Cite this: Chem. Commun., 2012, 48, 5497–5499

COMMUNICATION

An iron catalyzed regioselective oxidation of terminal alkenes to aldehydes[†]

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Received 21st March 2012, Accepted 14th April 2012 DOI: 10.1039/c2cc32051g

Fe(BF₄)₂·6H₂O with pyridine-2,6-dicarboxylic acid and PhIO can efficiently catalyze the regioselective oxidation of terminal alkene derivatives to aldehydes under mild and benign reaction conditions.

The regioselective functionalization of terminal alkenes and alkynes is the most elementary reaction in organic synthesis as it allows easy introduction of various hetero-atom(s) into the existing molecular framework.¹ Though the catalytic anti-Markovnikov regioselective hydration of terminal alkynes to aldehydes has gained considerable research interest over the past decade,^{1a,2} the exclusive control of regioselectivity during transition metal catalyzed functionalization of terminal alkenes to aldehydes is emerging as a convenient approach to synthesize aldehydes.^{3–5}

Direct oxidation of alkenes to the corresponding carbonyl compounds is a widely employed chemical process due to their immense utility as an intermediate or a synthon in targeted organic synthesis.⁶ The well known palladium catalyzed Wacker oxidation usually yields ketones *i.e.* Markovnikov products from terminal alkenes,⁶ but the direct transformation of alkenes to aldehydes is rather scarcely reported.^{3–5} A Wacker type catalyst has also been shown to influence the anti-Markovnikov regioselectivity for alkene to aldehyde formation as a major product in the presence of a directing group like heteroatom(s) which facilitates the anti-Markovnikov regioselectivity *via* chelation to palladium.⁴ However, exclusive anti-Markovnikov regioselectivity with broad substrate scope has recently been achieved using iron and ruthenium porphyrin based catalysts through a tandem epoxidation–isomerization (E–I) pathway.⁵

The exclusive anti-Markovnikov regioselectivity is known to be achieved *via stoichiometric* multi-step hydroboration– oxidation reaction.¹ However the generation of a large amount of non-recyclable waste from boron and peroxide makes this process industrially undesirable. So, there is an urgent need to develop an efficient method for synthesizing aldehydes from terminal alkene functionalities.^{7,8} An immediate economical and environmentally benign option is to use iron as a catalyst because of its low toxicity and increasing (high) price as well as limited availability of palladium, rhodium or cobalt.⁹ Very recently, we have developed a reliable and direct method for iron catalyzed *anti-Markovnikov* acetal formation from styrene derivatives.¹⁰ As a part of our ongoing research program of iron catalyzed *anti-Markovnikov* regioselection process under mild reaction conditions, the present communication highlights the iron-catalyzed conversion of aromatic or aliphatic alkenes to aldehydes with mechanistic insight (Scheme 1).

The initial screening of suitable reaction conditions is investigated in detail with styrene as a substrate. Fe(BF₄)₂· $6H_2O$ (1) has been established to be much more selective and efficient than other iron, ruthenium, copper and cobalt salts in the presence of various commercially available ligands and PhIO in CHCl₃ at room temperature (Table 1). Similar to our earlier observation, only dipic (dipic: pyridine-2,6dicarboxylic acid) is found to have excellent activity and selectivity over other ligands in the presence of 1 and PhIO as an oxidant (entries 14–20, Table 1).¹⁰ The electron rich dianionic dipic ligand facilitates the *in situ* formation of the active catalyst, *i.e.* high valent iron-oxo species, which in turn exhibits the best activity (entry 20, Table 1). Consequently, the analogous but monoanionic pic ligand (pic: pyridine-2carboxylic acid) renders only moderate activity (entry 18, Table 1).

The said catalytic system has initially been tested in different solvents but reasonable activity is obtained only in chlorinated solvents, and CHCl₃ is found to be most effective (Table S1, ESI†). Notably reasonable conversion has been achieved only with PhIO among the large variety of oxidants (Table S2, ESI†). In general, an *in situ* generated complex derived from **1** and dipic has led to significant activity and 2-phenylacetaldehyde has been isolated in 92% yield (Table 1).

The optimized reaction conditions facilitate the oxidation of alkene derivatives, **2a–s**, to the aldehydes (**3a–s**) using only 2 mol% **1** and dipic, PhIO as an oxidant and 3 Å molecular sieves in chloroform under an aerial atmosphere (Table 2). The change of reaction conditions to an inert atmosphere does not alter the yield and selectivity at all. Also, molecular sieves have



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[†] Electronic supplementary information (ESI) available: Experimental procedures, detailed characterizations, additional tables, figures and schemes. See DOI: 10.1039/c2cc32051g

 Table 1
 Catalytic oxidation of styrene to aldehydes^a

| Entry | Catalyst ^b | Conversion (%) | Yield ^c (%) |
|-------|--|----------------|------------------------|
| 1 | RuCl ₃ ·xH ₂ O/dipic | <1 | 0 |
| 2 | Ru(acac) ₃ /dipic | <1 | 0 |
| 3 | [Ru(p-cym) ₂ Cl ₂] ₂ /dipic | 51 | 0 |
| 4 | Ru(trpy)Cl ₃ /dipic | 46 | 0 |
| 5 | Ru ₃ (CO) ₁₂ /dipic | <1 | 0 |
| 6 | Fe ₂ O ₃ /dipic | 10 | 0 |
| 7 | CoCl ₂ ·6H ₂ O/dipic | 26 | <1 |
| 8 | $Co(acac)_2(H_2O)_2/dipic$ | 35 | <1 |
| 9 | FeCl ₃ ·6H ₂ O/dipic | 65 | 45 |
| 10 | FeCl ₃ ·6H ₂ O/dppf | 5 | <1 |
| 11 | FeCl ₂ /dipic | 60 | 25 |
| 12 | Fe(acac) ₃ /dipic | 10 | <5 |
| 13 | Fe(OAc) ₂ /dipic | 75 | 52 |
| 14 | $Fe(BF_4)_2 \cdot 6H_2O$ | <1 | <1 |
| 15 | Fe(BF ₄) ₂ ·6H ₂ O/dppf | 25 | 12 |
| 16 | $Fe(BF_4)_2 \cdot 6H_2O/en$ | 21 | 16 |
| 17 | $Fe(BF_4)_2 \cdot 6H_2O/dppe$ | 17 | 6 |
| 18 | Fe(BF ₄) ₂ ·6H ₂ O/pic | 65 | 51 |
| 19 | Fe(BF ₄) ₂ ·6H ₂ O/trpy | 27 | 9 |
| 20 | Fe(BF ₄) ₂ ·6H ₂ O (1)/dipic | 100 | 92 ^d |
| 21 | Fe(ClO ₄) ₂ ·6H ₂ O/dipic | 100 | 70 |
| 22 | Cu(ClO ₄) ₂ ·6H ₂ O/dipic | 100 | 42 |
| 23 | Cu(BF ₄) ₂ ·6H ₂ O/dipic | 100 | 61 |

^{*a*} Reaction conditions: 2 mol% catalyst, 2 mol% L, styrene, 1.5 equiv. PhIO in 4 mL CHCl₃, 3 Å molecular sieves, RT, 20 h. See ESI for 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*} Isolated yield.

shown a prominent effect on conversion.¹⁰ Epoxides have not been detected at all at the end of the reaction. Interestingly, completely regioselective Markovnikov ethyl ketone is formed from both (Z)/(E)- β -methyl styrene (2e–2f). Such entirely reversal of regioselectivity from substrates like 2e or 2f has been reported earlier, which provides the necessary justification about the mechanism; especially the nature of the intermediate (vide infra).^{3a,11} Unlike mono- and di-substituted alkenes, products from the tri-substituted alkenes (1-phenylcyclohexene, 21) undergo alkyl migration during isomerization; indicating the existence of the E-I mechanism.5c Furthermore, under similar optimized reaction conditions, various aliphatic alkenes (20-s) have been screened to give aldehydes (30-s) but at an elevated temperature (60 °C) using 2 equiv. of PhIO (Table 2). The very poor conversion (<10%) from substrates like 2-allylphenol or eugenol is probably due to the chelating nature of the hydroxyl group with iron. Remarkably, unlike earlier observations,⁵ the present catalytic protocol functions smoothly in the absence of either base or silver additives. In essence, both terminal aromatic and aliphatic alkenes can be regioselectively oxidized to aldehydes when 1 is used as a catalyst under optimized reaction conditions.

A tentative mechanism is depicted in Scheme 2. Interaction of the active iron-oxo species (**1a**) with the terminal alkenes *via* a side-on approach leads to the formation of aldehydes by following the two alternate pathways: (a) the tandem E-I mechanism (path a, Scheme 2) and (b) a pinacol like rearrangement (path b, Scheme 2).^{5,12} Initially, **1a** catalyzes the oxidation of alkenes to epoxides followed by isomerization to

5498 Chem. Commun., 2012, **48**, 5497–5499

| Table 2 | Iron catalyzed | oxidation | of alkene | functionalities ^a |
|---------|----------------|-----------|-----------|------------------------------|
|---------|----------------|-----------|-----------|------------------------------|



^{*a*} Reaction conditions: 2 mol% 1, 2 mol% dipic, substrate, 1.5 equiv. PhIO in 4 mL CHCl₃, 3 Å molecular sieves, RT, 20 h. See ESI for details. Isolated yields are given. ^{*b*} NMR yield. ^{*c*} Markovnikov ketone from (*Z*)-β-methyl styrene (**2e**). ^{*d*} Markovnikov ketone from (*E*)-β-methyl styrene (**2f**). ^{*e*} Small amount of benzaldehyde is also obtained. ^{*f*} Isomerized product from 1-phenylcyclohexene (**2l**). ^{*g*} 2 equiv. of PhIO, 60 °C, 48 h, the rest is unreacted alkene.



aldehydes by 1.⁵ The formation of epoxides during the course of the reaction has also been established (Fig. S1, ESI[†]). ¹H and ¹³C NMR spectra of a control reaction with styrene as a model substrate at a lesser reaction time reveal the existence of the final product, 2-phenylacetaldehyde, intermediary styrene oxide and unreacted styrene (Fig. S2-S3, ESI[†]). Moreover, the direct treatment of styrene oxide with 2 mol% of 1 and dipic in CHCl₃ at RT for 6 h affords 3a in 99% yield. Hence, under identical reaction conditions 1 is the active catalyst for isomerization, which indeed supports the proposed E-I mechanism (path a, Scheme 2).⁵ Subsequently, 3a can also be produced directly via a pinacol like rearrangement from the cationic intermediate (1b) as postulated earlier by Groves and Collman et al. (path b. Scheme 2 and Scheme S1. ESI[†]).¹² Such an intermediate may also be imagined to arrive from metallaoxetene via Fe- C_{α} bond cleavage (Scheme S2, ESI[†]).¹² The cis C_{β} -H bond is eventually aligned for the requisite rearrangement or migration to 2-phenylacetaldehyde due to conformational preference of the cyclic four-membered ring of metallaoxetene which finally results in the carbonoxygen double bond as well as subsequent cleavage of the Fe-C_a bond.^{12b} This in turn provides indirect justification in favor of the completely opposite regioselectivity from 2e or 2f. Either greater stabilization of the carbocation at the benzylic over allylic position or the relatively stable Fe– C_β bond due to benzylic resonance presumably influences such reversal of regioselectivity (Scheme S3, ESI†).^{11,12} Benzylic resonance facilitates C_{β} -H to coordinate to iron to form a σ -agostic structure ($\sigma_{C\alpha-H}$ serves as an electron donor and high lying $\sigma^*_{C\alpha-H}$ acts as a π -acceptor), which accounts for the Markovnikov product formation.^{1*a*,11} Additionally, treatment of styrene with PhIO and HCO2H and its subsequent reaction with K₂CO₃ under similar catalytic conditions give 2-phenylacetaldehyde and 1-phenylethane-1,2-diol (via ring opening of epoxide), implying the simultaneous existence of both pathways.^{5c} However, the influential role of strong Lewis acidic iron and BF₄⁻ cannot be excluded.¹³ Nevertheless, a similar conversion even in the presence of a radical scavenger and absolute retention of the strained four membered ring of α -pinene essentially rule out the alternate possibility of a radical intermediate in the present case.¹⁴

In conclusion, an efficient and reliable catalytic protocol has been developed for anti-Markovnikov oxidation to aldehydes from terminal alkene functionalities under mild reaction conditions. The present catalytic system functions well at room temperature in most cases with the abundant, cheap, benign and simple iron-catalyst, which is currently considered as an ideal option to replace any precious metal in homogeneous catalysis.⁹ Both the tandem epoxidation–isomerization and pinacol like rearrangement are found to be operational in the present catalytic process. Further improvement of the present catalytic protocol with respect to the effective use of more benign oxidants and non-chlorinated solvents is in progress.

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

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