# Deaminative Radical Formation from Primary Amine

**Literature Seminar** 

2020/11/14 Koichi Hagiwara

# Contents

1. Introduction of primary amine

#### 2. Reductive deaminative carbon radical formation

#### 3. Oxidative deaminative carbon radical formation

# **Primary Amines**

•Primary amines in natural products and pharmaceuticals



•Pfizer's internal chemical inventry: 47,000 alkyl primary amines 28,000 primary and secondary alkyl halides

# **Representative Preparation of Primary Amines**

•Gabriel amine synthesis



### **Representative Reactions of Primary Amines**



For a recent study, see 200425\_LS\_Tsukasa\_Shimakawa.

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•Transformation of other functional groups



# **Cleavage of the C-N Bond**



for transition metal chemistry, to cleave strong C-N bond, amines should be located at allylic or benzylic position (electronic activation) or cyclized (aziridine, strain activation)



**B(OH)**<sub>3</sub> seemed to activate the amine and contribute to increasing the yield.

Li, M.-B.; Wang, Y.; Tian, S.-K. Angew. Chem., Int. Ed. 2012, 51, 2968.

## **Carbon Radical Generation via C-N Cleavage**

How could we cleave C-N bond homolytically (i.e. alkyl radical generation) ?





# Katritzky Pyridinium Salt



•2,4,6-Triphenylpyrylium tetrafluoroborate is commercially available (25 g  $\pm$  36,160), but easily prepared as follows



1) Dimroth, K.; Reichardt, C.; Voget, K. Org. Synth. **1969**, 49, 121.

2) Schonbauer, D.; Sambiagio, C.; Noel, T.; Schnurch, M. Beilstein J. Org. Chem. 2020, 16, 809.

# **Reductive Carbon Radical Generation** from Pyridinium Species



1) Basch, C. H.; Liao, J.; Xu, J.; Piane, J. J.; Watson, M. P. *J. Am. Chem. Soc.* **2017**, *139*, 5313. 2) Grimshaw, J.; Moore, S.; Trocha-Grimshaw, J. *Acta Chem. Scand., Ser. B* **1983**, *37*, 485.

### **How Does Single Electron Reduction Occur?**



How does single electron reduction proceed in the reaction system?

- 1. By metal species. ex) Ni<sup>I</sup>→Ni<sup>II</sup>, Mn<sup>0</sup>→Mn<sup>I</sup>
- 2. By photocatalyst. ex) Ir<sup>III\*</sup>→ Ir<sup>IV</sup>
- 3. By electron donor acceptor complex.

For a review, see: Correia, J. T. M.; Fernandes, V. A.; Matsuo, B. T.; Delgado, J. A. C.; de Souza, W. C.; 10 Paixao, M. W. *Chem. Commun.* **2020**, *56*, 503.

### **Deaminative Suzuki-Miyaura Coupling**



Basch, C. H.; Liao, J.; Xu, J.; Piane, J. J.; Watson, M. P. J. Am. Chem. Soc. 2017, 139, 5313.



Basch, C. H.; Liao, J.; Xu, J.; Piane, J. J.; Watson, M. P. J. Am. Chem. Soc. 2017, 139, 5313.

#### **Deaminative Minisci-Type Reaction**



Klauck, F. J. R.; James, M. J.; Glorius, F. Angew. Chem., Int. Ed. 2017, 56, 12336.

# Plausible Mechanism for Deaminative Minisci-Type Reaction



Correia, J. T. M.; Fernandes, V. A.; Matsuo, B. T.; Delgado, J. A. C.; de Souza, W. C.; Paixao, M. W. *14 Chem. Commun.* **2020**, *56*, 503.

# **Reaction with Indole**



When they mixed 1a abd 2a, the solution color changed.



electron donor-acceptor (EDA) complex formation?

Photocatalyst would not need?

1) Klauck, F. J. R.; James, M. J.; Glorius, F. *Angew. Chem., Int. Ed.* **2017**, 56, 12336. 2) James, M. J.; Strieth-Kalthoff, F.; Sandfort, F.; Klauck, F. J. R.; Wagener, F.; Glorius, F. *Chem. Eur. J.* **2019**, 25, 8240.



James, M. J.; Strieth-Kalthoff, F.; Sandfort, F.; Klauck, F. J. R.; Wagener, F.; Glorius, F. *Chem. Eur. J.* **2019**, *25*, 8240.

# **Plausible Mechanism**



Correia, J. T. M.; Fernandes, V. A.; Matsuo, B. T.; Delgado, J. A. C.; de Souza, W. C.; Paixao, M. W. *Chem. Commun.* **2020**, *56*, 503.

#### **Further Development and Limitation**



•Major limitations:  $\alpha$ -tetra-substituted primary amine does not form pyridinium salt



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•If imines could be single-electron-oxidized,



Ashley, M. A.; Rovis, T. J. Am. Chem. Soc. 2020, 142, 18310.

carbon radical

NH

R

# Oxidative Carbon Radical Generation from Aromatic Imine



# **Optimization of Reaction Conditions**



#### deviation

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acceptor (2 eq.), K<sub>3</sub>PO<sub>4</sub> (2 eq.), PhCF<sub>3</sub> (0.1 M): 46%
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acceptor (2 eq.), K<sub>3</sub>PO<sub>4</sub> (2 eq.), PhCF<sub>3</sub> (0.1 M), [lr(dF(Me)ppy)<sub>2</sub>(dtbbpy)]PF<sub>6</sub>: 19%

tetramethylguanidine (1 eq.): 72%

tetramethylguanidine (0 eq.): 40%

no 427 nm LEDs: 0% no photocatalyst, 427 nm LEDs: 0% no photocatalyst, 75 °C: 0%



 $[Ir(dF(CF_3)ppy)_2(dtbbpy)]PF_6: R = CF_3$  $[Ir(dF(Me)ppy)_2(dtbbpy)]PF_6: R = CH_3$ 

#### **Substrate Scope 1 - Preparation of Imine -**



#### Substrate Scope 2 - Imines -



#### Substrate Scope 3 - Electron-Deficient Olefin -



53%

Ashley, M. A.; Rovis, T. *J. Am. Chem. Soc.* **2020**, *142*, 18310.

35%

#### **Kinetic and Quenching Study**



R<sup>2</sup> = 0.98

15

Ashley, M. A.; Rovis, T. J. Am. Chem. Soc. 2020, 142, 18310.

ΌМе

MeO

0

3

6

9

quencher (mM)

# **Spin Density of Radical Cation Intermediate**

•Calculation of spin density



1. Nitrogen radical cation A acts as a hydrogen atom transfer reagent toward red-H.

2. Base (TMG) deprotonates red-H of radical cation.

# **Competition Experiment**



•Plaisible pathway for imidiyl radical formation



#### **Plausible Mechanism**



# Limitation

•Low yield in the case of imine derived from  $\alpha$ -tri-substituted primary amine



### Summary

