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Diarylmethyl ethers and Pd salts or complexes: a perfect combination for the protection and deprotection of alcohols

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ABSTRACT

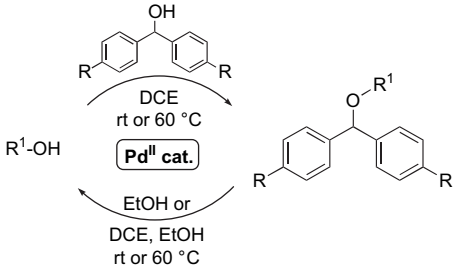
Primary and secondary alcohols are easily protected as diphenylmethyl (DPM) or bis(methoxyphenyl)methyl (BMPM) ethers in good yield using $PdCl_2(CH_3CN)_2$ as catalyst in dichloroethane at 60 or 20 °C, respectively. These conditions are compatible with other functional and protecting groups such as halides, esters, acetal, benzyl, *para*-methoxybenzyl, benzyloxycarbonyl, and *tert*-butyldiphenylsilyl. Good selectivity was observed in favor of primary over secondary alcohols. Deprotection of diphenylmethyl or bis(4-methoxyphenyl)methyl ethers was efficiently achieved at room temperature using $PdCl_2(CH_3CN)_2$ in dichloroethane in the presence of 10 equiv of ethanol.

1. Introduction

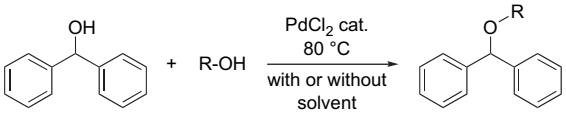
The syntheses of highly functionalized molecules usually require several steps dealing with the protection and deprotection of those functional groups.[1,2] The choice of protecting groups is often critical for synthesis success, specially for the total synthesis of complex natural products and analogs.[2,3]

Benzyl type protecting groups are among the most commonly used, due to their deprotection conditions7 orthogonal to other protecting and functional groups,[1–3] and they have been applied to the protection of alcohols, thiols, amines, and acids.[1,2] Nevertheless, their introduction is not always simple due to the basic or acid condition required.[2]

In order to solve this problem, we recently described new chemoselective conditions for the protection and deprotection of alcohols as diphenylmethyl (DPM) ether (Scheme 1, R=H), offering an interesting mild alternative and an orthogonal complement to the common benzyl type ethers (Scheme 2).[4] Herein, we describe improved conditions to introduce DPM protecting group, and we also describe the use of bis(4-methoxyphenyl)methyl (BMPM) ethers (Scheme 1, R=OMe) as a new protecting group. The scope and limitations of both protecting groups are reported, as well as their specific deprotection methods (Scheme 1).



Scheme 1. Pd-catalyzed protection of alcohols as DPM (R=H) or BMPM (R=OMe) ethers and deprotection of their ethers in alcohols.



Scheme 2. $PdCl_2$-catalyzed protection of alcohols as DPM ethers.

2. Results and discussion

Our preliminary investigations revealed that palladium dichloride was, among various metal Lewis acids, the best catalyst for the protection of alcohols as DPM ethers (Scheme 2).[4] This protection could be performed either without solvent in an environmentally friendly process or in the presence of solvent for more synthetic purposes.

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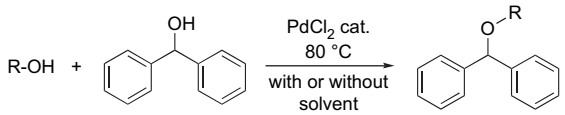
Table 1
Effect of solvent and palladium catalysts on DPM ether formation[a]



Entry	Alcohols	Catalysts	Solvents	Time (h)	Yield[b] (%)
1	BnOH	$PdCl_2$	DCE	4	92
2	BnOH	$PdCl_2$	Benzene	24	90
3	BnOH	$PdCl_2$	Toluene	24	90
4	BnOH	$PdCl_2$	CH_3CN	24	86
5	BnOH	$PdCl_2$	Ethyl acetate	24	Degradation
6	BnOH	$PdCl_2$	Dioxane	24	Degradation
7	BnOH	$PdCl_2$	DMF	24	Degradation
8	11-Bromoundecanol	$PdCl_2$	DCE	48	88
9	11-Bromoundecanol	$PdCl_2$	DCE/1% CH_3CN	24	87
10	11-Bromoundecanol	$PdCl_2(CH_3CN)_2$	DCE	1	88
11	11-Bromoundecanol	$PdCl_2(PPh_3)_2$	DCE	24	No reaction
12	BnOH	$PdCl_2(CH_3CN)_2$	DCE	2.2	91
13	BnOH	$PdCl_2(PPh_3)_2$	DCE	24	No reaction

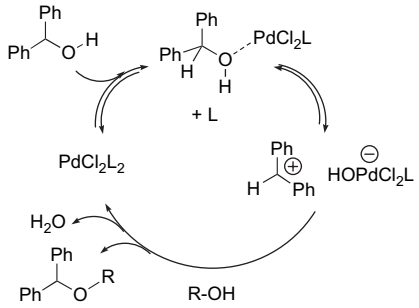
[a] Reaction conditions: [Alcohol]=[DPMOH]=0.2 M in solvent, 10 mol % Pd^{II} salt or complex, 80 °C.
[b] Yield estimated from NMR analysis.

2.1. Catalyst survey and mechanism

In the latter case, dichloroethane proved to be the best choice, although benzene and toluene were almost as effective (Table 1, entry 1 vs 2, 3). However, $PdCl_2$ is not fully soluble in these solvents,[5] a fact, which could explain the longer reaction time (24 h vs 4 h, entries 2, 3 vs 1). Running the reaction in more polar solvents did not help but rather led to decomposition except in acetonitrile (entries 5–7 vs 4). During our screening studies, we also noticed that long chain aliphatic alcohols, such as 11-bromoundecanol, afforded the corresponding DPM ether in high yield but after 2 days at 80 °C (entry 8). This difference (entry 1 vs 8) could also be ascribed to solubility problems. Both aspects led us to look at the role of coordinating and polar solvents, and we found that adding acetonitrile in the reaction with 11-bromoundecanol induced a remarkable rate acceleration (entry 9 vs 8).

These results suggested that not only solubility but also coordination could be the key factors in this reaction. To check this hypothesis, we performed the reaction in the presence of the more soluble bis(acetonitrile)palladium dichloride or bis(triphenylphosphane)palladium dichloride as catalyst in dichloroethane. As expected, we were pleased to observe very rapid reactions in the presence of bis(acetonitrile)palladium dichloride in DCE (entry 10 vs 8, 9 and entry 12 vs 1). However, no reaction was observed in the presence of bis(triphenylphosphane)palladium dichloride (entry 11 vs 10 and entry 13 vs 12).

As suspected, these results revealed that solubility and mainly coordination, especially the strength of the palladium-ligand bond, played key roles in this reaction. The stronger the ligand coordination, the lower the reaction efficiency, in agreement with a ligand exchange process.[6] Such critical role of the coordination around palladium has already been pointed out in selective oxidation studies.[7] Therefore, a similar mechanism is probably involved in this protection reaction (Scheme 3).[8] Upon addition, diphenylmethanol probably compete for Pd^{II} complexation, according to the observed ligand effect. The resulting complex would then evolve toward diphenylmethyl carbocation, and as shown by the solvent effect, most probably as intimate ion pair. Trapping this carbocation with alcohols would then give the DPM protected alcohols with concomitant formation of water and regeneration of the palladium catalyst.[9]



Scheme 3. Proposed mechanism for the $PdCl_2(CH_3CN)_2$-catalyzed DPM protection of alcohols.

With such a mechanism, it seems that the more stable the cation, the easier the reaction should be. This is indeed what was observed in our effort for improving the selectivity and efficiency of this novel protection method (see Section 2.4).

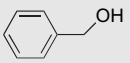
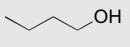
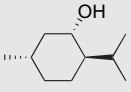
2.2. Condition optimization

As $PdCl_2(CH_3CN)_2$ seemed to be more effective than $PdCl_2$, we then compared the efficiency of both catalysts for a series of representative alcohols and tried to find the best conditions for the protection of alcohols as DPM ethers (Table 2).

The more reactive benzyl alcohol was converted in high yield to its DPM ether within a few hours with net changes in reaction times depending on the catalyst and the temperature (entries 2, 3 vs 1). 1-Butanol was among the most reactive alcohols and it was also rapidly converted in high yield to its DPM ether with $PdCl_2$ as catalyst and the reaction was twice faster in the presence of $PdCl_2(MeCN)_2$ at the same temperature too (entry 5 vs 4). With the latter catalyst, decreasing the temperature did not significantly change rate and yields at 60 °C (entry 6 vs 5) but lowered the reaction rate at 40 °C (entry 7 vs 5–6). Interestingly, a similar but more pronounced effect was observed with secondary alcohols such as menthol (entries 9, 10 vs 8) and isopropanol (entries 12 and 13 vs 11). Phenol remained non-reactive whatever the catalyst and the conditions, giving very poor yields despite long reaction times (entries 14 and 15).

These results showed that milder conditions with lower temperature and reaction time could be achieved by using $PdCl_2(MeCN)_2$. This catalyst is thus an interesting alternative to $PdCl_2$ for the protection of alcohols as DPM ether.

Table 2
Effect of Pd catalysts and temperature on DPM ether formation[a]

Entry	Substrate	Catalyst	Temp (°C)	Time (h)	Yield[b] (%)
1		$PdCl_2$	80	4	92
2		$PdCl_2(MeCN)_2$	80	2.2	88
3			60	2.5	89
4		$PdCl_2$	80	4	83
5		$PdCl_2(MeCN)_2$	80	2	83
6			60	2	81
7			40	4	79
8		$PdCl_2$	80	48	65
9		$PdCl_2(MeCN)_2$	80	2.5	68
10			60	5.5	69
11		$PdCl_2$	80	48	86
12		$PdCl_2(MeCN)_2$	80	2	71
13			60	3.5	72
14		$PdCl_2$	80	96	4
15		$PdCl_2(MeCN)_2$	80	24	<5

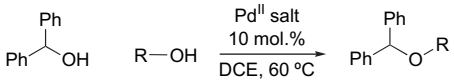
[a] [Alcohol]=[DPMOH]=0.2 M in DCE, 10 mol % Pd salt.
[b] Yields of isolated pure products.

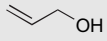
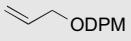
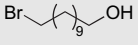
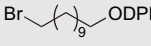
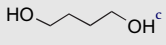
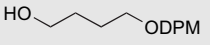
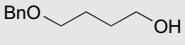
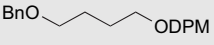
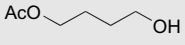
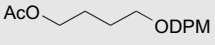
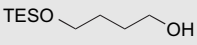
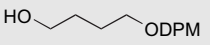
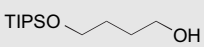
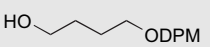
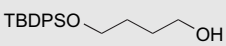
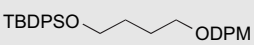
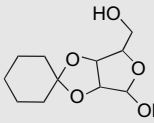
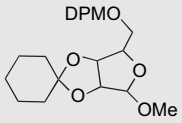
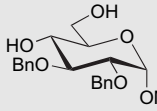
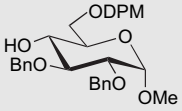
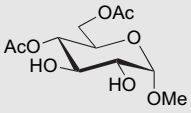
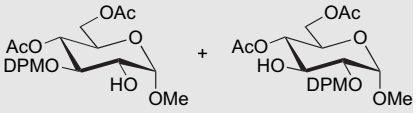
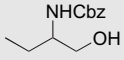
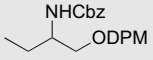
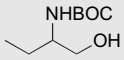
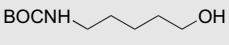
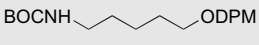
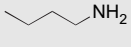
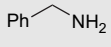
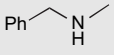
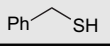
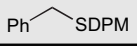
2.3. Scope and limitation

With this new procedure in hand, we then evaluated its scope and limitations, focusing our attention to the tolerance of the improved reaction conditions toward other protecting groups (Table 3).

As benzyl alcohol, allyl alcohol was very reactive toward this Pd^{II}-catalyzed protection,[4] and its DPM ether was obtained in good

Table 3
Scope of the $PdCl_2(CH_3CN)_2$-catalyzed DPM ether formation[a]



Entry	Substrate	Time (h)	Yield[b] (%)	Product
1		3	71	
2		2.5	86	
3		0.75[c]	73[d]	
4		1.5	85	
5		3.5	88	
6		1.5	20[e]	
7		1.5	22[f]	
8		1.5	41[g]	
9		6	69	
10		1	57[h]	
11		24	25+14	
12		5	82	
13		10	No reaction	—
14		12	10[i]	
15		16	No reaction	—
16		16	No reaction	—
17		16	No reaction	—
18		2	24[j]	

[a] Reactions performed in dichloroethane at 60 °C with 10 mol % $PdCl_2(CH_3CN)_2$ and [Alcohol]=[DPMOH]=0.2 M.
[b] Yields of isolated pure products.
[c] Diol (4 equiv) was used, at 80 °C.
[d] The diprotected derivative was also isolated (8%).
[e] The diprotected derivative was also isolated (35%).
[f] The diprotected derivative was also isolated (37%).
[g] The diDPM derivative was also isolated (21%).
[h] The diprotected derivative was also isolated (4%).
[i] The starting material was recovered (90%).
[j] No further evolution could be noticed upon longer time.

yield after 3 h (Table 3, entry 1). As mentioned above, bromide was fully compatible with these conditions (entry 2). With a 4:1 ratio of the starting materials, butan-1,4-diol mostly gave the monoprotected DPM ether as the major product in good yield (entry 3).

To look at protecting group compatibility, a series of butan-1,4-diol derivatives monoprotected with various group were prepared according to known methods.[10] Benzyl and ester groups were stable under such conditions and the corresponding DPM ether was obtained in high yields (entries 4 and 5). However, silyl groups such as triisopropylsilyl (TIPS) and triethylsilyl (TES) groups proved to be non-compatible with our conditions (entries 6 and 7), whereas *tert*-butyldiphenylsilyl (TBDPS) was compatible (entry 8). Indeed, 4-triisopropylsilyloxybutan-1-ol and 4-triethylsilyloxybutan-1-ol did not give the desired TIPS or TES and DPM protected product but rather a mixture of mono- and diDPM-protected butanediols. Reaction monitoring indicated that deprotection occurred first, even for TIPS, followed by the formation of the DPM ether.[11] The less acid sensitive TBDPS group was less rapidly cleaved in these conditions than other silyl groups, and the expected 1-*tert*-butyldiphenylsilyloxy-4-diphenylmethyl oxybutane was isolated, although in modest yield (entry 8). The diDPM-protected butanediol could also be isolated.

Acetal cleavage has been reported in the presence of $PdCl_2(CH_3CN)_2$ in a mixture of acetonitrile and water at room temperature.[12] However, our $PdCl_2$-catalyzed DPM protection[4] as well as the present $PdCl_2(CH_3CN)_2$-catalyzed version proved to be fully compatible with acetal groups (entry 9). Therefore, glycosides could be engaged in such reactions (entries 10 and 11). This allowed us to explore the selectivity between primary and secondary alcohols in various environments. The primary alcohol of methyl α-D-2,3-*O*-dibenzylglucopyranoside[13] was selectively protected, while its secondary alcohols remained mostly untouched (entry 10). However, the difference of the reactivity of two secondary alcohols in methyl α-D-4,6-di-*O*-acetylglucopyranoside[14] was not strong enough to give a good selectivity. Nevertheless, a 2:1 selectivity was obtained in favor of the alcohol at position 3 (entry 11), in agreement with the nucleophilicity of such alcohols.[15] Identification of both mono-DPM protected sugars was achieved by comparing H-2 multiplicity on both ethers. Indeed, while the starting material exhibited a broad doublet at 3.75 ppm (J=9.3 Hz), the 3-DPM ether gave a signal at 3.61 ppm split into a doublet of triplet due to its coupling with H-1 (J=3.8 Hz) and H-3 ($J\sim$9 Hz) as well as with the labile hydroxyl hydrogen at the 2-position ($J=\sim$9 Hz). In contrast, the 2-DPM ether exhibited for the same hydrogen H-2 a simpler signal (dd, J=9.6, 3.6 Hz) at 3.45 ppm, the hydroxyl coupling constant being missing. Interestingly, the H-4 proton resonated at the same frequency in the starting material and in the 2-DPM ether (5.13 ppm) but at a higher one (5.30 ppm) in the 3-DPM, experiencing anisotropy from the adjacent phenyl rings.

Protected aminoalcohols[16] gave different results depending on the nature of the protected group on the nitrogen atom. Carbobenzyloxy group proved to be fully compatible with our DPM protections conditions, even in position where metal chelation could occur (entry 12). In sharp contrast, the *tert*-butyloxycarbonyl group seemed to preclude any DPM etherification of adjacent free alcohol, whatever the relative position of the two functional groups (entries 13, 14 vs 12). Surprisingly, no *N*-BOC deprotection occurred and the starting materials were mostly recovered, suggesting that *N*-BOC could act as ligand toward Pd^{II}.

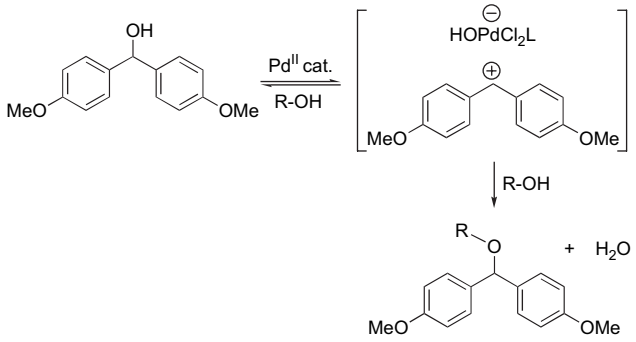
In order to broaden applications, we also applied these DPM protection conditions to amines and thiols. Unfortunately, no reaction occurred with primary and secondary amines (entries 15–17) and thiols proved to be not reactive enough (entry 18). Both groups are good ligand toward palladium, and thus their competitive coordination probably blocks further evolution, as phosphane do (see Table 1, entries 11, 13).

This reaction screening and the preceding one[4] clearly showed that the $PdCl_2$- and $PdCl_2(CH_3CN)_2$-catalyzed DPM protections of alcohol are compatible with a large variety of functional groups, but that these protection conditions can not be applied to thiols or amines.

2.4. Extension to other diarylmethyl derivatives

The proposed mechanism involving diphenylmethyl carbocation (Scheme 3) suggested that placing electron-donating group(s) on the aromatic rings would first reinforce the coordination to the Lewis acid Pd^{II} species and mainly favor the breakage of the C–O bond by liberating a more stabilized cation. If right, this mechanism suggested improving the protection rate with electro-enriched diphenylmethyl derivatives.

Bis(4-methoxyphenyl)methanol (BMPMOH) being commercially available, it was tempting to check its behavior in our protection conditions. A few representative alcohols were thus submitted to $PdCl_2$ or $PdCl_2(CH_3CN)_2$ catalysts in dichloroethane and indeed, the corresponding bis(4-methoxyphenyl)methyl (BMPM) ethers were rapidly obtained in high yields, even at room temperature (Scheme 4 and Table 4).



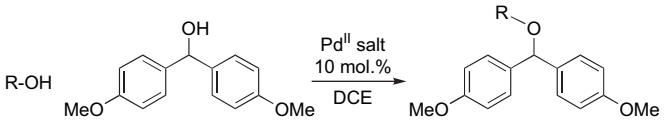
Scheme 4. Pd-catalyzed BMPM ether formation.

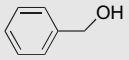
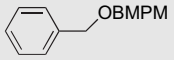
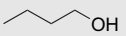
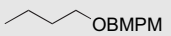
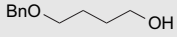
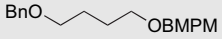
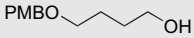
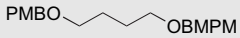
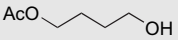
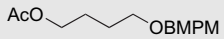
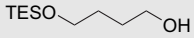
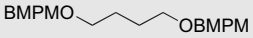
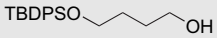
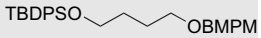
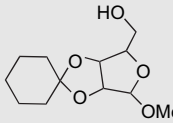
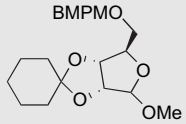
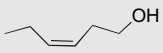
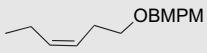
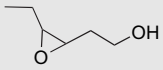
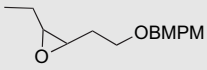
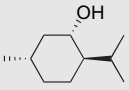
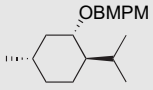
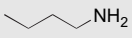
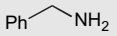
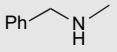
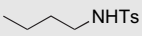
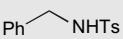
As expected, bis(4-methoxyphenyl)methanol was far more reactive than diphenylmethanol and it can be used at room temperature in most cases. Here again, the use of $PdCl_2(CH_3CN)_2$ as catalyst induced a dramatic improvement in reaction rate in dichloroethane compared to other Pd^{II} catalysts. For example, the reactive benzyl alcohol was cleanly protected as BMPM ether at room temperature, but this protection required 19 h with $PdCl_2$ as catalyst but only 20 min with $PdCl_2(CH_3CN)_2$ as catalyst (Table 4, entry 2 vs 1). These results could be compared to those obtained with DPM for which 2.2 to 4 h at 80 °C were required depending on the catalyst (see Table 2, entries 1 and 2). Similar comparisons could be achieved with butanol or the monobenzylated 1,4-butanediol[10] (entries 3, 4 and 5, 6, respectively, vs Table 2, entries 4, 5 and Table 3, entry 4). $PdCl_2(CH_3CN)_2$ as catalyst in dichloroethane at room temperature is thus clearly the ideal conditions for BMPM protection.

Looking again for compatibility with other functional groups, we screened butanediols monoprotected with various groups.[10,17] Benzyl, *para*-methoxybenzyl, ester and acetal proved to be compatible with these conditions, the corresponding BMPM ethers being always cleanly obtained in high yields within very short times (entries 6–8 and 11). Interestingly, *tert*-butyldiphenylsilyl ether was now stable whereas triethylsilyl group was again removed under these conditions despite their mildness (entry 10 vs 9).

As expected from the results gained during the DPM protection study, acetals were fully compatible with the milder BMPM protection conditions, as well as double bond or epoxy groups.[17] Primary alcohols containing such groups were protected as the corresponding BMPM ethers in good yields (entries 11–13).

Table 4
Pd-catalyzed BMPM ether formation[a]



Entry	Substrate	Catalyst	Temp (°C)	Time (h)	Yield[b] (%)	Product
1		$PdCl_2$	20	19	80	
2		$PdCl_2(MeCN)_2$	20	0.3	95	
3		$PdCl_2$	20	2	85	
4		$PdCl_2(MeCN)_2$	20	0.3	95	
5		$PdCl_2$	20	5	81	
6		$PdCl_2(MeCN)_2$	20	0.6	78	
7		$PdCl_2(MeCN)_2$	20	0.3	71	
8		$PdCl_2(MeCN)_2$	20	0.3	82	
9		$PdCl_2(MeCN)_2$	20	0.3	31	
10		$PdCl_2(MeCN)_2$	20	1	70	
11		$PdCl_2(MeCN)_2$	20	12	73	
12		$PdCl_2(MeCN)_2$	20	0.3	81	
13		$PdCl_2(MeCN)_2$	20	0.3	81	
14		$PdCl_2(MeCN)_2$	0	0.5	78	
15		$PdCl_2(MeCN)_2$	20	48	—[c]	—
16		$PdCl_2(MeCN)_2$	20	48	—[c]	—
17		$PdCl_2(MeCN)_2$	20	48	—[c]	—
18		$PdCl_2(MeCN)_2$	20	16	37[d]	$BMPM_2O$
19		$PdCl_2(MeCN)_2$	20	16	39[d]	$BMPM_2O$

[a] Reactions performed in dichloroethane at 20 °C with 10 mol % $PdCl_2(CH_3CN)_2$ and [Alcohol]=[BMPMOH]=0.2 M.
[b] Yields of isolated pure products.
[c] Starting materials recovered.
[d] Tosylated amines recovered.

Secondary alcohols, even hindered ones like menthol, could also be protected without any problem in a fast reaction (entry 14).

As for DPM protection, amines were again unreactive under these conditions, whatever their substitution (entries 15–17). More electro-deficient amines less prone to coordination, such as tosyl amines,[18] were not protected, remaining untouched (entries 18 and 19). However, in these cases, the BMPM alcohol was converted to its dimeric BMPM ether, revealing that the catalyst was still active and indeed not poisoned by the amino group (entries 18 and 19).

These results revealed that replacing diphenylmethanol by bis(4-methoxyphenyl)methanol allows to protect alcohols in similar yields but in very short reaction times. These results also strongly supported the proposed mechanism (see Section 2.1 and Scheme 3).

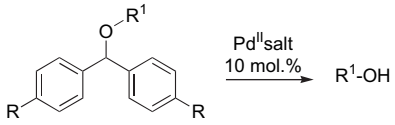
2.5. Deprotection of diarylmethyl ethers

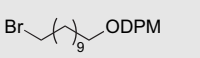
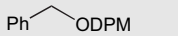
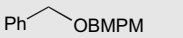
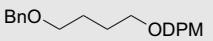
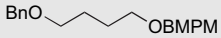
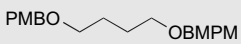
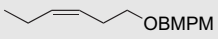
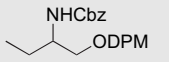
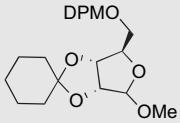
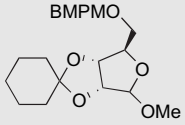
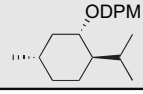
Based again on mechanistic considerations (Scheme 3), it seemed that the overall process should be reversible. Therefore, it should be possible to deprotect DPM or BMPM ether in the

presence of an excess of either water or a reactive alcohol upon catalysis by mild Lewis acids $PdCl_2$ or $PdCl_2(CH_3CN)_2$.

Several DPM and BMPM ethers were thus submitted to Pd catalysts either in pure ethanol or in dichloroethane containing small but sufficient amounts of ethanol (Table 5). Although efficient, the deprotection proved surprisingly long in pure ethanol, even on heating, and again, $PdCl_2(CH_3CN)_2$ proved more effective and rapid than $PdCl_2$ (entry 1 vs 2). In a mixture of dichloroethane–ethanol, the deprotection was by far faster (entry 3 vs 2) and these conditions were thus used throughout.

Table 5
Pd-catalyzed DPM and BMPM ether deprotection[a]



Entry	Substrate	Catalyst	Solvent	Temp (°C)	Time (h)	Yield[b] (%)
1		$PdCl_2$	EtOH	60	36	90
2		$PdCl_2(MeCN)_2$	EtOH	60	24	92
3			DCE,[c] EtOH	60	7	92
4		$PdCl_2(MeCN)_2$	DCE,[c] EtOH	60	5	89
5		$PdCl_2(MeCN)_2$	DCE,[c] EtOH	20	0.7	91
6		$PdCl_2(MeCN)_2$	DCE,[c] EtOH	60	6	89
7		$PdCl_2$	EtOH	20	18	94
8		$PdCl_2(MeCN)_2$	DCE,[c] EtOH	20	1.5	91
9			DCE,[c] EtOH	60	1	93
10		$PdCl_2$	EtOH	20	6	93
11		$PdCl_2(MeCN)_2$	DCE,[c] EtOH	20	2	92
12			DCE,[d] EtOH	60	2	<5[d]
13		$PdCl_2(MeCN)_2$	DCE,[c] EtOH	20	0.7	—[e]
14		$PdCl_2(MeCN)_2$	DCE,[c] EtOH	60	5	90
15		$PdCl_2(MeCN)_2$	DCE,[c] EtOH	60	5	89
16		$PdCl_2(MeCN)_2$	DCE,[c] EtOH	20	1	89
17			DCE,[c] EtOH	60	0.5	90
18		$PdCl_2(MeCN)_2$	DCE,[c] EtOH	60	2.5	91

[a] [Ether]=0.2 M, 10 mol % Pd salt.
[b] Yields of isolated pure deprotected alcohols.
[c] EtOH (10 equiv) was used.
[d] Deprotection of PMB-ether was also observed.
[e] Degradation.

Interested in selectivity, several diarylmethyl ethers containing different other benzyl type protecting groups were submitted to these conditions (entries 4–12). The diarylmethyl group of diphenylmethyl and bis(4-methoxyphenyl)methyl benzyl ethers were selectively deprotected in such conditions (entries 4 and 5). As expected on mechanistic basis, the BMPM proved easier to deprotect than DPM. A fast reaction occurred even at room temperature for BMPM benzyl ether (entry 5), while heating for 5 h was required for DPM benzyl ether (entry 4). Both reactions allowed to recover the unprotected benzyl alcohol in high yields.

Similarly, the DPM group in benzyl and DPM protected 1,4-butanediol could be selectively removed in high yields with $PdCl_2(CH_3CN)_2$ as catalyst at 60 °C (entry 6). In the analog benzyl-BMPM protected 1,4-butanediol, the BMPM group was more rapidly removed with $PdCl_2(CH_3CN)_2$ in a mixture of dichloroethane–ethanol at 60 °C (entry 9). As before, it could also be deprotected at room temperature with the same catalyst (entry 8). Even $PdCl_2$ at room temperature in pure ethanol was also able to deprotect the BMPM group, although a longer reaction time was required (entry 7 vs 8). With the *para*-methoxybenzyl and BMPM protected 1,4-butanediol, the deprotection with $PdCl_2$ in pure ethanol was reasonably rapid and gave the 4-*para*-methoxybenzyloxybutan-1-ol in high yield (entry 10). As expected, this reaction was faster with $PdCl_2(CH_3CN)_2$ as catalyst in dichloroethane–ethanol at room temperature (entry 10 vs 11). However, at higher temperature (60 °C), both BMPM and PMB groups were removed in these conditions (entry 12). It is worth noting that the latter conditions could thus be applied to the deprotection of *para*-methoxybenzyl ether.

The compatibility of the diarylmethyl ether deprotection conditions with other functional groups was also examined. Except for alkenyl (entry 13), various groups such as carbobenzyloxy and acetals were tolerated. For example, the *N*-Cbz DPM protected 2-aminobutan-1-ol was efficiently and rapidly cleaved at its ether moiety in the presence of $PdCl_2(CH_3CN)_2$ in dichloroethane–ethanol at 60 °C. The Cbz aminoalcohol was recovered in high yield (entry 14). Both the DPM and BMPM protected methyl 2,3-*O*-cyclohexyliden-β-D-ribofuranoside were cleanly deprotected in these conditions, leading in high yields to the corresponding riboside free at its 5-position (entries 15–17). The BMPM group was again removed faster than DPM, even at room temperature (entry 17 vs 16 vs 15).

As demonstrated with the preceding examples, primary alcohols can easily be deprotected. The secondary diphenylmethyl menthyl ether was deprotected in these conditions and in a short time, the free menthol was recovered in high yield (entry 18). As expected, the reaction proved faster with a secondary alcohol compared to other primary alcohols (entry 18 vs 3, 4, 6, 14, and 15).

3. Conclusion

A convenient and efficient method based on palladium catalysts has been developed for the protection of alcohols with diphenylmethanol and 4,4′-dimethoxydiphenylmethanol. Interestingly, the corresponding diphenylmethyl and 4,4′-dimethoxydiphenylmethyl ethers could also be selectively deprotected in similar conditions using palladium catalysts.

Both methods proved compatible with a variety of other functional groups, including protecting groups. Moreover, a high selectivity has been observed toward other related protecting groups, and a good selectivity was observed in the protection of primary versus secondary alcohols, especially for carbohydrates.

The mildness of these protection and deprotection methods as well as their selectivity render them very useful tools for total synthesis.

4. Experimental section

4.1. General

Unless otherwise noted, all reagents were obtained from commercial sources and used without further purification. DMF, THF, and CH_2Cl_2 were distilled from CaH_2. Extracts were dried over $MgSO_4$ or Na_2SO_4 and solvents were removed in vacuo via a rotary evaporator at aspirator pressure. TLC analysis was performed on Merck Alufolien silica gel 60 F254 TLC plates with detection either by UV-absorption (254 nm) or by staining with $KMnO_4$, *p*-anisaldehyde, or molybdophosphoric acid/$Ce(SO_4)_2\cdot 4H_2O$ solution. Flash chromatography (FC) was carried out on Merck silica gel Si 60 (40–63 mm). Melting points are uncorrected. ^1H and ^{13}C NMR spectra were recorded with a 300 MHz spectrometer and referenced to $CDCl_3$ or C_6D_6 peak(s) unless otherwise noted. IR spectra (neat) were recorded on IR alpha Bruker spectrophotometer. Mass spectra and high resolution mass spectra were obtained by electrospray (ESI) or electronic impact (EI) ionization method.

4.2. Starting materials

All starting materials, except methyl 2,3-*O*-cyclohexyliden-β-D-ribofuranoside, were prepared and characterized according to the literature.[10,13,14,16,17]

4.2.1. *Methyl 2,3-O-cyclohexyliden-β-D-ribofuranoside*

To a solution of D-ribose (10 g, 66.6 mmol) and concentrated sulfuric acid (4 mL) in methanol was added cyclohexanone (26 g, 4 equiv). After stirring at 60 °C for 3 h, the solution was cooled at room temperature and a saturated sodium carbonate solution (50 mL) was added. The mixture was then extracted with EtOAc (3×15 mL) and the organic layers were dried and concentrated under vacuum. The crude product was purified by flash chromatography (cHex/EtOAc 9:1) to afford a colorless viscous oil (12.5 g, 77%). ^1H NMR ($CDCl_3$, 300 MHz) δ 1.38–1.71 (m, 10H), 3.43 (s, 3H), 3.65 (m, 2H), 4.43 (t, 1H, J=2.8 Hz), 4.57 (d, 1H, J=5.9 Hz), 4.82 (d, 1H, J=5.9 Hz), 4.97 (s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 23.7, 24.0, 25.0, 34.3, 36.1, 55.5, 64.0, 81.0, 85.4, 88.5, 110.1, 112.9; IR (film) 3463, 1105, 1085, 1039, 939, 928 cm^{-1}; ESMS-ESI *m*/*z* for $C_{12}H_{20}O_5Li$ $[M+Li]^+$ calcd 251.1466, found 251.1478.

4.3. General procedure for DPM- and MDMP-ether formation (procedure A)

To a solution of diphenylmethanol (200 mg, 1.08 mmol) or 4,4′-dimethoxydiphenylmethanol (264 mg, 1.08 mmol) in DCE (5.4 mL) were added the alcohol (1 equiv) and the palladium catalyst, $PdCl_2$ (20 mg, 0.1 equiv) or $PdCl_2(CH_3CN)_2$ (28 mg, 0.1 equiv). The reaction was stirred at the desired temperature (20, 40, 60, or 80 °C) until disappearance of the starting material (TLC monitoring), filtered on a pad of silica gel using ethyl acetate as eluant. The solvents were evaporated under reduced pressure and the resulting crude product was purified by flash chromatography (0–50% EtOAc/cHex).

Final products that are already described in the literature were only characterized by ^1H and ^{13}C NMR.

4.3.1. *Diphenylmethyl benzyl ether*[19] *(Table 2, entries 1–3)*

^1H NMR ($CDCl_3$, 300 MHz) δ 4.65 (s, 2H), 5.55 (s, 1H), 7.32–7.51 (m, 15H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 70.6, 82.6, 127.2, 127.4, 127.6, 127.8, 128.5, 128.5, 138.5, 142.3.

4.3.2. *Diphenylmethyl n-butyl ether*[19] *(Table 2, entries 4–7)*

^1H NMR ($CDCl_3$, 300 MHz) δ 1.00 (t, 3H, J=7.5 Hz), 1.53 (tq, 2H, J=7.6 and 8.5 Hz), 1.73 (tt, 2H, J=6.6 and 8.7 Hz), 3.54 (t, 2H, J=6.7 Hz), 5.41 (s, 1H), 7.28–7.46 (m, 10H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 14.2, 21.0, 64.4, 82.5, 125.3, 127.0, 127.3, 128.6, 142.4.

4.3.3. *Diphenylmethyl menthyl ether (Table 2, entries 8–10)*

^1H NMR (300 MHz, $CDCl_3$) δ 0.77–0.80 (m, 6H), 0.88 (d, 3H, J=6.8 Hz), 1.07–1.17 (m, 1H), 1.37–1.97 (m, 8H), 3.57–3.62 (m, 1H), 5.51 (s, 1H), 7.23–7.42 (m, 10H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 19.6, 21.3, 21.4, 21.5, 25.8, 27.3, 30.1, 35.5, 45.6, 73.0, 80.1, 127.2, 127.4, 128.2, 143.1; IR (film) 2949, 2924, 1454, 698 cm^{-1}; ESMS-ESI *m*/*z* for $C_{23}H_{30}ONa$ $[M+Na]^+$ calcd 345.2189, found 345.2221.

4.3.4. *Diphenylmethyl isopropyl ether*[19] *(Table 2, entries 11–13)*

^1H NMR ($CDCl_3$, 300 MHz) δ 1.31 (d, 6H, J=6.2 Hz), 3.76 (sep, 1H, J=6.2 Hz), 5.58 (s, 1H), 7.26–7.49 (m, 10H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 22.4, 69.2, 80.1, 127.2, 127.5, 128.4, 143.1.

4.3.5. *Diphenylmethyl phenyl ether*[19] *(Table 2, entries 14 and 15)*

^1H NMR ($CDCl_3$, 300 MHz) δ 5.30 (s, 1H), 6.99–7.49 (m, 15H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 83.1, 115.1, 122.7, 127.2, 127.7, 128.5, 136.1, 160.3.

4.3.6. *Diphenylmethyl allyl ether*[19] *(Table 3, entry 1)*

^1H NMR ($CDCl_3$, 300 MHz) δ 4.09 (dd, 2H, J=1.6 and 5.4 Hz), 5.27 (dd, 1H, J=1.9 and 10.3 Hz), 5.38 (td, 1H, J=1.9 and 17.1 Hz), 5.48 (s, 1H), 6.05 (tdd, J=5.5, 10.3, and 17.1 Hz), 7.28–7.50 (m, 10H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 69.7, 82.7, 116.9, 127.5, 128.1, 128.4, 142.3.

4.3.7. *Diphenylmethyl 11-bromoundecanyl ether (Table 3, entry 2)*

^1H NMR ($CDCl_3$, 300 MHz) δ 1.34–1.50 (m, 14H), 1.67–1.76 (m, 2H, J=7.0 Hz), 1.85–1.95 (m, 2H, J=6.9 Hz), 3.44 (t, 2H, J=7.1 Hz), 3.51 (t, 2H, J=6.5 Hz), 5.40 (s, 1H), 7.26–7.45 (m, 10H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 26.3, 28.2, 28.8, 29.5, 30.0, 32.9, 34.1, 69.3, 83.6, 127.0, 127.4, 128.4, 142.7; IR (film) 2926, 2853, 1452, 1095, 1075, 699 cm^{-1}; EI *m*/*z* for $C_{24}H_{33}BrOLi$ $[M+Li]^+$ calcd 416.17, found 416.2.

4.3.8. *Diphenylmethyl 4-hydroxybutyl ether (Table 3, entry 3)*

^1H NMR ($CDCl_3$, 300 MHz) δ 1.73 (m, 4H), 2.30 (br s, 1H), 3.52 (t, 2H, J=5.7 Hz), 3.64 (t, 2H, J=6.1 Hz), 5.38 (s, 1H), 7.23–7.40 (m, 10H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 26.6, 30.0, 62.6, 69.1, 83.9, 127.0, 127.5, 128.5, 142.3; IR (film) 3393, 3337, 2940, 2866, 1493, 1452, 1093, 1061, 742, 698 cm^{-1}; ESMS-ESI *m*/*z* for $C_{17}H_{20}O_2Li$ $[M+Li]^+$ calcd 263.1618, found 263.1636.

4.3.9. *Diphenylmethyl 4-diphenylmethyloxybutyl ether (Table 3, entry 3)*

^1H NMR ($CDCl_3$, 300 MHz) δ 1.77–1.81 (m, 4H), 3.47–3.51 (m, 4H), 5.33 (s, 2H), 7.22–7.42 (m, 20H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 26.8, 69.0, 83.6, 127.0, 127.4, 128.4, 142.6; IR (film) 1102, 1077, 738, 696, 648 cm^{-1}; ESMS-ESI *m*/*z* for $C_{30}H_{30}O_2Na$ $[M+Na]^+$ calcd 445.2138, found 445.2157.

4.3.10. *Diphenylmethyl 4-benzyloxybutyl ether (Table 3, entry 4)*

^1H NMR ($CDCl_3$, 300 MHz) δ 1.81–1.85 (m, 4H), 3.53–3.58 (m, 4H), 4.56 (s, 2H), 5.40 (s, 1H), 7.27–7.44 (m, 15H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 26.7, 68.9, 70.3, 72.9, 83.7, 127.0, 127.3, 127.4, 127.6, 127.7, 128.4, 138.7, 142.6; IR (film) 1452, 1092, 1074, 1027, 741, 698 cm^{-1}; ESMS-ESI *m*/*z* for $C_{24}H_{26}O_2Na$ $[M+Na]^+$ calcd 369.1825, found 369.1863.

4.3.11. *Diphenylmethyl 4-acetoxybutyl ether (Table 3, entry 5)*

^1H NMR ($CDCl_3$, 300 MHz) δ 1.65–1.81 (m, 4H), 2.03 (s, 3H), 3.47 (t, 2H, J=6.1 Hz), 4.08 (t, 2H, J=6.2 Hz), 5.33 (s, 1H), 7.21–7.36 (m, 10H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 21.0, 25.6, 26.4, 64.4, 68.5, 83.7, 126.9, 127.4, 128.4, 142.4, 171.2; IR (film) 1737, 1242, 1093, 1053, 670 cm^{-1}; ESMS-ESI *m*/*z* for $C_{19}H_{22}O_3Li$ $[M+Li]^+$ calcd 305.1724, found 305.1656.

4.3.12. Diphenylmethyl 4-tert-butyldiphenylsilyloxybutanyl ether (Table 3, entry 8)

^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.04 (s, 9H), 1.62–1.80 (m, 4H), 3.45 (t, 2H, J=6.5 Hz), 3.68 (t, 2H, J=6.2 Hz), 5.31 (s, 1H), 5.31–5.50 (m, 2H), 7.18–7.45 (m, 16H), 7.60–7.71 (m, 4H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 19.2, 26.3, 26.8, 29.4, 63.7, 68.9, 83.6, 126.9, 127.3, 127.6, 128.3, 129.5, 134.0, 135.6, 142.6; IR (film) 1073, 1028, 738, 696, 503 cm^{-1}; ESMS-ESI m/z for $C_{33}H_{38}O_2SiLi$ $[M+Li]^+$ calcd 501.2796, found 501.2739.

4.3.13. Methyl 2,3-O-cyclohexyliden-5-O-diphenylmethyl-β-D-ribofuranoside (Table 3, entry 9)

^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.43–1.78 (m, 10H), 3.29 (s, 3H), 3.53 (m, 2H), 4.49 (t, 1H, J=7.3 Hz), 4.59 (dd, 1H, J=1.6 and 6.0 Hz), 4.74 (d, 1H, J=6.0 Hz), 5.01 (d, 1H, J=1.6 Hz), 5.41 (s, 1H), 7.28–7.42 (m, 10H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 19.6, 21.3, 21.4, 21.5, 25.8, 27.3, 30.1, 35.5, 73.0, 80.0, 127.2, 127.4, 128.2, 143.5; IR (film) 2935, 1108, 1086, 1049, 700 cm^{-1}; ESMS-ESI m/z for $C_{25}H_{30}O_5Li$ $[M+Li]^+$ calcd 417.2248, found 417.1954.

4.3.14. Methyl 2,3-di-O-benzyl-6-O-diphenylmethyl-α-D-glucopyranoside (Table 3, entry 10)

^{1}H NMR (C_6D_6, 300 MHz) δ 3.09 (s, 3H), 3.47 (dd, 1H, J=3.5 and 9.5 Hz), 3.65–3.71 (t, 1H, J=10.2 Hz), 3.69–3.78 (m, 2H), 3.88–3.94 (m, 1H), 3.98 (t, 1H, J=9.2 Hz), 4.39 (AB, 2H, J=11.2 Hz), 4.62 (d, 1H, J=3.5 Hz), 4.67 (d, 1H, J=11.9 Hz), 4.94 (d, 1H, J=11.7 Hz), 5.32 (s, 1H), 6.95–7.36 (m, 20H); ^{13}C NMR (C_6D_6, 75 MHz) δ 54.6, 69.0, 70.7, 71.3, 72.4, 75.0, 80.6, 81.4, 84.2, 98.0, 127.1, 127.3, 127.6, 127.8, 127.9, 128.2, 128.3, 138.8, 139.4, 142.5; IR (film) 1453, 1092, 1053, 1028, 740, 697 cm^{-1}; ESMS-ESI m/z for $C_{34}H_{36}O_6Li$ $[M+Li]^+$ calcd 547.2667, found 547.2712.

4.3.15. Methyl 2,3-di-O-benzyl-4,6-di-O-diphenylmethyl-α-D-glucopyranoside (Table 3, entry 10)

^{1}H NMR (C_6D_6, 300 MHz) δ 3.26 (s, 3H), 3.38 (dd, 1H, J=5.7 and 10.7 Hz), 3.58 (dd, 1H, J=3.5 and 9.7 Hz), 3.68 (dd, 1H, J=1.9 and 10.6 Hz), 3.88 (dd, 1H, J=8.6 and 9.9 Hz), 4.20 (ddd, 1H, J=1.6, 5.5 and 9.9 Hz), 4.59 (d, 1H, J=10.8 Hz), 4.72 (d, 1H, J=3.3 Hz), 5.05 (d, 1H, J=10.8 Hz), 5.17 (s, 1H), 6.17 (s, 1H), 7.01–7.42 (m, 30H); ^{13}C NMR (C_6D_6, 75 MHz) δ 54.3, 68.3, 70.6, 72.5, 75.4, 81.2, 82.6, 83.7, 83.8, 97.7, 126.6, 127.1, 127.2, 128.0, 128.3, 128.5, 138.9, 139.2, 142.6, 142.8, 143.1, 143.6; IR (film) 2921, 1494, 1045, 1027, 739, 697 cm^{-1}; ESMS-ESI m/z for $C_{47}H_{46}O_6Li$ $[M+Li]^+$ calcd 713.3450, found 713.3410.

4.3.16. Methyl 4,6-di-O-acetyl-3-O-diphenylmethyl-α-D-glucopyranoside (Table 3, entry 11)

^{1}H NMR (C_6D_6, 300 MHz) δ 1.53 (s, 3H), 1.70 (s, 3H), 2.81 (s, 3H), 3.52 (ddd, 1H, J=2.4, 4.6, and 10.9 Hz), 3.61 (dt, 1H, J=3.8 and 8.8 Hz), 3.81 (t, 1H, J=9.1 Hz), 4.01 (dd, 1H, J=2.5 and 12.3 Hz), 4.22 (dd, 1H, J=4.8 and 12.2 Hz), 4.33 (d, 1H, J=4.0 Hz), 5.30 (dd, 1H, J=9.0 and 10.4 Hz), 5.98 (s, 1H), 6.92–7.43 (m, 10H); ^{13}C NMR (C_6D_6, 75 MHz) δ 20.0, 20.2, 54.5, 62.1, 67.9, 69.3, 73.4, 78.2, 84.3, 99.3, 126.8, 127.1, 127.3, 127.8, 143.1, 143.5, 168.9, 170.2; IR (film) 1717, 1046, 1027, 1001, 738, 696 cm^{-1}; ESMS-ESI m/z for $C_{24}H_{28}O_8Li$ $[M+Li]^+$ calcd 451.1939, found 451.1903.

4.3.17. Methyl 4,6-di-O-acetyl-2-O-diphenylmethyl-α-D-glucopyranoside (Table 3, entry 11)

^{1}H NMR (C_6D_6, 300 MHz) δ 1.64 (s, 3H), 1.66 (s, 3H), 2.94 (s, 3H), 3.45 (dd, 1H, J=3.6 and 9.6 Hz), 3.76 (ddd, 1H, J=2.2, 4.7, and 10.2 Hz), 4.05 (dd, 1H, J=2.3 and 12.3 Hz), 4.19–4.29 (m, 2H), 4.33 (d, 1H, J=3.5 Hz), 5.13 (dd, 1H, J=9.2 and 10.3 Hz), 5.41 (s, 1H), 6.93–7.31 (m, 10H); ^{13}C NMR (C_6D_6, 75 MHz) δ 20.0, 20.1, 54.6, 62.2, 67.5, 70.8, 71.4, 79.6, 84.1, 98.0, 126.9, 127.3, 127.5, 128.2, 128.3, 143.2, 143.7, 168.8, 168.9; IR (film) 1754, 1086, 1074, 1050, 1028, 991, 737, 696 cm^{-1}; ESMS-ESI m/z for $C_{24}H_{28}O_8Li$ $[M+Li]^+$ calcd 451.1939, found 451.1923.

4.3.18. Diphenylmethyl 2-benzyloxycarbonylaminobutanyl ether (Table 3, entry 12)

^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.00 (t, 3H, J=7.3 Hz), 1.63–1.85 (m, 2H), 3.55 (d, 2H, J=4.0 Hz), 3.85 (d, 1H, J=7.3 Hz), 5.19 (s, 2H), 5.41 (s, 1H), 7.29–7.45 (m, 15H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 10.6, 25.2, 52.7, 66.6, 70.2, 83.9, 126.9, 127.0, 127.6, 128.1, 128.5, 128.6, 136.8, 142.1, 156.3; IR (film) 1719, 1690, 1540, 1278, 696 cm^{-1}; ESMS-ESI m/z for $C_{25}H_{27}NO_3Li$ $[M+Li]^+$ calcd 396.2146, found 396.2170.

4.3.19. Diphenylmethyl 5-butoxycarbonylaminopentanyl ether (Table 3, entry 13)

^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.36–1.53 (s, 13H), 1.62–1.71 (m, 2H), 3.10 (m, 2H), 3.45 (t, 2H, J=6.4 Hz), 4.50 (s, 1H), 5.33 (s, 1H), 7.21–7.41 (m, 10H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 23.6, 28.5, 29 .5, 29.9, 40.6, 68.9, 76.3, 83.7, 126.6, 127.4, 128.5, 143.8, 156.0; IR (film) 1493, 1017, 752, 734, 695, 651, 601 cm^{-1}; ESMS-ESI m/z for $C_{23}H_{31}NO_3Li$ $[M+Li]^+$ calcd 376.2459, found 376.2497.

4.3.20. Diphenylmethyl thiobenzyl ether[20] (Table 3, entry 18)

^{1}H NMR ($CDCl_3$, 300 MHz) δ 3.63 (s, 2H), 5.03 (s, 1H), 7.29–7.48 (m, 15H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 37.9, 54.7, 128.9, 129.1, 129.4, 130.7, 138.7, 141.8.

4.3.21. Bis(4-methoxyphenyl)methyl benzyl ether (Table 4, entries 1 and 2)

^{1}H NMR ($CDCl_3$, 300 MHz) δ 3.79 (s, 6H), 4.51 (s, 2H), 5.36 (s, 1H), 6.83–6.88 (m, 4H), 7.23–7.38 (m, 9H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 55.3, 70.2, 77.2, 81.5, 113.7, 127.5, 127.7, 128.3, 134.6, 138.6, 158.9; IR (film) 1508, 1241, 1169, 1029, 826, 810 cm^{-1}; ESMS-ESI m/z for $C_{22}H_{22}O_3Li$ $[M+Li]^+$ calcd 341.1724, found 341.1742.

4.3.22. Bis(4-methoxyphenyl)methyl n-butyl ether (Table 4, entries 3 and 4)

^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.92 (t, 3H, J=7.3 Hz), 1.43 (m, 2H), 1.63 (m, 2H), 3.44 (t, 2H, J=6.5 Hz), 3.79 (s, 6H), 5.28 (s, 1H), 6.83–6.89 (m, 4H), 7.24–7.28 (m, 4H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 14.0, 19.5, 32.1, 55.3, 68.7, 82.7, 113.9, 128.4, 135.1, 158.8; IR (film) 1508, 1240, 1169, 1087, 1032, 810 cm^{-1}; ESMS-ESI m/z for $C_{17}H_{24}O_3Na$ $[M+Na]^+$ calcd 323.1618, found 323.1684.

4.3.23. Bis(4-methoxyphenyl)methyl 4-benzyloxybutyl ether (Table 4, entries 5 and 6)

^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.74 (m, 4H), 3.48 (m, 4H), 3.79 (s, 6H), 4.51 (s, 2H), 5.26 (s, 1H), 6.83–6.88 (m, 4H), 7.23–7.29 (m, 4H), 7.30–7.36 (m, 5H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 26.6, 26.7, 55.2, 68.6, 70.2, 72.8, 82.7, 113.5, 127.5, 127.6, 128.1, 128.4, 135.0, 138.6, 158.8; IR (film) 1508, 1242, 1170, 1085, 1031, 812 cm^{-1}; ESMS-ESI m/z for $C_{26}H_{34}O_4Li$ $[M+Li]^+$ calcd 413.2304, found 413.2354.

4.3.24. Bis(4-methoxyphenyl)methyl 4-methoxybenzyloxybutyl ether (Table 4, entry 7)

^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.67–1.73 (m, 4H), 3.39–3.47 (m, 4H), 3.78 (s, 6H), 3.80 (s, 3H), 4.42 (s, 2H), 5.24 (s, 1H), 6.82–6.88 (m, 6H), 7.20–7.26 (m, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 26.6, 55.2, 68.6, 69.9, 72.5, 76.6, 82.6, 113.6, 113.7, 128.1, 129.2, 133.7, 135.0, 158.8; IR (film) 1508, 1241, 1169, 1082, 1030, 812 cm^{-1}; ESMS-ESI m/z for $C_{27}H_{32}O_5Li$ $[M+Li]^+$ calcd 443.2405, found 443.2464.

4.3.25. Bis(4-methoxyphenyl)methyl 4-acetoxybutyl ether (Table 4, entry 8)

^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.62–1.78 (m, 4H), 2.03 (s, 3H), 3.43 (t, 2H, J=5.8 Hz), 3.78 (s, 6H), 4.07 (t, 2H, J=6.3 Hz), 5.25 (s, 1H), 6.83–6.86 (m, 4H), 7.21–7.25 (m, 4H); ^{13}C NMR ($CDCl_3$, 75 MHz)

δ 24.8, 26.4, 29.2, 48.2, 55.3, 68.3, 71.0, 85.0, 107.5, 113.4, 128.1, 141.6; IR (film) 1734, 1604, 1508, 1240, 1168, 1029, 812 cm^{-1}; ESMS-ESI *m/z* for $C_{21}H_{26}O_5Li$ $[M+Li]^+$ calcd 365.1935, found 365.1984.

4.3.26. Bis(4-methoxyphenyl)methyl 4-tert-butyldiphenylsilyloxybutanyl ether (Table 4, entry 10)

^1H NMR ($CDCl_3$, 300 MHz) δ 1.03 (s, 9H), 1.61–1.78 (m, 4H), 3.41 (t, 2H, *J*=6.2 Hz), 3.67 (t, 2H, *J*=6.0 Hz), 3.78 (s, 6H), 5.23 (s, 1H), 5.31–5.50 (m, 2H), 6.80–6.89 (m, 4H), 7.18–7.25 (m, 4H), 7.32–7.45 (m, 6H), 7.61–7.70 (m, 4H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 26.3, 26.8, 26.9, 29.4, 55.2, 64.0, 68.7, 82.6, 113.7, 127.6, 127.7, 128.1, 129.5, 134.1, 135.6, 158.8; IR (film) 1073, 1027, 810, 738, 696, 503 cm^{-1}; ESMS-ESI *m/z* for $C_{35}H_{42}O_4SiNa$ $[M+Na]^+$ calcd 577.2745, found 577.2705.

4.3.27. Methyl 2,3-O-cyclohexyliden-5-(bis(4-methoxyphenyl)-methyl)- β-D-ribofuranoside (Table 4, entry 11)

^1H NMR ($CDCl_3$, 300 MHz) δ 1.33–1.76 (m, 10H), 3.26 (s, 3H), 3.39–3.51 (m, 2H), 3.78 (s, 6H), 4.42 (t, 1H, *J*=6.9 Hz), 4.55 (d, 1H, *J*=5.9 Hz), 4.68 (d, 1H, *J*=5.9 Hz), 4.97 (s, 1H), 5.29 (s, 1H), 6.84–6.88 (m, 4H), 7.24–7.28 (m, 4H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 23.8, 24.0, 25.1, 34.7, 36.3, 54.8, 55.2, 69.8, 81.8, 83.1, 84.9, 85.6, 109.6, 113.0, 113.7, 128.1, 128.2, 128.4, 134.5, 158.9; IR (film) 2933, 1609, 1463, 1169, 960, 827, 812, 562 cm^{-1}; ESMS-ESI *m/z* for $C_{21}H_{26}O_5Li$ $[M+Li]^+$ calcd 365.1935, found 365.1984.

4.3.28. Bis(4-methoxyphenyl)methyl (Z)-hex-3-enyl ether (Table 4, entry 12)

^1H NMR ($CDCl_3$, 300 MHz) δ 0.95 (t, 3H, *J*=7.5 Hz), 1.98–2.13 (m, 2H, *J*=7.2 Hz), 2.29–2.46 (m, 2H, *J*=6.7 Hz), 3.42 (t, 2H, *J*=7.0 Hz), 3.78 (s, 6H), 5.28 (s, 1H), 5.31–5.50 (m, 2H), 6.81–6.89 (m, 4H), 7.21–7.28 (m, 4H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 14.3, 20.7, 28.0, 55.3, 68.6, 77.2, 82.7, 113.7, 125.1, 127.7, 128.1, 134.9, 18.8; IR (film) 1508, 1240, 1169, 1032, 812 cm^{-1}; ESMS-ESI *m/z* for $C_{21}H_{26}O_3Na$ $[M+Na]^+$ calcd 349.1774, found 349.1784.

4.3.29. Bis(4-methoxyphenyl)methyl cis-3,4-epoxyhexyl ether (Table 4, entry 13)

^1H NMR ($CDCl_3$, 300 MHz) δ 1.03 (t, 3H, *J*=7.5 Hz), 1.43–1.64 (m, 3H, *J*=14.7 and 7.6 Hz), 1.72–1.98 (m, 2H), 2.91 (td, 1H, *J*=6.4 and 4.3 Hz), 3.12 (td, 1H, *J*=6.9 and 4.7 Hz), 3.60 (dd, 2H, *J*=7.1 and 5.9 Hz), 3.79 (s, 6H), 5.30 (s, 1H), 6.83–6.88 (m, 4H), 7.22–7.28 (m, 4H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 10.6, 21.2, 28.6, 55.3, 58.2, 66.2, 83.0, 113.7, 128.1, 134.8, 158.9; IR (film) 1508, 1240, 1170, 1083, 1030, 810, 558 cm^{-1}; ESMS-ESI *m/z* for $C_{21}H_{26}O_4Na$ $[M+Na]^+$ calcd 365.1723, found 365.1690.

4.3.30. Bis(4-methoxyphenyl)methyl menthyl ether (Table 4, entry 14)

^1H NMR ($CDCl_3$, 300 MHz) δ 0.77 (t, 6H, *J*=6.2 Hz), 0.84 (d, 3H, *J*=6.8 Hz), 1.04–1.19 (m, 1H), 1.24–2.02 (m, 9H), 3.52–3.56 (m, 1H), 3.79 (s, 6H), 5.38 (s, 1H), 6.82–6.88 (m, 4H), 7.22–7.28 (m, 4H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 19.6, 21.4, 25.8, 27.3, 30.1, 35.5, 45.6, 55.2, 68.0, 72.6, 79.1, 113.5, 128.4, 134.8, 158.8; IR (film) 1508, 1242, 1169, 1034, 812 cm^{-1}; ESMS-ESI *m/z* for $C_{25}H_{34}O_3Li$ $[M+Li]^+$ calcd 389.2663, found 389.2713.

4.4. General procedure for DPM- and BMPM-ether deprotection (procedure B)

To a solution of DPM- or BMPM-protected alcohol (1.08 mmol, 1 equiv) in ethanol (5.4 mL) were added the palladium catalyst, $PdCl_2$ (20 mg, 0.1 equiv), or $PdCl_2(CH_3CN)_2$ (28 mg, 0.1 equiv). The reaction was stirred at the desired temperature (20 or 60 °C) until disappearance of the starting material (TLC monitoring), filtered on a pad of silica gel using ethyl acetate as eluant. The solvents were evaporated under reduced pressure and the resulting crude product was purified by flash chromatography (0–100% EtOAc/cHex).

4.5. General procedure for DPM- and BMPM-ether deprotection (procedure C)

To a solution of DPM- or BMPM-protected alcohol (1.08 mmol, 1 equiv) in DCE (5.4 mL) were added ethanol (0.63 mL, 10 equiv) and then $PdCl_2(CH_3CN)_2$ (28 mg, 0.1 equiv). The reaction was stirred at the desired temperature (20 or 60 °C) until disappearance of the starting material (TLC monitoring), filtered on a pad of silica gel using ethyl acetate as eluant. The solvents were evaporated under reduced pressure and the resulting crude product was purified by flash chromatography (0–100% EtOAc/cHex).

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