

## Two Interesting Hydrogen-abstraction Applications of *N*-Hydroxyphthalimide in the Presence of Catalytic Amounts of Metallic Salts

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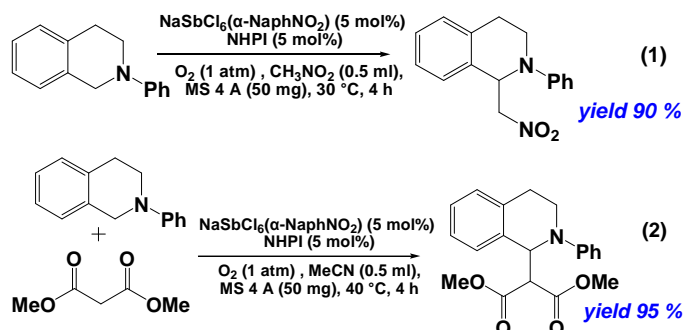
The recent emphasis on green and sustainable chemistry [1] has attracted an increasing interest in the academic areas towards direct functionalization of various kinds of C-H bonds in readily available organic substrates under mild conditions. Despite numerous methods have been reported in this respect [2,3], the ideal controllable selectivity and yields of targeted products under the scope of eco-friendly standards are still challenging. These trends are especially obvious for C-H bonds with strong strength or that in the complex macromolecules. Therefore, developing efficient methods for these selective transformations continues to be a research hotspot at present and in future.

One particular class of catalytic systems among recent numerous innovative scientific breakthroughs in the concerned field comprises *N*-hydroxyphthalimide (NHPI) and its analogues or derivatives [4-10] in the presence of various metallic, organic, photocatalytic, enzymatic, radical, inorganic, and electrocatalytic initiators [11]. They act as efficient carbon-radical-producing catalysts in the aerobic oxidation reactions [3-12], oxidation of cellulose fibers [14], nitration [14], amination [15,16], and so on. Due to their usefulness and also undeniable advantages over conventional C-H transformation protocols involving transition metal catalysts, they have received much attentions recently on the given topic, establishing desired high reactivity. Their main mechanistic profiles have been widely accepted as the hydrogen-abstraction processes from substrates by their nitroxy radicals, followed by the addition of concerned substances (e.g. dioxygen or other *in situ* generated radicals) to produce carbon-

centered radicals, ultimately leading to the formation of final products.

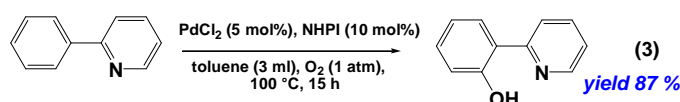
Recently, the application of NHPI has been extended to two new areas, namely cross-dehydrogenative coupling (CDC) [17] and direct aromatic C-H hydroxylation [18] reactions.

CDC reactions are very attractive for the construction of C-C bonds towards preparation of complex natural products and pharmaceutical molecules. However, previous strategies always use stoichiometric amounts of transition metal salts as catalysts, making it urgent to explore organocatalytic systems for the replacement of them. In 2013, Kobayashi and his coworkers [17] contributed significantly to this field by the employment of the catalytic amounts of NHPI and antimony (Sb) under aerobic conditions at room temperature (Eq.1 and Eq.2). This intriguing strategy has high yields of targeted products (ca. 90 %) in most cases, undoubtedly opening a new way towards greener CDC processes.



The strong nature of C-H bonds in aromatic rings has to be activated by transition metal catalysts with stoichiometric amounts. The most famous example is the utilization of palladium (Pd)

based catalysts. In this area, direct hydroxylation of aromatic C-H bonds of industrial importance remains a challenging task due to low efficiency, poor selectivity, and usage of harsh conditions [18]. In this context, Jiao and his coworkers [18] have developed a fascinating protocol with high isolated yields at relatively low temperature (100 °C) (Eq. 3) and also found that the combination of 10 mol% NHPI, 5 mol% PdCl<sub>2</sub>, and toluene were indispensable to the optimal performances for this method.



Though the significant advances have been achieved in both areas, their proposed possible mechanistic pathways still remain much room unresolved. In our opinion, for instance, the generation of phthalimide-*N*-oxyl radical (PINO) from NHPI by the oxygen radical anion in CDC reactions may not be the main route, as this radical may also be produced by Sb(V) salt with dioxygen via valence change, like other metals. In the case of aromatic C-H hydroxylation, the role of benzyl derivatives (like radicals) in situ generated from toluene is unclear yet, as it may also influence the product distributions to some extent. Of course, the utilization of NHPI at 100 °C would reduce its catalytic role due to its favorable decomposition over 80 °C. Alternatively, the higher reactivity of NHPI analogues [11,19] or derivatives [20] may overcome this shortage, and keep the similar performances under relatively lower temperature. It can also be anticipated that these catalysts will surely improve the overall performances of CDC reactions.

#### References:

- [1] P.J. Dunn, *The importance of green chemistry in process research and development*. Chem. Soc. Rev. 2012, **41** (4): p. 1452-1461.
- [2] A. Gunay and K. H. Theopold, *C-H bond activations by metal-oxo compounds*. Chem. Rev. 2010, **110** (2): p. 1060-1081.
- [3] P. B. Arockiam, et al., *Ruthenium(II)-catalyzed C-H bond activation and functionalization*. Chem. Rev. 2012, **112** (11): p. 5879-5918.
- [4] Y. Ishii, et al., *Innovation of hydrocarbon oxidation with molecular oxygen and related reactions*. Adv. Synth. Catal. 2001, **343** (5): p. 393-427.
- [5] Y. Ishii and S. Sakaguchi, *Recent progress in aerobic oxidation of hydrocarbons by N-hydroxyimides*. Catal. Today 2006, **117** (1-3): p. 105-113.
- [6] R.A. Sheldon and I.W.C.E. Arends, *Organocatalytic oxidations mediated by nitroxyl radicals*. Adv. Synth. Catal. 2004, **346** (9-10): p. 1051-1071.
- [7] F. Recupero and C. Punta, *Free radical functionalization of organic compounds catalyzed by N-hydroxyphthalimide*. Chem. Rev. 2007, **107** (9): p. 3800-3842.
- [8] S. Coseri, *Phthalimide-N-oxyl (PINO) radical, a powerful catalytic agent: Its generation and versatility towards various organic substrates*. Catal. Rev. 2009, **51** (2): p. 218-292.
- [9] L. Melone and C. Punta, *Metal-free aerobic oxidations mediated by N-hydroxyphthalimide. A concise review*. Beilstein J. Org. Chem. 2013, **9**: p. 1296-1310.
- [10] K. Chen, *Design and Mechanistic Investigations of N-Hydroxyimides as Organocatalysts for Aerobic Oxidation*. PhD Thesis, Zhejiang Univ., 2013.
- [11] K. Chen, et al., *Theoretical studies on multi-hydroxyimides as highly efficient catalysts for aerobic oxidation*. ChemPhysChem 2013, **14** (1): p. 179-184. The *in situ* PINO generated methods are briefly summarized in this paper.
- [12] K. Chen, et al., *Aerobic oxidation of β-isophorone catalyzed by N-hydroxyphthalimide: The key features and mechanism elucidated*. Phys. Chem. Chem. Phys. 2012, **14** (35): p. 12141-12146.
- [13] S. Coseria, et al., *Oxidized cellulose-Survey of the most recent achievements*. Carbohydr. Polym. 2013, **93** (1): p. 207-215.
- [14] S. Isozaki, et al., *Nitration of alkanes with nitric acid catalyzed by N-hydroxyphthalimide*. Chem. Commun. 2001: p. 1352-1353.
- [15] K. Chen, et al. *Highlight on direct amination of unreactive C-H bonds catalyzed by N-hydroxyphthalimide*. J. Postdoc. Res. 2013, **1** (8): p. 19-20.
- [16] Y. Amaoka, et al., *Radical amination of C<sub>(sp<sup>3</sup>)</sub>-H bonds using N-hydroxyphthalimide and dialkyl azodicarboxylate*. J. Org. Chem. 2012, **77** (22): p. 9959-9969.
- [17] A. Tanoue, et al., *Antimony/N-hydroxyphthalimide as a catalyst system for cross-dehydrogenative coupling reactions under aerobic conditions*. Adv. Synth. Catal. 2013, **355** (2-3): p. 269-273.
- [18] Y. Yan, et al., *PdCl<sub>2</sub> and N-hydroxyphthalimide co-catalyzed C<sub>sp<sup>2</sup></sub>-H hydroxylation by dioxygen activation*. Angew. Chem. Int. Ed. 2013, **52** (22): p. 5827-5831.
- [19] I. Hermans, et al., *Autoxidation catalysis with N-hydroxyimides: more-reactive radicals or just more radicals?* Phys. Chem. Chem. Phys. 2007, **9** (6): p. 686-690.
- [20] Y. Sun, et al., *Correlation analysis of the substituent electronic effects on the allylic H-abstraction in cyclohexene by phthalimide-N-oxyl radicals: A DFT study*. J. Phys. Chem. B 2010, **114** (14): p. 4862-4869.