Diastereodivergent Intermolecular 1,2-Diamination of Unactivated Alkenes Enabled by Iodine Catalysis

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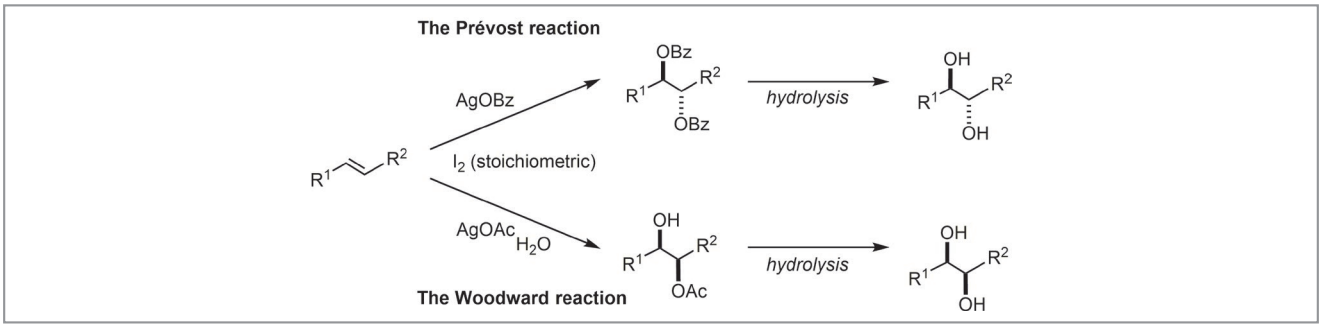
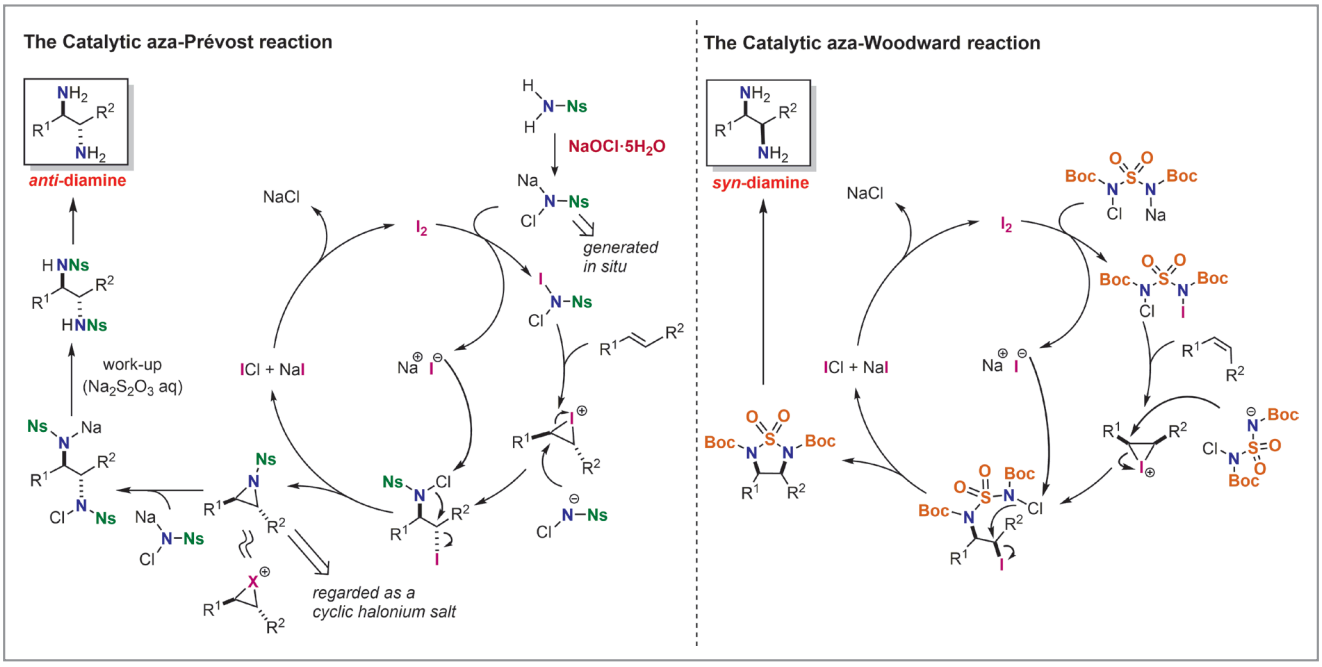
The 1,2-diamine motif is a ubiquitous feature of bioactive compounds, a ligand for organic transformations, and a valuable synthetic intermediate for the construction of complex molecules. Addition reactions to alkenes are upstream transformations in synthetic organic chemistry, because such structures are essential feedstocks in a wide variety of petrochemical processes. Thus, the development of a robust methodology for the 1,2-diamination of alkenes is highly desirable. "Controlling the relative configuration of two nitrogen moieties is crucial for the synthesis of diverse molecules, but there are no versatile and practical methods available for the *anti*- and *syn*-diamination of alkenes with complete control of the stereochemistry of the reaction," said Professor Satoshi Minakata from Osaka University (Suita, Japan). He and his research group are interested in developing fundamental organic transformations: "Even though a nitrogen atom is a ubiquitous atom that is as important as an oxygen atom in a variety of organic molecules, the nitrogen versions of dihydroxylation, i.e., the Prévost and Woodward reactions, remain unexplored," explained Professor Minakata, and this is indeed one of his group's research themes: the development of catalytic aza-Prévost and Woodward reactions (Scheme 1).

Professor Minakata's group has been exploring the molecular-iodine-catalyzed aziridination of alkenes utilizing commercially available and inexpensive *N*-chloro-*N*-sodio-*p*-toluenesulfonamide (chloramine-T) as a potential nitrogen source (*Tetrahedron* **1998**, *54*, 13485–13494; *Angew. Chem. Int. Ed.* **2004**, *43*, 79–81; *Acc. Chem. Res.* **2009**, *42*, 1172–1182). The observation that small amounts of the ring-opened product, a 1,2-diamine, form in the process prompted Professor Minakata to search for a suitable nitrogen source that could be used for both aziridine formation and ring opening. "This simple concept led to the successful *anti*-diamination of alkenes. The strategy also involves the formation of an intermediate, namely, a cyclic iodonium intermediate, which is a strong electrophile for ring opening. We reasoned that if it were possible to prepare a more electron-deficient aziridine – other than the *N*-Ts aziridine – the latter could be regarded as a cyclic halonium derivative that would easily undergo ring-opening," said Professor Minakata. After a series of investigations, an *o*-nitrobenzenesulfonyl (Ns) group was found to be the optimal group for achieving the desired iodine-catalyzed anti-diamination. "Since an Ns group can be readily cleaved by Fukuyama's method, thus leading to the formation of unsubstituted amino groups, the discovery of such Ns group is like *getting two diamonds for the price of one*," explained Professor Minakata (Scheme 2; left).

To achieve the *syn*-diamination of alkenes, Professor Minakata's group designed a bespoke nitrogen source. "If two nitrogen moieties in the same molecule could be added to an alkene in the same manner via iodine-catalyzed aziridination, the reaction would be predicted to proceed in a *syn*-mode," said Professor Minakata. "Since a chloramine salt induces iodine-catalyzed aziridination reactions, the chloramine salt of *N*,*N*′-bis(*tert*-butoxycarbonyl)sulfamide (chloramine-BBS) was designed. Although BBS is a known compound, it is not extensively used in organic synthesis. We were very pleased to find that this nitrogen source was applicable to iodine-catalyzed *syn*-diamination (Scheme 2; right)."

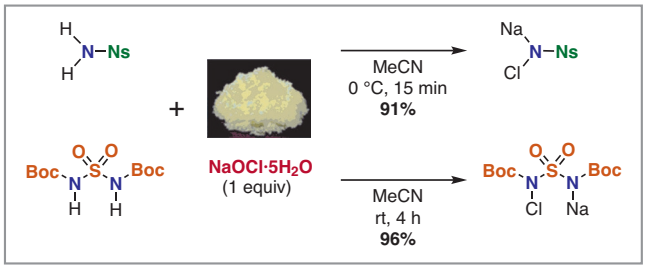


Scheme 1 The Prévost and Woodward reactions



Scheme 2 Diastereodivergent intermolecular 1,2-diamination of unactivated alkenes enabled by molecular iodine catalysis

Professor Minakata emphasized that chloramine salts bearing electron-withdrawing groups on the nitrogen are crucial for such iodine-catalyzed reactions. The group thought that a convenient method for preparing chloramine salts would be needed if the above *anti*- and *syn*-diamination was to be more practical. The finding in 2015 of sodium hypochlorite pentahydrate ($NaOCl{\cdot}5H_2O$) accelerated the development of the two strategies. "This unique reagent is manufactured and sold by the Nippon Light Metal Company, Ltd.," said Professor Minakata, who was focused on identifying a solid-state reagent that could be used in an organic solvent. As expected, both nitrogen sources, *o*-nitrobenzensulfonamide and *N*,*N*′-bis(*tert*-butoxycarbonyl)sulfamide, were efficiently transformed into the corresponding chloramine salts in acetonitrile (Scheme 3). In particular, chloramine-Ns could be generated in situ for *anti*-diamination reactions, meaning that the reagents needed for such *anti*-diamination reactions, including the catalyst, are all commercially available materials.



Scheme 3 Preparation of chloramine salts for *anti*- and *syn*-diamination reactions from simple amides with NaOCl pentahydrate

Concerning the applications of this approach and future perspectives of this powerful methodology, Professor Minakata noted: "As I wrote in the original paper, immediate applications include the N-modification of products and the aminofunctionalization of alkenes through the formation of reactive aziridine intermediates that can react with various other nucleophiles." He added: "As future prospects, considering that the 1,2-diamine moiety is an important structure that is found in anti-influenza drugs having neuraminidase inhibition properties (Tamiflu®, Relenza® and Inavir®), the developed methods could facilitate the early discovery of various new drugs, including those against new viruses that promise to pose an increasing threat to mankind in the future."

Professor Minakata concluded: "Our group succeeded in discovering reactions that had been seen before, but were new at the same time! These simple, efficient, convenient, robust, and practical methods have the potential to be used in the synthesis of various organic molecules. I strongly believe that the present diamination reaction could become a *Name Reaction* in the field of organic synthesis."

About the authors

Prof. S. Minakata

Satoshi Minakata was born in Wakayama in 1964. He received his Ph.D. in 1993 from Osaka University (Japan) under the direction of Professor Yoshiki Ohshiro. After spending two years (1993–1995) at Central Research Laboratories of DIC Corporation (Japan), he was appointed as an assistant professor of Department of Applied Chemistry in Professor Komatsu's group at Osaka University, and promoted to lecturer in 2000. From 1997 to 1998, he worked with Prof. Erick. M. Carreira at the California Institute of Technology (USA) as a visiting associate. In 2002, he was promoted to associate professor and since 2010, he has been a full professor at Osaka University. His research interest centers the development of new methodologies for synthesis of valuable organic molecules from simple molecules.

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Hayato Miwa was born in 1992. He received his Bachelor (2016) and Master (2018) of Engineering degrees from Osaka University (Japan) under the supervision of Professor Satoshi Minakata. Currently, he is working at a chemical company. During his Bachelor's and Master's degree programs, he focused on the development of direct *anti*-diamination of alkenes from nosylamide utilizing sodium hypochlorite pentahydrate enabled by iodine catalysis.

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Dr. S. Okumura

Sota Okumura was born in 1987. He received his Bachelor (2010), Master (2012) and PhD (2015) of Engineering degrees from Osaka University (Japan) under the supervision of Professor Satoshi Minakata. The title of his doctoral dissertation is *Development of Novel Synthetic Methods Utilizing Mono- or Trivalent Iodine Reagent*. Currently, he is working at a chemical company. Apart from research for his doctoral degree, he contributed to the early stages of this diamination chemistry.

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