ChemComm

Cite this: *Chem. Commun.*, 2012, **48**, 3448–3450

www.rsc.org/chemcomm

COMMUNICATION

A generalized approach for iron catalyzed chemo- and regioselective formation of anti-Markovnikov acetals from styrene derivatives†

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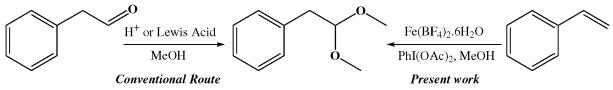
Received 17th December 2011, Accepted 9th February 2012
DOI: 10.1039/c2cc17889c

$Fe(BF_4)_2{\cdot}6H_2O$ in the presence of pyridine-2,6-dicarboxylic acid and $PhI(OAc)_2$ can efficiently catalyze the formation of chemoselective dialkyl acetals from styrene derivatives with anti-Markovnikov regioselectivity in good to high yields under mild and benign reaction conditions.

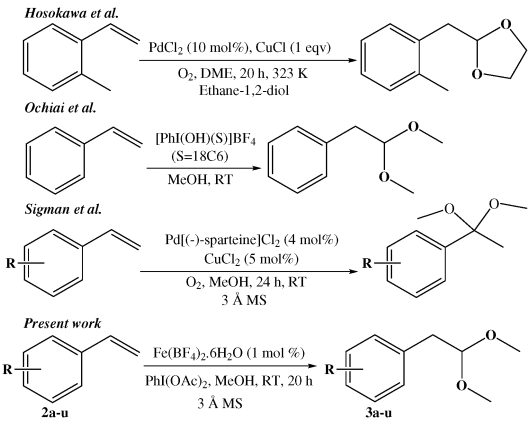
Acetalization is known to be the most popular and widely employed synthetic route towards the protection of aldehydic and ketonic functionalities during the manipulation of various multifunctional organic molecules.[1] Acetals can also be directly converted to other useful functional groups and hence can serve as an important intermediate in the course of organic synthesis.[1,2] Furthermore, hemiacetal formation is the mechanism by which pentoses and hexoses assume their cyclic forms. Additionally acetals have immense industrial importance particularly due to their potential utility as flavoring agent in distilled beverages, diesel additives and in plastic materials.[3]

Most of the existing methods for the synthesis of acetals involve the treatment of aldehydes or ketones by either a protic[1,4] or a Lewis acid[1,5] catalyst. But these methods have severe limitations, such as use of corrosive and costly reagents or additives, halogenated solvents, high temperature, inconvenient reaction conditions, large waste and high catalyst loading. In this context the recent report of ruthenium catalyzed direct transformation of alcohols to acetals is noteworthy as it avoids the use of expensive aldehydes or ketones as substrate.[6] Direct transformation of a *cheaper* terminal alkene to an acetal instead of using a *costlier* aldehyde or ketone as substrate is regarded as a challenging task. We therefore report here the direct and highly efficient catalytic conversion of various styrene derivatives to the corresponding terminal or anti-Markovnikov acetals under mild and environmentally benign reaction conditions using a cheap and readily available iron-based catalyst (Scheme 1).

Over the years styrene has emerged as an attractive alternative substrate for acetal synthesis (Scheme 2). Hosokawa *et al.* reported for the first time that styrene can be directly oxidized to acetal with high regioselectivity for the anti-Markovnikov



Scheme 1



Scheme 2

product by palladium catalyzed Wacker type oxidation protocol (Scheme 2).[7] On the contrary, complete reversal of regioselectivity *i.e.* the formation of Markovnikov acetals has been demonstrated recently by Sigman *et al.* during similar kind of Wacker type oxidation of styrene derivatives *but* by using $Pd[(-)\text{-sparteine}]Cl_2$ as a catalyst (Scheme 2).[8a] Here anti-Markovnikov acetals are also reported to form as a minor product from styrene containing an electron withdrawing functional group.[8a] Ochiai *et al.* have also shown the synthesis of anti-Markovnikov dimethyl acetal, (2,2-dimethoxyethyl)benzene, from styrene using $[PhI(OH)(18Crown6)]BF_4$ as the reagent in methanolic medium.[8b] However, the general regio- and chemoselective catalytic formation of anti-Markovnikov acetals from styrene derivatives under benign catalytic conditions has not been reported in the literature till date (Scheme 2).

During initial optimization of suitable reaction conditions different iron, ruthenium, copper and cobalt salts in the presence of various commercially available bi- and tridentate ligands have been screened in the presence of $PhI(OAc)_2$ as an oxidant in methanol (Table 1) using styrene as the model substrate. However, only iron based precursors have been found to deliver measurable activity and/or selectivity. Among them, both $Fe(BF_4)_2{\cdot}6H_2O$ (**1**) and $Fe(ClO_4)_2{\cdot}6H_2O$ have shown almost

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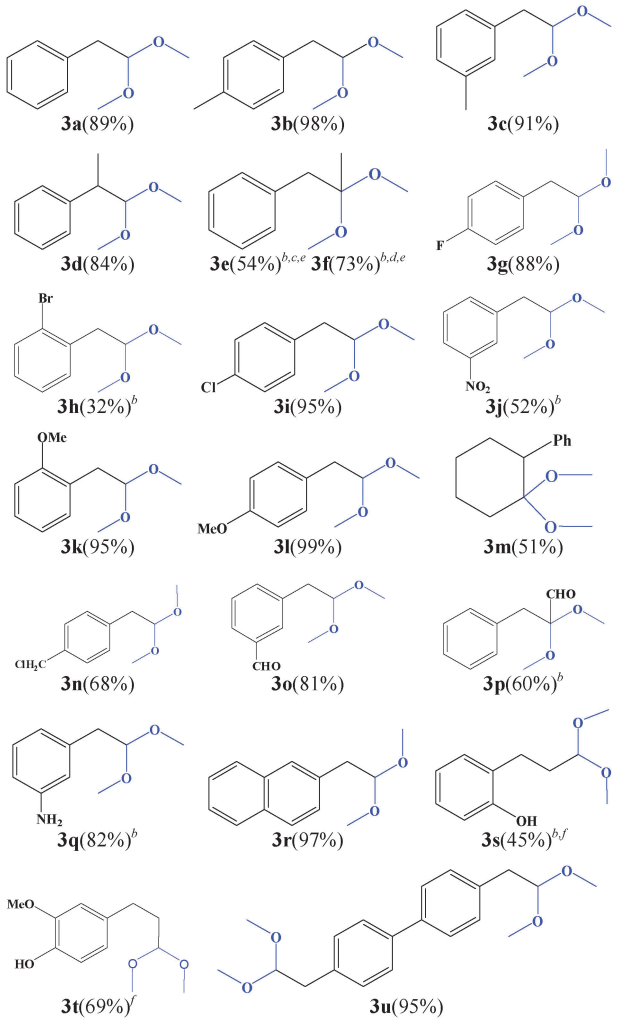
† Electronic supplementary information (ESI) available: Experimental procedure, characterization data, and additional tables and figures. See DOI: 10.1039/c2cc17889c

Table 1 Catalytic acetalization of styrene[a]

Entry	Catalyst[b]	Conversion (%)	Yield[c] (%)
1	$RuCl_3{\cdot}xH_2O$/dipic	<1	0
2	$RuCl_3{\cdot}xH_2O$/trpy	<1	0
3	$RuCl_3{\cdot}xH_2O$/dppf	<1	0
4	$Ru(acac)_3$/dipic	<1	0
5	$[Ru(p\text{-cym})_2Cl_2]_2$/dipic	3	0
6	$Ru(trpy)Cl_3$/dipic	11	0
7	$Ru(CO)_3(PPh_3)_3$/dipic	<1	0
8	Fe_2O_3/dipic	10	3
9	$FeCl_3{\cdot}6H_2O$/dipic	52	25
10	$FeCl_3{\cdot}6H_2O$/dppf	11	1
11	$FeCl_2$/dipic	60	31
12	$Fe(acac)_3$/dipic	12	5
13	$Fe(OAc)_2$/dipic	61	43
14	**$Fe(BF_4)_2{\cdot}6H_2O$ (1)/dipic**	**97**	**92(89)[d]**
15	$Fe(BF_4)_2{\cdot}6H_2O$/dppf	61	51
16	$Fe(BF_4)_2{\cdot}6H_2O$/en	56	44
17	$Fe(BF_4)_2{\cdot}6H_2O$/dppe	19	12
18	$Fe(BF_4)_2{\cdot}6H_2O$/pic	59	47
19	$Fe(BF_4)_2{\cdot}6H_2O$/trpy	32	21
20	$Fe(BF_4)_2{\cdot}6H_2O$	10	<1
21	$Fe(ClO_4)_2{\cdot}6H_2O$/dipic	81, 98[e]	77, 94[e]
22	$Fe(ClO_4)_2{\cdot}6H_2O$/dppf	56	43
23	$Cu(ClO_4)_2{\cdot}6H_2O$/dipic	58	39
24	$Cu(BF_4)_2{\cdot}6H_2O$/dipic	65	51
25	$CuSO_4{\cdot}5H_2O$/dipic	44	35
26	$CoCl_2{\cdot}6H_2O$/dipic	40	12
27	$Co(acac)_2(H_2O)_2$/dipic	35	9

[a] Reaction conditions: 1 mol% catalyst, 1 mol% L, styrene, 1.5 equiv. $PhI(OAc)_2$ in 4 mL methanol, RT, 20 h. See the experimental part for the details. [b] dipic = pyridine-2,6-dicarboxylic acid, trpy = 2,2′ : 6′,2″-terpyridine, dppf = 1,1′-bis(diphenylphosphino) ferrocene, en = ethylenediamine, dppe = 1,2-bis(diphenylphosphino)ethane, pic = pyridine-2-carboxylic acid, acac = acetylacetonate, *p*-cym = *p*-cymene or 4-isopropyltoluene. [c] Determined by GC using n-dodecane as an internal standard. [d] Determined by ^1H NMR with PhTMS as an internal standard. Isolated yield is given in parentheses. [e] 48 h.

Table 2 Iron catalyzed acetalization of styrene derivatives[a]



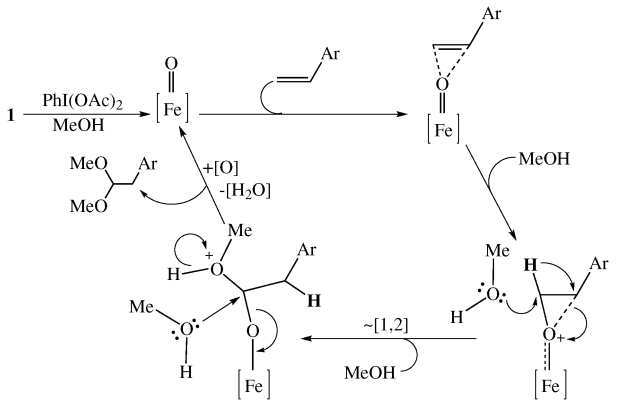
[a] Reaction conditions: 1 mol% **1**, 1 mol% dipic, substrate, 1.5 equiv. $PhI(OAc)_2$ in 4 mL methanol, RT, 20 h. Isolated yields are given. See ESI for details. [b] Yields based on ^1H NMR with PhTMS as an internal standard. [c] Substrate: *cis*-β-methyl styrene. [d] Substrate: *trans*-β-methyl styrene. [e] Isomerisation of unreacted substrate is not observed. [f] 2 equiv. of $PhI(OAc)_2$.

similar efficiency but the latter requires longer reaction time to achieve similar conversion (entries 14 and 21, Table 1). Thus, the *in situ* generated catalyst derived from $Fe(BF_4)_2{\cdot}6H_2O$ and dipic ligand (dipic: pyridine-2,6-dicarboxylic acid) has led to significant activity and resulted in (2,2-dimethoxyethyl)benzene in 92% yield (entry 14, Table 1). A large variety of oxidants have also been tested with the $Fe(BF_4)_2{\cdot}6H_2O$/dipic catalytic system and significant activity and selectivity have only been achieved by $PhI(OAc)_2$ (Table S1, ESI†). Moreover, only dipic exhibits excellent activity and selectivity over other ligands in the presence of **1** and $PhI(OAc)_2$ as oxidant (entries 14–20, Table 1).

In essence, only one combination along with $Fe(BF_4)_2{\cdot}6H_2O$ (**1**) extends promising activity in terms of both conversion and selectivity under specified reaction conditions. Notably, ruthenium precursors in combination with dipic failed to show any activity and other copper and cobalt catalysts display poor activity and/or selectivity with dipic under identical reaction conditions.

The optimized reaction conditions indeed allowed the oxidation of a wide variety of styrene derivatives (**2a–u**) to the corresponding anti-Markovnikov acetals (**3a–u**) using only 1 mol% **1**, 1 mol% dipic, $PhI(OAc)_2$ as oxidant (1.5 equiv.) and 3 Å molecular sieves in methanol under aerial atmosphere (Table 2 and ESI†). The same reaction conditions *but* an inert atmosphere do not alter the yield and selectivity at all. The effect of molecular sieves (MS) is highly prominent in the present case to achieve complete conversion to the acetal (*vide infra*). Similar role of MS has already been established earlier.[8a,9] Interestingly, Markovnikov acetals are not formed by any means from any styrene derivatives, **2a–u** in the present case. Excellent yields are obtained generally with styrene containing an electron donating functionality whereas poor yield has been observed with styrene having an electron withdrawing group. A slightly larger amount of oxidant is required to achieve good yield from the allylic derivatives.

The most remarkable feature of this work is that it proceeds in a highly chemoselective manner. Substrates like **2o** and **2p** having a formyl group on the ring and at the β-carbon, respectively, remain completely unaffected after the reaction, neither acetalized nor oxidized even under such an oxidizing environment. Moreover, the change of solvent from methanol to ethanol or ethylene glycol similarly gives anti-Markovnikov acetals in good to reasonable yields (Table S2, ESI†). Unfortunately, poor



Scheme 3

yield of anti-Markovnikov acetals is obtained from the long-chain alcohol, 1-pentanol (entry 3, Table S2, ESI†).[10a]

The dehydrating agent (MS) plays an additional crucial role here.[9] In its absence the reaction is considerably slow and the terminal aldehyde is also formed to a large extent.[10b] The time monitored model reaction with styrene as a substrate reveals the formation of a minute amount ($\lesssim$3%) of phenylacetaldehyde during the reaction (Fig. S1, ESI†). However, direct acetalization of phenylacetaldehyde produces *only* 38% (2,2-dimethoxyethyl)-benzene which in effect suggests that the acetalization of styrene instead of aldehyde is the *highly* favored pathway for the present catalytic system. The existence of *only* phenylacetaldehyde and complete *absence* of acetophenone and/or styrene oxide during the course of the reaction provides the necessary justification in favor of the observed exclusive regioselectivity towards anti-Markovnikov acetals (Fig. S1, ESI†). It should be noted that during other reported iron-catalyzed oxidation of a terminal alkene, acetal products were not detected.[11]

A tentative mechanism is proposed in Scheme 3. The active iron catalyst mediates the acetalization of a terminal alkene to an anti-Markovnikov acetal, where the alkene approaches the iron bound oxo-atom *via* a side on approach. It then undergoes a [1,2] hydride shift followed by two consecutive solvent (methanol) neucleophilic attacks at the β-carbon atom which eventually leads to the formation of selective anti-Markovnikov acetals. Lewis acidic feature of the substrate bound iron center may facilitate the selective neucleophilic attack of the solvent, which in turn governs the exclusive regio- and chemoselectivity. Since no epoxide has been detected during the reaction, the possibility of the well known E–I (tandem epoxidation–isomerization) mechanism can therefore be completely ruled out in the present case.[12a] Additionally, one model reaction with styrene oxide as a substrate resulted in 1,2-dimethoxyphenylethane which indeed rules out the alternate possibility of the formation of styrene oxide as an intermediate as well as the E–I mechanism. The role of weakly ligating strong Lewis acid, BF_4^-, cannot be excluded.[12b] Further mechanistic studies are underway.

In summary, an efficient and selective iron-catalyzed oxidation of styrene to anti-Markovnikov acetal has exclusively taken place in alcoholic medium under mild reaction conditions. This provides an unprecedented account of anti-Markovnikov acetal formation, where the only reported catalyst exhibits low catalytic activity.[7] The present catalytic system operates well at room temperature with an abundant, cheap and benign iron-catalyst which is currently considered an ideal option to replace any precious metal in homogeneous catalysis.[12b,c] The present report of iron-catalyzed chemo- and regioselective direct acetalization of styrene to its anti-Markovnikov acetal may extend an alternate route for targeted organic synthesis.

The financial support received from DST and CSIR (fellowship to A.D.C.), New Delhi, India, is gratefully acknowledged.

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10 (*a*) Maximum upto 36% of yield can be achieved from 1-decene as substrate; (*b*) In the absence of 3 Å MS, yield of (2,2-dimethoxyethyl)-benzene is only ~63% whereas phenylacetaldehyde is ~18% under identical reaction conditions.

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