Organic LETTERS

Letter

pubs.acs.org/OrgLett

p-Chlorobenzyl Ether: A *p*-Methoxybenzyl Ether in Disguise

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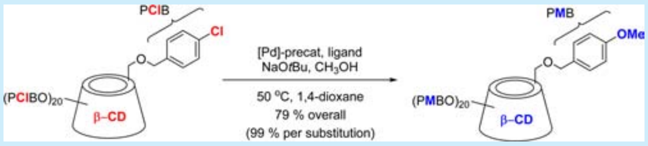
Supporting Information

ABSTRACT: In the chemistry of polyfunctionalized organic compounds, protecting groups that can undergo mild and selective cleavage while still being stable during the entire synthetic sequence are often required. In this work, we present a straightforward conversion of the robust *p*-chlorobenzyl ether into the more labile and well-described *p*-methoxybenzyl ether using palladium catalysis. This reaction was demonstrated to be high yielding and compatible with a wide range of functionalities, thereby providing a useful supplement to the conventional ether protecting groups.



The use of protecting groups is essential when working with organic synthesis on polyfunctionalized substrates such as carbohydrates and other natural products. Protecting groups are used to mask specific functionalities and render them unreactive to achieve specific chemical transformations on other reactive sites. In carbohydrate chemistry, the choice of protecting groups is often used to influence the reactivity and stereochemical outcome of the glycosylation reaction.[1,2]

Common types of hydroxyl protecting groups are the benzyl (Bn) and allyl (All) ethers. The benzyl ether is a very robust protecting group that is typically introduced as a permanent protecting group in the beginning of a synthetic sequence and cleaved in one of the final steps of the synthesis. The most commonly used conditions for the deprotection of benzyl ethers is palladium-catalyzed hydrogenolysis,[3] which is not compatible with functionalities such as alkenes or alkynes. Furthermore, it is our impression that benzyl ether removal by hydrogenolysis occasionally can be an unreliable reaction.

The allyl ether, on the other hand, is often used as a temporary protecting group, which is either cleaved directly[4] or in a two-step procedure starting with isomerization of the double bond and then cleavage.[5] The allyl deprotection can also be problematic due to low reactivity or competing side reactions.[6] An alternative for the protection of hydroxyl groups is the *p*-methoxybenzyl (PMB) ether group, which can easily be deprotected using a wealth of different methods.[5,7] The most popular of these deprotection strategies is either DDQ oxidation[8] or acidic treatment.[9] The mild deprotection conditions for PMB cleavage comes at the cost of lower stability, making this group unsuitable for some synthetic protocols.[10]

A less known hydroxyl protecting group is the *p*-chlorobenzyl (PClB) ether.[11] The PClB group is as stable as the benzyl ether, while also being found to have a stabilizing effect on glycosidic linkage due to its electron withdrawing nature.[12] Additionally the PClB group has been shown to induce crystallinity into molecules,[13] providing a straightforward way to obtain crystals from otherwise noncrystalline compounds.

While the PClB group has all the advantages of a permanent protecting group, it still suffers from the same drawbacks such as deprotection by hydrogenolysis as the benzyl group. However, preliminary results from our group have shown that employing the conditions developed by Cheung and Buchwald for the methoxylation of aryl chlorides[14] it was possible to convert PClB protecting groups into the well-known PMB group in good yield in the presence of ethers and an *O*,*S*-acetal in the form of a thioglycoside.[1]

Provided that conversion of PClB to PMB is a general transformation, we envision the former to be a valuable stable protecting group for introduction at an early stage of the synthesis and possess well-documented chemistry as its PMB congener.[5] PClB still has the option of being cleaved under hydrogenolysis conditions[1,5] but otherwise be cleaved over two steps as is the case for the allyl ether protecting group.

While our previous study has shown that the Pd-mediated (multiple) conversion of Cl into OCH_3 was possible in thioglycosides, we did not investigate functional group tolerance. For the utilization of the PClB group to be successful it is paramount that the conversion from PClB to PMB is able to take place in the presence of a wide range of functionalities. In order to investigate this we synthesized a total of 11 PClB protected carbohydrate derivatives as models of a densely functionalized small organic molecule. The protection of an alcohol functionality as a PClB ether was found to be uneventful following normal benzylation procedures (Scheme 1).[15]

For the methoxylation we decided to use Rockphos Pd G3 (5 mol %) and Rockphos ligand (5 mol %)[16] together with NaO*t*Bu and CH_3OH in 1,4-dioxane as we found these conditions to give high conversion[17] similar to the conditions reported by Cheung and Buchwald.[14]

These conditions resulted in high yields with PClB-protected primary alcohols of glucose and galactose (Table 1, entries 1 and 4) and secondary alcohols (entry 2) as well as anomeric

Received: September 6, 2016
Published: October 31, 2016

DOI: 10.1021/acs.orglett.6b02672
Org. Lett. 2016, 18, 5773–5775

Scheme 1. General Reaction Scheme

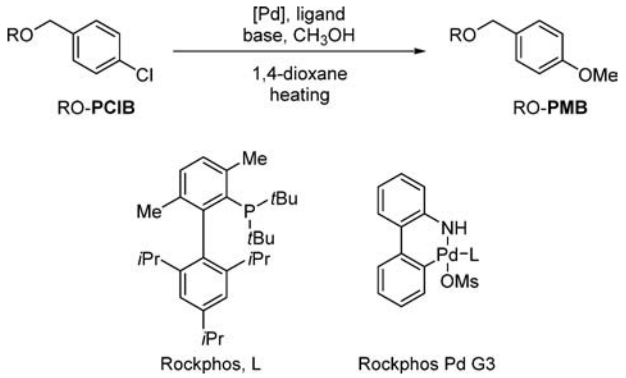


Table 1. Conversion of Aryl Chlorides into Aryl Methoxides According to the General Reaction Scheme*

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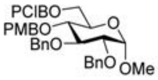
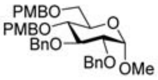
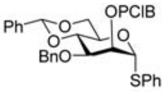
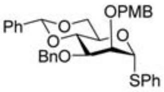
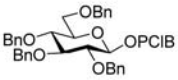
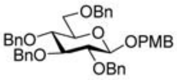
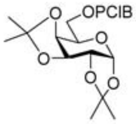
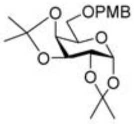
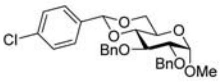
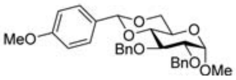
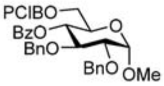
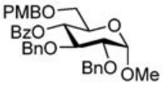
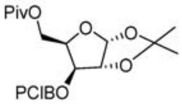
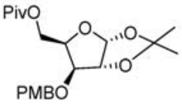
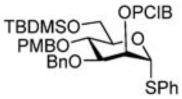
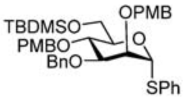
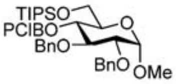
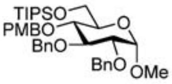
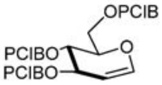
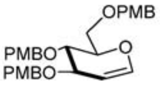
1			20	82
2			21	83
3			19	84
4			20 ½	97
5			22 ½	83

*Reaction conditions: RockPhos Pd G3 (5 mol %), RockPhos ligand (5 mol %), 1.4 equiv of NaO*t*Bu, 5 equiv of CH_3OH, 50 °C. [a]Isolated yields after chromatography.

PClB-protected glucose (entry 3). The method was also fully compatible with the presence of ethers (entries 1 and 3), thioacetals (entry 2), and acetals (entry 2, 4, and 5). It was also possible to employ the reaction conditions directly on *p*-chlorobenzylidene-protected glucose, converting it into the *p*-methoxybenzylidene in 83% yield (entry 5).

With these promising results in hand, we continued to investigate if the method was compatible with more challenging substrates containing functionalities that are labile under basic conditions. For this purpose, we chose to use substrates containing functionalities such as esters, silyl ethers, and alkenes (Table 2). We found that both the benzoyl and pivaloyl esters were labile using the conditions described above with NaO*t*Bu as the base. Changing the base to Cs_2CO_3 as described by Cheung and Buchwald[14] and heating the reaction to 60 °C in order to shorten the reaction time allowed us to obtain the PMB ether in the presence of a pivaloyl ester in high yield in only 1.5 h (entry 2). The benzoyl ester was unfortunately still labile under these conditions. Using the conditions on a TBDMS-protected compound gave a very sluggish reaction that only showed 50% conversion after 20 h as well as deprotection of the silyl ether (entry 3). On the other hand, switching to the more stable TIPS ether gave good results, with a yield of 90% after only 2.5 h (entry 4). Lastly, testing the reaction on tri-*p*-chlorobenzylated glucal gave us conversion of all three benzyl ethers in 64% isolated yield, corresponding to 86% per substitution (entry 5).

Table 2. Conversion of Aryl Chlorides into Aryl Methoxides According to the General Reaction Scheme in the Presence of Base-Sensitive Functionalities*

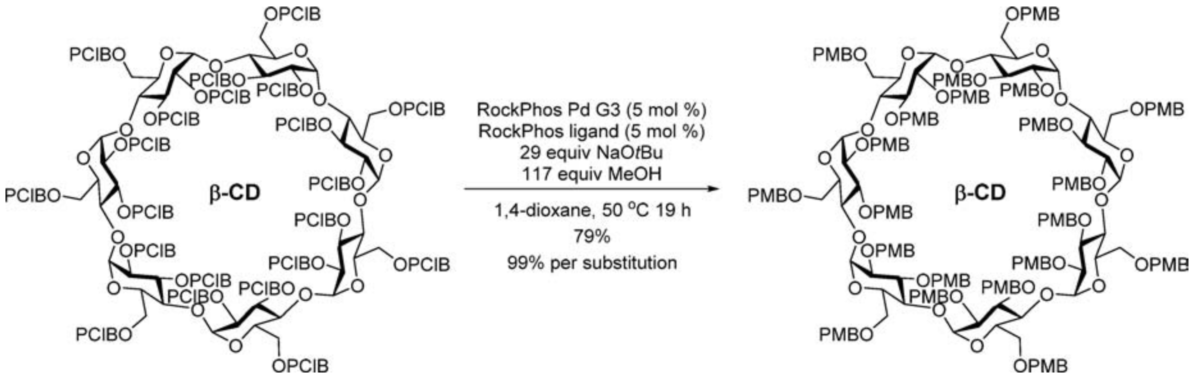
entry	starting material	product	time (h)	yield (%)[a]
1			1 ½	only benzoyl removal
2			1 ½	84
3			20	38 also silyl ether removal
4			2 ½	90
5[b]			5 ½	64

*Reaction conditions: RockPhos Pd G3 (5 mol %), RockPhos ligand (5 mol %), 1.4 equiv of NaO*t*Bu, 5 equiv of CH_3OH, 60 °C. [a]Isolated yields after chromatography. [b]Conditions using 4.2 equiv of Cs_2CO_3 and 15 equiv of CH_3OH.

As a final example of the effectiveness of this protocol, we were able to synthesize per-PClB-protected β-cyclodextrin and convert all 21 PClB groups into PMB groups in only 19 h in 79% isolated yield, corresponding to a yield of 99% per substitution (Scheme 2).

In conclusion, we have explored the scope of the Pd-catalyzed conversion of PClB ethers into the well-studied PMB ethers and found that this reaction is high yielding and versatile. The reaction conditions were found to be compatible with a wide range of functionalities, including acetals, thioacetals, silyl ethers, esters, and alkenes. We believe that the PClB protecting group is a valuable tool for the general organic chemist, providing a good supplement to the conventional protecting groups such as benzyl, allyl, and *p*-methoxybenzyl protecting groups due to its chameleon-like properties of superior stability and ease of deprotection.

Scheme 2. Conversion of All 21 PClB Ethers in Per-PClB-Protected β-Cyclodextrin into 21 PMB Ethers



■ ASSOCIATED CONTENT

Ⓢ Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b02672.

General procedures and NMR spectra of all synthetic compounds. (PDF)

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We thank Dr. Christian Marcus Pedersen (University of Copenhagen) and Mr. Rasmus Telving (Aarhus University) for running MALDI experiments and the Villum Foundation for funding.

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(15) See the Supporting Information
(16) (a) Wu, X.; Fors, B. P.; Buchwald, S. L. *Angew. Chem., Int. Ed.* **2011**, *50*, 9943. (b) Bruno, N. C.; Buchwald, S. L. *Org. Lett.* **2013**, *15*, 2876. (c) Bruneau, A.; Roche, M.; Alami, M.; Messaoudi, S. *ACS Catal.* **2015**, *5*, 1386.
(17) Conditions: 1.4 equiv of base and 5 equiv of methanol per PClB group, while the catalyst load is kept at 5 mol % regardless of the number of PClB groups in the molecule.