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COMMUNICATION

Metal-Free, Catalytic Regioselective Oxidative Conversion of Vinylarenes: A Mild Approach to Phenylacetic Acid Derivatives

Received 00th January 20xx,
Accepted 00th January 20xx

DOI: 10.1039/x0xx00000x

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A new synthetic approach towards the synthesis of phenylacetic acids from aromatic alkenes has been developed for the first time under mild conditions by employing non-toxic reagents such as molecular iodine and oxone. This metal-free catalytic regioselective oxygenation of vinylarenes proceeds *via* tandem iodofunctionalization/de-iodination induced rearrangement.

The selective oxidation methods for the conversion of readily available and cheap hydrocarbons towards value-added oxygenated products as versatile building blocks or fine chemicals under mild conditions have been found to be indispensable tools in modern organic synthesis.[1] In particular, the regioselective catalytic oxidative functionalization of carbon-carbon double bond of alkenes is of utmost importance for the synthesis of a wide variety of organic products, because they are manufactured on very large scales. For example, the Pd(II)-catalyzed direct oxidation of olefins to methyl ketones (Markovnikov products), usually known as the Tsuji–Wacker oxidation, has found widespread applications in both academia and industry.[2] Nevertheless, the achievement of anti-Markovnikov selectivity in the oxidation of alkenes is a difficult process and has been listed as one of the top ten challenges to be addressed by catalysis since 1993.[3] Over the past few years, considerable efforts have been made toward the historical challenge of anti-Markovnikov functionalization of alkenes.[4,5] However, the regioselective oxidation of aromatic alkenes has not been reported so far for the synthesis of arylacetic acid derivatives.

Phenylacetic acids are important class of compounds found in many natural products and pharmaceuticals,[6] which exhibit significant biological activities including anti-inflammatory, antifungal, antityrosinase, and antimicrobial activity. For example, the nonsteroidal anti-inflammatory drugs, such as Ibuprofen and Diclofenac contain a phenylacetic acid moiety in their structures (Fig. 1). The particular high importance among these compounds made attentive the chemists to develop an assortment of synthetic protocols for their preparation. The conventional methods for the synthesis of phenylacetic acids involve the carbonylation of benzyl halides/benzyl alcohols using transition metal catalysts

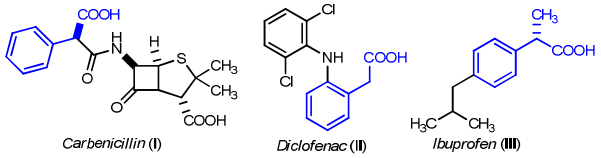
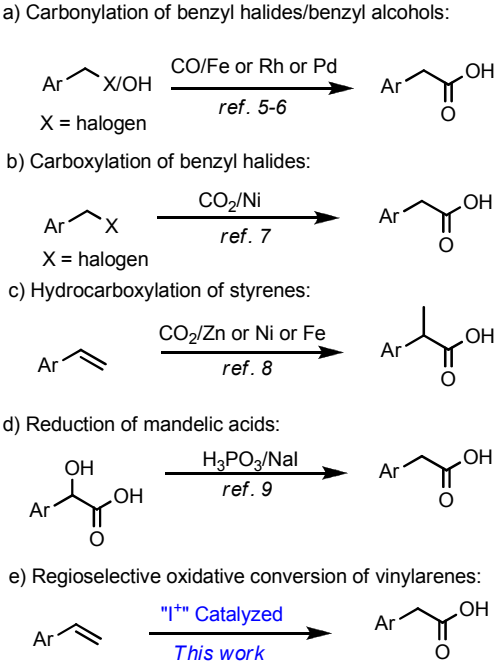


Figure 1. Representative biologically active compounds containing phenylacetic acid moieties.



Scheme 1. Different methods for the synthesis of phenylacetic acids.

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Electronic Supplementary Information (ESI) available: Experimental procedures and NMR spectra (^{1}H and ^{13}C). See DOI: 10.1039/x0xx00000x

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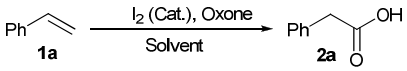
(Scheme 1a).[7-8] In recent years, the carboxylation of benzyl halides,[9] hydrocarboxylation of alkenes[10] and reduction of mandelic acids[11] have provided direct access to phenylacetic acids (Scheme 1b-d). However, since most of these standard protocols rely on the use of transition metals (in catalytic amounts or in over stoichiometric amounts), costly and/or corrosive reagents, harsher reaction conditions and sometimes require prior synthesis of their precursors, there is still an apparent need for methodology improvement with respect to environmental and economic issues. Indeed, the metal-free catalytic regioselective oxygenation of vinylarenes would enable the ecologically and economically viable production of arylacetic acid derivatives.

Over the past few years, the iodine catalysts have been increasingly employing as environmentally benign and promising alternatives to many transition metal catalysts used in various carbon-carbon and carbon-hetero atom bond formation reactions.[5,12] Nonetheless, to the best of our knowledge, these catalysts have never been utilized for the regioselective oxygenation (in an anti-Markovnikov fashion) of vinylarenes for the preparation of phenylacetic acid moieties. Being interested in important biological activities of phenylacetic acids, we, herein, report the first non-metal catalyzed protocol for the synthesis of phenylacetic acid derivatives from aromatic alkenes employing mild reagents such as molecular iodine and oxone at room temperature.

We initiated our investigation by choosing styrene (**1a**) as model substrate, molecular iodine as the source of electrophilic iodine and oxone as terminal oxidant. To our delight, the reaction of **1a** with iodine and oxone in aqueous media indeed occurred to give the desired phenylacetic acid product **2a** in 42% yield at room temperature (Table 1, entry 1). In an attempt to improve the yield of **2a**, various co-solvent systems (homogeneous and biphasic system) have been investigated and found that the combination of 1,2-dimethoxyethane (DME) and water (4:1; 5 mL) is the best for achieving the maximum yield (88%) of phenylacetic acid (**2a**) (Table 1, entries 2-8). Next, we screened the amount of reagents (iodine and oxone) and other oxidants to further enhance the reaction yield. But, either increasing or decreasing the amounts of reagents or replacing the oxone with various oxidants such as *m*-CPBA, $K_2S_2O_8$, aq.H_2O_2 and aq.TBHP did not improve the yield of the reaction (Table 1, entries 9-17).

With the optimized reaction conditions in hand, we then focused our attention on assessing the scope of the reaction against a variety of alkenes (Table 2 and Table 3). As shown in Table 2, all the terminal aromatic alkenes reacted smoothly to afford moderate to excellent yields of the corresponding anti-markovnikov products. Styrene (**1a**) produced the respective acid **2a** in high yield (88%). In order to determine the influence of substitution on aromatic ring of styrene on the reaction path with this reagent system, we considered the reaction with different substitutions. The alkyl substituted styrenes **1b-1d** were successfully converted into the corresponding acids **2b-2d** in 45-86% yields (Table 2, entries 2-4) and the lower yield of 2,4-dimethyl styrene **(1c)** probably due to steric hindrance of *ortho* substituted methyl group.

Table 1. Optimization study for metal-free catalytic conversion of styrene (**1a**) to phenylacetic acid (**2a**).[a,b]

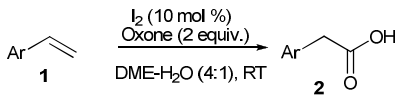


Entry	Solvent	Oxone (equiv.)	Time (h)	Yield (%)
1	H_2O	2	3	42
2	CH_3CN-H_2O (4:1)	2	4	63
3	**DME-H_2O (4:1)**	2	**6**	**88**
4	$CHCl_3$-H_2O (4:1)	2	6	-
5	DCM-H_2O (4:1)	2	6	-
6	CCl_4-H_2O (4:1)	2	6	-
7	DCE-H_2O (4:1)	2	6	-
8	DME-H_2O (1:4)	2	2	70
9	DME-H_2O (4:1)	1.5	6	75
10	DME-H_2O (4:1)	3	6	88
11	DME-H_2O (4:1)	0.5	6	20
12[c]	DME-H_2O (4:1)	2	6	83
13[d]	DME-H_2O (4:1)	2	6	88
14[e]	DME-H_2O (4:1)	2	6	<5
15[f]	DME-H_2O (4:1)	2	6	-
16[g]	DME-H_2O (4:1)	2	6	-
17[h]	DME-H_2O (4:1)	2	6	-

[a] Reaction conditions: Unless otherwise stated, styrene (1 mmol), I_2 (10 mol %), oxone, solvent (5 mL). [b] Isolated yields. [c] I_2 (5 mol %). [d] I_2 (15 mol %). [e] *m*-CPBA was used as an oxidant instead of oxone. [f] $K_2S_2O_8$ was used as an oxidant instead of oxone. [g] aq.H_2O_2 was used as an oxidant instead of oxone. [h] aq.TBHP was used as an oxidant instead of oxone.

Highly activated styrenes **1e** and **1f** furnished the corresponding products **2e** and **2f**, respectively, in moderate yields (Table 2, entries 5-6). Halo substituents at para position of styrenes including **1g-1i** were efficiently oxidized to give the corresponding products **2g-2i** in 77-91% yields possibly due to

Table 2. Regioselective metal-free catalytic oxidative conversion of terminal aromatic olefins.[a,b]



Entry	Olefin **1**	Time (h)	Product **2**	Yield (%)
1	Ar = Ph; **1a**	6	**2a**	88
2	Ar = 4-MeC_6H_4; **1b**	2.5	**2b**	86
3	Ar = 2,4-diMeC_6H_3; **1c**	3	**2c**	45
4	Ar = 4-*t*-BuC_6H_4; **1d**	4	**2d**	76
5	Ar = 4-$MeOC_6H_4$; **1e**	2	**2e**	48
6	Ar = 2-$MeOC_6H_4$; **1f**	3.5	**2f**	54
7	Ar = 4-FC_6H_4; **1g**	4	**2g**	91
8	Ar = 4-ClC_6H_4; **1h**	3	**2h**	77
9	Ar = 4-BrC_6H_4; **1i**	4	**2i**	83
10	Ar = 3-BrC_6H_4; **1j**	5	**2j**	52
11	Ar = 3-$NO_2C_6H_4$; **1k**	24	**2k**	50
12	Ar = C_5H_5N; **1l**	24	**2l**	00

[a] Reaction conditions: substrate (1 mmol), I_2 (10 mol %), oxone (2 mmol), DME-H_2O (4:1, 5 mL), RT. [b] Isolated yields.

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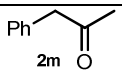
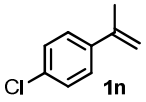
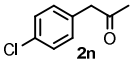
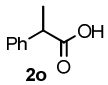
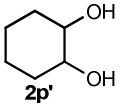
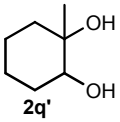
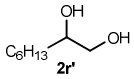
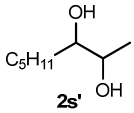
Table 3. Regioselective metal-free catalytic oxidative conversion of aromatic (disubstituted) and aliphatic olefins.[a,b]

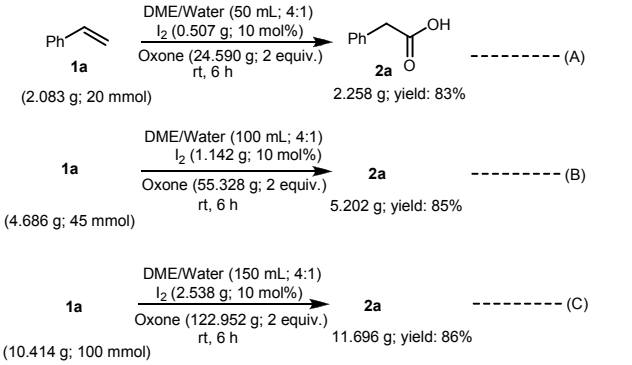
Entry	Olefin 1	Time (h)	Product 2 or 2'	Yield (%)
1	 1m	3	 2m	76
2	 1n	3	 2n	80
3	 1o	3	 2o	35
4	 1p	1	 2p'	91
5	 1q	1.5	 2q'	63
6	1-octene (**1r**)	4	 2r'	56
7	*trans*-2-octene (**1s**)	5	 2s'	58

[a] Reaction conditions: substrate (1 mmol), I_2 (10 mol %), oxone (2 mmol), DME-H_2O (4:1, 5 mL), RT. [b] Isolated yields.

the inductive and resonance effect of halogen (F, Cl and Br) groups (Table 2, entries7-9). However, the halo substituent, for example bromo group, at *meta* position provided lesser yield than that obtained for *para* position (Table 2, entry 10). Similarly, styrene containing strong electron with-drawing group i.e. 3-nitro styrene (**1k**) also yielded the corresponding product **2k** in 50% yield even after prolonged the reaction time for 24 h (Table 2, entry 11). In contrast, the hetero aromatic alkene i.e., 2-vinylpyridine (**1l**) did not react under optimized conditions and the only starting material (100%) was recovered after 24 h (Table 2, entry 12).

Next, we investigated the efficiency of this method with a few 1,1-disubstituted, internal and aliphatic olefins (Table 3). The reactions of α- and β-substituted styrene derivatives **1m-1o** under standard conditions provided the corresponding anti-Markovnikov products **2m-2o** in 35-80% yields (Table 3, entries 1-3). These results suggesting that the reactions of styrene derivatives may involve the rearrangement of aryl group under the standard conditions. However, the aliphatic alkenes (cyclic and acyclic) **1p-1s** yielded the corresponding vicinal diols **2p'-2s'** in 56-91% yields instead of desired anti-Markonikov (rearranged) products **2p-2s** (Table 3, entries 4-7).

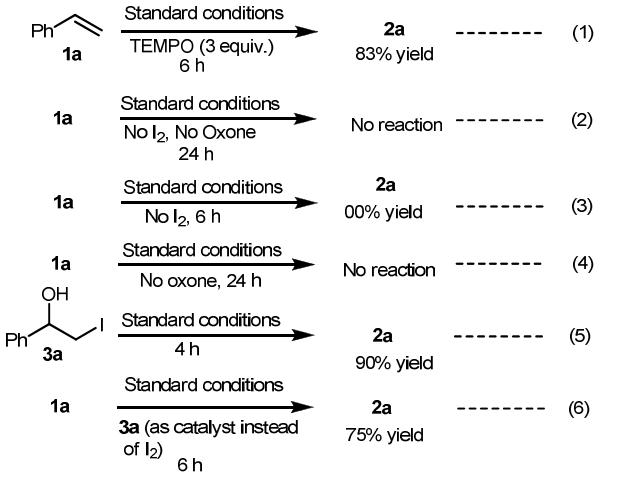
To illustrate the practical utility of this protocol, we have performed the large-scale reactions (20, 45 and 100 mmol scale) of styrene (**1a**) under optimized conditions. As outlined



Scheme 2. Large-scale experiments for the synthesis of phenylacetic acid (**2a**) from styrene (**1a**)

in Scheme 2, all the preparative-scale reactions proceed smoothly with excellent yields.

In order to establish the reaction pathway for the formation of phenylacetic acids from aromatic olefins, we performed several control experiments and are outlined in Scheme 3. The reaction of styrene (**1a**) under optimal conditions in the presence of a radical inhibitor, such as



Scheme 3. Control experiments.

TEMPO (2,2,6,6-tetramethyl piperidine 1-oxy) had no significant effect on the yield of the desired product (Scheme 3, eq. 1), indicating the absence of a radical mechanism. The reaction in the absence of I_2 and oxone did not occur to provide the product **2a** (Scheme 3, eq. 2). When the reaction was performed without I_2, the reaction failed to deliver the desired product (Scheme 3, eq. 3). The product **2a** was also not formed in the absence of oxone (Scheme 3, eq. 4). These results collectively indicated the importance of iodine catalyst and oxidant in this reaction. When the co-iodo intermediate **3a** was subjected to the standard reaction conditions, the formation of **2a** was observed in 90% yield (Scheme 3, eq. 5). Also, the reaction of **1a** was investigated using 3a as the catalyst instead of I_2, and obtained the product **2a** in 75% yield (Scheme 3, eq. 6). These reactions indicating that **3a** may be

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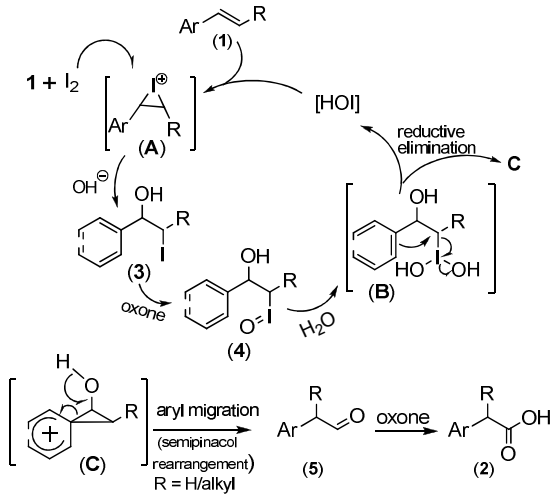
the intermediate in the anti-Markovnikov selective oxidation process.



Scheme 4. Plausible mechanism for the I_2/oxone mediated catalytic conversion of vinylarenes to arylacetic acids.

Based on the above investigated results and literature reports, a plausible mechanism is proposed and is outlined in Scheme 4. Initially, the I_2 reacts directly with an alkene **1** to form a co-iodo intermediate **3** (or reacts with oxone to form transient HOI species,[5c] which readily reacts with **1** to form 3). The de-iodination of **3** *via* its oxidation to hypervalent iodine intermediate **4** followed by reductive elimination led to HOI and a short lived phenonium ion intermediate **C**.[5c] The intermediate **C** undergoes aryl group migration to form corresponding aldehyde **5**, which upon oxidation in presence of oxone led to the desired arylacetic acid **2**. The HOI generated in the first cycle continues the catalytic cycle until the complete consumption of starting material into the product.

Conclusions

In conclusion, we have developed the first non-metal mediated catalytic protocol for the synthesis of phenylacetic acid derivatives from readily available starting materials using simple and non-toxic reagents such as molecular iodine and oxone. This new metal-free catalytic approach offers several advantages such as mild conditions, simple work up procedures, use of eco-friendly and readily available reagents and the exclusion of the need for transition metals. Moreover, the scope and limitations of this process are demonstrated with various terminal and internal alkenes. Furthermore, a plausible mechanism also proposed for the formation of phenylacetic acid derivatives from vinylarenes under metal-free catalytic conditions.

Acknowledgements

We thank the CSIR Network project CSC-0125 for financial support. K.S. P.S. and B. R. acknowledge the UGC, India and M.N. and C.D. acknowledge the CSIR, India for financial support in the form of fellowships.

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Metal-Free, Catalytic Regioselective Oxidative Conversion of Vinylarenes: A Mild Approach to Phenylacetic Acid Derivatives

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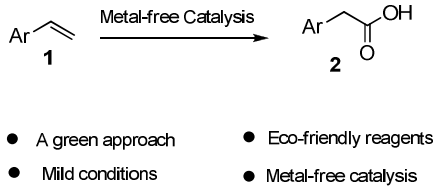

A first metal-free catalytic approach for the synthesis of phenylacetic acid derivatives from aromatic olefins is reported.

RSC Advances Accepted Manuscript