the scope and limitations of using $SnCl_4$ to selectively debenzylate esters and carbamates. Benzyl (and some other) ethers, benzyl amines, benzyl amides, alkyl esters, double bonds and triple bonds are inert to these reaction conditions. Although it is widely understood that Lewis acids often effect O-R cleavage, the selectivity of $SnCl_4$ to induce benzyl ester and carbamate cleavage over benzyl ethers and amines has not yet been realised.

Results and discussion

Benzyl esters are often used in pyrrole syntheses to protect, and easily deprotect, the 2-position of pyrroles.[4] Deprotection is routinely achieved via hydrogenolysis, enabling facile and orthogonal pyrrole 2-carboxylate deprotection over alkyl ester substituents. We were thus intrigued when a Friedel-Crafts acylation of **2** resulted not only in the anticipated product **3** but also the debenzylated analog **4** after acidic work-up (Scheme 1, note that the ethyl ester moiety within **4** was intact).



Scheme 1. Benzyl ester cleavage accompanied $SnCl_4$-promoted Friedel-Crafts acylation

A careful review of literature pertaining to the cleavage of esters and ethers using Lewis acids (Table 1) revealed that each reagent promotes its own characteristic reactivity. For example, $AlCl_3$ in combination with anisole or *N*,*N*-dimethylaniline is the most commonly used Lewis acid for the cleav-

age of benzyl esters,[5-7] yet this system exhibits poor selectivity as it also cleaves *tert*-Bu[5] esters as well as benzyl and PMB ethers[8,9] (entry 1). Alkyl esters can be hydrolyzed using a combination of $AlCl_3$ and *N*,*N*-dimethylaniline, thereby only the use of $AlCl_3$-anisole[6] allows for the selective deprotection of benzyl esters and ethers in the presence of alkyl esters. BCl_3 has been used for benzyl ether debenzylation,[10] and has some application for benzyl[11-14] and alkyl ester[11] cleavage (Entry 2). Indeed, the hydrolysis of alkyl esters requires higher loading of BCl_3 and/or longer reaction times,[11,15] and thus selective benzyl ether cleavage is possible in the presence of alkyl esters.[10] It is also possible to selectively deprotect a benzyl ester in the presence of an alkyl ester using BCl_3,[16,17] but no selectivity seems possible between a benzyl ester and a benzyl ether.[18,19] $TiCl_4$,[5,20-22] $FeCl_3$,[23-25] $(Re(CO)_4Br)_2$[23] and $Sc(CTf_3)_3$[26] are used to a lesser extent to remove the benzyl moiety from esters, and their selectivity towards other functionalities is not evident from the literature (Entries 3-6): however, they all cleave benzyl ethers. $CeCl_3$ is highly selective for the hydrolysis of *tert*-Bu esters and PMB ethers, leaving benzyl esters and benzyl ethers untouched (Entry 7).[27-29] It is nevertheless possible to reduce an alkyl or benzyl ester to its corresponding alcohol using a combination of $CeCl_3$ and $NaBH_4$.[30,31] The use of $ZrCl_4$ was also studied for its ability to cleave PMB esters and PMB ethers selectively over other ethers (Entry 8).[32]

$SnCl_4$ has been shown to induce the de-*O*-benzylation[33] of particular polybenzyl ethers in monosaccharides, whereby precise stereochemical orientation of multiple ethereal groups is essential to pre-complexing the Lewis acid to achieve the desired reactivity (Entry 9). The use of $SnCl_4$ was also reported for the hydrolysis of cephalosporin *tert*-Bu esters.[20] Furthermore, a dimeric tin adduct has been used to cleave acetates of substituted uridines,[34] and TBTO [bis(tri-*n*-butyltin)oxide] has been used to cleave alkyl and benzyl esters of amino acids.[35] However, to the best of our knowledge, $SnCl_4$ has not been reported as a reagent by which to achieve the debenzylation of benzyl esters. Furthermore, Table 1 reveals that Lewis acids have not previously been reported to effect selective debenzylation of esters over ethers.

Table 1. Literature review of alkyl and benzyl ester and ether cleavage using Lewis acids; "✓" indicates complete conversion to the corresponding acid or alcohol; n.r. = no reaction.

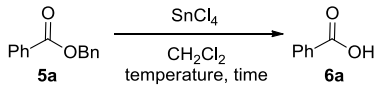
Entry	Lewis acid	RCO_2Bn	RCO_2PMB	RCO_2tBu	RCO_2Me	ROBn	ROPMB
1	$AlCl_3$	[a] ✓ [5,6]	[b] ✓ [7]	[b] ✓ [5]	[c] ✓ [6]	[a] ✓ [8,9]	[c] ✓ [9]
2	BCl_3	✓ [12,16,17]		✓ [14]	✓ [11,15]	✓ [10]	✓ [13]
3	$TiCl_4$	✓ [5]		✓ [20]		✓ [21]	✓ [22]
4	$FeCl_3$	✓ [23]			✓ [24]	✓ [23,25]	
5	$(Re(CO)_4Br)_2$	✓ [23]				incomplete [23]	
6	$Sc(CTf_3)_3$	✓ [26]				✓ [26]	✓ [26]
7	$CeCl_3$	n.r. [27]		✓ [28]	n.r. [28]	n.r. [29]	✓ [29]
8	$ZrCl_4$		✓ [32]			n.r. [32]	✓ [32]
9	$SnCl_4$			✓ [20]		[d] ✓ [33]	

[a]in combination with anisole or *N,N*-dimethylaniline; [b]in combination with anisole; [c]in combination with *N,N*-dimethylaniline; [d]only with elaborate polyol substrate.

To investigate the utility of $SnCl_4$ as a reagent for the debenzylation of esters, benzyl benzoate was used as a model substrate. At room temperature and using 1.2 equiv $SnCl_4$, benzoic acid was thus isolated in 79 % yield (Table 2, Entry 1). We then discovered that just 0.5 equiv $SnCl_4$ was sufficient for the debenzylation to be achieved in good yield. Furthermore, the reaction was tolerant to the presence of trace amounts of water. The use of DCE as solvent gave comparable results, yet the reaction yielded only starting material when THF and CH_3CN were employed, presumably due to Lewis acid/base adduct formation. With 0.5 equiv $SnCl_4$ in CH_2Cl_2 the reaction proceeded efficiently at reflux temperature (Table 2, Entry 2), and so these became our conditions of choice, although complete conversion was also observed using either hexane or toluene at 40°C. To verify that the observed benzyl

deprotection was not caused by hydrolysis of $SnCl_4$ and thus liberation of HCl, benzyl benzoate was reacted with 2.4 equiv of an anhydrous hydrochloric acid solution in ether with 1 equiv water. After 24 h, no reaction was observed and the benzyl ester was isolated with 98% recovery. We also ascertained that SnO_2 (the byproduct of the quench of $SnCl_4$ with water) was not the reaction catalyst: reacting 0.5 equiv of SnO_2 with benzyl benzoate in CH_2Cl_2 for 16 h did not result in cleavage of the benzyl ester.

Table 2. $SnCl_4$-induced ester debenzylation

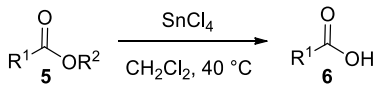


entry	equiv $SnCl_4$	temperature (ºC)	time (h)	isolated yield of **6a** (%)
1	1.2	25	19	79
2	0.5	40	6	80

To further explore the scope of $SnCl_4$-induced ester debenzylation, compounds incorporating additional functionality were explored. Aryl esters bearing electron-withdrawing and electron-donating groups underwent smooth cleavage to give excellent yields of the corresponding benzoic acids (Table 3, Entries 2-3). Benzyl alkanoates were debenzylated in an equally successful manner (entries 4-6), as was a benzyl phenyl acetate (Entry 7). Remote and conjugated double bonds were stable to the $SnCl_4$-induced debenzylation reaction conditions, and enabled isolation of unsaturated carboxylic acids as well as cinnamic acid (Entries 8 and 9). Triple bonds also proved stable (Entry 10). *p*-Methoxybenzyl esters underwent smooth deprotection (Entries 11-13).

Table 3. Scope of $SnCl_4$-induced debenzylation of esters

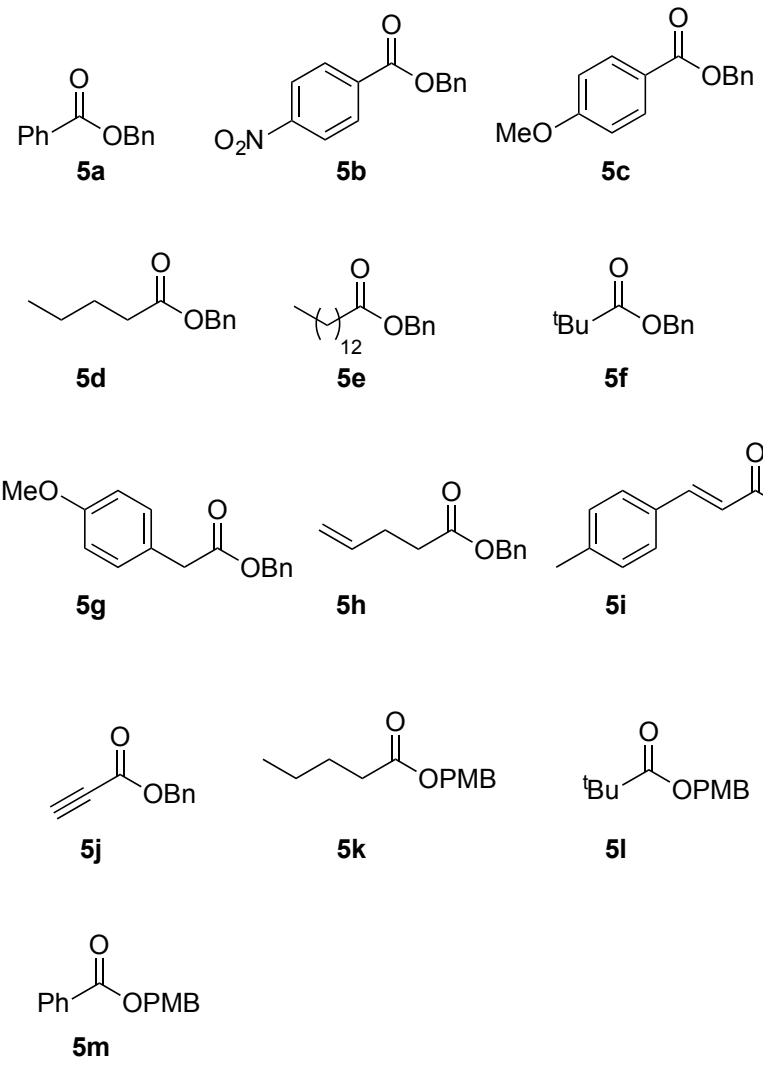
1



entry	5	6 (yield, %)[a]	entry	5	6 (yield, %)[a]
1	**5a**	**6a** (80)	8	**5h**	**6h** (quant)
2	**5b**	**6b** (quant)	9	**5i**	**6i** (90)
3	**5c**	**6c** (92)	10	**5j**	**6j** (quant)[c]
4	**5d**	**6d** (82)	11	**5k**	**6d** (85)
5	**5e**	**6e** (80)[b]	12	**5l**	**6f** (80)
6	**5f**	**6f** (quant)	13	**5m**	**6a** (86)
7	**5g**	**6g** (96)			

2 [a]isolated yields of ***6*** after complete reaction of **5** according to analysis using TLC; [b]1.2 equiv $SnCl_4$; [c]performed in NMR

3 tube, quantitative

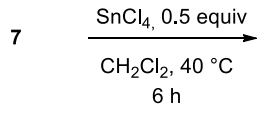


To further study the scope of cleaving benzyl esters using $SnCl_4$, several β-carbonyl-α-benzyl ester pyrroles were subjected to the reaction conditions. However, only moderate yields of the corresponding acids could be obtained, and analysis using TLC suggested that decomposition of the products occurred under the reaction conditions, making the purification challenging. A recent study reported the ability of $SnCl_4 \bullet 5H_2O$ to promote the ring-opening of 4,5-dihydropyrroles,[36] supporting the notion that this Lewis acid can invoke a multitude of mechanisms involving the carbonyl moiety.

Nevertheless, with efficient conditions in hand we investigated whether the cleavage strategy was general for esters or selective to the benzyl moiety and subjected several substrates to our optimised reaction conditions (Table 4, $SnCl_4$ 0.5 equiv, DCM, 40 °C, 6h). In agreement with the literature, a *tert*-Bu ester was cleaved in the presence of $SnCl_4$, but with only 0.5 equiv (Lit:[20] 4 equiv $SnCl_4$ used, Entry

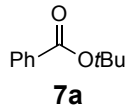
1). Gratifyingly, only starting material was returned when ethyl benzoate **7b** (Entry 2) was treated with $SnCl_4$, even when the stoichiometry was increased to 1.2 equiv $SnCl_4$. Thus a benzyl ester could be easily removed in the presence of an ethyl ester (Entry 3). Benzyl amines and amides are inert to the deprotection reaction conditions (Entry 4-5). In contrast, the benzyl carbamate **7f** was successfully cleaved, albeit using 1.5 equiv $SnCl_4$, to presumably allow for non-productive complexation to the nitrogen heteroatom (Entry 6). Importantly, no reaction occurred using the same conditions with the Troc-like benzyl carbamate **7g** and the starting material was completely recovered after 20 h (Entry 7).

Table 4. Scope of the reactivity of $SnCl_4$ with various protecting groups

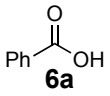


entry	substrates	recovered compounds (yield, %)[a]
1	**7a**	**6a** (76)
2	**7b**	SM[b] (96)
3	**7c**	**8c** (79)
4	**7d**	SM[b] (99)
5	**7e**	SM[b] (quant)
6	**7f**	**8f** (79)[c]
7	**7g**	SM (quant)[c]

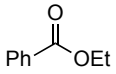
[a]isolated yield; [b]SM = smarting material; [c]1.5 equiv of $SnCl_4$, 20 h.



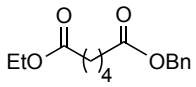
7a



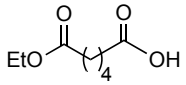
6a



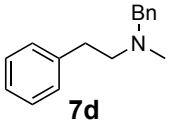
7b



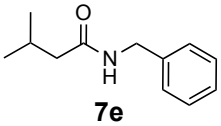
7c



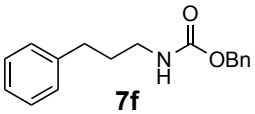
8c



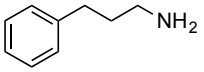
7d



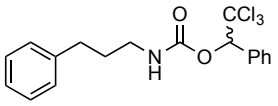
7e



7f



8f

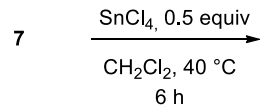


7g

We then assessed the stability/reactivity of other alcohol protecting groups in the presence of $SnCl_4$ (Table 5). Primary benzyl alkyl ethers were inert to the reaction conditions (Entry 1). Although the secondary benzyl alkyl ether **7h** was recovered in 95% yield, traces of the alcohol were observed using TLC (Entry 2). Phenol benzyl ethers substituted with an electron withdrawing group remained untouched in the presence of $SnCl_4$ (Entry 3), yet phenol benzyl ethers substituted with electron donating groups were quantitatively cleaved (Entry 4-5), indicating that the use of benzyl groups to protect (poly)phenols can be engineered so that selective deprotection may be achieved via the use of $SnCl_4$. The tosyl protecting group was inert under the reaction conditions (Entry 6). THP was readily removed in just a few minutes (Entry 7). Removal of the MOM group under the reaction conditions was observed, as were several side products (Entry 8). The TBDMS protecting group was partially cleaved in

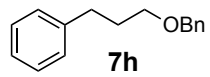
the presence of $SnCl_4$, but more robust TIPS-protected alcohol was recovered (85%) after 6 h of reaction and only traces of the alcohol were observed using TLC (Entry 9-10).

Table 5. Scope of the reactivity of $SnCl_4$ with alcohol protecting groups

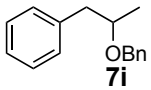


entry	substrates	compounds (yield, %)[a]
1	**7h**	SM[b] recovered (quant)
2	**7i**	SM[b] recovered (97)[c]
3	**7j**	SM[b] recovered (95)
4	**7k**	**8k**[d]
5	**7l**	**8l**[d]
6	**7m**	SM[b] recovered (quant)
7	**7n**	**8n** (84)[e]
8	**7o**	-[f]
9	**7p**	SM[b] recovered (85)[c]
10	**7q**	SM[b] recovered (36)

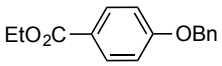
[a]isolated yield; [b]SM = starting material; [c]traces of deprotected material could be observed using TLC; [d]not isolated, complete conversion according to analysis using TLC; [e]5 minutes of reaction; [f]partial conversion and formation of side-products



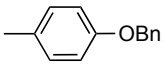
7h



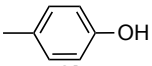
7i



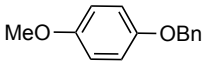
7j



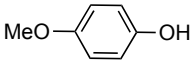
7k



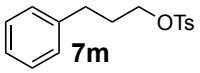
8k



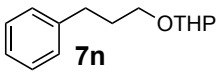
7l



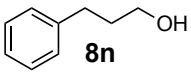
8l



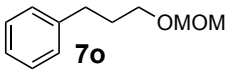
7m



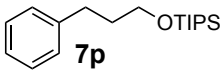
7n



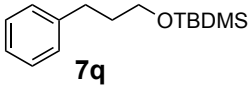
8n



7o



7p



7q

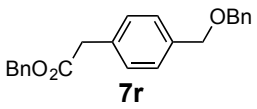
The orthogonal deprotection of benzyl-protected carboxylic acids within difunctional substrates was then attempted, first in the presence of a benzyl ether (**7r**, Table 6, Entry 1) and also in the presence of a benzyl amine (**7s**,[37,38] Entry 2). However, although complete consumption of the starting materials was observed in both cases, intractable mixtures resulted, with the ^{1}H NMR spectra of the crude reaction mixtures suggesting only decomposition. Fuelled by recent work regarding the relevance of evaluating the scope and tolerance of new methodology by using multi-functional substrates vs. using multiple additives each bearing different functional groups,[39] we were intrigued by our results, given that the benzyl ethers **7h** and **7i** (Table 5), and the benzyl amine **7d** (Table 4), had been stable in the presence of

$SnCl_4$. We thus performed an experiment involving benzyl benzoate and $SnCl_4$, dissolved in CD_2Cl_2 alongside one equivalent of diethyl ether as an additive. The reaction did not reach completion after the expected 5 h at 40 °C, despite the fact that benzyl benzoate underwent complete cleavage in the absence of diethyl ether (Table 3, Entry 1). Instead, ^{1}H NMR analysis of the reaction mixture after 24 h indicated a benzyl benzoate/benzoic acid ratio of 1:7.3, alongside complexation of the diethyl ether to $SnCl_4$ as suggested by the chemical shift of the CH_2 protons (*cf*. Supporting Information). Clearly the complexation of the ether to the $SnCl_4$ reagent slowed down the desired ester debenzylation process. This was confirmed when using the dibenzyl-containing serines **7t** and **7u** (Table 6, Entries 3 and 4, respectively), both of which required 1 equivalent of $SnCl_4$ to produce the expected substrates via chemoselective debenzylation, albeit in moderate yield. Although mono benzyl ethers are stable under our reaction conditions (Table 5), a poly benzyl ether (**7u**) was partially deprotected, and 57% of starting material was recovered (Table 6, Entry 5) presumably because of the close proximity of functional groups capable of complexation to the Lewis acid.[33] Those experiments demonstrate the limitations of the use of $SnCl_4$ as a debenzylating agent for some substrates. Indeed, the strong Lewis acid properties of this reagent, as well as its complexation properties, should always be anticipated when considering the use of $SnCl_4$ to effect debenzylation.

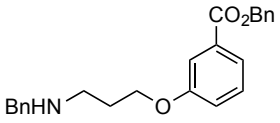
Table 6: Scope of the reactivity of $SnCl_4$ with substrates bearing multi-functionality.

entry	substrates	compounds (yield, %)[a]
1	**7r**	Decomp.
2	**7s**	Decomp.[b]
3	**7t**	**8t** (55)[b]
4	**7u**	**8u** (30)[b] SM[c] (24)
5	**7v**[d]	SM[c] recovered (57)[e]

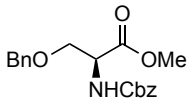
[a]isolated yield; [b]1 equiv of $SnCl_4$, overnight; [c]SM = starting material; [d]α/β 1:6.2; [e] α/β 3.2:1



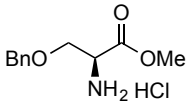
7r



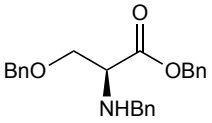
7s



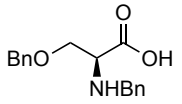
7t



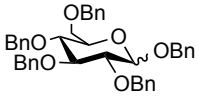
8t



7u



8u



7v

Turning to the potential mechanism for $SnCl_4$-induced ester debenzylation, we used NMR studies (Figure 1) to follow the course of benzyl benzoate deprotection. As expected, ^1H spectra recorded over time revealed the decrease of the CH_2 signal of the benzyl ester (originally at 5.4 ppm), alongside the gradual appearance of aryl signals corresponding to benzoic acid. Curiously, the characteristic benzylic signal of benzyl chloride appeared at 4.6 ppm, yet the signal intensity decreased with extension of the reaction time (compare Figure 1c recorded after 1 hour to Figure 1e recorded after 6 h). The formation of benzyl chloride was previously observed upon the deprotection of poly benzyl ethers using $SnCl_4$,[33] and this Lewis acid has been reported to induce calixarene formation from 4-*tert*butyl phenol,[40] lending support to the belief that the liberated benzyl moiety undergoes further reaction to form a polymeric species.

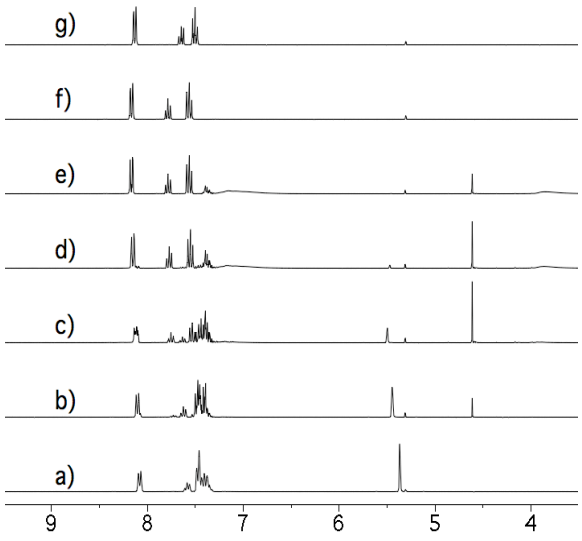


Figure 1. ^1H NMR (300 MHz) of benzyl benzoate deprotection at 30 °C; (a) benzyl benzoate in CD_2Cl_2; (b) addition of $SnCl_4$ (0.5 equiv); (c) reaction after 1 h; (d) reaction after 3 h; (e) reaction after 6 h; (f) benzoic acid and $SnCl_4$ (0.5 equiv) in CD_2Cl_2; (g) benzoic acid in CD_2Cl_2. Note that the broad areas across (d) and (e) at δ 3.8 and 7.1 ppm are indicative of the by-product (**9**).

We also noted that the reactions produced a by-product (**9**). Upon isolation as a crystalline white solid, compound **9** exhibited ^1H NMR characteristics (see Supporting Information) that matched the

broad aryl and benzylic signals that appeared as the ester debenzylation proceeded (see Figure 1d and 1e). Analysis using $APCI^+$ mass spectrometry revealed that **9** was polymeric, with a repeating benzylic unit (mass 90 *m/*z, see Supporting Information). Furthermore, the reaction of benzyl chloride with 0.5 equiv of $SnCl_4$ in CH_2Cl_2 for 21 hours, gave a crystalline white solid. The corresponding ^1H NMR spectrum exhibited the same two broad signals as the material isolated after the ester debenzylation reaction (7.1 and 3.8 ppm), with similar polymeric mass spectral data (see Supporting Information). A related polybenzyl species was observed after benzyl ester cleavage using a rhenium catalyst, and can be prevented using mesitylene as a scavenger of the benzylic cation.[23] Anisole has been shown to play the same role when using $AlCl_3$ for removal of the benzyl moiety from benzyl esters.[5]

The coordination of $SnCl_4$ to ethyl esters has previously been demonstrated using IR spectroscopy.[41] Based on the postulated mechanism for $SnCl_4$-induced debenzylation of polybenzyl ethers,[33] we propose an ester debenzylation mechanism whereby pre-coordination of tin to the oxygen atoms of the benzyl ester facilitates delivery of chloride to the electrophilic benzylic position. Such delivery would not occur in the case of alkyl esters, since the corresponding O–CH_2R functionality would be insufficiently activated. In this respect, the distinguishing electronic properties of the benzylic position render benzyl esters, and not benzyl ethers, uniquely susceptible to $SnCl_4$. However, the presence of other moieties capable of coordinating to $SnCl_4$ would evidently disrupt the desired coordination to the ester functionality thus slowing the debenzylation and/or altering the course of the reaction and so, as for most deprotection strategies, each substrate should be considered for its functionality and its likelihood to interact with $SnCl_4$ in the desired manner. We analysed NMR data for signs of coordination of $SnCl_4$ to benzyl carboxylates. The ^{119}Sn NMR spectrum of a sample of benzyl benzoate and 2.5 equiv $SnCl_4$ reveals an upfield shift (Figure 2b) c.f. $SnCl_4$ alone (Figure 2a), and significant signal broadening. Such broadening and coordination is less dramatic for $SnCl_4$ and benzoic acid (Figure 2c), indicating much greater Sn interaction with benzyl esters than carboxylic acids.

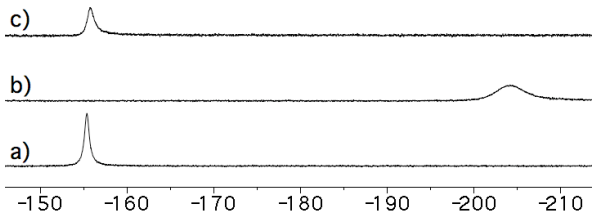


Figure 2. ^{119}Sn NMR (112 MHz), -80 °C; (a) $SnCl_4$ in CD_2Cl_2, δ -155.4 ppm; (b) ten mins after addition of benzyl benzoate, δ -204.1 ppm; (c) benzoic acid and $SnCl_4$ in CD_2Cl_2 after ten mins, δ -155.7 ppm.

Conclusion

In summary, $SnCl_4$ cleaves benzyl esters and carbamates yet leaves benzyl amides, double bonds and triple bonds intact. Benzyl alkanoates and aryl esters were successfully cleaved in high yields. While simple benzyl ethers remain unreacted, the suitability of $SnCl_4$ should be considered carefully when the substrate presents multiple benzyl ethers as tin complexation to multiple oxygen atoms can induce benzyl ether cleavage. The orthogonality of cleaving benzyl esters and carbamates, cf. benzyl ethers, is substrate dependant, presumably due to the intrinsic strong Lewis acid properties of $SnCl_4$. NMR analysis suggests that a crucial coordination of $SnCl_4$ with the oxygen atoms of the ester facilitates chloride attack at the benzylic position to cleave the O–CH_2Ph bond. Alongside the requisite carboxylic acid, the reaction produces a polybenzylic material. Although the method suffers some limitations we believe that benzyl deprotection using $SnCl_4$ offers an alternative route for the debenzylation of esters for organic and total synthesis. The potential to use $SnCl_4$ for the chemoselective cleavage of benzyl esters and carbamates, over benzyl ethers, amides and amines complements strategies that use catalytic transfer hydrogenation,[42] NBS,[43] silica-supported $NaHSO_4$,[44] $NiCl_2/NaBH_4$[45] and Raney Ni.[46]

EXPERIMENTAL SECTION

General Experimental Procedures: All reactions were carried out under a nitrogen atmosphere using septa-sealed solvents under anhydrous conditions. All reagents and solvents, including anhydrous CH_2Cl_2, were used as received unless otherwise stated. $SnCl_4$ (99%) was anhydrous and fuming, hexanes and dichloromethane used for chromatography were obtained crude and were purified via distillation under air and at 1 atm. before use. Column chromatography was performed using 230-400 mesh ultra pure silica gel. Mass spectra were obtained using TOF and LCQ Duo ion trap instruments operating in ESI+ or APCI+ mode. ^{1}H NMR, ^{13}C NMR and ^{119}Sn spectroscopy were used for chemical characterization and purity analysis using 300 and 500 MHz spectrometers. All chemical shifts are expressed in parts per million (ppm). The $CDCl_3$ singlet was calibrated to 7.26 ppm for ^{1}H NMR and 77.36 ppm for ^{13}C NMR; the $CDCl_2$ signal was set to 5.31 ppm for ^{1}H NMR and 53.80 ppm for ^{13}C NMR; the DMSO signal was set to 2.50 ppm for ^{1}H NMR; the CD_3OD signal was set to 3.31 ppm for ^{1}H NMR; ^{119}Sn spectra were referenced against $SnMe_4$ set to 0 ppm as an internal reference. Coupling constants (*J*) are reported in Hertz (Hz). Splitting patterns are indicated as; broad (br), singlet (s), doublet (d), triplet (t), apparent triplet (at), quartet (q), apparent quartet (aq), quintet (qn), sextet (se), multiplet (m).

The following compounds were prepared via established procedures: monoethyl glutarate (**1**),[47] benzyl 3,5-dimethyl-1*H*-pyrrole-2-carboxylate (**2**),[48] benzyl benzoate (**5a**),[49] benzyl 4-nitrobenzoate (**5b**),[50] benzyl 4-methoxybenzoate (**5c**),[51] benzyl pentanoate (**5d**),[52] benzyl tetradecanoate (**5e**),[53] benzyl pivalate (**5f**),[54] benzyl 2-(4-methoxyphenyl)acetate (**5g**),[55] benzyl pent-4-enoate (**5h**),[56] 4-methoxybenzyl pivalate (**5l**)[57] and 4-methoxybenzyl benzoate (**5m**), [50] *tert*-butyl benzoate (**7a**),[58] ethyl benzoate (**7b**),[59] *N*-benzyl-*N*-methyl-2-phenylethanamine (**7d**),[60] N-benzyl-3-methylbutanamide (**7e**),[61] benzyl (3-phenylpropyl)carbamate (**7f**),[62] (3-(benzyloxy)propyl)benzene (**7h**),[63] ethyl 4-(benzyloxy)benzoate (**7j**),[64] 1-(benzyloxy)-4-methylbenzene (**7k**),[65] 1-(benzyloxy)-4-methoxybenzene (**7l**),[66] 3-phenylpropyl 4-methylbenzenesulfonate (**7m**),[67] 2-(3-phenylpropoxy)tetrahydro-2H-pyran (**7n**)[68] (NMR data were in agreement with the literature),[69] triisopropyl(3-phenylpropoxy)silane (**7p**) and

tert-butyldimethyl(3-phenylpropoxy)silane (**7q**),[70] benzyl 2,3,4,6-tetra-*O*-benzyl-D-glucopyranoside (**7v**).[71]

Preparation of starting material 3, 4, 5 and 7:

Benzyl 4-(5-ethoxy-5-oxopentanoyl)-3,5-dimethyl-1*H*-pyrrole-2-carboxylate (3) and 4-(5-ethoxy-5-oxopentanoyl)-3,5-dimethyl-1*H*-pyrrole-2-carboxylic acid (4): To monoethyl glutarate 1[47] (3.75 g, 23.4 mmol), thionyl chloride (2.1 mL, 29.3 mmol) was added. The reaction was heated to 60°C for 30 minutes and then 80 °C for 1 h. Thionyl chloride was removed *in vacuo* to afford the acid chloride as a yellow oil which was used without further purification (4.2 g, quantitative).

Benzyl 3,5-dimethyl-1*H*-pyrrole-2-carboxylate **2** (4.8 g, 21 mmol) was dissolved in anhydrous CH_2Cl_2 (50 mL) under nitrogen. While stirring at 0 °C, $SnCl_4$ (3 mL, 25 mmol) was slowly added. The resulting solution was stirred for 10 min at 0 °C. The previously synthesized acid chloride (3.75 g, 21 mmol) in anhydrous CH_2Cl_2 (30 mL) was then added. The reaction mixture was stirred for 2 h at 0 °C then quenched via the addition of HCl (1 M, 35 mL). After 15 min stirring the mixture was extracted with CH_2Cl_2 (3 × 50 mL). The combined organic layers were washed with brine and then dried (Na_2SO_4). After evaporation of the solvent under reduced pressure the crude material was purified using flash chromatography (SiO_2, EtOAc/hexane 3/7 to 4/6) to give compound **3** as an off white solid (5.1 g, 66%) and compound **4** as a white solid (1.2 g, 24%). Benzyl 4-(5-ethoxy-5-oxopentanoyl)-3,5-dimethyl-1H-pyrrole-2-carboxylate **(3)**: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.24 (t, *J* = 7.0 Hz, 3H), 2.02-2.04 (m, 2H), 2.40 (t, *J* = 7.0 Hz, 2H) 2.49 (s, 3H), 2.60 (s, 3H) 2.80 (t, *J* = 7.0 Hz, 2H), 4.11 (q, *J* = 7.0 Hz, 2H) 5.31 (s, 2H), 7.33-7.42 (m, 5H) 8.98 (br s, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 13.2, 14.6, 15.6, 19.7, 33.9, 42.0, 60.6, 66.5, 117.9, 123.8, 128.6, 128.7, 129.0, 130.0, 136.3, 138.5, 161.5, 173.7, 197.4; HRMS-ESI (*m/z*): $[M+Na]^+$ calcd for $C_{21}H_{25}N_1Na_1O_5$, 394.1625; found, 394.1605. 4-(5-Ethoxy-5-oxopentanoyl)-3,5-dimethyl-1H-pyrrole-2-carboxylic acid **(4)**: ^{1}H NMR (DMSO, 300 MHz) δ 1.17 (t, *J* = 7.2 Hz, 3H), 1.75-1.85 (m, 2H), 2.33 (t, *J* = 7.5 Hz, 2H) 2.42 (s, 3H), 2.47 (s, 3H) 3.30 (t, *J* = 6.9 Hz, 2H), 4.06 (q, *J* = 7.2 Hz, 2H), 11.7 (br s, 1H); ^{13}C NMR (DMSO, 125 MHz) δ 12.3, 14.1, 14.4, 19.2,

32.9, 40.7, 59.7, 122.2, 128.0, 137.9, 142.6, 162.4, 172.8, 196.2; HRMS-ESI (*m/z*): $[M+Na]^+$ calcd for $C_{14}H_{19}N_1Na_1O_5$, 304.1155; found, 304.1143.

(*E*)-Benzyl 3-(*p*-tolyl)acrylate 5i: To a suspension of (*E*)-4-methylcinnamic acid (500 mg, 3.08 mmol) in CH_2Cl_2 (10 mL) was added EDC (525 mg, 3.39 mmol), DMAP (414 mg, 3.39 mmol) followed by benzyl alcohol (480 µL, 4.62 mmol). The resulting solution was stirred for 18 h, and then water was added (50 mL). The mixture was extracted with CH_2Cl_2 (3 × 30 mL). Then the combined organic layers were washed with brine and then dried (Na_2SO_4). After evaporation of the solvent under reduced pressure the crude was purified using flash chromatography (SiO_2, EtOAc/hexanes 1/9) to give a white solid (380 mg, 49%). Mp 86 °C; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 2.37 (s, 3H), 5.25 (s, 2H), 6.45 (d, *J* = 15.7 Hz, 1H), 7.20 (d, *J* = 8 Hz, 2H), 7.33-7.43 (m, 7H), 7.71 (d, *J* = 15.7 Hz, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 21.6, 66.4, 116.9, 128.2, 128.4 (2C), 128.7, 129.8, 131.7, 136.3, 140.9, 145.3, 167.1; HRMS-ESI (*m/z*): $[M+Na]^+$ calcd for $C_{17}H_{16}Na_1O_2$, 275.1043; found, 275.1050.

Benzyl propiolate 5j: To a suspension of potassium carbonate (4.47 g, 32.3 mmol) in DMF (15 mL), propiolic acid (2.00 mL, 32.3 mmol) in DMF (8 mL) was added and stirred at 0°C. After 10 minutes, benzyl bromide (3.20 mL, 26.9 mmol) was added and reaction mixture was warmed to 25 °C. The resulting solution was stirred for 2 h, then water was added (45 mL). The mixture was extracted with EtOAc/hexanes 1/1 (3 x 30 mL). The combined organic layers were washed with brine and then dried (Na_2SO_4). After evaporation of the solvent under reduced pressure the crude material was purified using flash chromatography (SiO_2, EtOAc/hexanes 1/19) to give a colorless oil (4.31 g, quantitative). ^{1}H NMR (CD_2Cl_2, 500 MHz) δ 2.96 (s, 1H), 5.20 (s, 2H), 7.35-7.40 (m, 5H); ^{13}C NMR (CD_2Cl_2, 125 MHz) δ 68.3, 74.8, 75.2, 128.9, 129.01, 129.04, 135.2, 152.8; HRMS-ESI (*m/z*): $[M+Na]^+$ calcd for $C_{10}H_8NaO_2$, 183.0417; found, 183.0417.

4-Methoxybenzyl pentanoate 5k: To a stirring solution of 4-methoxybenzyl alcohol (0.30 mL, 2.42 mmol) in DCM (8.0 mL) at 0 °C, triethylamine (0.49 mL, 4.83 mmol) and valeroyl chloride (0.29 mL, 2.42 mmol) was added. The reaction was stirred for 1 h and then a further aliquot of valeroyl chloride

(0.17 mL, 1.45 mmol) was added. The reaction mixture was quenched with water (15 mL), and then extracted into CH_2Cl_2 (3 x 15 mL). The combined organic layers were washed with brine and then dried (Na_2SO_4). After evaporation of the solvent under reduced pressure the crude material was purified using flash chromatography (SiO_2, EtOAc/hexanes 1/9) to give a colorless oil (336 mg, 63%). ^{1}H NMR (CD_2Cl_2, 500 MHz) δ 0.89 (t, *J* = 7.5 Hz, 3H) 1.33 (se, *J* = 7.5 Hz, 2H), 1.58 (qn, *J* = 7.5 Hz, 2H), 2.30 (t, *J* = 7.5 Hz, 2H), 3.78 (s, 3H), 5.01 (s, 2H), 6.87 (d, *J* = 8.5 Hz, 2H), 7.28 (d, *J* = 8.5 Hz, 2H); ^{13}C NMR (CD_2Cl_2, 125 MHz) δ 13.8, 22.6, 27.4, 34.4, 55.6, 66.1, 114.2, 128.9, 130.2, 160.0, 173.8; HRMS-ESI (*m/z*): $[M+Na]^+$ calcd for $C_{13}H_{18}Na_1O_3$, 245.1148; found, 245.1137.

Benzyl ethyl adipate 7c: to a solution of 6-ethoxy-6-oxohexanoic acid (1.1 g, 6.3 mmol) in anhydrous DCM (5 mL) was added $SOCl_2$ (570 µL, 7.9 mmol) and the reaction mixture was heated at 45 °C for two hours. Then benzyl alcohol (720 µL, 6.9 mmol) was added at room temperature. The reaction mixture was heated at 40 °C for 3 hours then cooled to room temperature. An aqueous solution of NaOH (10%, 20 mL) was added and the mixture was extracted with CH_2Cl_2 (3 × 20 mL). The combined organic layers were washed with brine (50 mL), and then dried (Na_2SO_4). After evaporation of the solvent under reduced pressure the crude material was purified using flash chromatography (SiO_2, EtOAc/hexanes 1/9) to give a colorless oil (600 mg, 36%). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.24 (t, *J* = 7.0 Hz, 3H), 1.65-1.70 (m, 4H), 2.31 (t, *J* = 7.0 Hz, 2H) 2.38 (t, *J* = 7.0 Hz, 2H), 4.12 (q, J = 7.0 Hz, 2H), 5.11 (s, 2H), 7.33-7.37 (m, 5H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 14.3, 24.5, 34.0, 60.4, 66.3, 128.3, 128.7, 136.1, 173.2, 173.4; HRMS-ESI (*m/z*): $[M+Na]^+$ calcd for $C_{15}H_{20}Na_1O_4$, 287.1254; found, 287.1259.

2,2,2-Trichloro-1-phenylethyl (3-phenylpropyl)carbamate 7g: To a solution of 3-phenylpropan-1-amine (314 µL, 2.2 mmol) in anhydrous CH_2Cl_2 (12 mL) was added CDI (390 mg, 2.4 mmol) and the reaction mixture was stirred at 40 °C for 2h30. It was cooled to room temperature, then water (30 mL) was added and the mixture was extracted with Et_2O (3 × 30 mL). The combined organic layers were

washed with brine (50 mL), dried (Na_2SO_4) and the solvent were removed under reduced pressure to give *N*-(3-phenylpropyl)-1*H*-imidazole-1-carboxamide as a white solid (500 mg, quant.)

To a solution of 2,2,2-trichloro-1-phenylethanol (250 mg, 1.1 mmol)[72] in anhydrous THF (2 mL) was added NaH (60% in oil, 1.33 mmol) at 0°C. The reaction was run at this temperature for 30 min then a solution of *N*-(3-phenylpropyl)-1*H*-imidazole-1-carboxamide (250 mg, 1.1 mmol) in anhydrous THF (2mL) was added. The reaction mixture was stirred 3 h at room temperature then quenched by the addition of water (10 mL) and extracted with Et_2O (3 × 30 mL). The combined organic layers were washed with brine (50 mL), and then dried (Na_2SO_4). After evaporation of the solvent under reduced pressure the crude material was purified using flash chromatography (SiO_2, CH_2Cl_2/hexanes 5/5) to give a colorless oil (311 mg, 70%). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.86 (quint., J = 7.4 Hz, 2H), 2.65 (t, J = 7.6 Hz, 2H), 3.17-3.31 (m, 2H), 4.99 (br s, 1H), 6.30 (s, 1H), 7.14-7.21 (m, 3H), 7.25-7.28 (m, 2H), 7.38-7.41 (m, 3H), 7.59-7.62 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 31.5, 33.1, 41.0, 83.3, 126.2, 128.0, 128.5, 128.6, 129.7, 129.8, 133.6, 141.3, 154.2. HRMS-ESI (*m/z*): $[M+Na]^+$ calcd for $C_{18}H_{18}Cl_3N_1Na_1O_2$, 408.0295; found, 408.0278.

(2-(Benzyloxy)propyl)benzene 7i: Following a literature procedure,[73] 1-phenylpropan-2-ol (500 mg, 3.67 mmol) was dissolved in $MeNO_2$ (20 mL) then benzaldehyde (440 μL, 4.3 mmol), $FeCl_3$ (35 mg, 5 mol%) and Et_3SiH (590 mL, 3.67 mmol) were added under N_2. The reaction mixture was stirred two hours then quenched through the addition of phosphate buffer (pH = 7, 20 mL). The reaction mixture was extracted with EtOAc (3 × 30 mL) and the combined organic layers were washed with brine (50 mL) then dried (Na_2SO_4). After evaporation of the solvents under reduced pressure the crude material was purified using flash chromatography (SiO_2, EtOAc/hexanes 0.3/99.7) to give a colorless oil (730 mg, 94%). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.20 (d, J = 6.0 Hz, 3H), 2.70 (dd, J = 13.5, 6.3 Hz, 1 H), 2.97 (dd, J = 13.5, 6.3 Hz, 1 H), 3.74 (se. J = 6.3 Hz, 1H), 4.46 (d, J = 12.0 Hz, 1H), 4.56 (d, J = 12.0 Hz, 1H), 7.19-7.38 (m, 10H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 19.7, 43.4, 70.7, 76.3, 126.2, 127.5, 127.7,

128.3, 128.4, 129.7, 139.0, 139.2; HRMS-ESI (*m/z*): $[M+Na]^+$ calcd for $C_{16}H_{18}Na_1O_1$, 249.1250; found, 249.1253.

(3-(Methoxymethoxy)propyl)benzene 7o: To a solution of 1-phenylpropan-2-ol (500 mg, 3.67 mmol) in anhydrous THF (15 mL) was added DIPEA (1.4 mL, 8.07 mmol) followed by MOMCl (300 μL, 4.01 mmol). The reaction mixture was stirred for 16 h then quenched with a saturated aqueous solution of NH_4Cl (15 mL) for 15 min. The reaction mixture was then extracted with EtOAc (3 × 30 mL) and the combined organic layers were washed with brine (50 mL) and then dried (Na_2SO_4). After evaporation of the solvent under reduced pressure the crude material was purified using flash chromatography (SiO_2, EtOAc/hexanes 0.5/99.5) to give a colorless oil (450 mg, 68%). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.88-1.97 (m, 2H), 2.72 (t, *J* = 7.8 Hz, 2H), 3.38 (s, 3H), 3.56 (t, *J* = 6.5 Hz, 2H), 4.64 (s, 2H), 7.16-7.21 (m, 3H), 7.26-7.31 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 31.6, 32.6, 55.3, 67.3, 96.6, 126.0, 128.5, 128.6, 142.0; HRMS-ESI (*m/z*): $[M+Na]^+$ calcd for $C_{11}H_{16}Na_1O_2$, 203.1043; found, 203.1043.

Benzyl 2-(4-((benzyloxy)methyl)phenyl)acetate 7r:[73] To a solution of benzyl 2-(4-(hydroxymethyl)phenyl)acetate[74] (500 mg, 3.67 mmol) in nitromethane (20 mL) under nitrogen was added benzaldehyde (440 μL, 4.3 mmol), $FeCl_3$ (35 mg, 5 mol%) and then triethylsilane (590μL, 3.67 mmol). The reaction mixture was stirred for 2 h under nitrogen then was quenched by the addition of a phosphate buffer (50 mL, pH = 7). The crude mixture was extracted with EtOAc (3 × 20 mL) and the combined organic layers were washed with brine and then dried (Na_2SO_4). After evaporation of the solvent under reduced pressure the crude material was purified using flash chromatography (SiO_2, EtOAc/hexanes 0.5/99.5) to give a colorless oil (730 mg, 94%). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 3.68 (s, 2H), 4.56 (s, 4H), 5.14 (s, 2H), 7.27-7.38 (m, 14H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 41.2, 66.8, 71.9, 72.2, 127.8, 127.9, 128.1, 128.3, 128.4, 128.5, 128.7, 129.5, 133.4, 136.0, 137.4, 138.4, 171.5. HRMS-ESI (*m/z*): $[M+Na]^+$ calcd for $C_{23}H_{22}Na_1O_3$, 369.1461; found, 369.1448.

Benzyl 3-(3-(benzylamino)propoxy)benzoate 7s: To a solution of benzyl 3-hydroxybenzoate[37] (500 mg, 2.2 mmol) in DMF (10 mL) at 0 °C under nitrogen was added NaH (60% in grease, 2.6 mmol). The

suspension was stirred for 30 min at room temperature then cooled to 0 °C. A solution of 3-((*tert*-butoxycarbonyl)amino)propyl 4-methylbenzenesulfonate[38] in DMF (10 mL) was then added and the reaction mixture was stirred for a further 3 h at room temperature. The reaction was quenched through the addition of water (100 mL) and the reaction mixture was extracted with EtOAc (3 × 30 mL). The combined organic layers were washed with water (50 mL), brine (50 mL) and then dried (Na_2SO_4). After evaporation of the solvent under reduced pressure the crude material was purified using flash chromatography (SiO_2, EtOAc/hexanes 2/8 then 3/7) to give benzyl 3-(3-((*tert*-butoxycarbonyl)amino)propoxy)benzoate as a white solid (570 mg, 67%). Mp 80 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.44 (s, 9H), 1.99 (qn, *J* = 6.3 Hz, 2H), 3.33 (q, *J* = 6.3 Hz, 2H), 4.05 (t, *J* = 6.0 Hz, 2H), 4.74 (br s, 1H), 5.36 (s, 2H), 7.09 (ddd, *J* = 8.4, 2.7, 0.9 Hz, 1H), 7.31-7.46 (m, 5H), 7.58 (dd, *J* = 2.7, 1.6 Hz, 1H), 7.67 (dt, *J* = 7.8, 1.2 Hz, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 28.5, 29.7, 38.1, 66.1, 66.9, 115.1, 120.0, 122.4, 128.3, 128.4, 128.7, 129.6, 131.6, 136.2, 156.1, 158.9, 166.4; HRMS-ESI (*m/z*): $[M+Na]^+$ calcd for $C_{22}H_{27}N_1Na_1O_5$, 408.1781; found, 408.1795.

Benzyl 3-(3-((*tert*-butoxycarbonyl)amino)propoxy)benzoate (520 mg, 1.34 mmol) was dissolved in CH_2Cl_2 (5 mL) then TFA (1 mL) was added. The reaction mixture was stirred for 3 h at room temperature then water (50 mL) was added. The crude mixture was then extracted with DCM (3 × 20 mL) then the combined organic layers were washed with $NaHCO_3$ (50 mL), brine (50 mL) and then dried (Na_2SO_4). The obtained oil (430 mg, 1.34 mmol) was dissolved in DCM (3 mL) and $MgSO_4$ (160 mg, benzaldehyde (180 μL, 1.8 mmol) and triethylamine (250 μL, 1.8 mmol) were added under nitrogen. The reaction was stirred overnight then filtered through a pad of Celite using CH_2Cl_2. The filtrate was concentrated under reduce pressure then the resulting oil was dissolved in MeOH (5 mL). $NaBH_4$ (68 mg, 1.8 mmol) was added in portions at 0 °C then the reaction mixture was stirred at room temperature for 1 h. The reaction was quenched through the addition of water (20 mL) and the reaction mixture was then extracted with CH_2Cl_2 (3 × 20 mL). The combined organic layers were washed with brine (50 mL) and then dried (Na_2SO_4). After evaporation of the solvent under reduced pressure the crude mate-

rial was purified using flash chromatography (Al_2O_3 neutral Brockman type III, CH_2Cl_2 100% then CH_2Cl_2/MeOH 99/1) to give **7s** colorless oil (300 mg, 53%). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.46 (br s, 1H), 2.00 (qn, *J* = 6.5 Hz, 2H), 2.83 (t, *J* = 7.0 Hz, 2H), 3.81 (s, 2H), 4.09 (t, *J* = 6.5 Hz, 2H), 5.36 (s, 2H), 7.08 (dd, *J* = 8.0, 2.5 Hz, 1H), 7.22-7.26 (m, 1H), 7.29-7.40 (m, 8H), 7.44-7.45 (m, 1H), 7.59 (br s, 1H), 7.66 (d, *J* = 7.5 Hz, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 29.9, 46.3, 54.2, 66.7, 66.9, 115.1, 120.0, 122.2, 127.1, 128.2, 128.3, 128.4, 128.5, 128.7, 129.5, 131.6, 136.2, 140.5, 159.1, 166.5. HRMS-ESI (*m/z*): $[M+H]^+$ calcd for $C_{24}H_{26}N_1O_3$, 376.1907; found, 376.1915.

***N*-Benzylcarbamate-*O*-Benzyl-L-serine methyl ester 7t**: (*S*)-Methyl 2-(((benzyloxy)carbonyl)amino)-3-hydroxypropanoate[75] (200 mg, 0.79 mmol) was dissolved in CH_2Cl_2 (3 mL) then BnBr (100 μL, 0.87 mmol) and silver oxide (274 mg, 1.18 mmol) were added. The suspension was stirred in the dark for 20 h then filtered. After evaporation of the solvent under reduced pressure the crude material was purified using flash chromatography (SiO_2, EtOAc/hexanes 3/7) to give a colorless oil (150 mg, 55%). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 3.70 (dd, *J* = 9.6, 3.3 Hz, 1H), 3.75 (s, 3H), 3.89 (dd, *J* = 9.6, 3.3 Hz, 1H), 4.45-4.56 (m , 3H), 5.12 (s, 2H), 5.63 (d, *J* = 8.7 Hz, 1H), 7.24-7.37 (m, 10H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 52.7, 54.5, 67.2, 69.9, 73.4, 127.7, 128.0, 128.2, 128.3, 128.6, 128.7, 136.4, 137.6, 156.1, 170.9; HRMS-ESI (*m/z*): $[M+Na]^+$ calcd for $C_{19}H_{21}N_1Na_1O_5$, 366.1312; found, 366.1299.

***N*-Benzyl-*O*-Benzyl-L-serine benzyl ester 7u**: Following the previous procedure and starting from (*S*)-benzyl 2-(benzylamino)-3-hydroxypropanoate,[76] **7u** was obtained as a colorless oil (110 mg, 20%). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.46 (br s, 1H), 3.60-3.67 (m, 3H), 3.73-3.79 (m, 2H), 3.90 (d, *J* = 13.5 Hz, 2H), 5.25 (aq, *J* = 11.8 Hz, 2H), 7.23-7.33 (m, 10H), 7.39-7.43 (m, 5H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 55.0, 59.5, 62.0, 66.6, 127.6, 128.6, 128.7, 128.8, 129.1, 135.8, 138.8, 171.3 (6 carbon signals non accounted for); HRMS-ESI (*m/z*): $[M+Na]^+$ calcd for $C_{24}H_{25}N_1Na_1O_3$, 398.1727; found, 398.1720.

Compounds from Table 3:

General procedure for deprotection of benzyl esters/carbamates (GPD): The benzyl protected material (**5**) (0.826 mmol, 1 equiv) was dissolved in anhydrous CH_2Cl_2 (1.8 mL) under nitrogen. While stirring, $SnCl_4$ (0.413 mmol, 0.5 equiv) was added. The reaction vessel was then sealed and heated to 40°C overnight (for convenience, although analysis using TLC indicated that many reactions progressed at room temperature and/or were complete in just a few hours). The reaction was quenched with HCl (1 M, 1 mL) then extracted with CH_2Cl_2 (3 × 5 mL). The combined organic layers were washed with brine then dried (Na_2SO_4) and the product was purified via recrystallization or column chromatography.

Benzoic acid 6a from benzyl benzoate 5a: Following GPD**, 6a** was synthesized from **5a** (white crystalline solid, 80%). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.46-7.51 (m, 2H), 7.60-7.66 (m, 1H), 8.15 (d, J = 9 Hz, 2H). NMR data matches that previously reported for this compound.[77]

Benzoic acid 6a from 4-methoxybenzyl benzoate 5m: Following GPD**, 6a** was synthesized from **5m** (white crystalline solid, 86%). ^{1}H NMR (DMSO, 300 MHz) δ 7.50 (t, J = 7.7 Hz, 2H), 7.62 (t, J = 7.5 Hz, 1H), 7.94 (d, J = 7.0 Hz, 2H), 12.96 (s, 1H). NMR data matches that previously reported for this compound.[77]

4-Nitrobenzoic acid 6b: Following GPD**, 6b** was synthesized from **5b** (white yellow/white crystalline solid, quantitative). ^{1}H NMR (DMSO, 300 MHz) δ 8.17 (d, J = 8.8 Hz, 2H), 8.32 (d, J = 8.8 Hz, 2H), 13.64 (br s, 1H). NMR data matches that previously reported for this compound.[77]

4-Methoxybenzoic acid 6c: Following GPD**, 6c** was synthesized from **5c** (off-white solid, 92%). ^{1}H NMR (DMSO, 500 MHz) δ 3.82 (s, 3H), 7.01 (d, J = 8.5 Hz, 2H), 7.89 (d, J = 8.5 Hz, 2H), 12.65 (br s, 1H). NMR data matches that previously reported for this compound.[77]

Pentanoic acid 6d from benzyl pentanoate 5d: Following GPD**, 6d** was synthesized from **5d** (colorless oil, 82%). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.93 (t, J = 7.5 Hz, 3H), 1.39 (qn, J = 7.5 Hz, 2H), 1.63 (qn, J = 7.5 Hz, 2H), 2.36 (t, J = 7.5 Hz, 2H). NMR data matches that previously reported for this compound.[78]

Pentanoic acid 6d from 4-methoxybenzyl pentanoate 5k: Following GPD**, 6d** was synthesized from **5k** (colorless oil, 85%). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 0.92 (t, J = 7.5 Hz, 3H), 1.37 (qn, J = 7.5 Hz, 2H), 1.63 (qn, J = 7.5 Hz, 2H), 2.36 (t, J = 7.5 Hz, 2H). NMR data matches that previously reported for this compound.[78]

Tetradecanoic acid 6e: Following GPD**, 6e** was synthesized from **5e** (white crystalline solid, 80%). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.88 (t, J = 6.9 Hz, 3H), 1.26-1.33 (m, 20H), 1.58-1.68 (m, 2H), 2.35 (t, J = 7.2 Hz, 2H). NMR data matches that previously reported for this compound.[79]

Pivalic acid 6f from benzyl pivalate 5f: Following GPD**, 6f** was synthesized from **5f** (white/colorless crystalline solid, quantitative). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.22 (s, 9H). NMR data matches that previously reported for this compound.[80]

Pivalic acid 6f from 4-methoxybenzyl pivalate 5l: Following GPD**, 6f** was synthesized from **5l**, white/colorless crystalline solid (80%). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.24 (s, 9H). NMR data matches that previously reported for this compound.[80]

2-(4-Methoxyphenyl)acetic acid 6g: Following GPD**, 6g** was synthesized from **5g** (off-white flaky solid, 96%). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 3.59 (s, 2H), 3.80 (s, 3H), 6.87 (d, J = 8.5 Hz, 2H), 7.20 (d, J = 9 Hz, 2H). NMR data matches that previously reported for this compound.[81]

Pent-4-enoic acid 6h: Following GPD**, 6h** was synthesized from **5h** (colorless solid, quantitative). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 2.37-2.41 (m, 2H), 2.45-2.48 (m, 2H), 5.02-5.10 (m, 2H), 5.80-5.88 (m, 2H). NMR data matches that previously reported for this compound.[82]

(*E*)-3-(*p*-Tolyl)acrylic acid 6i: Following GPD**, 6i** was synthesized from **5i** (white solid, 90%). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.39 (s, 3H), 6.41 (d, J = 15.9 Hz, 1H), 7.21 (d, J = 8.1 Hz, 2H), 7.45 (d, J = 8.1 Hz, 2H), 7.76 (d, J = 15.9 Hz, 1H). NMR data matches that previously reported for this compound.[83]

Propiolic acid 6j: Since propiolic acid is highly water soluble, rendering product isolation challenging and thus the yield inaccurate, this reaction was performed and monitored in an NMR tube. Benzyl propiolate **5k** (0.132 g, 0.826 mmol) was dissolved in deuterated dichloromethane (1.0 mL) in an NMR

tube. At 25°C the reaction was initiated via the addition of $SnCl_4$ (47 μL, 0.413 mmol). Reaction progress was monitored via collection of ^1H NMR and ^{119}Sn NMR spectra immediately after initiation and then after 1, 3, 5 and 21 h. A ^{13}C NMR spectrum was collected after 21 h. 100% conversion based on NMR data. The data for this crude sample was compared to commercially obtained propiolic acid. ^1H NMR (CD_2Cl_2, 500 MHz) δ 3.17 (s, 1H), 3.82 (br s, polymer), 7.14 (br s, polymer), 10.82 (br s, 1H); ^{13}C NMR (CD_2Cl_2, 125 MHz) δ 73.9, 78.4, 126.3 (polymer), 128.7 (polymer), 129.1 (polymer), 129.2 (polymer), 157.3.

Compounds from Table 4:

Benzoic acid 6a from *tert*-butyl benzoate 7a: Following GPD**, 6a** was synthesized from **7a** (white crystalline solid, 76%). ^1H NMR ($CDCl_3$, 300 MHz) δ 7.46-7.52 (m, 2H), 7.60-7.66 (m, 1H), 8.12-8.15 (m, 2H). NMR data matches that previously reported for this compound.[77]

Ethyl benzoate 7b: Was subjected to GPD conditions and isolated after extraction as a white solid (340 mg, 96%). ^1H NMR ($CDCl_3$, 300 MHz) δ 1.39 (t, J = 7.2 Hz, 3H), 4.38 (q, J = 7.2 Hz, 2H), 7.39-7.45 (m, 2H), 7.51-7.56 (m, 1H), 8.03-8.06 (m, 2H). NMR data matches that previously reported for this compound.[59]

6-Ethoxy-6-oxohexanoic acid 8c: Following GPD**, 8c** was synthesized from **7c** (white solid 79%). ^1H NMR ($CDCl_3$, 300 MHz) δ 1.25 (t, J = 7.2 Hz, 3H), 1.66-1.71 (m, 4H), 2.30-2.41 (m, 4H), 4.13 (q, J = 7.2 Hz, 2H). NMR data matches that previously reported for this compound.[84]

***N*-Benzyl-*N*-methyl-2-phenylethanamine 7d**: Was subjected to GPD conditions and isolated after extraction (yellow film, 99%). ^1H NMR ($CDCl_3$, 300 MHz) δ 2.26 (s, 3H), 2.64-2.65 (m, 2H), 2.80-2.83 (m, 2H), 3.55 (s, 2H), 7.13-7.16 (m, 3H), 7.20-7.27 (m, 7H). NMR data matches that previously reported for this compound.[60]

***N*-Benzyl-3-methylbutanamide 7e**: Was subjected to GPD conditions and isolated after extraction (colorless oil, quant). ^1H NMR ($CDCl_3$, 300 MHz) δ 0.96 (d, J = 6.6 Hz, 6H), 2.10-2.23 (m, 3H), 4.45 d,

J = 5.7 Hz, 2H), 5.73 (br s, 1H), 7.26-7.37 (m, 5H). NMR data matches that previously reported for this compound.[61]

3-Phenylpropylamine 8f: Following GPD but using 1.5 equiv of $SnCl_4$**, 8f** was synthesized from **7f** (colorless oil, 79%). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.25 (br s, 2H), 1.75-1.81(m, 2H), 2.66 (t, J = 7.5 Hz, 2H), 2.73 (t, J = 7.5 Hz, 2H), 7.17-7.20 (m, 3H), 7.26-7.29 (m, 2H). NMR data matches that previously reported for this compound.[85]

2,2,2-Trichloro-1-phenylethyl (3-phenylpropyl)carbamate 7g: Was subjected to GPD conditions and isolated after extraction (colorless oil, quant). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.86 (qn, J = 7.4 Hz, 2H), 2.65 (t, J = 7.6 Hz, 2H), 3.24 (qn, J = 6.4 Hz ,2H), 5.03 (br s, 1H), 6.31 (s, 1H), 7.15-7.21 (m, 3H), 7.28-7.31 (m, 2H), 7.38-7.42 (m, 3H), 7.60-7.62 (m, 2H). NMR data matches that of the starting material.

Compounds from Table 5

(3-(Benzyloxy)propyl)benzene 7h: Was subjected to GPD conditions and isolated after extraction (colorless oil, quant). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.81-1.91 (m, 2H), 2.64 (t, J = 6.3 Hz, 2H), 3.41 (t, J = 6.3 Hz, 2H), 4.43 (s, 2H), 7.08-7.11 (m, 3H), 7.16-7.27 (m, 7H). NMR data matches that previously reported for this compound.[63]

(2-(Benzyloxy)propyl)benzene 7i: Was subjected to GPD conditions and isolated after purification using column chromatography (SiO_2, EtOAc/hexanes 1/9) (colorless oil, quant). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.19 (d, J = 6.0 Hz, 3H), 2.70 (dd, J = 13.5, 6.3 Hz, 1 H), 2.97 (dd, J = 13.5, 6.3 Hz, 1 H), 3.73 (q, J = 6.3 Hz, 1H), 4.46 (d, J = 12.0 Hz, 1H), 4.55 (d, J = 12.0 Hz, 1H), 7.18-7.31 (m, 10H). NMR data matches that of the starting material.

Ethyl 4-(benzyloxy)benzoate 7j: Was subjected to GPD conditions and isolated after purification using column chromatography (SiO_2, EtOAc/hexanes 1/9) (white solid, 95%). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.38 (t, J = 7.2 Hz, 3H), 4.35 (q, J = 7.2 Hz, 2H), 5.12 (s, 2H), 6.99 (d, J = 9.0 Hz, 2H), 7.34-7.45 (m, 5H), 8.00 (d, J = 9.0 Hz, 2H). NMR data matches that previously reported for this compound.[64]

1-(Benzyloxy)-4-methylbenzene 7k: Was subjected to GPD conditions and followed by TLC. TLC showed complete conversion of **7k** to *p*-cresol.

1-(Benzyloxy)-4-methoxybenzene 7l: Was subjected to GPD conditions and followed by TLC. TLC showed complete conversion of **7l** to 4-methoxyphenol along with byproducts.

3-Phenylpropyl 4-methylbenzenesulfonate 7m: Was subjected to GPD conditions and isolated after extraction (colorless oil, quant). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.91-2.01 (m, 2H), 2.46 (s, 3H), 2.65 (t, J = 7.5 Hz, 2H), 4.04 (t, J = 6.3 Hz, 2H), 7.05-7.08 (m, 2H), 7.17-7.27 (m, 3H), 7.34 (d, J = 7.8 Hz, 2H), 7.79 (d, J = 8.4 Hz, 2H). NMR data matches that previously reported for this compound.[67]

3-Phenylpropan-1-ol 8n: Following GPD**, 8n** was synthesized from **7n** and isolated after purification using column chromatography (SiO_2, EtOAc/hexanes 6/4) (colorless oil, 84%). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.33 (br s, 1H), 1.90-2.00 (m, 2H), 2.76 (t, J = 7.6 Hz, 2H), 3.73 (t, J = 6.4, 2H), 7.23-7.26 (m, 3H), 7.30-7.36 (m, 2H). NMR data matches that previously reported for this compound.[86]

Triisopropyl(3-phenylpropoxy)silane 7p: Was subjected to GPD conditions and isolated after purification using column chromatography (SiO_2, EtOAc/hexanes 0.3/99.7) (colorless oil, 85%). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.05-1.09 (m, 21H), 1.81-1.91 (m, 2H), 2.71 (t, J = 7.6 Hz, 2H), 3.72 (t, J = 6.3 Hz, 2H), 7.17-7.31 (m, 5H). NMR data matches that previously reported for this compound.[70]

***Tert*-butyldimethyl(3-phenylpropoxy)silane 7q**: Was subjected to GPD conditions and isolated after purification using column chromatography (SiO_2, EtOAc/hexanes 1/9) (colorless oil, 36%). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.05 (s, 6H), 0.91 (s, 9H), 1.79-1.89 (m, 2H), 2.65-2.70 (m, 2H), 3.64 (t, J = 6.3 Hz, 2H), 7.17-7.20 (m, 2H), 7.25-7.28 (m, 3H). NMR data matches that previously reported for this compound.[70]

Compounds from Table 6:

***O*-Benzyl-L-serine methyl ester hydrochloride 8t:** Following GPD conditions from **7t** but using 1.0 equiv of $SnCl_4$. The reaction was quenched with HCl (1M), and the pH then adjusted to pH 7 using $NaHCO_3$. The aqueous layer was extracted with CH_2Cl_2 (3 ×10 mL). The combined organic layers were washed with brine then dried (Na_2SO_4). After evaporation of the solvent, the crude product was dissolved in Et_2O (3 mL) and a solution of HCl (2 M) in Et_2O (300 μL) was added. The white solid obtained was collected using filtration (white solid, 55%). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 3.76 (s, 3H), 3.94-4.00 (m, 1H), 4.08-4.11 (m, 1H), 4.36 (br s, 1H) 4.49 (d, *J* = 12.0 Hz, 1H), 4.68 (d, *J* = 12.0 Hz, 1H), 7.23-7.31 (m, 5H), 8.86 (br s, 3H). NMR data matches that previously reported for this compound.[87]

***N*-Benzyl-*O*-Benzyl-L-serine 8u**: Following GPD conditions, from **7u** but using 1.0 equiv of $SnCl_4$. The reaction was quenched with a saturated aqueous solution of $NaHCO_3$ and purified using flash chromatography (SiO_2, CH_2Cl_2/MeOH 9/1) (colorless oil, 30%). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 3.65 (t, J = 3.9 Hz, 1H), 3.88-3.99 (m, 4H), 4.04 (d, *J* = 7.8 Hz, 2H), 7.18-7.26 (m, 10H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 55.3 (2C), 59.0, 63.6, 128.6 (2C), 129.1 (2C), 129.6 (2C), 135.5 (2C), 172.4; HRMS-ESI (*m/z*): $[M+Na]^+$ calcd for $C_{17}H_{19}N_1Na_1O_3$, 308.1257; found, 308.1259.

Benzyl 2,3,4,6-tetra-*O*-benzyl-D-glucopyranoside 7v: Was subjected to GPD conditions and isolated after purification using column chromatography (SiO_2, EtOAc/hexanes 1/9) (white solid, 57%). ^{1}H NMR ($CDCl_3$, 300 MHz) δ selected data on *α*-**7v** 4.04 (t, *J* = 9.3 Hz, 1H). NMR data matches that previously reported for this compound.[88]

ASSOCIATED CONTENT

Supporting Information. NMR spectra for new compounds and mass spectral data. This material is available free-of-charge via the Internet at http://pubs.acs.org.

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