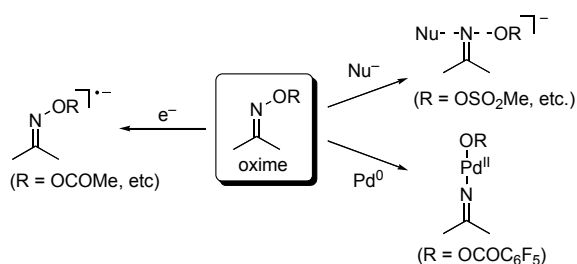


# SYNTHETIC ORGANIC CHEMISTRY

## Annual Research Highlights

### (1) “Amination with Oximes”

The S<sub>N</sub>2 reaction has been well recognized not to occur at sp<sup>2</sup> carbons, while such an S<sub>N</sub>2-type substitution reaction was found to proceed readily at the sp<sup>2</sup> nitrogen of oximes. Ab initio MP2 calculations show that the activation energy of the nucleophilic substitution at the sp<sup>2</sup> nitrogen is almost same as that of the Beckmann rearrangement. By the intramolecular S<sub>N</sub>2-type reaction at the oxime nitrogen, various aza-arenes and cyclic imines, such as quinolines, aza-spiro compounds, and dihydropyroles, can be synthesized. Intermolecular substitution of oximes with organometallic reagents such as Grignard reagents also proceeds. Anion radicals, generated by one-electron reduction or photo-induced process of oximes, act as iminyl radical equivalents to allow the transformation of  $\gamma,\delta$ -unsaturated oximes to dihydropyroles. Oxidative addition of oximes to palladium(0) complexes generates alkylideneamino-palladium(II) species, which are utilized as key intermediates in C–N bond formation. Various aza-heterocycles, including pyrroles, pyridines, isoquinolines, spiroimines, and azaazulenes, are synthesized from *O*-(pentafluorobenzoyl)oximes having olefinic moieties via the intramolecular Heck-type reaction (amino-Heck reaction) by treatment with a catalytic amount of a Pd(0) complex.



1.(1)-1) *Heterocycles*, **65**, 273–277 (2005)

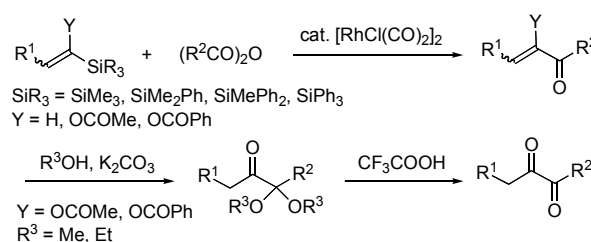
1.(1)-4) *Tetrahedron Lett.*, **46**, 2373–2376 (2005)

1.(1)-5) *Bull. Chem. Soc. Jpn.*, **78**, 1659–1664 (2005)

### (2) “Rhodium- or Palladium-Mediated Preparation of Carbonyl Compounds”

Simple methods for preparation of carbonyl compounds have been established by using metal exchanges between chromium–palladium and silicon–rhodium as key steps. We found that acylchromates act as unmasked acyl anion

equivalents in the presence of electron deficient palladium(II) complexes. Acyl groups are easily introduced into alkenes such as norbornenes to give multi-acylated compounds. Vinylsilanes undergo desilylative acylation with acid anhydrides and [RhCl(CO)<sub>2</sub>]<sub>2</sub> catalyst. The reaction provides a catalytic transformation of vinylsilanes into  $\alpha,\beta$ -unsaturated ketones, whereas conventional methods require more than a stoichiometric amount of Lewis acid. Mechanistic investigations revealed that a metal exchange between transition metal and silicon occurred without any activation reagents such as fluoride salts.



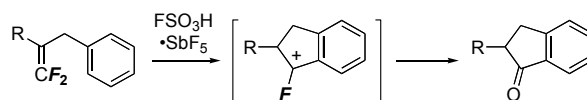
1.(1)-2) *Bull. Chem. Soc. Jpn.*, **78**, 331–340 (2005)

1.(1)-3) *Bull. Chem. Soc. Jpn.*, **78**, 477–486 (2005)

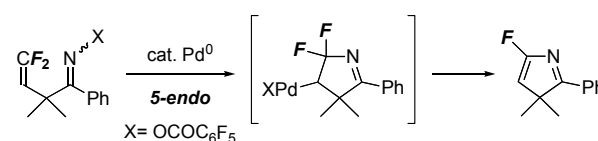
1.(1)-6) *Bull. Chem. Soc. Jpn.*, **78**, 1665–1672 (2005)

### (3) “Construction of Cyclic Systems via Electrophilic Activation of Fluoroalkenes”

Fluorine possesses  $\alpha$ -carbocation stabilizing effect caused by donation of an unshared electron pair, despite its high electronegativity. By the use of this effect, we have developed electrophilic cyclizations of fluoroalkenes. The Friedel–Crafts-type cyclization of difluoroalkenes bearing aryl groups is promoted by Magic Acid to yield fused bicyclic ketones.



The palladium-catalyzed Heck-type cyclizations of difluoroalkenes have been accomplished via a “normally disfavored” 5-*endo*-mode alkene insertion to afford fluorine-containing five-membered hetero- and carbocyclic compounds.



1.(1)-7) *Synthesis*, **2005**, 39–46

1.(1)-10) *Chem. Commun.*, **2005**, 4684–4686

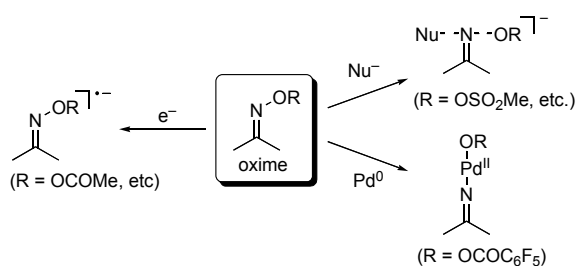
# 有機合成化学研究室

## 研究ハイライト

### (1) オキシム類を用いるアミノ化反応

SN2型反応は、sp<sup>2</sup>炭素原子上では進行しないとされる。これに対し我々は、オキシム誘導体のsp<sup>2</sup>窒素原子上でSN2型反応が進行することを見いだした。このSN2型反応を分子内反応に利用すると、キノリン、ジヒドロピロールなど、様々な含窒素芳香族化合物や環状イミンを合成できる。さらに分子間反応では、Grignard反応剤など有機金属化合物の求電子的アミノ化が行える。

また、オキシム類の一電子還元、光照射、遷移金属触媒による活性化が可能であることも示した。すなわち、オキシム類の一電子還元や光照射によりイミニルラジカル等価体が生成する。これを分子内アルケンにより補足することで、環状イミン類が得られる。また、*O*-ペンタフルオロベンゾイルオキシムをパラジウム(0)錯体に作用させると、酸化的付加が進行しアミノパラジウム(II)錯体が生成する。これを用いると、ピロール、ピリジン、イソキノリン、スピロイミン、アザブレンなど、含窒素環状化合物を触媒的に合成できる。



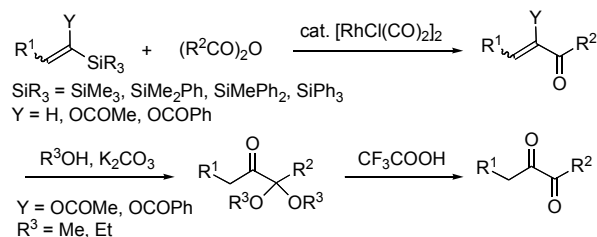
- 1.(1)-1) *Heterocycles*, **65**, 273–277 (2005)
- 1.(1)-4) *Tetrahedron Lett.*, **46**, 2373–2376 (2005)
- 1.(1)-5) *Bull. Chem. Soc. Jpn.*, **78**, 1659–1664 (2005)

### (2) ロジウム(I)錯体、パラジウム(II)錯体を用いるカルボニル化合物の合成

我々は、アシルクロマト錯体とパラジウム(II)錯体の金属交換が、低温で速やかに進行することを見いだした。この手法を用いると、ノルボルネンなどのアルケンに複数のアシル基を簡便に導入することができる。また、ビニルシラン類をカルボン酸無水物と触媒量のロジウム(I)カルボニル錯

体存在下で加熱すると、脱シリルアシル化が進行する。この変換反応は従来、化学量論量以上のルイス酸を必要としていたが、触媒的変換が初めて可能となった。

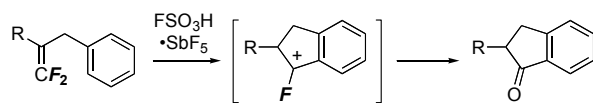
このように電子不足ロジウム、パラジウム錯体を用いることで、カルボニル化合物の簡便な調製法を開発した。



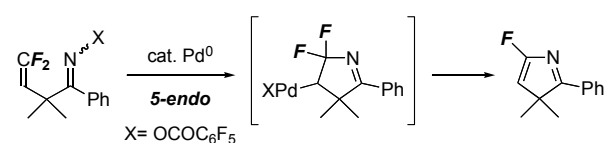
- 1.(1)-2) *Bull. Chem. Soc. Jpn.*, **78**, 331–340 (2005)
- 1.(1)-3) *Bull. Chem. Soc. Jpn.*, **78**, 477–486 (2005)
- 1.(1)-6) *Bull. Chem. Soc. Jpn.*, **78**, 1665–1672 (2005)

### (3) フルオロアルケン類の求電子的活性化による環構築

フッ素は、電子求引性を持ちながら、その非共有電子対によりα-カルボカチオンを安定化することができる。これを利用すると、アリール基を有するgem-ジフルオロアルケンにMagic酸を作用させることによって、α-フルオロカルボカチオンが生成し、Friedel-Crafts型の環化を経て効率良く二環式ケトンが合成できる。



また、分子内Heck反応による環化は広く利用されているが、5-endo型のアルケン挿入は不利とされ、極めて希である。我々は、gem-ジフルオロアルケンでこうしたアルケン挿入を行い、新たな5-endo Heck型環化を達成した。これにより、五員環の炭素環および含窒素ヘテロ環が構築できる。



- 1.(1)-7) *Synthesis*, **2005**, 39–46
- 1.(1)-10) *Chem. Commun.*, **2005**, 4684–4686

## 1. 原著論文

### (1) Refereed Journals

- 1) M. Kitamura, H. Yanagisawa, M. Yamane, and K. Narasaka, "Palladium(0)-Catalyzed Amino-Heck Reaction of  $\gamma,\delta$ -Unsaturated Ketone *N,N,N*-Trimethylhydrazonium Salts", *Heterocycles*, **65**, 273-277 (2005).
- 2) M. Yamane, Y. Kubota, and K. Narasaka, "Palladium-Catalyzed Carboacylation of Alkenes by Using Acylchromates as Acyl Donors", *Bull. Chem. Soc. Jpn.*, **78**, 331-340 (2005).
- 3) M. Yamane, K. Uera, and K. Narasaka, "Rhodium-Catalyzed Acylation of Vinylsilanes with Acid Anhydrides", *Bull. Chem. Soc. Jpn.*, **78**, 477-486 (2005).
- 4) M. Kitamura, Y. Mori and K. Narasaka, "Photochemical Radical Cyclization of  $\gamma,\delta$ -Unsaturated Ketone Oximes to 3,4-Dihydro-2*H*-pyrroles", *Tetrahedron Lett.*, **46**, 2373-2376 (2005).
- 5) K. Tanaka, M. Kitamura, and K. Narasaka, "Synthesis of  $\alpha$ -Carbolines Copper-Catalyzed Radical Cyclization of  $\beta$ -(3-Indolyl) Ketone *O*-Pentafluorobenzoyloximes", *Bull. Chem. Soc. Jpn.*, **78**, 1659-1664 (2005).
- 6) C. H. Cho, S. Kim, M. Yamane, H. Miyauchi, and K. Narasaka, "Radical Cyclizations of Alkenyl Acylphosphonate Derivatives under Thermal and Photochemical Conditions", *Bull. Chem. Soc. Jpn.*, **78**, 1665-1672 (2005).
- 7) J. Ichikawa, H. Jyono, T. Kudo, M. Fujiwara, and M. Yokota, "Friedel-Crafts Cyclization of 1,1-Difluoro-1-alkenes: Synthesis of Benzene-Fused Cyclic Ketones via  $\alpha$ -Fluorocarocations", *Synthesis*, **2005**, 39-46.
- 8) T. Mori, Y. Iwai, and J. Ichikawa, "Cyclization of *o*-Functionalized  $\alpha$ -Trifluoromethylstyrenes: Synthesis of Isoquinoline Derivatives Bearing Fluorinated One-Carbon Units", *Chem. Lett.*, **34**, 778-779 (2005).
- 9) T. Saitoh, and J. Ichikawa, "Bis(triarylmethyl)mediated Diaryl Ether Synthesis: Oxidative Arylation of Phenols with *N,N*-Dialkyl-4-Phenylthioanilines", *J. Am. Chem. Soc.*, **127**, 9696-9697 (2005).
- 10) K. Sakoda, J. Mihara, and J. Ichikawa, "Heck-Type 5-*endo-trig* Cyclization Promoted by Vinylic Fluorines: Synthesis of 5-Fluoro-3*H*-Pyrroles", *Chem. Commun.*, **2005**, 4684-4686.

## 2. 総説・解説

- 1) K. Narasaka and M. Kitamura, "Amination with Oxime", *Eur. J. Org. Chem.*, **2005**, 4505-4519.

## 3. 著書

- 1) J. Ichikawa, "Synthetic Methods for the Preparation of Ring-Fluorinated Heterocycles via Intramolecular Vinylic Substitution of *gem*-Difluoroalkenes" in *Fluorine-Containing Synthons*, ACS Symposium Series #911, V. A. Soloshonok, Ed., Oxford University Press/American Chemical Society, Washington, D.C., 2005; Chapter 3, pp. 262-275.