

Literature Report

Radical induced remote Csp³ – H Functionalization

Reporter: Changcheng Wang
Supervisor: Zhang-Jie Shi

Fudan University
2019-12-13

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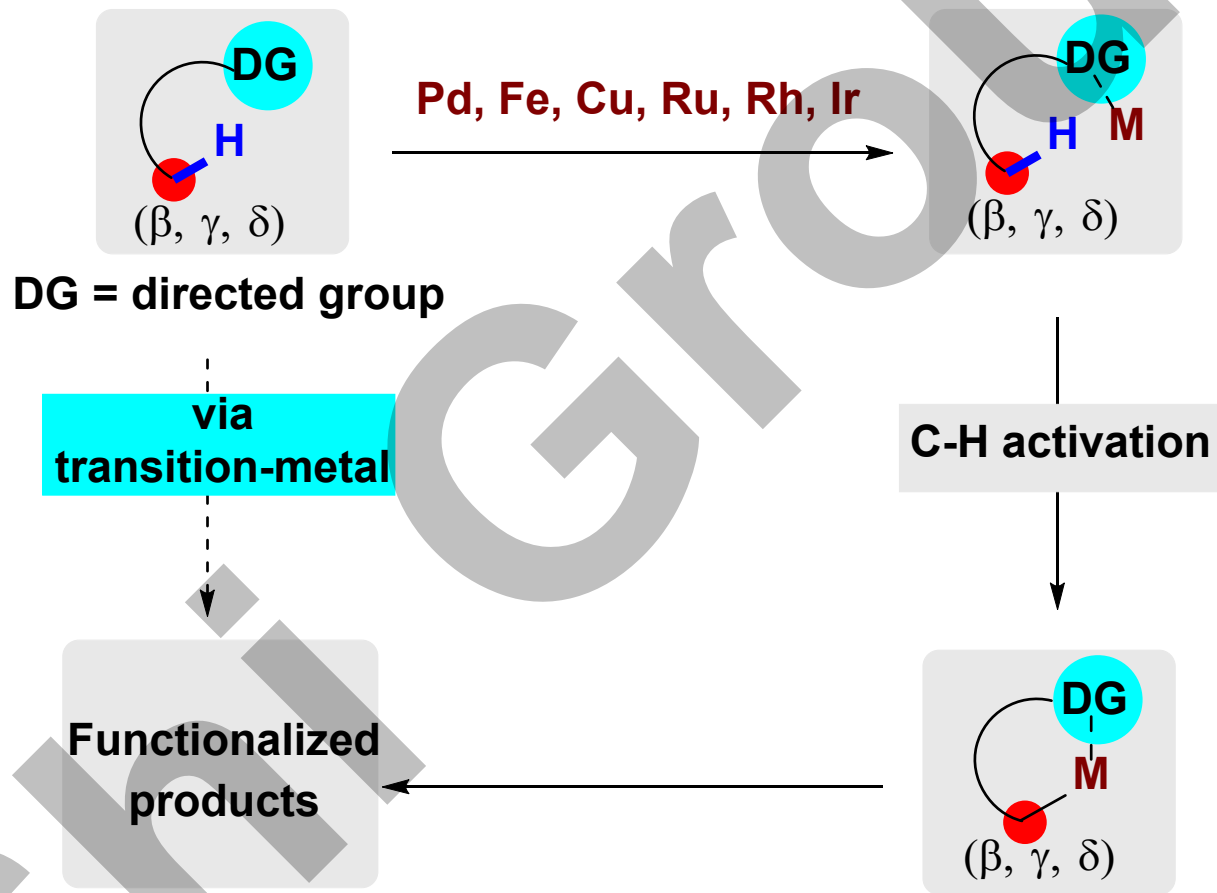
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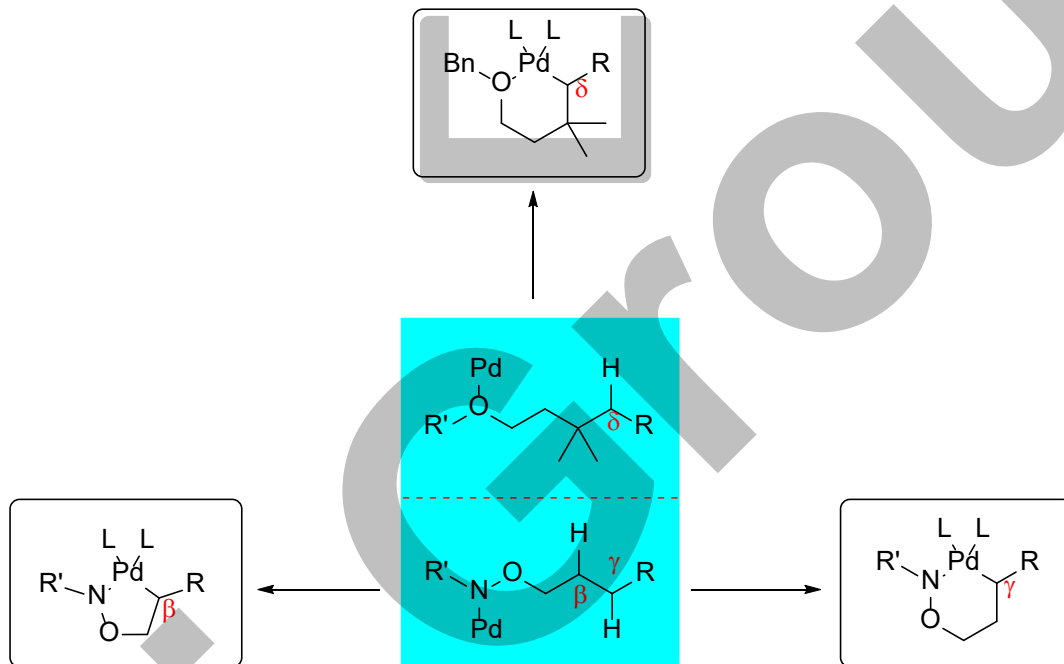
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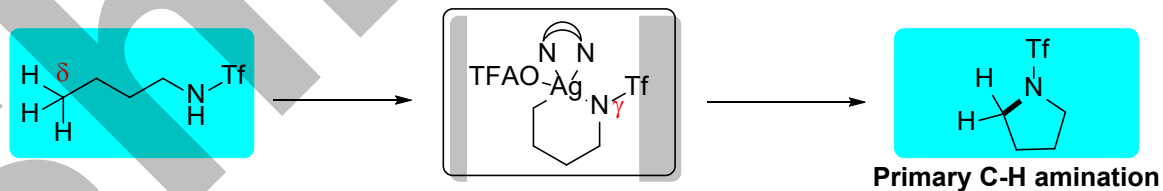
Background

Yu, J. Q. and co-authors. *J. Am. Chem. Soc.* **2019**, *141*, 15494.



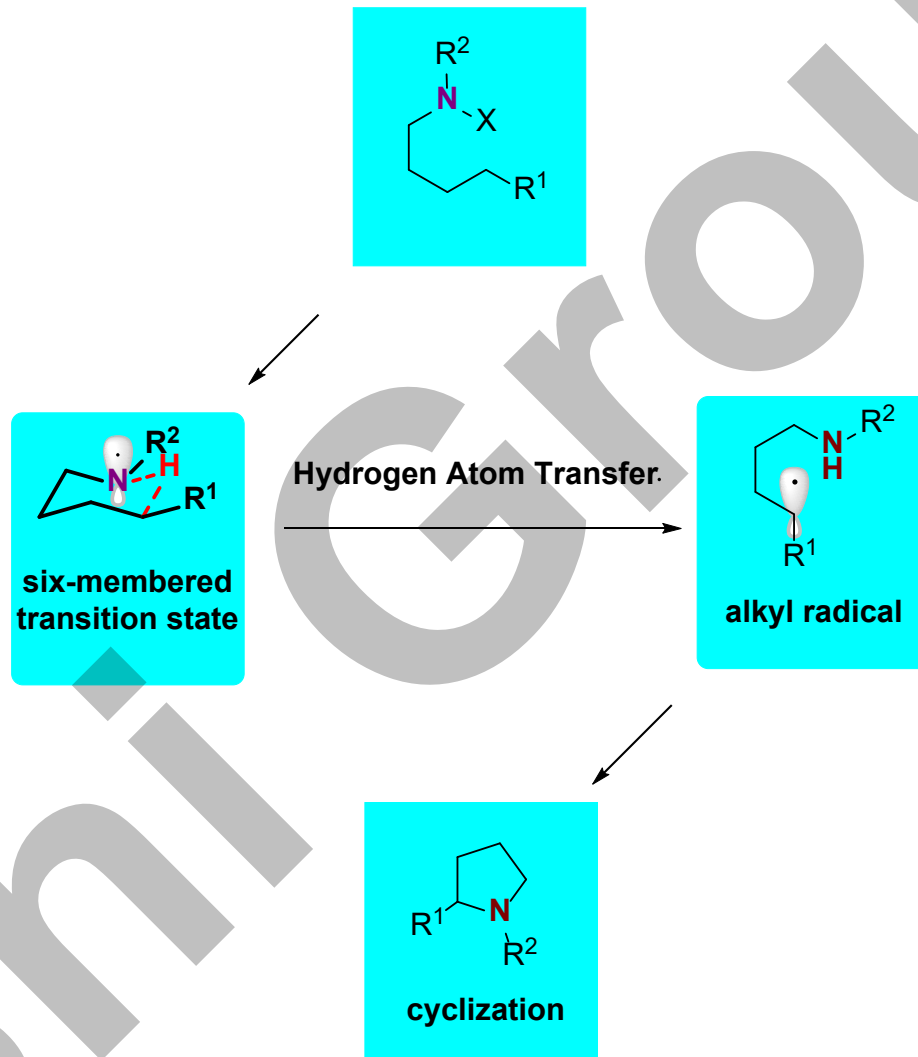
Xu, D. Q. and co-authors. *Angew. Chem., Int. Ed.* **2018**, *57*, 14085.

Yu, J. Q. and co-authors. *Nat. Chem.* **2019**, *11*, 571.



Shi, Z. J. and co-authors. *Nat. Commun.* **2014**, *5*, 1.

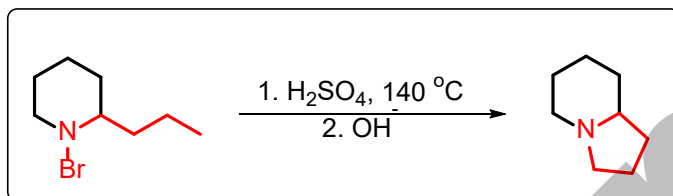
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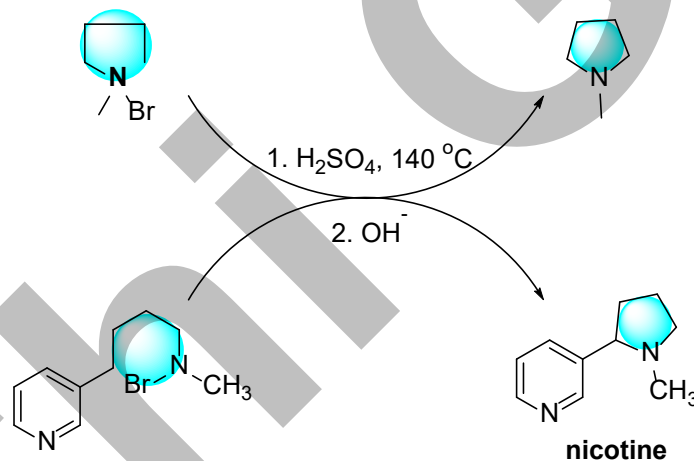
Background

CYCLIZATION OF N-HALOGENATED AMINES (The Hofmann-Löffler Reaction)

Wolff, M. E. and co-authors. *Chem. Rev.* **1963**, *63*, 55.



Hofmann, A. W. and co-authors. *Ber. Dtsch. Chem. Ges.* **1883**, *16*, 558.



Löffler, K.; Freytag, C. *Ber. Dtsch. Chem. Ges.* **1909**, *42*, 3427.

Löffler, K. and co-authors. *Ber. Dtsch. Chem. Ges.* **1909**, *42*, 3421.

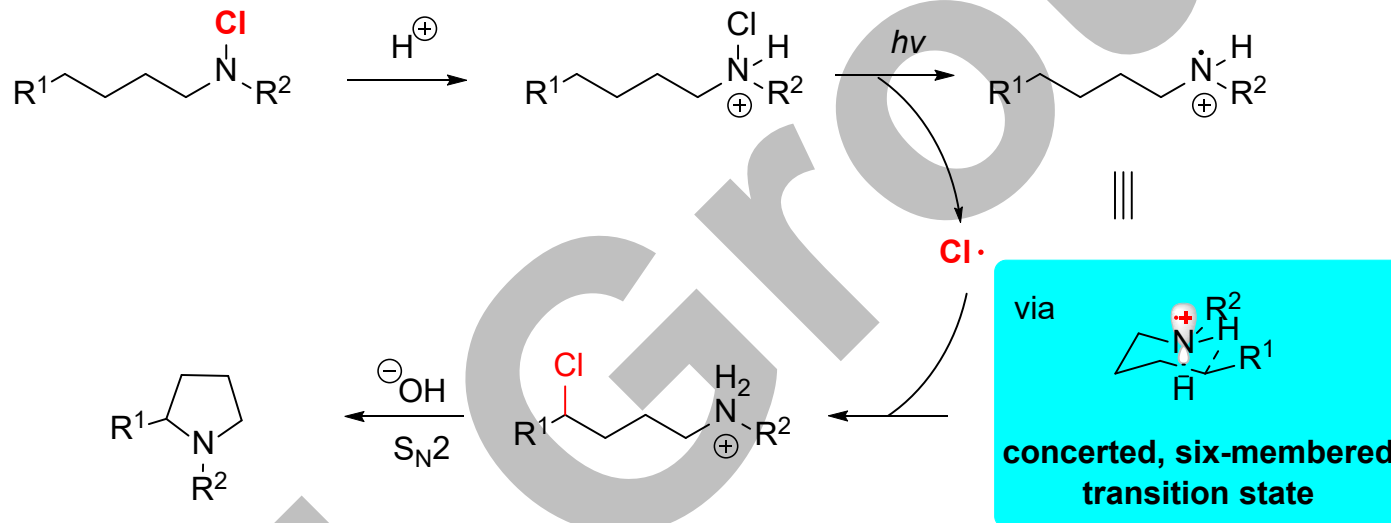
Löffler, K. and co-authors. *Ber. Dtsch. Chem. Ges.* **1910**, *43*, 2025.



August Wilhelm von Hofmann
(1818–1892)

Background

Mechanism:

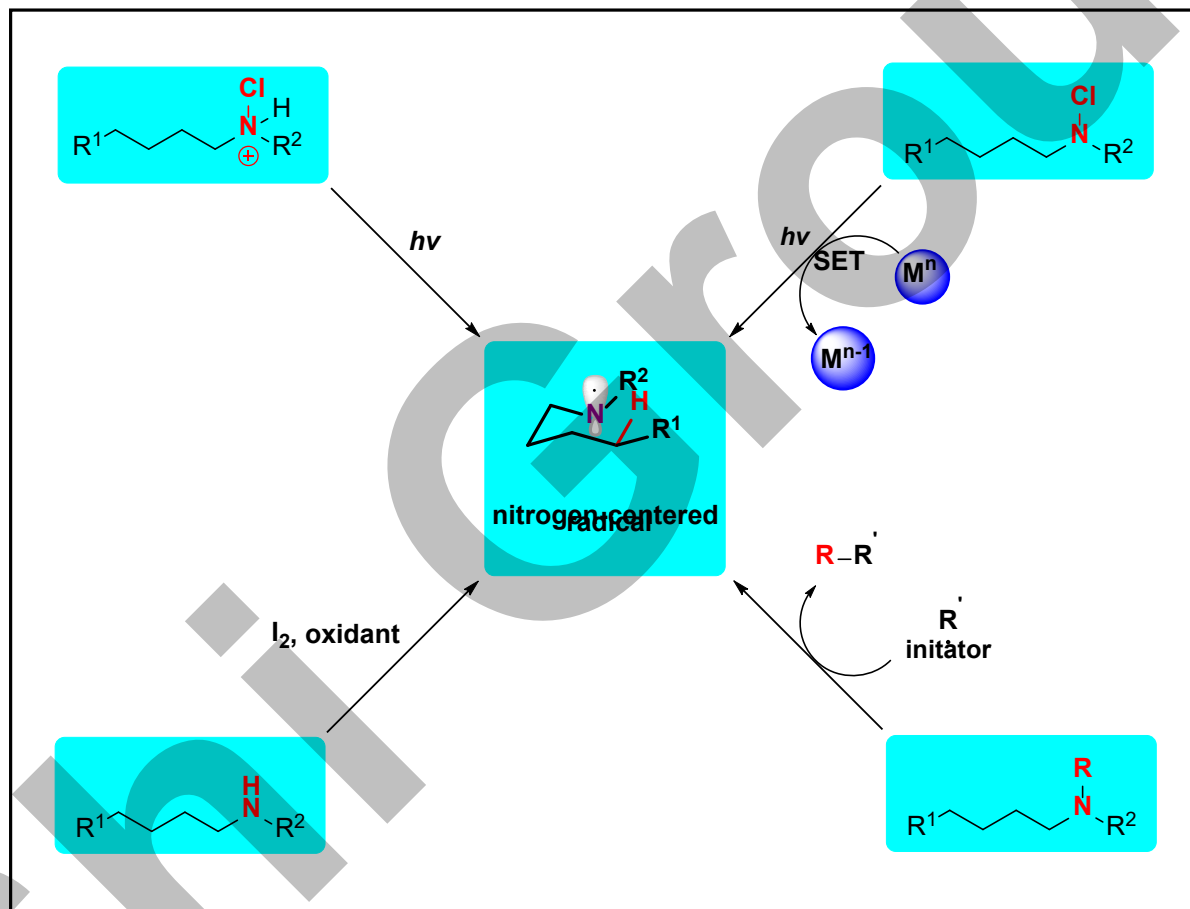


Wawzonek, S. and co-authors. *J. Am. Chem. Soc.* **1950**, 72,

2118.

Corey, E. J. and co-authors. *J. Am. Chem. Soc.* **1960**, 82, 1657.

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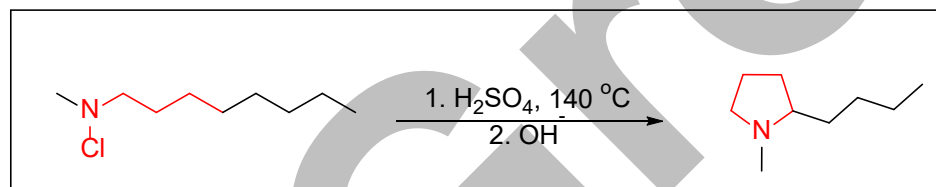
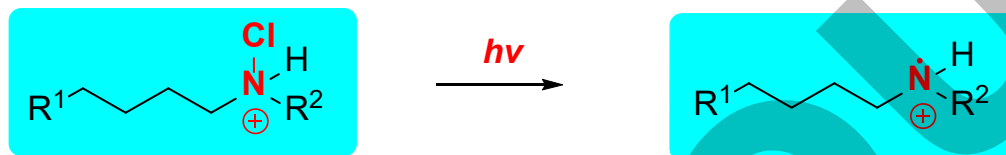
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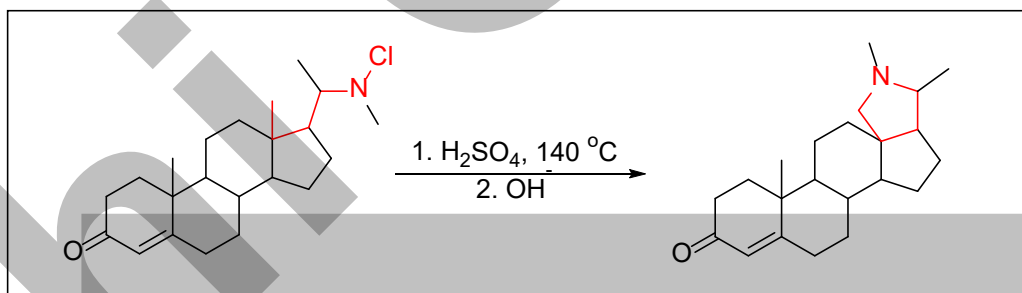
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-----*N*-Chloroamines to form the *N*-centered radical



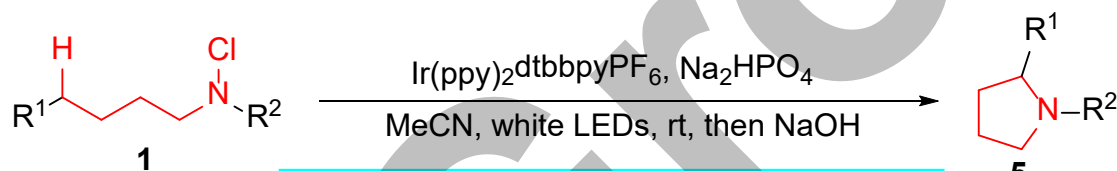
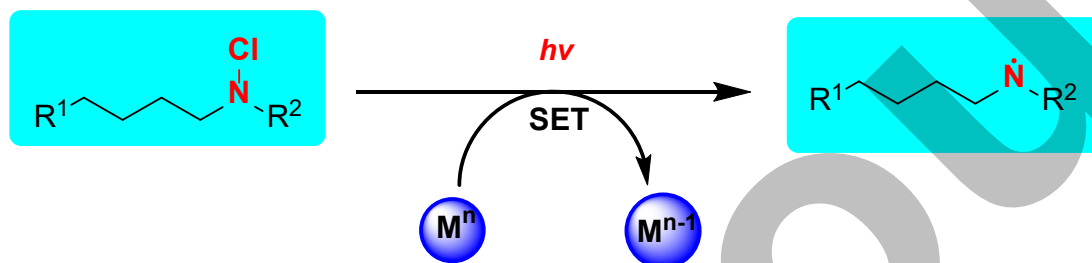
Coleman, G. H. and co-authors. *Proc. Iowa Acad. Set.* **1939**, 46, 217.



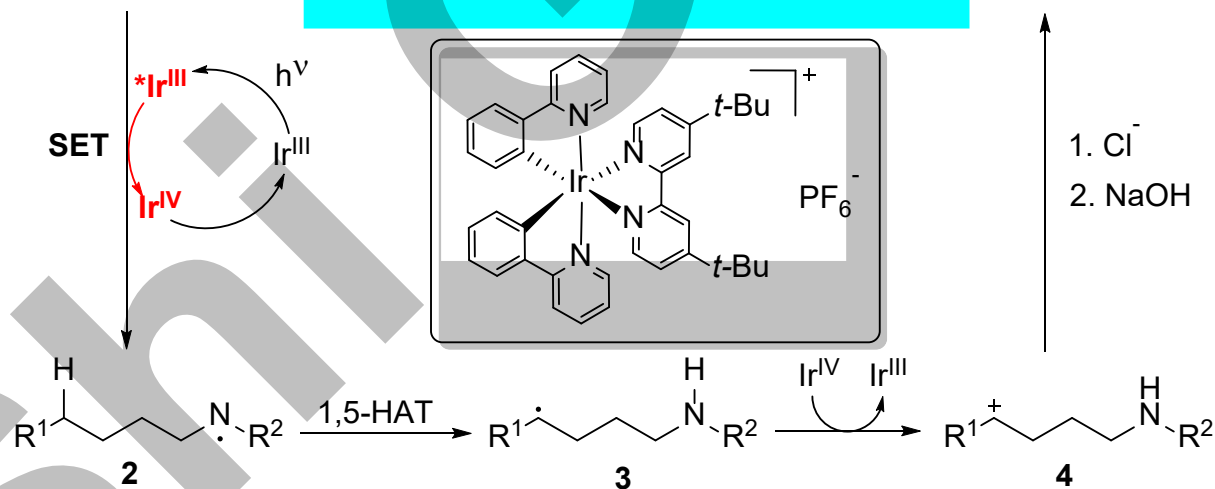
Georgian, V. and co-authors. *J. Org. Chem.* **1962**, 27, 3628.

Nitrogen-centered radicals induced remote C(sp³)-H Functionalization

-----N-Chloroamines to form the N-centered radical



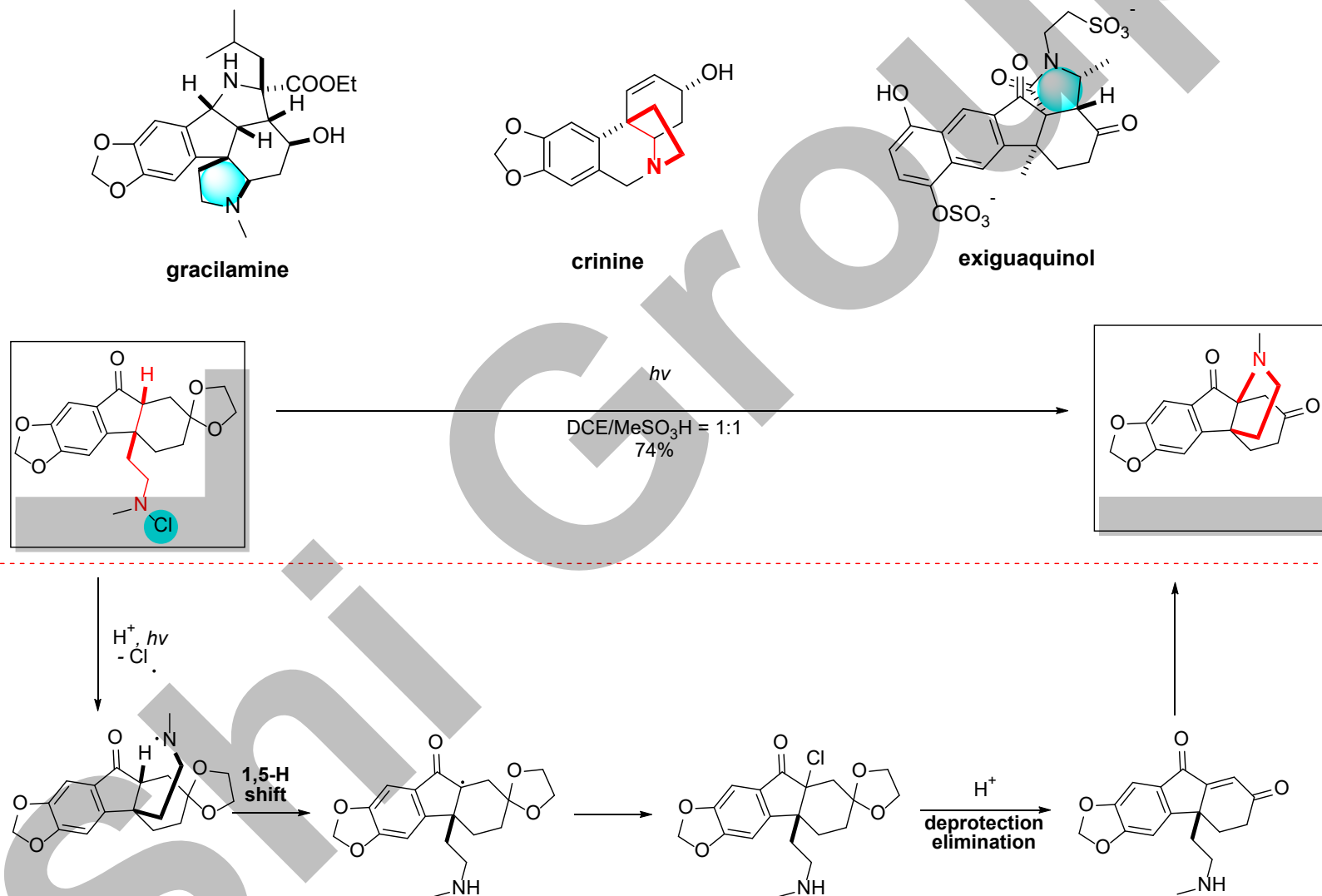
under mild condition
avoid ultraviolet photolysis, strong acid



Yu, S. Y. and co-authors. *Org. Lett.* **2015**, *17*, 1894.

Nitrogen-centered radicals induced remote C(sp³)-H Functionalization

-----*N*-Chloroamines to form the *N*-centered radical



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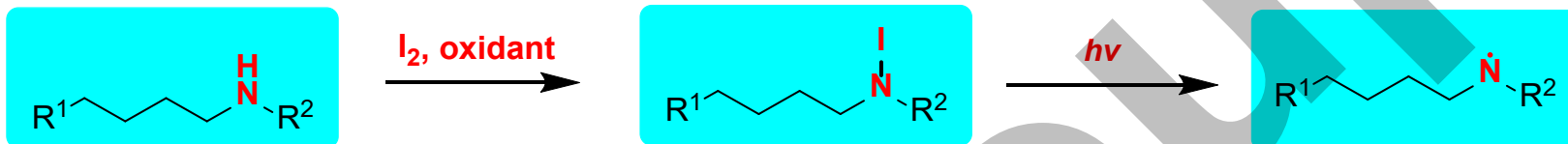
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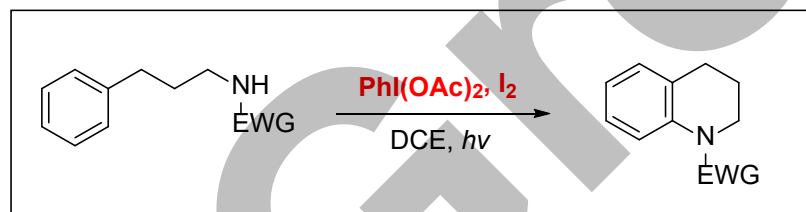
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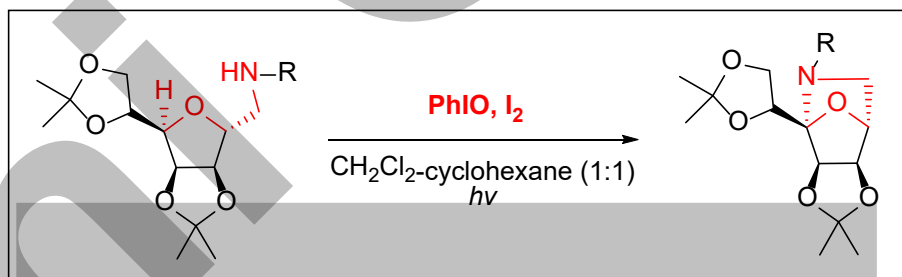
-----Amine to form the N-centered radical



Suárez, E. and co-authors. *Tetrahedron Lett.* **1987**, 28, 2533.



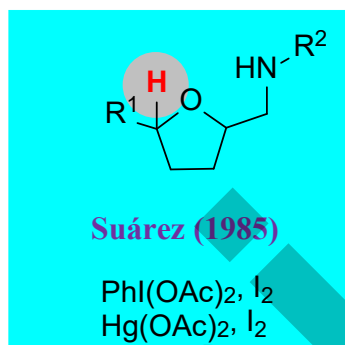
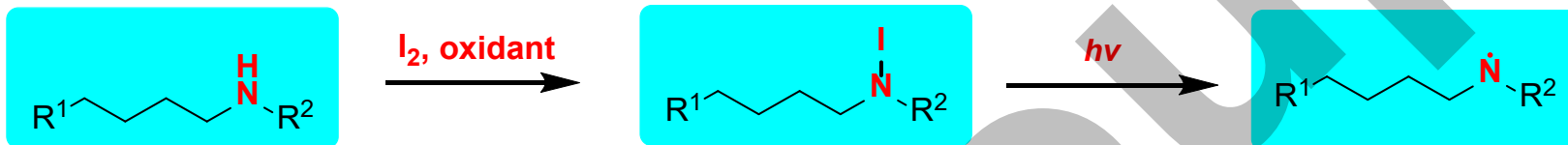
Yokoyama, M. and co-authors. *J. Org. Chem.* **1998**, 63, 5193.



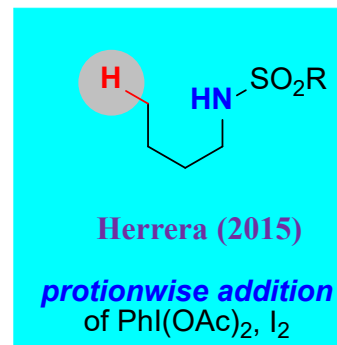
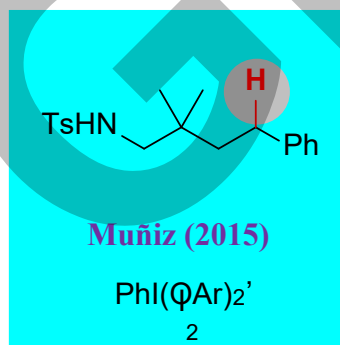
Suárez, E. and co-authors. *J. Org. Chem.* **2003**, 68, 1012.

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-----Amine to form the N-centered radical



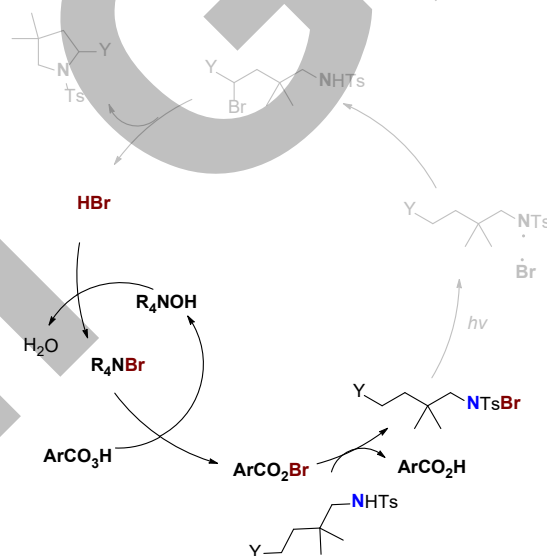
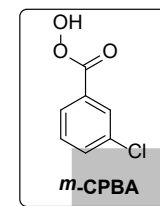
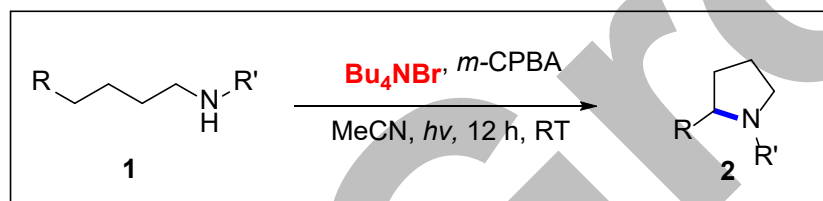
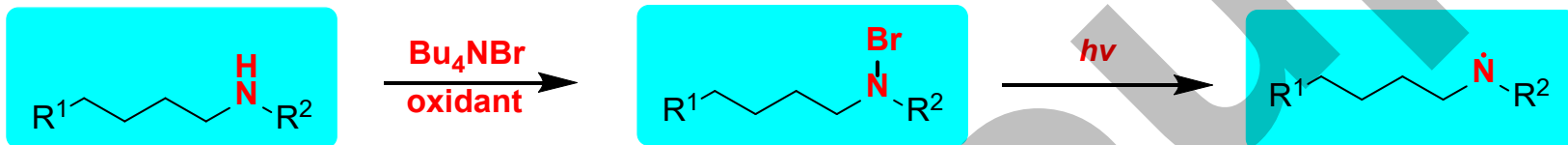
weak C-H (tertiary, benzylic, α-oxy)



primary C-H

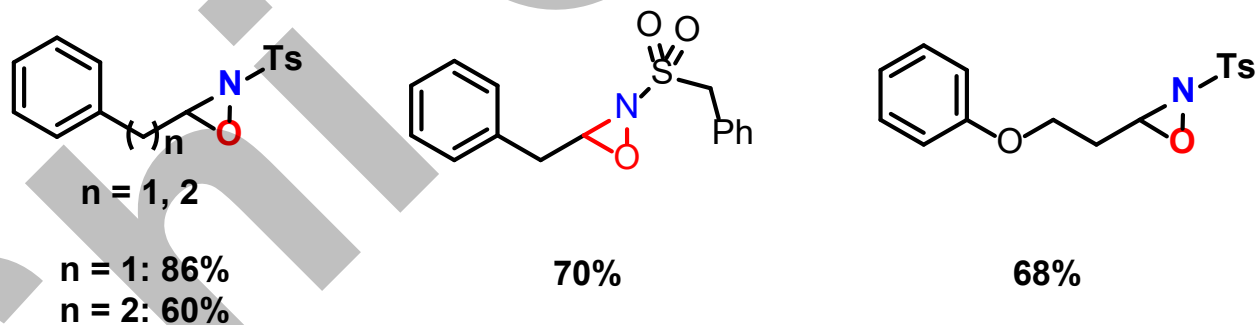
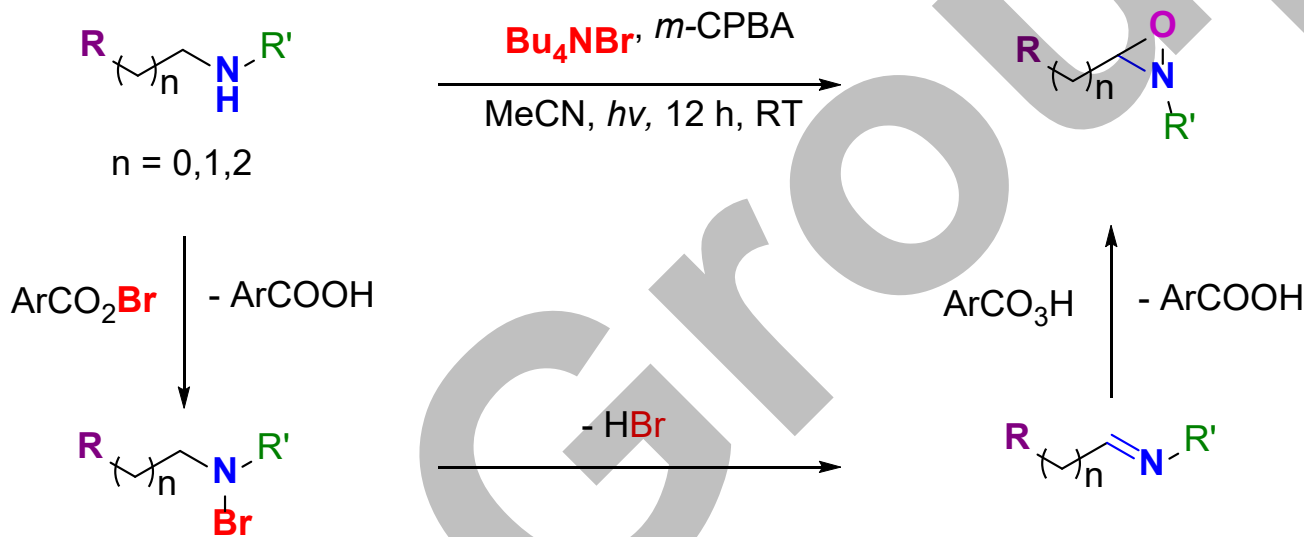
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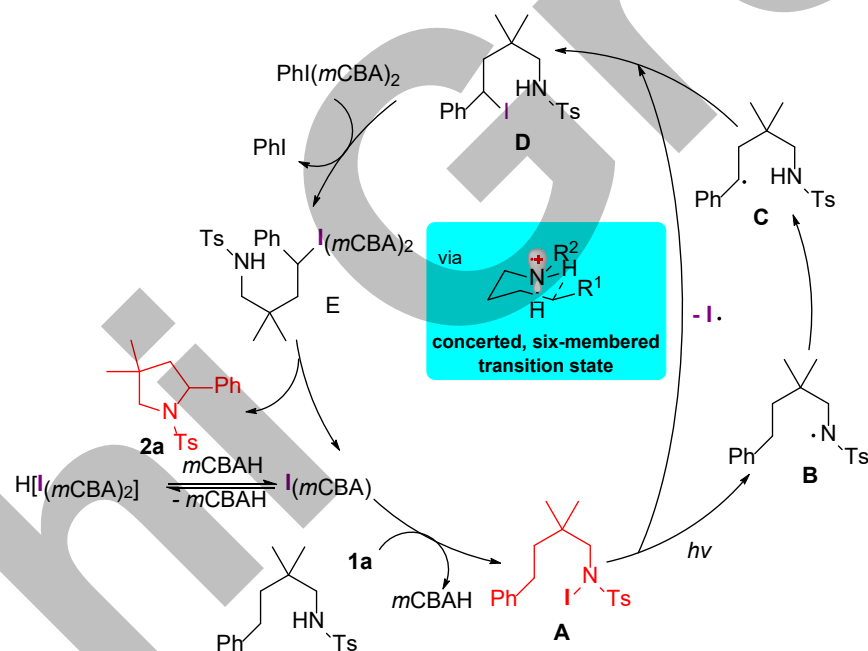
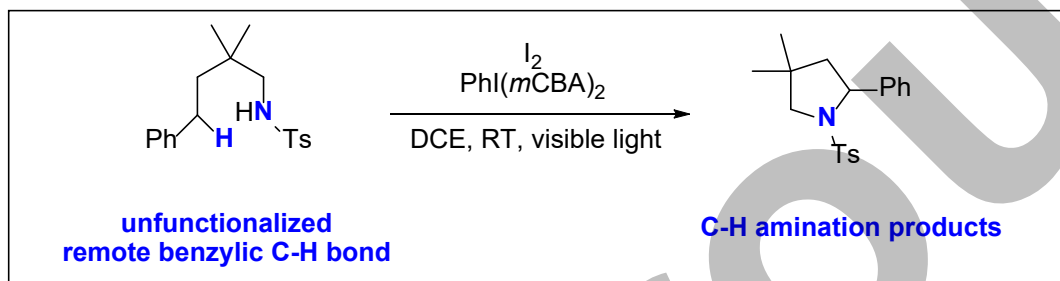


Nitrogen-centered radicals induced remote C(sp³)-H Functionalization

-----Amine to form the N-centered radical



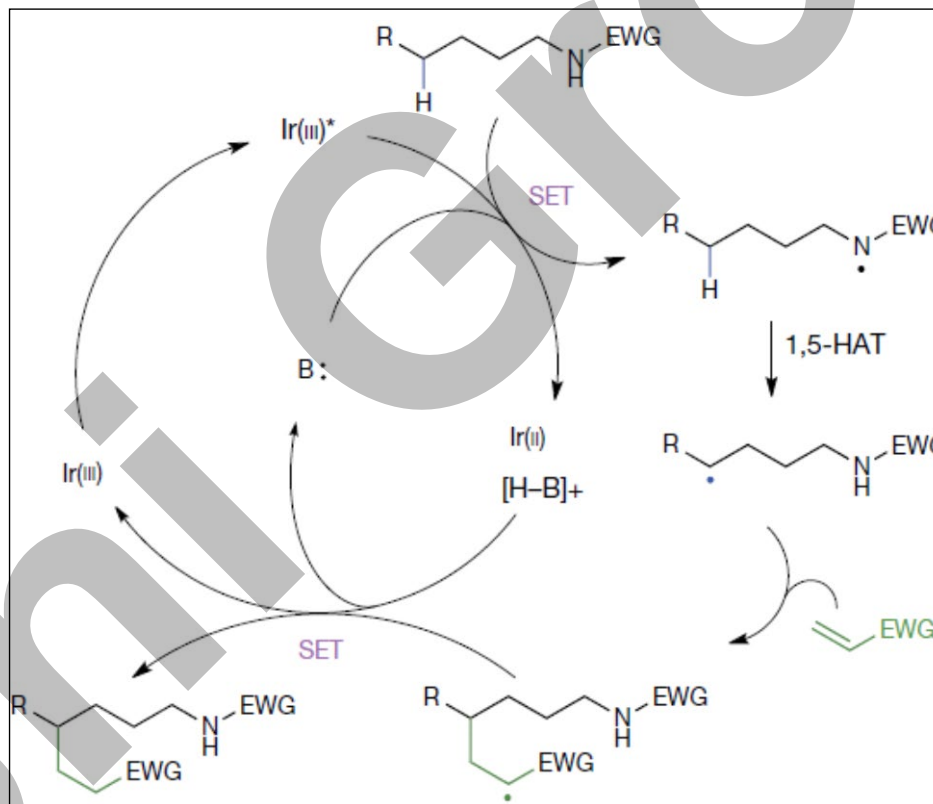
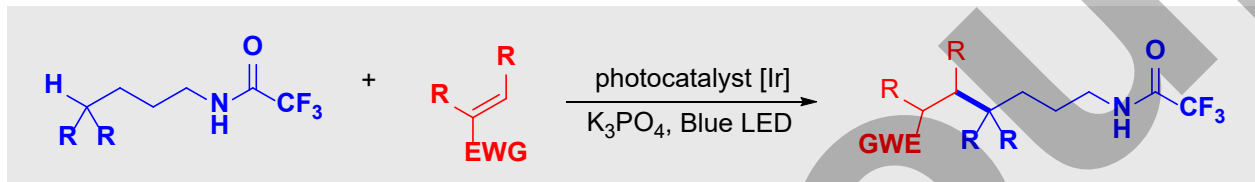
Nitrogen-centered radicals induced remote C(sp³)-H Functionalization



Muñiz, K. and co-authors. *Angew. Chem. Int. Ed.* **2015**, *54*, 8287.

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-----Amine to form the N-centered radical



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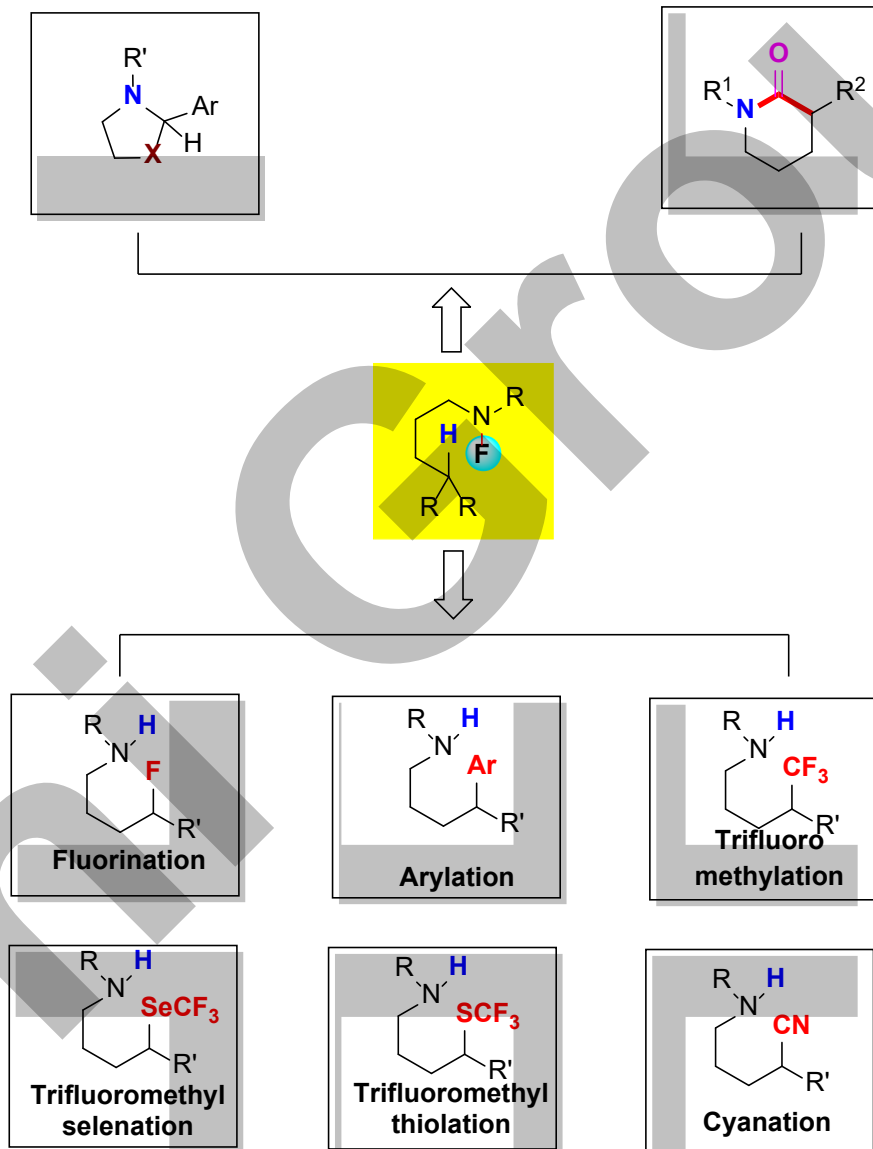
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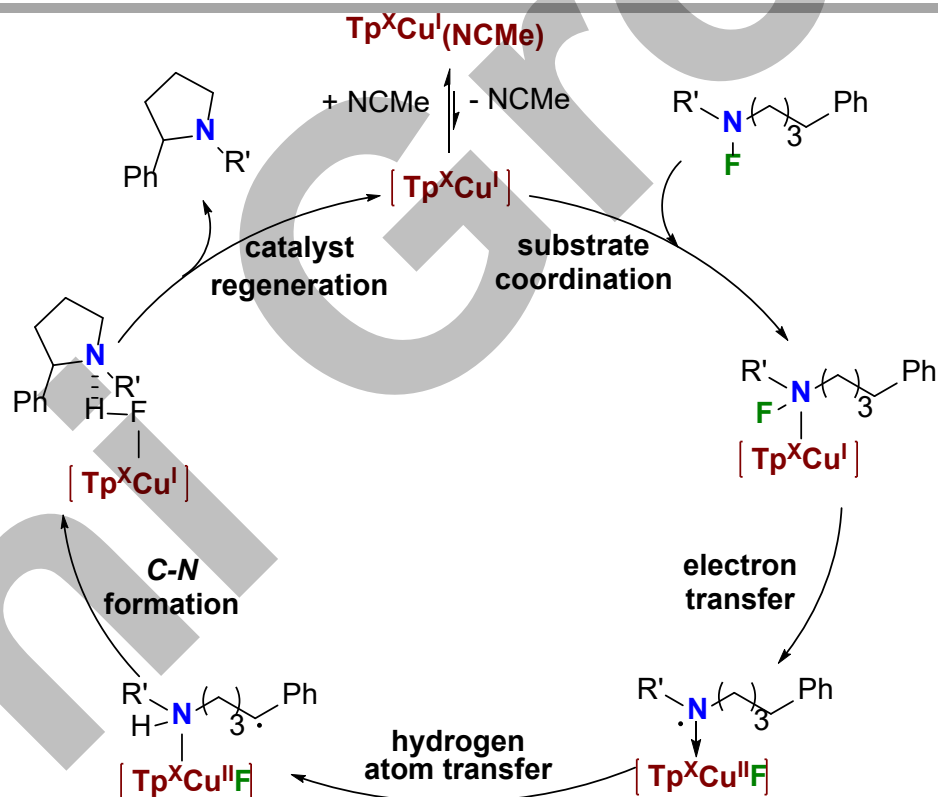
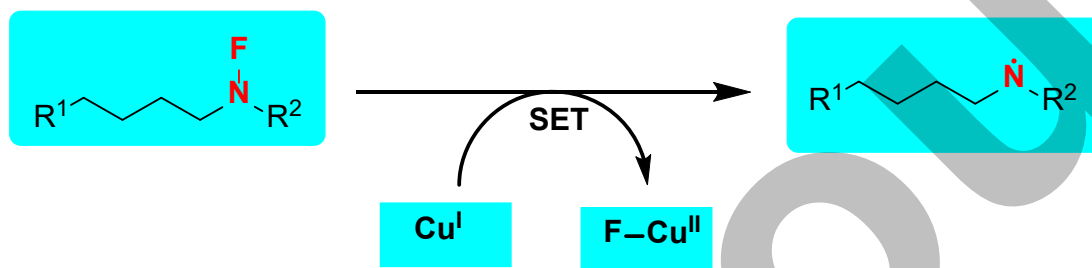
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-----*N*-Fluoroamines to form the *N*-centered radical



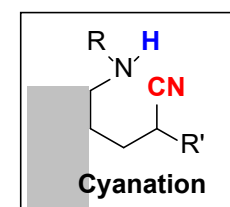
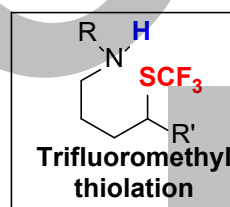
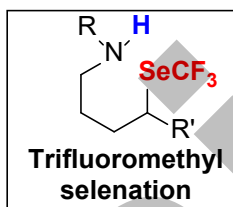
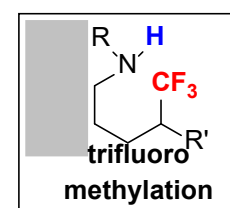
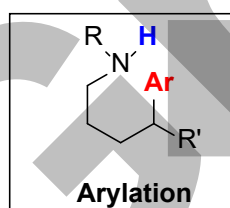
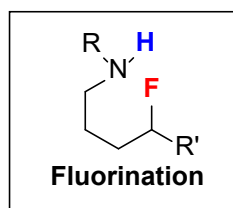
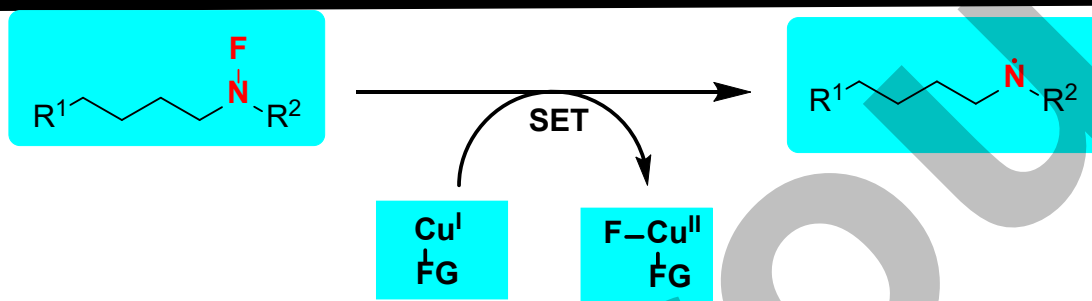
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-----N-Fluoroamines to form the N-centered radical



Nitrogen-centered radicals induced remote C(sp³)-H Functionalization

-----N-Fluoroamines to form the N-centered radical



Cook, S. P. and co-authors. *J. Am. Chem. Soc.* **2016**, *138*, 12771.

Nagib, D. A. and co-authors. *Chem. Sci.* **2019**, *10*, 1207.

Zhu, J. P. and co-authors. *Angew. Chem. Int. Ed.* **2018**, *57*, 13288.

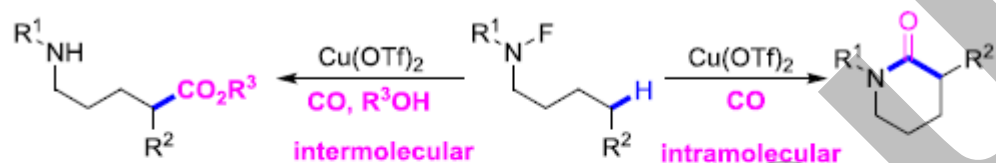
Li, C. Z. and co-authors. *Angew. Chem. Int. Ed.* **2019**, *58*, 2510.

Cook, S. P. and co-authors. *J. Am. Chem. Soc.* **2019**, *141*, 18405.

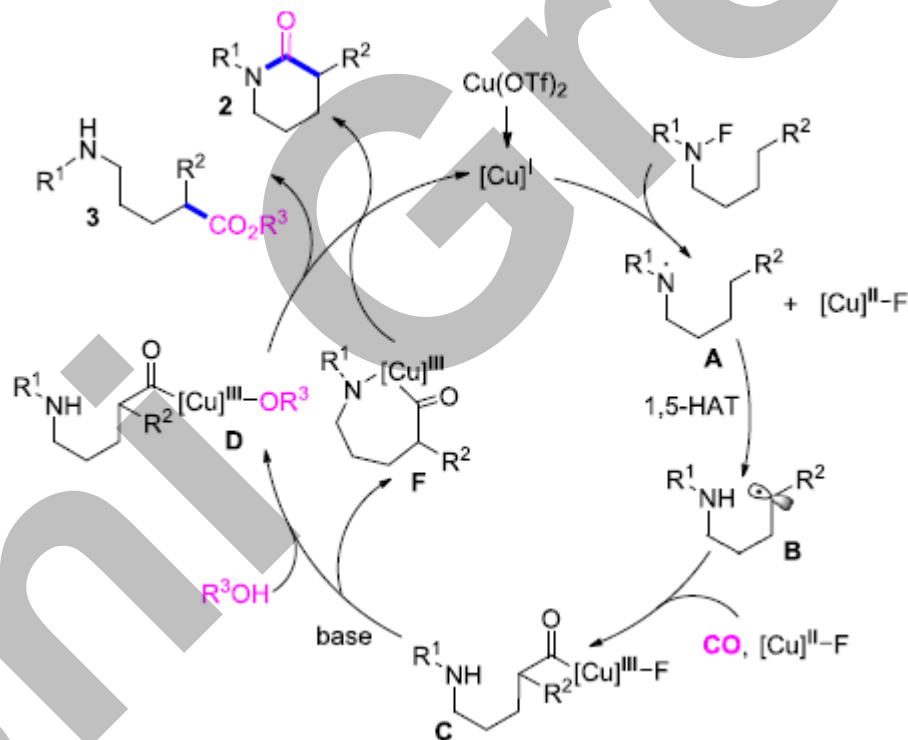
Jiang, C. Y. and co-authors. *Org. Lett.* **2019**, *21*, 1921.

Nitrogen-centered radicals induced remote C(sp³)-H Functionalization

-----*N*-Fluoroamines to form the *N*-centered radical

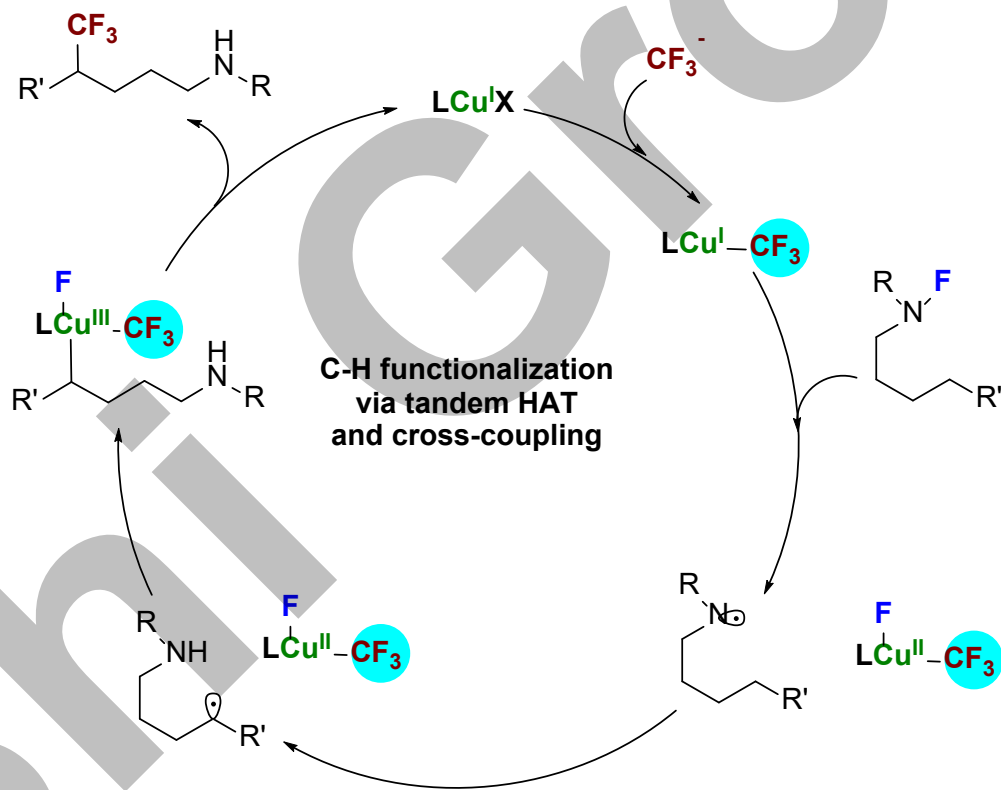
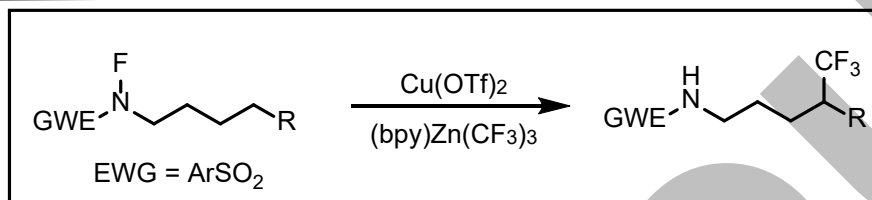


- Oxidant free
- Regioselectivity
- Mild reaction condition
- Broad substrate scope
- Intra- and intermolecular reactions
- Late-stage functionalization



Nitrogen-centered radicals induced remote C(sp³)-H Functionalization

-----N-Fluoroamines to form the N-centered radical



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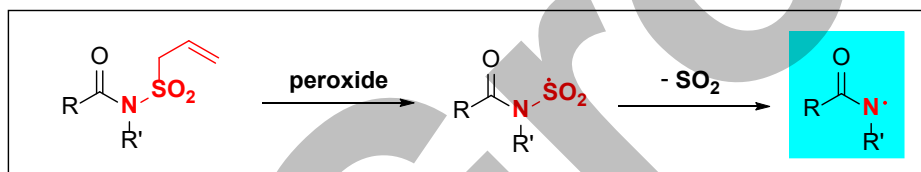
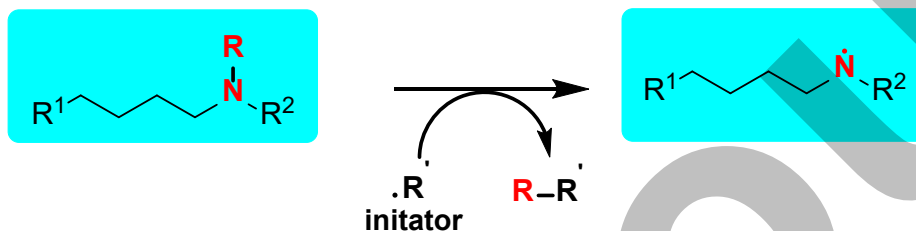
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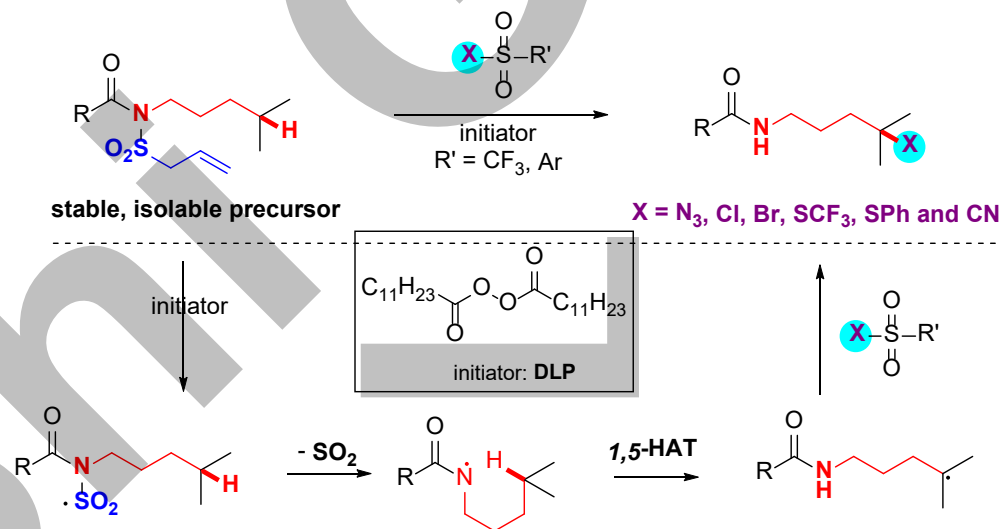
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Nitrogen-centered radicals induced remote C(sp³)-H Functionalization

-----N-Allylsulfonyl to form the N-centered radical



Zard, S. Z. and co-authors. *Chem. Commun.* **2004**, 1848.



Studer, A. and co-authors. *Angew. Chem. Int. Ed.* **2018**, 57, 12940.

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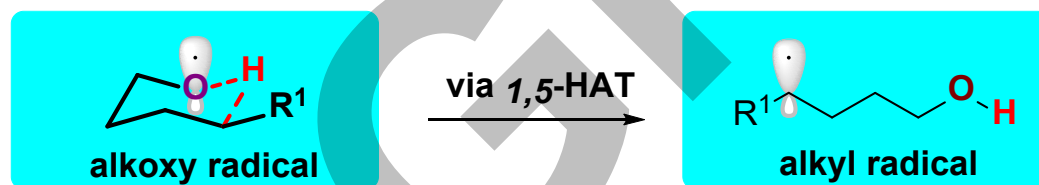
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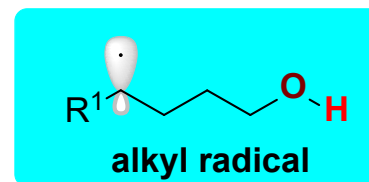
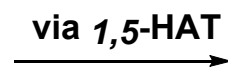
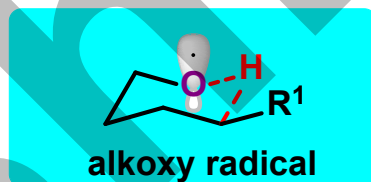
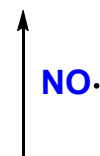
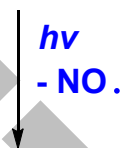
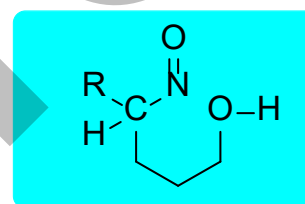
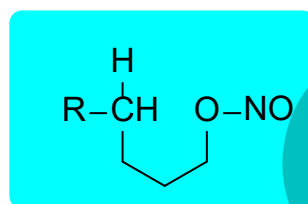
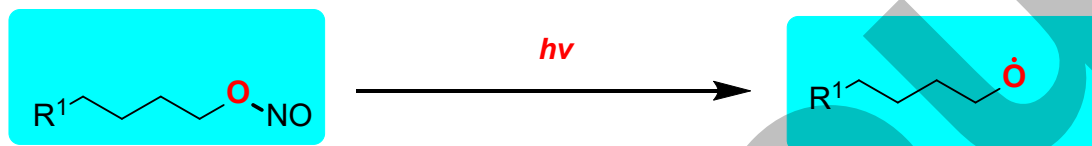
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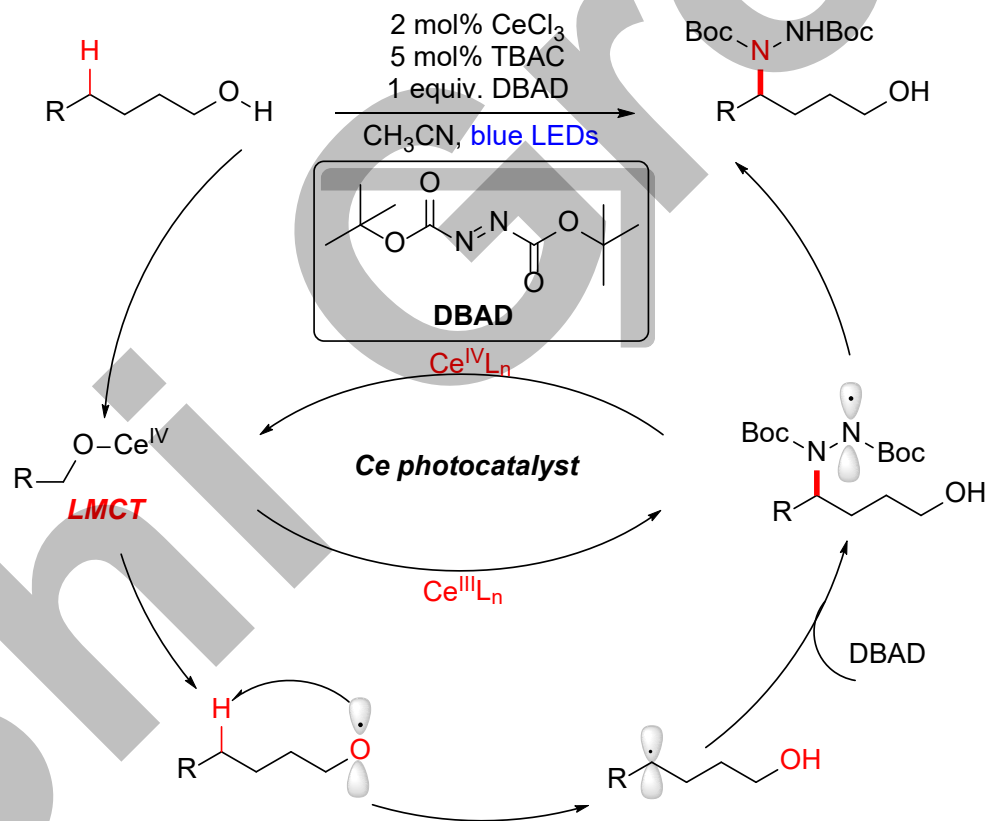
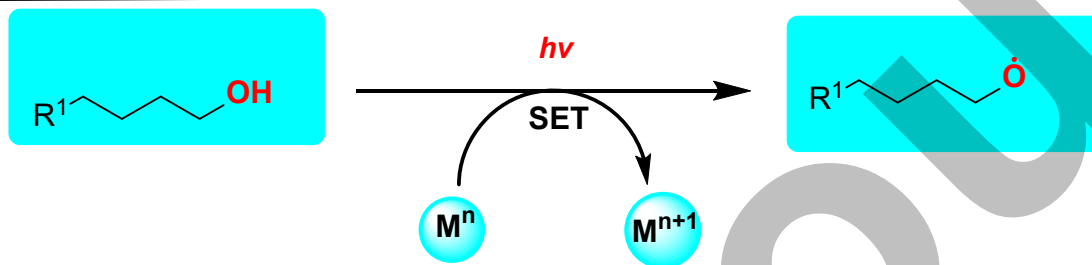
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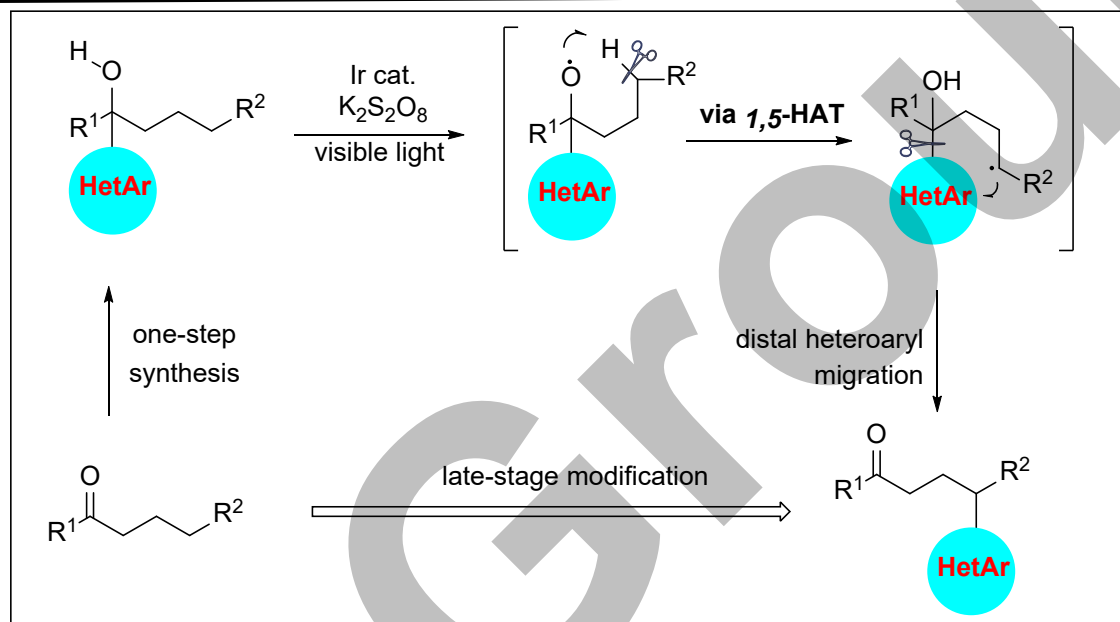
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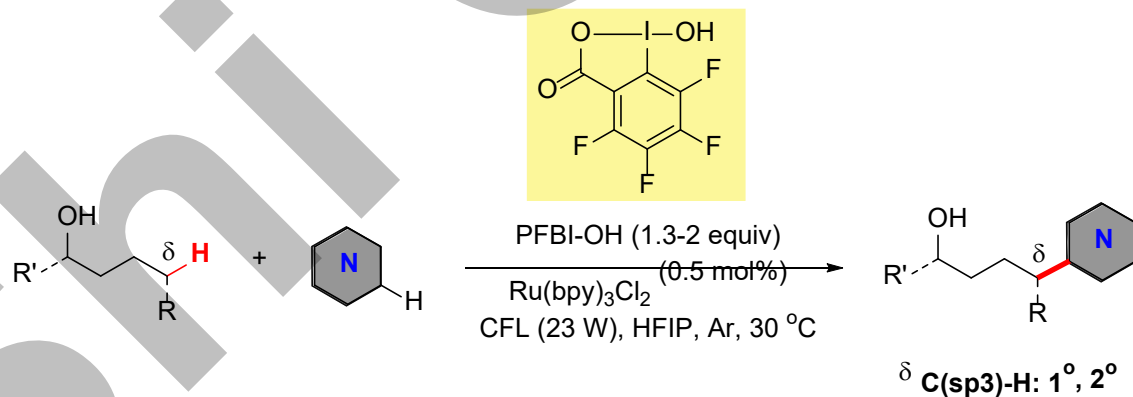
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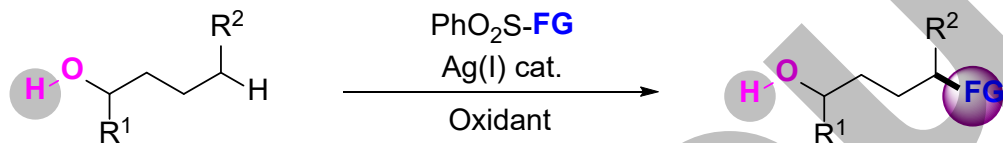


Zhu, C. and co-authors. *Angew. Chem. Int. Ed.* **2018**, *57*, 1640.

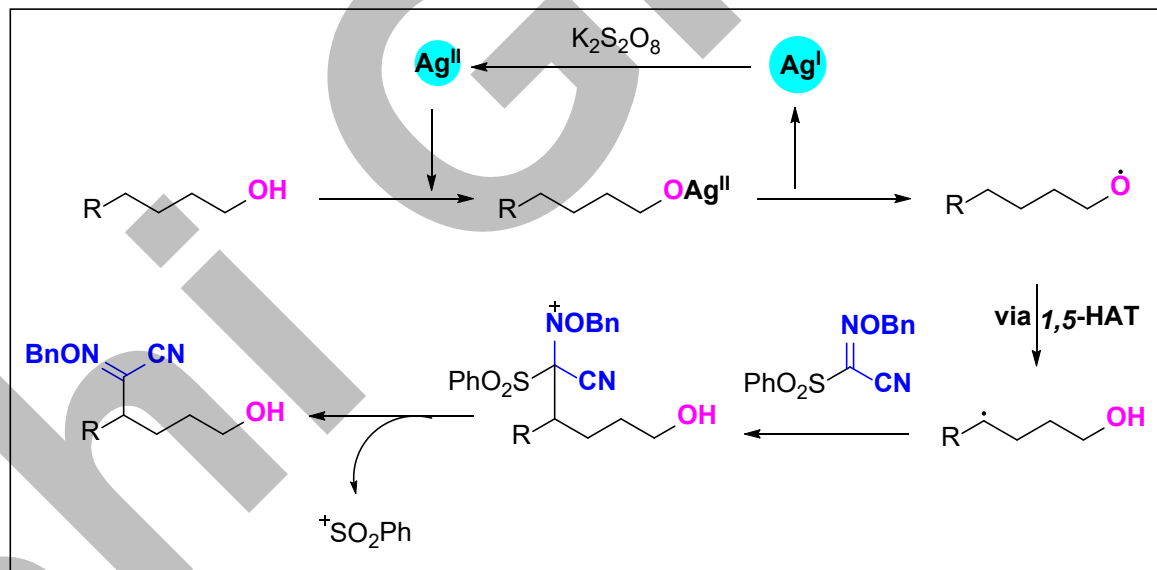


Chen, G. and co-authors. *Chem. Sci.* **2019**, *10*, 688.

Alkoxy radicals induced remote C(sp³)-H Functionalization



- Mild reaction conditions
- Carbon-carbon bond formation
- Broad substrate scopes
- Excellent regio-selectivity



Jiao, N. and co-authors. *Nat. Commun.* **2018**, *9*, 2625.

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N-Allylsulfonyl to form the *N*-centered radical

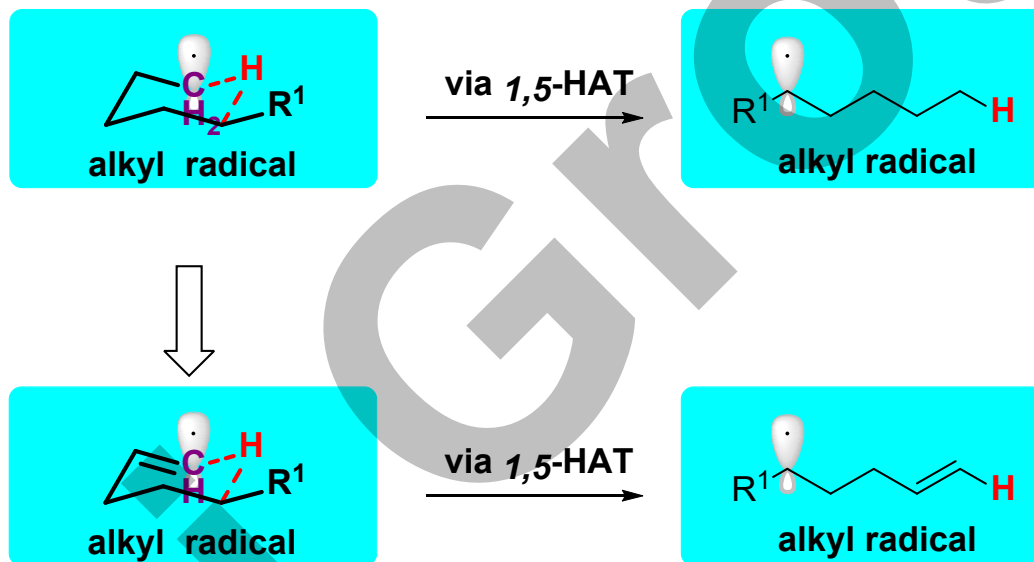
III. Alkoxy radicals induced remote C(sp³)-H Functionalization

IV. Alkyl radicals induced remote C(sp³)-H Functionalization

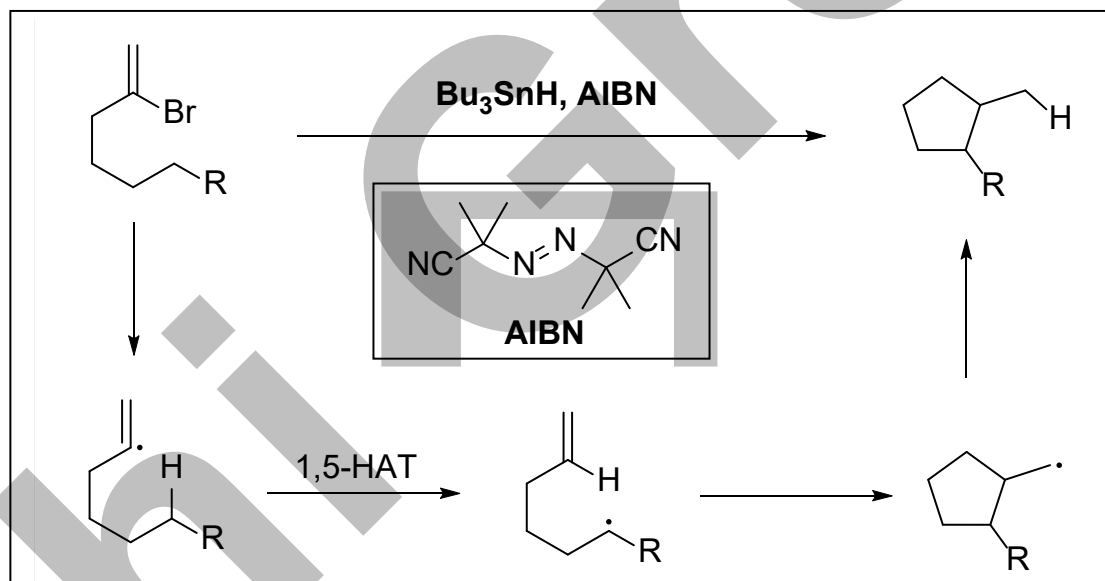
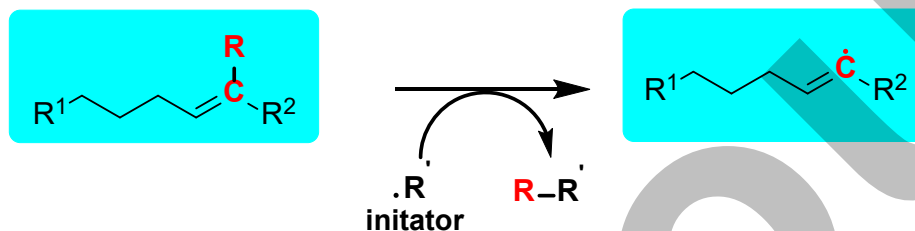
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Alkyl radicals induced remote C(sp³)-H Functionalization

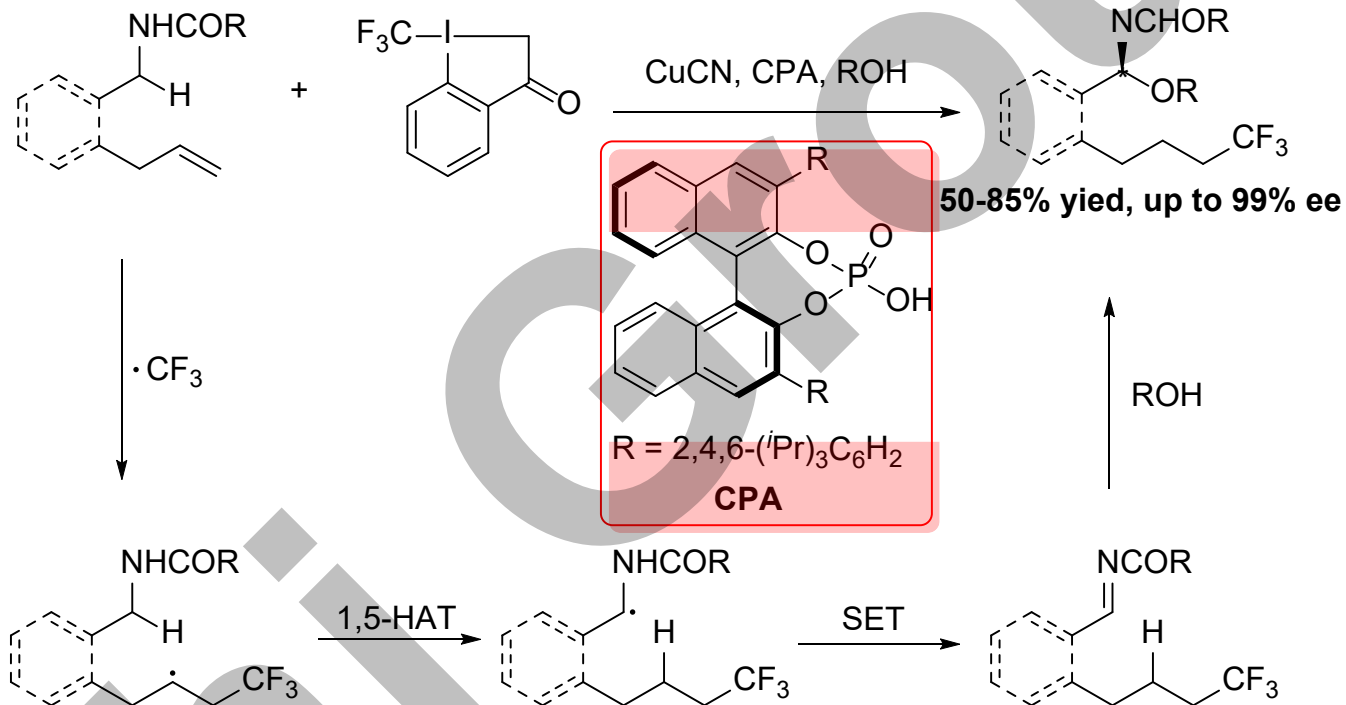


Alkyl radicals induced remote C(sp³)-H Functionalization



Liu, H. T. and co-authors. *J. Am. Chem. Soc.* **1988**, *110*, 5900.

Alkyl radicals induced remote C(sp³)-H Functionalization



Liu, X. Y. and co-authors. *Angew. Chem. Int. Ed.* **2014**, *53*, 1.

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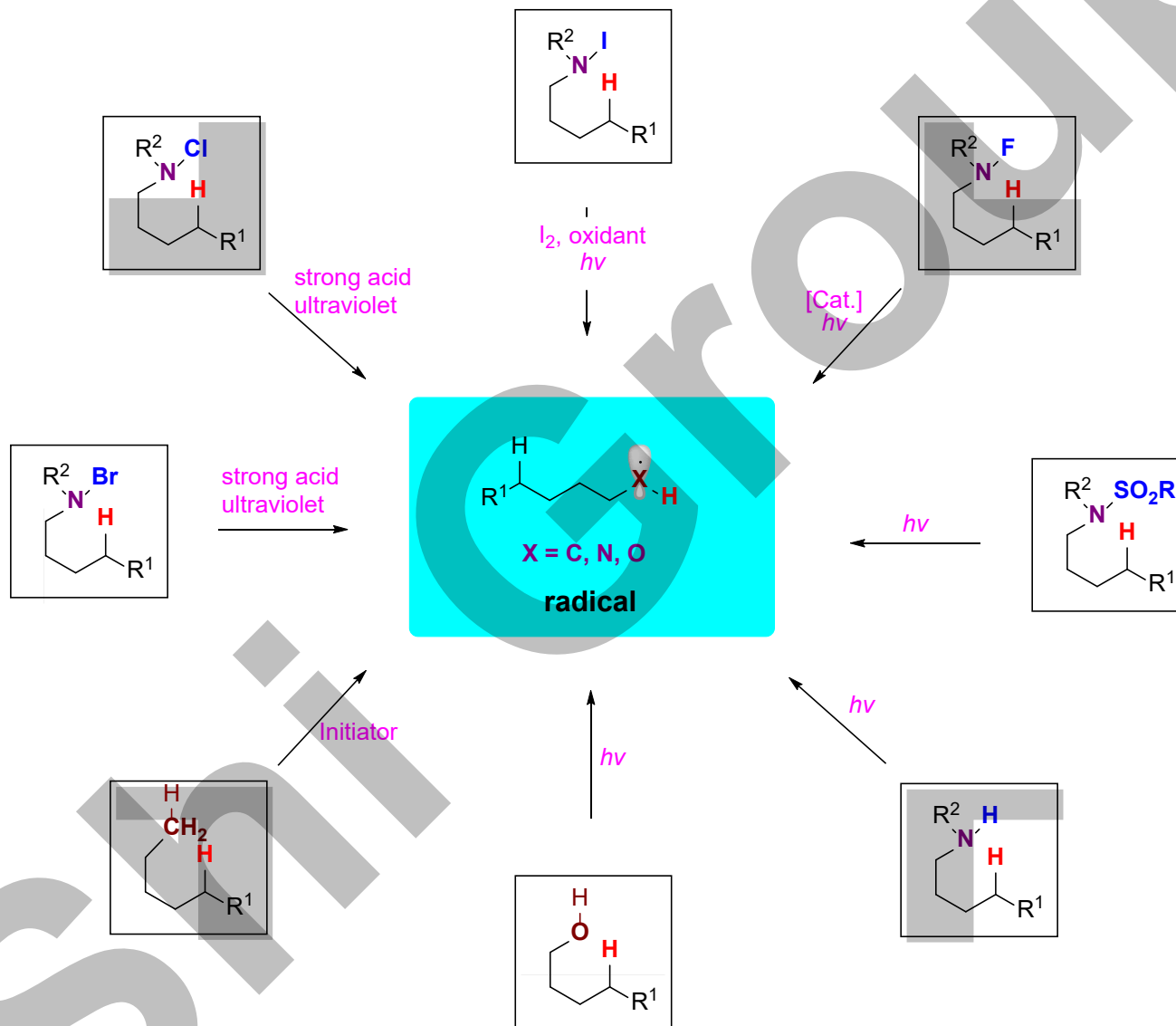
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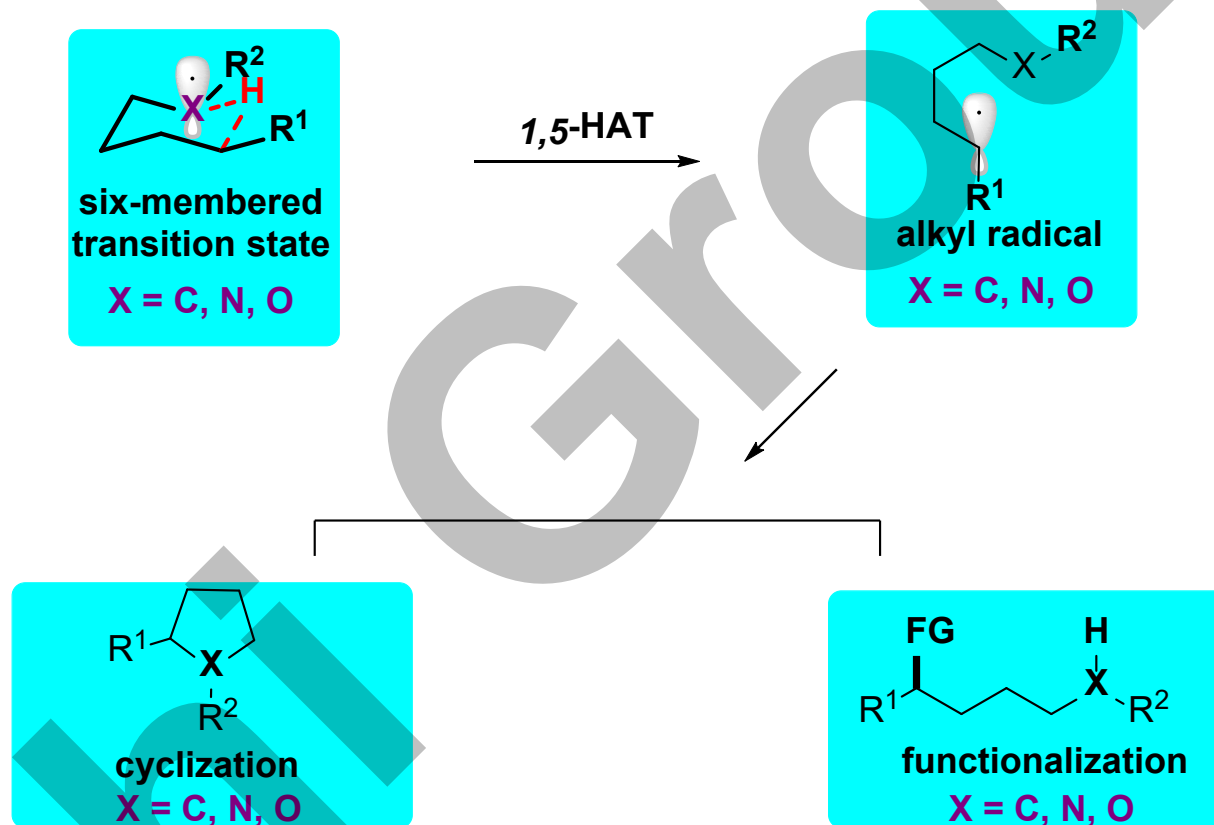
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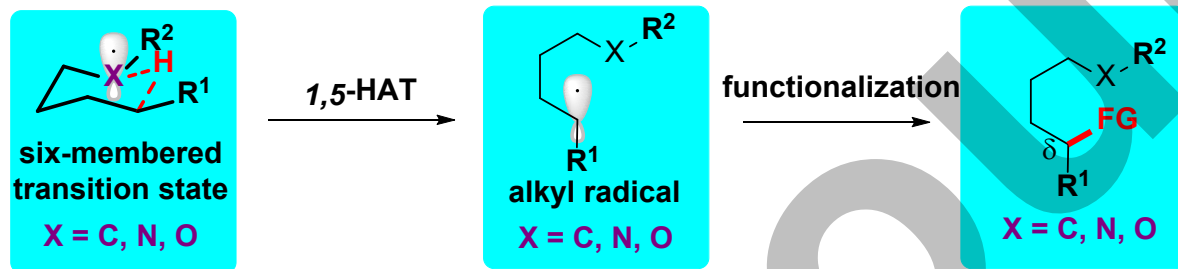
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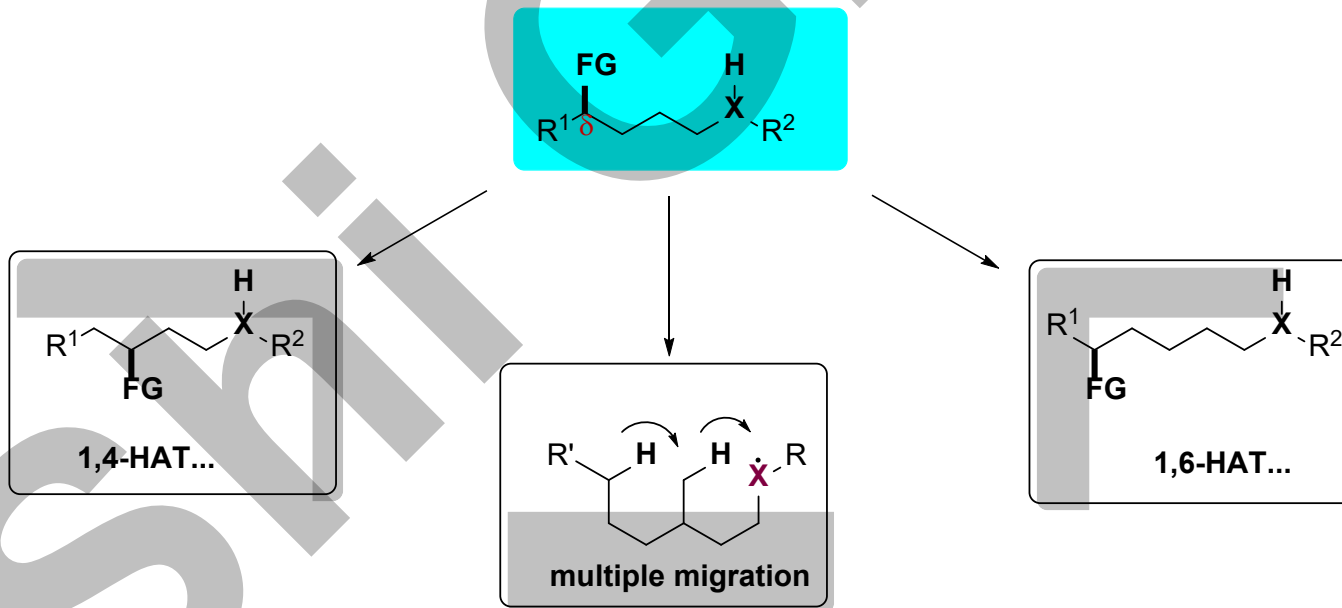
VI. Prospective

Prospective



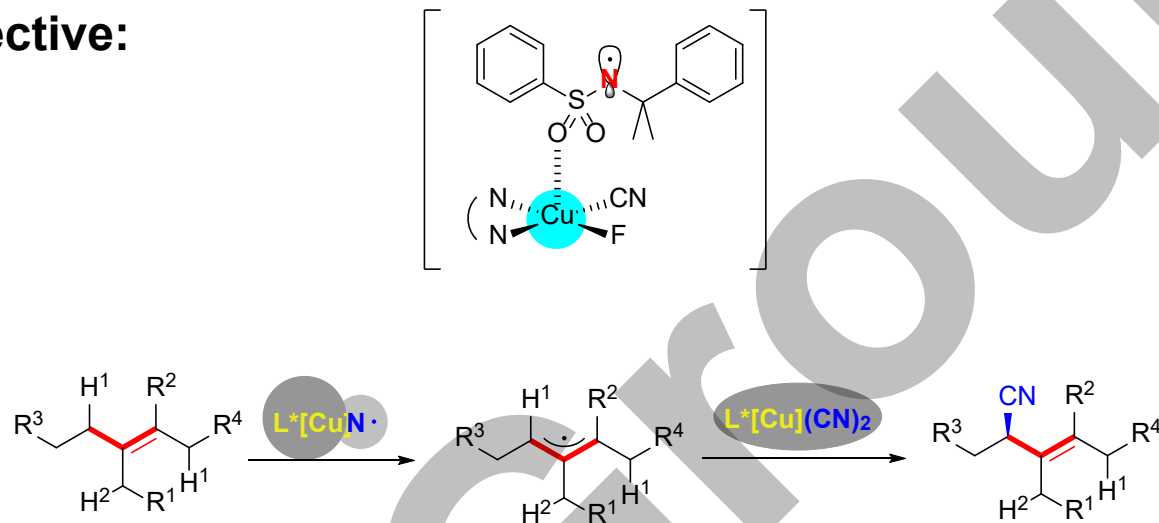
◆ single site selectivity

◆ no enantioselective

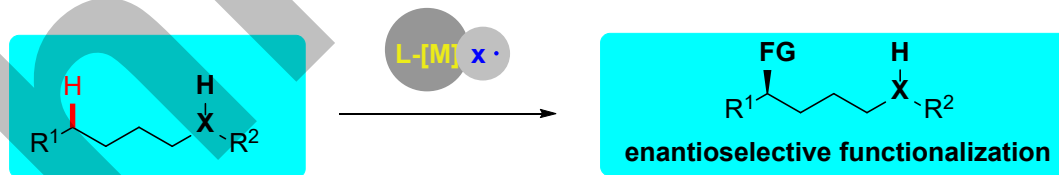


Prospective

Enantioselective:



Liu, G. S. and co-authors. *Nature*. 2019, 574, 516.



Thanks!

Shi Group