Tetrahedron xxx (2015) 1–4

Contents lists available at ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

Copper-catalyzed C–O coupling of styrenes with *N*-hydroxyphthalimide through dihydroxylamination reactions

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ARTICLE INFO

Article history:
Received 10 July 2015
Received in revised form 16 September 2015
Accepted 18 September 2015
Available online xxx

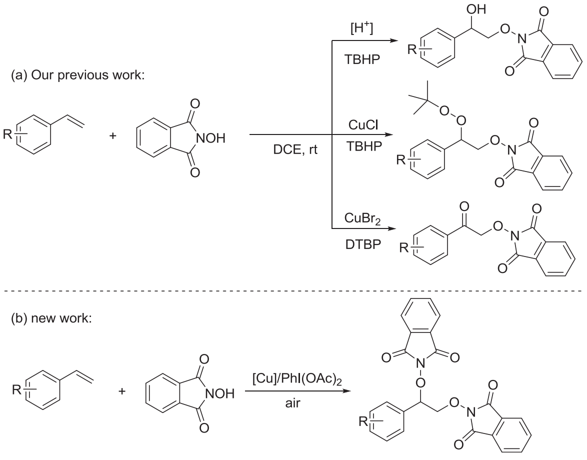
Keywords:
Copper-catalyzed
1,2-Dihydroxylamination
Styrenes
N-Hydroxyphthalimide
Radical addition

ABSTRACT

An efficient method of copper-catalyzed 1,2-dihydroxylaminations of alkenes have been demonstrated under air conditions by using $PhI(OAc)_2$ as oxidant to furnish the dioxygenated products in 20–81% yields. This provided an alternative methodology to synthesis of dioxygenated products, which were easily transformed into diols under the reductive conditions. Furthermore, a free-radical addition mechanism was proposed in this transformation.

1. Introduction

Alkenes are abundant simple chemical feedstocks and organic molecules, which have been widely applied in organic synthesis, and methods for their efficient, selective functionalization are attractive to construct more complex molecules.[1] Among these methods, direct 1,2-difunctionalization of alkenes has attracted considerable attention, providing the most efficient strategy for the construction of functionalized organic compounds.[2] In recent years, a series of metal-catalyzed dioxygenation of alkenes have been developed,[3] particularly, where Sharpless asymmetric dihydroxylation has been applied in the industry.[4] Despite the significance of these reactions, these kinds of 1,2-dihydroxylaminations were rarely reported. It was revealed that *N*-hydroxyphthalimide (NHPI) can generate the phthalimide *N*-oxyl (PINO) radical under the oxidizing conditions, which is an active catalytic species to realize C–H bond functionalization.[5] Recently, NHPI was also utilized as a stoichiometric reactant in organic synthesis to construct the C–O bond.[6] Very recently, our group found that NHPI can be also utilized as a stoichiometric reactant for radical addition of alkenes,[7] and a variety of 1,2-dioxygenation products can be easily obtained using NHPI under ambient conditions (Scheme 1-a).[7b] Herein, we found that when using $PhI(OAc)_2$ as oxidants, copper-catalyzed dihydroxylaminations of alkenes could be realized (Scheme 1-b).



Scheme 1. Hydroxylamination of alkenes.

2. Results/Discussion

We started this research by investigating the reaction of styrene **1a** with NHPI **2a** using CuCl as a catalyst, *N*-fluorobis(phenylsulfonyl)amine (NFSI) as the oxidant in 1,2-dichloroethane (DCE), and **3a** was produced with 65% yield (Table 1, entry 1). When the oxidant was changed to $PhI(OAc)_2$, a much better yield was obtained (entry 2). Increasing the loading of $PhI(OAc)_2$ to 2.2 equiv,

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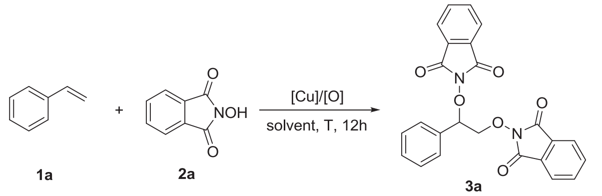
http://dx.doi.org/10.1016/j.tet.2015.09.040

Please cite this article in press as: Xia, X.-F.; et al., Tetrahedron (2015), http://dx.doi.org/10.1016/j.tet.2015.09.040

Table 1
Optimization of reaction conditions for **3a**[a]



Entry	Catalyst	Oxidant	Solvent	T (°C)	Yield (%)[b]
1	10% CuCl+10% Phen	1.5 equiv NFSI[c]	DCE	80	65%
2	10% CuCl+10% Phen	1.5 equiv PhI(OAc)$_2$	DCE	80	78%
3	10% CuCl	1.5 equiv PhI(OAc)$_2$	DCE	80	66%
4	**10% CuCl**	**2.2 equiv PhI(OAc)$_2$**	**DCE**	**80**	**80%**
5	10% CuBr	2.2 equiv PhI(OAc)$_2$	DCE	80	70%
6	10% CuI	2.2 equiv PhI(OAc)$_2$	DCE	80	67%
7	10% Cu(OAc)$_2$	2.2 equiv PhI(OAc)$_2$	DCE	80	56%
8	10% CuCl$_2$	2.2 equiv PhI(OAc)$_2$	DCE	80	76%
9	10% CuBr$_2$	2.2 equiv PhI(OAc)$_2$	DCE	80	58%
10	10% CuCl	2.2 equiv PhI(OAc)$_2$	CH$_3$CN	80	60%
11	10% CuCl	2.2 equiv PhI(OAc)$_2$	Toluene	80	40%
12	10% CuCl	2.2 equiv PhI(OAc)$_2$	DMF	80	0%
13	10% CuCl	2.2 equiv PhI(OAc)$_2$	CH$_3$CH$_2$OH	78	0%
14	—	2.2 equiv PhI(OAc)$_2$	DCE	80	68%

The entry in bold means the best reaction conditions.

[a] Reaction conditions: **1a** (0.3 mmol), **2a** (2.2 equiv, 0.66 mmol), and solvent (2.0 mL), 12 h.

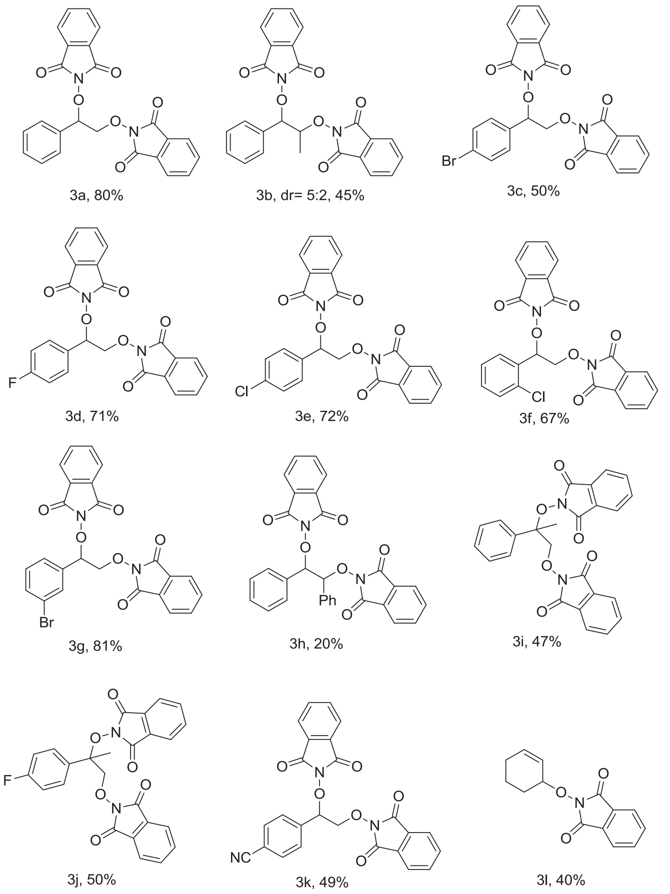
[b] Isolated yield.

[c] NFSI=*N*-fluorobis(phenylsulfonyl)amine.

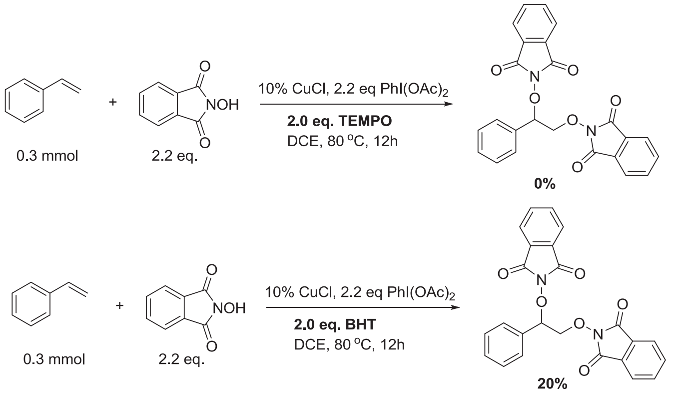
the yield was increased to 80% (entry 4). Next, other copper catalysts were screened including CuBr, CuI, Cu(OAc)$_2$, CuCl$_2$, and CuBr$_2$, where CuCl gave the best result (entries 4–9). In addition, other solvents were also screened, such as, CH$_3$CN, toluene, DMF, and CH$_3$CH$_2$OH, and DCE was found to be the better one. No product was observed using DMF or CH$_3$CH$_2$OH as solvents (entries 12 and 13). When copper catalyst was omitted, a 68% yield of **3a** was obtained (entry 14). In our opinion, the copper catalyst can accelerate the reaction.

With the optimal reaction condition in hand (Table 1, entry 4), we subsequently investigated the substrate scope of this highly selective method (Scheme 2). A series of substituted styrenes can readily be converted into the corresponding products in good to excellent yields. (*E*)-Prop-1-enylbenzene can be well tolerated in this reaction, providing a mixture of diastereoisomers (**3b**, dr=5:2) in 45% yield. When 4-bromostyrene was used, a 50% yield of the product **3c** was obtained. 4-Fluorostyrene can give a 71% yield of the product **3d**, and 4-chlorostyrene gave a similar result (**3e** in 72% yield). When a sterically demanding *ortho* substituted Cl was imbedded in styrene, a slightly lower yield was obtained (**3f** in 67% yield). 3-Bromostyrene gave a better result (**3g** in 81% yield). (*E*)-1,2-Diphenylethene was also tolerated, and a very low yield was obtained due to the steric hindrance (**3h** in 20% yield). α-Methyl styrene gave the corresponding product **3i** in moderate yield. Similarly, 4-fluoro-α-methyl styrene can deliver a 50% yield of product **3j**. The styrene with an electron-withdrawing group (**CN**) can also give the product **3k** in 49% yield. However, the styrene with an electron-donating group (**OAc**) gave a mixed product. When cyclohexene was employed as a substrate, cyclohexenyl-PINO (**3l**) was selectively obtained in moderate yield. Unfortunately, the reaction couldn't happen when norbornene was used as substrate under the standard conditions.

In order to gain insight into the mechanism, the control experiments were carried out (Scheme 3). When 2.0 equiv of TEMPO (2,2,6,6-tetramethyl-1-piperidinyloxy) was added into the reaction system, the desired transformation was found to be completely inhibited. In addition, when 2.0 equiv of BHT (2,6-di-*tert*-butyl-4-methylphenol) was applied in the reaction system, a 20% yield of the product was separated, providing further evidence that a radical addition mechanism was involved in this transformation.



Scheme 2. Scope of the reaction.



Scheme 3. Mechanistic experiment.

According to the results of mechanistic experiment and previous report,[6c,7] a possible reaction pathway is shown in Scheme 4. First, NHPI is oxidized to give the oxygen-centered radical PINO in the presence of copper catalyst and PhI(OAc)$_2$. PINO then quickly reacts with styrene to give radical **A**, which can be further oxidized to cation **B** in the presence of PhI(OAc)$_2$. Last, cation **B** was attacked by nucleophile NHPI to give the product **3a**. In our previous work,[7b] when acid was used as catalyst, water as nucleophile can quickly attack the cation intermediate **B**, and alcohol product was obtained. Under this reaction condition, alcohol products were not observed.

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