Academic Program [Oral B] | 14. Organic Chemistry -Aromatic, Heterocyclic, and Heteroatom Compounds-：Oral B

Sat. Mar 29, 2025 1:00 PM - 2:20 PM JST | Sat. Mar 29, 2025 4:00 AM - 5:20 AM UTC [F]2303(2303, Bldg. 2, Area 4 [3F])

[[F]2303-4pm] 14. Organic Chemistry -Aromatic, Heterocyclic, and Heteroatom Compounds-

Chair: Fumitoshi Shibahara, Yoshiyuki Mizuhata

Japanese
1:00 PM - 1:20 PM JST | 4:00 AM - 4:20 AM UTC
[[F]2303-4pm-01]
Enzymatic Radical Ring-opening Reaction of Cyclic Ketoxime via Iminyl Radial Generation Catalyzed by Aldoxime Dehydratase

○Haruka Nishiwaki[1], Keiji Endo[1], Shunsuke Kato[1], Takashi Hayashi[1] (1. Osaka University)

Japanese
1:20 PM - 1:40 PM JST | 4:20 AM - 4:40 AM UTC
[[F]2303-4pm-02]
Alkylation of tertiary amides with a novel active species, carbocationoid

○Daichi Shimada[1], Hikaru Fujita[1], Munetaka Kunishima[1,2] (1. Faculty of Pharmaceutical Sciences, Institute of Medical, Pharmaceutical, and Health Sciences, Kanazawa University, 2. Faculty of Pharmaceutical Sciences, Kobe Gakuin University)

Japanese
1:40 PM - 2:00 PM JST | 4:40 AM - 5:00 AM UTC
[[F]2303-4pm-03]
Synthesis and Reactivity of Chalcogenosilanes and -Germanes: Dearomative Cascade-Type Cycloaddition

○Ryosuke Masuda[1], Taisei Kuroki[1], Hiroyuki Kusama[1] (1. Gakushuin University)

English
2:00 PM - 2:20 PM JST | 5:00 AM - 5:20 AM UTC
[[F]2303-4pm-04]
Synthesis and Model Studies on Biologically Relevant Reactions of Reactive Supersulfides Utilizing Molecular Cavities

○Satoru Kuwano[1], Hinata Ikeda[1], Masato Goto[1], Kei Goto[1] (1. Institute of Science Tokyo)

アルドキシム脱水酵素を用いたイミニルラジカルを経由する環状ケトキシムのラジカル的開環反応

（阪大院工）○西脇 春香・遠藤 慶治・加藤 俊介・林 高史

Enzymatic Radical Ring-opening Reaction of Cyclic Ketoxime via Iminyl Radical Generation Catalyzed by Aldoxime Dehydratase (*Graduate School of Engineering, Osaka University*)

○Haruka Nishiwaki, Keiji Endo, Shunsuke Kato, Takashi Hayashi

Direct generation of iminyl radicals from non-activated oximes via N–OH bond cleavage remains challenging due to competitive O–H bond cleavage and low leaving ability of the OH group. In contrast, in nature, aldoxime dehydratases are known to catalyze the N–OH bond cleavage of aldoximes to form nitriles, which is promoted by the coordination of heme and the interaction with surrounding amino acid residues. Taking advantage of this unique catalytic mechanism of natural enzymes, we here developed a biocatalytic radical ring-opening reaction of cyclobutanone oximes using aldoxime dehydratase. Consequently, aldoxime dehydratase from *N. simplex* was found to catalyze the ring-opening reaction to afford γ-cyanosulfinic acid derivatives as a main product in the presence of dithionite.

Keywords : Radical Reaction, Biocatalysis, Oxime, Hemoprotein, Aldoxime dehydratase

オキシムの直接的 N–OH 結合の切断によるイミニルラジカル形成は、競合する O–H 結合の切断や OH 基の低い脱離能のため、未だに挑戦的なラジカル形成様式として知られている。一方、自然界においてアルドキシム脱水酵素は、ヘムと周辺のアミノ酸残基の働きによりアルドキシムの N–OH 結合開裂を促進し、イミニルラジカルを経由する反応機構でニトリルを合成することで知られている。本研究ではこのユニークな酵素の反応機構に着目し、環状ケトキシムのラジカル的開環反応を検討した。*N. simplex* 由来アルドキシム脱水酵素を含む溶液に種々のシクロブタノンオキシム誘導体を加えたところ、N–O 結合の開裂を駆動力とするシクロブタノン骨格の開環反応が進行した。特に、2-フェニルシクロブタノンオキシムを基質として用い、ジチオナイト存在下で反応を行った場合、室温 10 分の短時間でγ-シアノスルフィン酸が高収率で得られることが判明した。

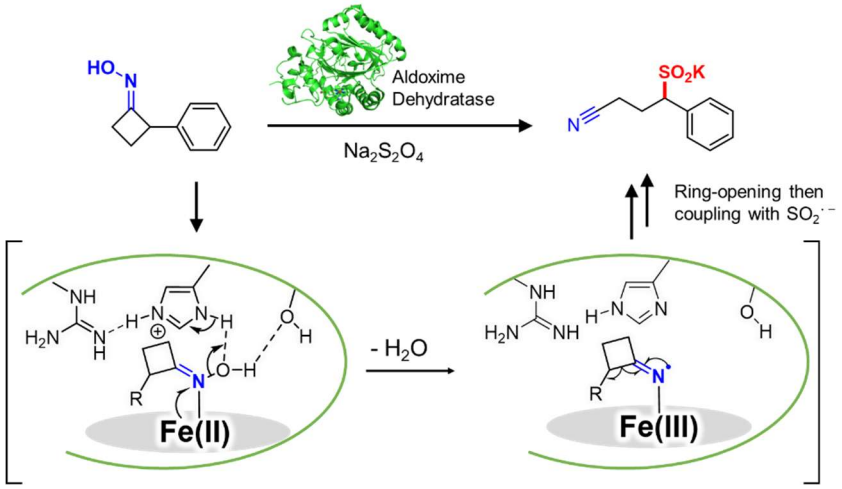


Figure 1. Radical ring-opening reaction of cyclic ketoxime catalyzed by aldoxime dehydratase.

新規活性種カルボカチオノイドを用いた第三級アミドのアルキル化反応

（金沢大院医薬保 [1]・神戸学院大薬 [2]）○島田 大地 [1]・藤田 光 [1]・国嶋 崇隆 [1,2]
Alkylation of tertiary amides with novel active species carbocationoids ([1]*Faculty of Pharmaceutical Sciences, Institute of Medical, Pharmaceutical, and Health Sciences, Kanazawa University*, [2]*Faculty of Pharmaceutical Sciences, Kobe Gakuin University*) ○ Daichi Shimada,[1] Hikaru Fujita,[1] Munetaka Kunishima[1,2]

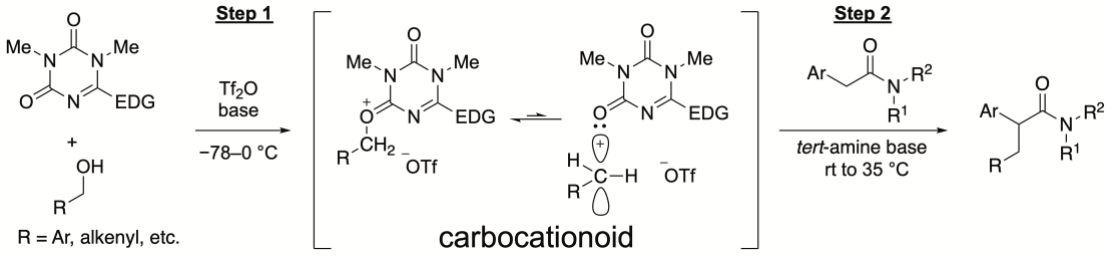
Recently, we have developed a method to preserve carbocations, highly reactive intermediates in S_N1 reactions, as novel active species termed “carbocationoids” in solution by coordinative stabilization with triazinedione compounds. These active species, even under weakly basic conditions, have a reactivity as carbocation species to facilitate alkylation reactions with high efficiency.

In this study, we developed a new alkylation reaction for tertiary amides using carbocationoids. This reaction does not require the generation of enolates beforehand using strong bases, such as LDA, as is customary in conventional methods. The new reaction achieved the direct alkylation of tertiary amides under mild basic conditions in the presence of tertiary amines as the base.

Keywords : Carbocationoids; Tertiary amides; Alkylation

最近我々は、S_N1 反応の高活性中間体であるカルボカチオンをトリアジンジオン化合物により配位安定化することで、新規活性種「カルボカチオノイド」として溶液中に保存する独自の方法論を開発した [1)]。本活性種はたとえ弱塩基性条件下でもカルボカチオン種としての反応性を示し、高効率にアルキル化反応を進行させる。

今回我々は、このカルボカチオノイドを用いることで、第三級アミドの新たなアルキル化反応を開発した。本反応では、従来法のような LDA などの強塩基を用いたエノラートの事前発生は不要であり、第三級アミンを共存塩基とする温和な塩基性条件下にて、第三級アミドを直接的にアルキル化することが可能である。



1) H. Fujita, D. Shimada, J. Kudo, K. Kosha, S. Kakuyama, H. Terasaki, M. Kunishima, *Commun. Chem.* **2024**, *7*, 55.

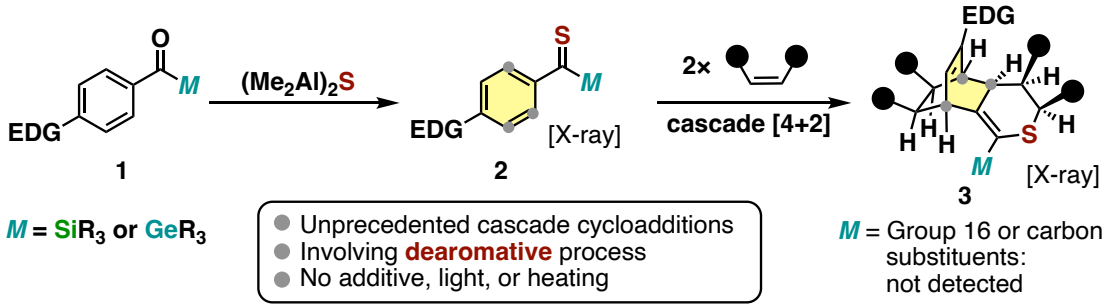
カルコゲノアシルシランおよびゲルマンの合成と反応: 脱芳香族化を伴うカスケード型環化反応

（学習院大理）○増田 涼介・黒木 大生・草間 博之
Synthesis and Reactivity of Chalcogenoacylsilanes and -Germanes: Dearomative Cascade-Type Cycloaddition (*Faculty of Science, Gakushuin University*) ○Ryosuke Masuda, Taisei Kuroki, Hiroyuki Kusama

Although the synthesis and reactivities of acylsilanes and acylgermanes have been well-explored, those of thioacylsilanes and -germanes have been poorly understood. Herein, we report the synthesis and reactivity of thioacylsilanes and -germanes; their reactions with electron-deficient alkenes gave the heterocycle bearing bicyclo[2.2.2] backbone without any additives. Notably, this reaction proceeded via the unprecedented dearomative *nucleophilic* reactivity of thioacyl Group 14 metalloids and their cascade-type cycloaddition, which was supported by the theoretical calculations.
Keywords : Chalcogens; Silicon; Germanium; Dearomatization; Cascade Reactions

カルボニルの隣に 14 族元素 (Si, Ge, Sn, Pb) が置換した化合物群は 14 族アシルメタロイドと呼ばれるが、これらのカルボニルをチオカルボニルに置き換えた化合物群はチオアシルシランのみに限られる [1a]。さらにその反応性については、主にジエノフィルや求電子剤としての性質が知られるのみである [1b]。以前我々は、チオアシルゲルマンの初めての合成を報告している [2]。今回、チオアシルシランおよびゲルマンが求核的に働くことによる、新奇な脱芳香族化反応を発見したため報告する。

対応するケトン **1** に対し $(Me_2Al)_2S$ を作用させることにより、チオアロイルシランおよびゲルマン **2** を緑色固体として高収率で単離できた。これらに対し電子不足アルケンを作用させたところ、基質 1 分子とアルケン 2 分子から構成される多環式化合物 **3** がほぼ定量的に得られた。本反応は室温中性条件下、添加剤なしに **2** の脱芳香族化が進行するユニークな反応である。本反応は他のチオカルボニル化合物では全く進行せず、チオアシルシランおよびゲルマンに固有な反応性に由来することが明らかとなった。中間体の単離や理論計算による反応機構検討も行ったため、併せて報告する。



1) Bonini, B. F. et al. a) *J. Chem. Soc. Chem. Commun.* **1981**, 822. b) *J. Chem. Soc. Perkin Trans 1* **1987**, 2643. 2) Kuroki, T.; Masuda, R.; Kusama, H. The 104th CSJ Annual Meeting, E1133-2am-05 (2023).

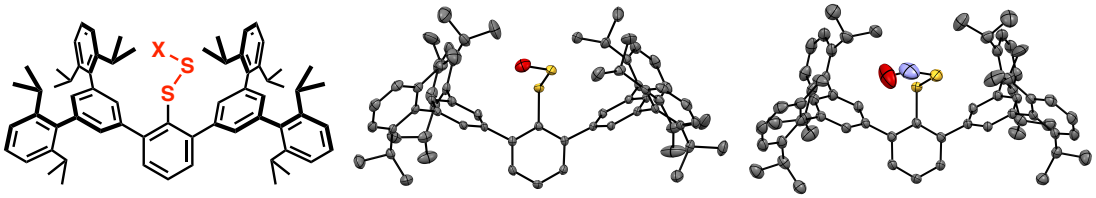
Synthesis and Model Studies on Biologically Relevant Reactions of Reactive Supersulfides Utilizing Molecular Cavities

(*School of Science, Institute of Science Tokyo*) ○Satoru Kuwano, Hinata Ikeda, Masato Goto, Kei Goto

Keywords: Reactive Supersulfides; Molecular Cavities; Biologically Relevant Reactions; Model Study

Reactive supersulfides, such as perthiosulfenic acid (R-SSOH) and *S*-nitrosodithioperoxol (R-SSNO), generated via oxidative modification of dithioperoxol (R-SSH) have been proposed as important intermediates in redox regulation and signal transduction. However, synthetic examples of stable compounds of reactive supersulfides have not been reported due to their susceptibility to decomposition via bimolecular reactions. Previously, we developed cavity-shaped substituents, the Bpq and Bpsc groups, which can effectively suppress undesired bimolecular reactions while maintaining sufficient space around the central functionality. In this study, we successfully synthesized and isolated several kinds of reactive supersulfides by utilizing these protective groups. Furthermore, we conducted model studies on biologically relevant reactions.

R-SSOH has been attracting much attention as a novel class of intermediates in redox regulation.[1] However, the synthesis of R-SSOH is challenging due to its inherent instability. Inspired by the synthetic approach for R-SOH, we successfully synthesized Bpq-SSOH by the thermal decomposition of a thiosulfinate precursor. R-SSNO has been postulated to be involved in nitric oxide release in biological systems.[2] However, as with R-SSOH, there has been no example of even observation of the species due to its instability. After careful optimization of reaction conditions, nitrosation of Bpq-SSH using ethyl nitrite at −30 °C provided Bpq-SSNO, presenting the first synthesis of the stable R-SSNO. Model studies using R-SSNO (R = Bpq or $BpqCH_2$) provided chemical evidence supporting the NO-release mechanism postulated in biological investigation. We also discovered a spontaneous desulfurization of R-SSNO yielding R-SNO, a reaction pathway that had not been anticipated in either chemistry or biology.



Bpq-SSX (X = OH, NO) **Bpq-SSOH** **Bpq-SSNO**

1) D. E. Heppner, M. Hristova, T. Ida, A. Mijuskovic, C. M. Dustin, V. Bogdándi, J. M. Fukuto, T. P. Dick, P. Nagy, J. Li, T. Akaike, A. Vliet, *Redox Biol.* **2018**, *14*, 379. 2) J. Zarenkiewicz, C. Perez-T., V. Kojasoy, C. McGinity, V. S. Khodade, J. Lin, D. J. Tantillo, J. P. Toscano, A. J. Hobbs, M. J. Fukuto, *Free Radical Biol. Med.* **2022**, *188*, 459.