Division of Synthetic Chemistry
– Synthetic Organic Chemistry –

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Prof WILLIARD, Paul Brown University, U.S.A., 27 September

Scope of Research

The research interests of the laboratory include the development of advanced molecular transformation, total synthesis of biologically active products, and molecular recognition. Programs are active in the areas of asymmetric alkylation of carbonyl compounds based on “memory of chirality”, organocatalysis for fine organic syntheses, synthesis of unusual amino acids and nitrogen heterocycles, regioselective functionalization of carbohydrates, and the structural and functional investigation of heterochiral oligomers.

KEYWORDS

Organocatalysis
Regioselective Functionalization
Dynamic Chirality
Unusual Amino Acid
Molecular Recognition

Selected Publications

Kawabata, T.; Matsuda, S.; Kawakami, S.; Monguchi, D.; Moriyama, K., Stereochemical Diversity in Asymmetric Cyclization via Memory of Chirality, *J. Am. Chem. Soc.*, **128,** 15394-15395 (2006).

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Yoshida, K.; Furuta, T.; Kawabata, T., Organocatalytic Chemoselective Monoacylation of 1,n-Linear Diol, *Angew. Chem. Int. Ed.*, **50,** 4888-4892 (2011).

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Tomohara, K.; Yoshimura, T.; Hyakutake, R.; Yang, P.; Kawabata, T., Asymmetric α-Arylation of Amino Acid Derivatives by Clayden Rearrangement of Ester Enolates via Momory of Chirality, *J. Am. Chem. Soc.*, **135,** 13294-13297 (2013).

Yoshimura, T.; Tomohara, K.; Kawabata, T., Asymmetric Induction via Short-Lived Chiral Enolates with Chiral C-O Axis, *J. Am. Chem. Soc.*, **135,** 7102-7105 (2013).

A Properly Positioned Carboxylate in a DMAP Skeleton Accelerates Acylation Reactions

The DMAP catalyzed acylation of alcohols with acid anhydrides has been widely used for the synthesis of esters. It has been proposed that the carboxylate ion of the reactive acylpyridinium salt acts as a general base, and deprotonates the alcohols at the transition state. Therefore, the carboxylate ion plays a crucial role not only in the reactivity, but also in the regio- and stereoselectivity of the acylation reaction. We investigated the proper location of the carboxylate ion that accelerates the DMAP-catalyzed acylation of alcohols. Catalytic profiles of **1a**, **2**, **3** and **4** with an internal carboxylate and the corresponding ester **1b** and **1c** were investigated, and the relative catalytic activities were shown in Figure 1a. The transition state structure of the *N*-acetylpyridinium salts derived from the most relative catalyst **1a** with MeOH calculated by the B3LYP/6-31G* level showed that the carboxylate ion proximal to the pyridine ring in face to face geometry works as an effective general base to promote the acylation reaction (Figure 1b).

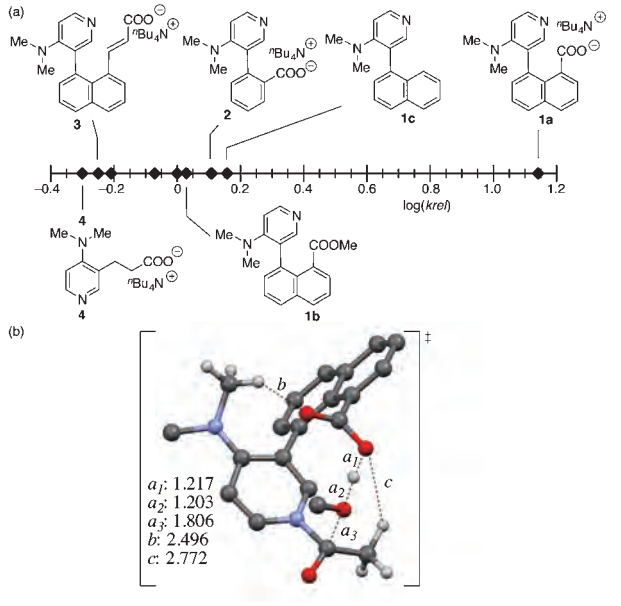

Figure 1. (a) Relative catalytic activities for acetylation of cyclohexanol. (b) Transition state structure for acetylation of *N*-acetylpyridinium ion of **1a** with MeOH.

Chemoselective Oxidation by an Electronically Tuned Nitroxyl Radical Catalyst

Nitroxyl radical **5** was disclosed to be an efficient catalyst for the oxidation of secondary alcohols. The oxoammonium generated from **5** was found to be highly reactive due to the adjacent electron-withdrawing ester groups (electronic tuning effect: Figure 2a), irrespective of the steric congestion around the active site as seen in a typical nitroxyl radical catalyst, TEMPO. Catalyst **5** promoted highly chemoselective oxidation of benzylic alcohols in the presence of aliphatic alcohols. The oxidation of the benzylic alcohols was proposed to proceed via rate-determining hydride transfer (Figure 2b).

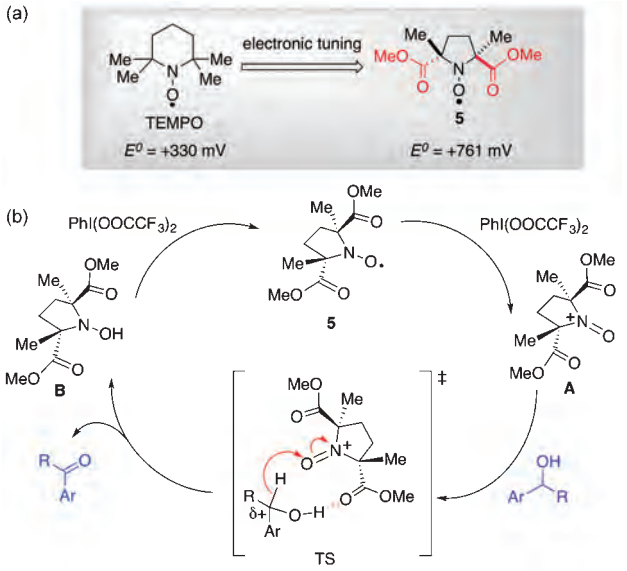

Figure 2. (a) Design of nitroxyl radical oxidation catalyst based on electronic tuning. (b) A possible reaction path via the rate-determining hydride-transfer.

The First Example of Asymmetric Synthesis via Inherently Chiral Enolates with a Chiral C-O Axis

A Novel method for asymmetric cyclization of chiral alkyl aryl ethers has been developed. The reactions were assumed to proceed via short-lived chiral enolate intermediates with a chiral C-O axis to give cyclic ethers with tetrasubstituted carbon in up to 99% ee. The half-lives of racemization of the chiral enolate intermediate was roughly estimated to be ~1 sec at –78 °C. This is the first example of asymmetric reactions that proceed via inherently chiral enolate intermediates based on the restricted rotation around a C-O bond.