Organic LETTERS

Letter

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Organocatalytic Aerobic Oxidation of Benzylic sp^3 C−H Bonds of Ethers and Alkylarenes Promoted by a Recyclable TEMPO Catalyst

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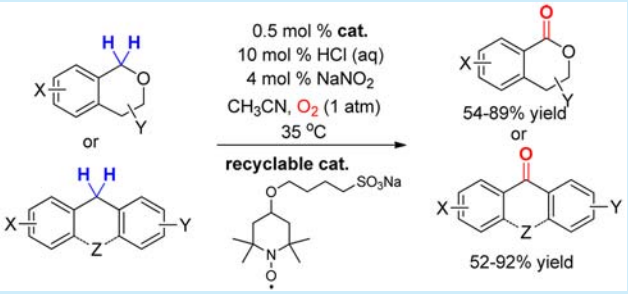
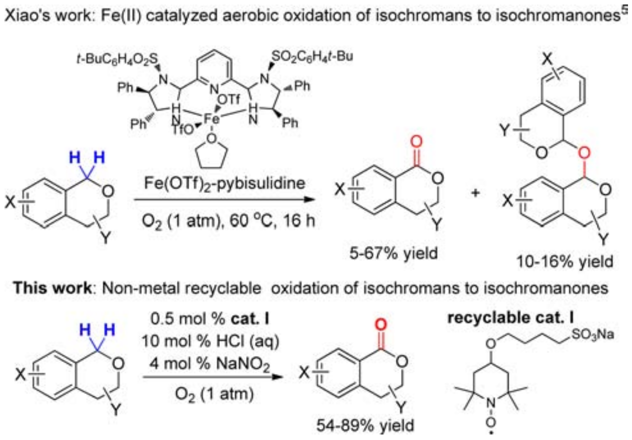
S Supporting Information

ABSTRACT: An entirely metal-free catalyst system consisting of an easily prepared recyclable new TEMPO derived sulfonic salt catalyst, and mineral acids ($NaNO_2$ and HCl) has been developed for selective aerobic oxidation of structurally diverse benzylic sp^3 C−H bonds of ethers and alkylarenes. The mild reaction conditions allow for the generation of synthetically and biologically valued isochromanones and xanthones from readily accessible alkyl aromatic precursors in good yields.



The development of practical benzylic oxidation reactions has long been pursued by synthetic chemists because, as one of the most useful transformations in organic synthesis, the process offers straightforward access to highly synthetically valued building blocks and scaffolds from readily accessible alkyl aromatic precursors.[1] The classic benzylic oxidation reactions normally employ a stoichiometric amount of oxidizing reagents under harsh reaction conditions.[2] Significant efforts have been directed toward the development of more efficient catalytic processes in the recent past. These processes largely rely on the transition metal complex promoters in the presence of a stoichiometric amount of expensive terminal oxidants such as *tert*-butyl hydroperoxide (TBHP), phenylmethylsulfoxide (PMSO), *N*-hydroxyphthalimide (NHPI), and their derivatives.[3] Research efforts have also been made on the use of environmental friendly oxygen as the oxidant in the presence of precious, toxic transition metals.[4] Recently, Xiao and coworkers disclosed an interesting catalytic system of $Fe(OTf)_2$ with pybisulidine ligands and oxygen as the oxidant for the dehydrogenative α-oxygenation of ethers to esters (Scheme 1).[5] Unfortunately, the low conversion of starting materials led to poor yields with typical values around 20−50% for the reactions studied. Moreover, in addition to the cost concern of using the complex pybisulidine ligands for the oxidation process, mixed products of esters and 1,1′-oxidiisochromans for isochroman substrates were obtained. Clearly there is an urgent demand for new synthetic paradigms, able to achieve useful transformation in a more cost-effective and green manner.

Scheme 1. Catalytic Aerobic Oxidation of Benzylic C−H Bonds



Toward this end, we wish to disclose an entirely metal-free organocatalytic, aerobic oxidation of benzylic sp^3 C−H bonds of isochroman ethers to isochromanones with significantly improved yields under aerobic conditions (1 atm of O_2) (Scheme 1). Moreover, the catalytic strategy can be extended to the oxidation of benzylic sp^3 C−H bonds of alkylarenes to ketones with high efficiency for the first time. The application of the useful protocol in the synthesis of value targets has also been demonstrated. TEMPO, a shelf-stable radical species, is the catalyst of choice in industry[6] and has been widely used for the oxidation of alcohols to carbonyls.[7,8] Despite the great success, their use for oxidative functionalization of other functionalities represents an important challenge and the examples are very limited.[9]

In our continuing efforts on developing useful ogranocatalytic reactions,[10] we are particularly interested in new green and cost-effective catalytic processes. Along this line, we designed a

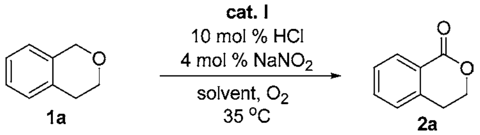
Received: October 4, 2015
Published: October 29, 2015

DOI: 10.1021/acs.orglett.5b02877
Org. Lett. 2015, 17, 5492−5495

novel class of recyclable TEMPO derived sulfonate organocatalysts including **I** (Scheme 1).[11] We pursued employing cheap metal-free mineral acid from $NaNO_2$ and HCl aqueous solution as the cocatalyst[12] and O_2 as the oxidant for large-scale applications. The amphiphilic feature renders the catalyst able to perform the reaction efficiently in a mixture of organic solvent and requisite HCl aqueous solution. On the other hand, the catalyst could be conveniently recovered by simple water extraction. Therefore, the successful realization of **I** promoted oxidation reactions will produce truly efficient green processes, which may increase its application potential in industrial settings.

The low yields in the oxidation of isochromans reported by Xiao[5] promoted us to test our catalyst for this process. In the initial study, isochroman **1a** was treated with 2 mol % TEMPO catalyst **I**, 4 mol % $NaNO_2$ (solid), and 10 mol % concn HCl (12.0 M) aq solution with an O_2 balloon in 3 mL of CH_3CN at rt (Table 1). To our delight, the resulting homogeneous reaction mixture went smoothly to give the desired product isochromanone **2a** in 59% yield after 12 h (entry 1). The starting material **1a** was completely consumed within 8 h in 83% yield when the temperature was raised to 35 °C (entry 2). Probing the catalyst loading revealed the use of as low as 0.5 mol % without sacrificing reaction yields (entries 3–5). The screening of solvents suggested that the reactions could be performed in all solvents probed, but the yields varied significantly. CH_3CN was the reaction medium of choice for the process (entries 6–9). No gain resulted by decreasing the amount of $NaNO_2$ and HCl used (14%, entry 10). These studies led to establishing the optimal reaction conditions: a 0.5 mol % of TEMPO sulfonic sodium catalyst **I** with 4 mol % $NaNO_2$ and 10 mol % HCl in CH_3CN at 35 °C with an O_2 balloon (entry 4).

Table 1. Optimization Reaction for Catalytic Aerobic Oxidation of Isochromans[a]



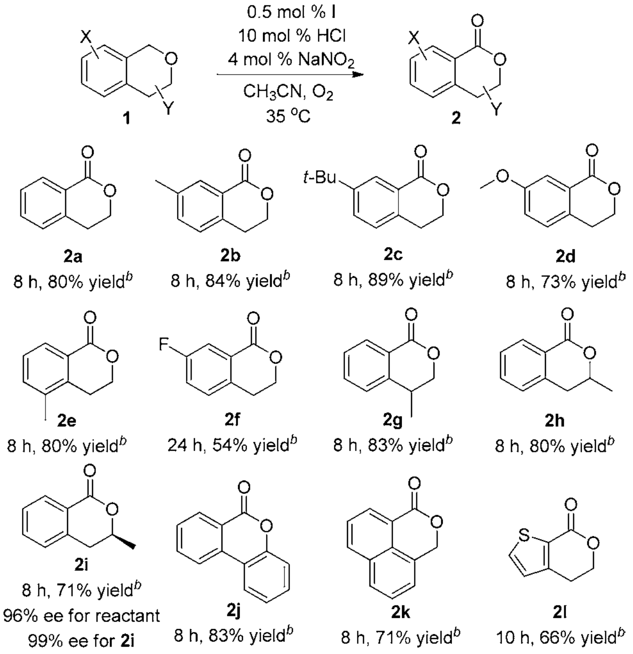
entry	solvent	**I** (mol %)	*t* (h)	yield (%)[b]
1[c]	CH_3CN	2	12	59
2	CH_3CN	2	8	83
3	CH_3CN	1	8	77
4	CH_3CN	0.5	8	80
5	CH_3CN	0.3	12	67
6	$ClCH_2CH_2Cl$	0.5	8	57
7	THF	0.5	8	34
8	DMF	0.5	8	51
9	H_2O	0.5	8	21
10[d]	CH_3CN	0.5	8	14

[a] Unless specified, a mixture of isochroman **1a** (5.0 mmol), **I**, $NaNO_2$ (0.2 mmol), and HCl (12.0 M, 0.5 mmol) in 3.0 mL of CH_3CN equipped with an O_2 balloon was heated at 35 °C for a specified time. [b] Isolated yields. [c] The reaction was run at rt. [d] $NaNO_2$ (0.05 mmol) and HCl (0.1 mmol) used.

With the optimized reaction conditions in hand, we then probed the scope of the new catalytic benzylic oxidation of substituted isochromans (Scheme 2). The results showed that this process serves as a general approach to structurally diverse isochromanones **2** with good yields. It is noteworthy that isochromanones are important structures found in a number of natural products and bioactive molecules.[13] Furthermore, under the mild reaction conditions, we did not obtain the dimer byproducts, observed in Xiao's studies.[5] First, the substitution pattern of isochromans on the aromatic ring was investigated.

Generally, the substrates with electron-neutral or -rich arenes displayed high reactivity and provided products **2a**–**2e** in good yields (73–89%). It appears that the reaction with an electron-withdrawing group became sluggish and gave a relatively poorer yield (**2f**). Next, we examined the reactions for isochromans with a methyl group as the representative substituent on the saturated 'O' ring (**2g**–**2i**). Again, the processes proceeded smoothly with high yields (71–83%). It is noted that the mild reaction conditions can retain the enantioselectivity when chiral isochroman was used as the reactant (**2i**) (see Supporting Information (SI)). Finally, we enabled extension of this protocol to the polycyclic systems including 6*H*-benzo[*c*]chromene (**2j**) and 1,3-dihydrobenzo[*de*]isochromene (**2k**). Furthermore, the mild oxidation method could selectively oxidize the thienopyran-contained structure to give the dehydrogenative *α*-oxygenation product **2l** in acceptable yield without affecting the sensitive heterocyclic ring.

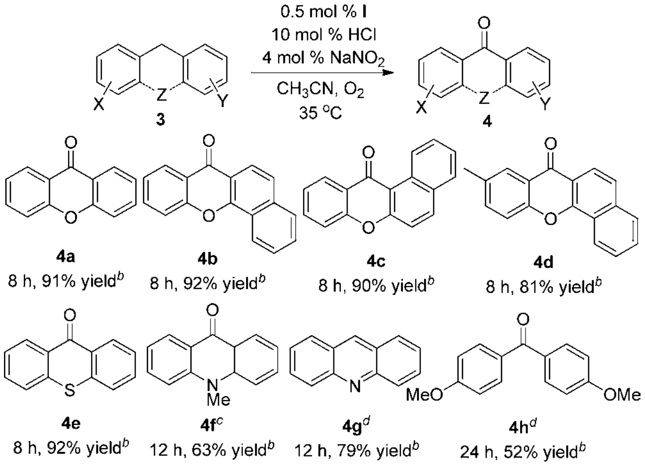
Scheme 2. Catalytic Aerobic Oxidation of Isochromans to Isochromanones[a]



[a] Unless specified, a mixture of **1** (5.0 mmol), **I** (0.025 mmol), $NaNO_2$ (0.2 mmol), and HCl (12.0 M, 0.5 mmol) in 3.0 mL of CH_3CN with a O_2 balloon was heated at 35 °C for a specified reaction time. [b] Isolated yield.

Having showed the viability of the mild catalytic system in efficient oxidization of isochromans, we turned our attention to the oxidation of other benzylic substrates (Scheme 3). "Privileged" structure xanthones, as secondary metabolites of fungi, lichens, and bacteria, are widespread in a diverse range of biologically interesting and medicinal compounds.[14] Generally strong oxidants such as H_2O_2 and TBHP (*tert*-butyl hydroperoxide) in the presence of homo- or heterogeneous transition metal catalysts are employed for these transformations in industry.[15] Herein we demonstrated the metal-free organo-

Scheme 3. Catalytic Aerobic Oxidation of Alkylarenes to Ketones[a]



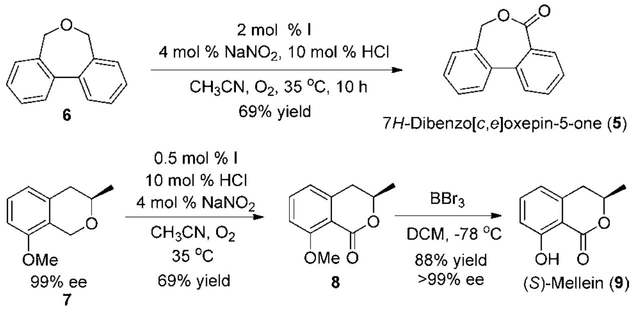
[a]Unless specified, a mixture of **3** (5.0 mmol), **I** (0.025 mmol), $NaNO_2$ (0.2 mmol), and HCl (0.5 mmol) in 3.0 mL of CH_3CN with an O_2 balloon was heated at 35 °C. [b]Isolated yields. [c]0.1 mmol of **I** was used. [d]0.25 mmol of **I** was used.

catalytic protocol as an effective route for preparation of xanthones in good to excellent yields (**4a**–**4d**). Moreover, thioxanthene was selectively oxidized into thioxanthen-9-one without touching "S" in high isolated yield (**4e**). In addition to "O" and "S", "N"-containing heterocycle could also participate in the processes (**4f**–**4g**). It was found that the "N" form played a role in the products produced. *N*-Methyl gave 10-methyl-9,10-dihydroacridine (**4f**), while 9,10-dihydroacridine led to aromatic acridine (**4g**).

Finally, acyclic bis(4-methoxyphenyl)methane can also be oxidized to deliver ketone (**4h**). An important feature of the TEMPO sulfonic salt catalyst **I** bestowed the recyclable capacity. The stability and reusability of **I** was fulfilled by oxidization of isochroman and xanthene in six continuous runs (Table S1 in SI).[16] The proposed mechanism for this catalytic oxidation was discussed in the SI.

The power of the newly developed reaction has also been demonstrated as key steps in the synthesis of valuable targets. 7*H*-Dibenzo[*c*,*e*]oxepin-5-one (**5**), an important intermediate for preparation of curable polymeric materials,[17] could be obtained via oxidation of the corresponding ether precursor **6** under the slightly modified conditions using 2 mol % cat. **I** in 69% yield (Scheme 4). However, the previous method used a stoichiometric amount of highly toxic bromine to perform the oxidation, and the yield is unsatisfactory (45%).[18] Natural product (*S*)-mellein[19] possesses antifungicidal, antibacterial, and HCV protease-inhibitory properties.[20] The reported synthetic protocol employed the Jones oxidation of isochroman **7** and then BBr_3 mediated cleavage of the methyl group resulting in a total 50% yield for the two steps.[20b] By using this greener catalytic oxidation method, (*S*)-mellein could be obtained in 61% yield over the two steps while no racemization was observed in the oxidation reaction and deprotection processes (see SI).

Scheme 4. Synthetic Applications



In summary, an entirely metal-free catalyst system has been developed for aerobic oxidation of structurally diverse benzylic sp^3 C–H bonds of ethers and alkylarenes for the first time. A new easily prepared recyclable TEMPO derived sulfonic salt catalyst is designed and combined with cheap mineral acids ($NaNO_2$ and HCl) as the cocatalyst in the presence of O_2 as the oxidant. The mild reaction conditions allow for the generation of synthetically and biologically valued isochromanones and xanthones from readily available alkyl aromatic precursors with a broad substrate scope and functional group tolerance. The application of the mild protocol in the synthesis of valued targets has also been demonstrated. Further exploration of new organic transformations and the application of this methodology in the synthesis of biologically relevant molecules are under investigation in our laboratories.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b02877.

> Experimental procedures and ^1H and ^{13}C NMR and HRMS data for experimental procedures and characterization of the products **2**, **4**, **5**, and **9** (PDF)

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Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENTS

Financial support of this research from the program for Professor of Special Appointment (Eastern Scholar) at Shanghai Institutions of Higher Learning (No. 201226, H. L.), the National Science Foundation of China (21372073, 21572054 and 21572055), the Fundamental Research Funds for the Central Universities and East China University of Science and Technology, and the China 111 Project (Grant B07023) is gratefully acknowledged.

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