

# Isocyanides: Anionic Methods for Dearomatizations to Complex Cyclohexadienes

**Bilal Altundas**  
Denmark Group Meeting  
10/25/2022

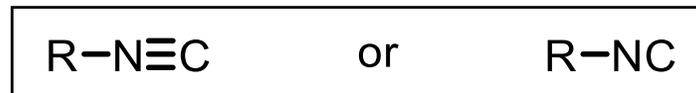
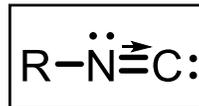
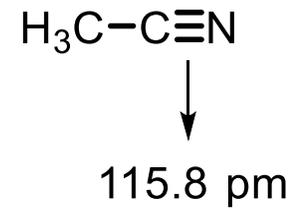
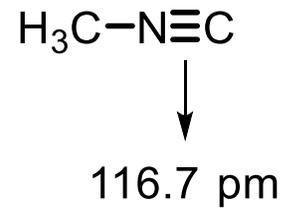
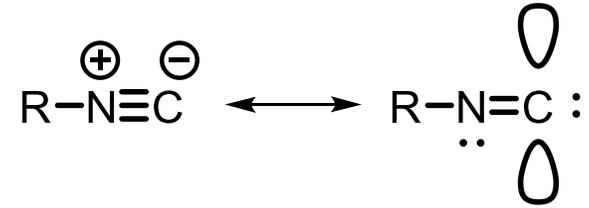


# Agenda

- Isocyanide Chemistry – Metalated Isocyanides
- The Chemistry of Anisylsulfanylmethylisocyanide (Asmic)
- Dearomatization of Asmic derivatives to complex cyclohexadienes
- Synthesis and Isolation of Sulfonium Salts

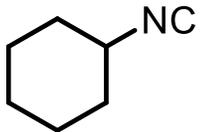


# Isocyanides 101

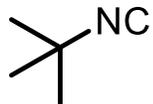




# Commercially available Isocyanides



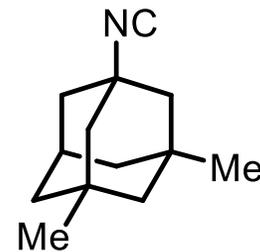
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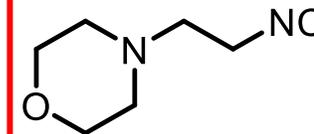
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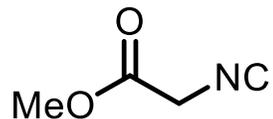
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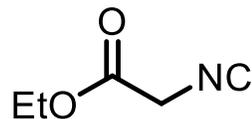
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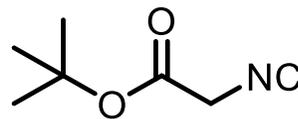
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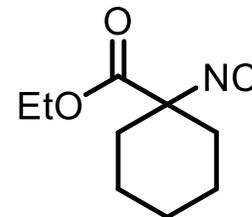
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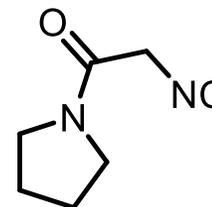
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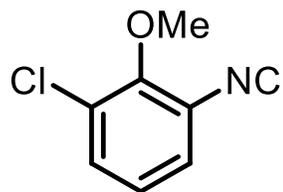
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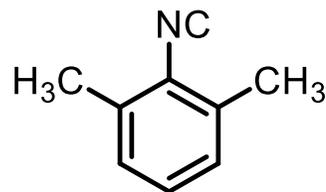
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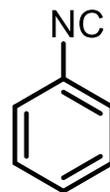
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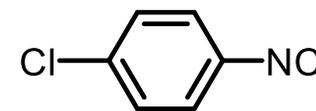
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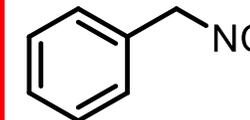
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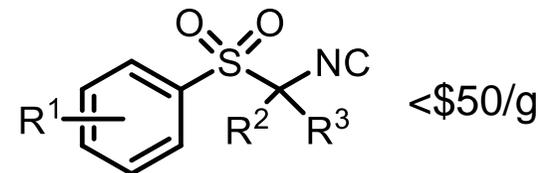
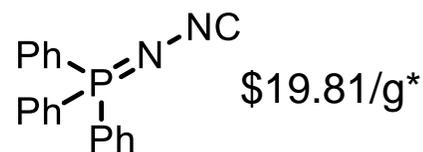
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\$7.6/g\*\*



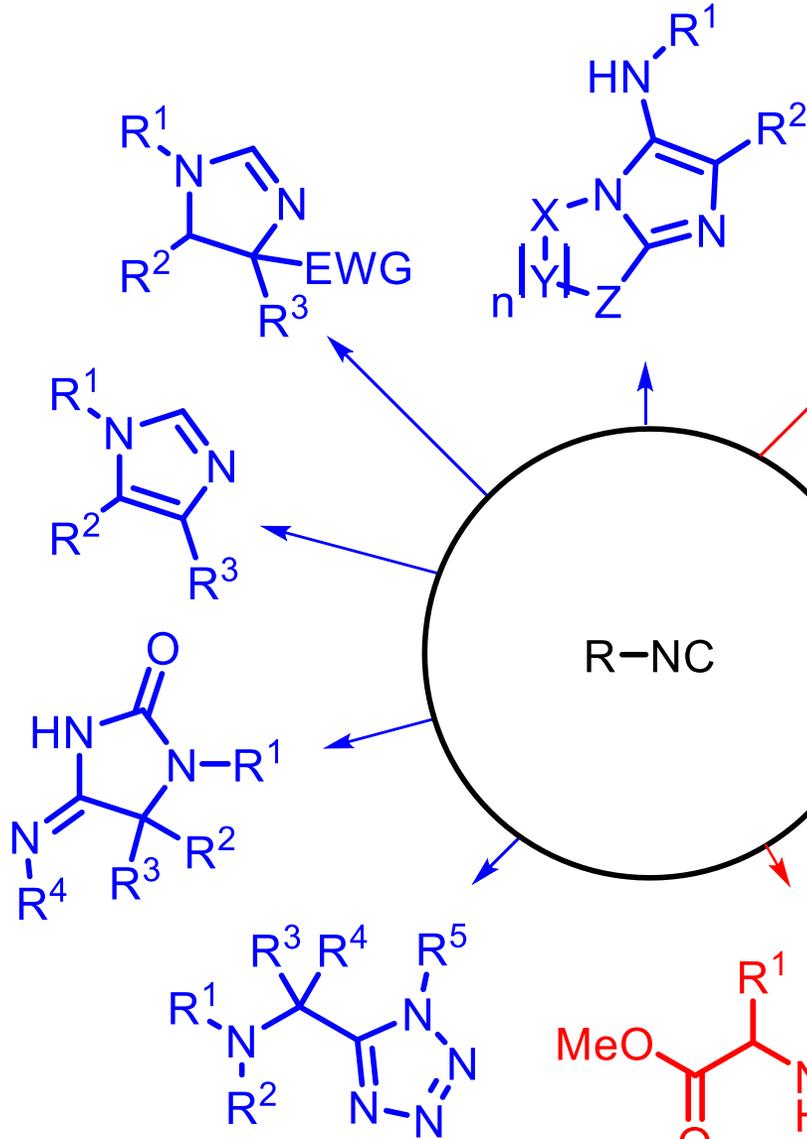
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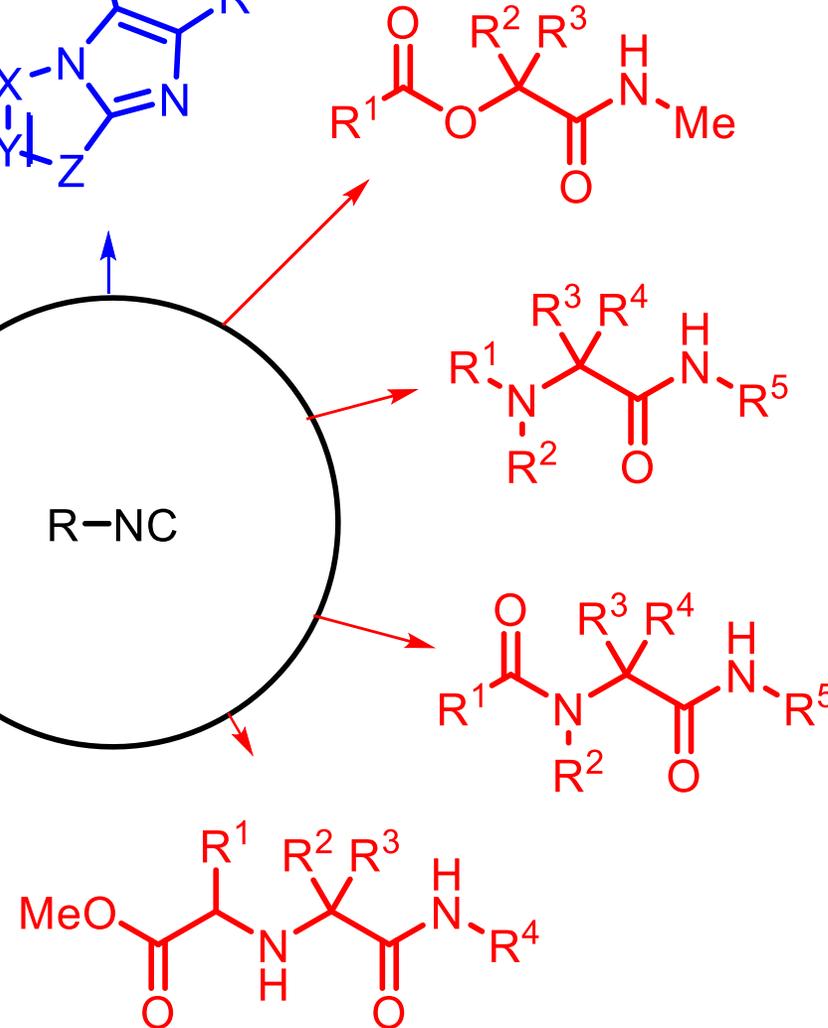


# Isocyanides 101

**Heterocyclic  
Scaffolds**

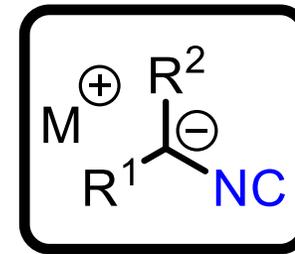
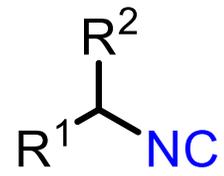
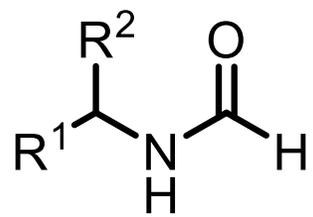


**Peptidomimetic  
Scaffolds**



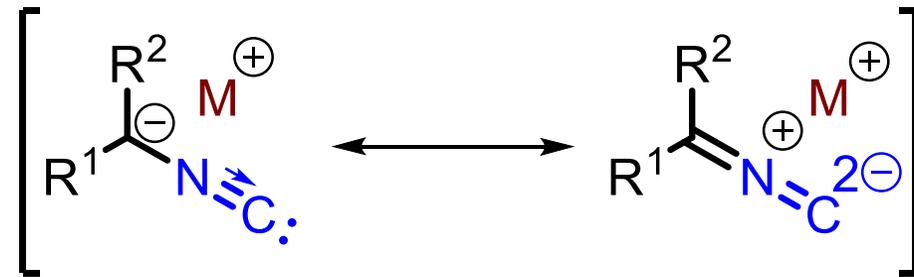
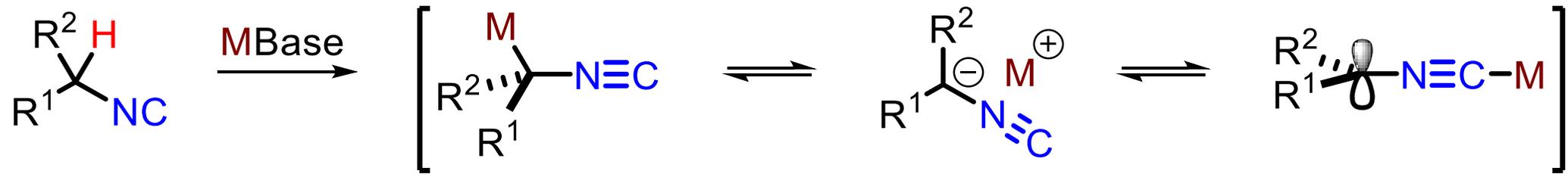


# Isocyanides 101



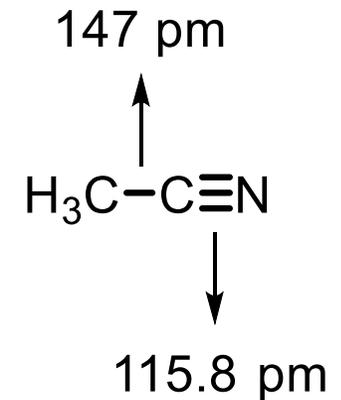
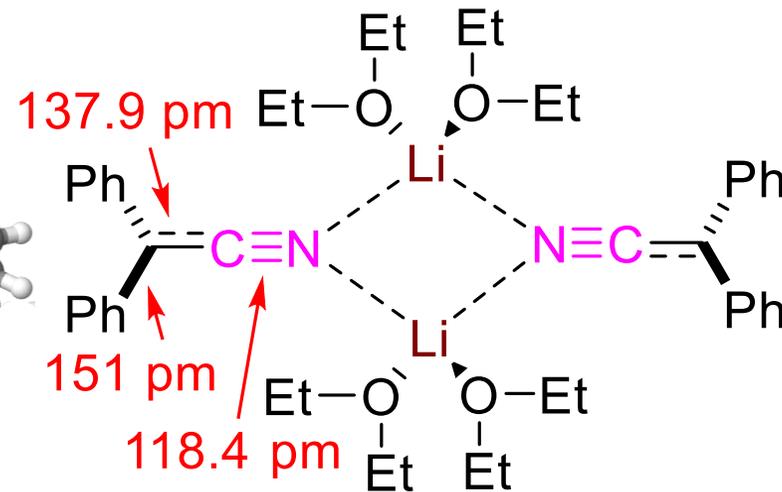
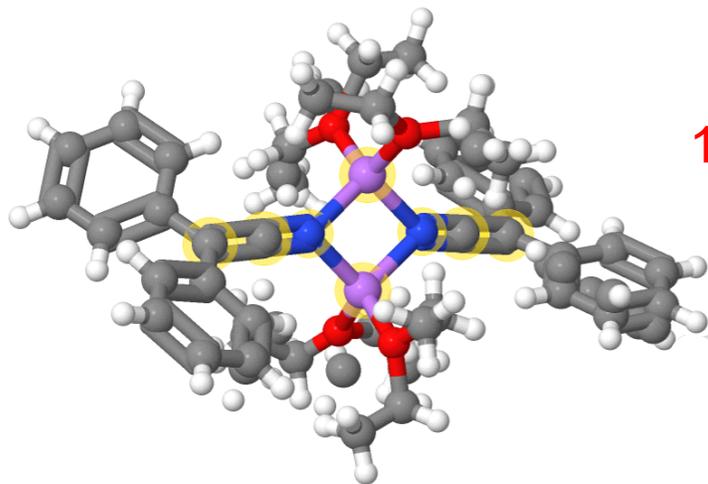
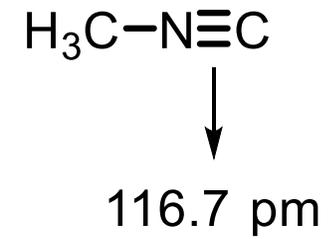
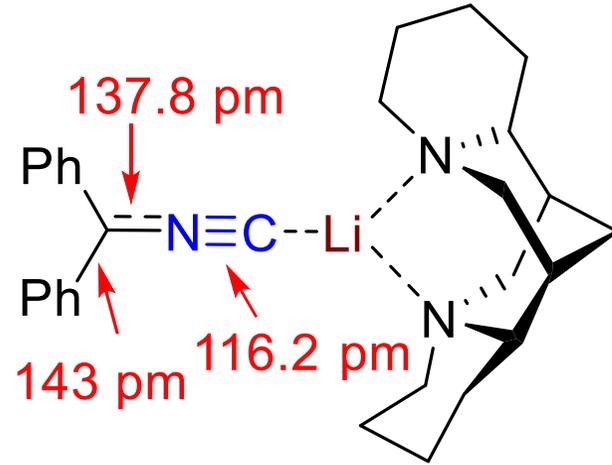
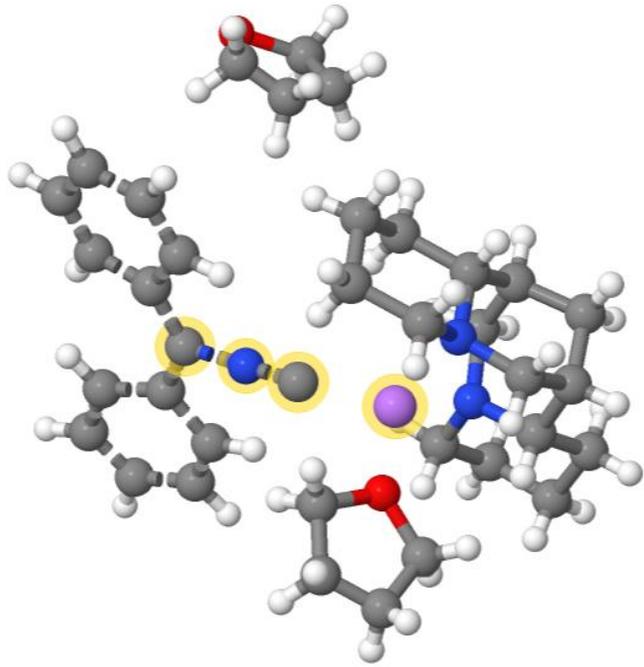


# Metalated Isocyanides



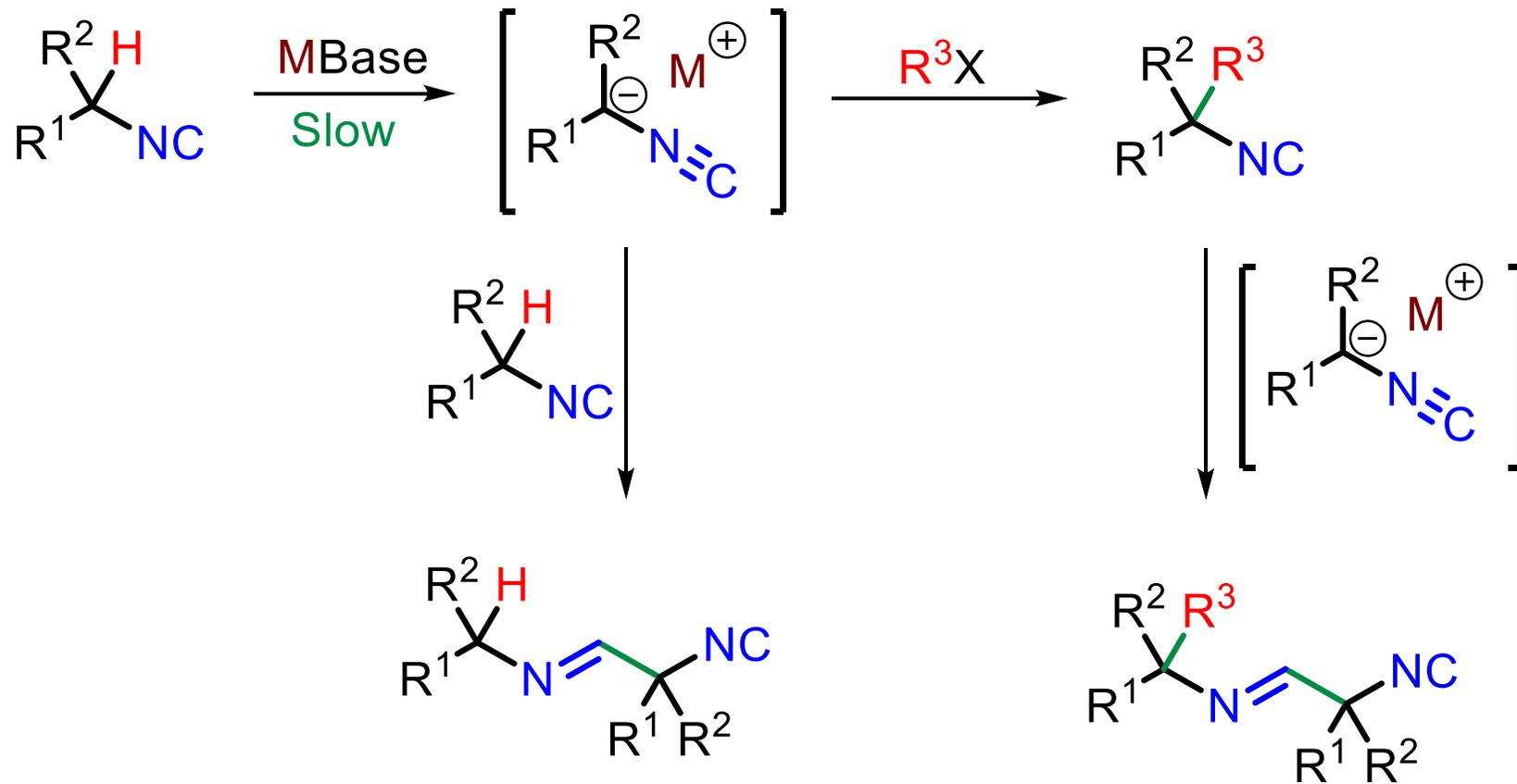


# Structure of Metalated Isocyanides



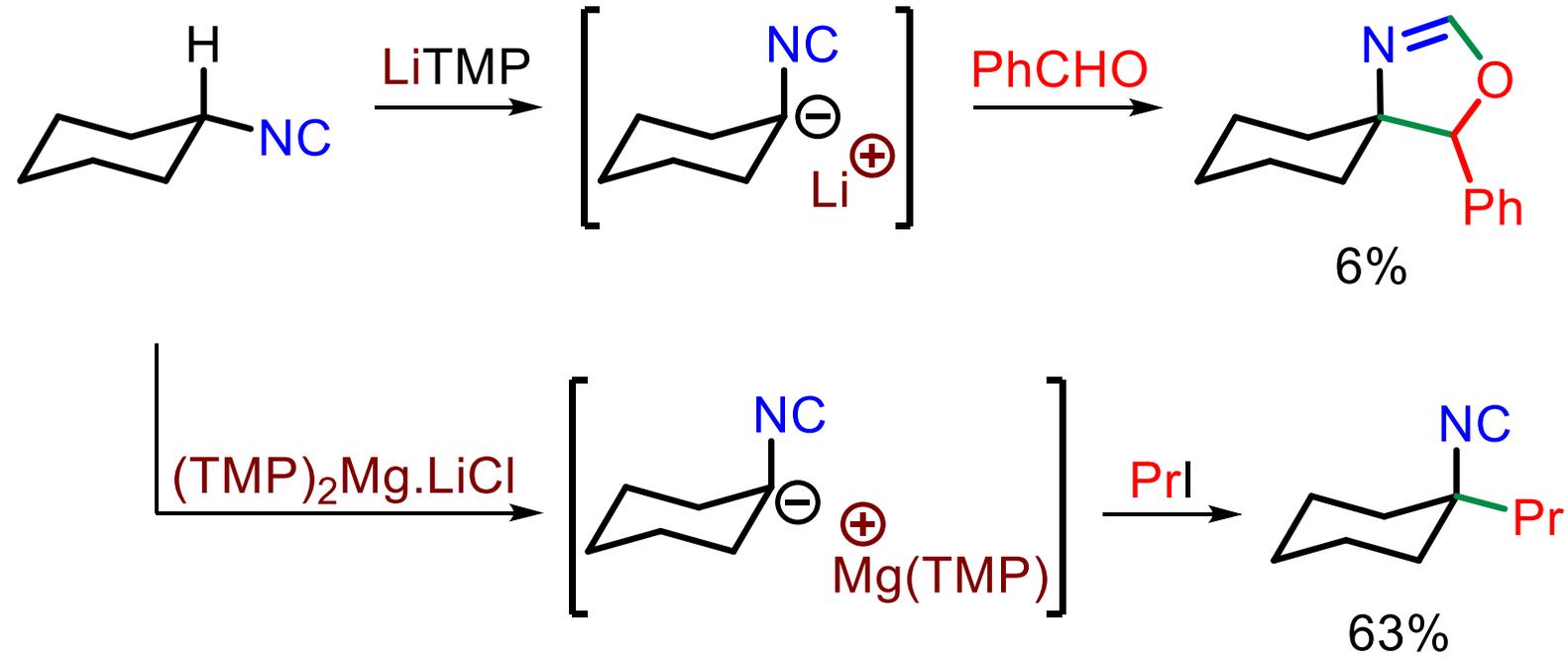


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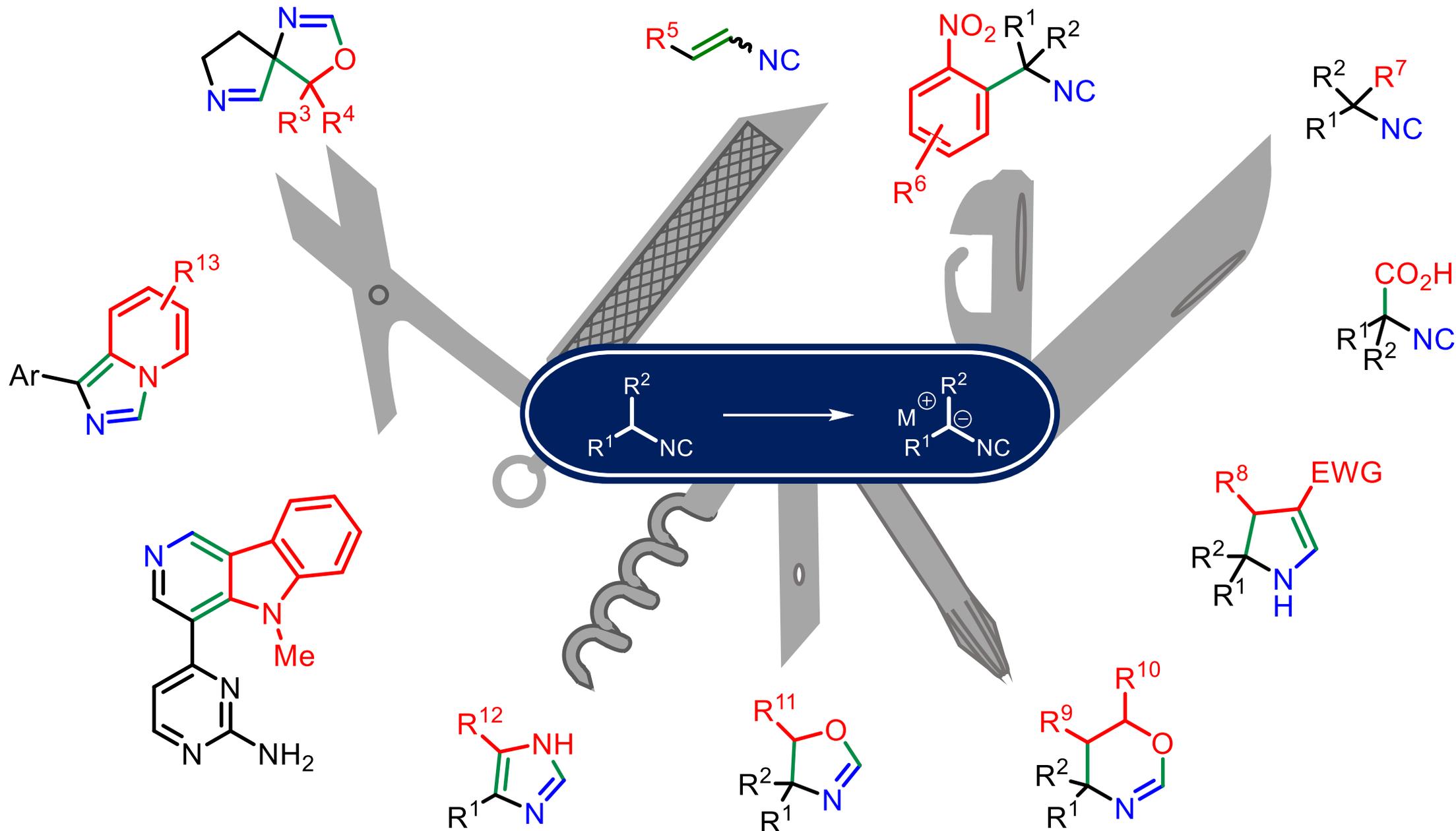


# Metalated Isocyanides





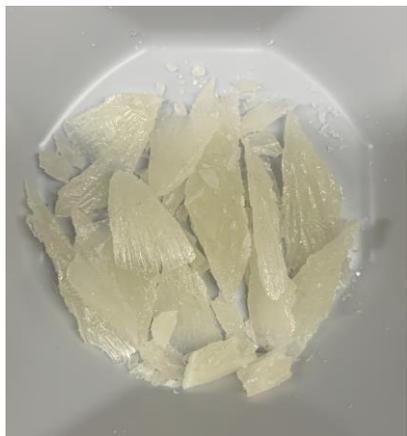
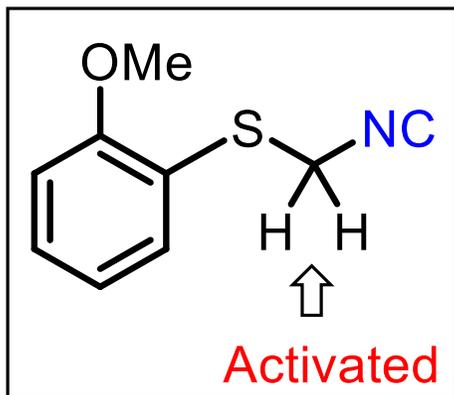
# Utility of Metalated Isocyanides



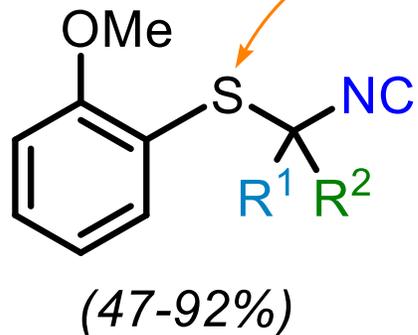


# ASMIC

**ASMIC** = AnisylSulfanylMethylisocyanide

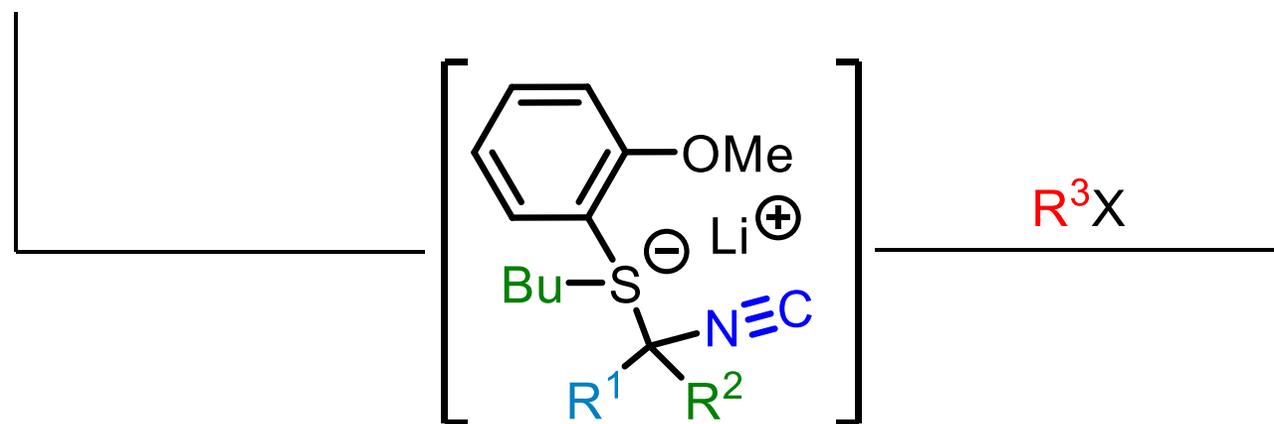
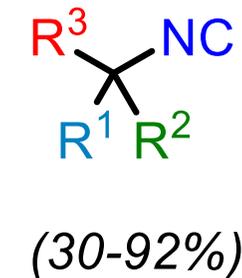


1. Base,  
 $R^1X$   
2. Base,  
 $R^2X$



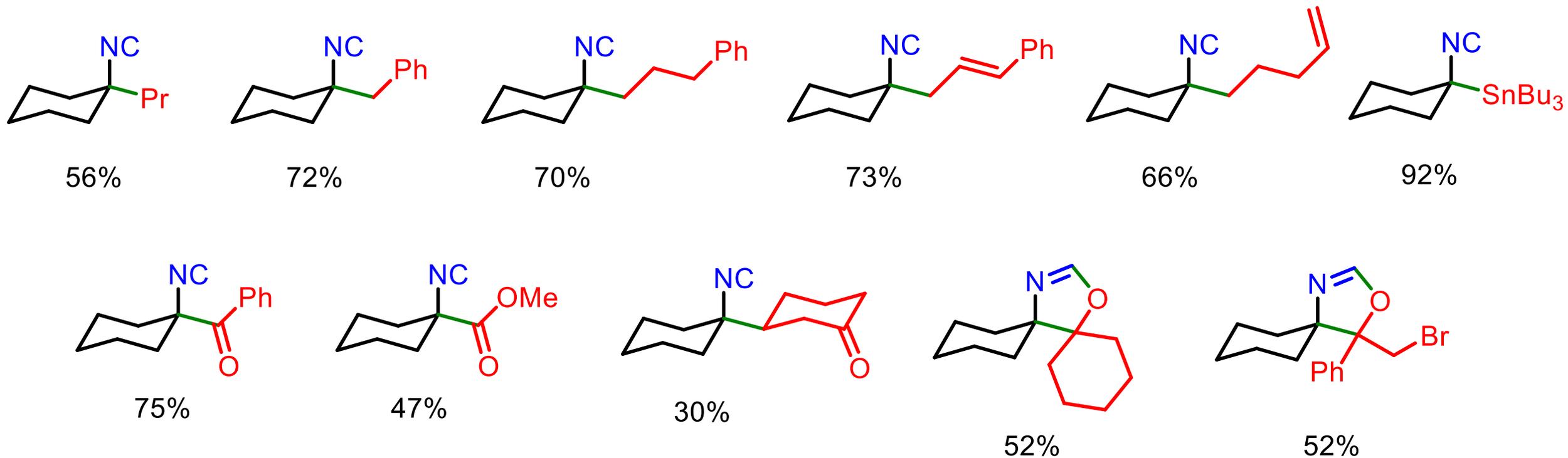
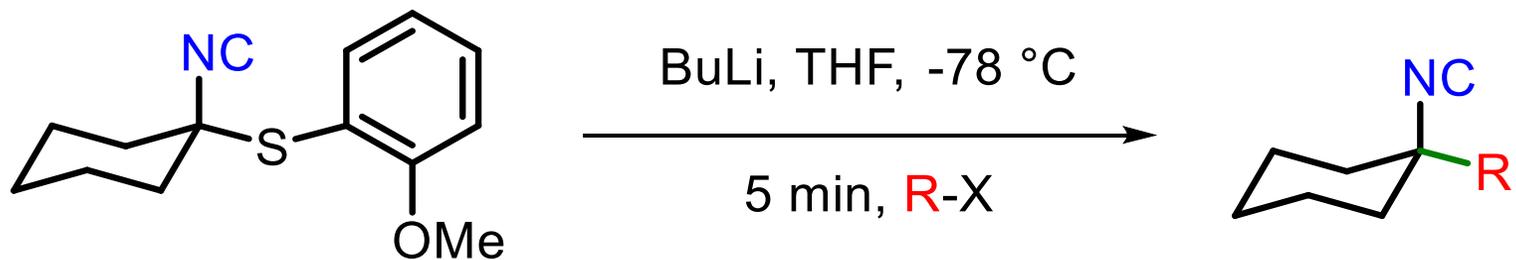
$Bu-Li$ , TMEDA,  $R^3X$

Trisubstituted  
Isocyanide





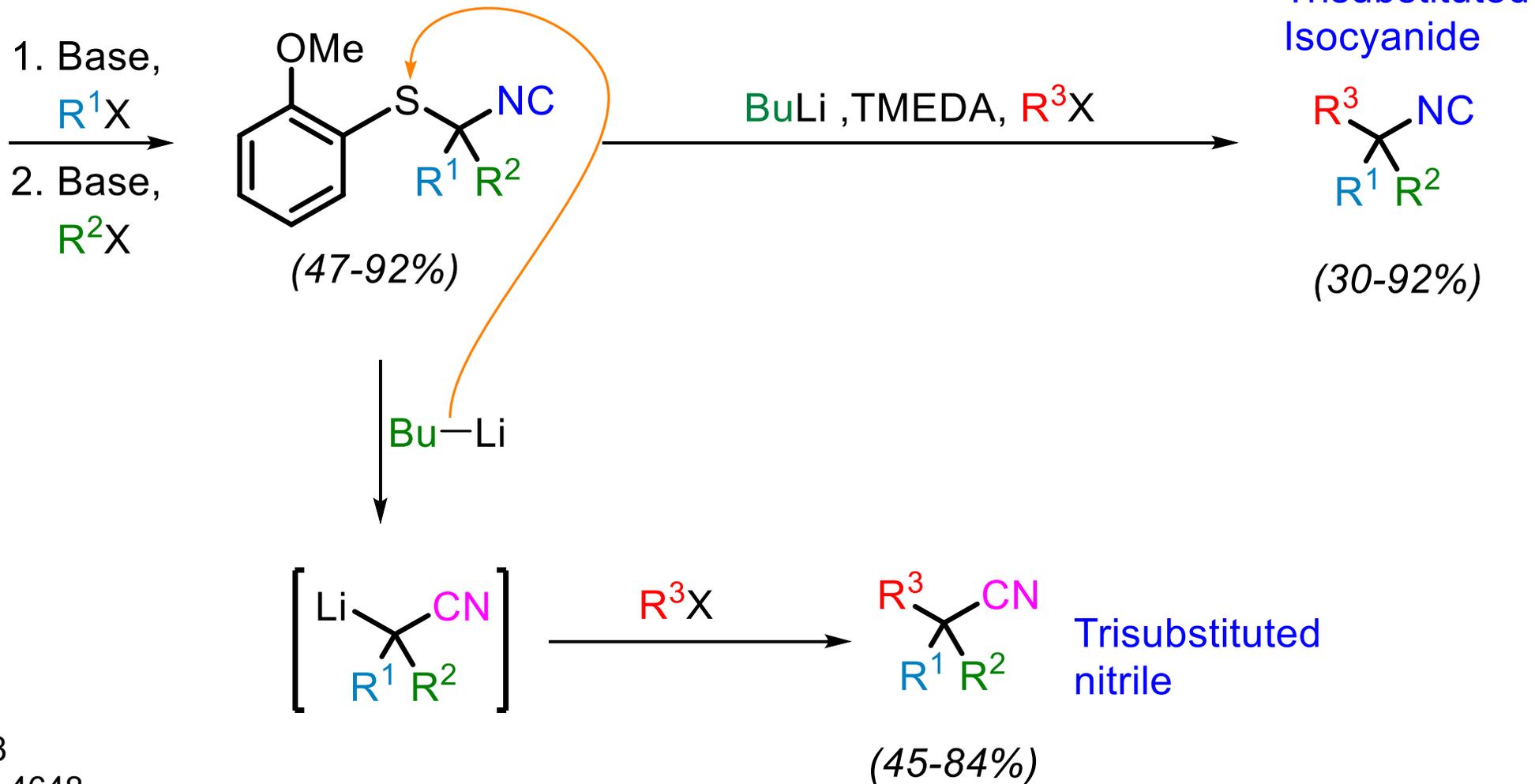
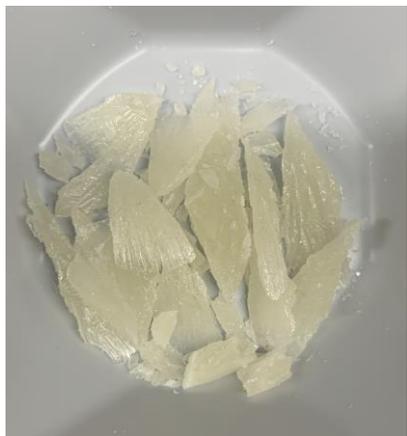
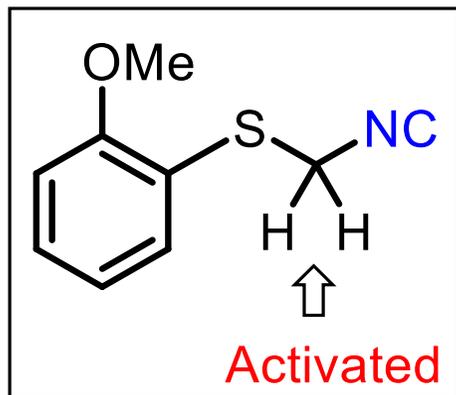
# Functionalized Cyclohexylisocyanides





# ASMIC

**ASMIC** = AnisylSulfanylMethylIsocyanide



*Org. Lett.* **2018**, 20, 5910–5913

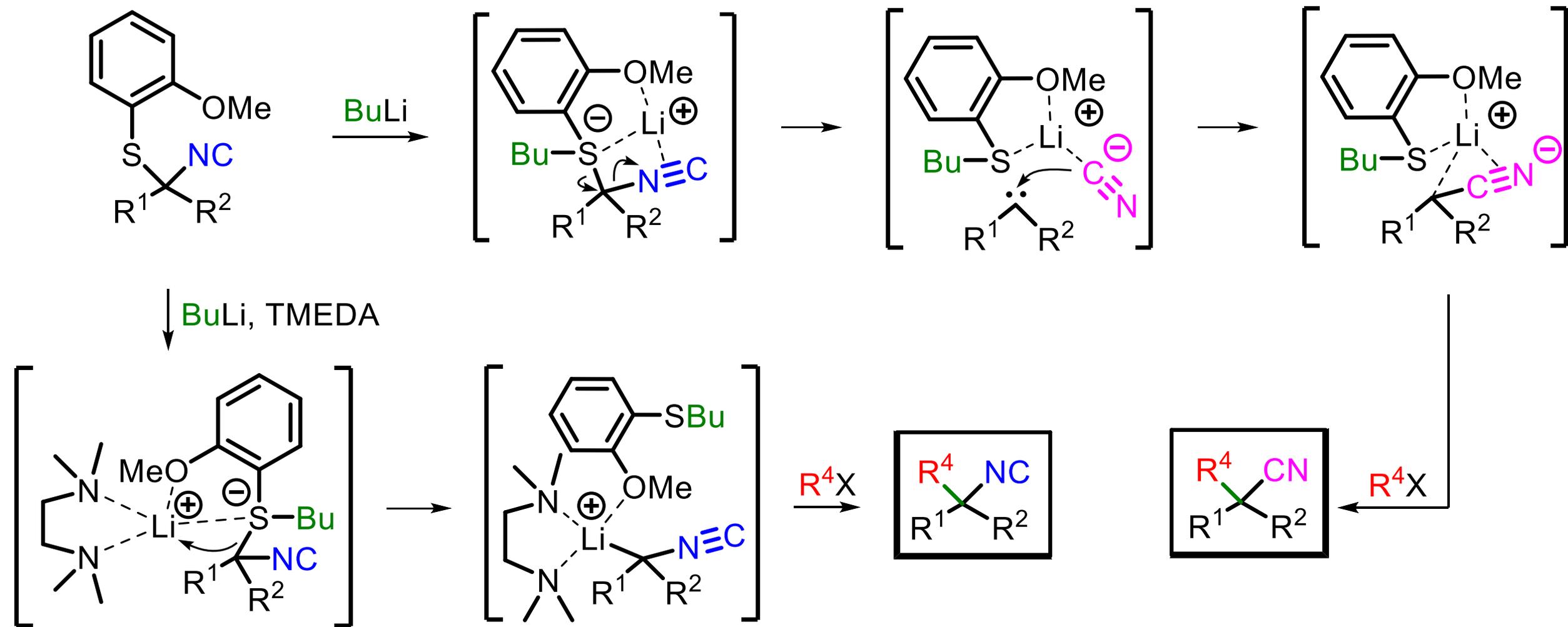
*Eur. J. Org. Chem.* **2019**, 4644–4648

*e-EROS*, **2020**

*Org. Synth.* **2021**, 98, 147-170

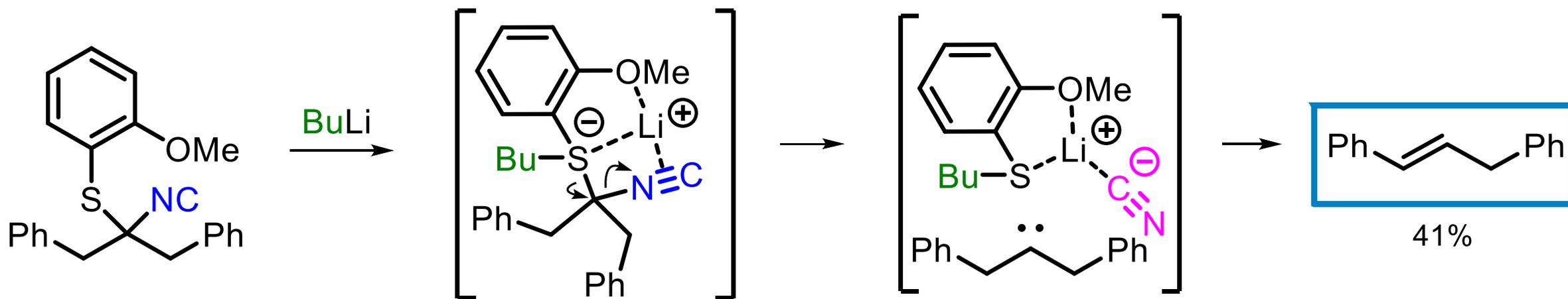


# Isocyanide to Nitrile Isomerization



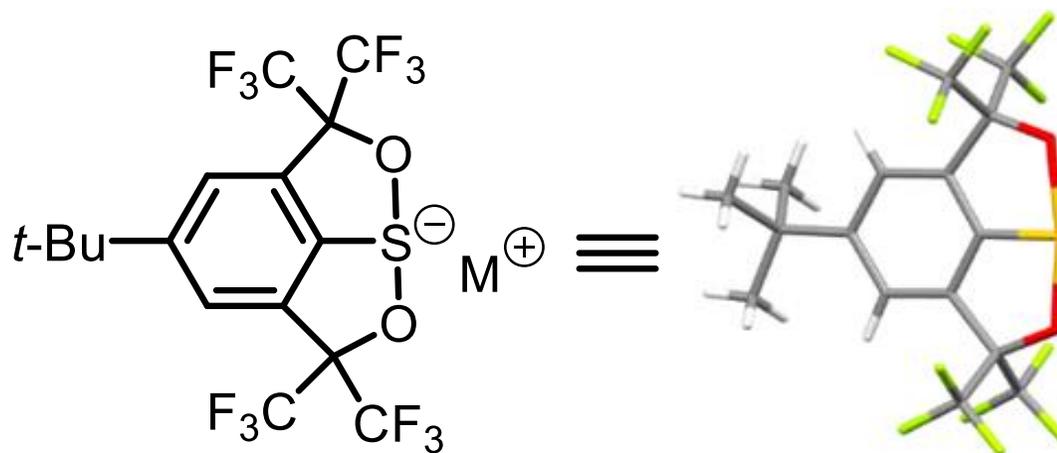
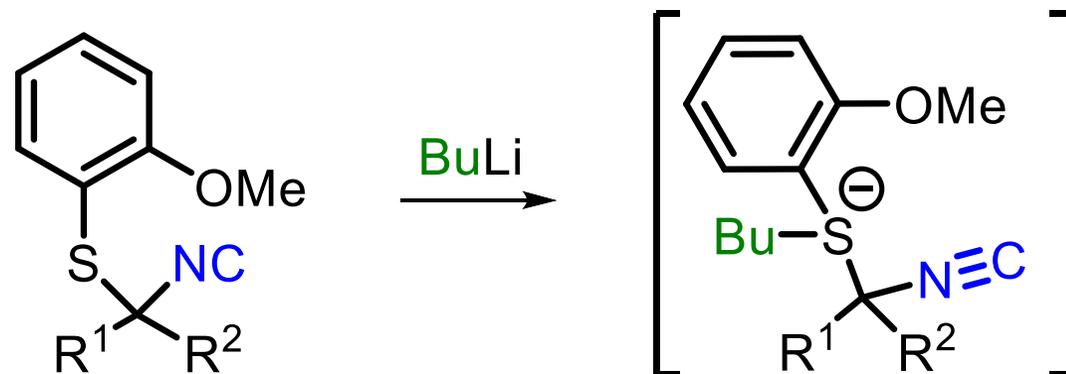


# Evidence for Carbene Formation



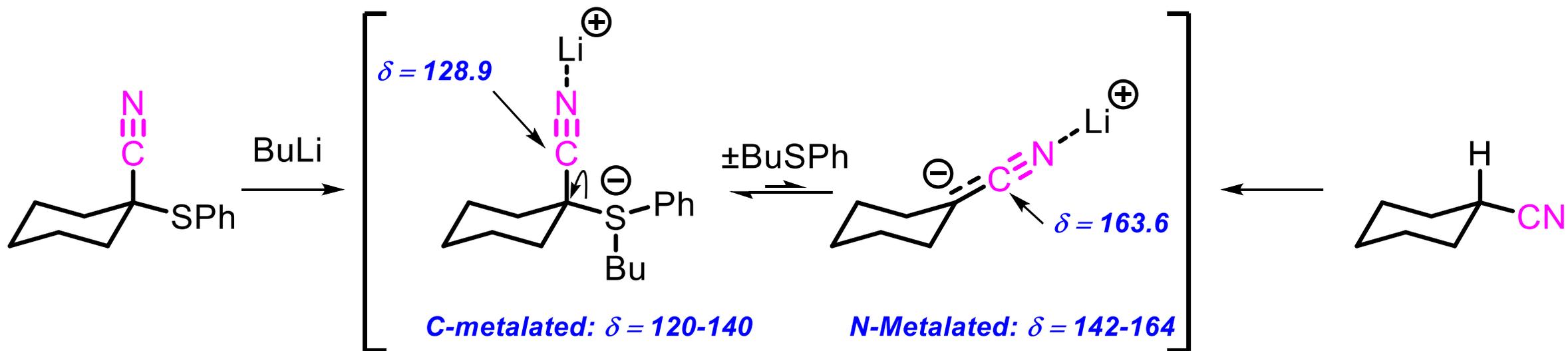


# 10-S-3 Sulfuranides



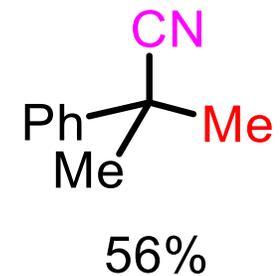
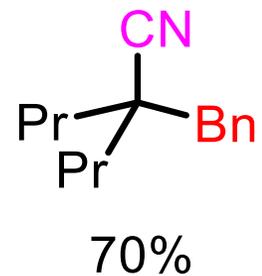
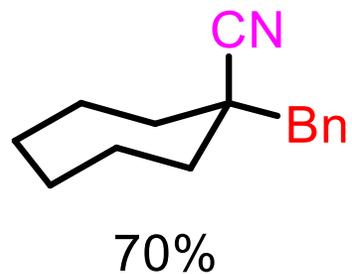
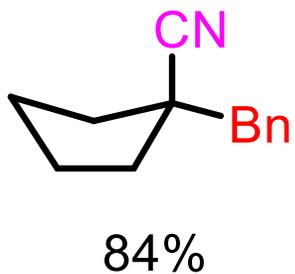
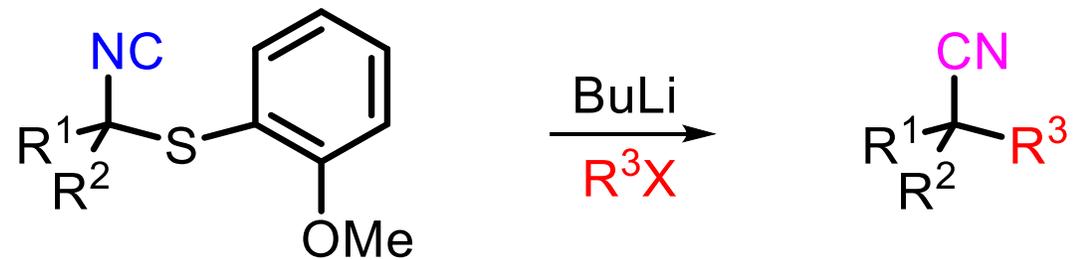


# Precedent for 10-S-3 Sulfuranides



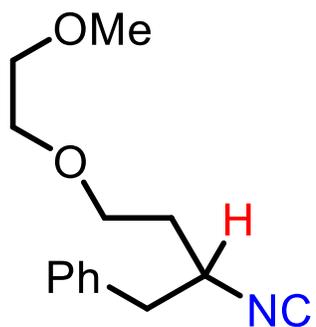
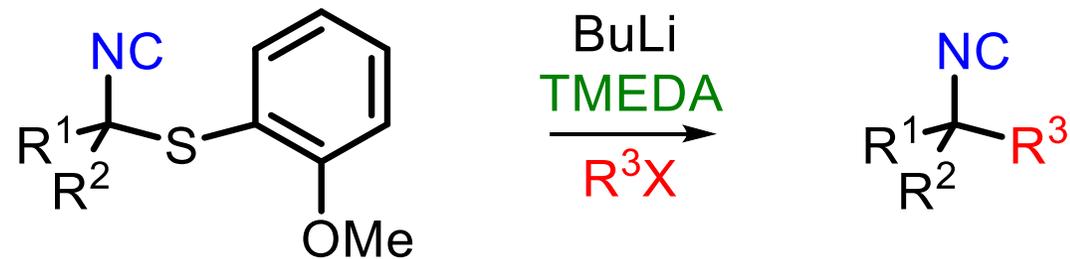


# Trisubstituted Nitriles from Asmic

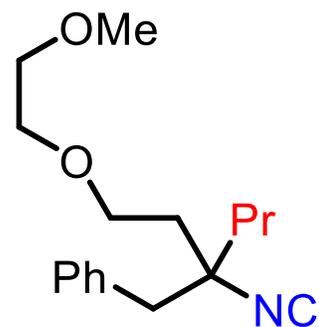




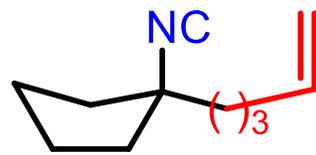
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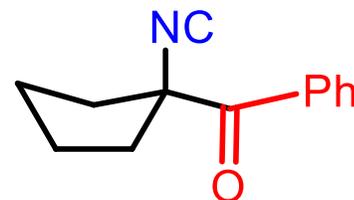
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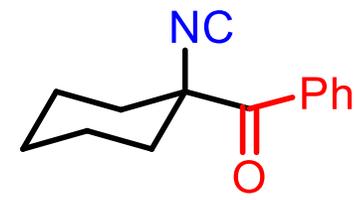
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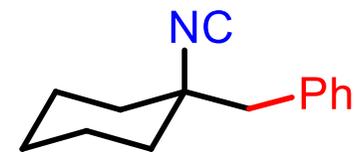
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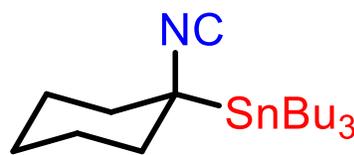
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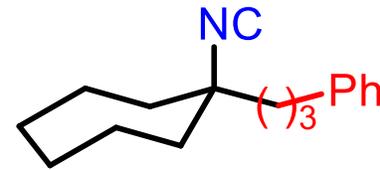
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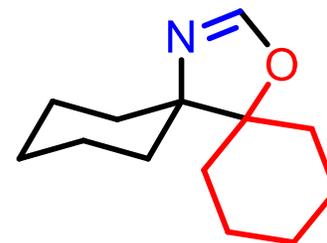
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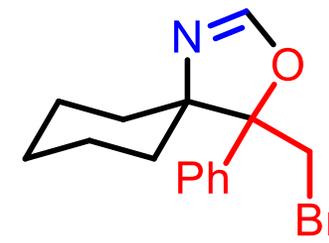
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60%



52%



53%

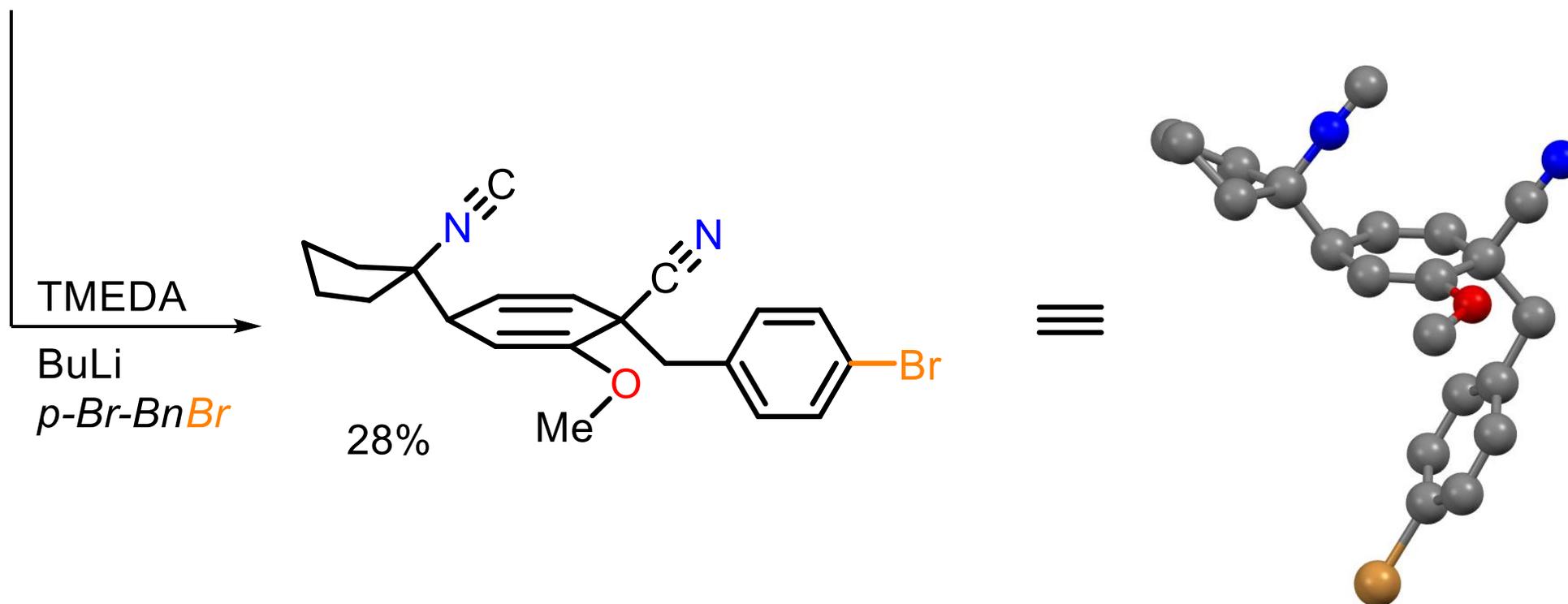
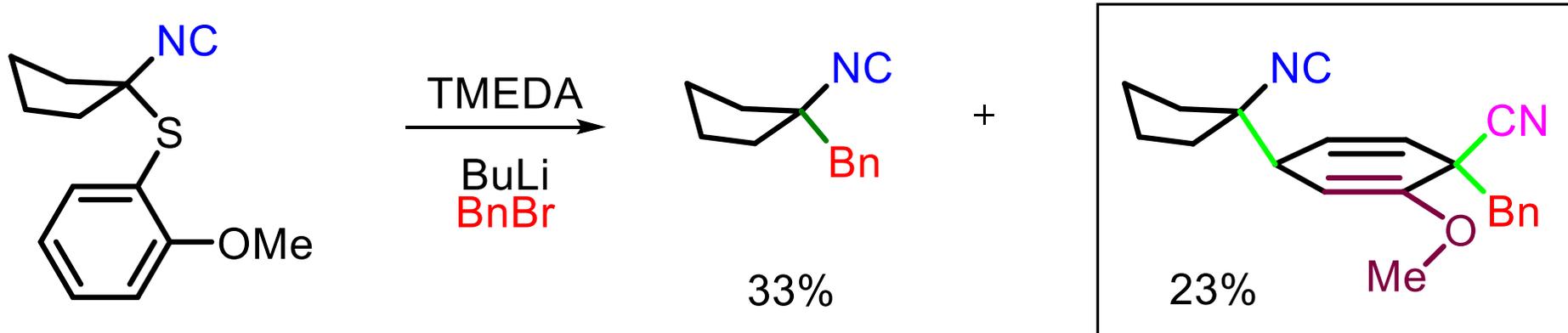


# A Novel Dearomatization



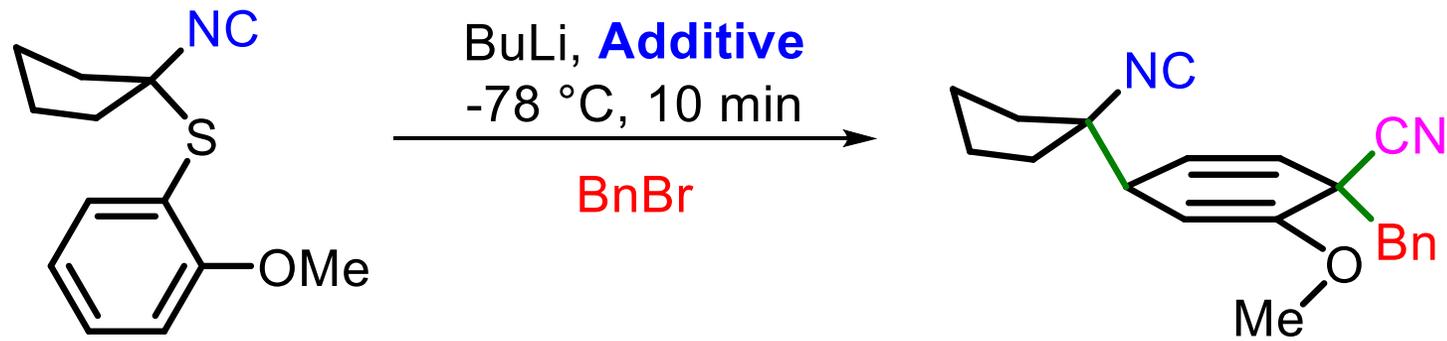


# Complexity from Simplicity



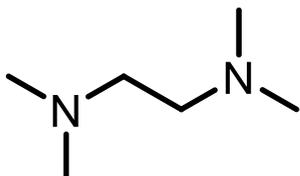


# Additive Screening

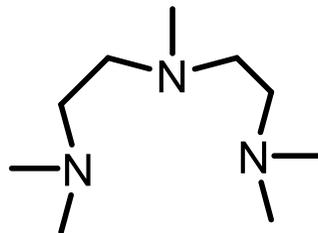


Additive	Yield
TMEDA	23%
TMEDA-LiCl (2 equiv)	42%
PMDTA	59%
<b>HMTETA</b>	<b>78%</b>

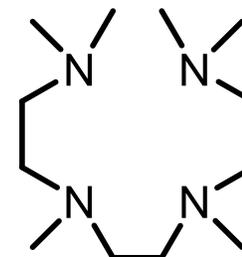
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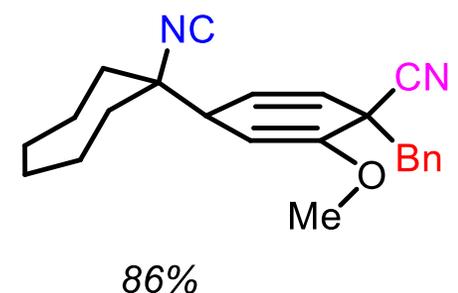
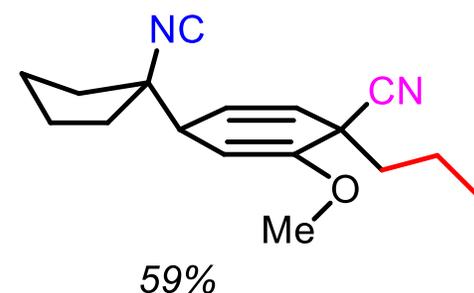
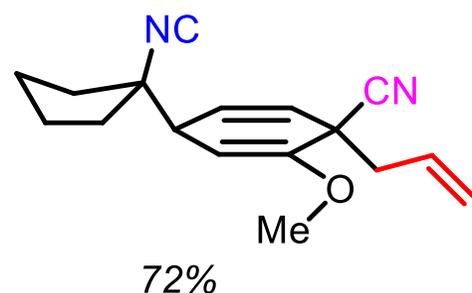
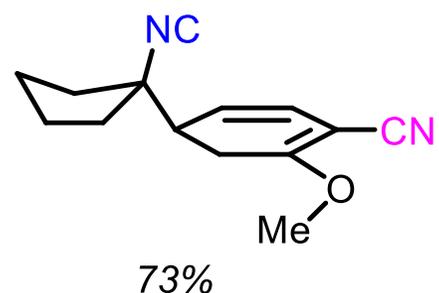
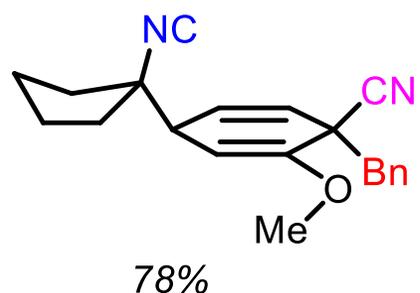
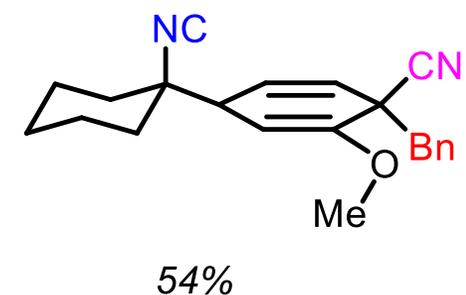
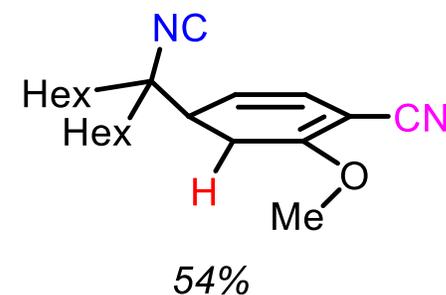
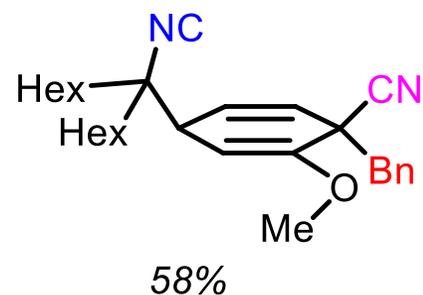
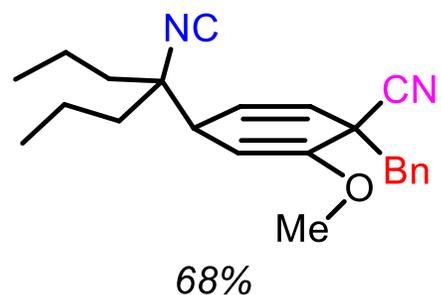
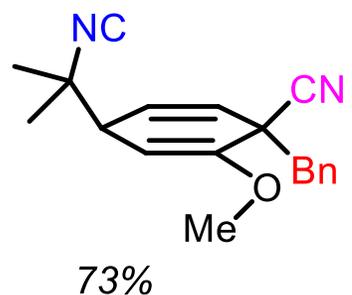
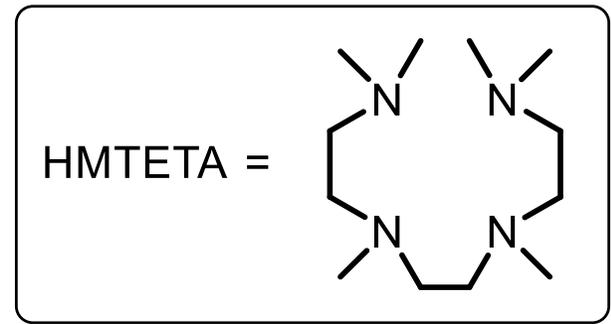
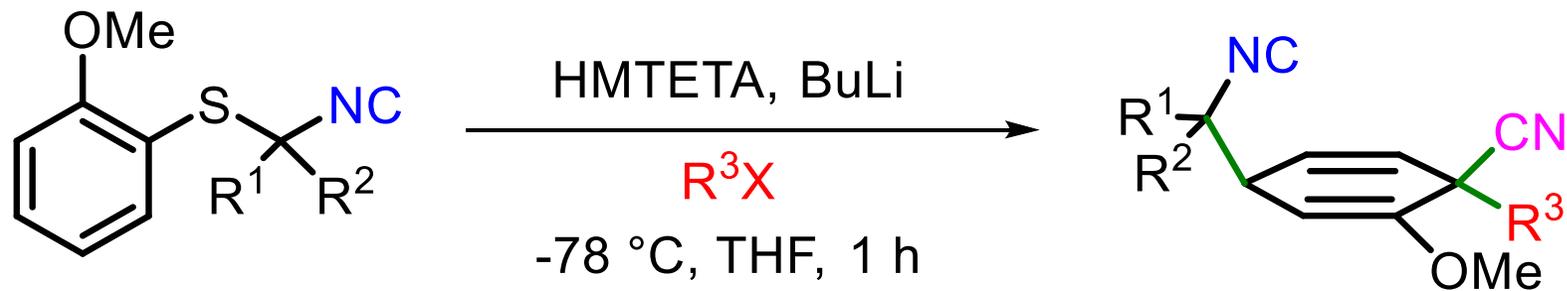


HMTETA =



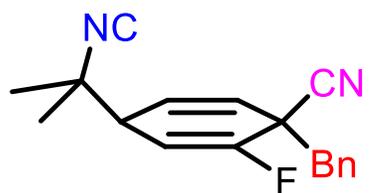
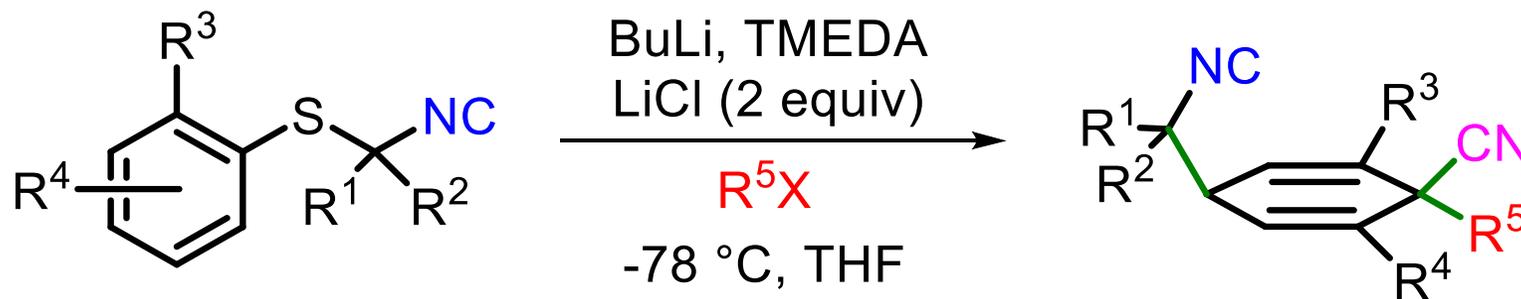


# Cyclohexadienes from Dialkyl Asmics

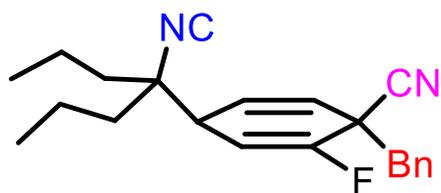




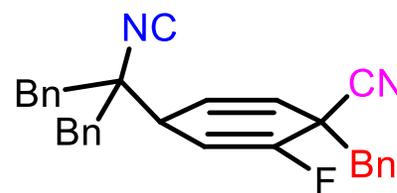
# Diversity of the Aromatic



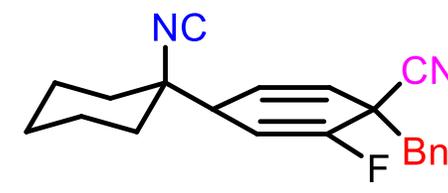
75%



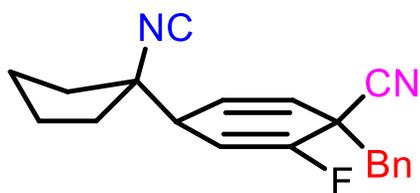
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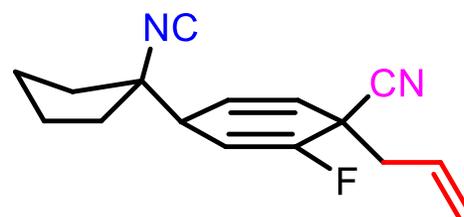
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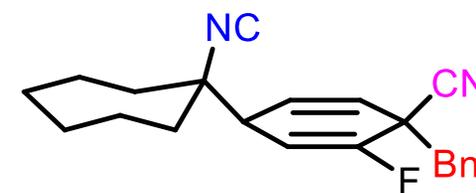
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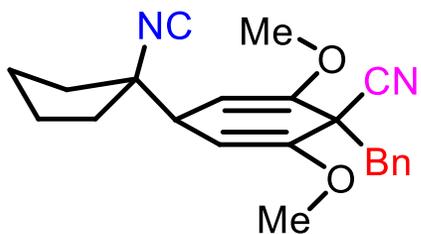
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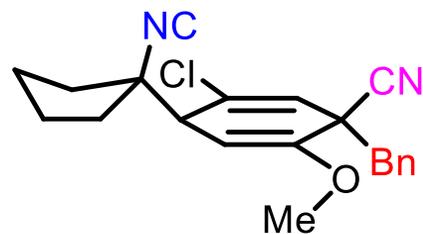
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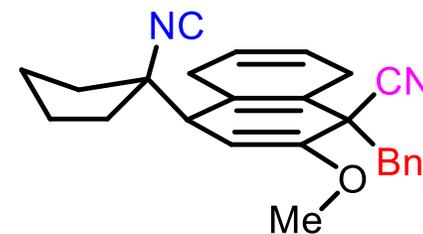
88%



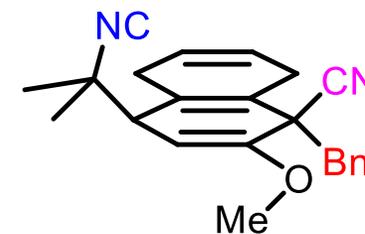
81%



69%



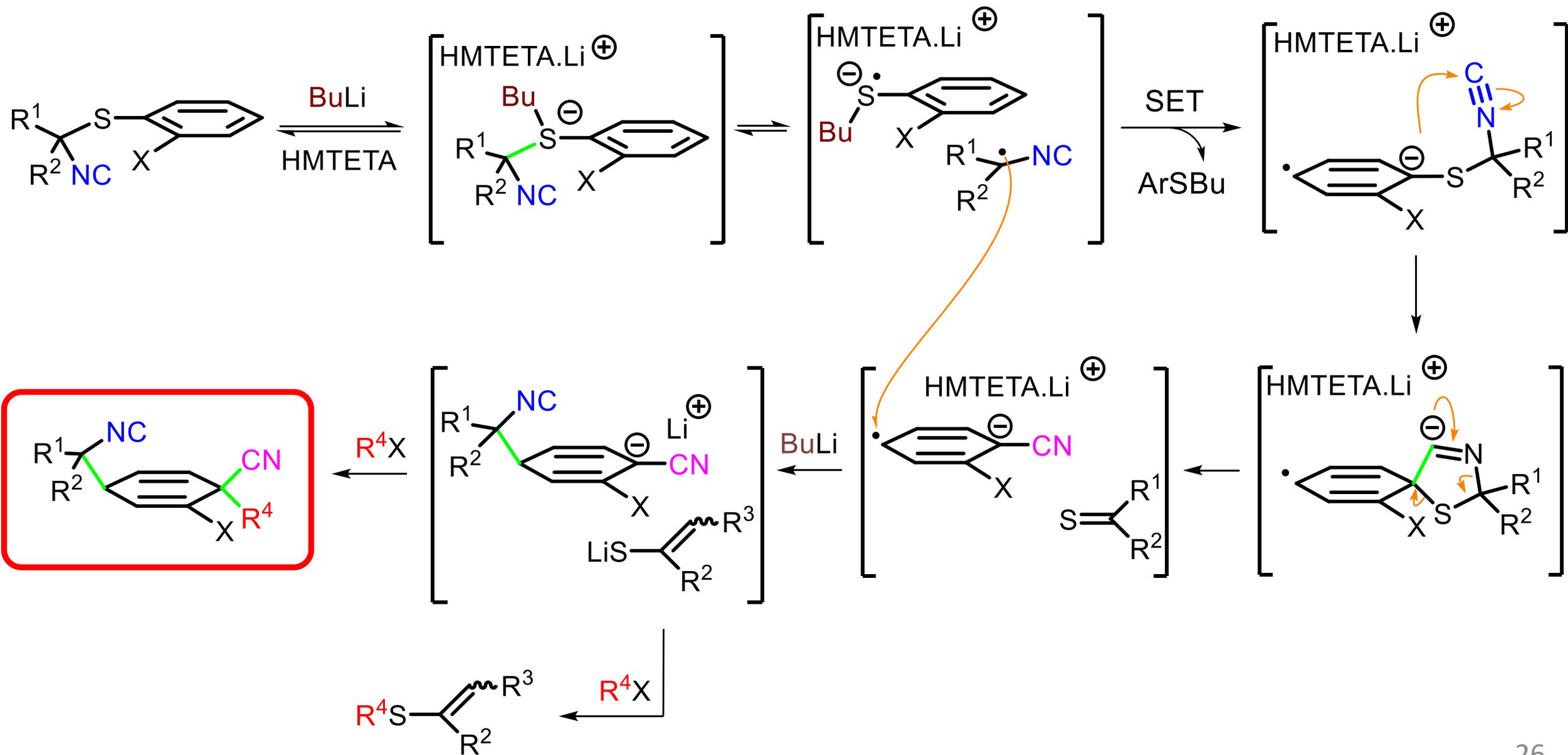
78%



69%

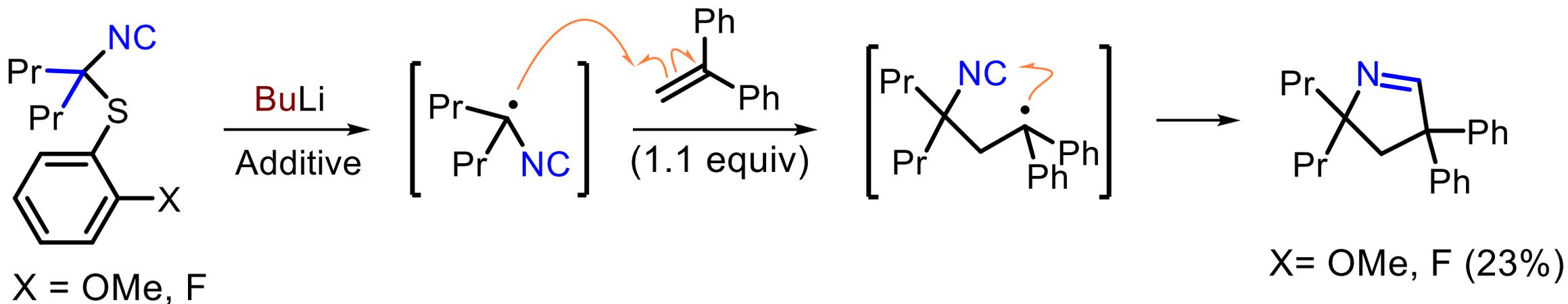
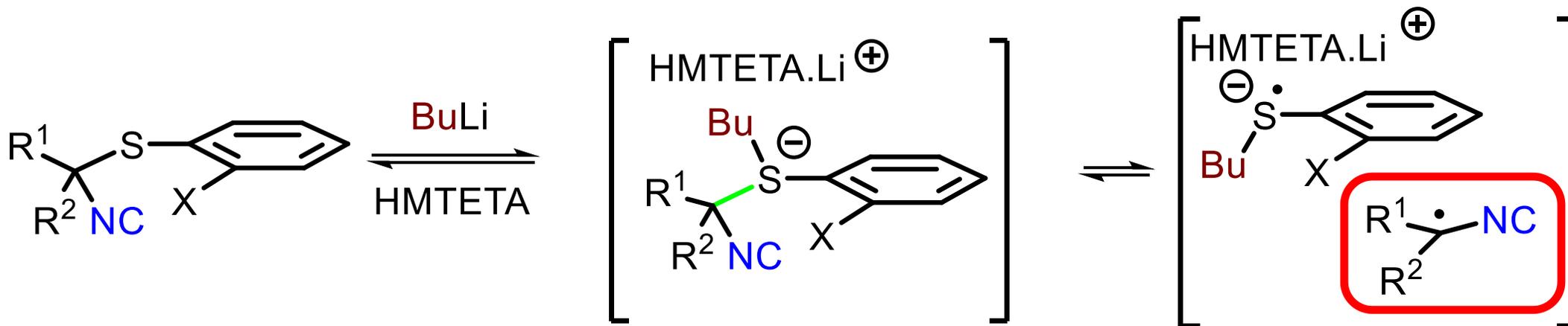


# Proposed Mechanism



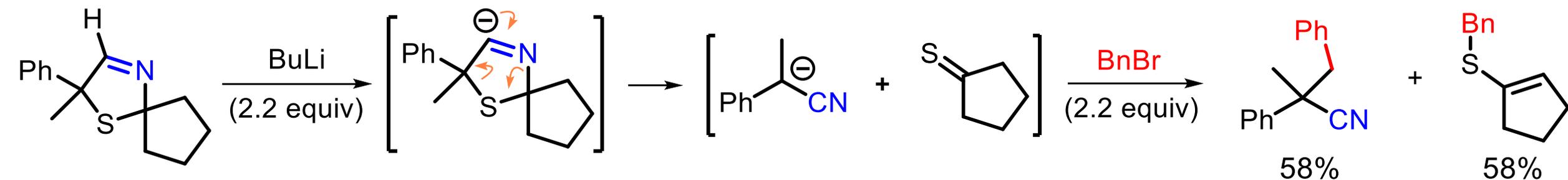
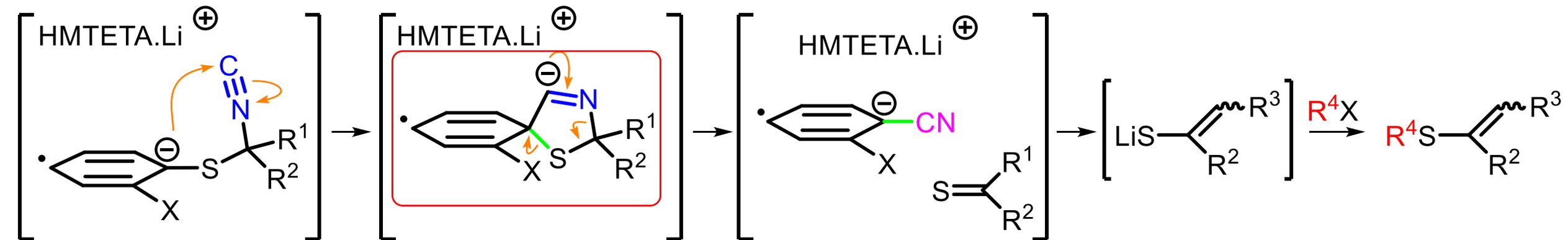


# Evidence



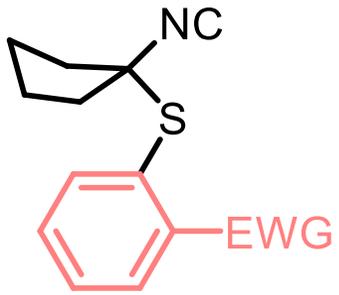


# Evidence



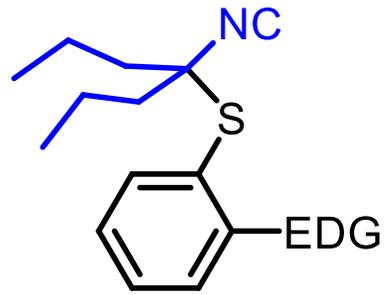


# Crossover Dearomatization



Acceptor

+

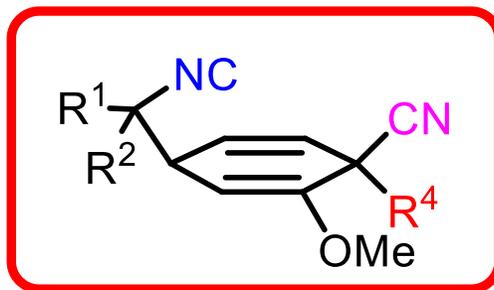
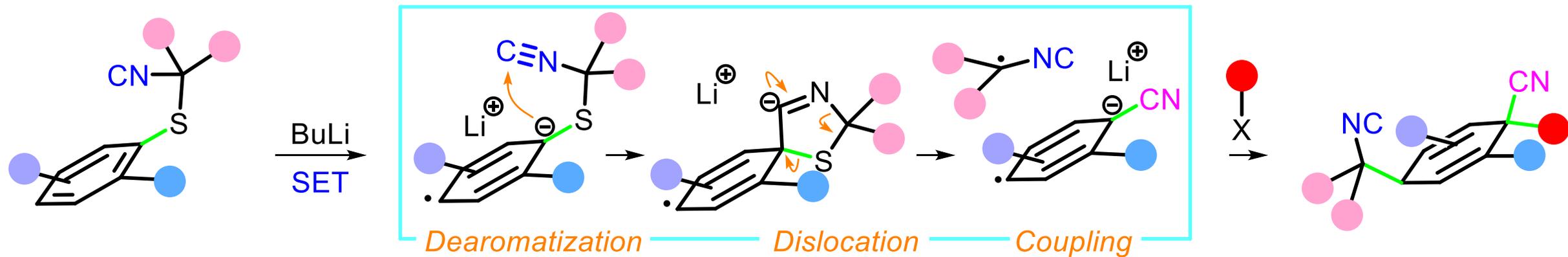


Donor





# Outlook



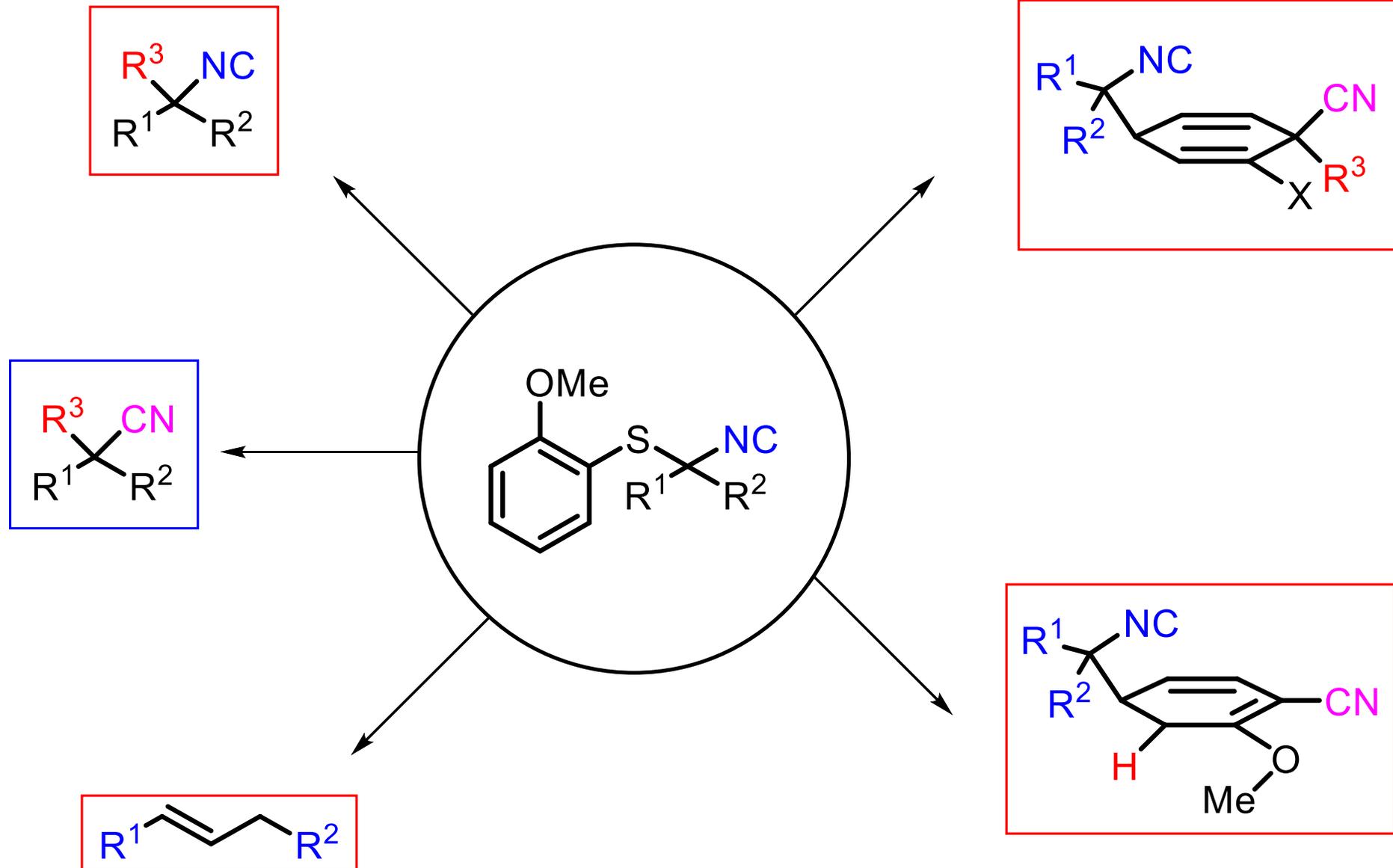


# Preparation of ASMIC



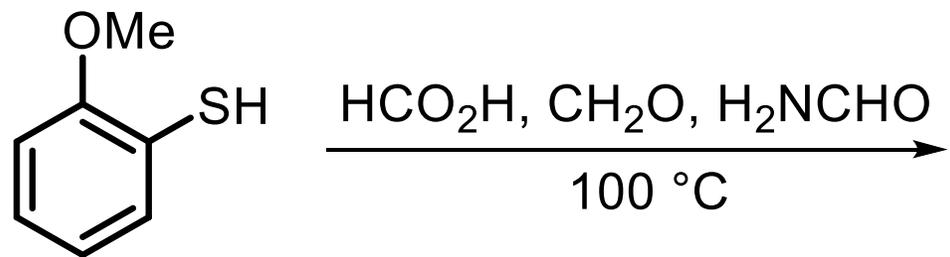


# Diversity

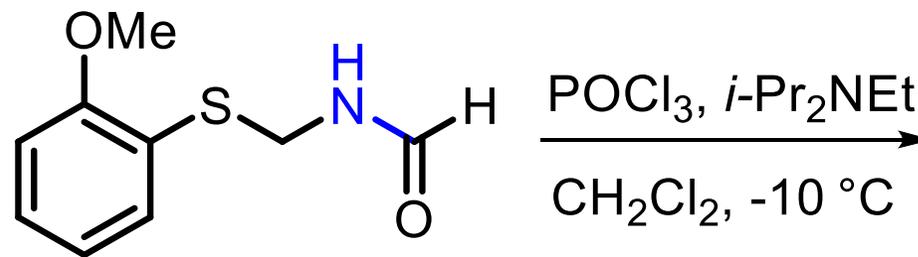




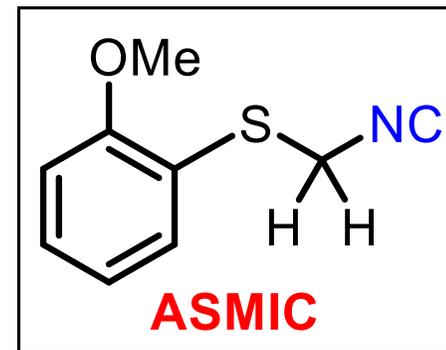
# Development of a Large Scale ASMIC Synthesis



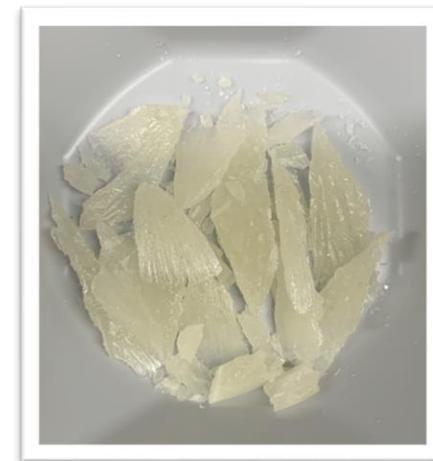
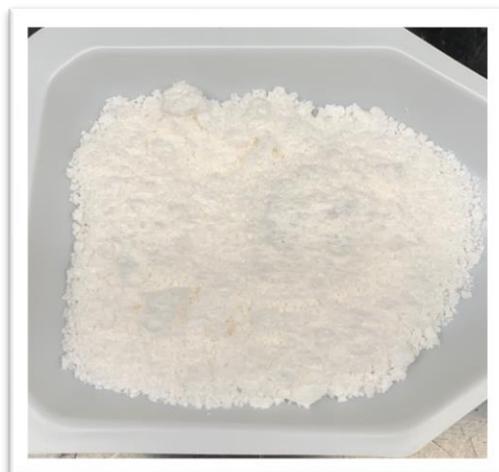
20 g  
10 g



19 g, 68%  
12.3 g, 87%



14.2 g, 85%  
7.65 g, 84%



**Formamide**

**ASMIC**

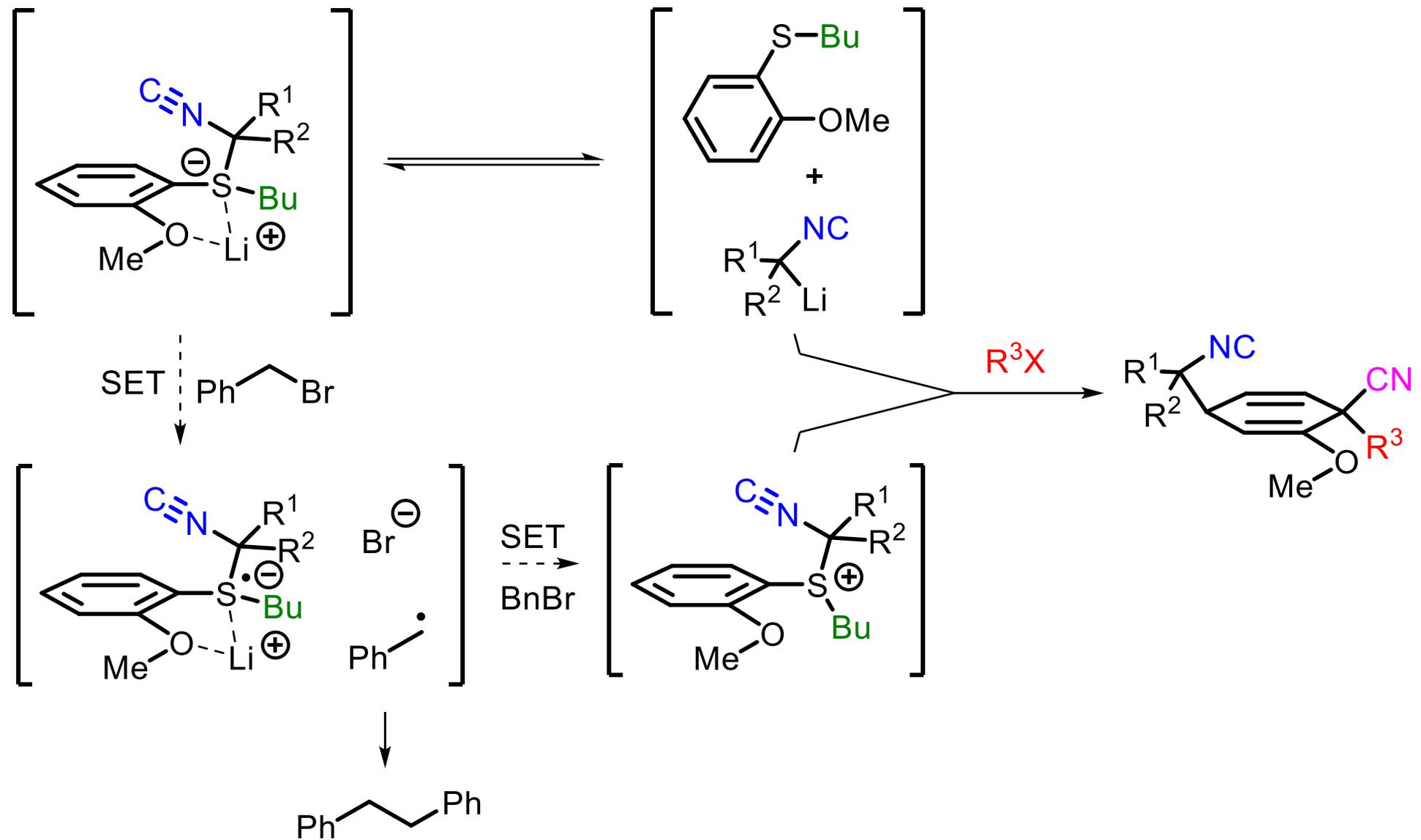


# Synthesis and Isolation of Sulfonium Salts



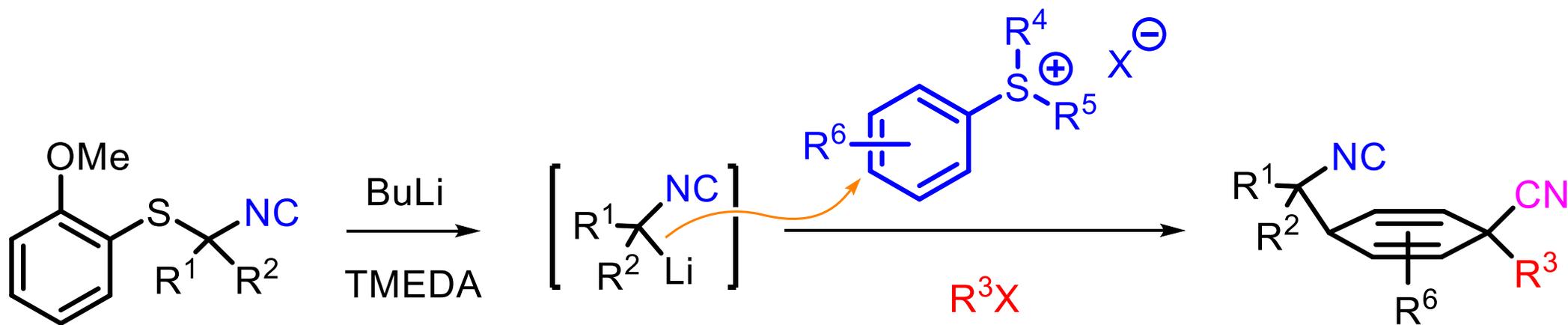


# Sulfonium Salts as Precursors



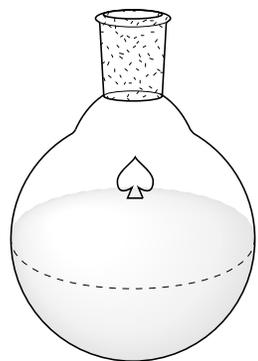
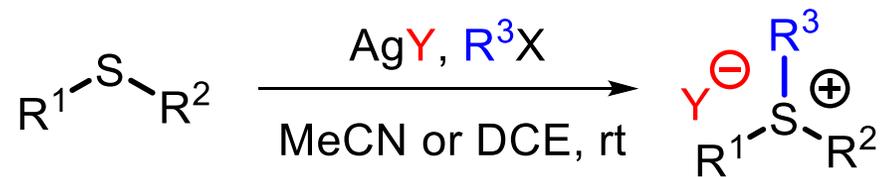


# Sulfonium Salts as Precursors



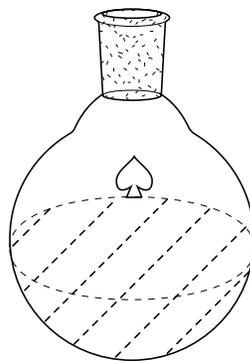


# Synthesis and Isolation of Sulfonium Salts



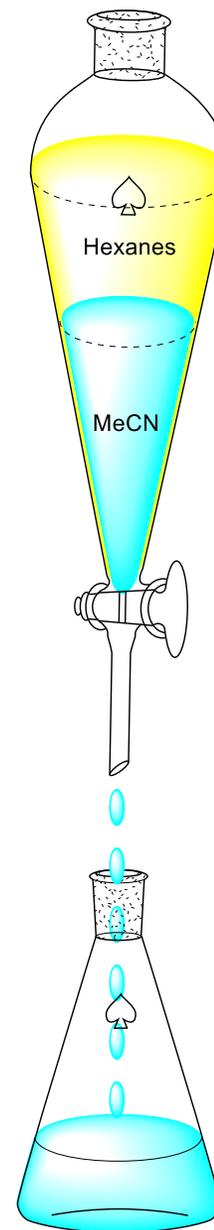
*Crude rxn mixture  
containing AgX ppt*

Filtration



*Impure sulfonium salt*

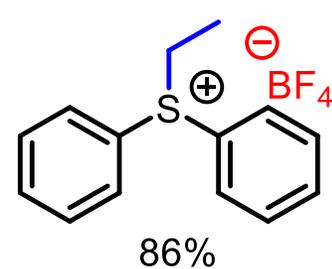
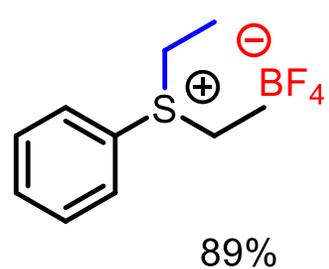
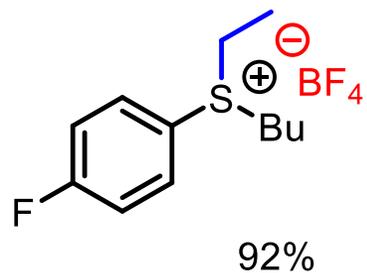
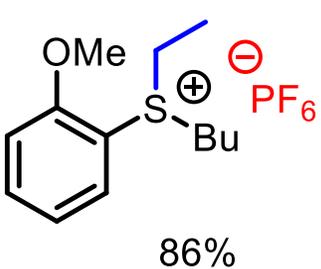
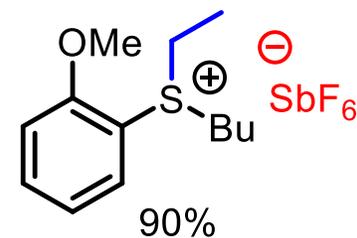
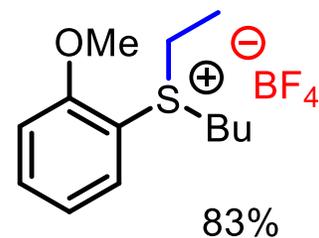
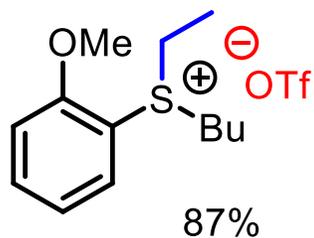
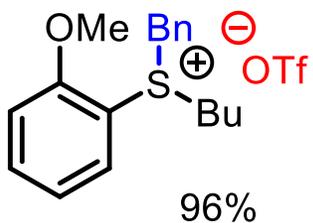
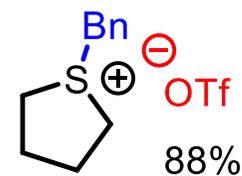
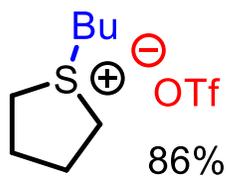
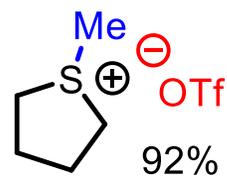
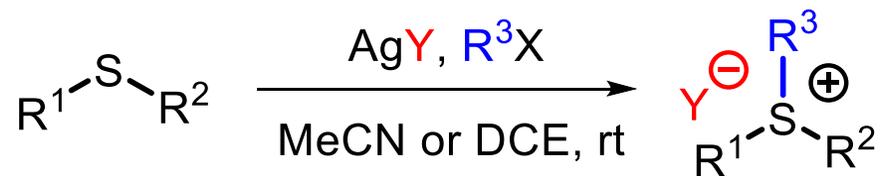
MeCN:Hexanes  
(1:3, by volume)



**Pure sulfonium  
salt**

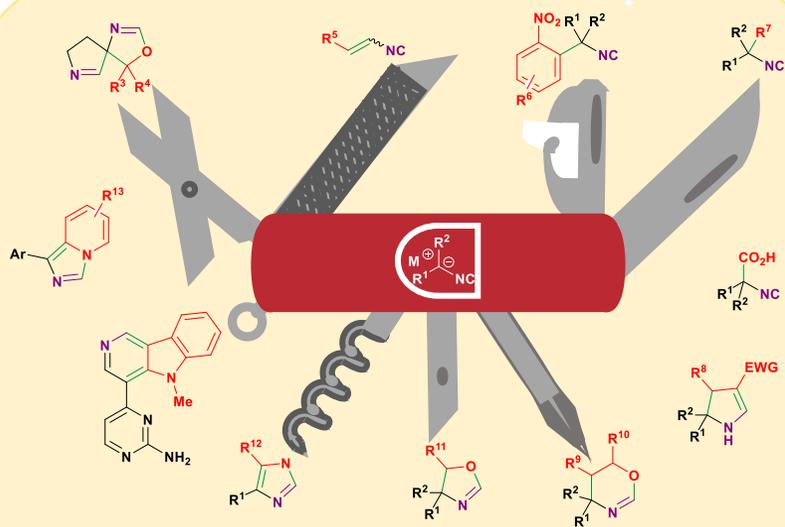


# Synthesis and Isolation of Sulfonium Salts

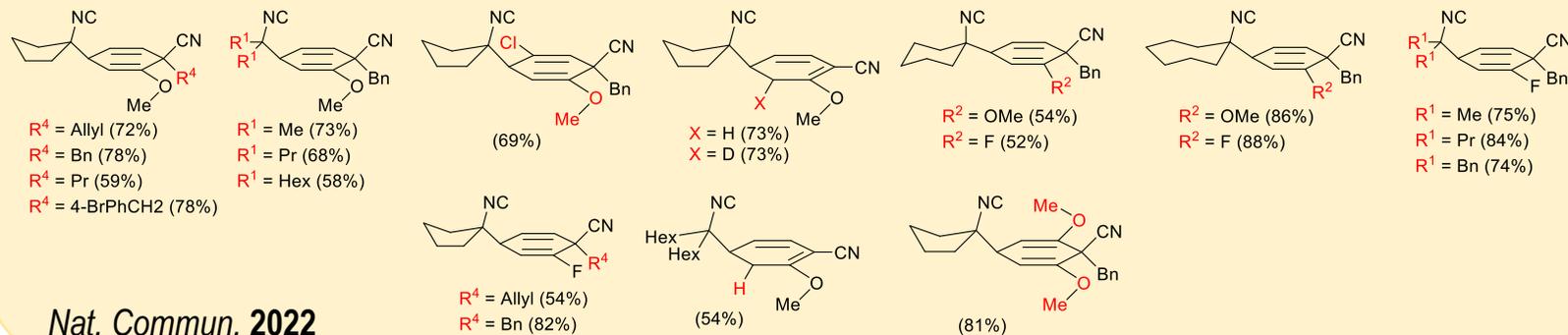
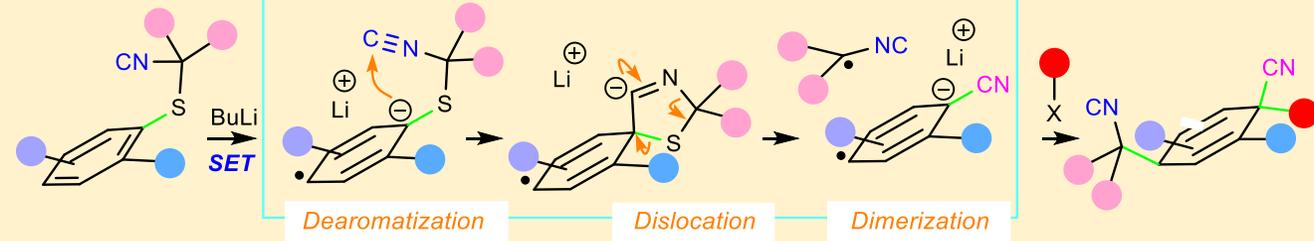




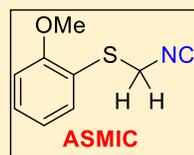
# Conclusion



*Org. Biomol. Chem.* **2020**, *18*, 6467-6482



*Nat. Commun.* **2022**



*e-EROS* **2020**

*Org. Synth.* **2021**, *98*, 147-170

**10 examples**  
**83-96% yield**

**Pure sulfonium salt**

Crude rxn mixture containing AgX ppt

Impure sulfonium salt



Filtration

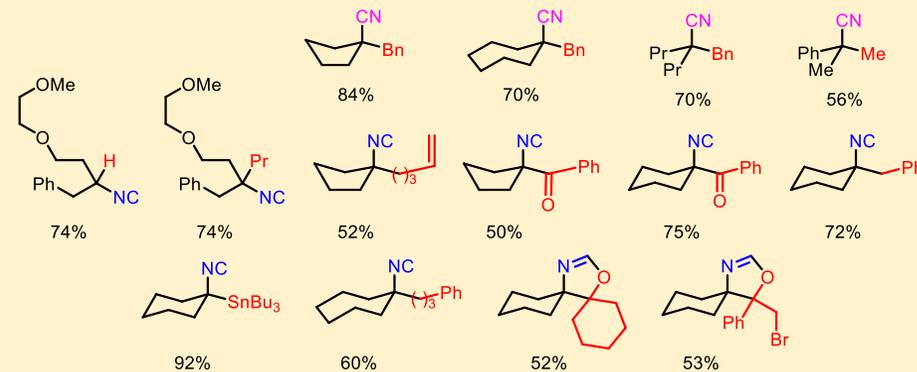
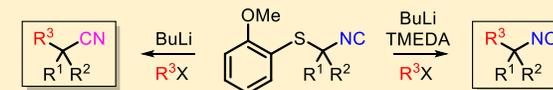


MeCN:Hexanes  
(1:3, by volume)



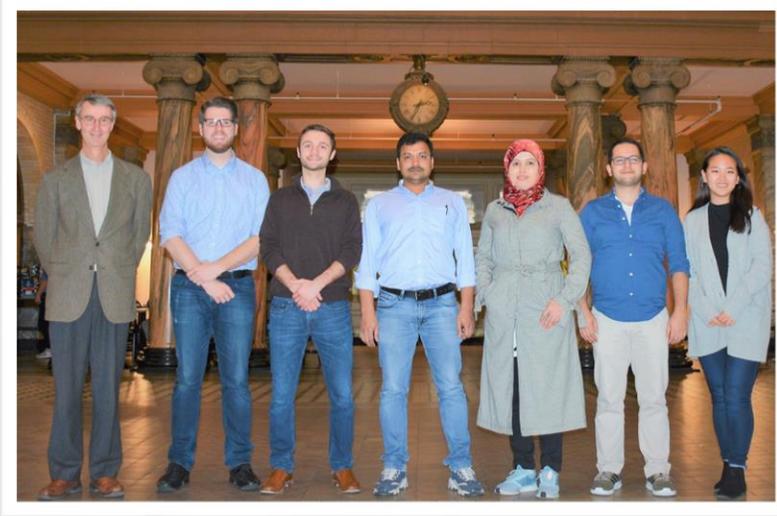
*ACS Omega* **2020**, *5*, 13384-13388

*Eur. J. Org. Chem.* **2019**, *2019*, 4644-4648





# Acknowledgements



DREXEL UNIVERSITY  
College of  
Arts and Sciences