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A mild and efficient selective tetrahydropyranylation of primary alcohols and deprotection of THP ethers of phenols and alcohols using $PdCl_2(CH_3CN)_2$ as catalyst

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Abstract—Primary alcohols were selectively tetrahydropyranylated in good to excellent yields at room temperature using $PdCl_2(CH_3CN)_2$ as catalyst in tetrahydrofuran (THF) in the presence of phenols, secondary, and tertiary alcohols. The tetrahydropyranyl (THP) group could be efficiently removed using $PdCl_2(CH_3CN)_2$ as catalyst in CH_3CN, while other protection groups such as *p*-toluenesulfonyl (Ts), *tert*-butyldiphenylsilyl (TBDPS), benzyloxycarbonyl (Cbz), allyl, benzyl (Bn), and benzoyl (Bz) remained intact under these conditions.

The choice of protection and deprotection strategy in a synthetic sequence is inevitable, owing to chemoselective transformations in the presence of various functional groups.[1] The 2-tetrahydropyranyl ether is the most versatile protecting group for alcohols in organic syntheses because of its low cost, ease of installation, general stability to most nonacidic reagents and the ease with which it can be removed.[1] A variety of reagents have been developed to introduce the THP protection group, which include mainly protic acids,[2] Lewis acids,[3] basic conditions,[4] neutral conditions,[5] transition metal catalysts,[6] and heterogeneous catalysts.[7] On the other hand, a method that would effect the selective removal of tetrahydropyranyl (THP) ethers in the presence of other sensitive functional groups still remains as a goal. The deprotection of these ethers was carried out under acidic,[1,2d,i,l,6h,j,7e,8] neutral,[9] and reductive conditions.[10] $PdCl_2(CH_3CN)_2$ was reported to catalyze acetal/ketal hydrolysis/exchange reaction[11] and deprotect *tert*-butyldimethylsilyl (TBDMS) ethers.[12] These results promoted us to investigate the possibility of deprotecting THP ethers using $PdCl_2(CH_3CN)_2$. We were delighted to discover that THP ethers could be removed smoothly. Herein we report our results on chemoselective protection of primary alcohols to THP ethers in the presence of phenols, secondary, and tertiary alcohols, and on chemoselective removal of the THP protecting group in phenols and alcohols in the presence of other sensitive protecting groups by using $PdCl_2(CH_3CN)_2$ as the catalyst.

The investigation of reaction conditions for the protection of 2-phenylethanol (**1**) with DHP using $PdCl_2(CH_3CN)_2$ demonstrated that 0.1 equiv of palladium catalyst in anhydrous THF at room temperature was optimal for the desired tetrahydropyranylation (Table 1). Other palladium catalysts were utilized to protect alcohol **1** at the same reaction conditions. As the results showed in Table 2, $PdCl_2(CH_3CN)_2$ and $PdCl_2$ (Table 2, entries 1–3) were effective for this reaction while $Pd_2(dba)_3$, $Pd(OAc)_2$, and $Pd(PPh_3)_4$ were ineffective (Table 2, entries 3–5). Among the described palladium catalysts, $PdCl_2(CH_3CN)_2$ was the most effective.

This novel method for tetrahydropyranylation was applied to a variety of phenols and alcohols.[13] The protection of primary alcohols **3**–**6** by using $PdCl_2(CH_3CN)_2$ in anhydrous THF afforded the corresponding THP-protected alcohols in good to excellent yields (Table 3, entries 1–4). Notably, secondary alcohol **7**, tertiary alcohol **8**, and phenols **9**–**10** gave poor yields or did not react under the same conditions (Table 3, entries 5–8). We then investigated the possibility for selective tetrahydropyranylation of alcohols in the presence of phenols within the same molecules. The

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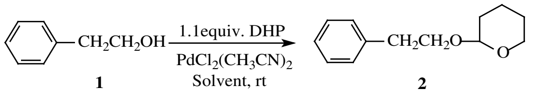
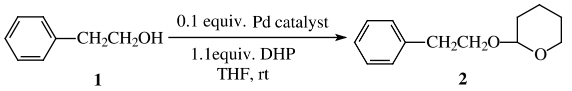
Table 1. Tetrahydropyranylation reactions of 2-phenylethanol catalyzed by $PdCl_2(CH_3CN)_2$ under a variety of conditions at room temperature



Entry	$PdCl_2(CH_3CN)_2$ (equiv)	Solvent	Reaction time (h)	Yield (%)[a]
1	0.1	THF	1.0	91
2	0.05	THF	3.5	80
3	0.1	Et_2O	12	22
4	0.1	CH_2Cl_2	1.0	84
5	0.1	Dioxane	5.5	67
6	0.1	CH_3CN	12	35
7	0.1	Acetone	1.0	85
8	0.1	DMF	12	39

[a] Isolated yield (average of two runs).

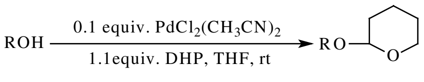
Table 2. Tetrahydropyranylation reactions of 2-phenylethanol catalyzed by a variety of palladium catalysts in THF at room temperature



Entry	Palladium catalyst	Reaction time (h)	Yield (%)[a]
1	$PdCl_2(CH_3CN)_2$	1.0	91
2	$PdCl_2$	12	85/trace[b]
3	$Pd_2(dba)_3$	12	No reaction
4	$Pd(OAc)_2$	12	Trace
5	$Pd(PPh_3)_4$	12	No reaction

[a] Isolated yield (average of two runs).
[b] Reaction was performed for 1 h.

Table 3. Tetrahydropyranylation of various phenols and alcohols catalyzed by $PdCl_2(CH_3CN)_2$ in THF at room temperature



Entry	Substrate		Reaction time (h)	Yield (%)[a]
1	$CH_3(CH_2)_6CH_2OH$	**3**	40 min	84
2	$C_6H_5CH_2OH$	**4**	1.0	72
3	$4\text{-}NO_2C_6H_4CH_2OH$	**5**	6.5	81
4	$C_6H_5CH_2CH_2OH$	**6**	1.0	90
5	*c*-$C_6H_{11}OH$	**7**	1.0	49
6	*t*-C_4H_9OH	**8**	48	Trace
7	$4\text{-}ClC_6H_4OH$	**9**	5.0	Trace
8	$4\text{-}CH_3OC_6H_4OH$	**10**	5.0	Trace

[a] Isolated yield (average of two runs).

results are summarized in Table 4. These results show a selective protection of primary alcohols in the presence of secondary, tertiary alcohols, and phenols.

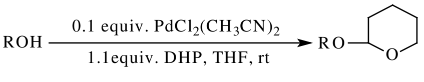
At the same time, the tetrahydropyranylation reaction using $PdCl_2(CH_3CN)_2$ could protect alcohols in the presence of other commonly used functional groups (Table 5). As the results show, under these reaction conditions, some other functional groups such as sulfonate (Ts, Table 5, entry 1), *tert*-butyldimethylsilyl (TBS, Table 5, entry 2), *tert*-butyldiphenylsilyl (Table 5, entry 3), benzyloxycarbonyl (Table 5, entry 4), allyl (Table 5, entry 5), and benzyl (Table 5, entry 6) are all stable.

We also investigated the possibility of deprotection of tetrahydropyranyl (THP) group using $PdCl_2(CH_3CN)_2$ as catalyst. It was found that the THP group could be removed efficiently by refluxing under 0.1 equiv $PdCl_2(CH_3CN)_2$ in wet CH_3CN. Some examples are listed in Table 6.[14]

The THP ethers of both phenols and primary alcohols could be deprotected in good to excellent yields under the reaction conditions, while the THP ethers of secondary and tertiary alcohols could not be deprotected in satisfied yields (Table 6, entries 5–6). At the same time, the chemoselective deprotection of THP ethers (**29**, **31**–**35**) in the presence of other commonly used functional groups within the same molecules was also investigated (Table 6, entries 9, 11–15). Our results showed that TBS ether **30** was hardly removed (Table 6, entry 10).

$PdCl_2(CH_3CN)_2$ is usually known as one of Lewis acid catalysts. However, the generation of protic acids through hydrolyis of metal complexes is a known, but often underestimated phenomenon in Lewis acid catalysis.

Table 5. Tetrahydropyranylation of alcohols in the presence of other commonly used functional groups catalyzed by $PdCl_2(CH_3CN)_2$ at room temperature



Entry	Substrate		Reaction time (h)	Yield (%)[a]
1	$TsO(CH_2)_6OH$	**15**	2.0	86
2	$TBSO(CH_2)_4OH$	**16**	1.0	80
3	$TBDPSO(CH_2)_4OH$	**17**	2.0	86
4	$CbzO(CH_2)_4OH$	**18**	1.5	79
5	$AllylO(CH_2)_4OH$	**19**	35 min	82
6	$BnO(CH_2)_4OH$	**20**	40 min	83

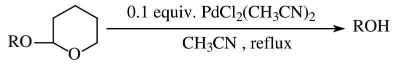
[a] Isolated yield (average of two runs).

Table 4. Chemoselective tetrahydropyranylation of alcohols in the presence of phenols catalyzed by $PdCl_2(CH_3CN)_2$ at room temperature

Entry	Substrate		Product		Reaction time (h)	Yield (%)[a]
1	*p*-$HOC_6H_4CH_2OH$	**11**	*p*-$HOC_6H_4CH_2OTHP$	**13**	2.5	79
2	*p*-$HOC_6H_4CH_2CH_2OH$	**12**	*p*-$HOC_6H_4CH_2CH_2OTHP$	**14**	5.5	90

[a] Isolated yield (average of two runs).

Table 6. Deprotection of tetrahydropyranyl ethers of phenols and alcohols catalyzed by $PdCl_2(CH_3CN)_2$



Entry	R		Reaction time (h)	Yield (%)[a]
1	$CH_3(CH_2)_6CH_2$	**21**	11.5	82
2	$C_6H_5CH_2$	**22**	11	75
3	$4\text{-}NO_2C_6H_4CH_2$	**23**	11	87
4	$C_6H_5CH_2CH_2$	**24**	15	93
5	$c\text{-}C_6H_{11}$	**25**	18	37
6	$t\text{-}C_4H_9$	**26**	48	Trace
7	$4\text{-}ClC_6H_4$	**27**	6.0	95
8	$4\text{-}CH_3OC_6H_4$	**28**	6.0	91
9	$TsO(CH_2)_6$	**29**	14	89
10	$TBSO(CH_2)_4$	**30**	12	Trace[b]
11	$TBDPSO(CH_2)_4$	**31**	16	72
12	$CbzO(CH_2)_4$	**32**	13	85
13	$AllylO(CH_2)_4$	**33**	11	59
14	$BnO(CH_2)_4$	**34**	12	80
15	$BzO(CH_2)_4$	**35**	8.0	88[c]

[a] Isolated yield (average of two runs).

[b] TBS was deprotected under the reaction conditions.

[c] The product is 4-benzoyl-1-butanol (**36**).

Recently, Spencer and co-workers[15] demonstrated that protons, rather than metal ions, were the active catalysts in $PdX_2(CH_3CN)_2$ mediated hetero-Michael addition reactions in the presence of small amount of water. Based on these facts, it is possible that protons from the hydrolyis of $PdCl_2(CH_3CN)_2$ in CH_3 CN (with a small amount of water) under reflux act as the active catalysts in our deprotection reaction. The researches on the mechanism of this catalytic reaction are in progress.

In conclusion, we have developed an efficient and facile method for the formation and cleavage of THP ethers. Primary alcohols could be chemoselectively tetrahydropyranylated in the presence of phenols, secondary, and tertiary alcohols by using $PdCl_2(CH_3CN)_2$ in anhydrous THF at room temperature. Meanwhile, chemoselective deprotection of THP ethers of phenols and primary alcohols was achieved using $PdCl_2(CH_3CN)_2$ in wet MeCN at reflux temperature. The THP-protected secondary and tertiary alcohols as well as Ts-, TBDPS-, Bn-, Allyl-, Bz-, and Cbz-protected alcohols are stable under these conditions.

Acknowledgements

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13. General procedure: a mixture of alcohol **1** (122 mg, 1 mmol), DHP (92 mg, 1.1 mmol), and $PdCl_2(CH_3CN)_2$ (26 mg, 0.1 mmol) in anhydrous THF (1.0 mL) was stirred at room temperature under nitrogen until the reaction was finished as indicated by thin-layer chromatography (TLC). The reaction mixture was filtered through Celite, and THF was removed under reduced pressure. The crude material was extracted with ethyl acetate, washed with water and brine. After drying (Na_2SO_4) and solvent removal, the crude product was purified by flash column chromatography over silica gel using ethyl acetate/hexane (1:20) as eluent to afford the corresponding THP ether **2** (188 mg, 91%).
14. General procedure: a mixture of THP ether **2** (206 mg, 1 mmol) and $PdCl_2(CH_3CN)_2$ (26 mg, 0.1 mmol) in wet CH_3CN (1.0 mL) was refluxed until the reaction was finished as indicated by thin-layer chromatography (TLC). The reaction mixture was filtered through Celite, and the CH_3CN removed under reduced pressure. The residue was extracted with ethyl acetate, washed with water and brine. After drying (Na_2SO_4) and solvent removal, the crude product was purified by flash column chromatography over silica gel using ethyl acetate/hexane (1:20) as eluent to afford the corresponding alcohol **1** (113 mg, 93%).
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