Polyhedron 29 (2010) 238–243

Contents lists available at ScienceDirect

Polyhedron

journal homepage: www.elsevier.com/locate/poly

High-valent $[Sn^{IV}(Br_8TPP)(OTf)_2]$ as a highly efficient and reusable catalyst for selective methoxymethylation of alcohols and phenols: The effect of substituted bromines on the catalytic activity

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ARTICLE INFO

Article history:
Available online 25 July 2009

Keywords:
Methoxymethylation
Alcohol
Phenol
Tin(IV) porphyrin
Formaldehyde dimethyl acetal

ABSTRACT

High-valent tin(IV)octabromotetraphenylporphyrinato trifluoromethanesulfonate, $[Sn^{IV}(Br_8TPP)(OTf)_2]$, was used for selective methoxymethylation of alcohols and phenols with formaldehyde dimethyl acetal (FDMA) at room temperature. Different primary, secondary and tertiary alcohols as well as phenols were converted to their corresponding methoxymethyl ethers with FMDA in the presence of an electron deficient tin(IV) porphyrin. The catalyst was reused several times without significant loss of its activity.

1. Introduction

The protection of functional groups is of great importance in the multi step synthesis. Amongst them, hydroxyl group is a versatile functional group and a wide variety of methods such as trimethylsilylation, tetrahydropyranylation, acetylation and methoxymethylation have been used for protection of hydroxyl groups [1,2]. Methoxymethyl ethers (MOM) are frequently prepared by the reaction of an alcohol or phenol with chloromethyl methyl ether, but the application of this methoxymethylating agent has been restricted due to its high carcinogenicity [3]. To solve this problem, methoxymethyl ethers are synthesized by the reaction of alcohols or phenols with formaldehyde dimethyl acetal (FDMA) [4]. But FDMA has low methoxymethylating power in the absence of a suitable catalyst. To overcome this limitation, a number of catalysts such as P_2O_5 [5], *p*-toluenesulfonic acid [6], Nafion-H [7], TMSI [8], BF_3 [9], Envirocat [10], NaY-zeolite [11], expansive graphite [12], sulfated metal oxides [13], silica sulfuric acid [14], $Sc(OTf)_3$ [15], $Bi(OTf)_3$ [16], $ZrCl_4$ [17], $MoO_2(acac)_2$ [18], $H_3PMo_{12}O_{40}$ [19], anhydrous $FeCl_3$ dispersed on 3A molecular sieve [20], TiO_2/SO_4^{2-} [21], $H_3PW_{12}O_{40}$ [22] and $H_3PW_{12}O_{40}$ supported on silica and zirconia [23] have been reported.

Electron-deficient metalloporphyrins have been used as mild Lewis acid catalysts [24–29]. Suda group has reported the use of chromium and iron porphyrins in organic synthesis. They used Cr(tpp)Cl for regioselective [3, 3] rearrangement of aliphatic allyl vinyl ethers and for Claisen rearrangement of simple aliphatic allyl vinyl ethers, Fe(tpp)OTf for rearrangement of α,β-epoxy ketones into 1,2-diketones and Cr(tpp)OTf for highly regio- and stereoselective rearrangement of epoxides to aldehydes [30–33]. Recently, Suda and coworkers used an electron-deficient chromium–phthalocyanine complex, Cr(TBPC)OTf, as a highly efficient and recyclable Lewis acid catalyst for the regio- and stereoselective rearrangements of epoxides to aldehydes [34].

Recently, we reported the use of $[Sn^{IV}(TPP)(ClO_4)_2]$ [35,36], $[Sn^{IV}(TPP)(OTf)_2]$ [37,38] and $[Sn^{IV}(TPP)(BF_4)_2]$ [39,40] in organic transformations.

In this paper, an efficient method for methoxymethylation of alcohols and phenols with FMDA catalyzed by high-valent $[Sn^{IV}(Br_8TPP)(OTf)_2]$ at room temperature is reported (Scheme 1).

2. Experimental

Chemicals were purchased from Merck chemical company. ^1H NMR spectra were recorded in $CDCl_3$ solvent on a Bruker AM 80 MHz or a Bruker AC 500 MHz spectrometer using TMS as an internal standard. Infrared spectra were run on a Philips PU9716 or Shimadzu IR-435 spectrophotometer. Tetraphenylporphyrin was prepared, brominated and metallated according to the literature [41–43].

2.1. Preparation of $[Sn^{IV}(Br_8TPP)(OTf)_2]$

A solution of $AgCF_3SO_3$ (0.54 g, 2 mmol) in THF (10 mL) was added to a solution of $[Sn(Br_8TPP)Cl_2]$ (1.71 g, 1 mmol) in THF

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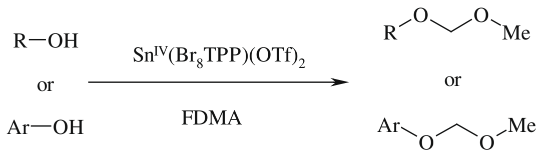
doi:10.1016/j.poly.2009.07.041



Scheme 1. Methoxymethylation of alcohols and phenols with FDMA catalyzed by Sn^{IV}(Br$_8$TPP)(OTf)$_2$.

(100 mL), at 55 °C. The solution was stirred at 55 °C for 30 min. The AgCl precipitate was filtered through a 0.45 μM filter. The resulting solution was evaporated at room temperature and the [Sn^{IV}(Br$_8$TPP)(OTf)$_2$] crystals were obtained by extraction with CH$_2$Cl$_2$ [38]. The purple crystals of [Sn^{IV}(Br$_8$TPP)(OTf)$_2$] was obtained by evaporation of solvent at room temperature. Visible spectrum: 468 (Soret), 598, 655 nm; ν_{max} (CHCl$_3$): 1026, 1172, 1225, 1295 cm^{-1} (belong to SO$_3$ groups and porphyrin ring); CHNS *Anal.* Calc. for: C, 33.27; H, 1.22; N, 3.37; S, 3.86. Found: C, 32.95; H, 1.24; N, 3.38; S, 3.80%.

2.2. General procedure for the methoxymethylation of alcohols and phenols catalyzed by [Sn^{IV}(Br$_8$TPP)(OTf)$_2$]

Alcohol or phenol (1 mmol), FDMA (7 mmol) and [Sn^{IV}(Br$_8$TPP)(OTf)$_2$] (10 mg, 0.006 mmol) were mixed and stirred at room temperature. The progress of the reaction was monitored by TLC. At the end of the reaction, the FDMA was evaporated, Et$_2$O (15 mL) was added and then the catalyst was filtered. The filtrates were washed with brine and dried over Na$_2$SO$_4$ and concentrated under reduced pressure to afford the crude product, which was confirmed by m.p., ^{1}H NMR and IR spectral data [21,44–46].

3. Results and discussion

3.1. Methoxymethylation of alcohols and phenols with FMDA catalyzed by [Sn^{IV}(Br$_8$TPP)(OTf)$_2$]

First, the ability of different tin(IV) porphyrins such as [Sn^{IV}(Br$_8$TPP)(OTf)$_2$], [Sn^{IV}(TPP)(OTf)$_2$] and [Sn^{IV}(TPP)Cl$_2$] was investigated in the methoxymethylation of 4-methoxybenzyl alcohol with FDMA. The results, which are summarized in Table 1, showed that [Sn^{IV}(Br$_8$TPP)(OTf)$_2$] is more efficient than the others. These observations show that replacement of chlorine with OTf as well as introducing of bromine in the β-position of porphyrin ring increased the electron deficiency of [Sn^{IV}(Br$_8$TPP)(OTf)$_2$] and therefore, the catalytic activity of this catalyst has been increased.

The optimized reaction conditions which were obtained for methoxymethylation of 4-methoxybenzyl alcohol were catalyst, FDMA and alcohol in a molar ratio of 1:7:167. Under these optimized conditions different primary, secondary and tertiary alcohols were converted efficiently to their corresponding MOM-ethers in excellent yields in the catalytic amounts of [Sn^{IV}(Br$_8$TPP)(OTf)$_2$] at room temperature. The results which are summarized in Table 2, show that all reaction were completed in 5–15 min for linear, aromatic and cyclic alcohols and no by-product was observed. In the case of 1,4-*bis*(hydroxymethyl)benzene both hydroxyl groups were methoxymethylated and 1,4-*bis*(methoxymethoxy)methyl benzene was obtained in high yield (Table 2, entry 10).

Table 1
Investigation of catalytic activity of different tin(IV) porphyrins in the methoxymethylation of 4-methoxybenzyl alcohol with FDMA.

Catalyst	Catalyst amount (mg, mol%)	Time (min)	Yield (%)[a]
[Sn^{IV}(Br$_8$TPP)(OTf)$_2$]	10 (0.6)	5	96
[SnIV(TPP)(OTf)$_2$]	10 (1)	5	47
[Sn^{IV}(TPP)Cl$_2$]	10 (1.2)	5	15

[a] Isolated yield.

Under the same reaction conditions, phenols were converted to their corresponding MOM-ethers with FDMA in the presence of [Sn^{IV}(Br$_8$TPP)(OTf)$_2$]. In the same way as for alcohols, the reactions were completed for all phenols and their corresponding MOM-ethers were obtained in excellent yields (Table 3).

All reactions were performed in air. It is important to note that the obtained results under nitrogen atmosphere were comparable with those obtained in air.

In order to demonstrate the chemoselectivity of the presented method, a set of competitive reactions was conducted between primary, secondary or tertiary alcohols and phenols (Table 4). Also in compounds containing both benzylic and phenolic hydroxyl groups, only benzylic hydroxyl groups were converted to their corresponding ethers with excellent chemoselectivity (entries 9 and 11, Table 2). The results indicated that the present protocol is potentially applicable for the chemoselective conversion of primary and secondary or tertiary alcohols to their MOM-ethers in the presence of phenols and alcohols.

It seems that the higher reactivity of primary alcohols in comparison with secondary and tertiary ones is due to the less steric hindrance of primary alcohols for attacking to methoxymethylating agent (**1**). Selective methoxymethylation of alcohols in the presence of phenols is attributed to higher nucleophilicity of alcohols. The methoxymethylation of bifunctional compounds containing both benzylic and phenolic hydroxyl groups such as 2-hydroxybenzyl alcohol and 3-methoxy-4-hydroxybenzyl alcohol, in which only alcoholic group was converted to its corresponding MOM-ether and the phenolic group remained intact, is a good indication of these observations.

The results obtained with this catalytic system have been compared with some of those reported in the literature for the methoxymethylation of hydroxyl compounds (Table 5). These results showed that [Sn^{IV}(Br$_8$TPP)(OTf)$_2$] which is a stable tin(IV) compound, shows high TOFs in the methoxymethylation reactions and the desired products were obtained in excellent yields with 100% selectivity in short reaction times. On the other hand, the catalyst can be reused several times which is important from economical and environmental point of views.

The actual mechanism of these protection reactions is not clear at present. It seems that the role of the catalyst is the activation of FDMA. The most probable interaction (according to the hard and soft concept) is coordination of the oxygen of FDMA to Sn(IV) species to afford **1**. This makes the FDMA susceptible to nucleophilic attack by alcohol to give **2** which in turn converts to the final product **3** and releases the catalyst for the next catalytic cycle (Scheme 2). If two FDMA molecules simultaneously coordinates to the porphyrin plane from above and below, due to the reduction of the electron deficiency of tin(IV), the catalytic activity of the catalyst will reduced.

Comparison of [Sn^{IV}(Br$_8$TPP)(OTf)$_2$] with [Sn^{IV}(TPP)(OTf)$_2$] [47] showed that introducing of bromines on the β-position of porphyrin ring, increases its catalytic activity. This is due to the electron-withdrawing nature of the Br which increases the electron deficiency of tin(IV) porphyrin. It is clear from the results that in the presence of [Sn^{IV}(Br$_8$TPP)(OTf)$_2$], both reaction times and catalyst mol% have reduced in comparison with [Sn^{IV}(TPP)(OTf)$_2$].

3.2. Catalyst recovery and reuse

The reusability of the catalyst was checked using multiple methoxymethylation of 4-chlorobenzylalcohol with FDMA. At the

Table 2
Protection of alcohols with FDMA catalyzed by $[Sn^{IV}(Br_8TPP)(OTf)_2]$ at room temperature.

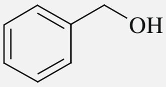
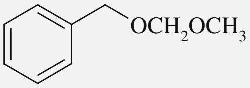
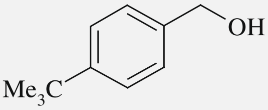
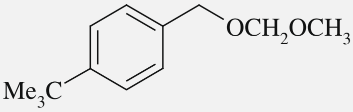
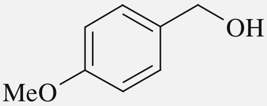
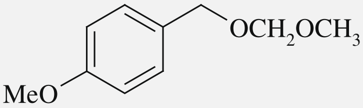
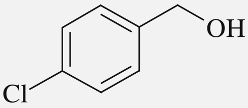
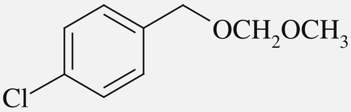
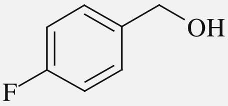
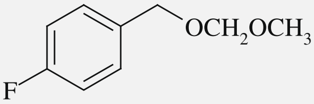
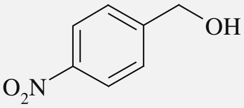
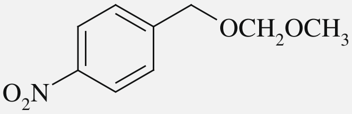
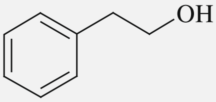
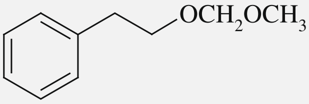
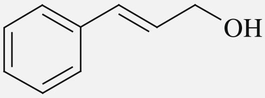
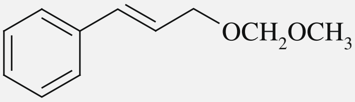
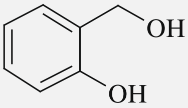
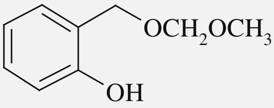
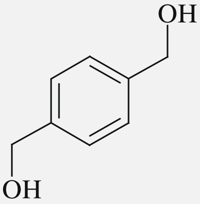
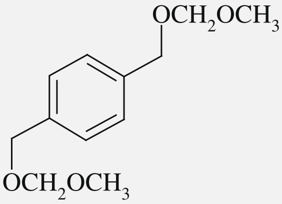
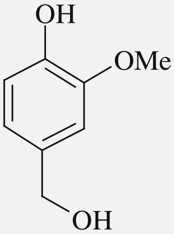
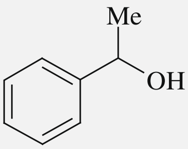
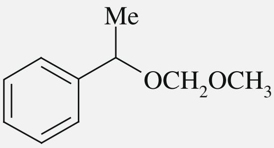
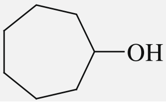
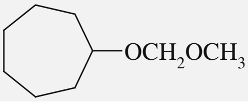
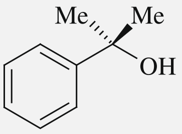
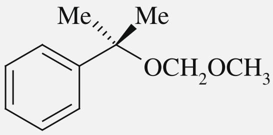
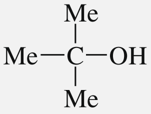
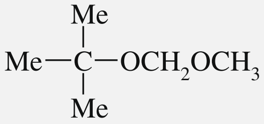
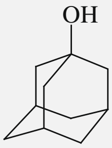
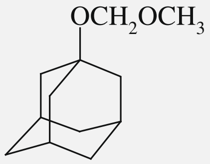
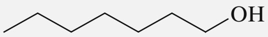
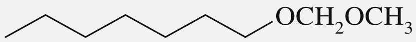
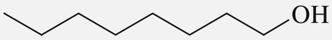
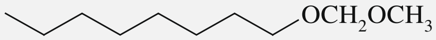
Entry	Alcohol	MOM-ether	Time (min)	Yield (%)[a,b]
1			5	97
2			15	95
3			5	97
4			10	96
5			10	96
6			15	95
7			15	95
8			5	95
9			10	95
10			10	94
11			10	93
12			10	95
13			10	94

Table 2 (*continued*)

Entry	Alcohol	MOM-ether	Time (min)	Yield (%)[a,b]
14			10	93
15			15	94
16			15	95
17			15	95
18			15	96

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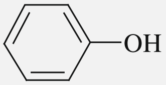
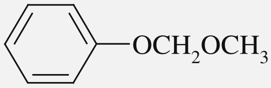
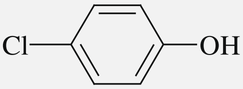
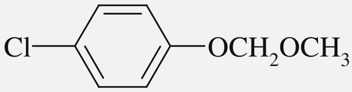
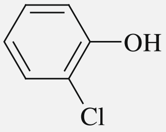
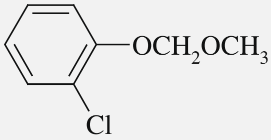
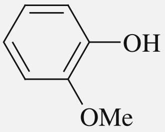
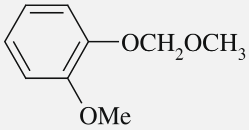
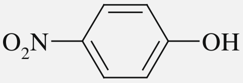
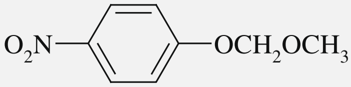
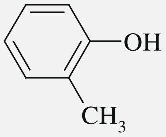
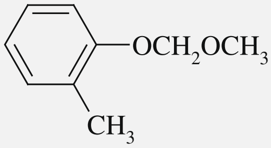
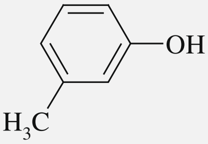
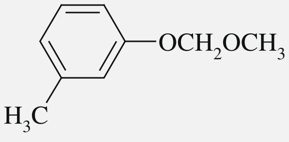
[a] Isolated yields.

[b] All of the isolated products are known compounds (except entries 9–11) and their spectral and physical data have been reported in the literature [21,43–45].

Table 3

Protection of phenols with FDMA catalyzed by $[Sn^{IV}(Br_8TPP)(OTf)_2]$ at room temperature.

Entry	Phenol	MOM-ether	Time (min)	Yield (%)[a]
1			10	95
2			10	95
3			10	94
4			10	97
5			10	95
6			10	94
7			10	95

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[a] Isolated yield.

end of the reaction, the catalyst was filtered and used in the next run. These results showed that after reusing the catalyst for several times (four consecutive runs was checked), no change was observed in its catalytic activity.

Table 4
Selective methoxymethylation of alcohols and phenols catalyzed by [$Sn^{IV}(Br_8TPP)(OTf)_2$].

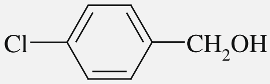
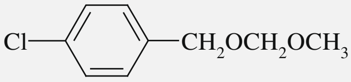
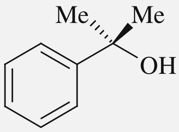
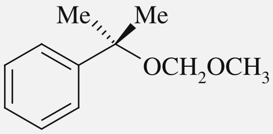
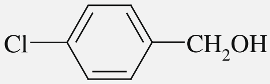
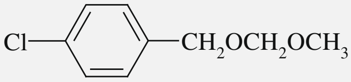
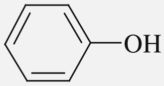
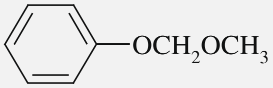
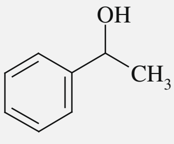
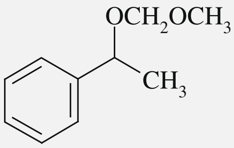
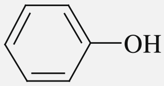
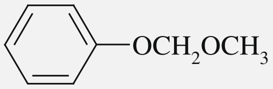
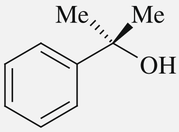
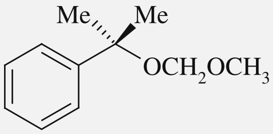
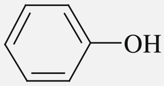
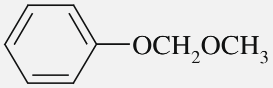
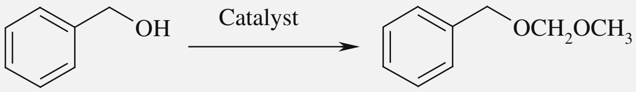
Row	ROH	MOM-ether	Time (min)	Yield (%)
1			10	96
				0
2			15	96
				0
3			10	95
				0
4			10	93
				0

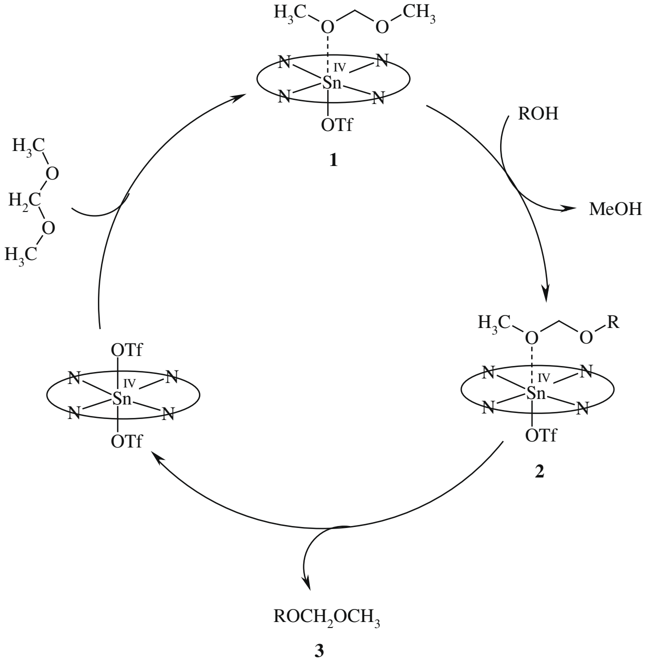
Table 5
Comparison of the results obtained for the methoxymethylation of benzyl alcohol catalyzed by [$Sn^{IV}(Br_8TPP)(OTf)_2$] with those obtained by the recently reported catalysts.



Entry	Catalyst	Catalyst (mol%)	Temperature	Time (h)	Yield (%)	TOF (h^{-1})	Reference
1	$Sn^{IV}(Br_8TPP)(OTf)_2$	0.6	R.T.	0.08	97	2020.83	
2	NaY-zeolite	27 mg	reflux	6	80		[11]
3	Expansive graphite	20 mg	reflux	6	91		[12]
4	Sulfated metal oxides	50 mg	R.T.	3	91		[13]
5	Silica sulfuric acid	200 mg	reflux	1.5	85		[14]
6	$Sc(OTf)_3$	5	reflux	3	98	6.53	[15]
7	$Bi(OTf)_3$	5	reflux	1	95	19.00	[16]
8	$ZrCl_4$	10	R.T.	1	97	9.70	[17]
9	$MoO_2(acac)_2$	2	reflux	4	85	10.63	[18]
10	$H_3PMo_{12}O_{40}$	5	reflux	3	90	6.00	[19]
11	Anhydrous $FeCl_3$ @ 3A molecular sieve	90	R. T.	1	90	1.00	[20]
12	TiO_2/SO_4^{2-}	20	reflux	6	92	0.77	[21]
13	$H_3PW_{12}O_{40}$	0.4	R.T.	3	91	75.83	[22]
14	$H_3PW_{12}O_{40}$@Silica	0.4	R.T.	1	94	235.00	[23]
15	$H_3PWo_{12}O_{40}$@Zirconia	0.4	R.T.	2.5	84	84.00	[23]

4. Conclusion

In conclusion, [$Sn^{IV}(Br_8TPP)(OTf)_2$] has been introduced as a stable tin(IV) compound. This catalyst is able to catalyze the reactions in which [$Sn^{IV}(TPP)Cl_2$] is not able to catalyze them. On the other hand, by introducing the bromines on the β-position of porphyrin ring, its catalytic activity has been increased in comparison with [$Sn^{IV}(TPP)(OTf)_2$]. This is due to the electron-withdrawing nature of the Br which increases the electron deficiency of tin(IV) porphyrin. In the presence of catalytic amounts of [$Sn^{IV}(Br_8TPP)(OTf)_2$], different primary and secondary as well as tertiary alcohols and phenols efficiently converted to their corresponding methoxy-



Scheme 2. Proposed mechanism for methoxymethylation of alcohols and phenols with FDMA catalyzed by $Sn^{IV}(Br_8TPP)(OTf)_2$.

methyl ethers (MOM-ethers) with formaldehyde dimethyl acetal (FDMA) at room temperature. Short reaction times, easy preparation of catalyst, high product yield, solvent free conditions and applicability for both alcohols and phenols are the advantages of this catalytic system.

5. Selected spectral data

2-(Methoxymethoxy)methyl phenol (entry 9, Table 2): Oil. IR ν_{max} (KBr, cm^{-1}): 3400, 2800, 1310, 1270, 1100, 1050, 730, 700. ^1H NMR (500 MHz, $CDCl_3$) δ = 1.98 (s, 3H, OCH_3), 2.02 (s, 2H, OCH_2), 3.98 (s, 2H, $ArCH_2$), 7.28–7.34 (m, 4H, Ar) ppm. CHN *Anal.* Calc. for: C, 64.27; H, 7.19. Found: 64.22; H, 7.21%.

1,4-Bis(methoxymethoxy)methyl benzene (entry 10, Table 2): m.p.: 68–70 °C. IR ν_{max} (KBr, cm^{-1}): 2800, 1210, 1080, 1010, 1000, 810. ^1H NMR (500 MHz, $CDCl_3$) δ = 4.55 (s, 6H, $2 \times CH_3$), 4.64 (s, 4H, OCH_2O), 4.70 (s, 4H, $2 \times ArCH_2$), 7.37 (s, 4H, Ar) ppm. CHN *Anal.* Calc. for: C, 63.70; H, 8.02. Found: 63.52; H, 7.99%.

2-Methoxy-4-((methoxymethoxy)methyl) phenol (entry 11, Table 2): m.p.: 71–73 °C. IR ν_{max} (KBr, cm^{-1}): 3300, 2900, 1200, 1000, 1060, 820, 790. ^1H NMR (500 MHz, $CDCl_3$) δ = 4.12 (s, 3H, OCH_3), 4.56 (s, 2H, OCH_2O), 4.66 (s, 3H, *o*-OCH_3), 4.84 (s, 2H, $ArCH_2$), 7.26–7.36 (m, 3H, Ar) ppm. CHN *Anal.* Calc. for: C, 60.59; H, 7.12. Found: 60.45; H, 7.10%.

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