Reversible Bonds-Manipulation to Access Functionalized Molecules

Tristan Delcaillau

Zhu group

LSPN - EPFL

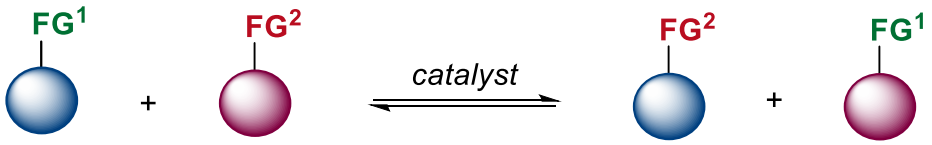
10/11/2022

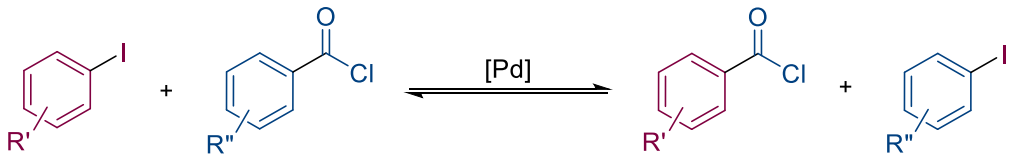
Prof. Bill Morandi

- Born in Fribourg, Switzerland
- PhD in Carreira group, ETH – Switzerland (2008-2012)
- Postdoc in Grubbs group, Caltech – US (2012-2014)
- Independent leader at MPI – Germany (2014-2018)
- Prof. at ETH Zürich – Switzerland (2018-)

Chemistry of Morandi group

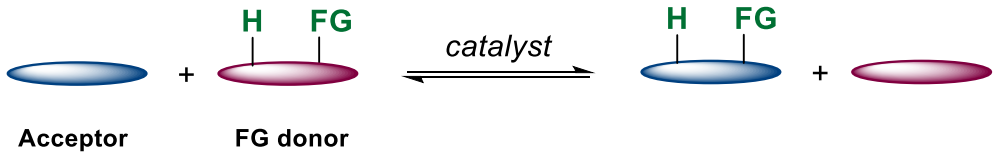
Functional group metathesis

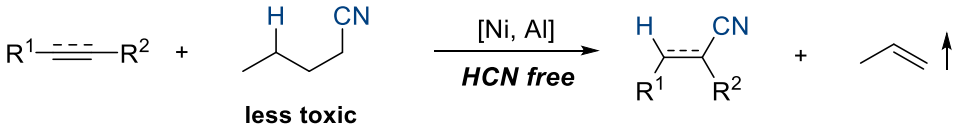




Nat. Chem. **2018**, *10*, 1016

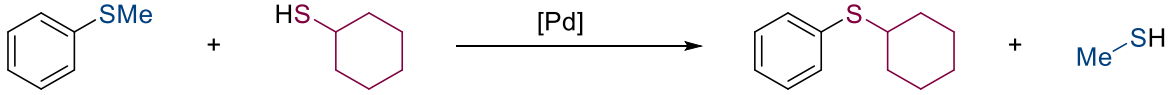
Shuttle Catalysis



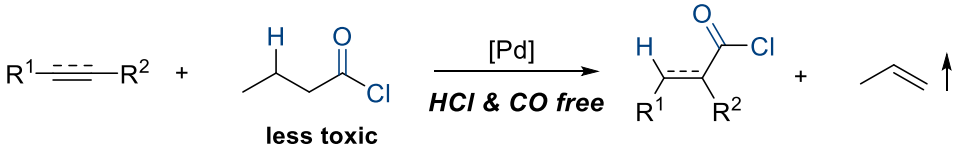


Science **2016**, *351*, 832–836

Single-bond metathesis



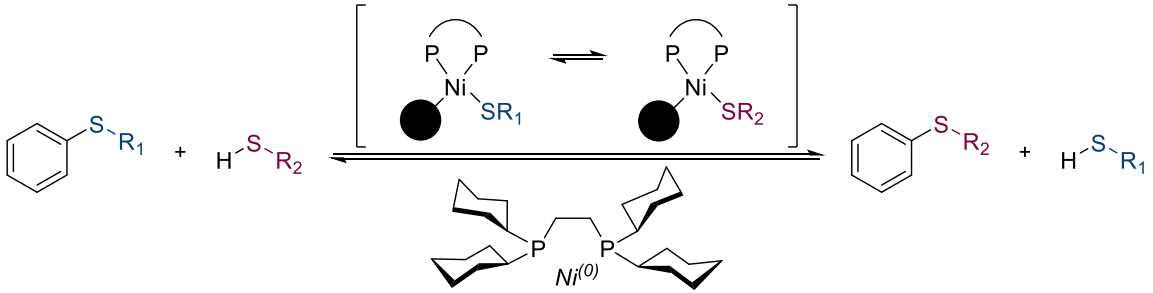
Science, **2017**, *356*, 1059–1063



Nat. Chem. **2017**, *9*, 1105-1109

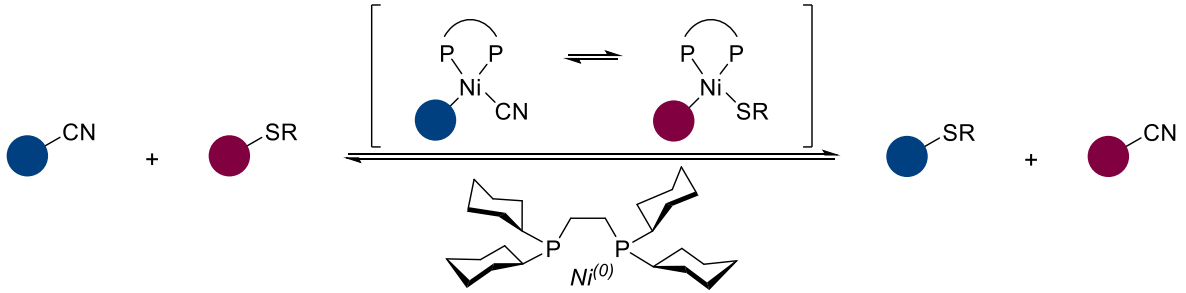
Overview

Aryl thioether metathesis



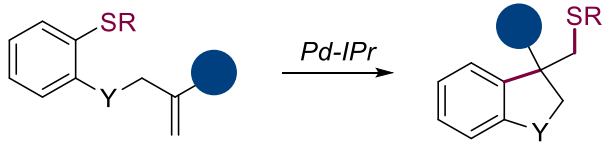
Angew. Chem. Int. Ed. **2020**, *59*, 2110–2114.

Functional group metathesis between ArCN and ArSR



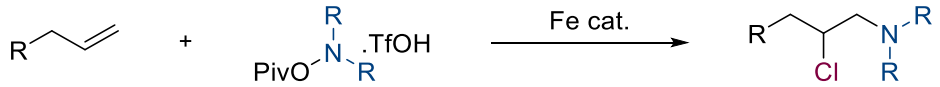
J. Am. Chem. Soc. **2021**, *143*, 3723–3728.
Chem. Eur. J. **2021**, *27*, 11823-11826.
Org. Lett. **2021**, *23*, 18, 7018-7022.

C(sp2)-S / C(sp3)-S metathesis



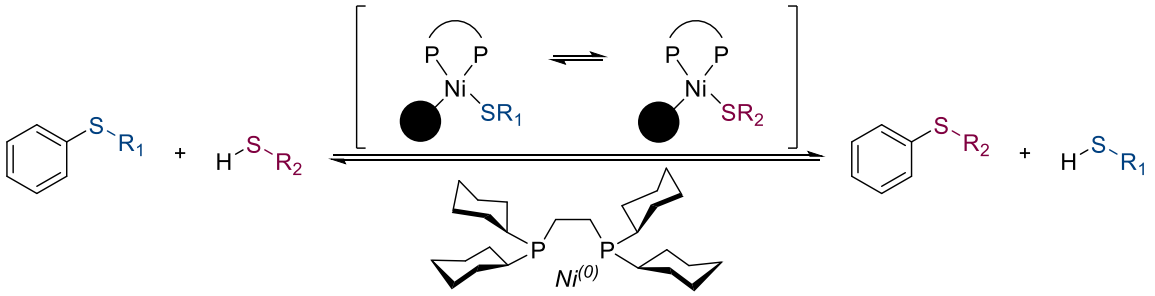
ACS Catal. **2022,** *12*, 6081–6091.

Amination of alkenes



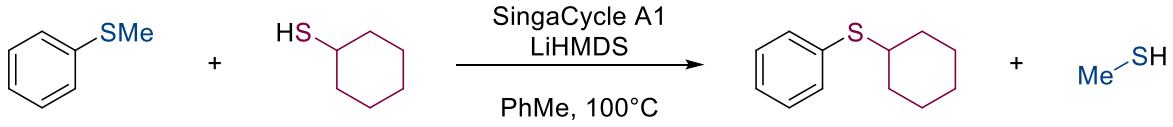
Angew. Chem. Int. Ed. **2020**, *59*, 21064.
Science **2018**, *362*, 434-439.

Reversible Inter- and Intramolecular Aryl Thioether Metathesis

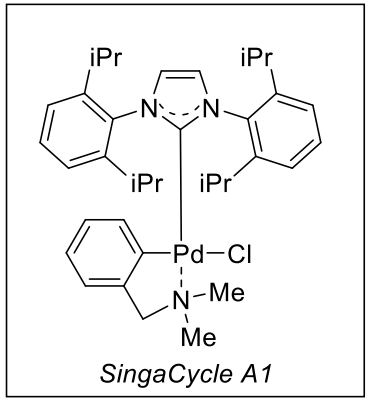


Reversible Inter- and Intramolecular Aryl Thioether Metathesis

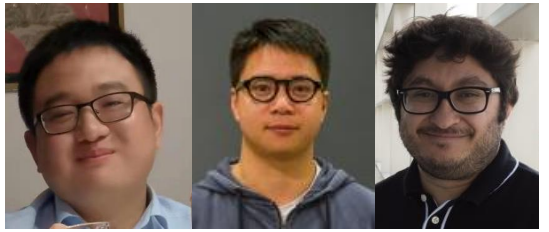
Aryl thioether metathesis



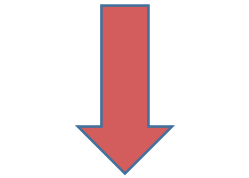
Science, **2017**, *356*, 1059–1063



SingaCycle A1



- Limited scope
- Expensive Pd cat.



28 $3d^8 4s^2$

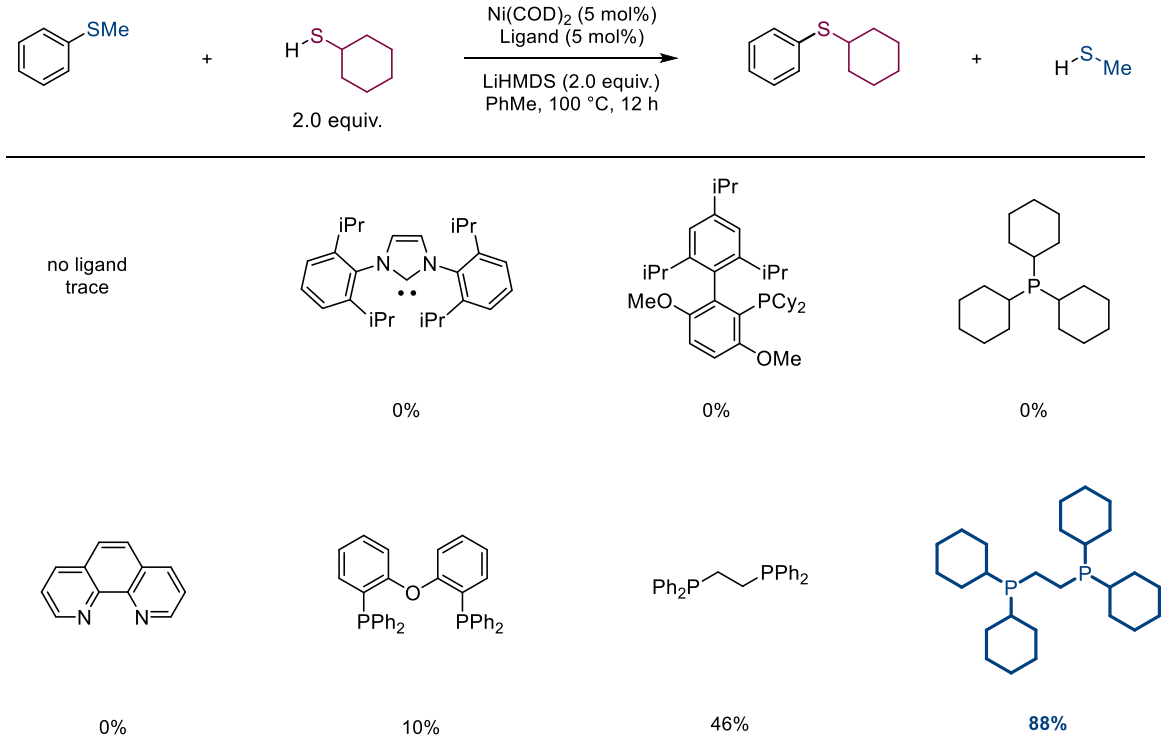
Ni

Nickel

58.693

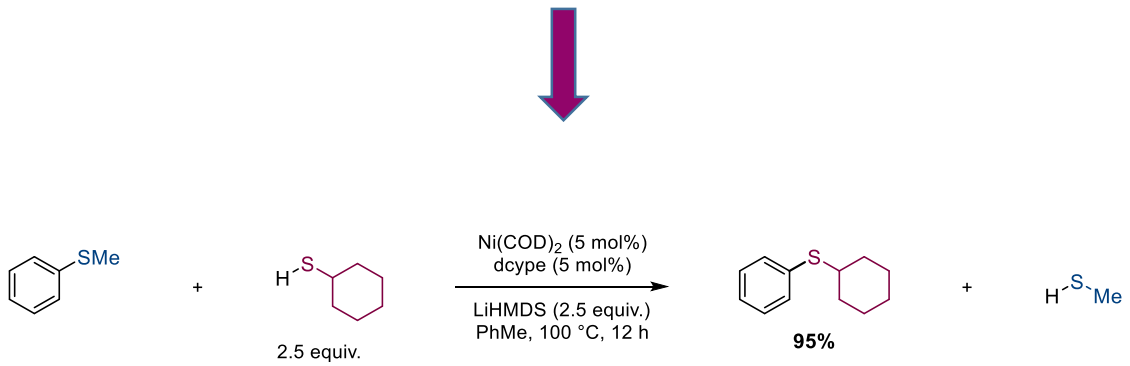
Reversible Inter- and Intramolecular Aryl Thioether Metathesis

Optimization



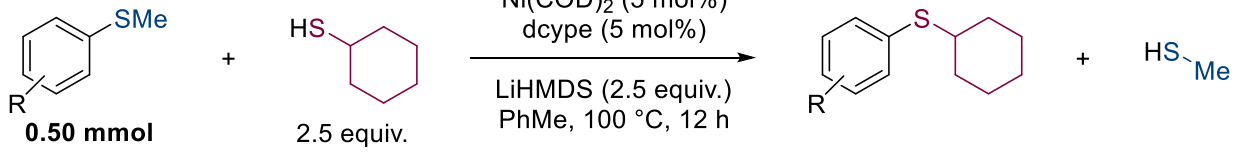
Further optimization

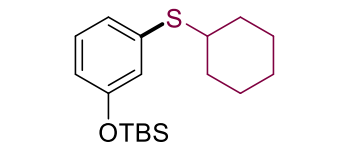
- Nickel loading
- Ligand loading
- Temperature
- Time
- Solvent
- Base
- Amount of thiol
- Amount of base



Reversible Inter- and Intramolecular Aryl Thioether Metathesis

ArSMe scope





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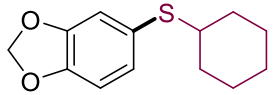

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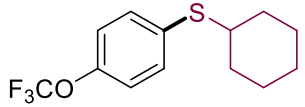

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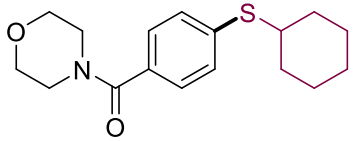

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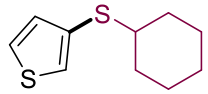

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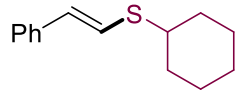

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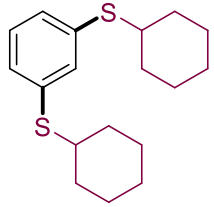

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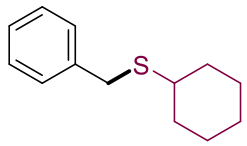

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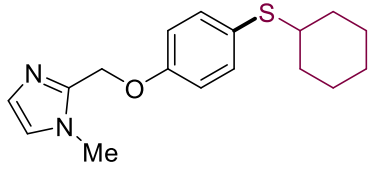
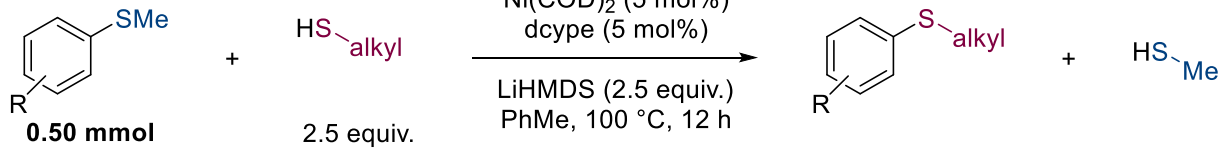
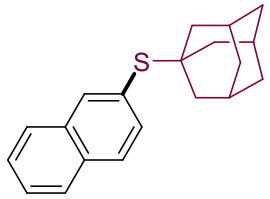


75%
Fexinidazole derivative

Thiol scope





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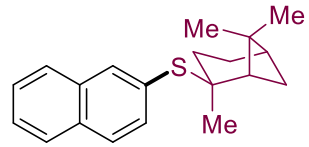

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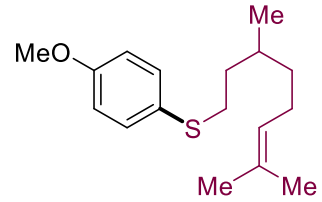

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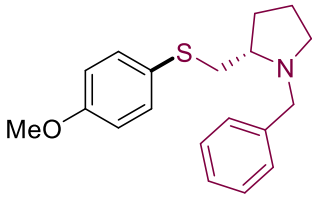

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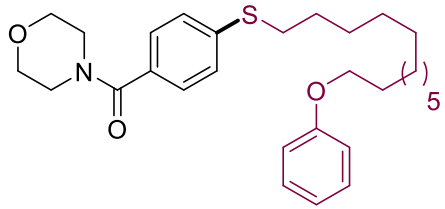

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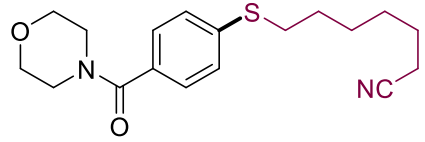

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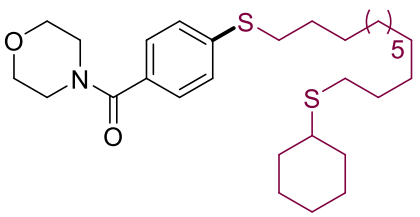

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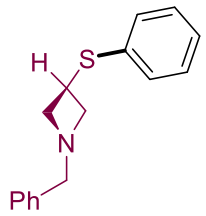

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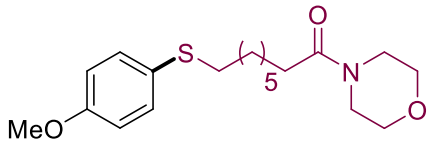

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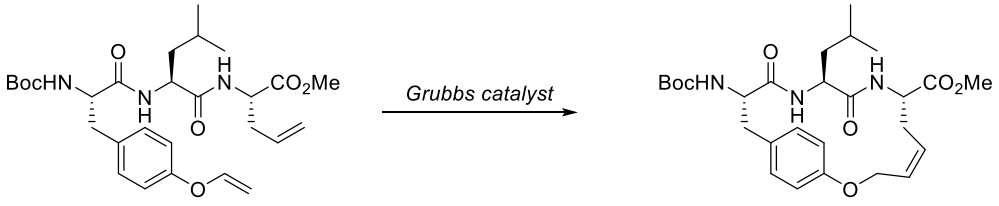
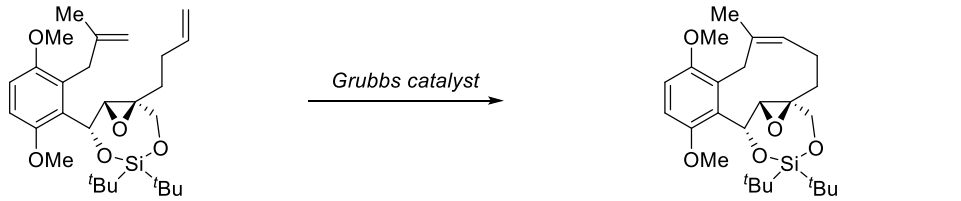
Reversible Inter- and Intramolecular Aryl Thioether Metathesis

Olefin metathesis



Chem. Sci. **2015**, *6*, 4561-4569

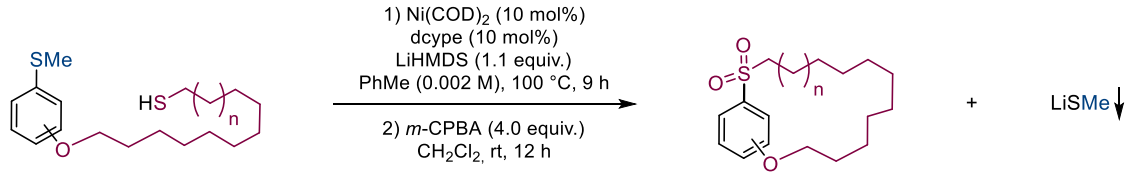


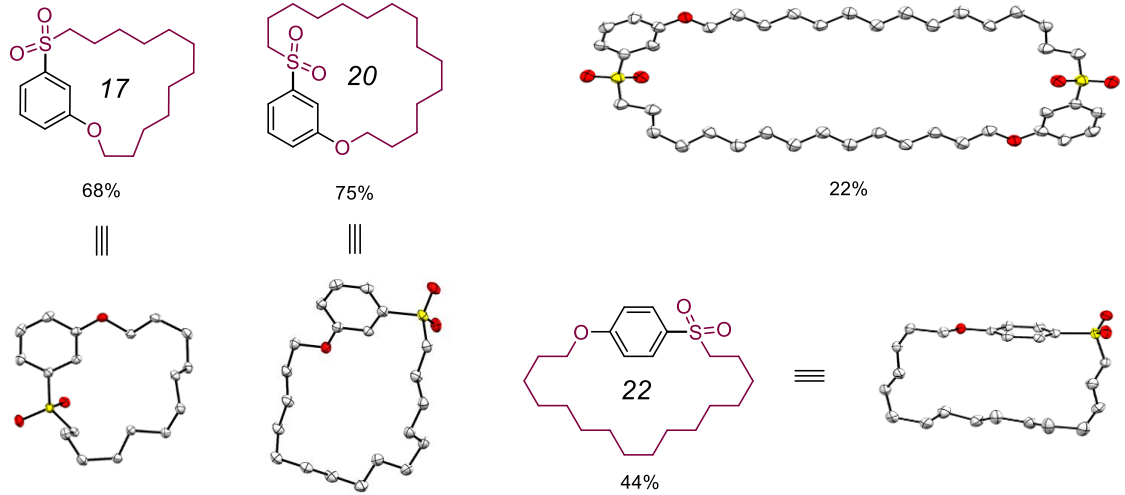
Intermediate en route to (+)-Clavilactone A

Org. Lett. **2013**, *15*, 5582–5585

Parameters

- Concentration
- Catalyst loading
- Time
- Temperature

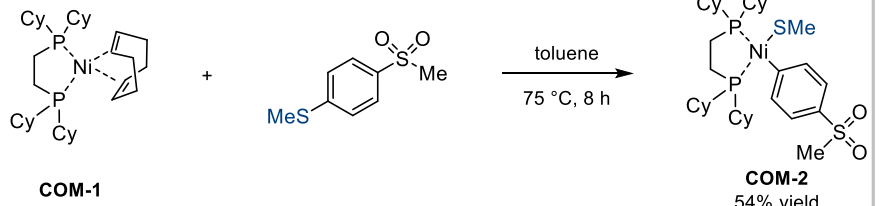




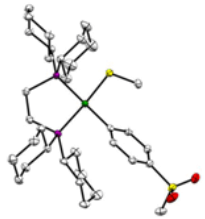
Reversible Inter- and Intramolecular Aryl Thioether Metathesis

Mechanistic study

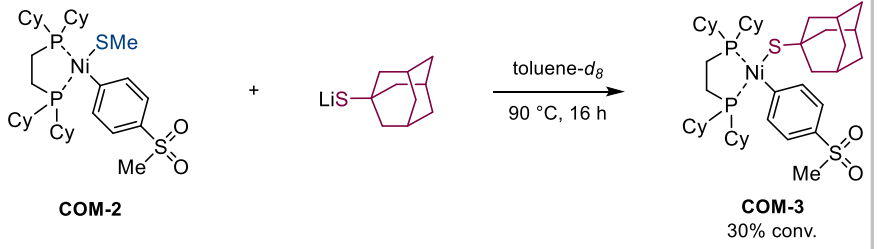
Oxidative addition



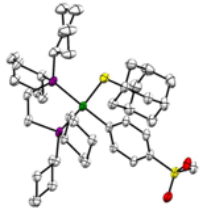
X-ray structure of COM-2



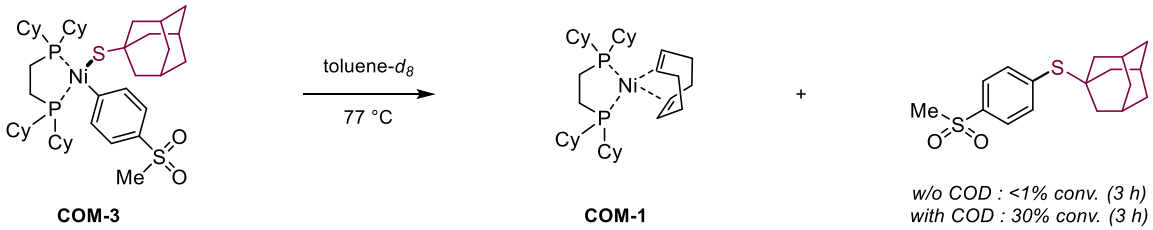
Ligand exchange



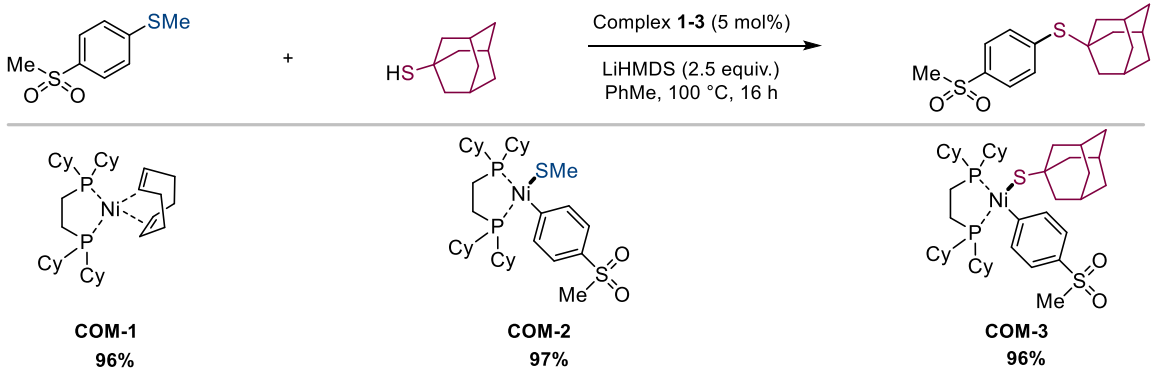
X-ray structure of COM-3



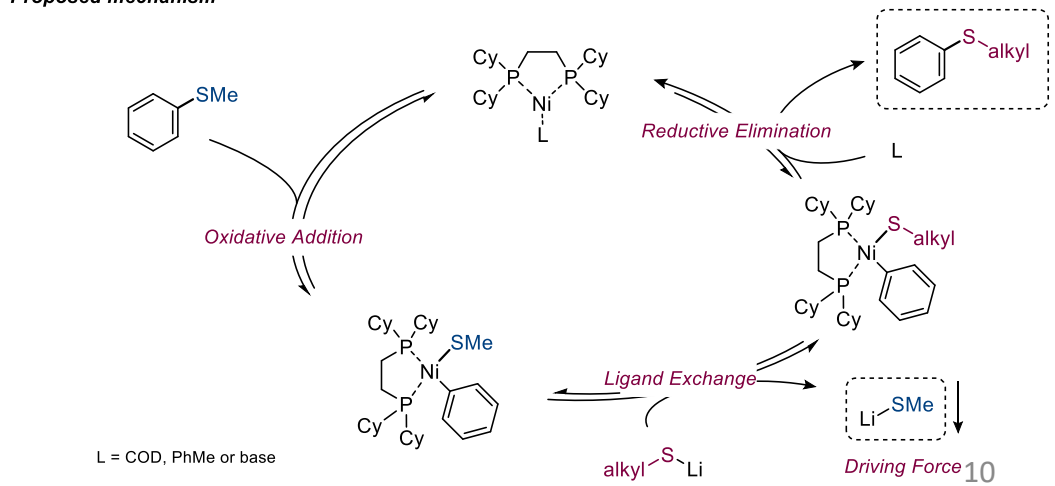
Reductive elimination



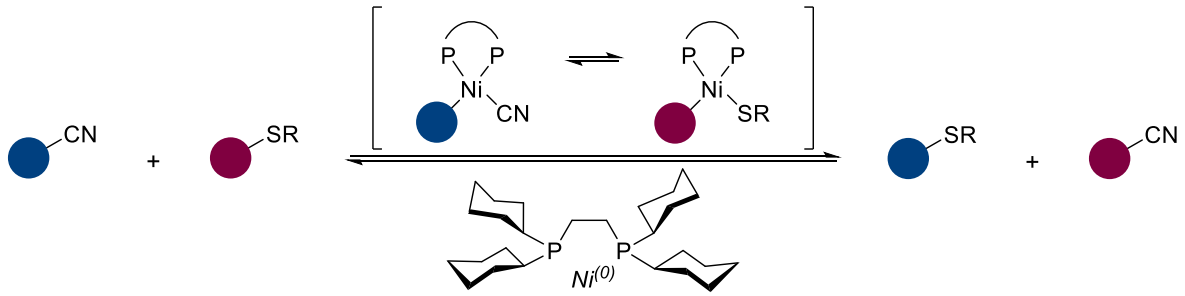
Catalytic competence



Proposed mechanism

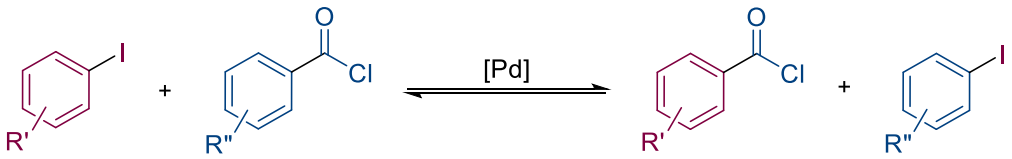


Reversible Functional Group Metathesis between ArCN and ArSR

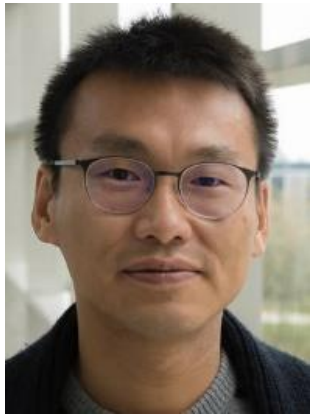


Reversible Functional Group Metathesis between ArCN and ArSR

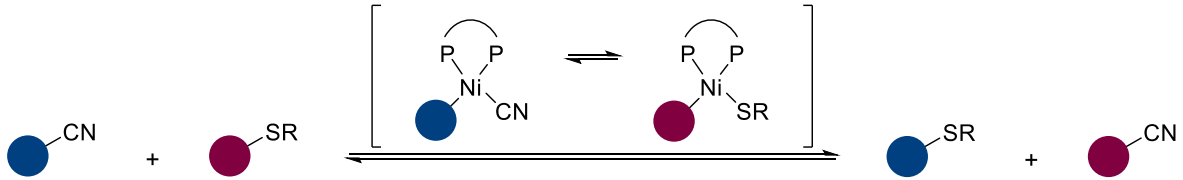
ArI - ArC(O)Cl metathesis



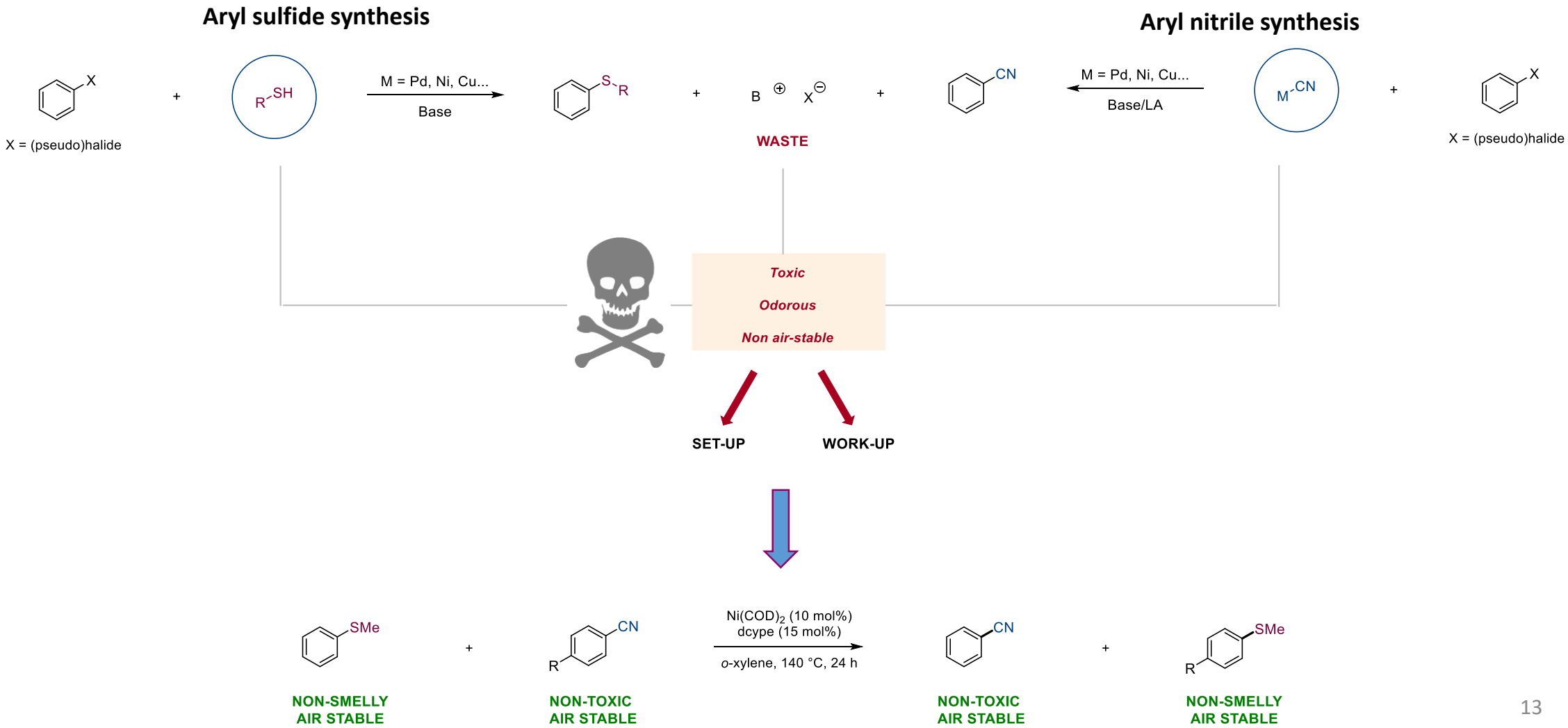
Nat. Chem. **2018**, *10*, 1016



Reaction design

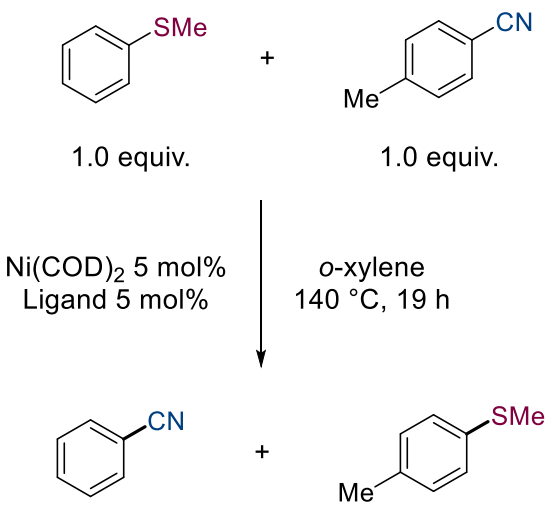


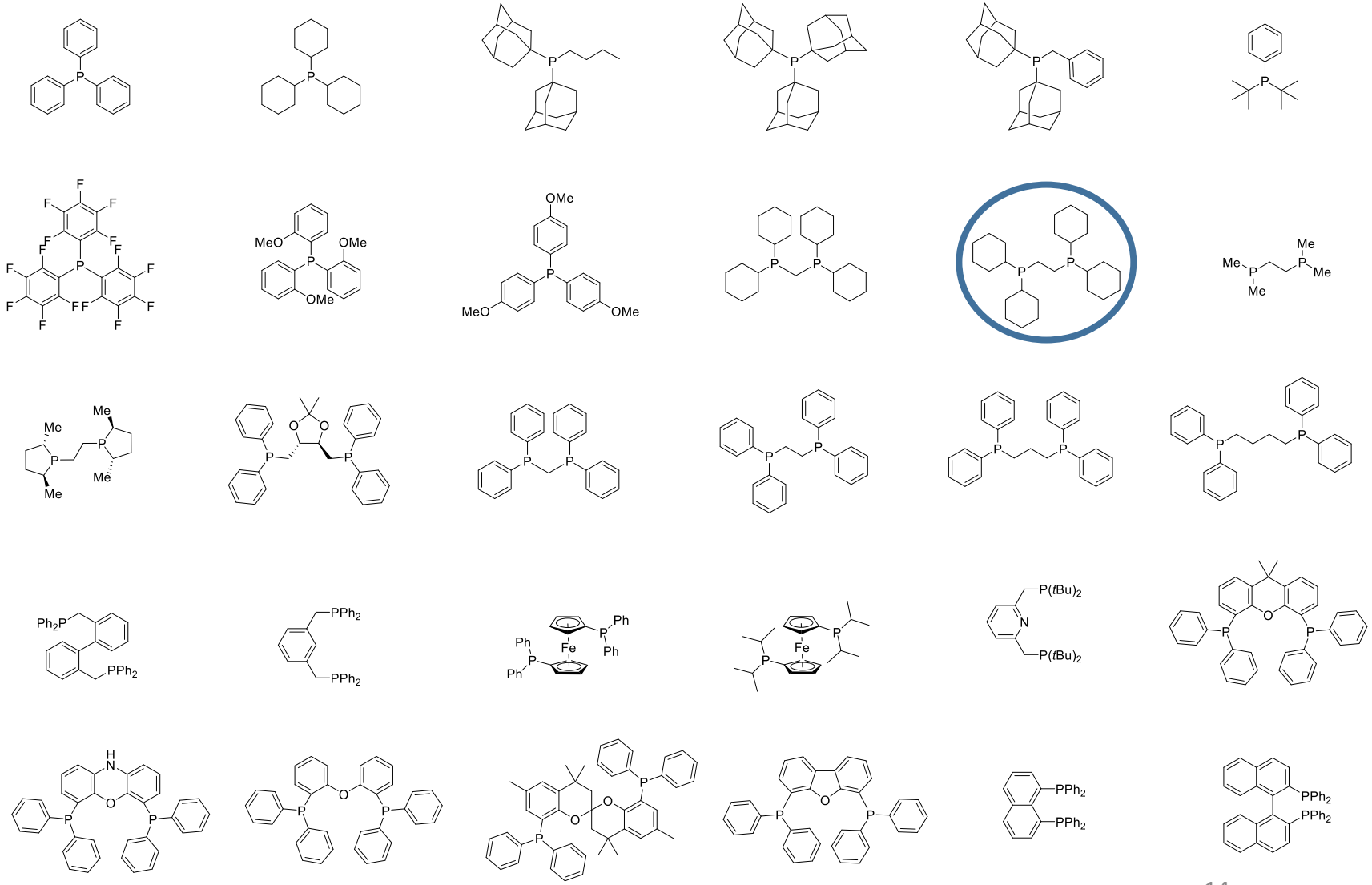
Reversible Functional Group Metathesis between ArCN and ArSR



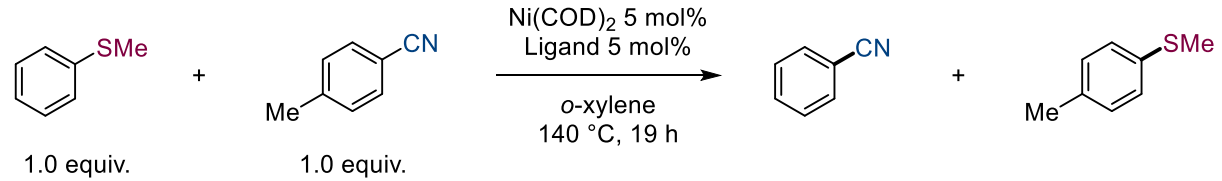
Reversible Functional Group Metathesis between ArCN and ArSR

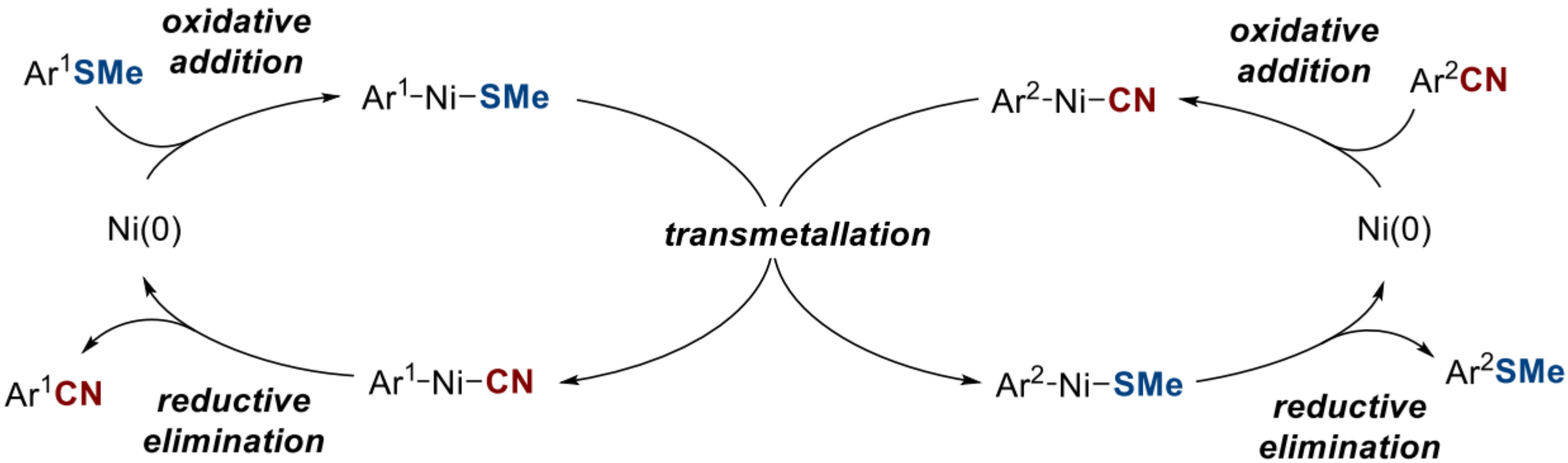
Optimization





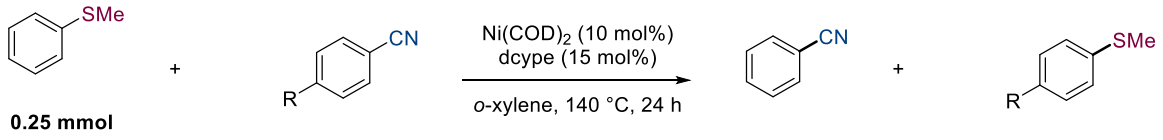
Reversible Functional Group Metathesis between ArCN and ArSR

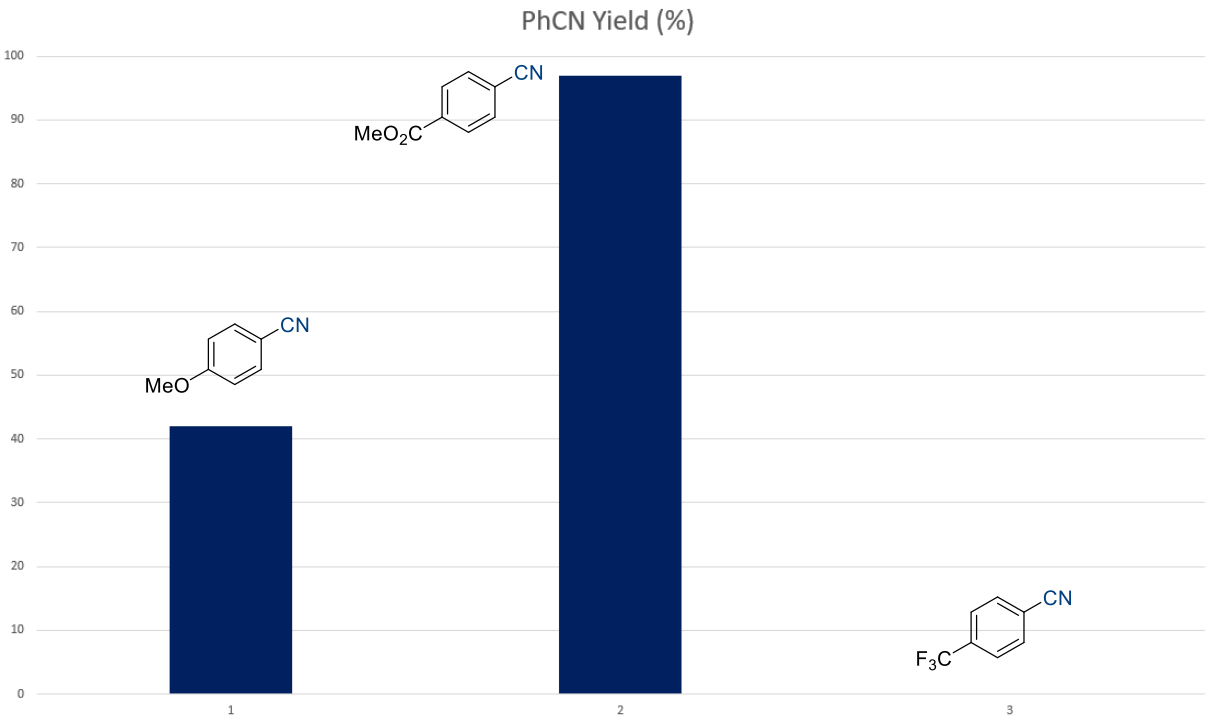




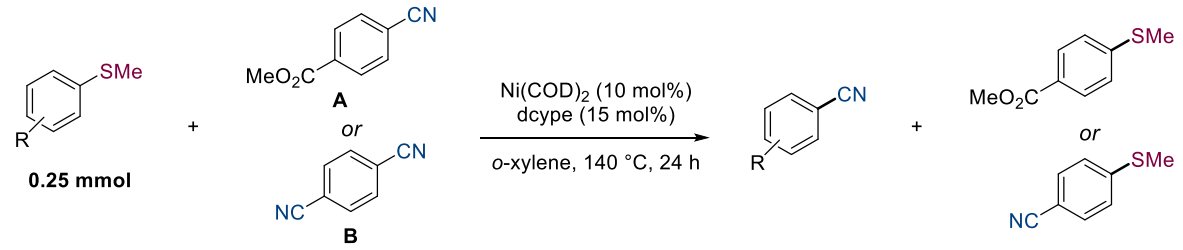
Reversible Functional Group Metathesis between ArCN and ArSR

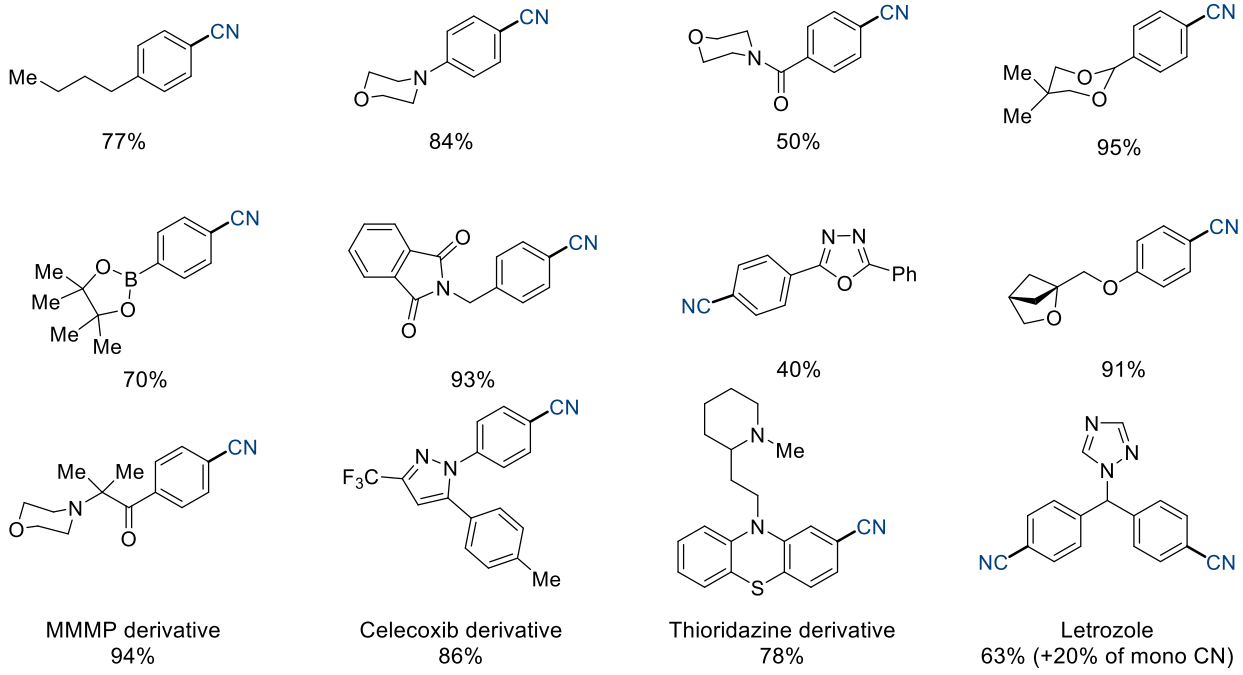
Driving the equilibrium





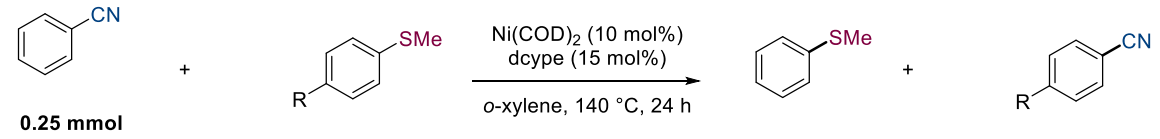
Scope Cyanation (Forward)



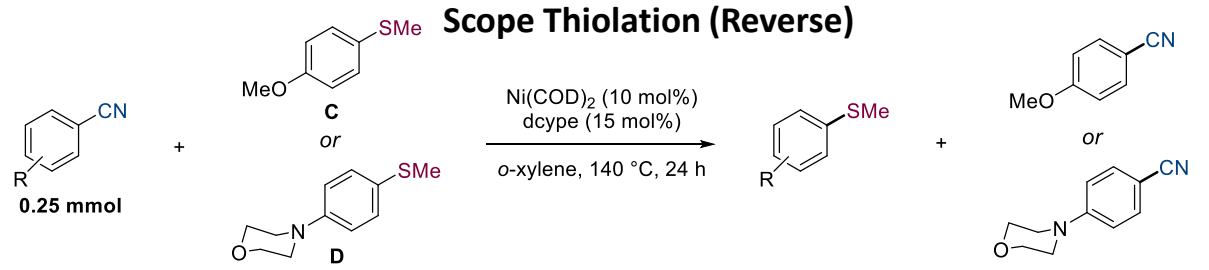


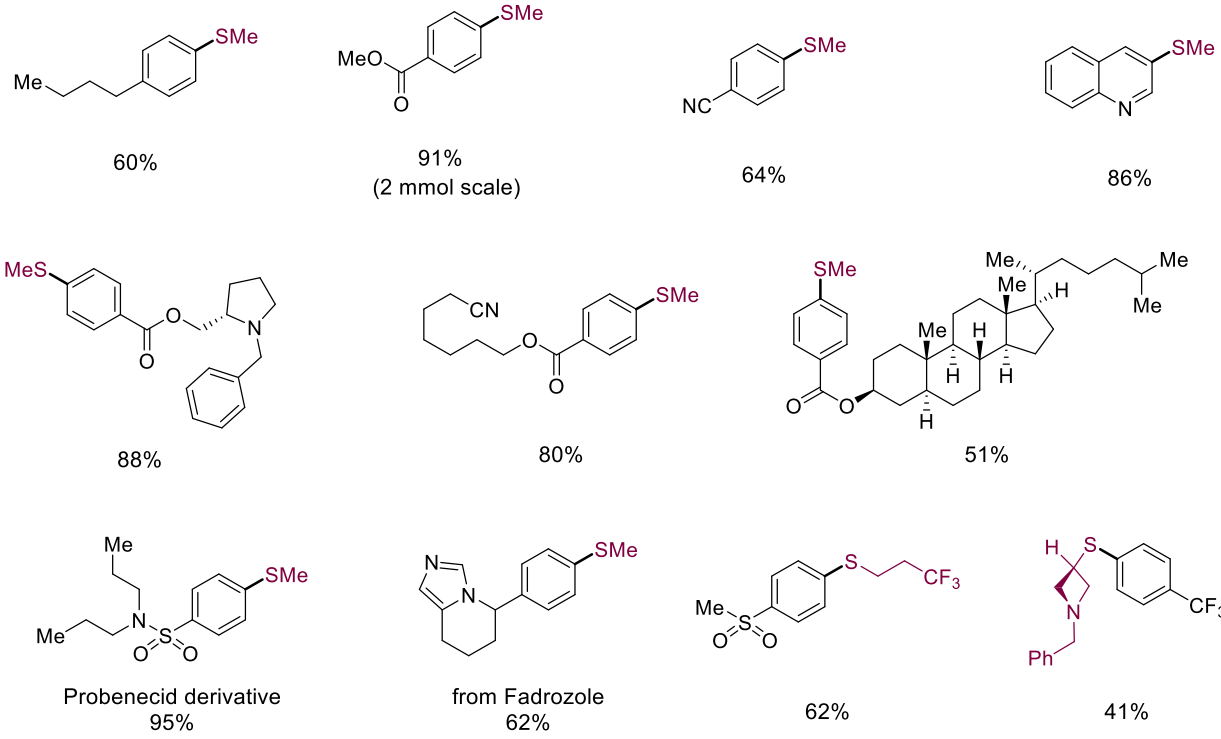
Reversible Functional Group Metathesis between ArCN and ArSR

Driving the equilibrium



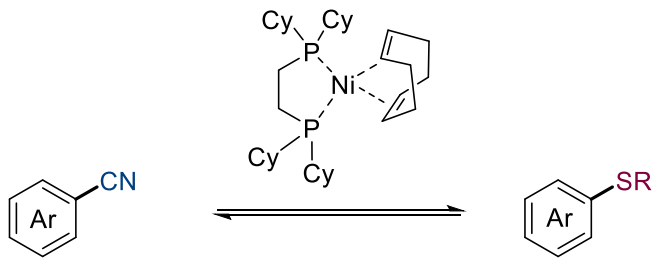
Scope Thiolation (Reverse)





Reversible Functional Group Metathesis between ArCN and ArSR

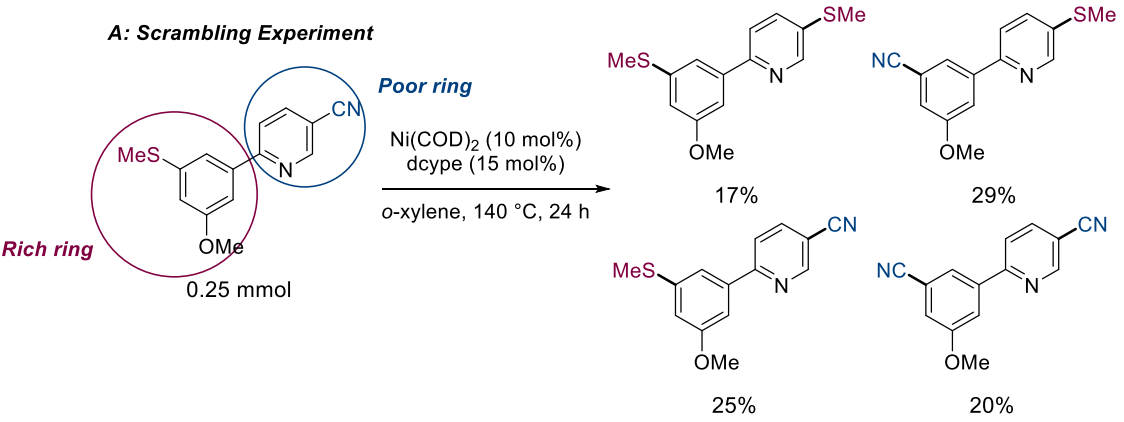
Antagonist properties of CN & SR functionnal groups

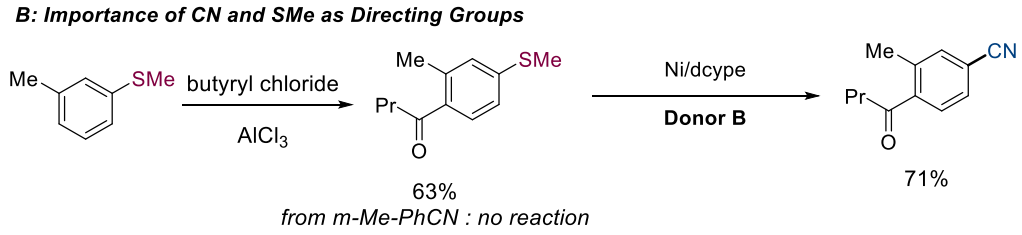


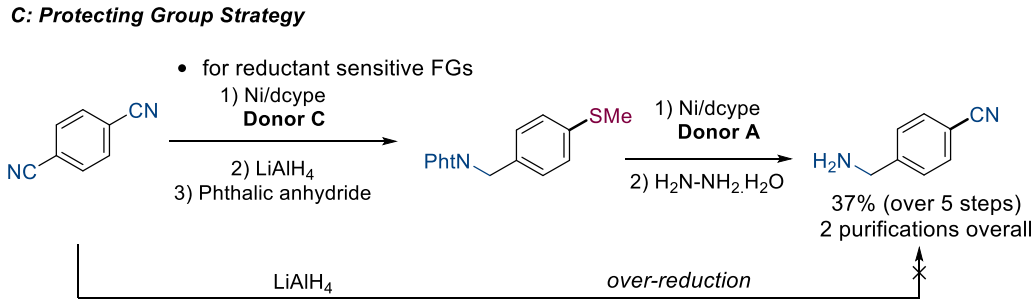
Oxidant tolerant	Oxidant intolerant
Reductant intolerant	Reductant tolerant
Acid and base intolerant	Acid and base tolerant
Electron-poor	Electron-rich

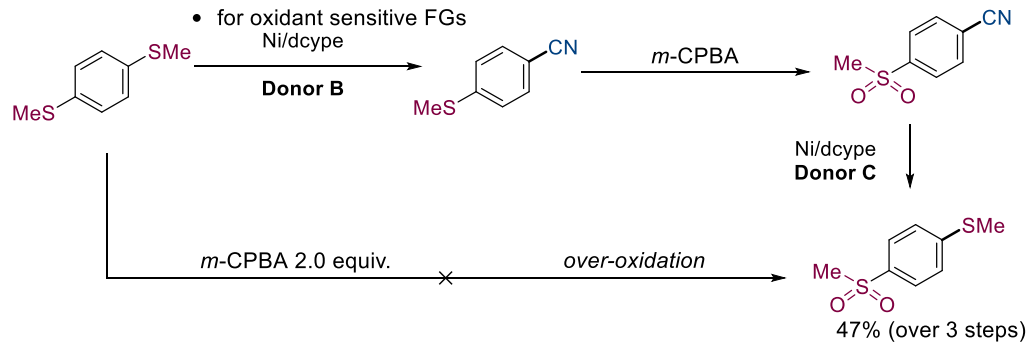
Reversible Functional Group Metathesis between ArCN and ArSR

Synthetic applications



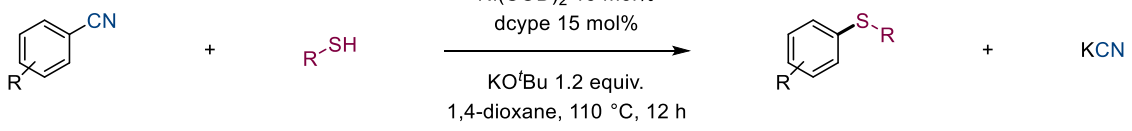


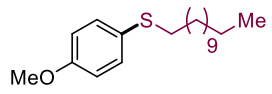




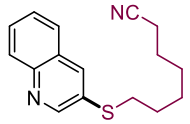
Reversible Functional Group Metathesis between ArCN and ArSR

Thiolation with a thiol

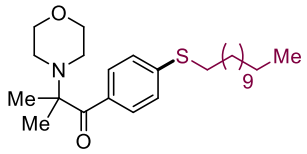




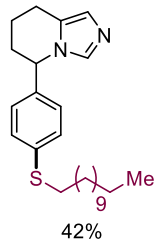
91%



63%



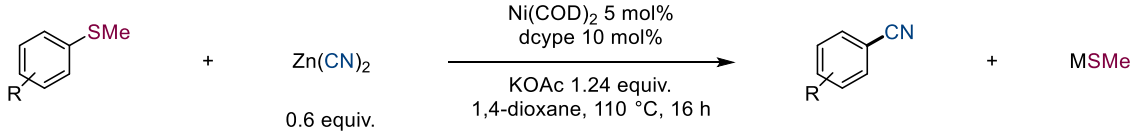
82%

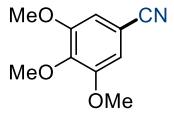


42%

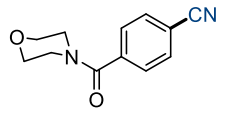
Chem. Eur. J. **2021**, *27*, 11823– 11826

Cyanation with $Zn(CN)_2$

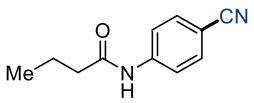




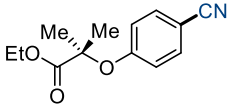
94%



97%



55%



77%
Clofibrate derivative

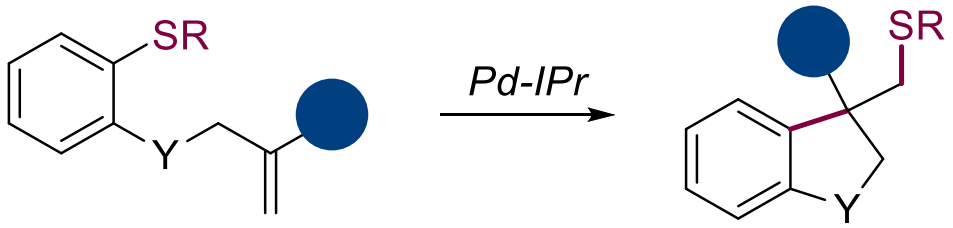
Depolymerization of a polymer

M_n ~10,000

58%

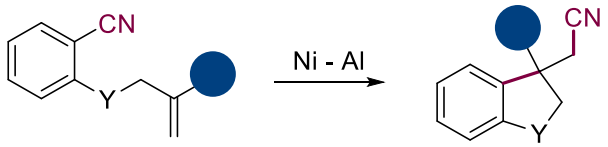
Org. Lett. **2021**, *23*, 7018–7022

Carbothiolation of unsaturated of alkenes and alkynes

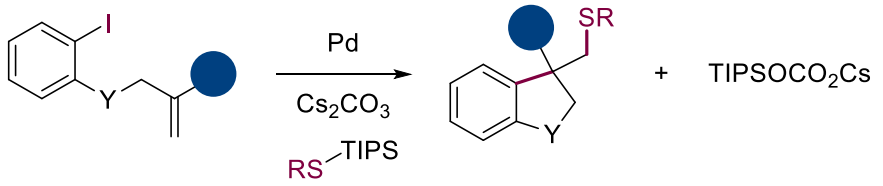


Carbothiolation of unsaturated of alkenes and alkynes

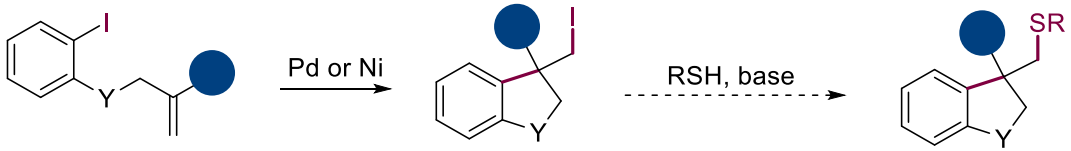
Background



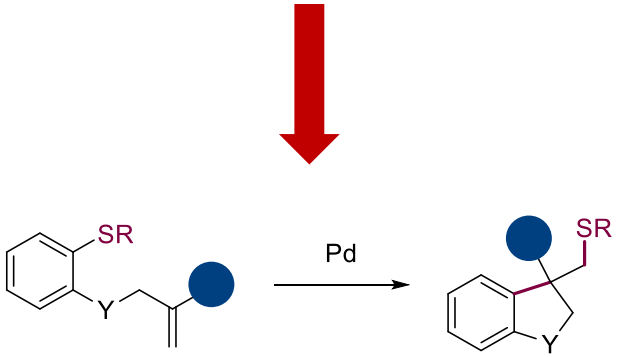
Hiyama, *J. Am. Chem. Soc.* **2008**, *130*,12874–12875
Jacobsen, *J. Am. Chem. Soc.* **2008**, *130*, 12594–12595



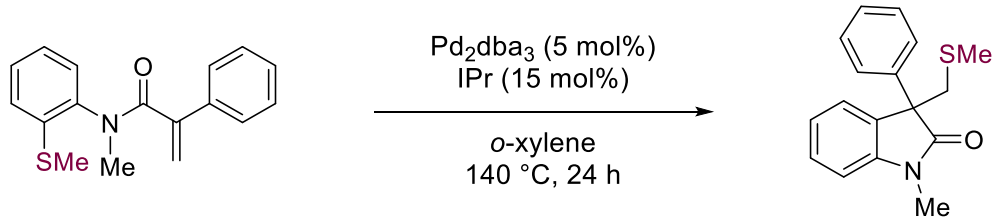
Nakada, *Org. Lett.* **2019**, *21*, 8280–8284

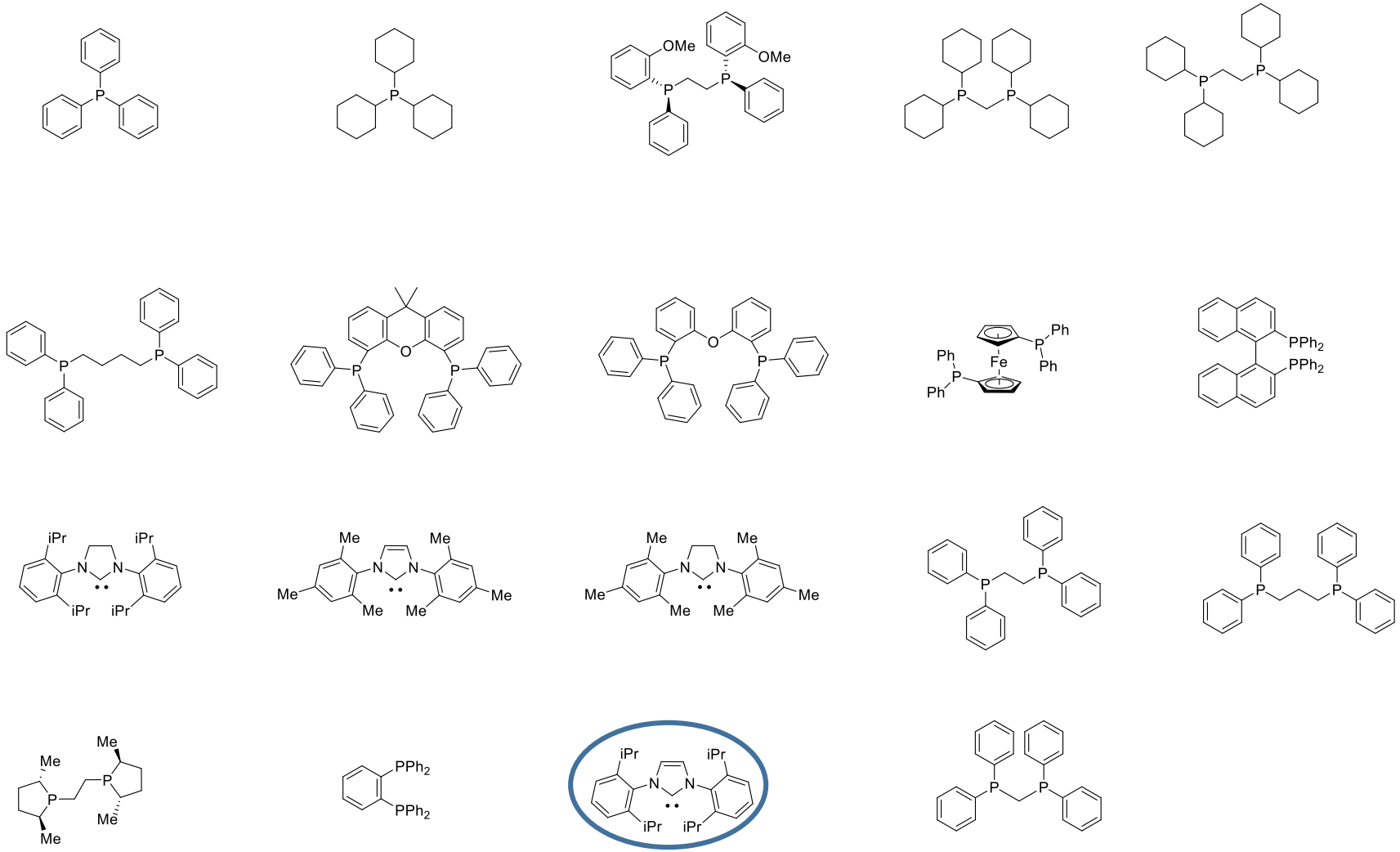


Lautens, *J. Am. Chem. Soc.* **2011**, *133*, 1778–1780
Tong, *J. Am. Chem. Soc.* **2011**, *133*, 6187–6193



Carbothiolation



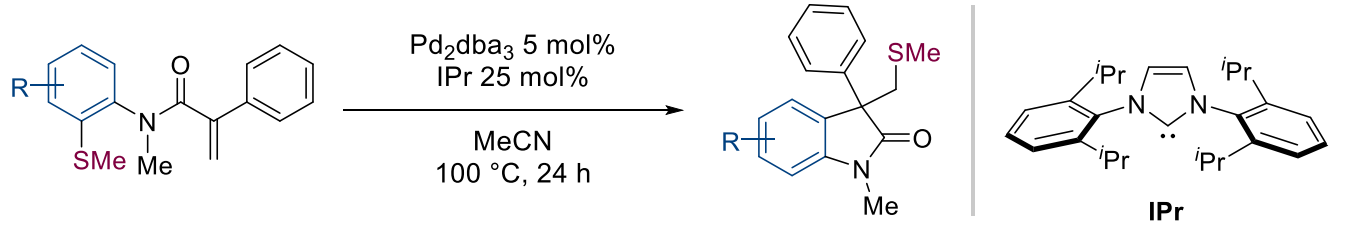


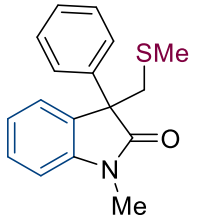
Further screening:

- Cat. Load.
- Pd source
- Solvent
- Temperature

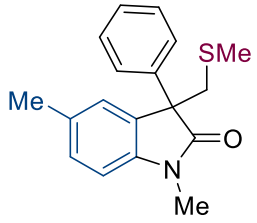
89% yield

Carbothiolation

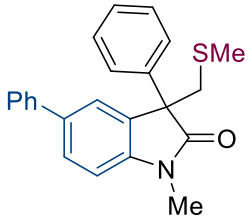




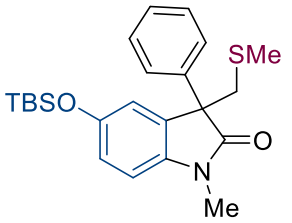
1, 89%
85% **[5 mmol scale]**



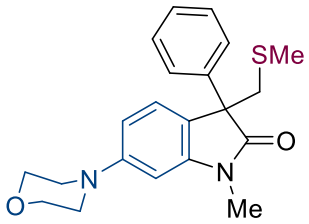
2, 90%[b]



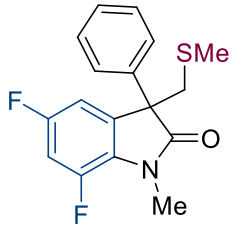
4, 97%



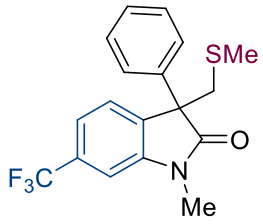
6, 84%



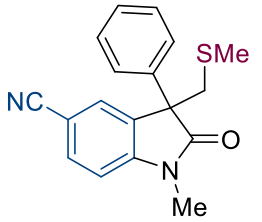
7, 81%



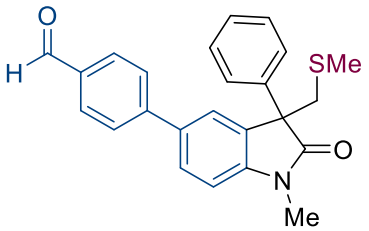
9, 87%



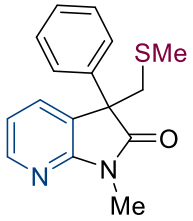
11, 92%



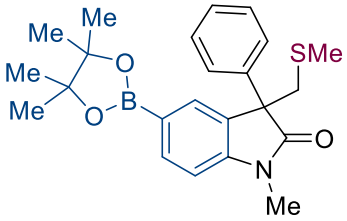
12, 94%



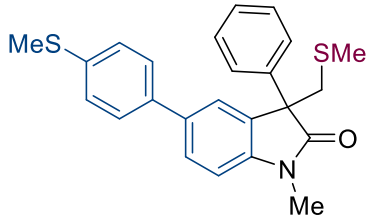
13, 51%



14, 60%

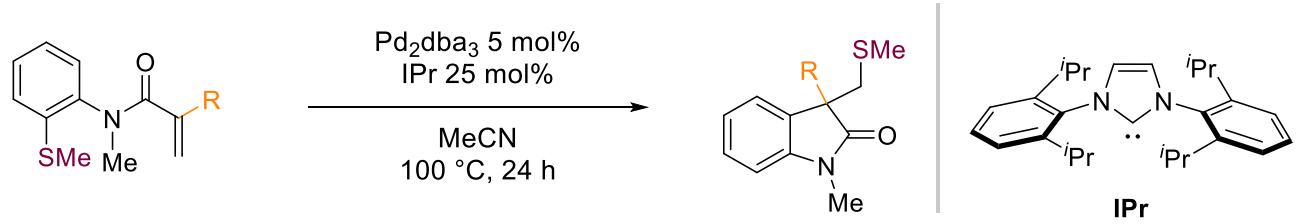


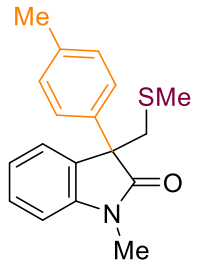
16, 93%



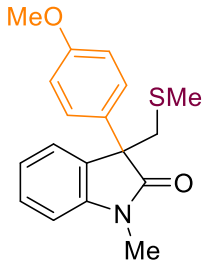
17, 89%

Carbothiolation

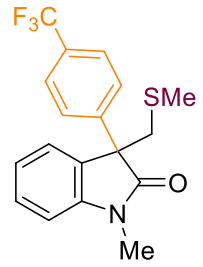




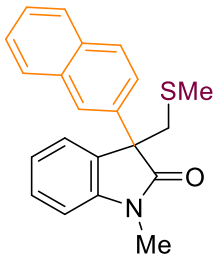
18, 69%



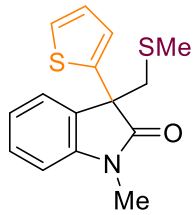
19, 61%



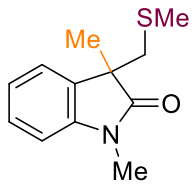
20, 56%



22, 72%

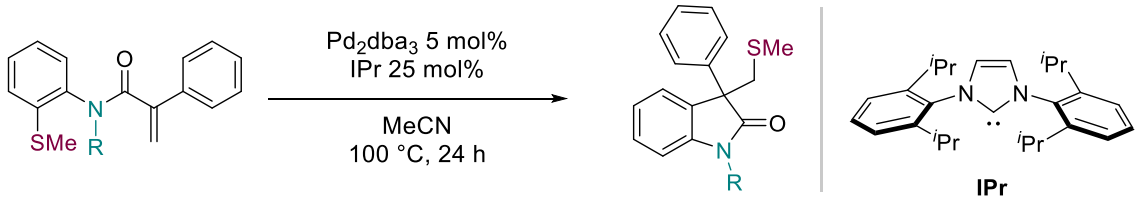


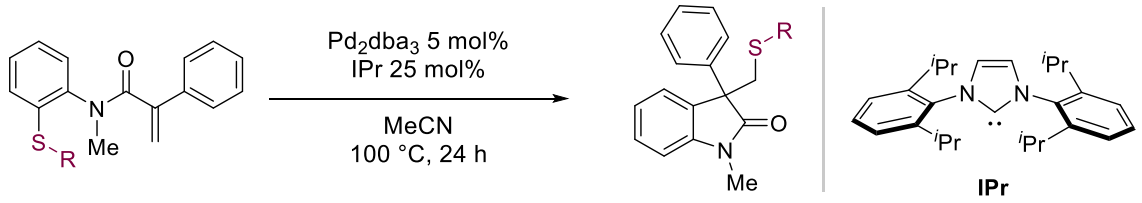
24, 82%

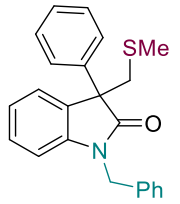


25, 97%

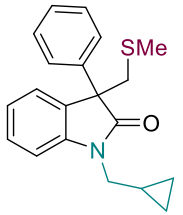
Carbothiolation



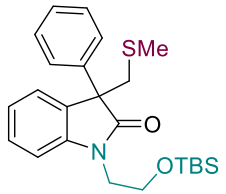




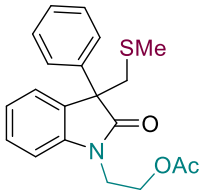
27, 81%



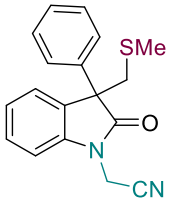
28, 82%



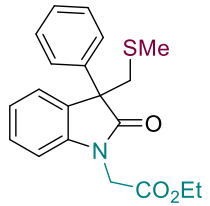
29, 71%



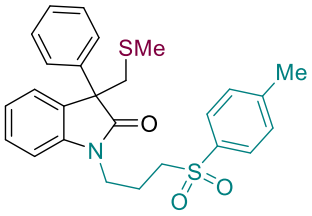
30, 85%



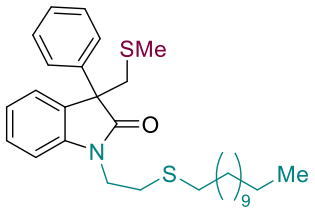
31, 59%



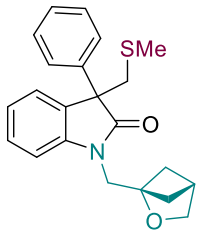
32, 81%



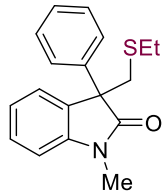
33, 93%



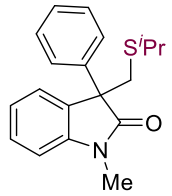
34, 50%



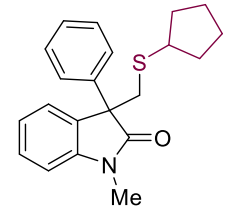
35, 91%



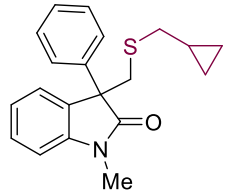
36, 96%



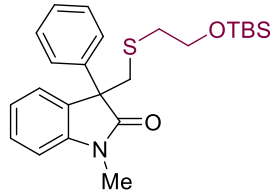
37, 47%



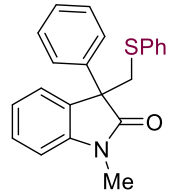
38, 55%



39, 32%

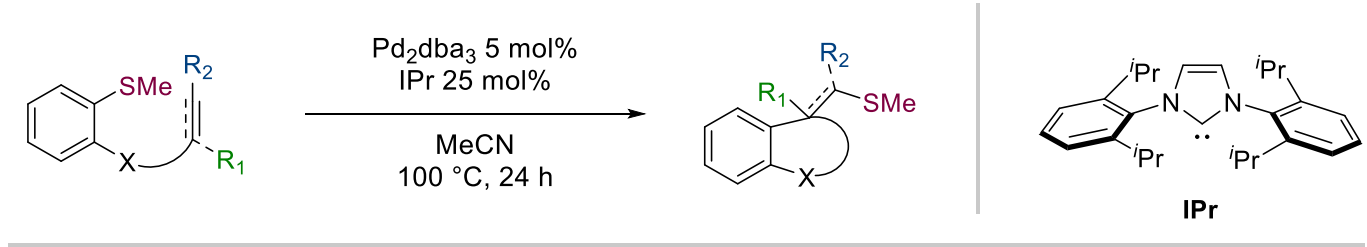


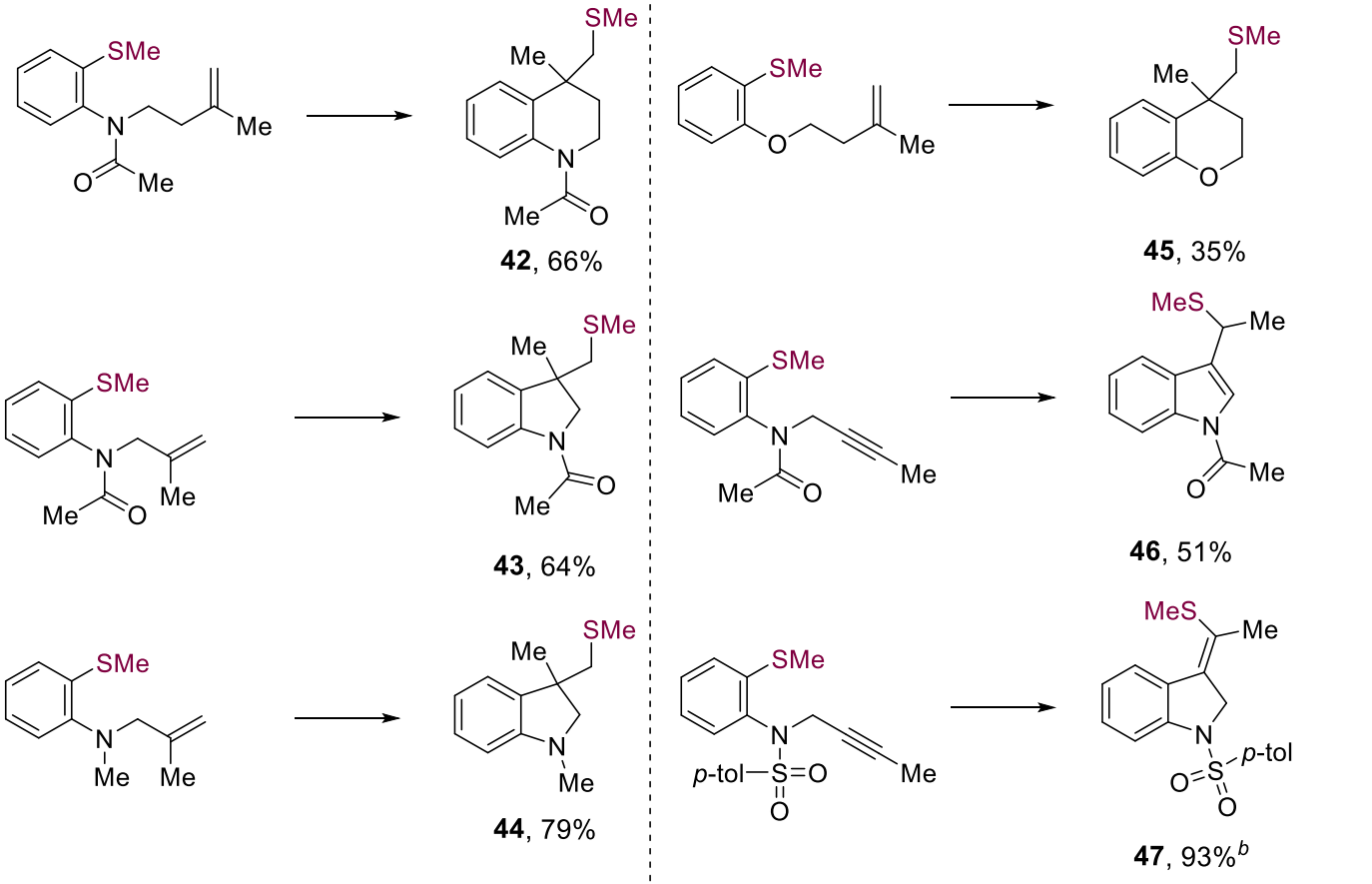
40, quant.

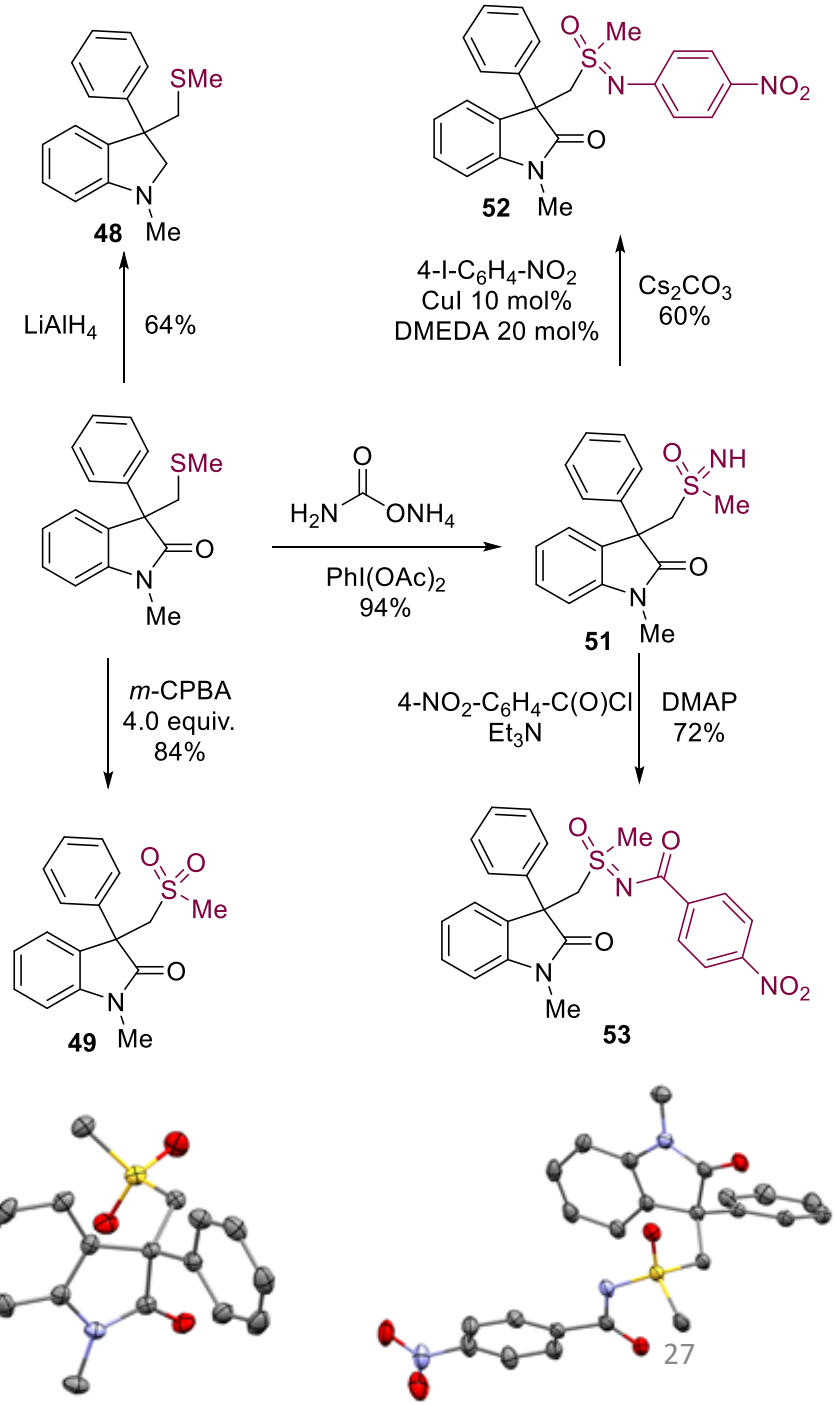


41, 87%

Carbothiolation







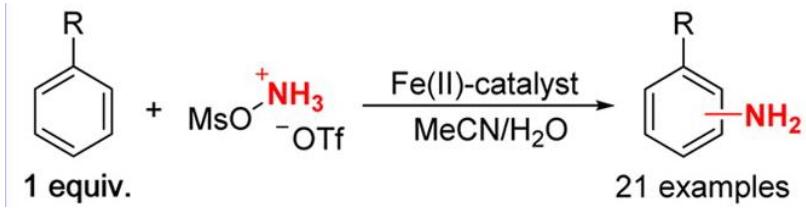
Other projects

RO–NH_2.TfOH

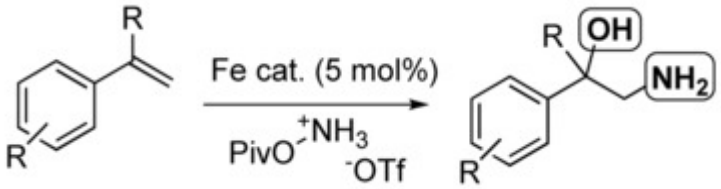
|||

"NH_3^+"

Amination of alkenes

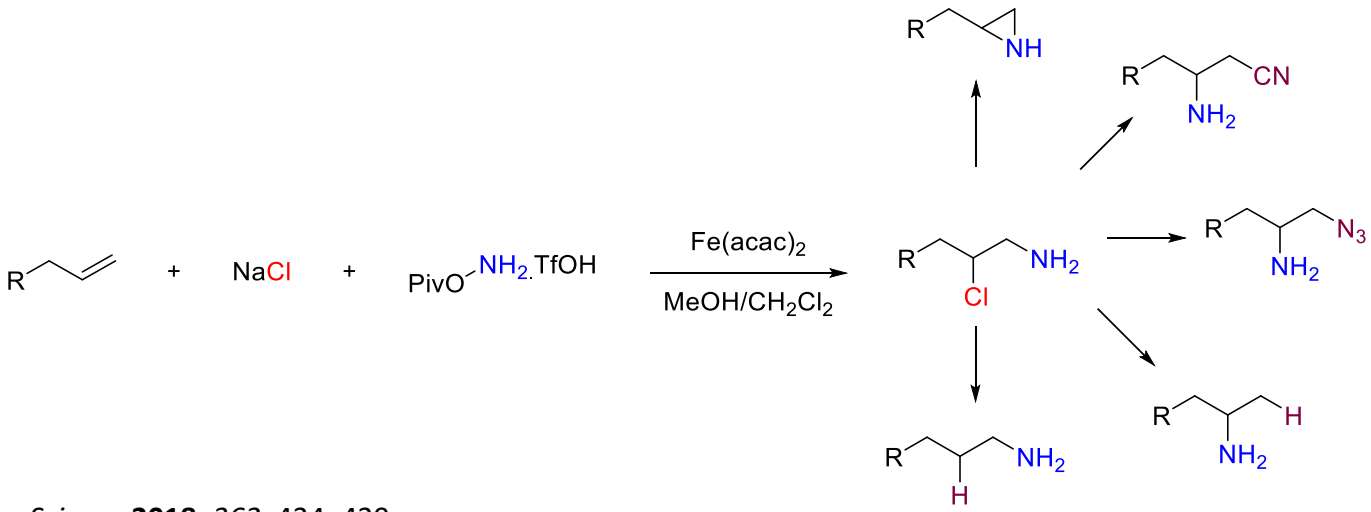


ACS Catal. **2016**, *6*, 8162-8165



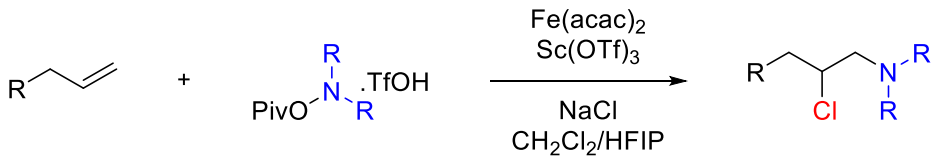
Angew. Chem. Int. Ed. **2016**, *55*, 2248-2251

Chloro-amination of alkenes



Science **2018**, *362*, 434–439

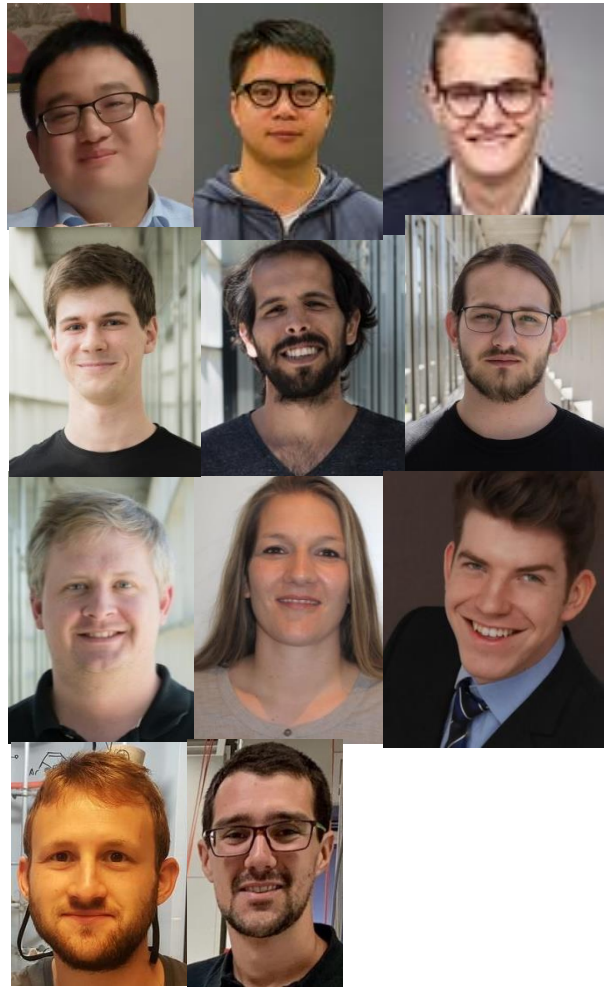
Chloro-alkyl amination of alkenes



Angew. Chem. Int. Ed. **2020**, *59*, 21064–21071

Acknowledgments

Prof. Dr. Bill Morandi



and all former group members.

ETH zürich

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