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Selective tetrahydropyranylation of alcohols and phenols using titanium(IV) salophen trifluoromethanesulfonate as an efficient catalyst

Maryam Yadegari* and Majid Moghadam

Titanium(IV) salophen trifluoromethanesulfonate, [Ti^{IV}(salophen)$(OSO_2CF_3)_2$], as a catalyst enables selective tetrahydropyranylation of alcohols and phenols with 3,4-dihydro-2*H*-pyran. Using this catalytic system, primary, secondary and tertiary alcohols, as well as phenols, were converted to their corresponding tetrahydropyranyl ethers in high yields and short reaction times at room temperature. Investigation of the chemoselectivity of this method showed discrimination between the activity of primary alcohols in the presence of secondary and tertiary alcohols and phenols. This heterogenized catalyst could be reused several times without loss of its catalytic activity. Copyright © 2016 John Wiley & Sons, Ltd.

Keywords: titanium Schiff base; alcohol; phenol; 3,4-dihydro-2*H*-pyran; tetrahydropyranyl ether

Introduction

The ability to recover a catalyst and reducing the amount of toxic waste must be considered as two important features when designing a catalytic synthesis system. Various heterogeneous solid support systems as catalysts are not environmentally suitable and use of large amounts of them, in the long run, results in a high quantity of toxic waste output. Metal Schiff base complexes, especially heterogeneous instances, with simple recovery capability can provide efficient catalysts. Salophen and salen tetradentate ligands with N_2O_2 arrangement and electron-deficient complexes have also been used to catalyse a wide variety of important chemical transformations, including oxidation of alcohols, sulfides, amines, alkanes and alkenes by complexes of chromium, iron, magnesium, ruthenium, cobalt and vanadium,[1] and titanium Schiff base complexes have also been used in developing reactions. For example, titanium binaphthyl-bridged Schiff base complex in regio and stereoselective epoxidation of allylic alcohols[2] and in oxidation of sulphides,[3] Ti(salen) complex in asymmetric ring opening of epoxides[4] and pinacol coupling reaction[5] and heterobimetallic Ti–Ga–salen system in enantioselective ring-opening reaction[6] could be mentioned.

Many protective groups have been developed for temporary blocking of reactive sites in multi-step reactions. For proposing a synthetic scheme, many factors must be considered like reaction conditions, reactants and their functional groups and compatibility of protective groups with reaction conditions. Hence, there is always a need for selective reagents. Tetrahydropyranylation of hydroxyl groups can be a good choice especially for most nonacidic reagents. Facile deprotection under mild acidic conditions is another advantage for this protecting route.[7]

Lewis acid and protonic catalysts such as $Bu_4N^+Br_3^-$,[8] $AlCl_3{\cdot}6H_2O$,[9] bis(trimethylsilyl)sulfate,[10] vanadyl(IV) acetate,[11] $K_5CoW_{12}O_{40}{\cdot}3H_2O$,[12] $In(OTf)_3$,[13] LiOTf,[14] $PdCl_2(CH_3CN)_2$,[15] $AlCl_3$@polystyrene,[16] $H_6P_2W_{18}O_{62}$,[17] silica-based sulfonic acid,[18,19] and homogeneous and heterogeneous [Sn^{IV}(TPP)$(OTf)_2$][20,21] and [V^{IV}(TPP)$(OTf)_2$][22] have been developed for tetrahydropyranylation of alcohols and phenols.

In the course of our studies on titanium salophen-catalysed reactions, we found them to be effective in catalysing acetylation and trimethylsilylation of alcohols and phenols and conversion of aldehydes to 1,1-diacetates.[23–25] Now we have extended the application of titanium salophen-catalysed reactions to tetrahydropyranylation of alcohols and phenols.

Experimental

All chemicals were purchased from Merck or Fluka. Fourier transform infrared spectra were obtained with potassium bromide pellets in the range 400–4000 cm^{-1} with a Nicolet Impact 400D spectrometer. GC experiments were performed with a Shimadzu GC-16 A instrument using a 2 m column packed with silicon DC-200 or Carbowax 20 m. In the GC experiments, *n*-decane was used as an internal standard. ^{1}H NMR spectra were recorded with a Bruker Avance AQS 400 MHz spectrometer.

* *Correspondence to: Maryam Yadegari, Department of Environmental Chemistry, Isfahan (Khorasgan) Branch, Islamic Azad University, Isfahan, Iran. E-mail: mym_yadegari@yahoo.com*

Department of Environmental Chemistry, Isfahan (Khorasgan) Branch, Islamic Azad University, Isfahan, Iran

Preparation of catalyst

After synthesis of salophen,[26] $[Ti^{IV}(salophen)(OSO_2CF_3)_2]$ as a catalyst was prepared according to the literature.[27]

General procedure for tetrahydropyranylation of alcohols and phenols with 3,4-Dihydro-2*H*-pyran (DHP) catalysed by $[Ti^{IV}(salophen)(OSO_2CF_3)_2]$

In a typical procedure, a solution of alcohol or phenol (1 mmol), $[Ti^{IV}(salophen)(OSO_2CF_3)_2]$ (0.01 mmol) and DHP (2 mmol per OH group) in CH_2Cl_2 (1 ml) was prepared and stirred at room temperature for an appropriate time. The progress of the reaction was monitored by GC and TLC. After completion of the reaction, the solvent was evaporated, *n*-hexane (10 ml) was added and the catalyst was filtered. The filtrates were washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure to afford the crude product, which was confirmed using ^1H NMR and IR spectral data.

Results and discussion

Tetrahydropyranylation of alcohols and phenols with DHP catalysed by $[Ti^{IV}(salophen)(OSO_2CF_3)_2]$

First, for optimization of the reaction parameters, tetrahydropyranylation of 4-chlorobenzyl alcohol with DHP was performed with various solvents and catalyst amounts. Among CH_2Cl_2, CH_3CN, EtOAc, chloroform and *n*-hexane, a higher yield was obtained in CH_2Cl_2 (Table 1). Since the catalyst has a heterogeneous nature in CH_2Cl_2, catalyst recovery in this solvent is simpler, and CH_2Cl_2 was used subsequently as a solvent. The presence of 0.01 mol of $[Ti^{IV}(salophen)(OSO_2CF_3)_2]$ for each mole of substrate (1 mol%) gave the highest yield. The amount of DHP was also optimized and the best result was obtained with a 2:1 molar ratio of DHP to alcohol as summarized in Table 2. Another factor investigated in this work is the effect of OSO_2CF_3 groups (OTf) on the catalytic activity of $[Ti^{IV}(salophen)(OSO_2CF_3)_2]$. For this purpose, the effect of introducing different groups such as Cl and OPh to the Ti(salophen) was compared with OTf groups in the tetrahydropyranylation of 4-chlorobenzyl alcohol with DHP. The

Table 1. Effect of solvent on the tetrahydropyranylation of 4-chlorobenzyl alcohol with DHP catalysed by $[Ti^{IV}(salophen)(OSO_2CF_3)_2]$[a]

Entry	Solvent	Time (min)	Yield (%)[b]
1	CH_2Cl_2	6	90
2	CH_3CN	6	79
3	EtOAc	6	38
4	$CHCl_3$	6	28
5	*n*-Hexane	6	16

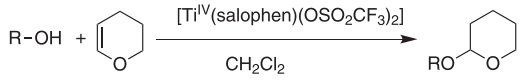
[a]Reaction conditions: 4-chlorobenzyl alcohol (1 mmol), catalyst (1 mol %), DHP (2 mmol), solvent (0.5 ml).
[b]Isolated yield.

Table 2. Effect of amount of DHP and $[Ti^{IV}(salophen)(OSO_2CF_3)_2]$ on the tetrahydropyranylation of 4-chlorobenzyl alcohol[a]

Entry	Solvent	Catalyst (mol%)	DHP/substrate (mmol)	Time (min)	Yield (%)[b]
1	CH_2Cl_2	2	2:1	6	90
2	CH_2Cl_2	1	2:1	6	90
3	CH_2Cl_2	0.5	2:1	6	75
4	CH_2Cl_2	1	3:1	6	90
5	CH_2Cl_2	1	1:1	6	78

[a]Reaction conditions: 4-chlorobenzyl alcohol, catalyst, DHP, solvent (0.5 ml).
[b]Isolated yield.

Table 3. Tetrahydropyranylation of alcohols catalysed by $[Ti^{IV}(salophen)(OSO_2CF_3)_2]$ at room temperature[a]



Entry	R	Time (min)	Yield (%)[b]
1	$C_6H_5CH_2$	4	90
2	$C_6H_5CH_2CH_2$	4	98
3	$C_6H_5CH_2CH_2CH_2$	4	95
4	2-$CH_3C_6H_4CH_2$	1	100
5	2-$CH_3OC_6H_4CH_2$	2	99
6	4-$NO_2C_6H_4CH_2$	2	100
7	3-$NO_2C_6H_4CH_2$	1	95
8	4-$ClC_6H_4CH_2$	6	90
9	2-$BrC_6H_4CH_2$	7	95
10	2-$NO_2C_6H_4CH_2$	16	80
11	4-$HOC_6H_4CH_2$	1	80
12	4-$CH_3OC_6H_4CH_2$	10	70
13	4-$FC_6H_4CH_2$	1	50
14	*n*-Octyl	6	96
15	$C_6H_5CH_2C(CH_3)_2$	4	98
16	Diphenylmethyl	20	90
17	Cyclohexyl	3	90
18	*t*-Butyl	9	90
19	1-Adamantyl	11	90

[a]Reaction conditions: alcohol (1 mmol), DHP (2 mmol), catalyst (1 mol%), CH_2Cl_2 (1 ml).
[b]Isolated yield.

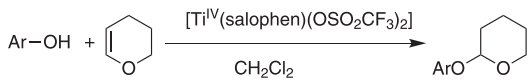
Table 4. Comparison of results obtained for tetrahydropyranylation of 4-nitrobenzyl alcohol catalysed by $[Ti^{IV}(salophen)(OSO_2CF_3)_2]$ with those obtained using recently reported catalysts

Entry	Catalyst	Catalyst (mol%)	*T* (°C)	Time (min)	Yield (%)	Ref.
1	$[Ti^{IV}(salophen)(OSO_2CF_3)_2]$	1	RT	2	100[a]	This work
2	$PdCl_2(CH_3CN)_2$	10	RT	390	81[a]	[15]
3	$[Sn^{IV}(TPP)(OTf)_2]$	1	RT	6	60[a]	[20]
4	$[Sn^{IV}(TNH_2PP)(OTf)_2]$ @CMP	1	RT	6	62[a]	[21]
5	Ps–$AlCl_3$	15	RT	90	91[a]	[16]
6	Silica chloride	10 mg	RT	15	92[a]	[28]
7	LiOTf	60	Reflux	180	92[a]	[14]
8	$K_5CoW_{12}O_{40}{\cdot}3H_2O$	1	RT	10	80[b]	[12]

[a]Isolated yield.
[b]GC yield.

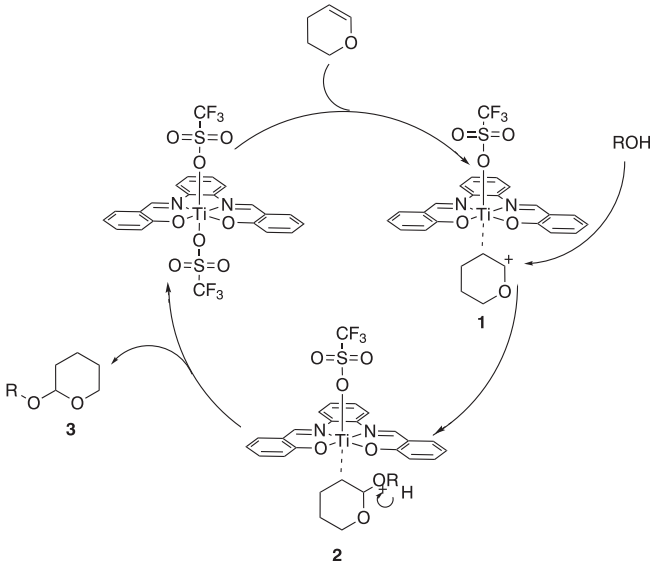
results of reactions are, respectively, 90, 51 and 29% for $[Ti^{IV}(salophen)(OSO_2CF_3)_2]$, $[Ti^{IV}(salophen)Cl_2]$ and $[Ti^{IV}(salophen)(OPh)_2]$. The order of activity of these catalysts clearly shows that by increasing the electron deficiency of the catalyst, catalytic activity increases.

Table 5. Tetrahydropyranylation of phenols with DHP catalysed by $[Ti^{IV}(salophen)(OSO_2CF_3)_2]$ at room temperature[a]



Entry	Ar	Time (min)	Yield (%)[b]
1	C_6H_5	5	97
2	4-ClC_6H_4	5	92
3	4-$NO_2C_6H_4$	20	67
4	4-$CH_3C_6H_4$	4	93
5	1-Naphthyl	7	90
6	3-$CH_3C_6H_4$	4	90
7	2-ClC_6H_4	7	90

[a]Reaction conditions: phenol (1 mmol), DHP (2 mmol), catalyst (1 mol%), CH_2Cl_2 (1 ml).
[b]Isolated yield.



Scheme 1. Proposed mechanism for tetrahydropyranylation of alcohols and phenols with DHP catalysed by $[Ti^{IV}(Salophen)(OSO_2CF_3)_2]$.

Under the optimized conditions, numerous types of primary, secondary and tertiary alcohols were transformed to their corresponding tetrahydropyranyl ethers in the presence of catalytic amounts of $[Ti^{IV}(salophen)(OSO_2CF_3)_2]$ at room temperature. The results, which are summarized in Table 3, showed that all primary, secondary and tertiary alcohols including aromatic, aliphatic and cyclic ones were converted efficiently to their corresponding tetrahydropyranyl ethers.

In the case of aromatic alcohols, the nature of substituents has no significant effect on the tetrahydropyranylation yield. But some derivatives of benzyl alcohol lead to very large yields. For example, 4-nitrobenzyl alcohol, 2-methoxybenzyl alcohol and 2-methylbenzyl alcohol give excellent yields in short reaction times. In order to show the advantage of this method, the tetrahydropyranylation of 4-nitrobenzyl alcohol with DHP catalysed by $[Ti^{IV}(salophen)(OSO_2CF_3)_2]$ is compared with some other available catalysts (Table 4). The results show that the present catalyst is superior in terms of catalyst amount, reaction time and product yield and also reusability. Therefore, this method can beneficial for alcohols that have been less perused or there are no eligible reports about them.

The tetrahydropyranylation of various phenols was also examined under the same reaction conditions as those applied for alcohols. The corresponding tetrahydropyranyl ethers were produced in high yields and short reaction times (Table 5).

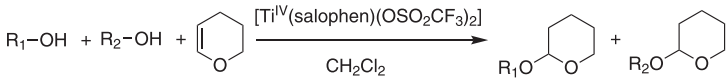
As shown in Scheme 1, a possible mechanism for these reactions is that DHP is first activated by $[Ti^{IV}(Salophen)(OTf)_2]$ to afford reactive agent **1**. Nucleophilic attack of alcohol on **1** affords **2** and final product **3** is formed after proton transfer, simultaneously releasing the catalyst for the next cycle.

It is noteworthy that this catalyst can be used for chemoselective tetrahydropyranylation of primary alcohols in the presence of secondary and tertiary alcohols and phenols (Table 6). The results indicated that primary alcohols are more reactive in the presence of secondary and tertiary alcohols and phenols.

Catalyst reusability

The reusability of $[Ti^{IV}(salophen)(OSO_2CF_3)_2]$ was also investigated in the multiple pyranylation of 4-chlorobenzyl alcohol with DHP under the optimized conditions. Then, the solvent was evaporated, and the catalyst was washed with Et_2O, filtered, dried and reused. It was observed that the activity of the catalyst did not decrease after four consecutive runs.

Table 6. Selective pyranylation of alcohols and phenols catalysed by $[Ti^{IV}(salophen)(OSO_2CF_3)_2]$ in CH_2Cl_2[a]



Entry	R_1	R_2	Time (min)	Yield 1 (%)[b]	Yield 2 (%)[b]
1	$C_6H_5CH_2$	$(Ph)_2CH$	4	90	10
2	$C_6H_5CH_2$	$C_6H_5CH_2C(CH_3)_2$	4	90	0
3	$C_6H_5CH_2$	*n*-Octyl	4	90	30
4	$C_6H_5CH_2$	C_6H_5	4	90	15

[a]Reaction conditions for a binary mixture: 1 mmol of each alcohol or phenol, DHP (2 mmol), catalyst (1 mol%), CH_2Cl_2 (1 ml).
[b]Isolated yield.

Conclusions

In this work, an efficient approach for tetrahydropyranylation of alcohols and phenols is presented. This catalytic system showed a good catalytic activity in these reactions.

Excellent yields, selectivity, easy work-up, extremely mild reaction conditions, applicability for alcohols and phenols, low amount required for reactions and reusability without significant decrease in initial activity are unique features and noteworthy advantages of this heterogeneous catalyst.

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