Highly efficient deprotection of phenolic tetrahydropyranyl and methoxymethyl ethers and sequel cyclization to indanones using $Sn(IV)Cl_4$ catalyst

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Highly efficient deprotection of phenolic tetrahydropyranyl and methoxymethyl ethers and sequel cyclization to indanones using $Sn(IV)Cl_4$ catalyst

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Abstract:

$Sn(IV)Cl_4$ catalyst provided a rapid and efficient deprotection method for the phenolic THP and MOM ethers and sequel intramolecular Friedel-Crafts alkylation reaction of THP and MOM protected chalcone epoxides under mild conditions. The reaction took 2-3 min to give the products in excellent yield (90-98%) at 0 ^{0}C without affecting the other functional groups.

Keywords*:* Alcohol, Phenol, $SnCl_4$, detetrahydropyranylation, demethoxymethylation, Friedel-Crafts alkylation.

Protection-deprotection of the functional groups is the most frequent used strategies in the multi-steps organic syntheses. In particular, the protection and the deprotection of hydroxyl group is extremely important because of its enormous demand for the synthesis of a number of compounds of biological and synthetic interest such as carbohydrates, macrolides, peptides, steroids, nucleotides and polyethers.[1] The protection of hydroxyl groups with 3,4-dihydro-2H-pyran is the most frequent used method due to stability of the resulting 2-tetrahydropyranyl ethers (THPEs) in the presence of strong bases or nucleophiles such as Grignard reagents, organolithium compounds, metal hydrides, catalytic hydrogenation, alkylating and acylating

agents.[2] Similarly, methoxymethyl chloride (MOMCl) is an another important reagent for the hydroxyl group protection.[3]

The deprotection of THP and MOM ethers therefore required efficient methods to avoid the decomposition of the products and/or loss of other functional groups in the products under harsh reaction conditions. Therefore, several catalysts have been explored for the detetrahydropyranylation of alcohols and phenols that include protic acids,[4] Lewis acids like BF_3-etherate,[5] LiBr,[6] $LiBF_4$,[7] LiOTf,[8] $LiClO_4$,[9] $Sc(OTf)_3$,[10] $In(OTf)_3$,[11] I_2,[12] $InCl_3$,[13] $ZrCl_4$,[14] $CuCl_2$,[15] and NH_4Cl,[16] expansive graphite,[17]clay materials,[18] silica-supported sulfuric acid,[19] and other miscellaneous catalysts.[20-25] Similarly, many catalysts have been used for the demethoxymethylation of alcohols and phenols such as HCl, BBr_3, pyridinium *p*-toluene sulphonate under strong acidic condition, mild Lewis acids $ZnBr_2$, and $TiCl_4$ in aprotic conditions and BBr_3 derivatives Me_2BBr, and $(i\text{-}PrS)_2BBr$.[26] Most of these methods have different drawbacks such as longer reaction time, low yields, refluxing at high temperature and the tedious work-up procedures. Hence, there is still a scope to develop mild and efficient methods in the deprotection of tetrahydropyranyl and methoxymethyl ethers.

In continuation of our interest to develop new methods for the synthesis and the acid catalysis reactions,[27] herein, we report an efficient deprotection method of the THP and the MOM ethers and sequel Friedel-Crafts alkylation reaction of the protected THP and MOM chalcone epoxides using $SnCl_4$ catalyst under mild reaction conditions.

The catalytic efficiency of different metal halides was screened (Table 1). The metal halides (Table 1, entries 1-5) showed poor to moderate catalytic activity. $InCl_3$ (Table 1, entry 6) was found to be a better catalyst at 10 mol% catalyst loading, which gave 90% yield of the cyclized products without deprotecting the THP or the MOM ethers. However, the reaction was

completed in 4-5 hours. $SnCl_4$ (Table 1, entries 7, 8) at less than 10 mol% catalyst loading gave lower yields in a longer reaction time. $SnCl_4$ (Table 1, entry 9) at 10 mol% catalyst loading was found to be the most efficient catalyst, which gave the optimal yield (98%) with deprotecting the THP and the MOM ethers within 2-3 min. Further, increase in the catalyst loading of $SnCl_4$ (Table 1, entry 10) gave the side-product as 3-(4-chlorophenyl)-2-chloro-2,3-dihydro indan-1-one along with the desider product. We also applied SnI_4 and $SnBr_4$ in 5, 10, and 20 mol% catalysts loading during the deprotection of THP and MOM ethers. However, it gave the desired products only 5-10% yields after stirring for 2-6 h at 0 ^oC.

[Table 1]

We observed the solvent effects using different solvents like CH_3COCH_3, $CHCl_3$, CH_2Cl_2 and THF. $CHCl_3$ and CH_2Cl_2 were found to be the desired solvents (Table 2, entries 4, 6).

[Table 2]

Under optimized reaction conditions, the deprotection of THP and MOM ethers in phenols, chalcone and chalcone epoxides were achieved using 10 mol% of $SnCl_4$ in excellent yields (90-98%) within 2-3 min at 0 ^0C in the presence of other functional groups. However, in the case of alcoholic THP and MOM ethers, even 20 mol% of catalyst loading gave less yield 10 and 25% respectively (Table 3, entry 1). In case of chalcones **6**-**13**, only THP or MOM removal was observed without intramolecular Friedel-Crafts alkylation. These products were characterized by comparing their physical and spectral data with the literature values.[22,28] Interestingly, the THP and MOM removal followed by the Friedel-Crafts alkylation was observed for the chalcone epoxides which gave the corresponding indanones **14-19** in excellent yield (90-98%) within 2-3 min at 0^oC (Table 3).

[Table 3]

The stereochemistry and the diastereomeric excess ratio of the indanone derivatives **14**-**19** were determined by the chiral column separation of racemic mixture of diastereomers. For example, in the synthesis of racemic indanone 3-(4-bromophenyl)-2-hydroxy-2, 3-dihydroindan-1-one (Scheme 1), the chiral HPLC purification gave peaks at 40.14 (51%) and 56.43 (49%) min. for the diastereomers (See Supporting Information). Then, we synthesized enantiomerically excess (ee) *trans*-chalcone epoxide of 2R, 3S-configuration from chalcone with α,α'-diphenyl-L-prolinol and TBHP in hexane which gave a good yield (58%) with 77.6% ee (Scheme 1). Asymmetric epoxides were characterized by comparing with the literature value of ^{1}H-NMR and enantiomeric excess was determined by chiral HPLC column and optical rotation in chloroform.[24]

[Scheme 1]

It was observed that during the ring opening of epoxides, the C-2 configuration remained same while the C-3 configuration changed due to S_N1-like mechanism therefore it gave the regio- and stereoselective intramolecular Friedel-Crafts alkylation. The protons at C-2 and C-3 positions are in *trans*-orientation which is confirmed by the coupling constant (J = 2.0 Hz) in ^{1}H-NMR spectrum. [24] The absolute configurations at C-2 and C-3 are confirmed as 2*R* and 3*S* respectively. The stereoselectivity and high yields for 1-indanones under acidic condition ($SnCl_4$) might be due to the variable oxidation state and availability of relatively low energy 5d-orbitals on tin. On ligation with epoxide oxygen, the tetrahedron structure of $SnCl_4$ was converted to a trigonal bipyramid/octahedron structure. This geometrical change enhanced the steric hindrance which results in a faster epoxide ring opening from β-carbon due to considerable electron deficient character at benzylic carbon. Therefore, the nucleophile attacked at β-carbon of carbonyl group.

A proposed reaction mechanism is shown in Scheme 2 for the MOM ether deprotection and the sequel intramolecular Friedel-Crafts alkylation, where ligation of $SnCl_4$ with MOM oxygen resulted in the removal of the methyl (methylene) oxonium group followed by its reaction with Cl^- generated the MOMCl.[23] Same time, the epoxide oxygen ligation with $SnCl_4$ might change the tetrahedron structure of $SnCl_4$ into trigonal bipyramid/octahedron structure. The geometry changes enhanced the steric hindrance which results in faster epoxide ring opening from *β*-carbon due to considerable electron deficient character at benzylic position not on α-carbon due to a 4-membered cyclobutanone (unstable intermediate). Therefore, the nucleophilic attack took place at *β*-carbon of carbonyl which gave a resonance stabilized benzyl intermediate. Finally, a base hydrolysis regenerated $SnCl_4$ catalyst which is used in the next catalytic-cycle.

[Scheme 2]

In conclusion, we have illustrated an optimized reaction conditions for the rapid and efficient deprotection of the phenolic THP and MOM ethers and sequel intramolecular Friedel-Crafts alkylation reaction of chalcone epoxides. All reactions were completed within 2-3 min and gave excellent yield (90-98%) at 0 ^{0}C for both the THP and the MOM ethers and sequel cyclization reactions without affecting the other functional groups.

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Supplementary Material

Experimental procedures and the characterization data ^{1}H, ^{13}C NMR spectra and chiral HPLC chromatogram associated with this article are available.

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28. General procedure for the deprotection of tetrahydropyranyl and methoxymethyl ethers of alcohols and phenols: $SnCl_4$ (10 moles %) was added to a stirred solution of THP/MOM

ethers (1 mmol) in CH_2Cl_2 (5 mL) at 0 °C. TLC monitoring, the reaction mixture was poured into 10% aqueous Na_2CO_3 solution and extracted with CH_2Cl_2. The combined organic layer was washed with brine solution, dried with anhyd. Na_2SO_4 and concentrated in *vacuo* to afford the corresponding alcohol or phenol, which was purified by silica gel column chromatography with hexane-EtOAc eluent to obtain the products **1**-**19** in excellent yield (90-98%). Characterization for example, *(E)-1-(4-chlorophenyl)-3-(4-hydroxy phenyl)prop-2-en-1-one(11):* ^{1}H NMR ($CDCl_3$, 500 MHz) δppm7.87 (d, *J* = 8.5 Hz, 2H), 7.54 (d, J = 8.5 Hz, 1H), 7.06 (d, 9 Hz, 1H), 6.95 (d, *J* = 9 Hz, 2H), 6.40 (s, 1H) 5.29 (t,7 Hz,1H), 5.22 (d, J = 1.5 Hz,1H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ ppm 195.55, 161.83, 137.36, 131.82, 131.42, 129.79, 125.99, 123.01, 116.23, 76.32, 63.53. GC-MS(m/z): 258 [$M^{+\cdot}$,$C_{15}H_{11}FO_3$]. *3-(4-bromophenyl)-2,5-dihydroxy-2,3-dihydroinden-1-one (13):* ^{1}H NMR ($CDCl_3$, 500 MHz) δppm 7.86 (d, *J* = 8.5 Hz, 2H), 7.54-7.52 (m, 1H), 7.05 (t, 7 Hz,1H), 6.95 (d, *J* = 9 Hz, 2H), 6.42 (s, 1H), 5.29 (t,7 Hz,1H), 5.22 (d, J = 1.5 Hz,1H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ ppm 195.57, 161.85, 137.38, 131.84, 131.45, 129.81, 126.01, 123.04, 116.25, 75.40, 63.55. GC-MS (m/z): 318 [$M^{+\cdot}$, $C_{15}H_{11}BrO_3$], 320 [M+2].

Caption to illustrations

Table 1. Optimization conditions in deprotection of the THP and the MOM ethers and sequel cyclization of phenolic compounds with different catalysts

Table 2. Solvent effects on yields in deprotection of the THP and the MOM ethers and sequel cyclization reaction

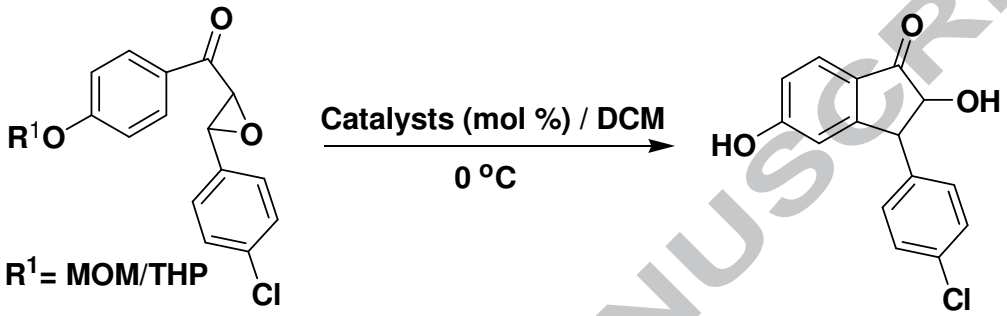
Table 3. Examples of the THP and MOM ethers deprotection and sequel cyclization reaction

Scheme 1. Synthesis of diastereoisomerically pure trans-3-(4-bromophenyl)-2-hydroxy-2,3-

dihydroindan-1-one

Scheme 2. A propose mechanism for the deprotection of MOM ethers followed by cyclization with $SnCl_4$

Table 1. Optimization conditions in deprotection of the THP and the MOM ethers and sequel cyclization of phenolic compounds with different catalysts



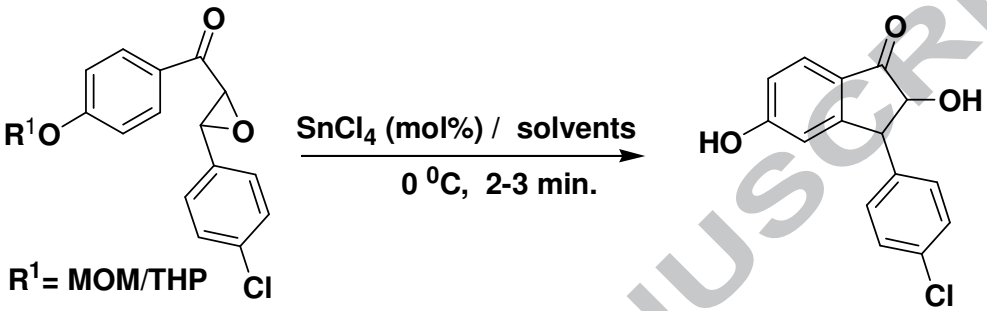
Entry	Catalyst	Mol %	Time	Yield (%)
1	$SbCl_3$	10	20-24 h	28[a]
2	SnI_4	10	6 h	7[b]
3	$SbCl_5$	10	20-24 h	20[a]
4	$MgCl_2$	10	18-24 h	18[a]
5	$SnBr_4$	10	6 h	10[b]
6	**$InCl_3$**	**10**	**4-5 h**	**90**[a]
7	$SnCl_4$	1	3 min	75[b]
8	$SnCl_4$	5	2 min	90[b]
9	**$SnCl_4$**	**10**	**3 min**	**98**[b]
10	$SnCl_4$	20	3 min	70+20[c]

[a] Gave only cyclization.

[b] Gave both THP and MOM ethers deprotection and sequel cyclization.

[C] Other product as 3-(4-chlorophenyl)-2-chloro-2,3-dihydro indan-1-one (20%).

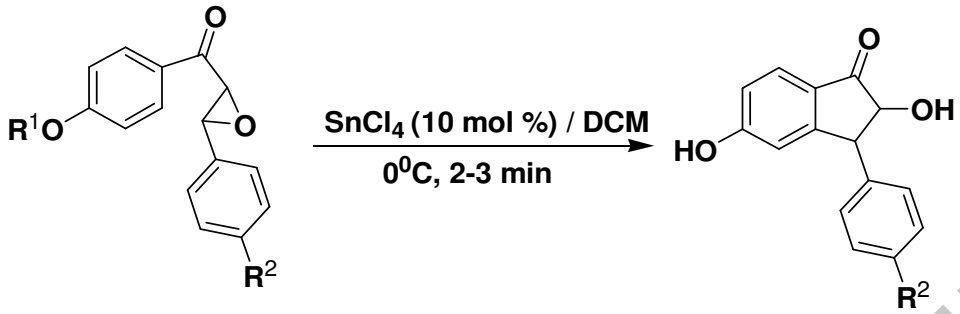
Table 2. Solvent effects on yields in deprotection of the THP and the MOM ethers and sequel cyclization reaction



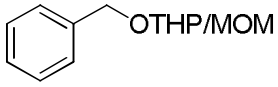
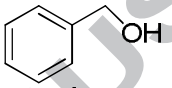
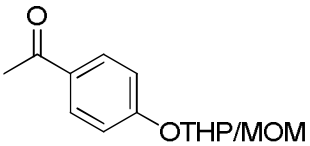
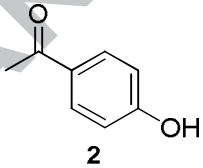
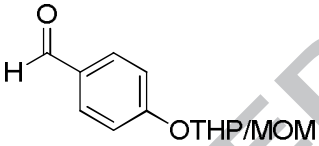
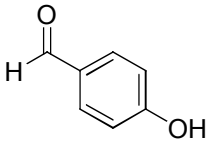
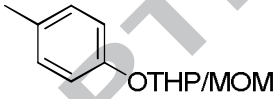
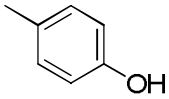
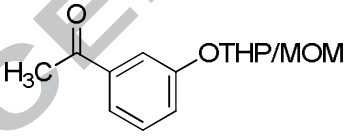
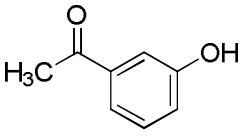
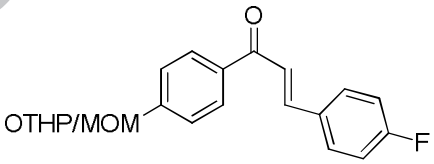
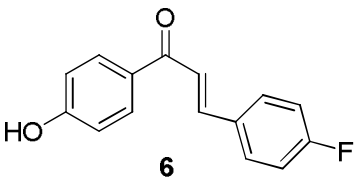
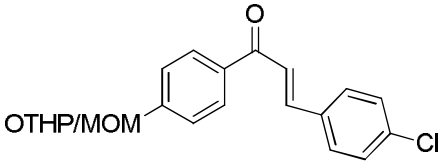
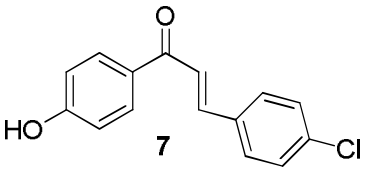
Entry	Mol%	Solvents	Yield (%)
1	1	Acetone	40[a]
2	5	Acetone	45 [a]
3	2	DCM	80 [b]
4	**10**	**DCM**	**98 [b]**
5	2	$CHCl_3$	85 [c]
6	**10**	**$CHCl_3$**	**96 [c]**
7	5	THF	52 [d]
8	10	THF	60 [d]

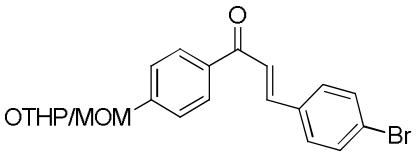
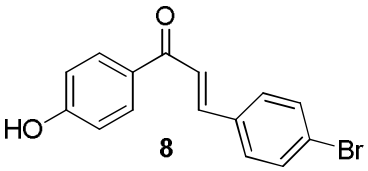
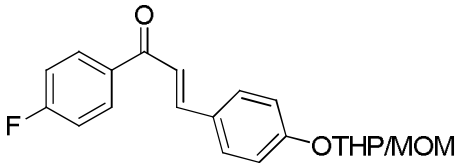
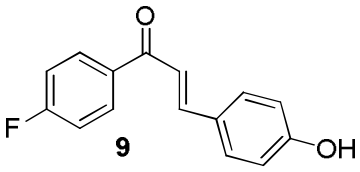
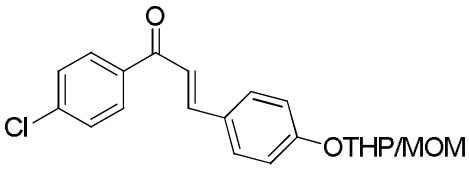
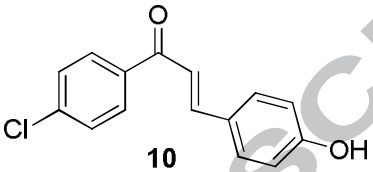
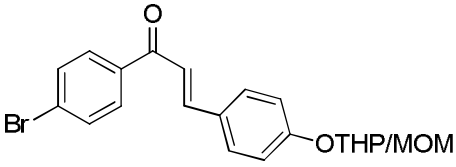
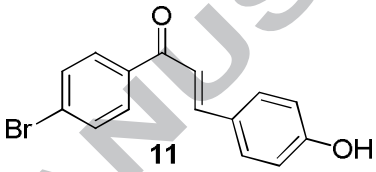
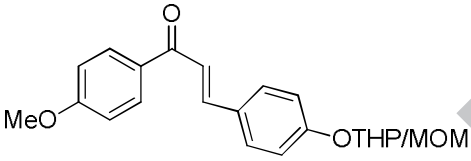
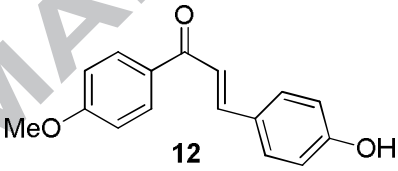
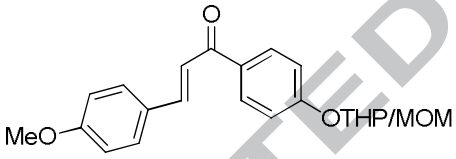
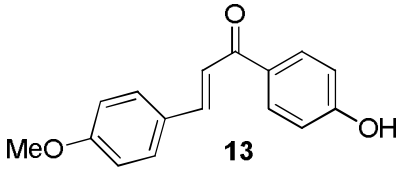
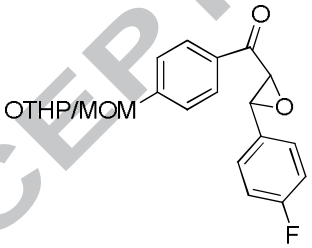
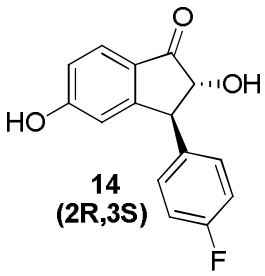
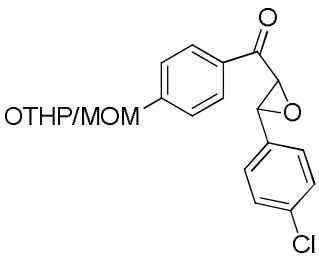
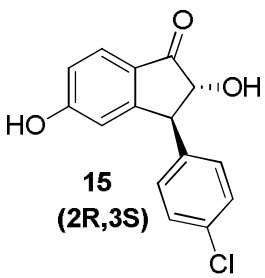
Reaction time: [a] 2h, [b,c] 3 min, [d] 3 h.

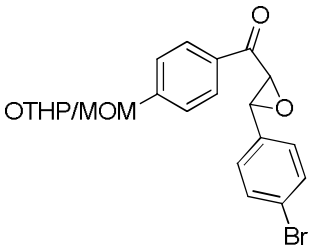
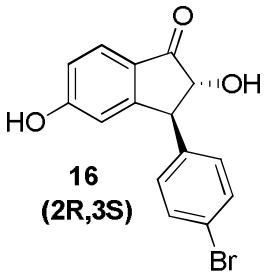
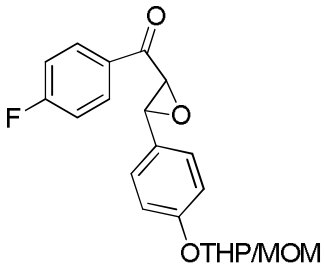
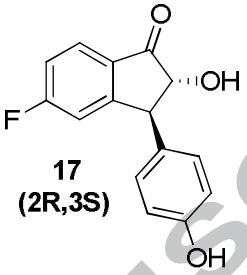
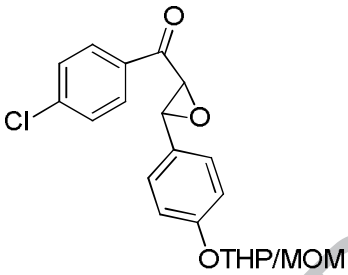
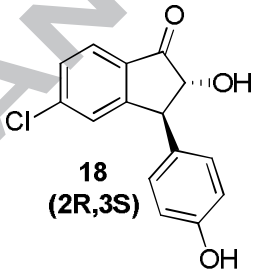
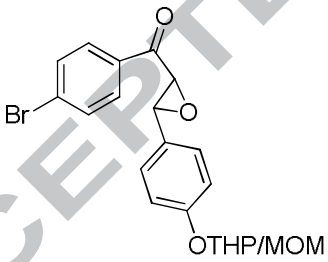
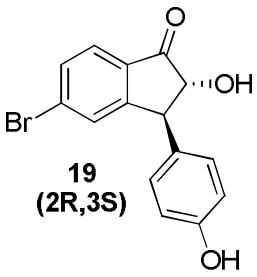
Table 3. Examples of the THP and MOM ethers deprotection and sequel cyclization reaction



214 **R^1= THP/MOM**

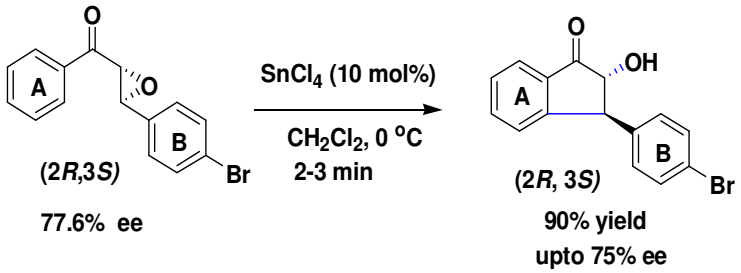
Entry	ROTHP/MOM	ROH	Time (min)	Yield (%)[a]	Yield (%)[b]
1		 **1**	2	10	25
2		 **2**	2	95	92
3		 **3**	2	96	95
4		 **4**	2	92	95
5		 **5**	2	90	92
6		 **6**	3	98	94
7		 **7**	3	96	98

8			2	97	94
9			2	96	93
10			3	95	92
11			3	96	95
12			2	90	92
13			3	95	95
14			3	96	93
15			2	98	98

16			2	95	94
17			3	96	93
18			3	95	92
19			2	92	92

Yield (**1-19**): [a] R-OTHP and [b] R-OMOM ethers deprotection.

Scheme 1. Synthesis of diastereoisomerically pure trans-3-(4-bromophenyl)-2-hydroxy-2,3-dihydroindan-1-one.



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221 **Scheme 2.** A propose mechanism for the deprotection of MOM ethers followed by cyclization

222 with $SnCl_4$

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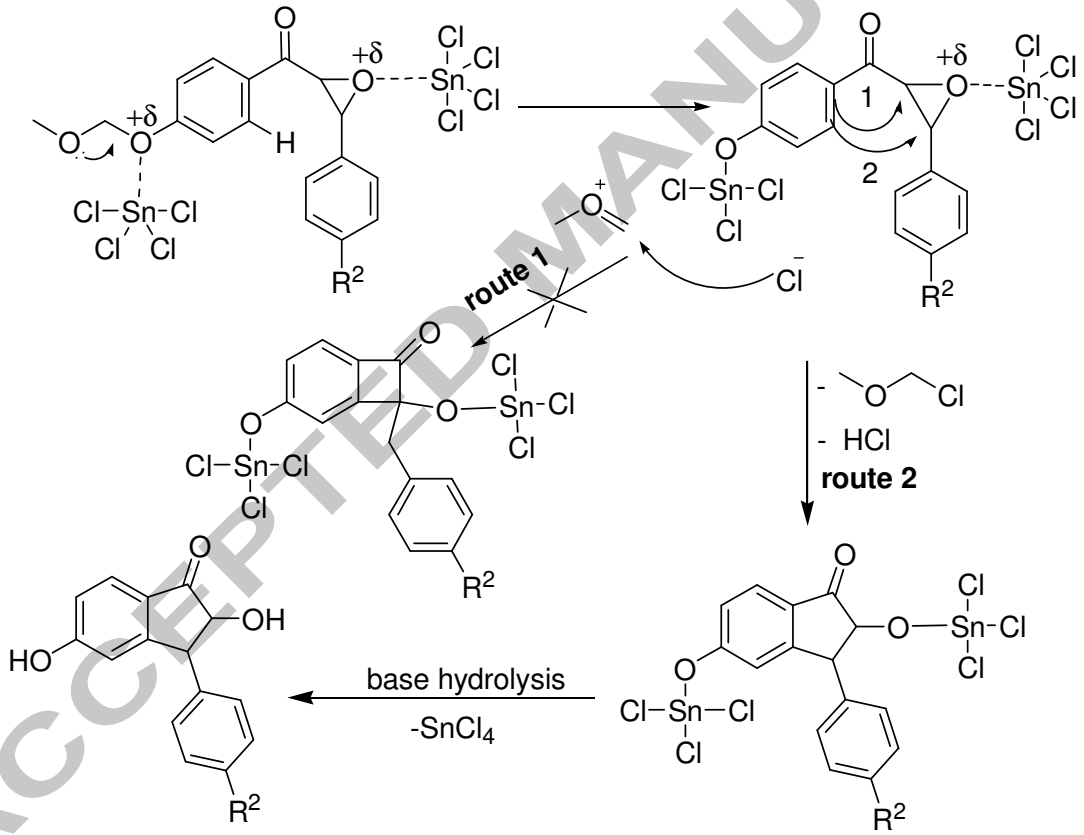

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Graphical Abstract

Highly efficient deprotection of phenolic tetrahydropyranyl and methoxymethyl ethers and sequel cyclization to indanones using Sn(IV)Cl_4 catalyst

Naseem Ahmed*, Gulab Khushalrao Pathe and B. Venkata Babu