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*n*Bu$_4$NI-Catalyzed Intermolecular C-O Cross-coupling Reactions: Synthesis of Alkyloxyamines

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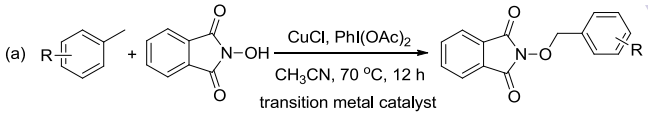
A practical and simple *n*Bu$_4$NI-catalyzed C-O bond formation for the synthesis of alkyloxyamines was achieved under metal-free conditions. The reaction is applicable to the coupling of a range of benzylic and allylic hydrocarbons with *N*-hydroxyphthalimide and is tolerant of various functional groups. The reaction mechanism was primarily investigated and a radical process was proposed.

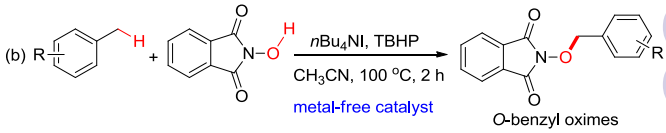
Selective direct C-H bond functionalization is emerging as a valuable tool for the synthesis of natural products and medicinal compounds.[1] The formation of C-O bonds is of fundamental importance in organic synthesis,[2] and alkyloxyamines are widely employed in the synthesis of pharmaceuticals and functional materials.[3] *N*-Hydroxyphthalimide (NHPI) is not only a cheap, nontoxic catalyst for C-H bond functionalization by using an in situ generated phthalimide N-oxyl (PINO) radical, but also a precursor of oxime ethers.[4] In recent years, NHPI has been also utilized as a stoichiometric reactant for the construction of the C-O bond in organic synthesis.[5] In 2008, Chang and co-workers reported a highly efficient protocol for the benzyl or allylic C-H functionalization of simple hydrocarbons using stoichiometric amounts of *N*-hydroxyphthalimide and PhI(OAc)$_2$ in the presence of CuCl catalyst (Scheme 1, equation a).[5b] Although the above-mentioned elegant methods appear to be general and efficient, new synthetic methods are still required.

In our previous communication, *n*Bu$_4$NI-catalyzed C-N cross coupling imidation reaction of C(sp^3)-H bond of simple ketones and N-H bond in imides with TBHP as an environmentally benign oxidant was described.[6] Taking the possible radical amination mechanism for C-H functionalization into account, we envisaged that benzylic and allylic C-H bond could be selectively oxygenated by using appropriate oxygen-centered radicals. Herein, we report a straightforward and versatile method to obtain alkyloxyamines by *n*Bu$_4$NI -catalyzed intermolecular highly selective benzylic and allylic C-O bond formation from readily available benzylic and allylic hydrocarbons with NHPI (Scheme 1, equation b). To the best of our knowledge, an example of a direct transformation from readily available hydrocarbons and NHPI to alkyloxyamines via a formal C(sp^3)-H functionalization under metal-free conditions has not been reported until this work.

Previous work:



This work:



Scheme 1 Different pathways for the synthesis of alkyloxyamines.

Initially, *o*-xylene **1a** and NHPI **2** were selected as the model substrates to optimize the reaction conditions (Table 1). To our delight, the combination of *n*Bu$_4$NI (0.2 equiv) and *tert*-butyl hydroperoxide (TBHP, 2 equiv) exhibited excellent catalytic activity and gave the desired product **3a** in 85% yield (entry 1). Ethyl acetate and dichloromethane (DCM) were effective to provide **3a** in 73% and 55% yield, respectively (Table 1, entries 2 and 3). Other catalysts such as KI, NH$_4$I, I$_2$ and NIS gave unsatisfactory results (Table 1, entries 4 - 7). TBHP was found to play an important role in the process. As shown in Table 1, TBHP was the most effective peroxide in the process. Other peroxides such as Na$_2$S$_2$O$_8$, *di-tert*-butylperoxide (TBP) and 30% H$_2$O$_2$ did not perform well (Table 1, entries 8 - 10). In addition, the reaction in the absence of *n*Bu$_4$NI or TBHP did not work (Table 1, entries 11 and 12). The best yield of **3a** (92%; entry 13) was obtained at 100 °C, whereas at higher temperatures no appreciable increase in yield was obtained. Upon decreasing the temperature to 90 °C or 70 °C, **3a** was obtained in 81% or 52% yield (Table 1, entries 14 and 15). It should be noted that this coupling reaction was performed under environmentally benign condition (with *tert*-butyl alcohol and water as by-product) without utilizing metal or stoichiometric amount of hypervalent iodine(III) species.[5b-f]

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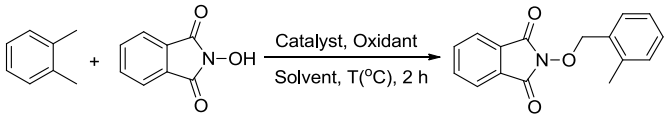
Table 1 Optimization of the Reaction Conditions[a]



1a 2 3a

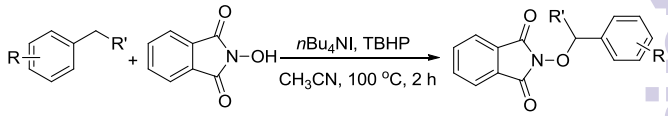
Entry	Oxidant[b]	Catalyst	Solvent	T (°C)	Yield(%)[c]
1	TBHP	*n*Bu$_4$NI	CH_3CN	130	85
2	TBHP	*n*Bu$_4$NI	EtOAc	130	73
3	TBHP	*n*Bu$_4$NI	DCM	130	55
4	TBHP	KI	CH_3CN	130	25
5	TBHP	NH_4I	CH_3CN	130	28
6	TBHP	I_2	CH_3CN	130	0
7	TBHP	NIS	CH_3CN	130	trace
8	$Na_2S_2O_8$	*n*Bu$_4$NI	CH_3CN	130	0
9	TBP	*n*Bu$_4$NI	CH_3CN	130	trace
10	H_2O_2[d]	*n*Bu$_4$NI	CH_3CN	130	0
11	-	*n*Bu$_4$NI	CH_3CN	130	trace
12	TBHP	-	CH_3CN	130	trace
13	**TBHP**	***n*Bu$_4$NI**	**CH_3CN**	**100**	**92**
14	TBHP	*n*Bu$_4$NI	CH_3CN	90	81
15	TBHP	*n*Bu$_4$NI	CH_3CN	70	52

[a] Reaction conditions: **1a** (1.5 mmol), **2** (0.3 mmol), oxidant (0.6 mmol), catalysts (0.06 mmol), solvent (3.0 mL), 2 h. [b] TBHP (70% in water). [c] Yield of the isolated product. [d] H_2O_2 30% in water.

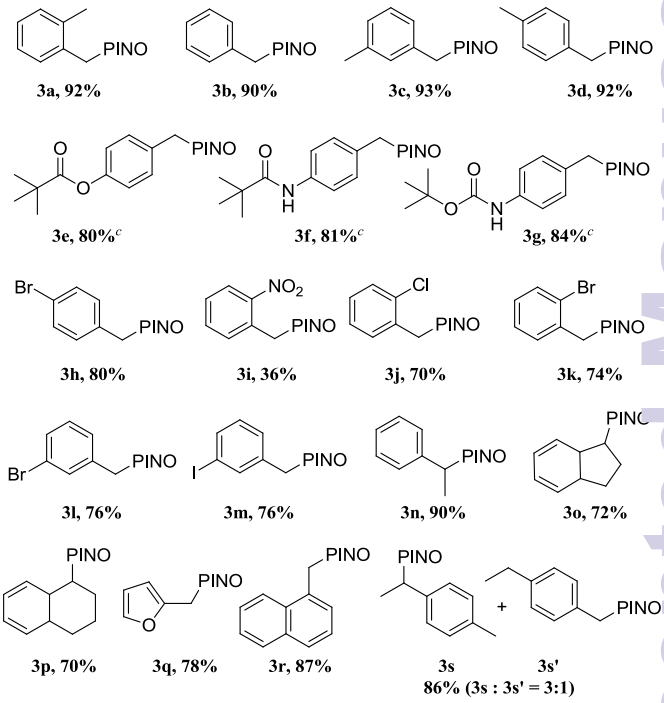
The generality of the C-H functionalization reaction was next examined. As described in Table 2, a broad range of toluene derivatives were investigated. Both toluene and xylenes could be successfully converted to the corresponding products in good to excellent yields (**3a-d**). Remarkably, the benzylic oxidation was also highly selective, affording only mono-oxidation products, and no multi-oxidation or aromatic C-H oxidation products were detected. Toluene substrates with various functional groups were effective. In general, Toluene substrates bearing electron-donating substituents provided higher yields than those containing electron-withdrawing substituents on the aromatic ring (**3d-i**). Halo-substituted toluene substrates (**1h**, **1j-m**) were tolerated in the oxidation reaction, and could be very useful for further transformations. In addition, starting from ethylbenzene (**1n**), Indane (**1o**) and 1,2,3,4-tetrahydronaphthalene (**1p**), **3n**, **3o** and **3p** could be obtained in 70-90% yields. Moreover, 2-methylfuran (**1q**) and 1-methylnaphthalene (**1r**) were also tolerated in this protocol, furnishing the desired products in good yields (**3q-r**). Next, the regioselectivity of the reaction was studied. 2-(1-(p-tolyl)ethoxy)isoindoline-1,3-dione (**3s**) and 2-((4-ethylbenzyl)oxy)isoindoline-1,3-dione (**3s'**) were obtained after 2 hours in 86% total yield in a ratio of 3:1 from 1-ethyl-4-methylbenzene (**1s**).

To further explore the potential of this efficient C-H functionalization reaction, several alkenes were examined as substrates to react with NHPI (**2**) under the optimized reaction conditions(Table 3). Alkenes **4a-d** led to linear (*E*)-allyl-PINO

Table 2 Oxygenation of benzyl C-H substrates with NHPI **2**[a,b]



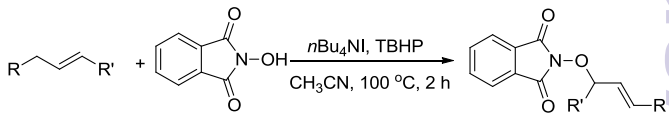
1 2 3



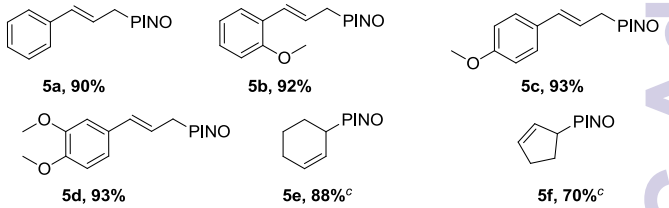
[a] Standard reaction conditions: **1** (1.5 mmol), **2** (0.3 mmol), TBHP (0.6 mmol, 70% in water), *n*Bu$_4$NI (0.06 mmol), CH_3CN (3.0 mL), 100 °C, 2 h. [b] Yield of the isolated products. [c] 0.9 mmol **1** was used.

derivatives **5a-d** in good yields and with high regioselectivity. In addition, cyclic alkenes such as cyclohexene **4e** and cyclopentene **4f** gave the corresponding compounds in 88% and 70% yields. Notably, under these conditions, the dioxygenation of alkenes products were not obtained in the works of Woerpel, Punniyamurthy and Liang et al.[5c-e]

Table 3 Oxygenation of allyl C-H substrates with NHPI **2**[a,b]

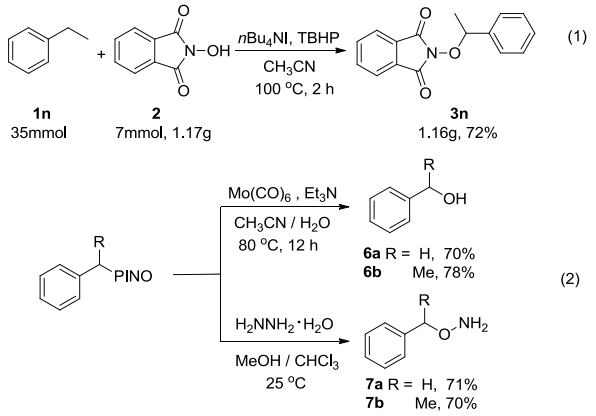


4 2 5

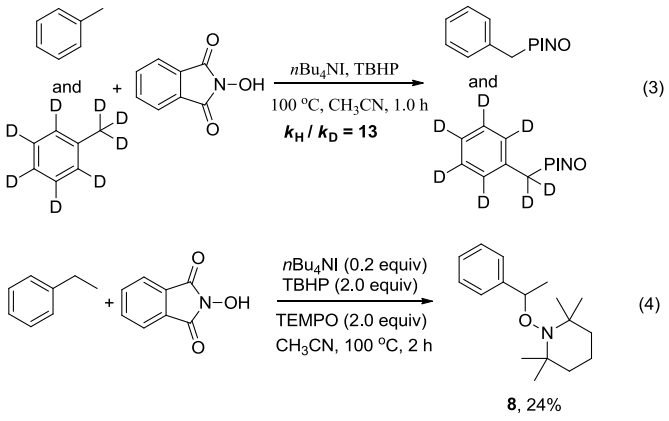


[a] Standard reaction conditions: **4** (0.9 mmol), **2** (0.3 mmol), TBHP (0.6 mmol, 70% in water), *n*Bu$_4$NI (0.06 mmol), CH_3CN (3.0 mL), 100 °C, 2 h. [b] Yield of the isolated products. [c] 1.5 mmol **4** was used.

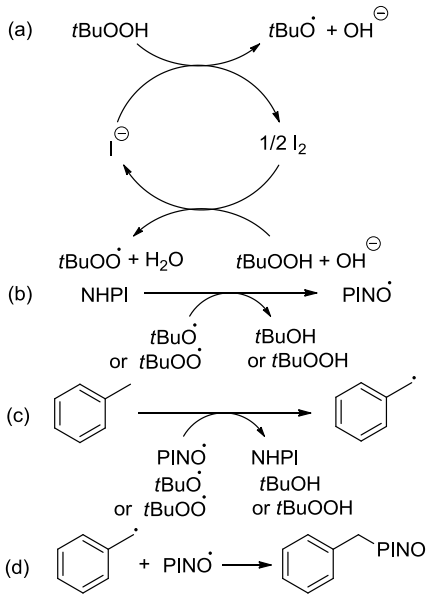
The protocol was further explored for the gram scale oxidation of ethylbenzene **1n** as a representative example (equation 1). As above, the reaction smoothly occurred with 72% yield. In addition, The obtained PINO adducts could be readily converted to the corresponding alcohols or hydroxylamine species (equation 2).[7] For example, product **3b** can be transformed into phenylmethanol **6a** in 70% yield by cleavage of the N–O bond with $Mo(CO)_6$, while **3n** underwent reaction to afford 1-phenylethanol **6b** in 78% yield. The reaction of **3b** with hydrazine produced *O*-benzylhydroxylamine **7a** in 71% yield. Similar results were observed with **3n**, furnishing *O*-(1-phenylethyl)hydroxylamine **7b** in 70% yield.



Several control experiments were performed to probe the reaction mechanism. The competitive oxidation involving toluene **1b** and its deuterated derivative **1b-d_8** were performed (equation 3). Obvious kinetic isotope effects (k_H/k_D=13/1) was observed, indicating that the cleavage of benzyl C-H bond is involved in the rate-determining step. When the radical scavenger 2,2,6,6-tetramethylpiperidine *N*-oxide (TEMPO, 2.0 equiv) was added to the reaction of ethylbenzene (**1n**) under the optimal condition, after 2 h, a TEMPO-captured product **8** was isolated (24%) and only a trace amount of **3n** was detected.The results indicates that the benzyl radical was involved under the catalytic system.[8]



Although the mechanistic details of this transformation are not very clear at the moment, based on the experimental results and literature precedent, a possible mechanism was proposed in Scheme 2. Initially, the *tert*-butoxyl and *tert*-butylperoxyl radicals form catalytically (Scheme 3a).[9] *tert*-Butoxyl or *tert*-butylperoxyl radicals then reacts with NHPI to generate NIPO radical, a fairly stable but highly reactive free radical, which has been proposed as a key intermediate in NHPI mediated oxidations (Scheme 3b).[4a,10] Subsequently *tert*-butoxyl, *tert*-butylperoxyl or NIPO radical induces the homolysis of a benzyl C-H bond to give the benzyl radical (Scheme 3c).[11] Finally, the recombination of the benzyl radical and PINO radical will lead to the PINO adducts **3b** (Scheme 3d).



Scheme 2 Proposed mechanism

In summary, we have reported a novel *n*Bu_4NI catalyzed operationally simple method for the C-H functionalization of hydrocarbons. Various alkyloxyamines products were obtained in good to excellent yields using TBHP (70% in water) as an inexpensive and environmentally friendly oxidant. Importantly, This metal-free catalyzed C-O bond formation makes use of simple, inexpensive starting materials and demonstrates excellent regioselectivity in all cases. Further investigations to gain a detailed mechanistic understanding of this reaction and apply this strategy in other oxidative coupling reactions are currently in progress.

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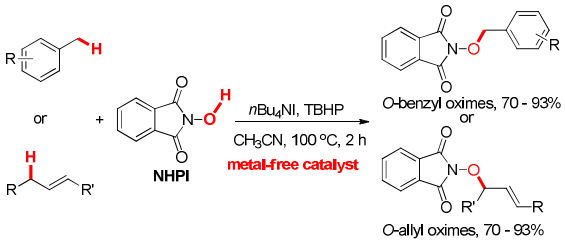

nBu_4NI-catalyzed cross-coupling of benzyl and allylic compounds with *N*-Hydroxyphthalimide for the synthesis of alkyloxyamines were realized for the first time.