Available online at www.sciencedirect.com

ScienceDirect

Tetrahedron Letters 48 (2007) 8895–8899

Tetrahedron Letters

$PdCl_2$, a useful catalyst for protection of alcohols as diphenylmethyl (DPM) ethers

Yann Bikard,[a,c] Jean-Marc Weibel,[a] Claude Sirlin,[b] Luc Dupuis,[c] Jean-Philippe Loeffler[c] and Patrick Pale[a,*]

[a] *Laboratoire de synthèse et réactivité organique, associé au CNRS, Institut Le Bel, Université L. Pasteur, 67000 Strasbourg, France*

[b] *Laboratoire de synthèses métallo-induites, associé au CNRS, Institut Le Bel, Université L. Pasteur, 67000 Strasbourg, France*

[c] *Laboratoire de signalisations moléculaires et neurodégénerescence, U 692, INSERM—Université Louis Pasteur, 11, rue Humann, 67085 Strasbourg, France*

Received 10 August 2007; revised 3 October 2007; accepted 10 October 2007

Abstract—Primary, secondary, benzylic and allylic alcohols are efficiently converted to the corresponding diphenylmethyl ethers in the presence of catalytic amounts of $PdCl_2$.

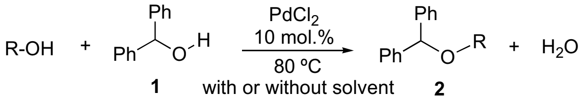
Total syntheses of complex molecules involve many steps, most of them being required to control functional groups and mainly to turn down their reactivity through modification with protecting groups.[1] The criteria involved in the choice of protecting groups are based on high yielding protection and deprotection steps and, if possible, chemoselectivity during those steps but also on orthogonality[1b] with other protecting and functional groups.

Usually, alcohols are temporarily converted to silyl and alkyl ethers, the benzyl and *para*-methoxybenzyl protecting groups being the most popular due to their deprotection conditions being orthogonal to each other.[1,2]

We present here new chemoselective conditions for the protection and deprotection of alcohols as diphenylmethyl (DPM) ether, offering an interesting alternative and an orthogonal complement to the common benzyl-type ethers.

Scarcely used in organic synthesis, the formation of DPM ethers usually involves the nucleophilic substitution of chloro- or bromodiphenylmethane by a metal alcoholate,[3] as for most benzyl-type ethers. A few other methods can nevertheless be found in the literature. Halogenodiphenylmethanes have been mentioned as starting materials toward DPM ethers by treatment with orthoformates at high temperature.[4] Diphenylmethanol in the presence of Brønsted acid,[5] strong Lewis acid,[6] or supported acids,[7] and other reagents such as diphenylmethylphosphate–trifluoroacetic acid[8] and diphenylmethyldiazomethane[8,9] have also been reported. Deprotection of DPM ethers is mostly achieved by simple hydrogenation as for any benzyl-type ethers,[10] but electrolytic reduction,[11] acidolysis[8a,12] and solvolysis[13] have also been reported. As a part of our program to develop new catalytic reactions using transition metals (especially Pd, Ag and Au salts),[14–16] we were interested in finding a more simple and environmentally friendly procedure for the formation of DPM ethers and their deprotection (Scheme 1).

To look for the best catalyst, we began our investigations by submitting diphenylmethanol **1** in ethanol in the presence of various metal salts (10 mol %) at 80 °C



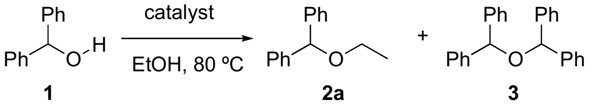
Scheme 1. Metal-catalyzed formation of DPM ethers.

---

[*] Corresponding author. Tel./fax: +33 390 24 15 17; e-mail: ppale@chimie.u-strasbg.fr

doi:10.1016/j.tetlet.2007.10.045

Table 1. Effect of transition metal salts on DPM ether formation



Entry	Catalyst	Time (h)	Recovered **1**[a] (%)	Yield **2a**[a] (%)	Yield **3**[a] (%)
1	$PdCl_2$	4.3	1	97	Traces
2	Pd/C 10%	16	30	Traces	0[b]
3	$Pd(OAc)_2$	24	27	Traces	0[b]
4	$NiCl_2$	48	100	0	0
5	AuCl	5.5	4	75	21
6	$NaAuCl_4$	24	2	76	8[c]
7	$AuCl_3$	5.5	3	12	85
8	AgOTf	1	100	0	0[d]
9	CuCl	24	95	5	0
10	$CuCl_2$	16	2	88	10
11	$CuSO_4{\cdot}5H_2O$	48	2	95	3

[a] Yield estimated from NMR analysis.

[b] Benzophenone and diphenylmethane were observed as major products.

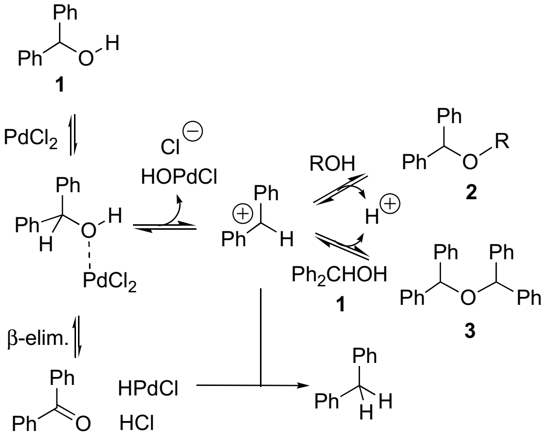
[c] Benzophenone was also detected.

[d] Formation of a silver mirror.

(reaction rates are dramatically lower without heating) (Table 1). Depending on the catalyst, two different products could be produced and easily isolated, the expected DPM protected ethanol **2a** and an ether resulting from dimerization of diphenylmethanol, compound **3**. Since the starting reagent **1** and products **2a** and **3** were clearly characterized by the chemical shift of their methyne proton at, respectively, 5.84, 5.37 and 5.41 ppm in $CDCl_3$, the reactions were followed by NMR and the product ratios determined by NMR (Table 1).

In the presence of $PdCl_2$ (entry 1), diphenylmethanol was rapidly and completely converted to its ether **2a**, nearly without formation of ether **3** or any other by-products. Surprisingly, palladium on charcoal, known to be often contaminated with $PdCl_2$ due to its preparation, gave a complex mixture mostly containing the starting materials, benzophenone and diphenylmethane, even after prolonged reaction time (entry 2). Other palladium salts, such as $Pd(OAc)_2$, gave almost the same results (entry 3). These results indicated that as expected, coordination of diphenylmethanol occurred but that the Lewis acid character of the salt could be balanced by β-elimination (see the mechanism below and Scheme 2).

To favor the Lewis acid pathway, we thus turned our attention to more acidic salts and to salts of metals less prone to β-elimination. Located in the same column as palladium in the Mendeleev periodic table, nickel salts are more acidic. Disappointedly, nickel chloride did not promote formation of the ether, starting material was recovered (entry 4). In contrast, gold salts gave high conversion (entries 5–7). Among them, AuCl gave ether **2** but in moderate yields together with relatively high amount of the dimeric ether **3** (entry 5). $NaAuCl_4$ gave similar results with reasonably low amount of **3** but the reaction required far longer time and was less clean, yielding a mixture of side-products (entry 6). The more acidic $AuCl_3$ gave predominately the undesired dimeric ether **3** (entry 7). Silver triflate (entry 8) and copper(I) chloride (entry 9) were not effective whereas copper(II) salts (entries 10 and 11) gave good results, copper sulfate being the best of them although the reaction required two days to be close to completion.

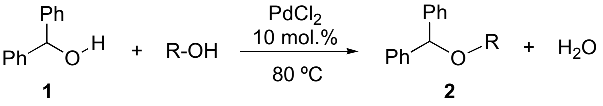


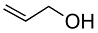
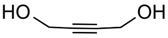
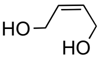
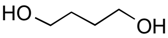
Scheme 2. Proposed mechanism for the $PdCl_2$-catalyzed DPM protection of alcohols.

This metal salt screening clearly showed that $PdCl_2$ is a very efficient catalyst for the protection of alcohols as DPM ethers, giving high conversion and almost quantitative yield in a few hours.

To rapidly evaluate the scope and the chemoselectivity of this novel protection procedure, we submitted representative examples of the different classes of alcohols in the presence of diphenylmethanol and $PdCl_2$, the alcohol acting as a reagent and solvent in an environmentally friendly procedure (Table 2). Primary alcohols, allylic and benzylic alcohols, were efficiently converted into their DPM ethers in a fast reaction under these conditions (entries 1, 4 and 5). Interestingly, α-unsaturated

Table 2. Formation of DPM ethers in alcohol (solvent-free conditions)[a]



Entry	Alcohol[a]	Time (h)	Yield[b] (%)	DPM ether (R)
1	EtOH	4.3	97	**2a** (Et)
2	*i*PrOH	24	97	**2b** (*i*Pr)
3	*t*BuOH	72	19	**2c** (*t*Bu)
4		1.7	88	**2d** ($CH_2CH{=}CH_2$)
5	Bn–OH	2.5	96	**2e** (CH_2Ph)
6	PhOH	24	0	—
7		1.5	Degrad.	—
8		1.7	Degrad.	—
9		16	95[c]	**2f**[c] ($(CH_2)_4OH$)

[a] [DPMOH] = 0.2 M in alcohol or phenol.

[b] Yield estimated by NMR analysis.

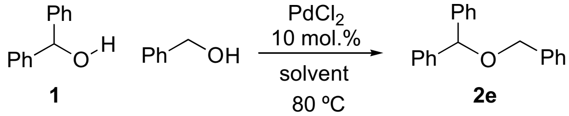
[c] Only the monoprotected product was obtained.

primary alcohols seem to be more reactive than saturated ones, as revealed by shorter reaction times (entries 4 and 5 vs entry 1). More interestingly, the secondary alcohol isopropyl alcohol, required much longer reaction time (entry 2) while the tertiary alcohol, *tert*-butanol, is even less reactive under the same conditions (entry 3). In a similar way, the less nucleophilic phenol did not react under these conditions (entry 6). Various primary diols (entries 7–9) were also examined, expecting monoprotection under these non-stoichiometric conditions. Surprisingly, only the saturated one was transformed and indeed monoprotected in excellent yield, while the unsaturated ones led to complex mixtures (entry 9 vs entries 7 and 8). This monoprotection, however, required longer time reaction than other primary alcohols (entry 9 vs entry 1).

This novel DPM protection thus offers useful selectivity, primary alcohols being more rapidly protected than secondary alcohols, while tertiary alcohols are scarcely protected and phenols do not react. To our knowledge, such chemoselectivity has not yet been reported for benzyl-type protecting groups.

Although the above-mentioned solvent-free protection of alcohols is very interesting as an environmentally friendly transformation (Green Chemistry), these conditions may not be very useful within the context of total synthesis. In multi-step synthesis, the alcohol is clearly the limiting species and it cannot be used as a solvent. We therefore developed stoichiometric conditions.

Table 3. Formation of benzyl DPM ethers in the presence of solvents. [Alcohol] = [DPMOH] = 0.2 M in solvent, 10 mol % $PdCl_2$, 80 °C, 16 h



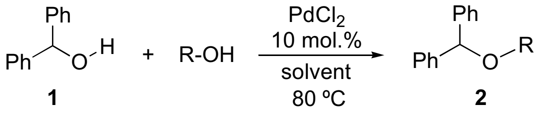
Entry	Solvents	Yield[a] (%)
1	DCE	94
2	Benzene	92
3	Toluene	91
4	Acetonitrile	90
5	Ethyl acetate	Degradation
6	Dioxane	Degradation
7	DMF	Degradation

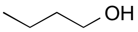
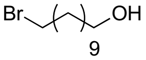
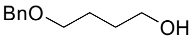
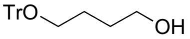
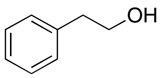
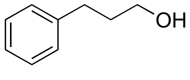
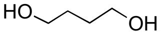
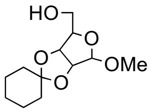
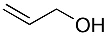
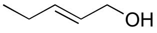
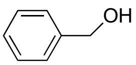
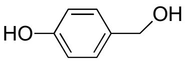
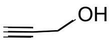
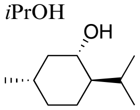
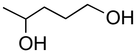
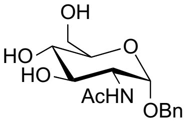
[a] Yield estimated by NMR analysis.

To do so, we looked for solvents compatible with these DPM protection conditions. The very reactive benzylic alcohol was chosen as the substrate and it was converted to its DPM ether in various solvents (Table 3). As expected, non-coordinating solvents gave the best results (entries 1–3) while coordinating and polar solvents led to messy reactions (entries 5–7). Among the solvents examined, acetonitrile occupied a peculiar position, allowing for an efficient reaction while being a polar solvent. The well known ability of acetonitrile to coordinate and stabilize Pd species and especially $PdCl_2$ is probably responsible for the behavior observed here. It is worth noting that either non-polar solvents or the relatively polar acetonitrile can thus be used for this protection, offering a large range to organic chemists. Rewardingly, reactions performed in apolar solvents were very clean and the diphenylmethanol dimer **3** can still be detected but only in less than 5%.

With these stoichiometric conditions in hands, we examined the scope of this protection in solution. Various alcohols were converted to their DPM ethers through this method. Aliphatic primary alcohols carrying or not other functional groups were easily protected as DPM ethers in high isolated yields (81–88%) (Table 4,

Table 4. $PdCl_2$ catalyzed formation of DPM ethers (conditions with solvent)[a]



Entry	Alcohols	Time (h)	Yield[b] (%)
1		4	83
2		48	88
3		24	83
4		24	87
5		48	87
6		48	81
7		1	73[c,d]
8		48	68
9		4	76
10		4	73
11		4	94
12		5	48[d,e,f]
13	PhOH	96	4[g]
14		24	0[g]
15	*i*PrOH	48	86
16		48	65
17		24	74[h]
18		3	56[c,f]
19		48	46[e,f]

[a] [Alcohol] = [DPMOH] = 0.2 M in dichloroethane unless otherwise stated, 10 mol % $PdCl_2$, 80 °C.
[b] Yield of pure product after column chromatography.
[c] Less than 10% of the diprotected diol was also isolated.
[d] 4 equiv of DPMOH was used.
[e] Performed in acetonitrile for solubility reasons.
[f] Only the primary hydroxyl was protected.
[g] The starting material was recovered.
[h] 2 equiv of DPMOH was used.

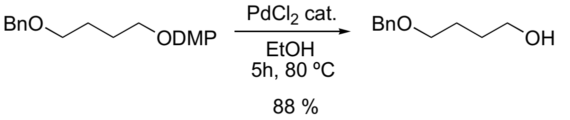
entries 1–6). Interestingly, the diol, which gave the monoprotected product under solvent-free conditions (Table 2), also led mostly to the same monoDPM ether **2f** (entry 7). More functionalized primary alcohol was also protected in good yield (entry 8).

As shown under the solvent-free conditions (Table 2), allylic and benzylic alcohols proved to be more reactive, giving the corresponding DPM ethers in good to excellent yield within a few hours (entries 9–11). However, decomposition occurred upon protection of *p*-hydroxymethylphenol probably due to the long reaction time. Increasing the amount of DMP-OH decreased the reaction time and allowed to isolate the monoprotected derivative in reasonable yield, the phenol moiety being untouched (entry 12). Indeed, simple phenol gave the ether in very low yield after 4 days (entry 13). Propargylic alcohols did not react under these conditions as shown for propynol, which was recovered even after 5 days (entry 14). Secondary alcohols reacted more or less rapidly depending on their bulkiness. Isopropanol cleanly afforded its ether in 86% yield, whereas L-menthol gave only 65% yield within 2 days (entry 16 vs entry 15). For the latter, the reaction rate was not high enough to impede the competitive formation of ether **3** but a slight excess of reagent avoided this problem, and the menthol DPM ether was isolated in good yields (entry 17). To check the selectivity observed without solvent (Table 2), we submitted a simple and more elaborated substrate exhibiting primary as well as secondary alcohols (entries 18 and 19). As expected, protection occurred at the primary alcohol in both cases.

This screening of alcohols revealed that this DPM protection is tolerant to other functional groups (entries 2–10, 12, 19), compatible with other protecting groups (entries 3 and 4, 8, 19) and selective toward primary alcohols (entries 12, 18 and 19).

The various products observed together with the expected DPM ether shed some light on the mechanism of the reaction. The formation of ether **3** resulting from dimerization of diphenylmethanol suggests the intervention of a benzhydryl carbocation (Scheme 2). The latter or, as shown by the solvent effect, most probably an intimate ion pair including this cation could react with the alcohol or with diphenylmethanol to give, respectively, the protected alcohol **2** or the dimeric ether **3**. The benzhydryl carbocation would be probably formed after coordination of alcohol oxygen atom to the mild Lewis acid Pd^{II}. The fact that, under some conditions (see Table 1), benzophenone and diphenylmethane were produced confirmed the intermediate formation of a Pd complex. Upon coordination of the hydroxyl group, the β-proton present in primary and secondary alcohols can be transferred to the palladium. This β-elimination would produce on the one hand benzophenone and on the other hand a hydridopalladium species able to reduce the carbocation also present in the medium (Scheme 2).

If correct, this mechanism shows that this DPM protection is reversible and probably displaced toward ether **2** either by the excess of alcohol in the solvent-free version and/or by removal of water by heating under both



Scheme 3. Deprotection of DPM ether using 10 mol % $PdCl_2$ in ethanol.

conditions. Interestingly, such proposal allows us to think that the conditions used for the protection would also be effective for the deprotection of DPM ethers. It also suggests that the deprotection should be selective for DPM ethers.

Rewardingly, this hypothesis was confirmed by the deprotection of one of the previously synthesized DPM ethers (Scheme 3). 1,4-Butanediol protected at one end as a benzyl ether and at the other as a DPM ether was cleanly and rapidly converted to the monobenzylated diol using $PdCl_2$ again as catalyst and ethanol to displace the DPM ether toward the free alcohol and the corresponding ethoxydiphenylmethane.

In conclusion, we have developed a novel and simple method for the synthesis of diphenylmethyl ethers from alcohols and diphenylmethanol using $PdCl_2$ as a catalyst. This reaction, showing interesting chemoselectivity, offers an alternative for the protection of alcohols. Moreover, a selective deprotection has been achieved under conditions orthogonal to other protecting groups. Both aspects will thus extend the tool box of organic chemists. Further works are now underway to expand the scope of this reaction and better understand its mechanism.

Typical procedure for the formation of DPM ethers from alcohols:

Solvent-free procedure: Diphenylmethanol (100 mg, 0.54 mmol, 1 equiv) was added to a solution of palladium chloride (10 mg, 0.054 mmol, 0.1 equiv) in alcohol (2.7 ml, 0.2 M). The reaction mixture was then heated at 80 °C until disappearance of the starting materials (TLC monitoring). Excess of alcohol was then removed in vacuum and the crude mixture obtained was purified by column chromatography when necessary.

Solution procedure: To a solution of alcohol (1 equiv) and diphenylmethanol (200 mg, 1.08 mmol, 1 equiv) in dichloroethane (5 ml/mmol) was added palladium chloride (20 mg, 0.108 mmol, 0.1 equiv). The reaction mixture was then heated at 80 °C until disappearance of the starting materials (TLC monitoring). The solvent was then removed in vacuum and the crude mixture obtained was purified by column chromatography.

Acknowledgments

The authors thank the 'CNRS' and the French Ministry of Research for financial support. Y.B thanks the 'Ministère de la Recherche et de la Technologie' for a doctoral fellowship.

References and notes

1. (a) Greene, T. W.; Wuts, P. G. M. *Protective groups in Organic Synthesis*, 3rd ed.; J. Wiley & Sons: New York, 1999; (b) Kocienski, P. J. *Protecting Groups*, 3rd ed.; G. Thieme: Stuttgart, New York, 2004.
2. For a recent review, see: Weissman, S. A.; Zewge, D. *Tetrahedron* **2005**, *61*, 7833, and references cited therein.
3. Dobson, D.; Todd, A.; Gilmore, J. *Synth. Commun.* **1991**, *21*, 601.
4. Gazizov, M. B.; Ibragimov, S. N.; Khamidullina, O. D.; Karimova, R. F.; Pudovik, M. A.; Sinyashin, O. G. *Russ. J. Gen. Chem.* **2005**, *75*, 1325.
5. (a) Sugsawa, S.; Fujiwara, K. *Org. Synth. Coll.* **1963**, *4*, 72; (b) Mairanovsky, V. G. *Angew. Chem., Int. Ed. Engl.* **1976**, *15*, 281; (c) Parades, R.; Perez, R. *Tetrahedron Lett.* **1998**, *39*, 2037.
6. (a) Sharma, G. V. M.; Prasad, T. R.; Mahalingam, A. K. *Tetrahedron Lett.* **2001**, *42*, 759; (b) Namboodiri, V. V.; Varma, R. S. *Tetrahedron Lett.* **2002**, *43*, 4593; (c) Stavber, S.; Zupan, M. *Tetrahedron Lett.* **1993**, *34*, 4355.
7. (a) Stanescu, M. A.; Varma, R. S. *Tetrahedron Lett.* **2002**, *43*, 7307; (b) Romanelli, G. P.; Ruiz, D. M.; Bideberripe, H. P.; Autino, J. C.; Baronetti, G. T.; Thomas, H. J. *Arkivoc* **2007**, *i*, 1.
8. (a) Kolovos, M.; Froussios, C. *Tetrahedron Lett.* **1984**, *25*, 3909; (b) Lapatsanis, L. *Tetrahedron Lett.* **1978**, *19*, 3943.
9. Roberts, J. D.; Watanabe, W. *J. Am. Chem. Soc.* **1950**, *72*, 4869.
10. Olah, G. A.; Prakash, G. K. S.; Narang, S. C. *Synthesis* **1978**, 825.
11. Mairanovsky, V. G. *Angew. Chem., Int. Ed. Engl.* **1976**, *15*, 281.
12. Froussios, C.; Kolovos, M. *Synthesis* **1987**, 1106.
13. Miyake, H.; Fujimura, M.; Tsumura, T.; Sasaki, M. *Chem. Lett.* **2006**, *35*, 778.
14. Selected references: with Pd (a) Halbes-Letinois, U.; Pale, P. Palladium-Catalyzed Synthesis of Enynes. In *Leading Edge Organometallic Chemistry Research*; Cato, M. A., Ed.; Nova: New-York, 2006; p 93, and references cited therein; (b) Halbes, U.; Vasiliev, A.; Pale, P. *Eur. J. Org. Chem.* **2005**, 2828; (c) Halbes, U.; Pale, P. *J. Organomet. Chem.* **2003**, *687*, 420.
15. Selected references: with Ag (a) Halbes-Letinois, U.; Weibel, J.-M.; Pale, P. *Chem. Soc. Rev.* **2007**, *36*, 759; (b) Orsini, A.; Vitérisi, A.; Bodlenner, A.; Weibel, J.-M.; Pale, P. A. *Tetrahedron Lett.* **2005**, *46*, 2259; (c) Vitérisi, A.; Orsini, A.; Weibel, J.-M.; Pale, P. A. *Tetrahedron Lett.* **2006**, *47*, 2779.
16. Selected references: with Au (a) Harkat, H.; Weibel, J.-M.; Pale, P. *Tetrahedron Lett.* **2006**, *47*, 6273; (b) Harkat, H.; Weibel, J.-M.; Pale, P. *Tetrahedron Lett.* **2007**, *48*, 1439.