ACS Catalysis

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Metal-Free, *n*-Bu_4NI-Catalyzed Regioselective Difunctionalization of Unactivated Alkenes

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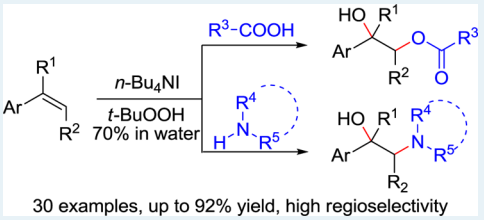
Supporting Information

ABSTRACT: A new synthetic approach toward difunctionalization of alkenes has been developed under metal-free conditions. Various carboxylic acids and amines could react smoothly with alkenes to give dioxygenation and oxyamidation products, respectively. This organocatalytic process delivers 2-hydroxy alcohols directly from simple alkenes with high levels of region control.



KEYWORDS: *alkene, dioxygenation, oxyamidation, metal-free, regioselective*

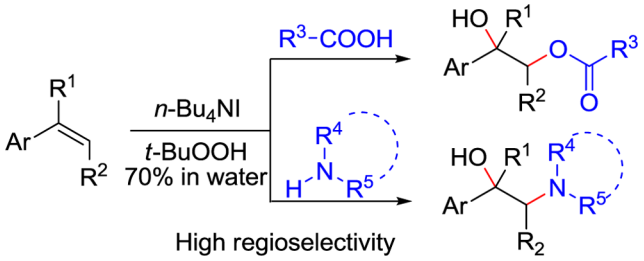
INTRODUCTION

Direct difunctionalization of alkenes has attracted considerable attention, providing the most attractive strategy for the assembly of functionalized organic compounds. In recent years, a number of transition-metal-catalyzed difunctionalizations of alkenes have been reported, such as dioxygenation,[1] oxyamidation,[2] oxyphosphorylation,[3] and diamination.[4] However, the cost, toxicity and environmental impact of these catalysts have hindered its further application. In this context, the development of a metal-free difunctionalization procedure provides a challenging and highly attractive target. Despite some remarkable progress that has been made, this area is considerably less established than their metal-based counterparts,[5−7] and regioselective difunctionalization of alkenes is still a challenge. Recently, the catalytic system "*n*-Bu_4NI−TBHP" has been a focus of interest because of high efficiency, lower toxicity, and environmental friendliness,[8] and some excellent results about C−O[9] and C−N[10] bond formations have been achieved. Herein, we report a protocol for an *n*-Bu_4NI-catalyzed regioselective difunctionalization of alkenes using TBHP as an oxidant (Scheme 1).

RESULTS AND DISCUSSION

Initially, the reaction of α-methylstyrene **1a** with 4-chlorobenzoic acid **2a** was selected as a model reaction. The dioxygenation product **3a** could be formed under the catalysis of *n*-Bu_4NI (Table 1, entry 1). Encouraged by this result, we investigated the reaction conditions in detail, and the results are summarized in Table 1. Among the catalysts screened, *n*-Bu_4NI showed the best catalytic efficiency (Table 1, entry 1). The use of *n*-Bu_4NBr, KI, or I_2 instead of *n*-Bu_4NI decreased the yields dramatically (Table 1, entries 2−4). Subsequently, various oxidants were evaluated in this process. The starting material **1a**

Scheme 1. Difunctionalization of Alkenes



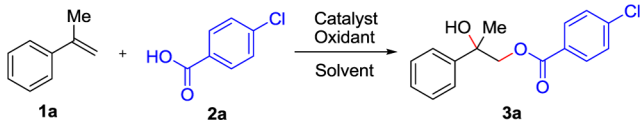
was rapidly consumed when $K_2S_2O_4$ was used as an oxidant; only a trace amount of product **3a** was detected (Table 1, entry 5). Other oxidants such as O_2, H_2O_2, and DTBP gave unsatisfactory results (Table 1, entries 6−8). To maximize the yields, different solvents were also tested. The results showed that *n*-hexane is a highly effective solvent, affording the product **3a** with the highest isolated yield (Table 1, entry 12). In addition, control experiments demonstrated that no **3a** could be identified when either *n*-Bu_4NI or TBHP was absent (Table 1, entries 13 and 14).

With the optimized reaction conditions established (Table 1, entry 12), the scope of our protocol was investigated (Table 2). First, a variety of alkenes were tested. Under the optimized conditions, α-methylstyrene and 1,1-diphenylethylene were converted to dioxygenation products in good isolated yields (Table 2, **3a** and **3b**). Styrene substrates bearing electron-withdrawing groups were converted into the corresponding products with higher yields than electron-donating groups

Received: April 1, 2013
Revised: May 16, 2013

   dx.doi.org/10.1021/cs400250m | *ACS Catal.* 2013, 3, 1365−1368

Table 1. Optimization of Reaction for the Alkene Dioxygenation[a]



entry	catalyst	oxidant	solvent	yield (%)[b]
1	*n*-Bu_4NI	TBHP[c]		75
2	*n*-Bu_4NBr	TBHP		trace
3	KI	TBHP		12
4	I_2	TBHP		23
5	*n*-Bu_4NI	$K_2S_2O_8$		trace
6	*n*-Bu_4NI	O_2[d]		N.D.[e]
7	*n*-Bu_4NI	H_2O_2[c]		N.D.
8	*n*-Bu_4NI	DTBP[c]		trace
9	*n*-Bu_4NI	TBHP	benzene	55
10	*n*-Bu_4NI	TBHP	DCE[c]	73
11	*n*-Bu_4NI	TBHP	EA[c]	78
12	*n*-Bu_4NI	TBHP	*n*-hexane	85
13		TBHP	*n*-hexane	trace
14	*n*-Bu_4NI		*n*-hexane	trace
15	*n*-Bu_4NI	TBHP[f]	*n*-hexane	85

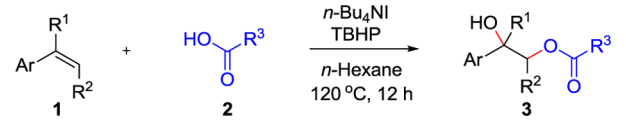
[a]Reaction conditions: **1a** (0.6 mmol), **2a** (0.3 mmol), catalyst (10 mol %), oxidant (0.9 mmol), 120 °C, 12 h. [b]Isolated yield. [c]TBHP, *tert*-butyl hydroperoxide 70% in water; H_2O_2 30% in water; DTBP, di-*tert*-butyl peroxide; DCE, 1,2-dichloroethane; EA, ethyl acetate. [d]Under an oxygen atmosphere (1.0 atm). [e]Not detected. [f]TBHP 5.5 M in decane.

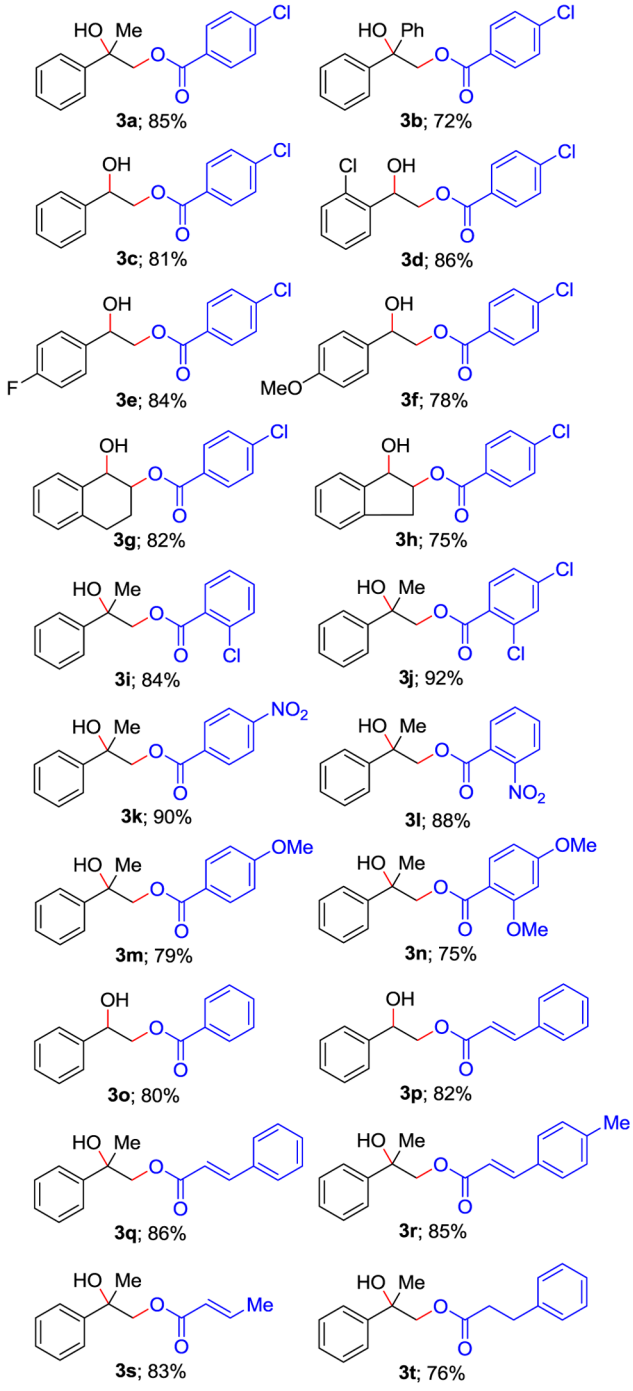
(Table 2, **3c**–**f**). 1,2-Dihydronaphthalene and 1*H*-indene were still very effective in our catalytic system and can give good results (Table 2, **3g** and **3h**). When styrene was replaced by tetraphenylethylene, allylbenzene, or cyclohexene, no difunctionalization product was detected. Subsequently, different aromatic acids were examined in this *n*-Bu_4NI-catalyzed reaction. In general, both electron-deficient and electron-rich aromatic acids were suitable for this protocol, and the corresponding dioxygenation products were obtained in good to excellent yields (Table 2, **3i**–**n**). To our delight, it was found that cinnamic acid derivatives were still very effective in our catalytic system and can give good results (Table 2, **3p**–**r**). When crotonic acid or aliphatic acid was employed, the reaction could proceed smoothly, leading to the desired product with high yield (Table 2, **3s** and **3t**).

The success of dioxygenation of alkenes encouraged us to further explore the scope of this protocol. Interestingly, we found that the reaction of styrene with benzotriazole **4a** at 100 °C for 12 h proceeded smoothly to afford the oxyamidation product **5a** with high efficiency (optimization of reaction conditions; see the Supporting Information). Encouraged by this result, the scope of oxyamidation of alkenes was investigated. As shown in Table 3, a variety of alkenes were tolerated in this process, affording the desired products in good yields (Table 3, **5a**–**f**). Notably, electron-withdrawing as well as electron-donating groups on the aromatic rings were compatible in the oxyamidation of alkenes. Furthermore, different benzotriazoles could react with alkenes in the presence of *n*-Bu_4NI to give the desired products in 89–91% yields (Table 3, **5f** and **5g**). Moreover, indazole, benzimidazole and imidazole were also tolerated in this protocol, furnishing the desired products in good yields (Table 3, **5h**–**j**).

To probe the mechanism of alkene dioxygenation, several control experiments were conducted (Scheme 2). The reaction

Table 2. The *n*-Bu_4NI-Catalyzed Dioxygenation of Alkenes[a]



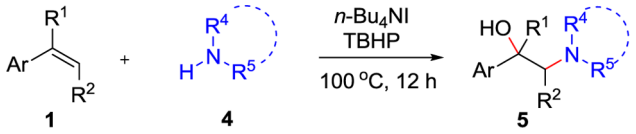


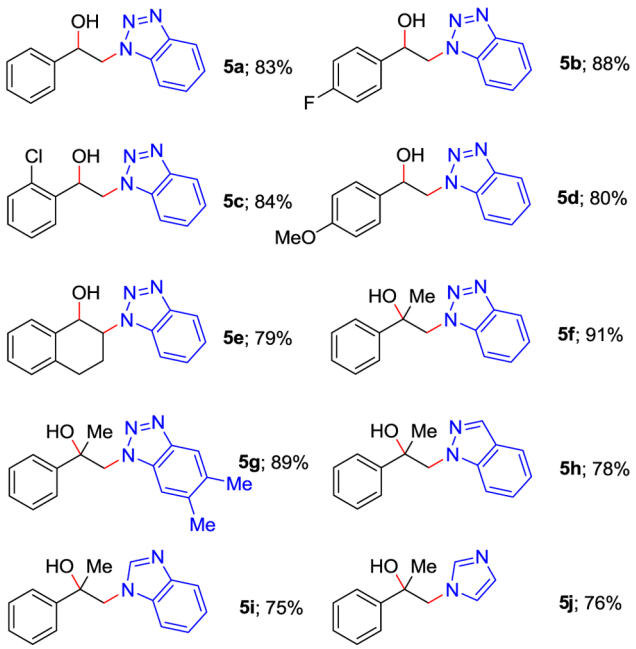
[a]Reaction conditions: **1** (0.6 mmol), **2** (0.3 mmol), *n*-Bu_4NI (10 mol %), TBHP 70% in water (0.9 mmol), *n*-hexane (1.0 mL), 120 °C, 12 h. Yields are for the isolated products.

of α-methylstyrene **1a** and sodium *p*-chlorobenzoate **6** did not result in the formation of **3a** (Scheme 2a). Interestingly, styrene oxide was rapidly consumed in this process; only a trace amount of **3a** was detected (Scheme 2b). The above results indicate that the carboxylate anion and epoxy compound were

dx.doi.org/10.1021/cs400250m | *ACS Catal.* 2013, 3, 1365–1368

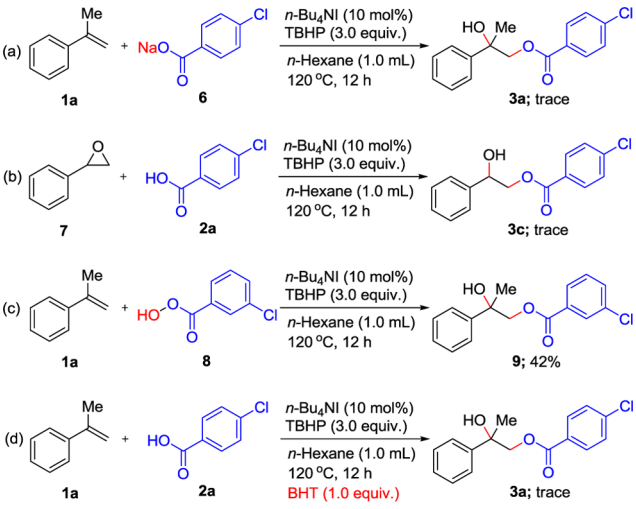
Table 3. *n*-Bu_4NI-Catalyzed Oxyamidation of Alkenes[a]





[a]Reaction conditions: **1** (0.6 mmol), **4** (0.3 mmol), *n*-Bu_4NI (10 mol %), TBHP 70% in water (0.9 mmol), 100 °C, 12 h. Yields are for the isolated products.

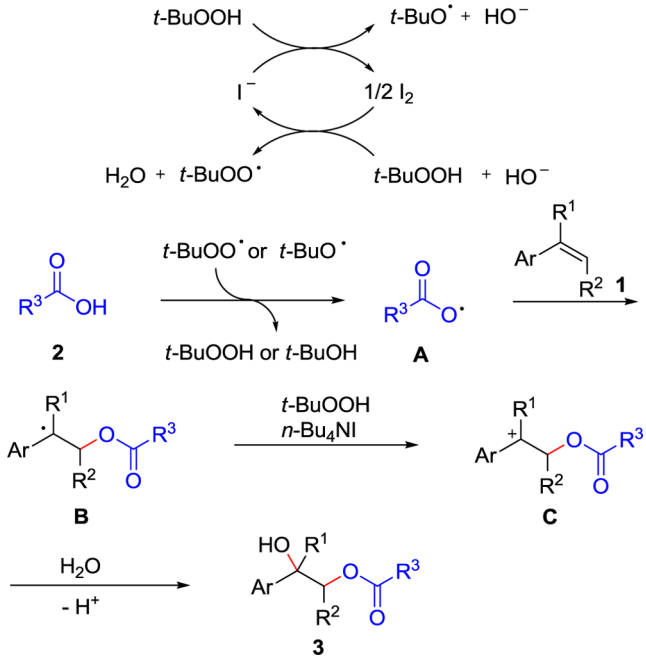
Scheme 2. Investigation into the Reaction Mechanism



not involved in this dioxygenation process. Furthermore, 3-chloroperoxybenzoic acid, a known acyloxy radical donor, was also tolerated in this protocol (Scheme 2c).[9a] Adding a radical inhibitor BHT (2,6-di-*tert*-butyl-4-methylphenol) to the reaction system, the formation of the dioxygenation product was completely suppressed (Scheme 2d).

On the basis of the above results, a plausible mechanism for *n*-Bu_4NI-catalyzed dioxygenation of alkenes is proposed in Scheme 3. Initially, *n*-Bu_4NI reacts with TBHP to give the *tert*-butoxyl and *tert*-butylperoxy radicals. Subsequently, these

Scheme 3. Proposed Reaction Mechanism for *n*-Bu_4NI-Catalyzed Dioxygenation of Alkenes



radicals abstract hydrogen atoms from the acid, **2**, to afford radical **A**,[9a,11] then it reacts with **1** to form intermdiate **B**. Oxidation of radical **B** forms the benzyl cation **C**.[12] Finally, the benzyl cation **C** reacts with water to form the desired product **3** (for the study of HRMS on the mechanism, see the Supporting Information). However, to disclose the exact mechanics of this transformation, further studies are needed.

CONCLUSIONS

In summary, we have successfully developed a novel *n*-Bu_4NI-catalyzed operationally simple method for difunctionalization of alkenes. Various dioxygenation and oxyamidation products were obtained in good to excellent yields using TBHP (70% in water) as an inexpensive and environmentally friendly oxidant. This metal-free process makes use of simple, inexpensive starting materials and demonstrates excellent regioselectivity in all cases. Further studies concerning the detailed mechanism are currently underway in our laboratory.

ASSOCIATED CONTENT

Supporting Information

Experimental procedures and spectroscopic characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENTS

We gratefully acknowledge the National Natural Science Foundation of China (21172106, 21074054), the National Basic Research Program of China (2010CB923303), and the Research Fund for the Doctoral Program of Higher Education

of China (20120091110010) for their financial support. J. Xie thanks the academic scholarship for doctoral candidates of MOE.

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