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Cu-Facilitated C–O Bond Formation Using *N*-Hydroxyphthalimide: Efficient and Selective Functionalization of Benzylic and Allylic C–H Bonds

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The direct C–H functionalization of simple hydrocarbons has emerged as a research topic of great interest in recent years due to the potential opportunity of developing novel methodologies in synthesis and chemical processes.¹ *N*-Hydroxyphthalimide (NHPI) has been used as a catalyst for the oxidation of certain types of hydrocarbons either in the absence or in the presence of metal cocatalysts to give alcohols, ketones, or carboxylic acids.² It was revealed that the phthalimide *N*-oxyl (PINO) radical, generated in situ from the NHPI precursor, is an active catalytic species responsible for the reaction.³ We envisaged that PINO can be also utilized as a stoichiometric reactant for the oxygenation of hydrocarbons, and the result of which is described herein.⁴

Using ethylbenzene as a test substrate with a stoichiometric amount of NHPI, the reaction efficiency was investigated upon the variation of metal species and oxidants (Table 1).⁵ While the oxygenated PINO adduct (**1**) was obtained in only 29% yield at 70 °C with PhI(OAc)₂ alone (entry 1),⁶ it was found that certain metal additives can significantly improve the reaction efficiency. For instance, CuCl or its variant bearing a *N*-heterocyclic carbene (NHC) ligand showed especially high reactivity (entries 2 and 3). The Cu-facilitated reaction proceeded even at room temperature, albeit with diminished efficiency (entry 4). However, other metals such as Co, Mn, or V species, known to be effective cocatalysts for the oxidation of hydrocarbons using NHPI,⁷ or Cu(II) displayed little improvement (entries 5 and 6). When PhI(OAc)₂ was absent, the reaction was very sluggish (entry 8). In addition, no reaction takes place in the absence of NHPI.

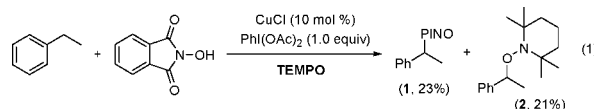
Table 1. Selected List of Screening for the Optimized Conditions^a

entry	catalyst	solvent	yield (%) ^b
1	none	CH ₃ CN	29
2	CuCl	CH ₃ CN	78
3	(NHC)CuCl	CH ₃ CN	77
4 ^c	CuCl	CH ₃ CN	51
5	Co(acac) ₃	CH ₃ CN	30
6	CuCl ₂	CH ₃ CN	46
7	CuCl ₃	CHCl ₃	43
8 ^d	CuCl	CH ₃ CN	10

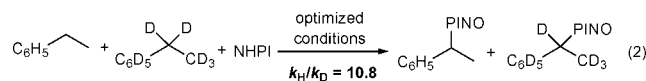
^a Ethylbenzene (5.0 equiv), NHPI (1.0 equiv), PhI(OAc)₂ (1.0 equiv), and catalyst (10 mol %) in solvent (0.3 M) at 70 °C for 12 h under Ar.
^b Determined by ¹H NMR. ^c Performed at 25 °C. ^d Without PhI(OAc)₂.

The present Cu-facilitated oxygenation of benzylic C–H bond was envisioned to proceed via a radical pathway based on a range of experimental data. When TEMPO (2,2,6,6-tetramethyl-1-piperidinyloxy), a well-known radical-capturing species, was added to the reaction mixture, a TEMPO-trapped compound **2** was isolated (21%) in addition to **1** (23%), thus suggesting that the reaction

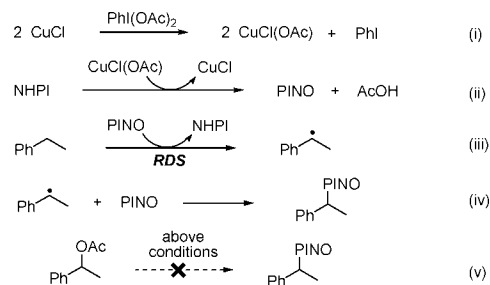
indeed involves a radical intermediate derived from ethylbenzene (eq 1).⁸ In addition, when the reaction mixture was subjected to the electron spin resonance (ESR) measurements, a triplet signal was obtained with *g* = 2.023.⁹



The relative rate constants of the intermolecular competition reaction were determined to be quite high (*k*_{rel} = 10.8, eq 2),⁵ suggesting a possible involvement of the quantum tunneling effect.¹⁰ The measured deuterium kinetic isotope effects (KIE) suggest that the hydrogen abstraction from ethylbenzene may be the rate-determining step during the oxygenation process.



The above observations led us to propose a plausible mechanistic pathway for the present oxygenation (Scheme 1). It is postulated that CuCl acts as a catalytic activator of PhI(OAc)₂,¹¹ leading to acetoxychlorocopper species, which in turn converts NHPI into the PINO radical (steps i and ii).¹² It is believed that an alkyl radical is generated upon the H abstraction from available hydrocarbons by PINO, being most likely the rate-determining step (step iii). Finally, the recombination of the alkyl and nitroxyl radical will lead to the PINO adducts (step iv).

Scheme 1

It should be mentioned that the PINO adduct is not produced by substitution of 1-phenylethyl acetate as an intermediate. In fact, when separately prepared 1-phenylethyl acetate was subjected to the reaction conditions, it remained intact (Scheme 1, step v). This result, combined with the fact that formation of 1-phenylethyl acetate is negligible (<1%) during the course of the oxygenation reaction, provides the basis for the exclusion of the stepwise substitution route as an alternative pathway.¹³

To explore the substrate scope, we examined a wide range of hydrocarbons (Table 2). It was observed that the electronic property

Table 2. Selective Oxygenation of Various Hydrocarbons^a

Entry	Substrate	Product	Yield (%) ^b
1 ^c			78
2 ^{c,d}			74
3			52
4			56
5			51
6 ^c			69
7			82
8			54
9			75
10			52
11 ^d			72
12			58
13			71
14 ^e			98
15			59
16 ^c			71
17 ^c			64
18 ^{d,f}			70
19			70
20			76
21			54

^a Substrate (10 equiv), NHPI (1.0 equiv), PhI(OAc)₂ (1.0 equiv), and CuCl (10 mol %) in CH₃CN (0.3 M) at 70 °C for 12 h under Ar. ^b Isolated yield. ^c Five equivalents of substrate was employed. ^d (NHC)CuCl (10 mol %) was used. ^e Twenty equivalents of substrate was used. ^f In neat conditions.

of substituents on ethylbenzene derivatives displayed little effects on the reaction efficiency (entries 1–5). Reactivity of 2-ethylpyridine was also similar to that of ethylbenzene (entry 6). Interestingly, a substrate bearing a radical-sensitive moiety was also efficiently oxygenated without rearrangement (entry 7), implying that recombination of two resultant radical species, PINO and cyclopropylcarbinyl in this case, is much faster than the ring-opening process of the later radical.¹⁴

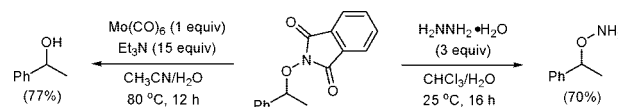
Reactions of bi- or tricyclic hydrocarbons also showed an excellent selectivity at the benzylic position (entries 9–11). Interestingly, among two available benzylic sites in dibenzosuberone and isochroman, the 1-position was exclusively oxygenated (entries 12 and 13), and its structure of the former product was determined by an X-ray crystallographic analysis.⁵ Toluene was smoothly reacted with NHPI to afford the benzyl–PINO adduct (entry 14), whereas reaction of *p*-xylene gave lower yield (entry 15).¹⁵ The observation that both 1-methylnaphthalene and 8-methylquinoline displayed similar efficiency implies that the plausible chelation effect is not appreciable in the present system (entries 16 and 17).¹⁶ Tetrahydrofuran was selectively converted to its α-PINO adduct in good yield (entry 18).

It was intriguing to observe that alkenes reacted with NHPI to allow for the introduction of the PINO group at the allylic position with the concurrent isomerization of double bond. For instance, when vinylcyclohexane was employed as a substrate, cyclohexyl-

idenemethyl–PINO was selectively obtained in good yield (entry 19). Similarly, allylbenzene was oxygenated to afford the isomerized cinnamyl–PINO adduct (entry 21).

The obtained PINO adducts could be readily converted to the corresponding alcohols or hydroxylamine species (Scheme 2),¹⁷ thus demonstrating the synthetic utility of the oxygenated products.

Scheme 2



In summary, we have developed a convenient protocol for the C–H functionalization of hydrocarbons. A broad range of substrates are selectively oxygenated at the benzylic or allylic position using stoichiometric amounts of *N*-hydroxyphthalimide and PhI(OAc)₂ in the presence of CuCl catalyst, thus offering a new possibility of the selective C–O bond-forming methodology.

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Supporting Information Available: The experimental procedures, analytical data, and copies of NMR spectra of products. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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