Synthesis of 1,3-Cycloalkadienes from Cycloalkenes: Unprecedented Reactivity of Oxoammonium Salts

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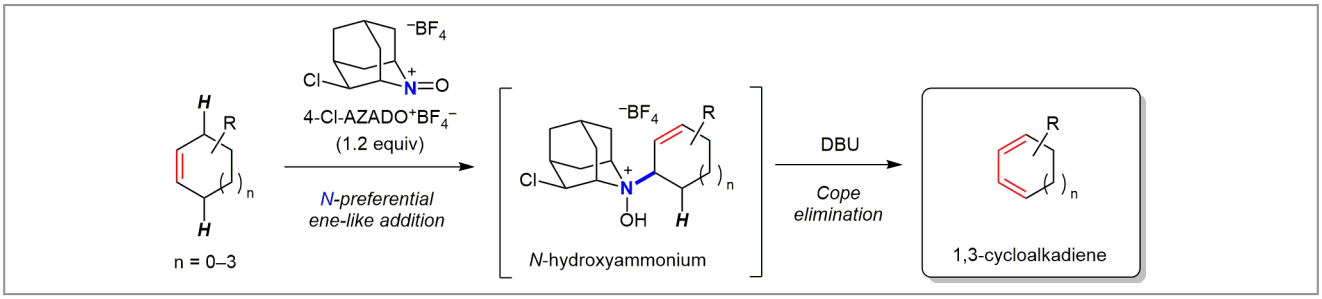
Cyclic 1,3-dienes or 1,3-cycloalkadienes are important chemicals that have a variety of synthetic applications in organic chemistry, but their preparation – particularly in the case of highly functionalized 1,3-cycloalkadienes – can be challenging, thus affecting the availability of these molecules as building blocks. A convenient one-pot synthesis of 1,3-cycloalkadienes via a regioselective dehydrogenation of the corresponding cycloalkenes has been developed recently by the group of Professor Yoshiharu Iwabuchi from Tohoku University (Japan). Professor Iwabuchi said: "The novel synthetic method stemmed from a serendipitous discovery during our attempt to expand the synthetic scope of oxoammonium salts. After extensive investigations, we realized that this dehydrogenation involves unprecedented reactivity of oxoammonium salts with cycloalkenes: an azaadamantane-type oxoammonium salt reacts with a cycloalkene to form a key *N*-hydroxyammonium intermediate via an N-preferential ene-like addition (Scheme 1)." Professor Iwabuchi revealed that PhD student Shota Nagasawa discovered the novel reactivity of the azaadamantane-type oxoammonium salt, and designed and conducted all the experiments covered in their paper as well as co-authoring it with Professor Yusuke Sasano and Professor Yoshiharu Iwabuchi.

Professor Iwabuchi continued: "Our investigation on the development and synthetic use of azaadamantane-*N*-oxyl (AZADO)-related compounds began in 2002 when I took over a laboratory from my mentor, Professor Emeritus Kunio Ogasawara at Tohoku University." The Ogasawara group had been preparing for publication of the seminal work entitled 'The Chiral Modification of Adamantane'.[1] "By learning the unique synthetic approach which employs an annulation of bicyclo[3.3.1]nonane skeleton to adamantane, inspiration dawned on the possible use of AZADO and its derivatives as a less-hindered congener of TEMPO that would mediate or catalyze oxidation of organic substrates," Professor Iwabuchi recalled. He continued: "The catalytic activity and the substrate applicability exhibited by AZADOs in alcohol oxidation were far beyond our expectation.[2] The discovery of the ultra-highly active catalyst spurred us to develop a commercial synthesis of AZADO. After productive collaboration with Nissan Chemical Industry, Ltd., a kilogram-scale synthesis process was established and AZADO (AZADOL®) is now widely distributed by several vendors.[3] The large-scale synthetic route to AZADO allowed us to enjoy the fertile chemistry of AZADO and related compounds: the less-hindered active site offers ultra-high activity and tunable redox potential. Either introducing electronegative substituents onto the azaadamantane skeleton[4] or coupling with different counter-anions significantly expanded the synthetic scope of the method.[5]"

Recently, the group's interests have expanded into reactions of AZADOs and related oxoammonium salts with alkenes. The reaction of oxoammonium salts with alkenes was first reported in 2006 by Bobbitt and co-workers: a TEMPO-derived oxoammonium salt (Bobbitt's salt) was found to react with trisubstituted alkenes selectively to give alkoxyamines.[6] "This new reaction, featuring the O-preferential ene-like addition of oxoammonium ion onto alkene, opened a new avenue for oxidation of alkenes, however, the substrate scope was limited to trisubstituted alkenes," said Professor Iwabuchi. "We envisioned that an electronically tunable AZADO-derived



Scheme 1 Dehydrogenation of cycloalkenes using an azaadamantane-type oxoammonium salt

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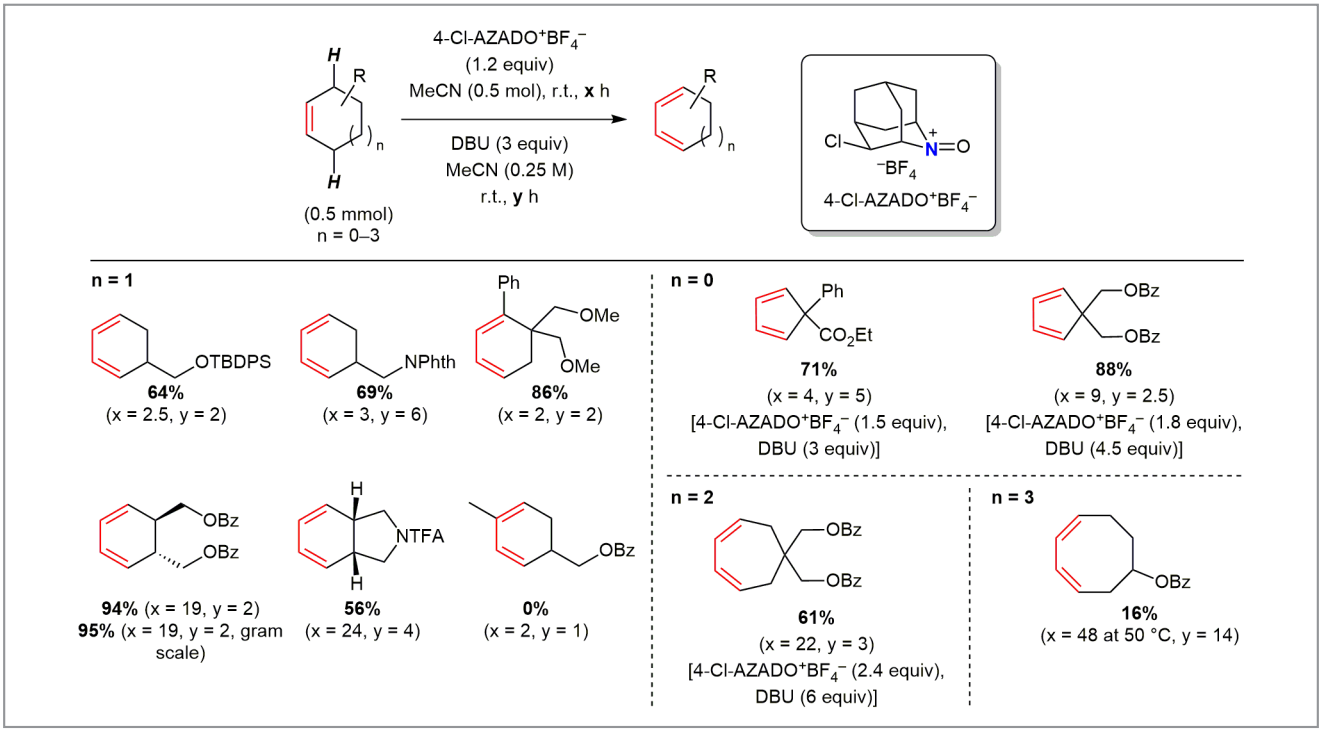
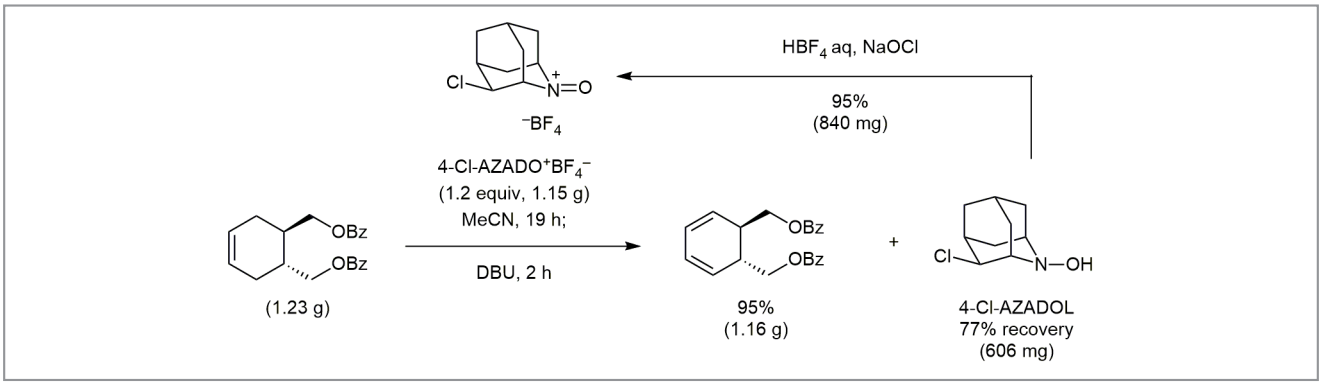
oxoammonium ion would acquire an enhanced electrophilic nature that would enable its attack onto disubstituted alkenes to give the corresponding adducts. The resulting story is described in detail in our *Angewandte* paper."

The selected scope of this reaction is shown in Scheme 2. "The most outstanding point of this reaction should be the complete regioselectivity in the dehydrogenation step," said Professor Iwabuchi. Dibromination–dehydrobromination sequence, which is a well-known method to synthesize cycloalka-1,3-dienes from cycloalkenes, often gives a regioisomeric mixture of cycloalka-1,3-dienes depending on structures of the substrates. In contrast, the Iwabuchi group's method gives cycloalka-1,3-dienes as a single isomer.

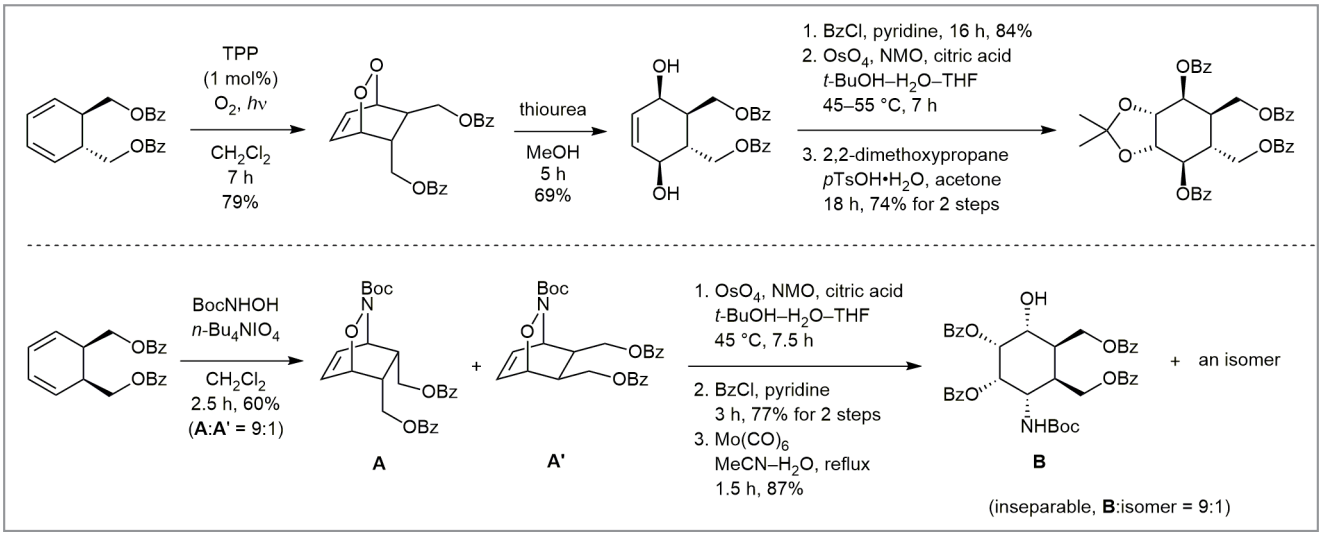
Professor Iwabuchi said: "A scalable synthesis of the key reagent 4-Cl-AZADO$^+$BF$_4^-$ has been developed on the basis of the kilogram-scale synthesis of AZADO. It should be stressed that 4-Cl-AZADO$^+$BF$_4^-$ can be recyclable: the corresponding hydroxylamine (4-chloro-2-azaadamantane-2-ol: 4-Cl-AZADOL) was recovered after the dehydrogenation and was converted into 4-Cl-AZADO$^+$BF$_4^-$ quantitatively (Scheme 3)."



Scheme 2 Substrate scope (selected)



Scheme 3 Large-scale experiment and regeneration of 4-Cl-AZADO$^+$BF$_4^-$



Scheme 4 Functionalization of the obtained 1,3-cyclohexadienes

Professor Iwabuchi remarked: "We demonstrated the synthetic use of the 1,3-cyclohexadiene products by the synthesis of carbasugar derivatives (Scheme 4). Since our method has a potential to afford various 1,3-cycloalkadienes (including unprecedented ones), various carbasugar derivatives could be synthesized."

Concerning future prospects and developments of this work, Professor Iwabuchi said: "In this paper, we reported the novel reactivity of oxoammonium species and the preliminary results of its applicability. Based on this finding, improvement of the efficiency (which includes the development of catalytic conditions) and expansion of the scope to other alkene substrates would be possible and are under way in our lab.

Furthermore, 4-Cl-AZADO$^{+}BF_4^{-}$, the key reagent in this reaction, is readily prepared in multigram scale and shows improved reactivity compared with previously developed oxoammonium salts," said Professor Iwabuchi. He concluded: "We believe that a sufficient supply of this oxoammonium salt should allow the research community to develop new reactions based on this chemistry, without the risk of missing opportunities because of difficulties connected with the availability of these compounds. Commercialization of 4-Cl-AZADO$^{+}BF_4^{-}$ is currently being discussed."

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About the authors

S. Nagasawa

Shota Nagasawa was born in Yamagata (Japan) in 1989. He studied at the Department of Pharmaceutical Sciences, Tohoku University (Japan), where he obtained his B.S. degree in 2012, and his M.S. degree in 2014 under the supervision of Professor Yoshiharu Iwabuchi. He is currently a Ph.D. candidate in the Iwabuchi group. His research interest is the development of novel reactions which has interesting reaction mechanism and makes the synthesis of complex molecules easy.

Prof. Y. Sasano

Yusuke Sasano was born in Sagamihara (Japan) in 1986. He studied at the Department of Pharmaceutical Sciences, Tohoku University (Japan), where he obtained his B.S. degree in 2008 and his Ph.D. in 2014 under the supervision of Professor Yoshiharu Iwabuchi. He was appointed as a Research Instructor in the Iwabuchi group in 2012, and has been an Assistant Professor in the same group since 2014. He worked as a Research Associate in Professor Ryan A. Shenvi's group at The Scripps Research Institute (USA) in 2014–2015. His current research interest is the development of selective oxidation methods.

Prof. Y. Iwabuchi

Yoshiharu Iwabuchi was born in Yamagata (Japan) in 1963. He studied at the Department of Pharmaceutical Sciences, Tohoku University (Japan), where he obtained his B.S. in 1986, and his Ph.D. in the laboratory of Professor Seiichi Takano under the guidance of Dr. Kunio Ogasawara in 1991. After a year of postdoctoral work with Professor K. C. Nicolaou in The Scripps Research Institute (USA), he joined the group of Dr. Ikuo Fujii at Protein Engineering Research Institute (Japan). In 1997 he was appointed Associate Professor in Professor Susumi Hatakeyama's group at Nagasaki University (Japan). In 2002 he returned to Tohoku University as a Full Professor. His research interests include the development of organocatalysts, asymmetric synthesis, and natural product synthesis.

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