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Highlight on Direct Amination of Unreactive C−H Bonds Catalyzed by *N*-hydroxyphthalimide

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The selectively direct heteratom-functionalization of unreactive C-H bonds of readily available organic substrates (e.g. methane [1]) or complex macromolecules *via* simplified synthetic routes under mild conditions is of crucial importance in the academic and industrial areas, which is a research hotspot at present and in furture. In particular, economic-friendly standards [2] require reagents, products, and conditions in such reactions to be capable of low environmental impact, namely green enough. Compared to conventional C-H transformation protocols, recently developed innovative *N*-hydroxyphthalimide (NHPI)-based catalytic systems by Ishii *et al.* [3-5] received great attentions [3-8] due to its environmental benign character and established desired high reactivity.

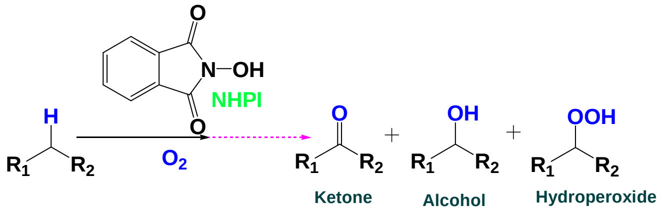

Figure 1. Aerobic oxidation of hydrocarbons under mild conditions catalyzed by *N*-hydroxyphthalimide (NHPI) in the presence or absence of any co-catalysts.

Generally, NHPI is mainly used in the aerobic oxidation reactions. Serving as an efficient carbon-radical-producing catalyst [4], its catalytic reactivity is induced by its *in situ* generated phthalimide *N*-oxyl radical (PINO) [9] via C-H activation; then the resultant carbon radicals combine the dioxygen to produce oxygenated compounds like alcohols, ketones, hydroperoxides, and carboxylic acids (Figure 1). Its utilization has covered the oxidation of a variety of hydrocarbons, including cholesterols [10,11], isophorones [12,13], cyclohexene [14] and toluenes [15]. The analogous catalysts [9,14,16,17] have also been designed, developed, and investigated for such purpose due to their similar catalytic features.

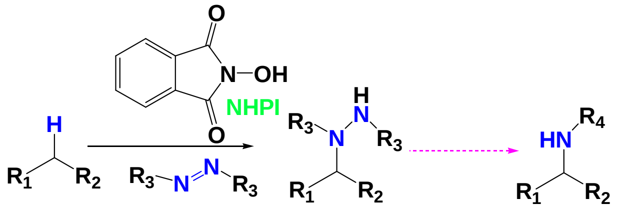

Figure 2. Radical amination of various C−H bonds by the combination of *N*-hydroxyphthalimide (NHPI) and dialkyl azodicarboxylate, reported by Inoue, *et al.* [18].

Recently, Japanese scientist Inoue and his cooperators [18] developed a novel method for direct radical amination of benzylic, propargylic, and aliphatic C(sp^3)−H bonds catalyzed by NHPI in combination of stoichiometric dialkyl azodicarboxylate (Figure 2), which is quite different from the above general reactions. C-N construction is very appealing as the occurrence of such bonds in nitrogen-substituted natural and non-natural biologically active molecules, e.g. alkaloids and potent pharmaceutical drugs [19], is quite universal. Such construction from unreactive C-H bonds requires predictable chemo-, regio-, and stereo-selective characters, making it one of the most challenging issues in organic synthesis. The fact that the traditional strategies through nitrene insertion commonly utilize transition metal catalysts [20] makes the exploitation of such catalytic reactions in a green manner urgent and vitally important. The novel metal-free strategy through radical routes developed by Inoue *et al.* [18] shows green features and high yields of nitrogen-containing products for a variaty of organic substrates, which sheds significant light on the state-of-the-art C-H amination, and will certainly give impetus to witness the feasibility of more efficient and sustainable C-N construction for natural products and pharmaceuticals under environmental benign conditions in future. It can also be anticipated from their studies that some of NHPI derivatives or analogs [9,14,16,17] can serve as appropriate catalysts for these or other transformations (e.g. C-F [20]), which still needs experimental evidence to make such a conclusion.

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