論文の内容の要旨

論文題目 Development of *N*-Hydroxy Activators and Oxidation State-Selective C(sp^3)–H Oxidation

(*N*-ヒドロキシル活性化剤と酸化度選択的C(sp^3)-H酸化反応の開発)

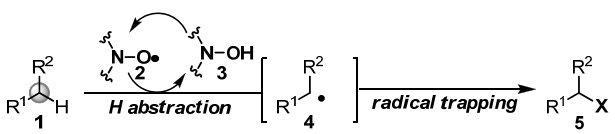
氏　名　　倪　積智

Introduction

In recent years, there has been a growing demand for the development of fundamentally new and environmentally benign catalytic systems for hydrocarbons which are operative in an industrial scale under mild conditions in a liquid-phase with a high degree of selectivity. Saturated hydrocarbons are inert because their carbon–hydrogen (C–H) bonds have high bond dissociation energy (~95–110 kcal/mol) and very low acidity and basicity. Functionalization of unactivated C–H bonds is currently under intensive investigation. Specifically, C(sp^3)–H functionalization can be a powerful tool for a streamlined synthesis of C(sp^3)-rich, drug lead complex molecules. Requiring no preactivation and prefunctionalization of the substrates for bond formations, it will dramatically streamline the synthesis of complex natural products and biologically active compounds. Radical C–H activation is a promising strategy because of radicals' inherently high reactivity and functional group tolerance.

As a representative of *N*-hydroxyimides, *N*-hydroxyphthalimide (NHPI) can generate phthalimide *N*-oxyl (PINO) radical species, which is active enough to abstract H atom from C(sp^3)–H bond.[1] Among the frontier challenges of modern synthetic chemistry, the design of catalysts for synthesis of organic molecules with high levels of efficiency is extremely important. To achieve general functionalization of C(sp^3)–H bonds under mild conditions, a two-stage transformation by employing an *N*-oxyl organocatalyst is shown in Scheme 1:Generated from its *N*-oxyl radical precursor **3**, *N*-oxyl radical **2** abstracts a H atom to give an alkyl radical **4**. Then the very reactive species is quickly captured by suitable trapping reagents, and hence

Scheme 1. *N*-Hydroxy Activator Catalyzed C(sp^3)-H Functionalization



diverse functional groups can be installed.

1. Catalytic Activation of C(sp^3)–H Bond by Novel *N*–Oxyl Radicals

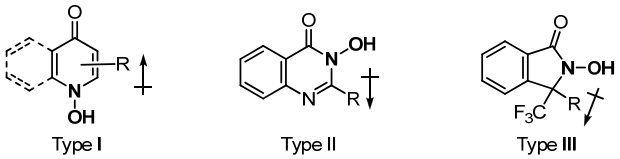
Research Background

Despite that extensive researches were devoted to the development of NHPI-catalyzed hydrocarbon transformations, the main drawbacks which may hinder its application are still remained untouched: 1) the instability of PINO under aerobic oxidation conditions, 2) the low solubility of polar NHPI in liquid hydrocarbon solvents, and 3) the structure and activity of NHPI which are not easy to tune.

Method and Result

To overcome the limitations of NHPI, I synthesized and investigated several *N*-hydroxy activators (Figure 1, Type I *N*-hydroxypyridone derivatives, Type II 3-hydroxy-4(3*H*)-quinazolinone derivatives and Type III *N*-hydroxyisoindolin-1-one derivatives) in order to obtain more stable and more reactive *N*-oxyl radical species. The activities of these compounds in the C–H activation were examined by a model reaction (conjugate addition of 2-methyl-1,3-dioxolane to *t*-butyl acrylate).[2]Among those compounds, Type II and III activators showed H atom abstraction activity. Especially, Type III proved much higher activity than the classic NHPI for this process and significantly improved solubility, which afforded a good direction for future modification of *N*-hydroxy catalysts.

Figure 1. Novel *N*-Hydroxyl Activators



2.Site- and Oxidation State-Selective Methylene Oxidation

Research Background

Hydroxy group is one of the most common functional groups in natural products and pharmaceutical reagents. If we can selectively convert specific C–H bond to C–O bond guided by a hydroxy group with use of molecular oxygen, it will be one of the most concise and green functionalizations. Especially, conversion of an unactivated C(sp^3)–H bond of a methylene carbon (CH_2) to a C–O single bond is attractive, but it is even more challenging due to undesired over-oxidation to ketone (C=O).

Method and Result

Inspired by NHPI chemistry, a novel directing activator (DA) was devised by Mr. Ozawa in our group. An *N*-oxyl radical generated from the *N*-hydroxyamide moiety of DA in the presence of cobalt catalyst and O_2 would homolytically cleave C(sp^3)–H bonds to produce carbon radical species. By covalently attaching the DA to the hydroxy group of substrate alcohols, this C(sp^3)–H activation step becomes an intramolecular process. As a result, our DA promoted very challenging simple methylene C(sp^3)–H oxygenation to produce γ-oxo product in good yields (Scheme 2, left).[3]

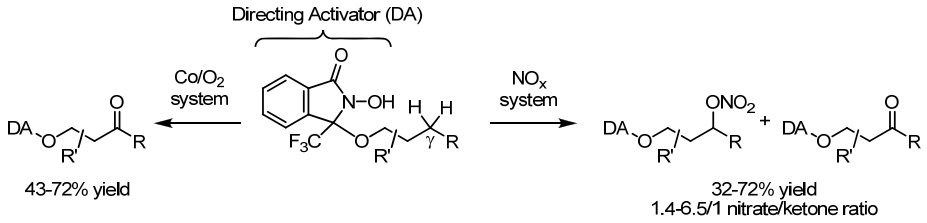
Since the BDE value of an α-oxy C–H bond is much lower than that of a methylene (CH_2), to control the oxidation state at the C–O single bond stage is quite challenging. I anticipated that a tentative protecting group could prevent further oxidation of the generated C–O single bond. Based on this consideration, I tried several radical trapping reagents. In addition, further oxidation of the generated radical to a carbocation followed by its nucleophilic trap was examined. However, no desired products were obtained under these conditions.

Interestingly, when NO_x source combined with oxygen was used, I obtained a nitrate product, which could serve as an alcohol surrogate (Scheme 2, right). The *in situ* generated NO_x species behaved as a strong oxidant for a more effective generation of PINO-like amidoxyl radical by hydrogen abstraction from the *N*-hydroxygroup.[4] Besides, NO_x trapped the generated alkoxy radicals, thus preventing undesired over-oxidation reactions. Based on this finding, I screened several NO_x sources and found that a metal nitrite salt combined with a Brønsted acid gave higher yield with the nitrate ester as the main product, despite a moderate ratio of nitrate/ketone.

The optimized reaction conditions were employed in different substrates oxidation. After aerobic C–H oxygenation, γ (and δ) position of the oxygen group was preferentially converted to a C–O single bond in moderate to good yields.[5] The diastereomer ratios were 1/1 in all these products.

The obtained nitrate ester ($R–ONO_2$) served as an alcohol precursor. After the N–O bond was reductively cleaved under hydrogen atmosphere at room temperature, the DA was smoothly removed by $LiAlH_4$, producing 1,3-diol in high yield.

Scheme 2. Oxidation State- and Site-Selective Methylene C(sp^3)-H Oxidation Using Directing Activator



Summary

Several *N*-hydroxy organocatalysts with H atom abstraction ability were newly synthesized. Some of them showed appealing merits (in terms of reactivity and solubility) comparing to the well-known NHPI.

By employing a new *N*-oxyl radical directing activator, very challenging acyclic methylene C(sp^3)–H bonds were converted to C=O bonds in a Co(II)/O_2 system, while C–O bonds were preferentially obtained via a NO_x/O_2 system under mild (moderate temperature) conditions. The reaction proceeded regioselectively at the γ (and δ) position(s), and α, β and other positions farther than the δ position were intact. These characteristics were resulted from the intramolecularity of the directing activator strategy. Efforts toward devising catalytic turnover of the directing activator are ongoing.

References

(1) For reviews of NHPI, see: (a) Ishii, Y,; Sakaguchi, S.; Iwahamab, T. *Adv. Synth. Catal.* **2001**, *343*, 393. (b) Recupero, F.; Punta, C. *Chem. Rev.* **2007**, *107*, 3800. (2) Hirano, K.; Iwahama, T.; Sakaguchi, S.; Ishii, Y.; *Chem. Commun*. **2000**, 2457. (3) Ozawa, J.; Ni, J.; Tashiro, M.; Oisaki, K.; Kanai, M. *Manuscript in preparation*. (4) (a) Sakaguchi, S.; Nishiwaki, Y.; Kitamura, T.; Ishii, Y. *Angew. Chem. Int. Ed.* **2001**, *40*, 222. (b) Nishiwaki, Y.; Sakaguchi, S.; Ishii, Y. *J. Org. Chem*. **2002**, *67*, 5663. (5) Ni, J.; Ozawa, J.; Oisaki, K.; Kanai, M. *Manuscript in preparation*.