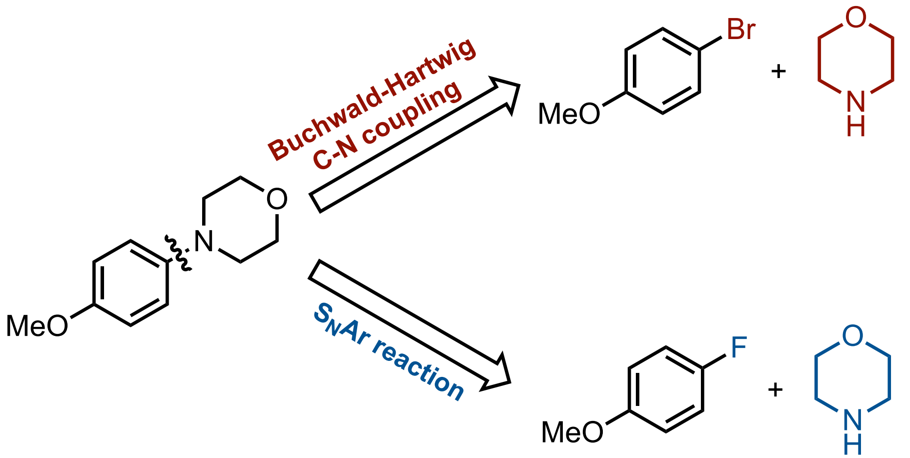
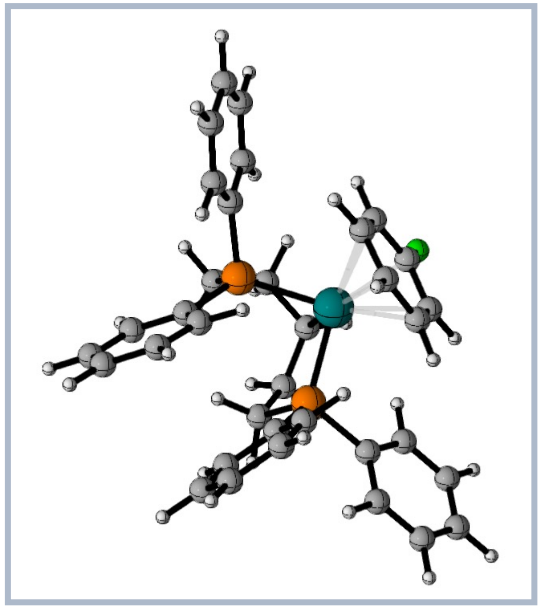
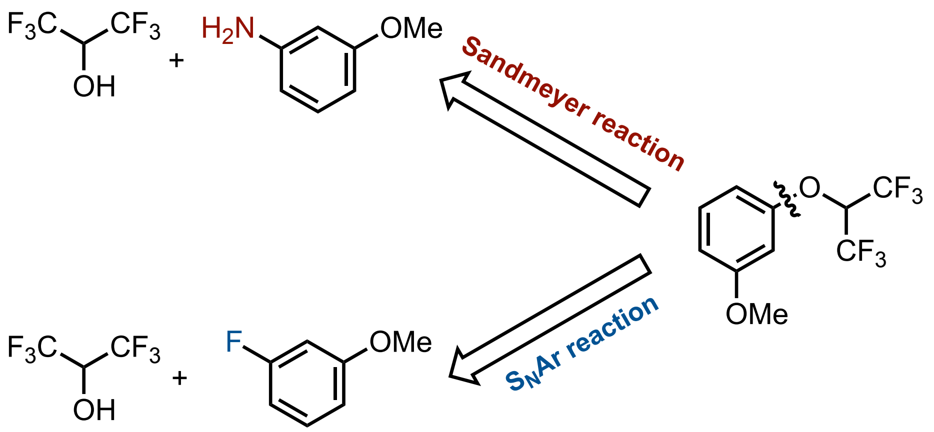
Recent Advances in S_NAr: π-Arene Activation via Lewis π-Acid



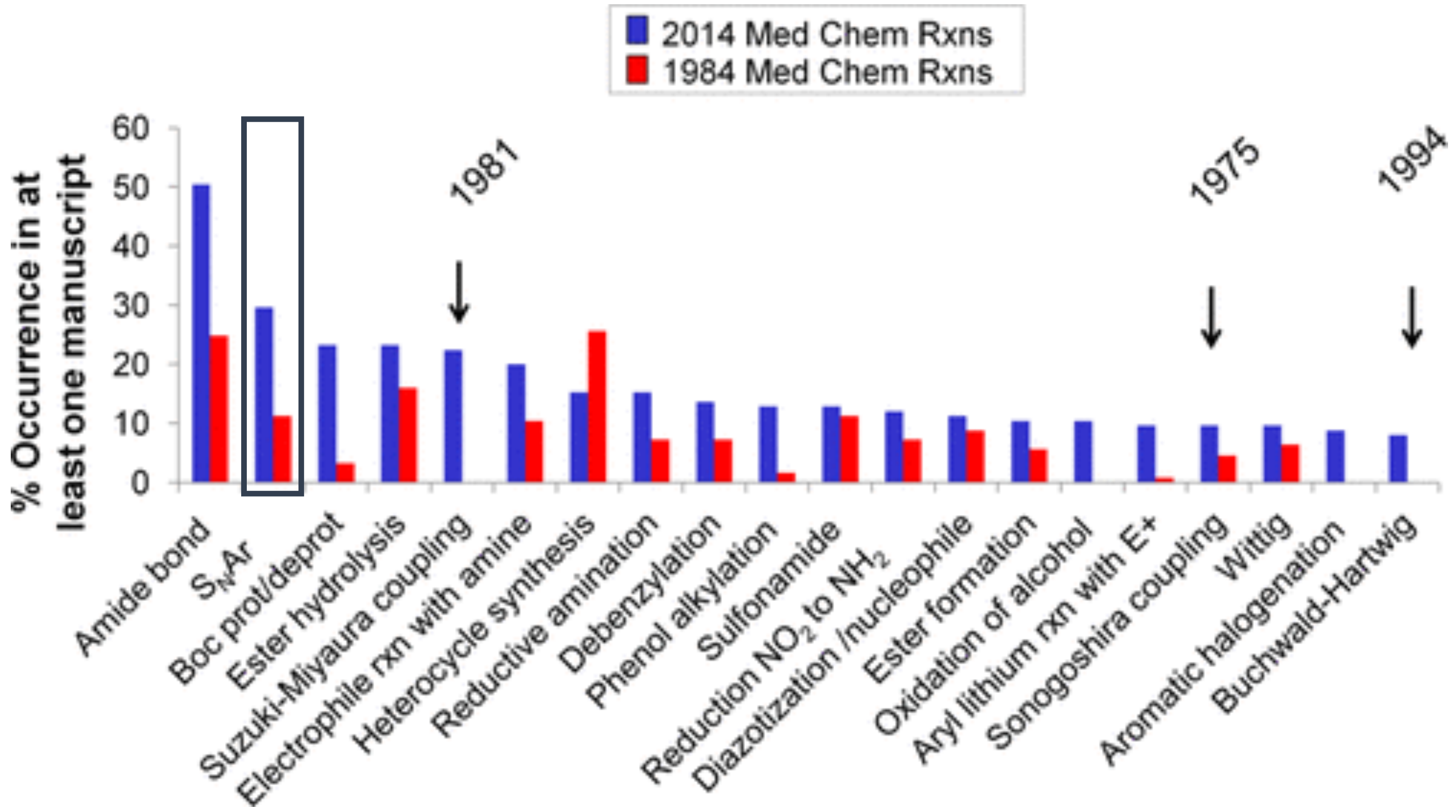




Dongchen Ouyang
Denmark Group Meeting

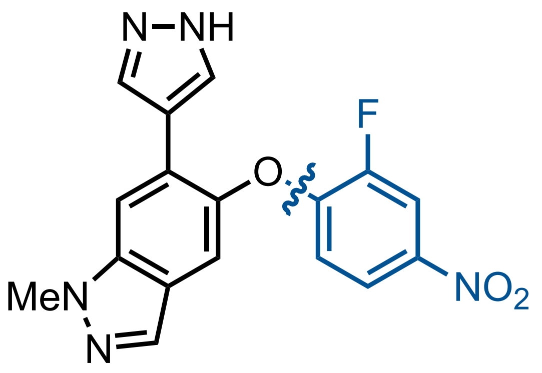
2025-01-28

S_NAR: the Second Most Frequently Used Transformation

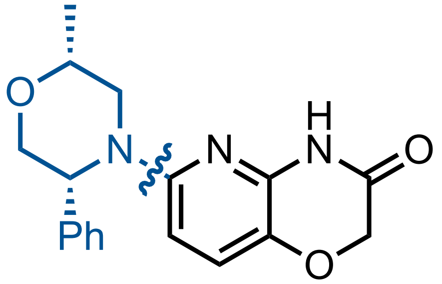


- *High chemoselectivity and robust reaction conditions*
- *Effective C(sp²)–heteroatom bond formation*
- *Functionalization of N-containing electrophilic heterocycles, such as pyridine and pyrimidine*

The primary limitation: the reaction substrates are restricted to electron-deficient arenes



Merestinib fragment

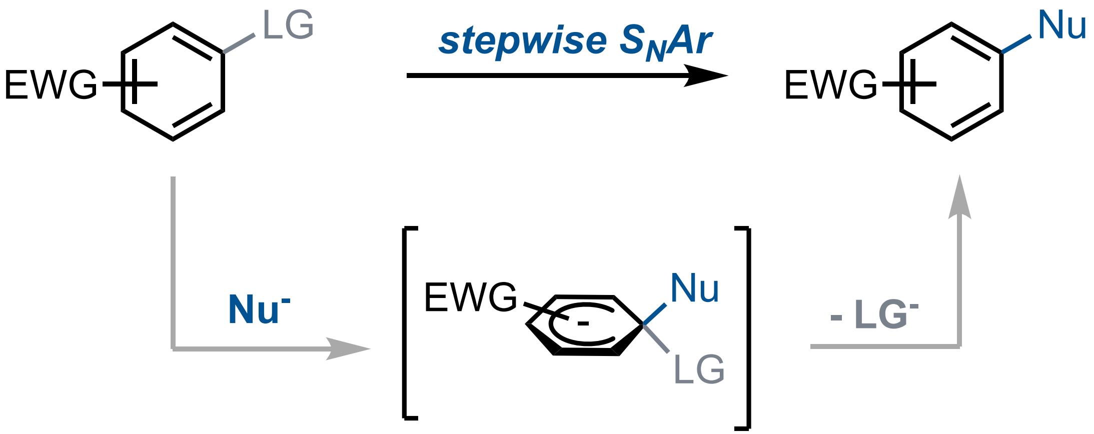


MR antagonist

Lu, Y.; Cole, K. P.; Fennell, J. W.; Maloney, T. D.; Mitchell, D.; Subbiah, R.; Ramadas, B. *Org. Process Res. Dev.* **2018**, *22* (3), 409–419.; Brown, D. G.; Boström, J. *J. Med. Chem.* **2016**, *59* (10), 4443–4458.; Sammons, M.; Jennings, S. M.; Herr, M.; Hulford, C. A.; Wei, L.; Hallissey, J. F.; Kiser, E. J.; Wright, S. W.; *Org. Process Res. Dev.* **2013**, *17* (6), 934–939.

S_NAR Mechanism: Stepwise VS Concerted

Traditional S_NAr Stepwise Mechanism

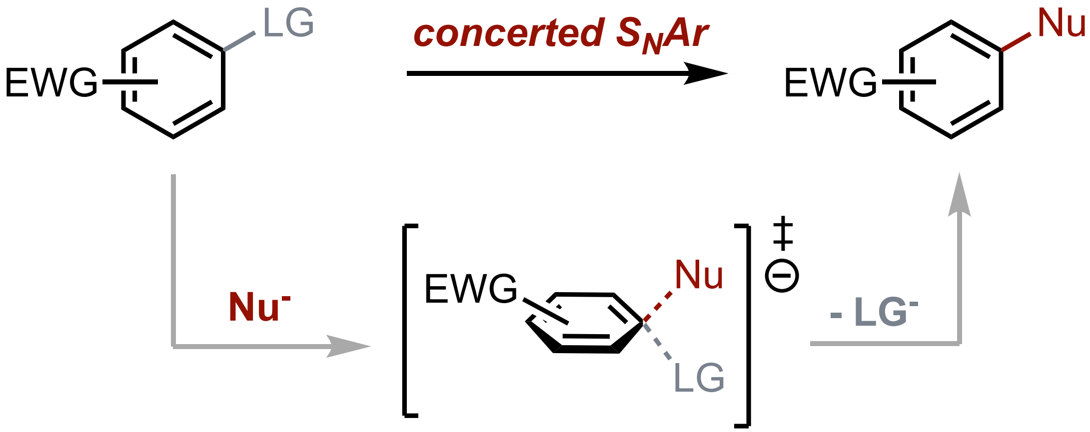


Meisenheimer interme

addition-elimination mechanism

- *Nucleophile adds to the aromatic ring by bonding interaction with π* orbitals, forming a anionic Meisenheimer intermediate (RDS).*
- *Reactivity of halides: ArF > ArCl > ArBr > ArI, primarily due to the polar effect*

Concerted S_NAr Mechanism



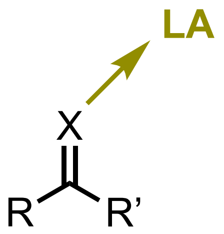
transition state

- *Meisenheimer intermediate cannot be sufficiently stabilized by electron-withdrawing groups (EWGs)*
- *Nucleophile's attack and the departure of the leaving group occur simultaneously*
- *cS_NAr is not able to fully address the challenge of insufficient substrate reactivity.*

Rohrbach, S.; Smith, A. J.; Pang, J. H.; Poole, D. L.; Tuttle, T.; Chiba, S.; Murphy, J. A. *Angew Chem Int Ed* **2019**, *58* (46), 16368–16388.; Carey, F. A.; Sundberg, R. J. *Advanced Organic Chemistry: Part A: Structure and Mechanisms*; Eds.; Springer US: Boston, MA, 2007; pp 771–831.

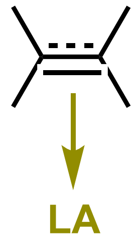
Lewis Acid: Unsaturated Bond Activation

Lewis acid activation



LA : $AlCl_3$, …

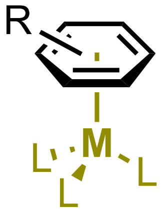
carbonyls
imines



LA: Pt(II), Au(I), …

alkenes
alkynes

enhance electrophilicity

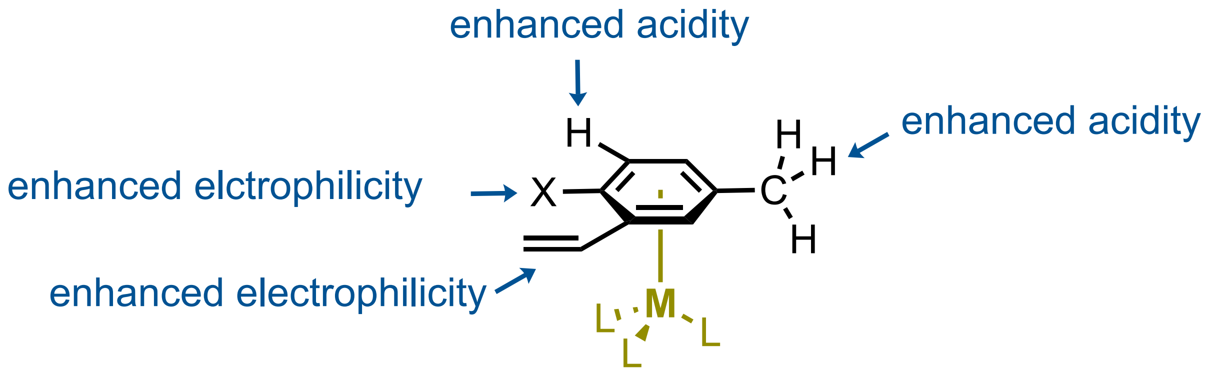


arenophilic π-acid

η^6-arene complexes

ML_n: $Cr(CO)_3$, $[Mn(CO)_3]^+$, $[Cp^*Ru]^+$, $[Cp^*Rh]^{2+}$, …

arenophilic π-acid activation



- *Activated C(sp²)–H bonds and benzylic C–H bonds: increased acidity*
- *Activated conjugated functional groups: styrene-related reaction*
- *Activated aromatic rings: dearomatization and S_NAr reaction*

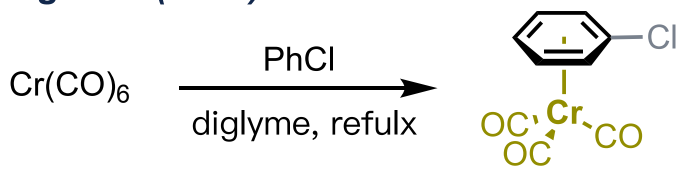
Williams, L. J.; Bhonoah, Y.; Wilkinson, L. A.; Walton, J. W. *Chemistry A European J* **2021**, *27* (11), 3650–3660.; Walton, J. W.; Wilkinson, L. A. π-Coordinated Arene Metal Complexes and Catalysis. In *Organometallic Chemistry*; Patmore, N. J., Elliott, P. I. P., Eds.; Royal Society of Chemistry: Cambridge, 2018; Vol. 42, pp 125–171; Takemoto, S.; Shibata, E.; Nakajima, M.; Yumoto, Y.; Shimamoto, M.; Matsuzaka, H. *J. Am. Chem. Soc.* **2016**, *138* (45), 14836–14839; Utsunomiya, M.; Hartwig, J. F. *J. Am. Chem. Soc.* **2004**, *126* (9), 2702–2703. Pigge, F. C.; Coniglio, J. J.; Fang, S. *Organometallics* **2002**, *21* (21), 4505–4512.

Outline

- **Historical perspective into Lewis π-Acid Activated S_NAr Reactions**
- **Lewis π-Acid Catalyzed S_NAr Reactions of Aryl Halides**
- **Lewis π-Acid Catalyzed S_NAr Reactions of Phenol**
- **Summary and Perspective**

Historical perspective into Lewis π-Acid Activated S_NAr Reactions

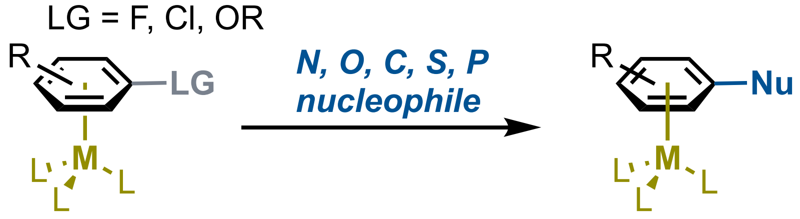
Whiting et al.(1959)



- *First example of Lewis π-acid activated S_NAr reactions*
- *Coordinated PhCl could be converted into the anisole complex*

This discovery marked the beginning of research into Lewis π-acid activated S_NAr reactions.

1980s–2000s



ML_n: $Cr(CO)_3$, $[Mn(CO)_3]^+$, $[CpFe]^+$, $[Cp^*Ru]^+$, $[Cp^*Rh]^{2+}$, …

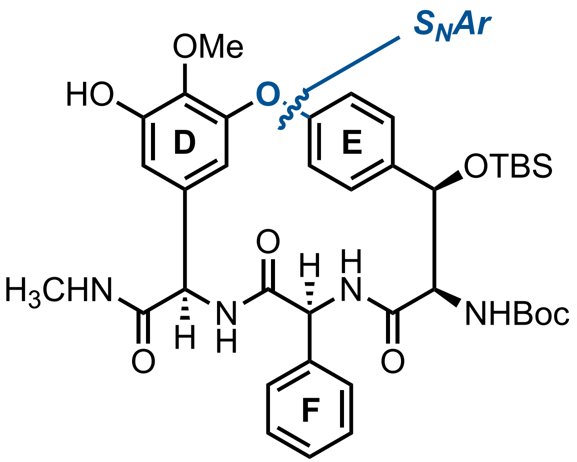
Diverse conditions

Metals: Fe, Ru, Rh, Cr, and Mn

Nucleophiles: N, O, C, P, and S

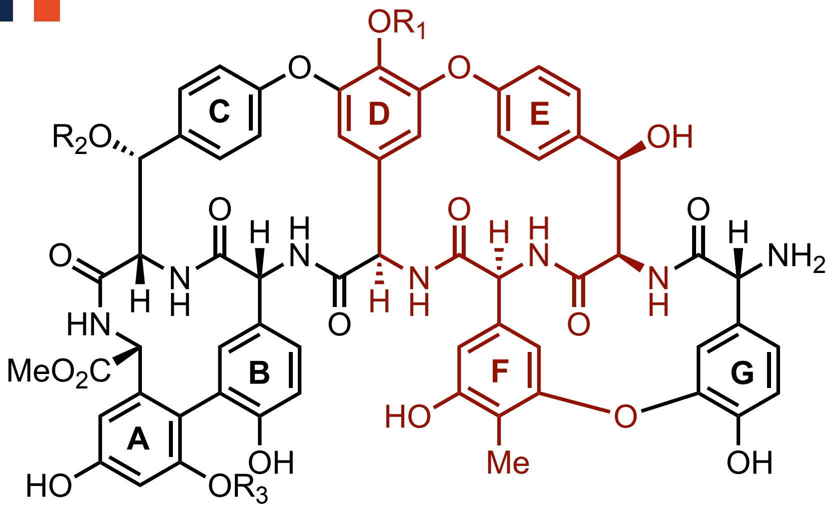
LG: F, Cl and OR

Substrates: electron-neutral and rich



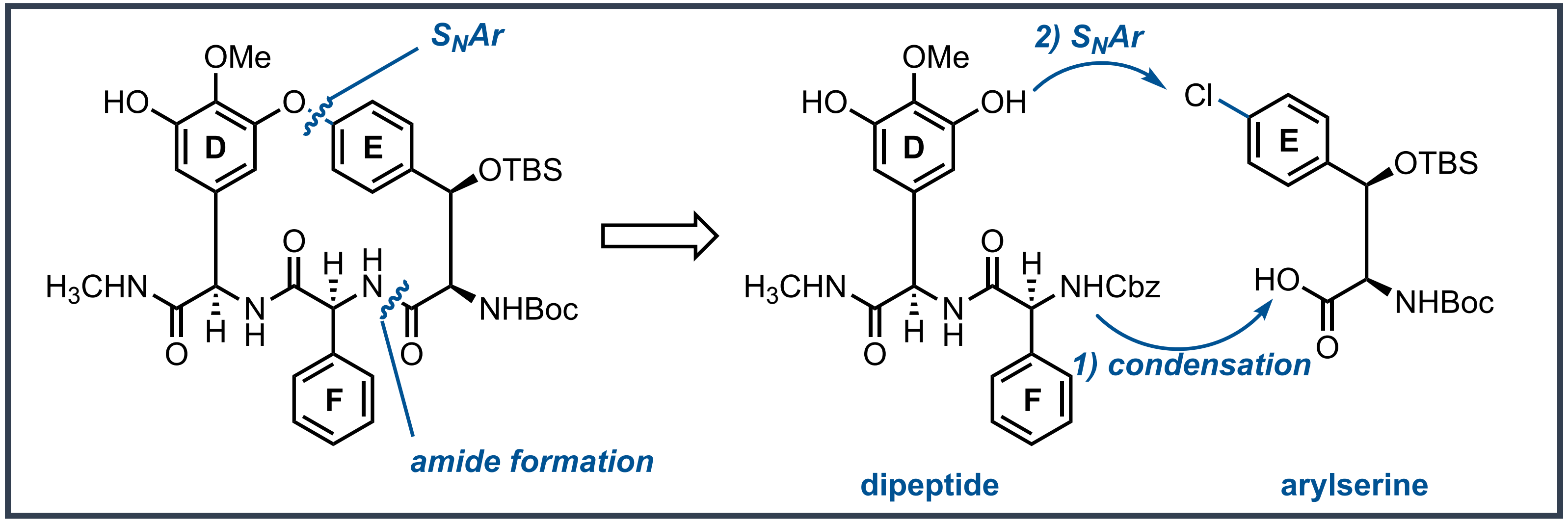
DEF ring system of ristocetin A

Synthetic Application of Ru-activated S_NAr Reaction

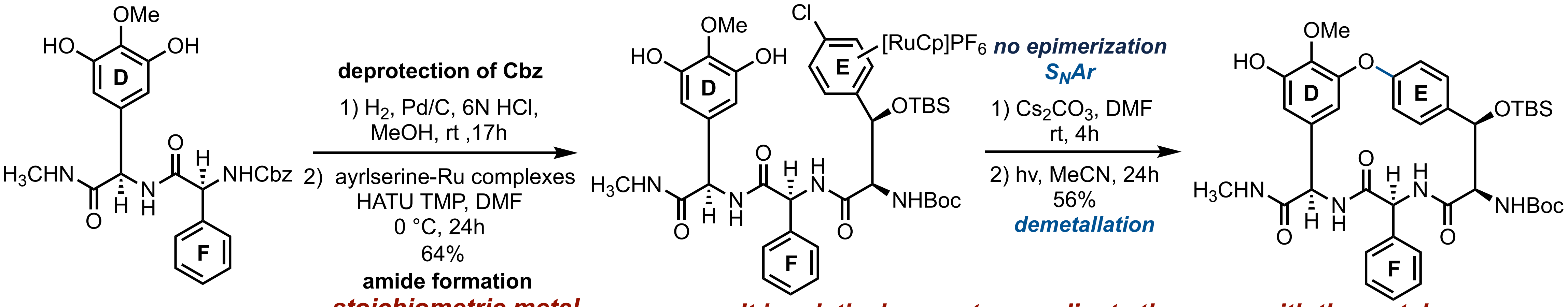


R_1, R_2, R_3 = sugars

ristocetin A
glycopeptide antibiotics



***Synthetic challenge**: base-sensitive amino acid residues* are prone to epimerization



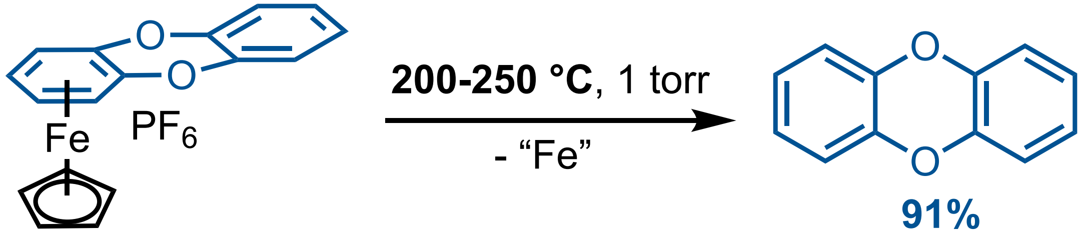
It is relatively easy to coordinate the arene with the metal, removing the metal afterwards is far more challenging

Pearson, A. J.; Heo, J.-N. *Tetrahedron Letters* **2000**, *41* (32), 5991–5996.

Four Strategies for Achieving Demetallation

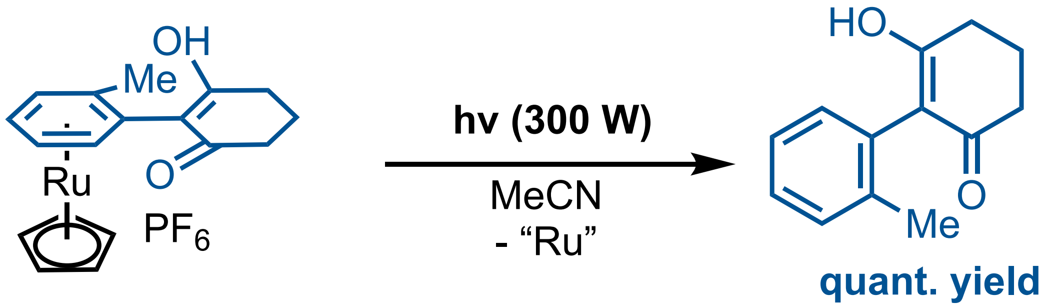
How can the reaction be rendered catalytic? How can the metal complex be effectively removed?

pyrolysis



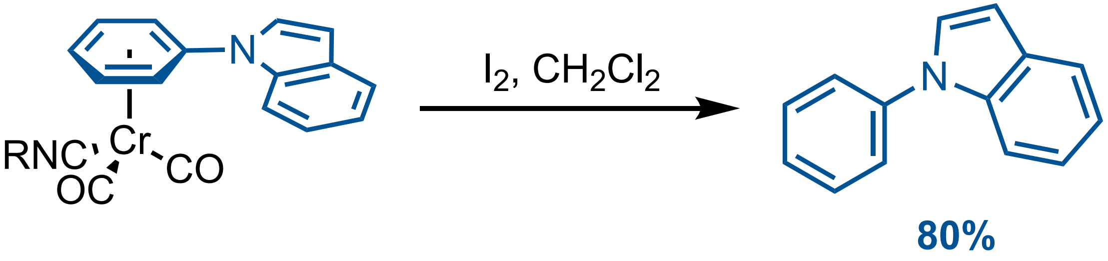
iron removal via pyrolytic sublimation

photolysis



Both pyrolysis and photolysis involve harsh conditions, significantly limiting their synthetic applications.

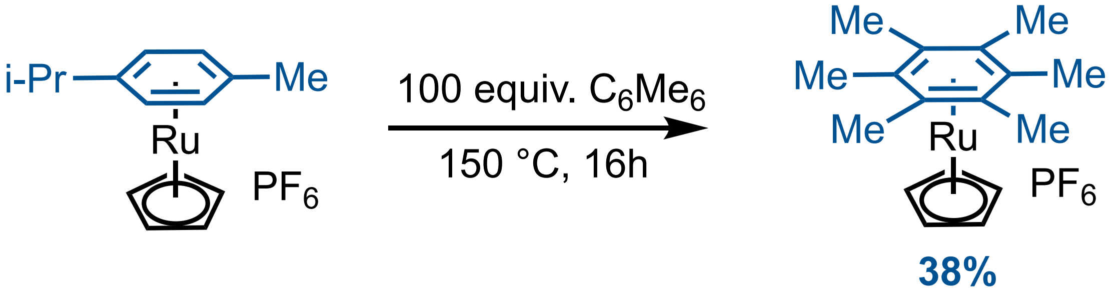
oxidation



other commonly used oxidants: CAN, DDQ, NBS

ligand exchange

demetallation without destroying scaffold of metal complexes



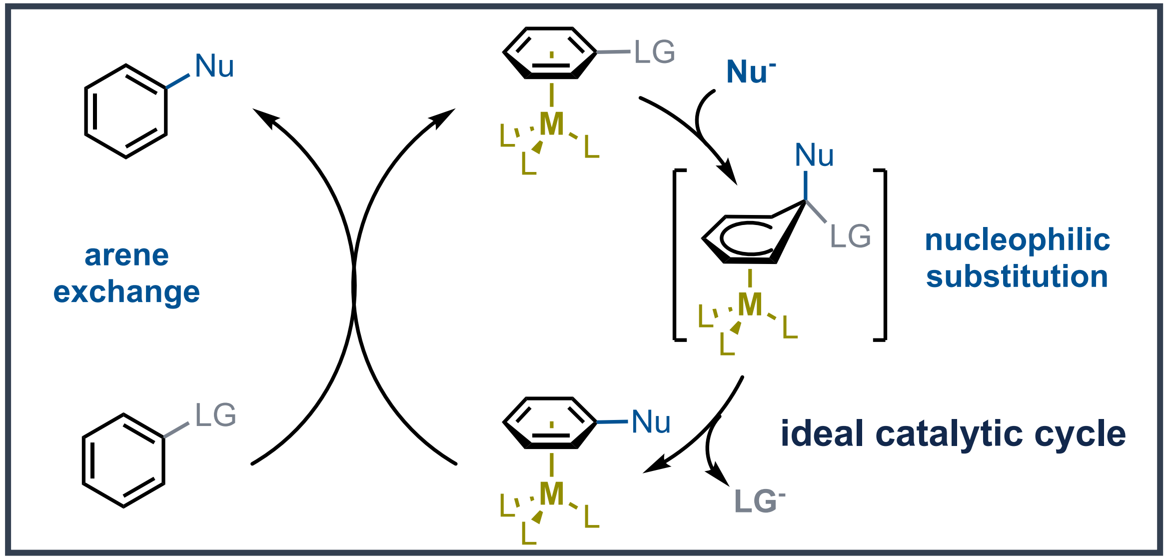
an ideal concept, though too slow in practice

Maiorana, S.; Baldoli, C.; Licandro, E.; Casiraghi, L.; De Magistris, E.; Paio, A.; Provera, S.; Seneci, P. *Tetrahedron Letters* **2000**, *41* (37), 7271–7275; Walton, J. W.; Williams, J. M. J. *Chem. Commun.* **2015**, *51* (14), 2786–2789.; Akana-Schneider, B.; Guo, Y.; Parnitzke, B.; Derosa, J.; *Dalton Trans.* **2024**, *53* (47), 18819–18827.; Sutherland, R. G.; Piórko, A.; Gill, U. S.; Lee, C. C. *Journal of Heterocyclic Chem* **1982**, *19* (4), 801–803.

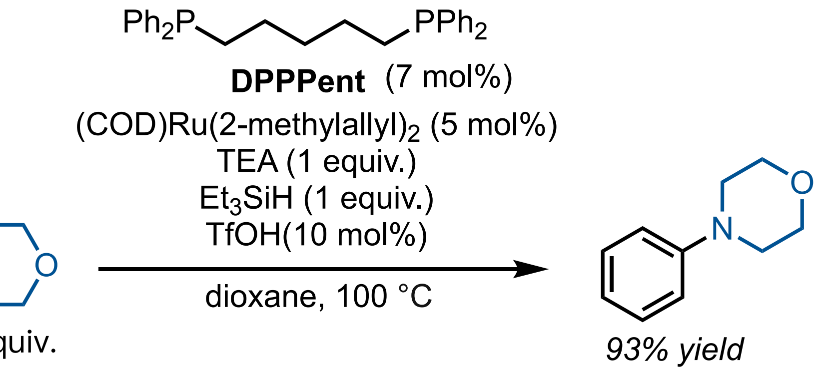
Outline

- Historical perspective into Lewis π-Acid Activated S_NAr Reactions
- **Lewis π-Acid Catalyzed S_NAr Reactions of Aryl Halides**
- Lewis π-Acid Catalyzed S_NAr Reactions of Phenol
- Summary and Perspective

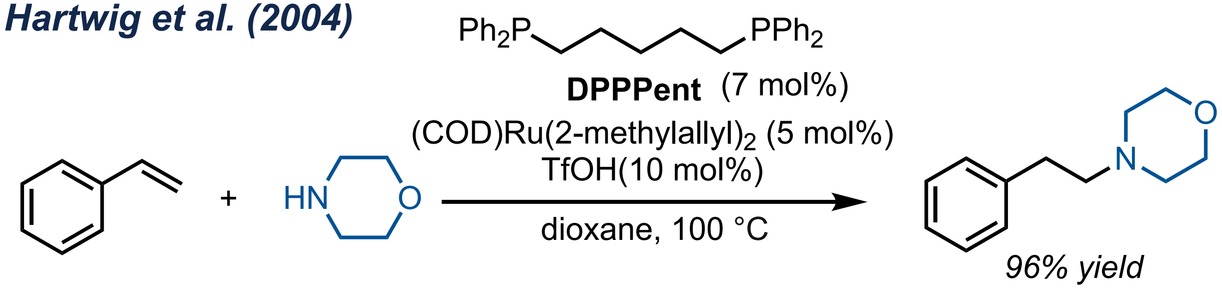
Lewis π-Acid Catalyzed S_NAr Reactions of Aryl Fluorides



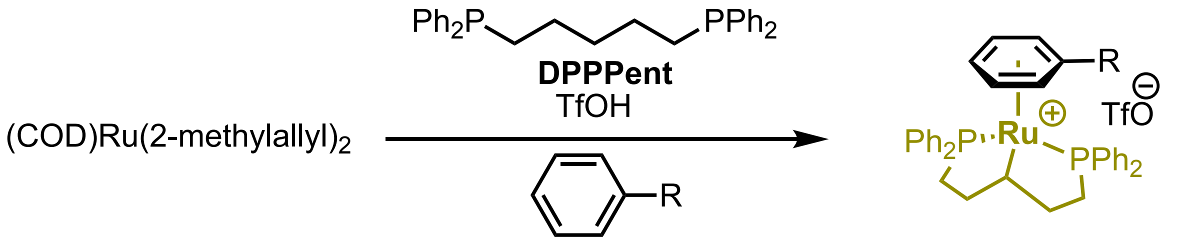
Shibata et al. (2010)
Schley et al. (2020)



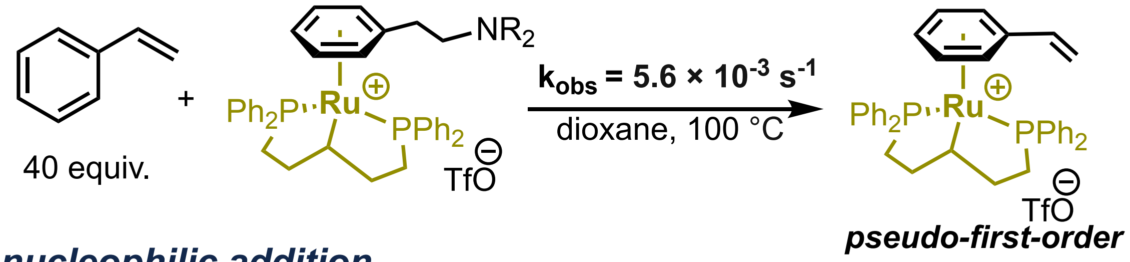
Hartwig et al. (2004)



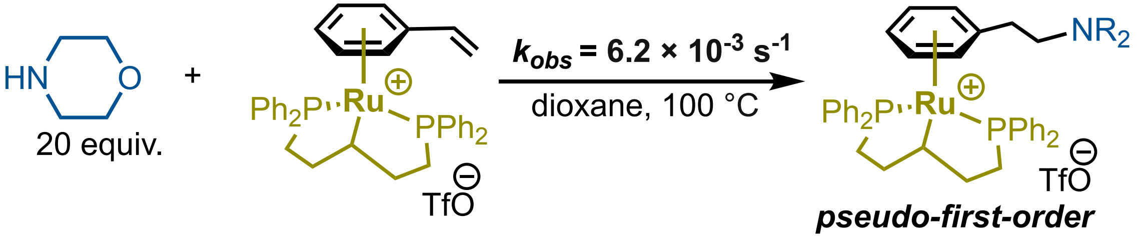
catalyst formation



arene exchange



nucleophilic addition

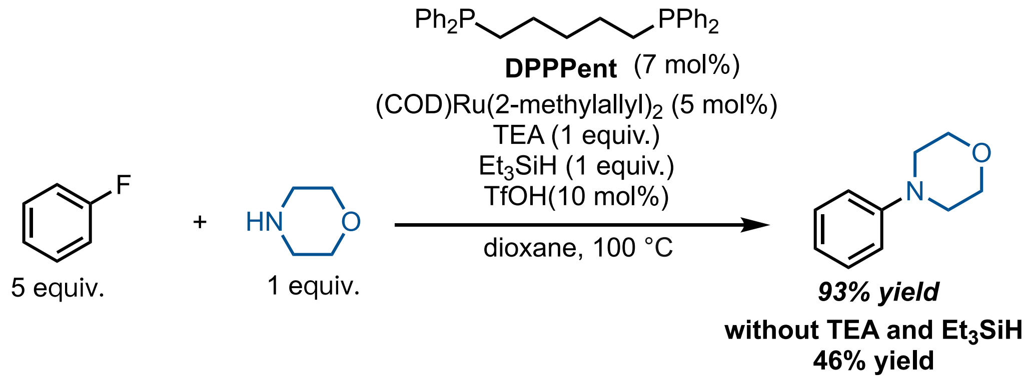


The rate of arene exchange is comparable to that of nucleophilic addition at 100 °C

Arene exchange is also the key step in S_NAr reaction

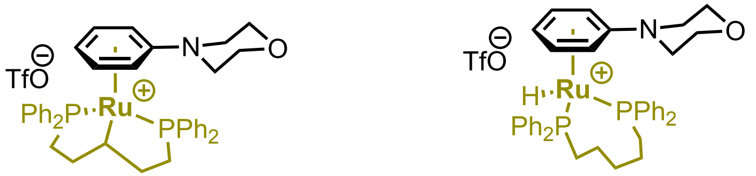
Otsuka, M.; Endo, K.; Shibata, T. *Chem. Commun.* **2009**, *46* (2), 336–338.
Takaya, J.; Hartwig, J. F. *J. Am. Chem. Soc.* **2005**, *127*(16), 5756–5757.

Lewis π-Acid Catalyzed S_NAr Reactions of Aryl Fluorides

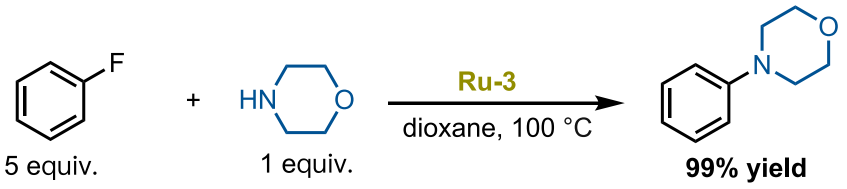


***with additives**: two intermediates were observed by ^31^P NMR*

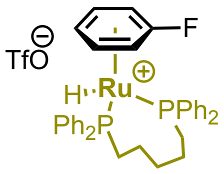
***without additives:** only one intermediate was observed by ^31^P NMR*



Ru-2 **Ru-3**

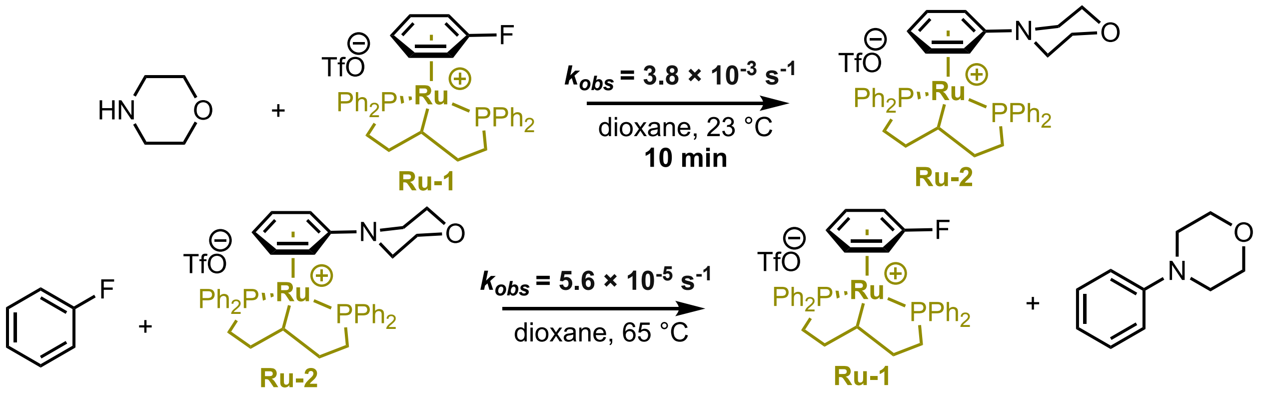


Ru-3 is kinetically competent under reaction condition
Ru-3 is the key intermediate

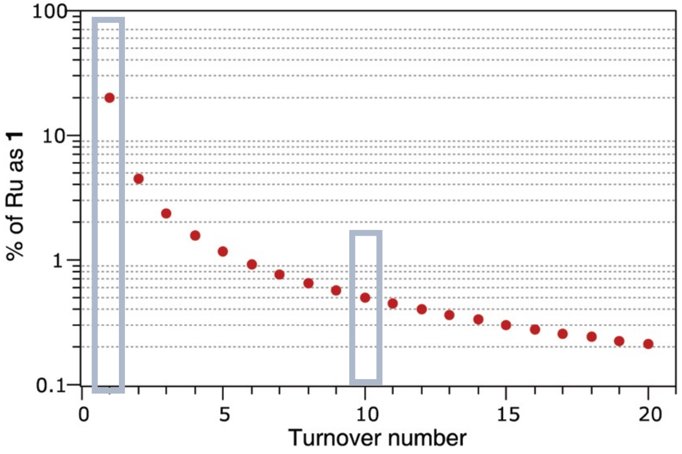


Ru-4
not formed

kinetic studies



thermodynamic studies ***K_{eq} = 1/2000, 100 °C***



1 turnover, Ru-1:Ru-2 = 1:4
10 turnovers, Ru-1:Ru-2 > 1:200

***Thermodynamic**: the product binds with roughly 2000 times greater affinity than the substrate leads to strong product inhibition*

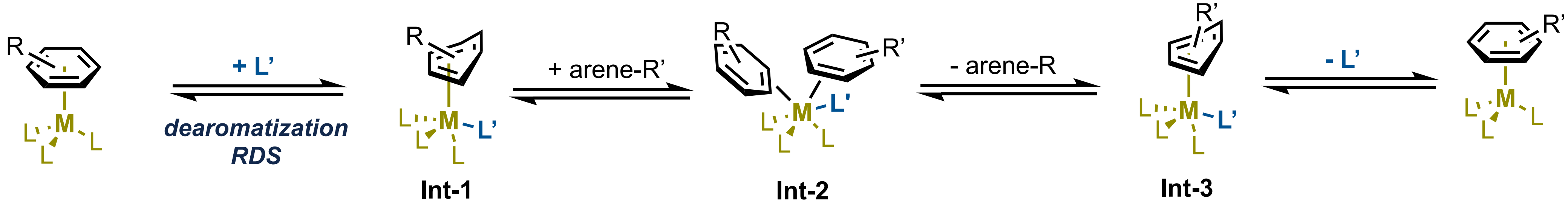
***Kinetic:** High temperature of this reaction is required by the kinetics of arene exchange instead of nucleophilic substitution*

Otsuka, M.; Endo, K.; Shibata, T. *Chem. Commun.* **2009**, *46* (2), 336–338.
Mueller, B. R. J.; Schley, N. D. *Dalton Trans.* **2020**, *49* (29), 10114–10119.

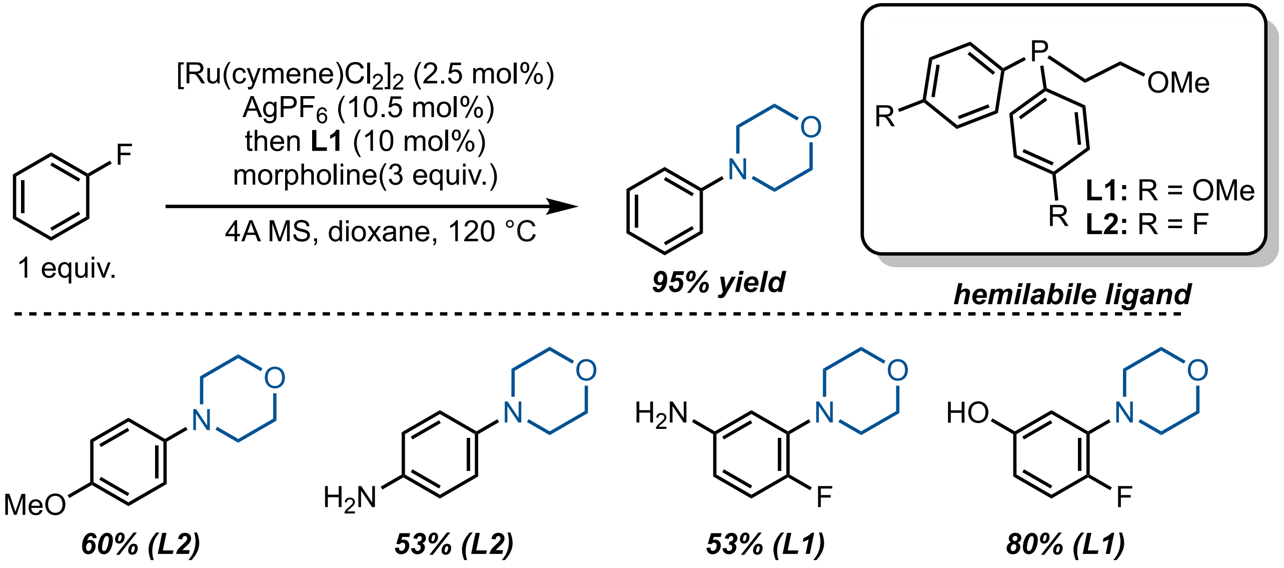
Mechanisms of Arene Exchange

The mechanism of arene exchange

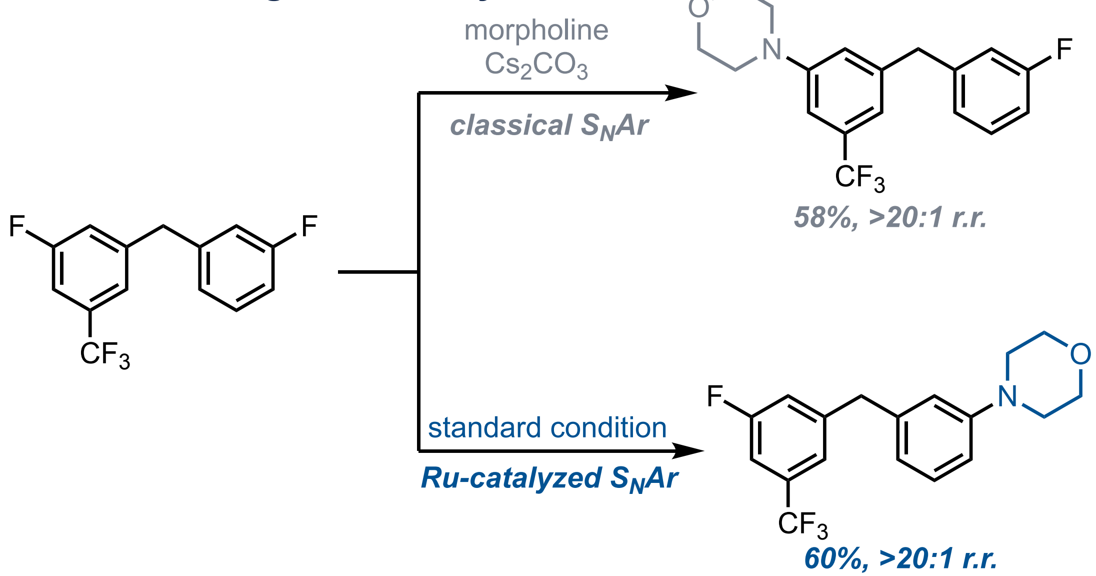
well-established for [(η^6-arene)$Cr(CO)_3$] complexes



Traylor, T. G.; Stewart, K.; Goldberg, M. . *J. Am. Chem. Soc.* **1984**, *106* (16), 4445–4454.



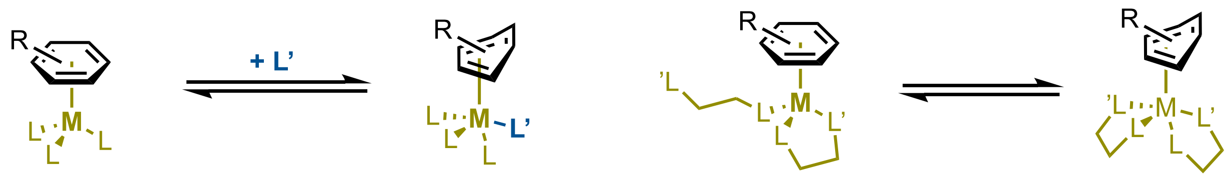
reversed regioselectivity



Kang, Q.-K.; Lin, Y.; Li, Y.; Shi, H. *J. Am. Chem. Soc.* **2020**, *142* (8), 3706–3711.

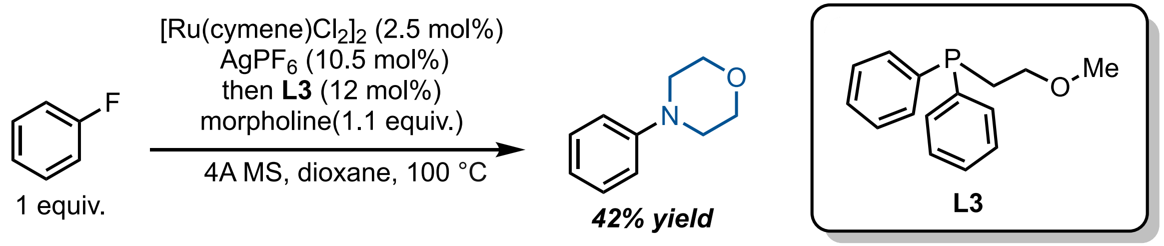
Ru(II)-Catalyzed Amination of Aryl Fluorides

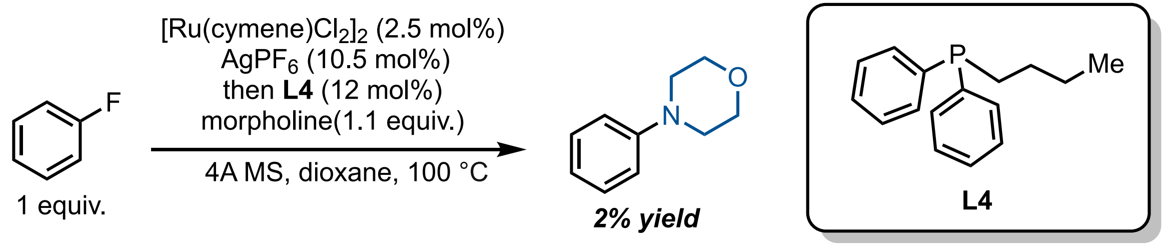
intermolecular **intramolecular**



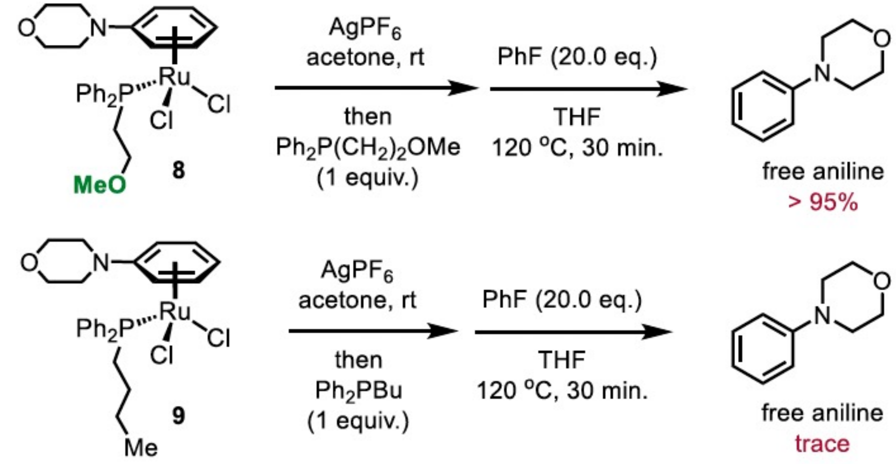
The side chain group L' temporarily coordinates with the transition metal

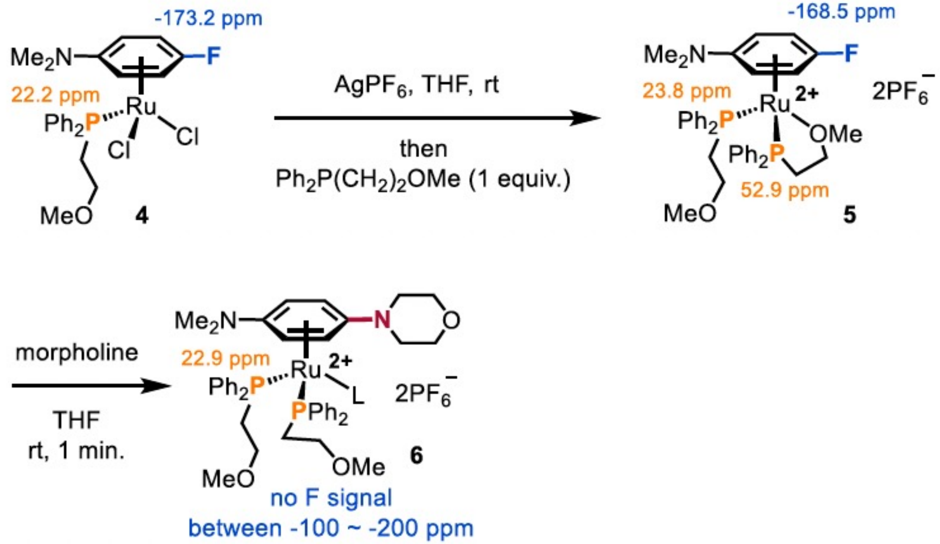
control experiment





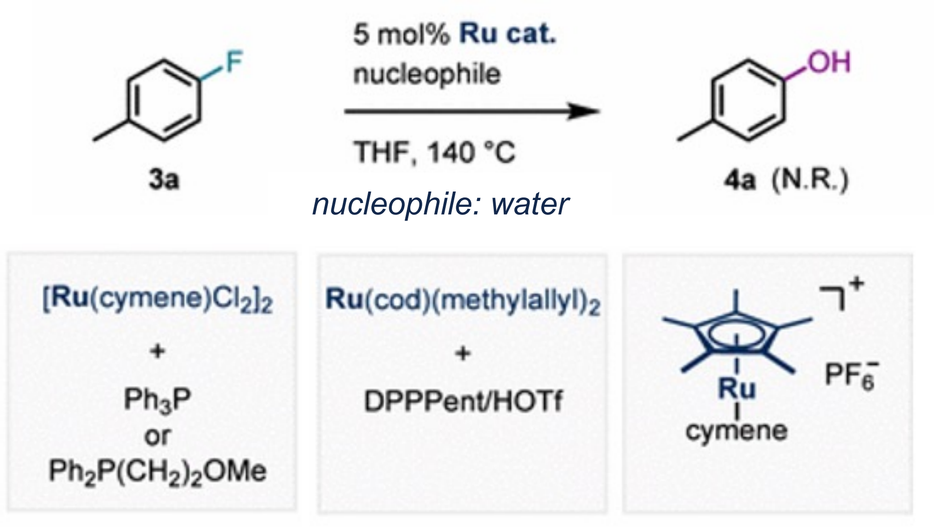
arene dissociation test

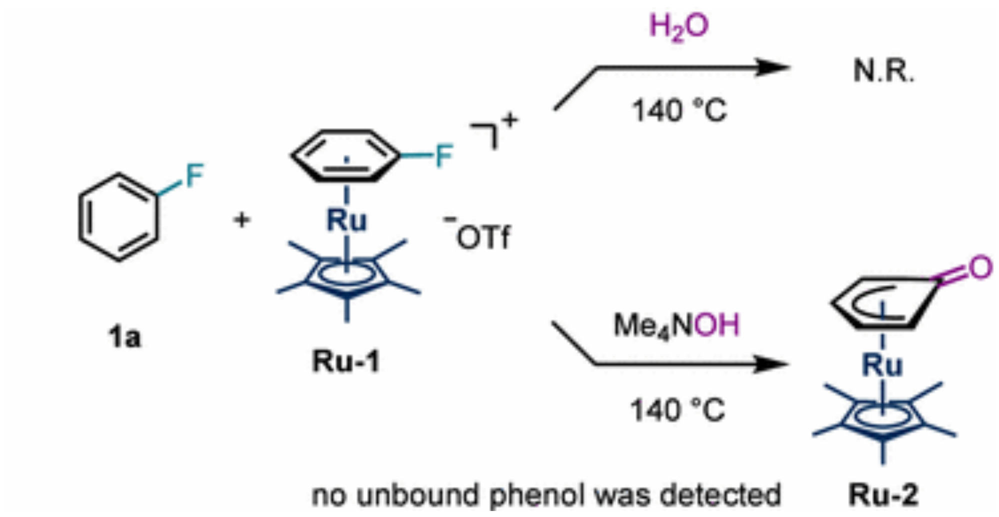




Kang, Q.-K.; Lin, Y.; Li, Y.; Shi, H. *J. Am. Chem. Soc.* **2020**, *142* (8), 3706–3711.

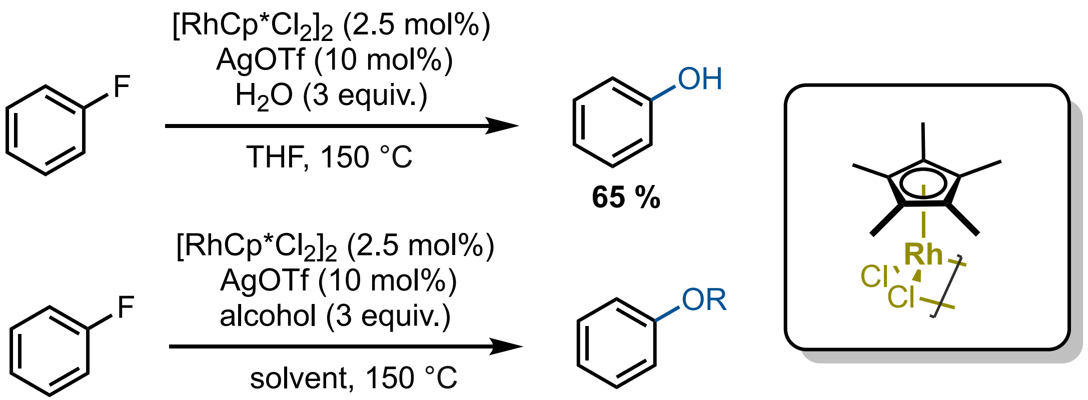
Rh(III)-Catalyzed Hyroxylation of Aryl Halides

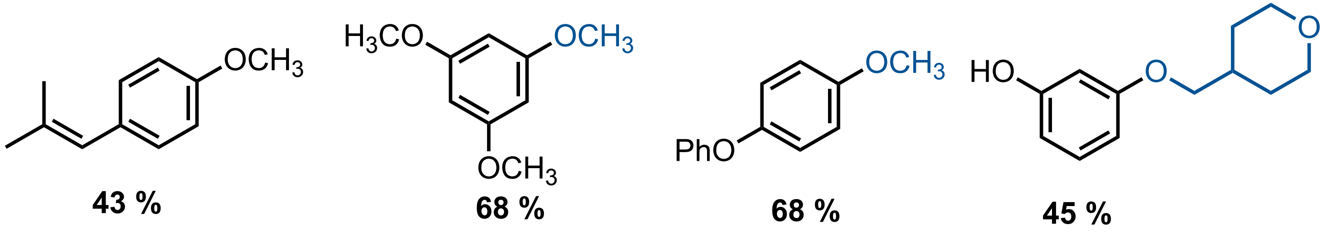




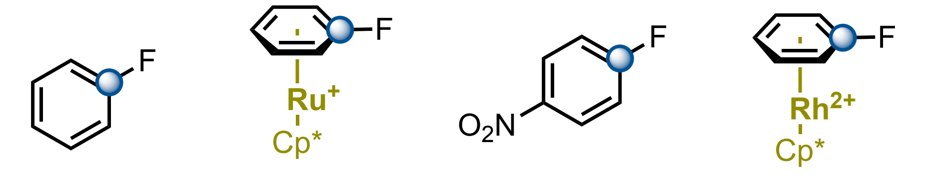
η⁵-phenoxo complex is resistant to arene exchange under basic condition

Stronger electron-withdrawing effects are needed to accommodate weak nucleophiles





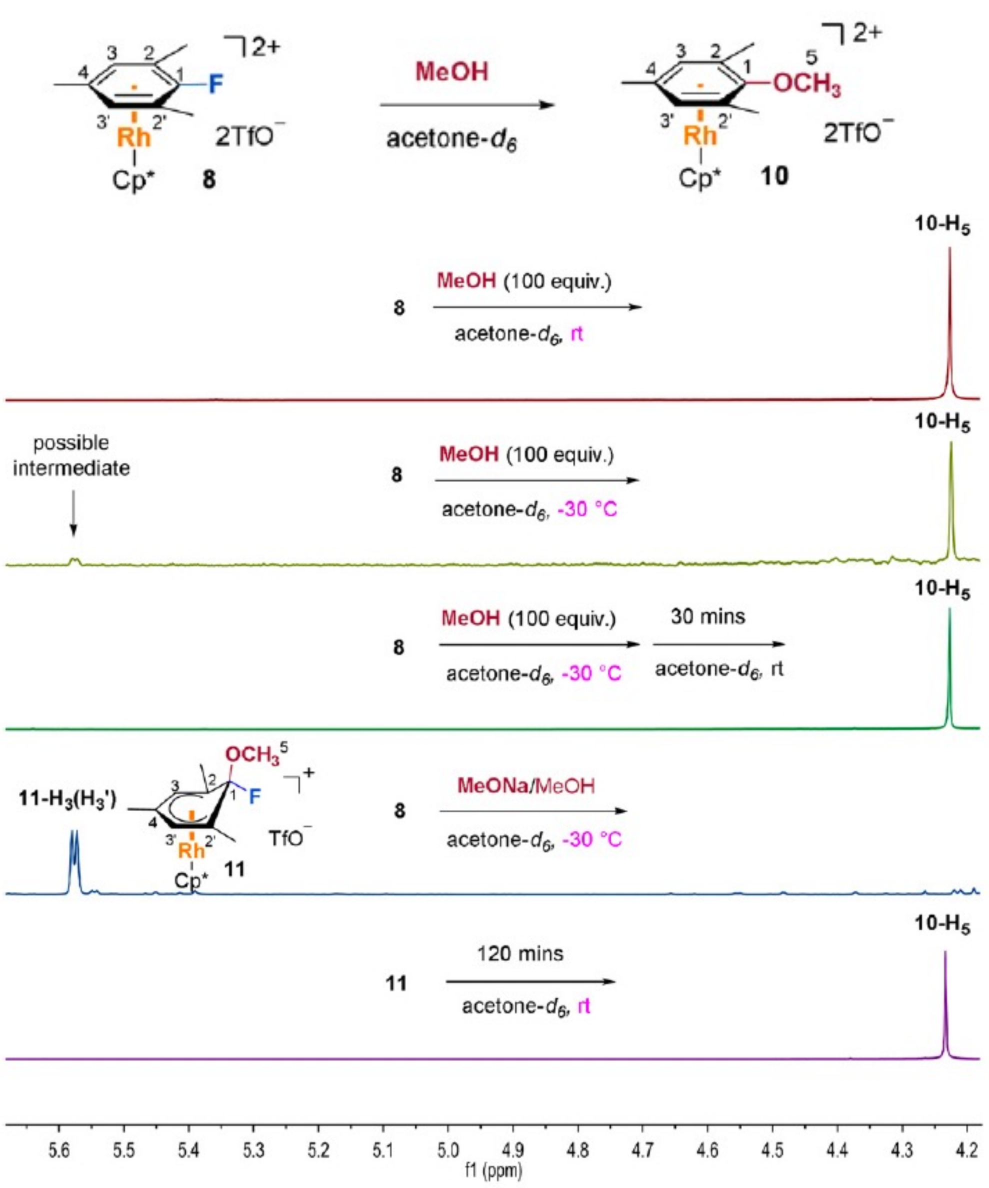
local electrophilicity indices ***Increasing***

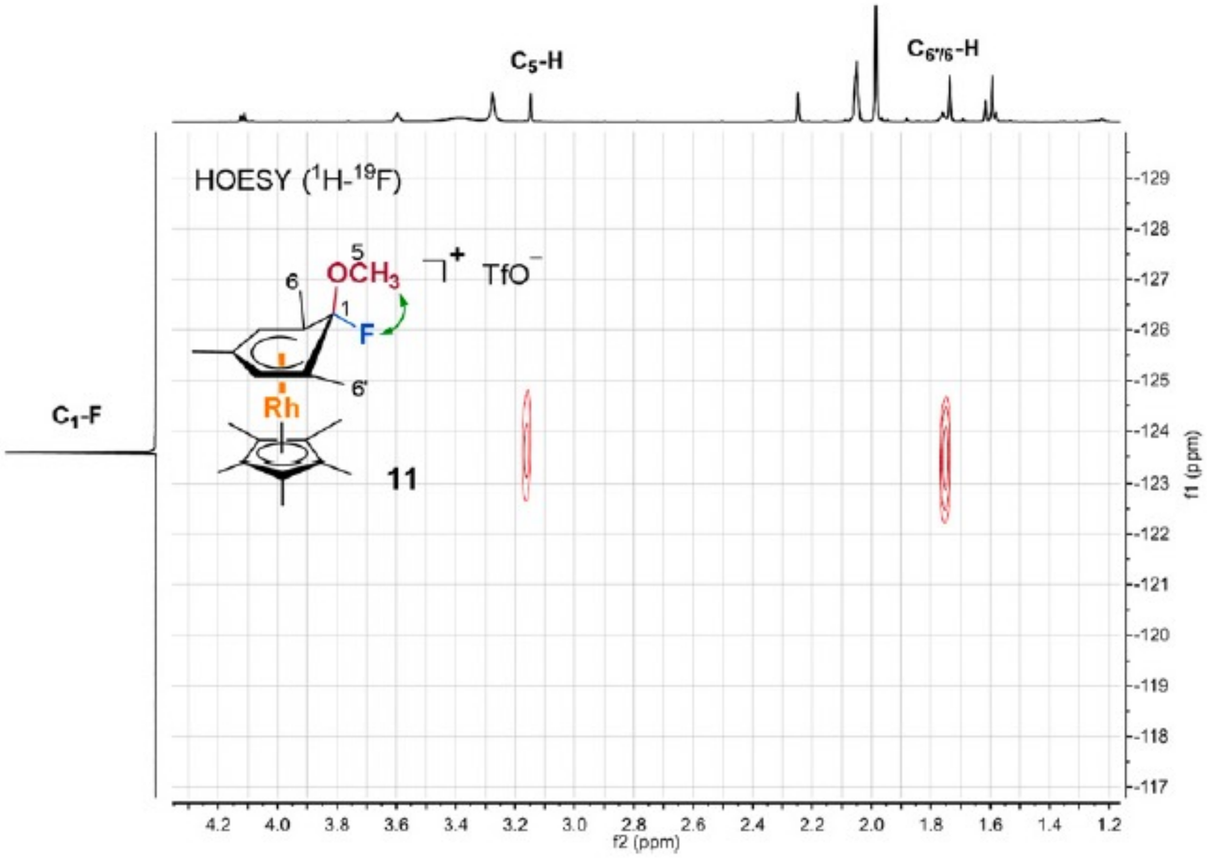


Rh(III) serves as a stronger activator compared to Ru(II)

Kang, Q.; Lin, Y.; Li, Y.; Xu, L.; Li, K.; Shi, H. *Angewandte Chemie* **2021**, *133* (37), 20554–20562.

Rh(III)-Catalyzed Hyroxylation of Aryl Halides





strong evidence for the stepwise mechanism of metal-catalyzed S_NAr

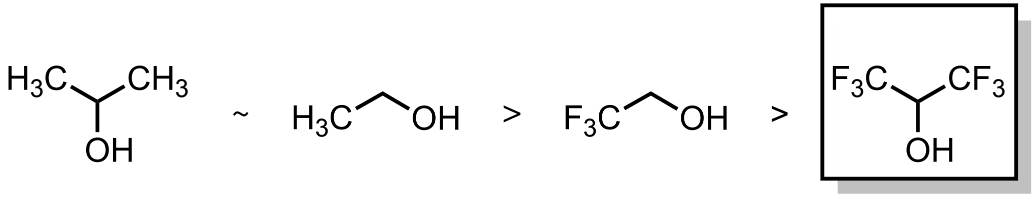
the first observation and characterization of Meisenheimer-type intermediate in metal-mediated S_NAr reaction

Kang, Q.; Lin, Y.; Li, Y.; Xu, L.; Li, K.; Shi, H. *Angewandte Chemie* **2021**, *133* (37), 20554–20562.

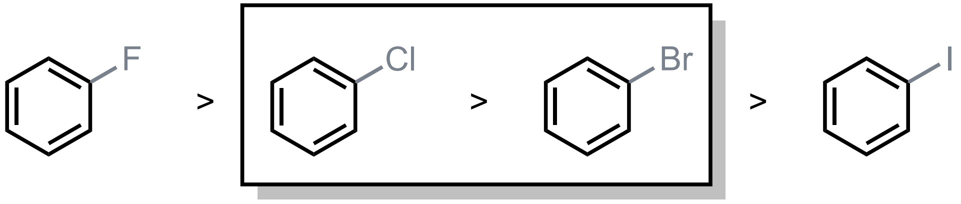
Rh(III)-Catalyzed Hexafluoroisopropoxylation of Aryl Halides

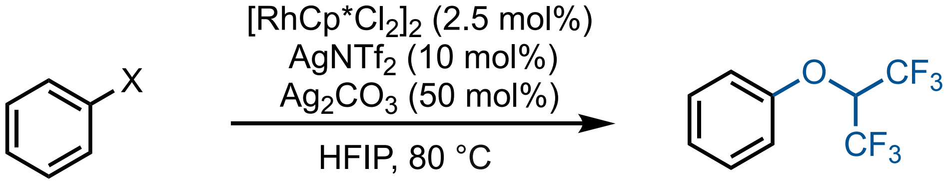
trends in S_NAr reaction

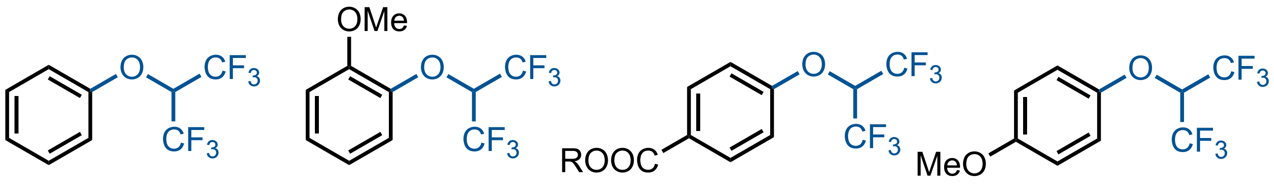
nucleophilicity



S_NAr reactivity

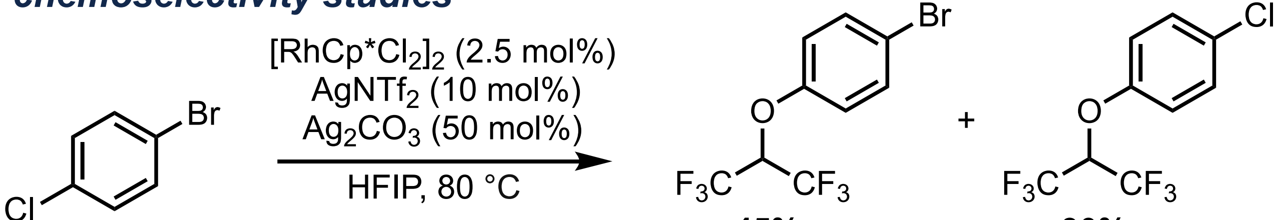






X = Cl, 98% X = Br, 95%	X = Cl, 84% X = Br, 88%	X = Cl, 48% (R = Et) X = Br, 55% (R = Me)	X = Cl, 84% X = Br, 84%

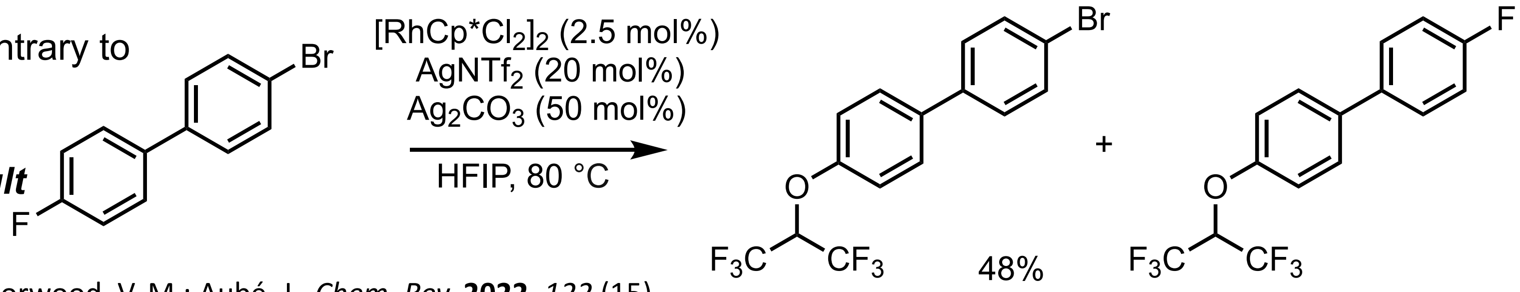
chemoselectivity studies



45% **30%**

The observed trends in the reactivity of Ar-Br and Ar-F are contrary to those of traditional S_NAr reactions

DFT calculation would be useful to explain the result



P-1 **P-1: P-2 = 1: 5.9** **P-2**

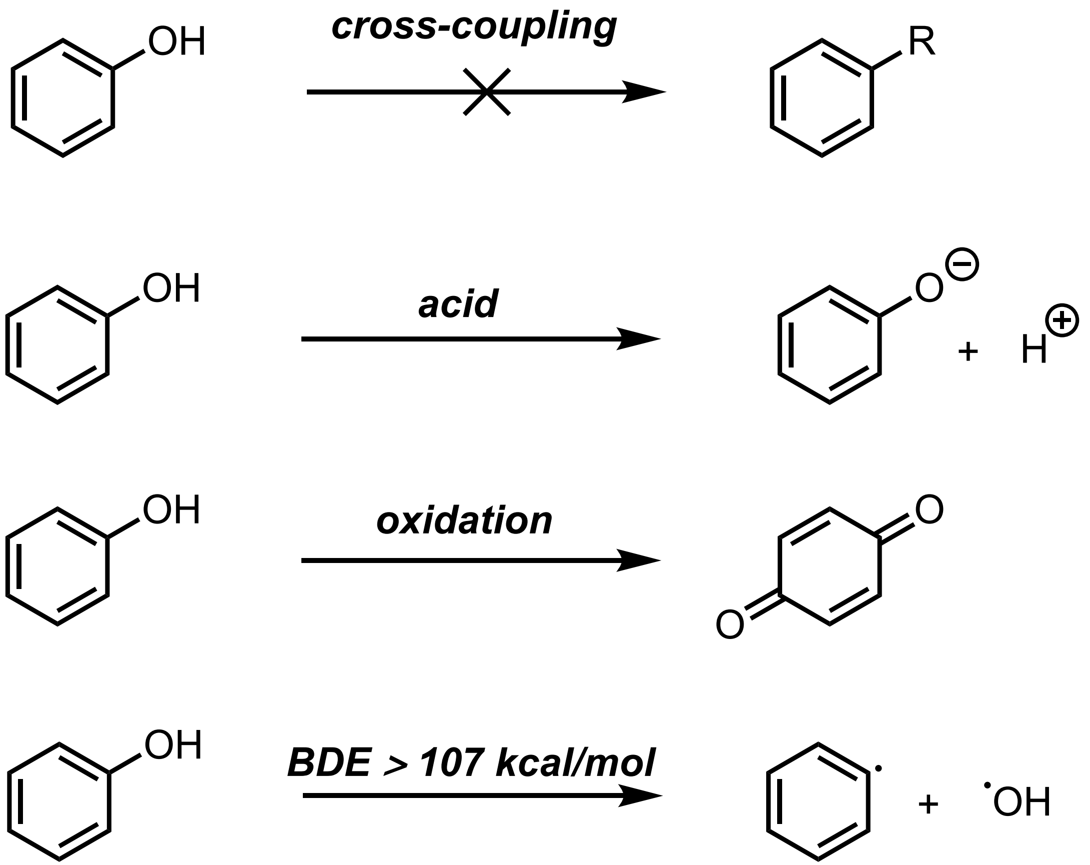
Motiwala, H. F.; Armaly, A. M.; Cacioppo, J. G.; Coombs, T. C.; Koehn, K. R. K.; Norwood, V. M.; Aubé, J. *Chem. Rev.* **2022**, *122* (15), 12544–12747.; Su, J.; Chen, K.; Kang, Q.; Shi, H. *Angew Chem Int Ed* **2023**, *62* (24), e202302908.

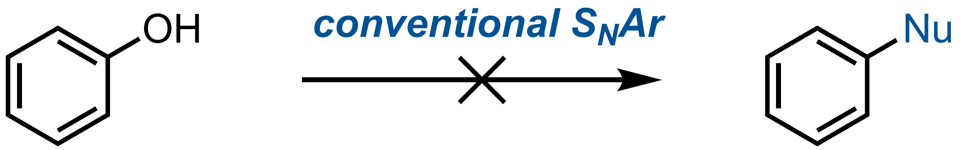
Outline

- Historical perspective into Lewis π-Acid Activated S_NAr Reactions
- Lewis π-Acid Catalyzed S_NAr Reactions of Aryl Halides
- **Lewis π-Acid Catalyzed S_NAr Reactions of Phenol**
- Summary and Perspective

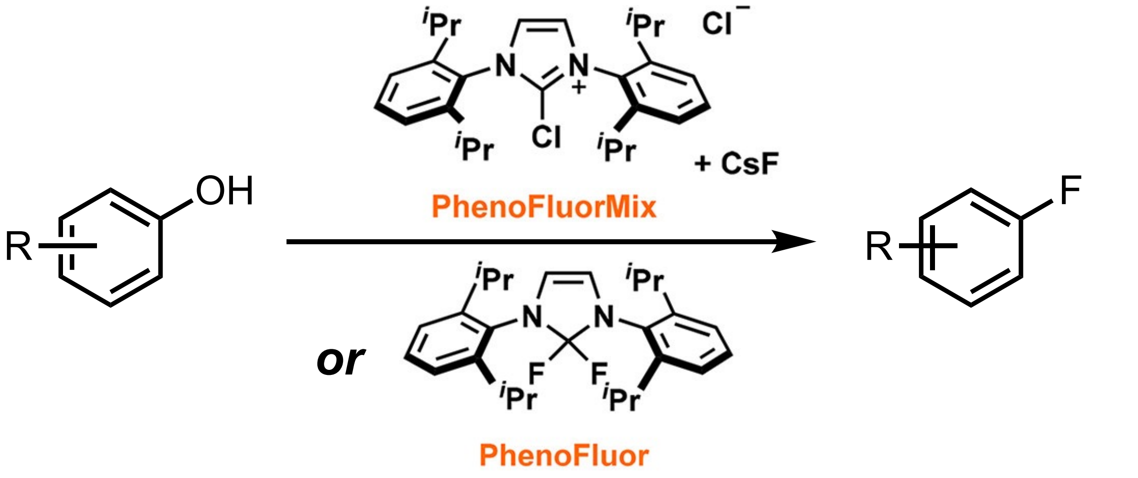
Catalytic Functionalization of Phenols

challenges in phenol functionalization

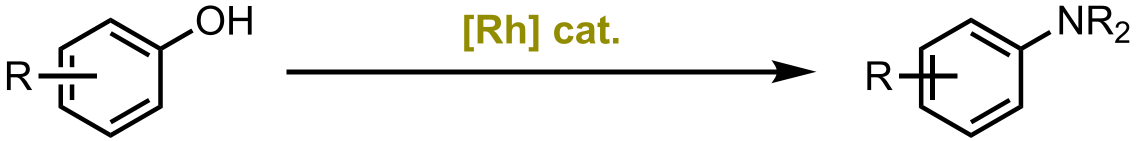




Ritter et al. (2011)



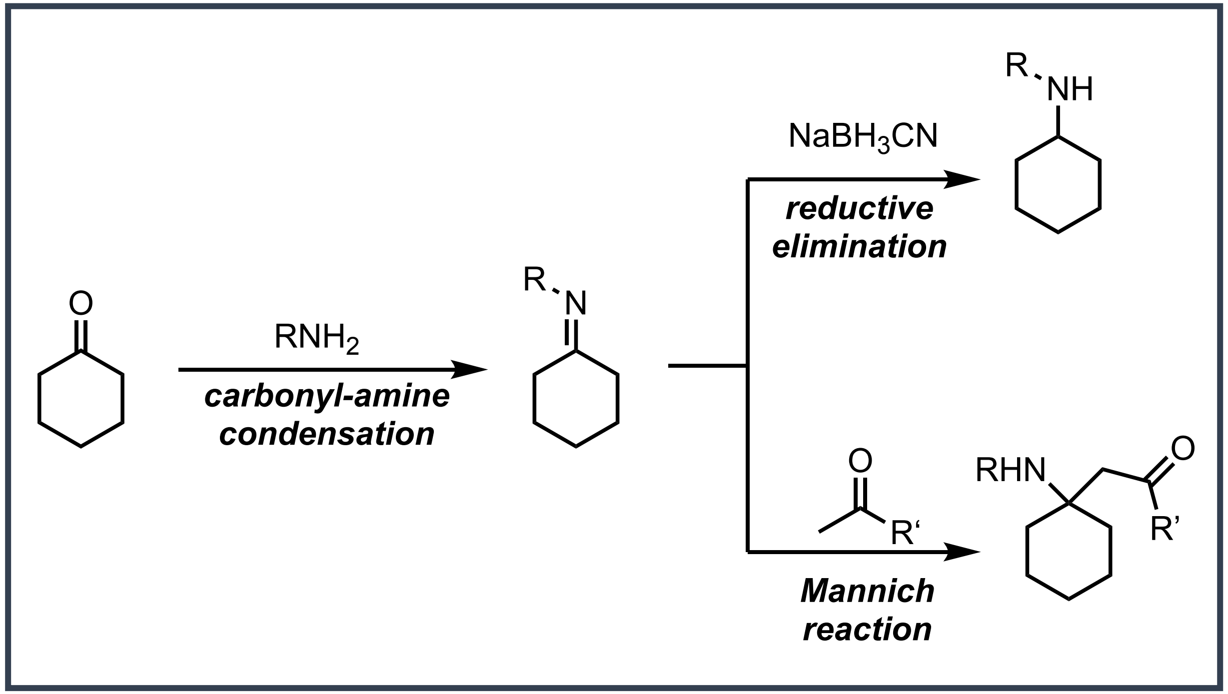
Mask reactive OH and convert it to a better LG

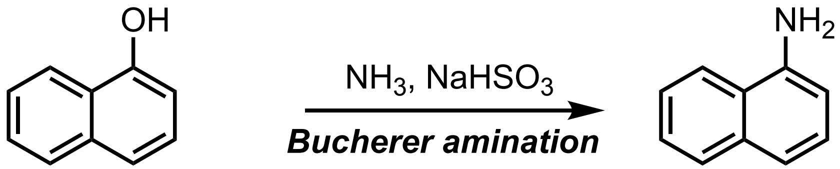


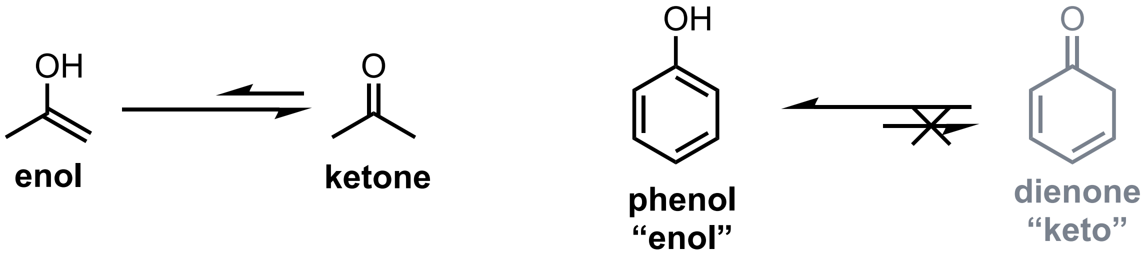
Eliminate the need for activating reagents and proceeds with direct substitution

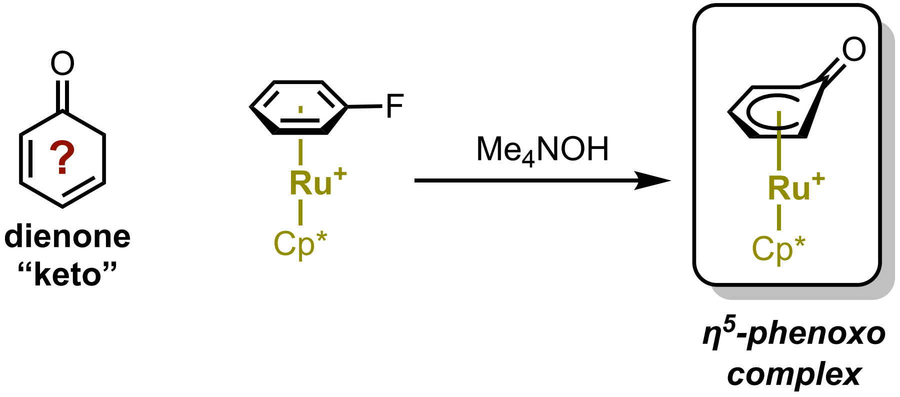
Chen, K.; Kang, Q.-K.; Li, Y.; Wu, W.-Q.; Zhu, H.; Shi, H. *J. Am. Chem. Soc.* **2022**, *144* (3), 1144–1151;
Neumann, C. N.; Ritter, T. *Acc. Chem. Res.* **2017**, *50* (11), 2822–2833.

Rh(III)-Catalyzed Amination of Phenols



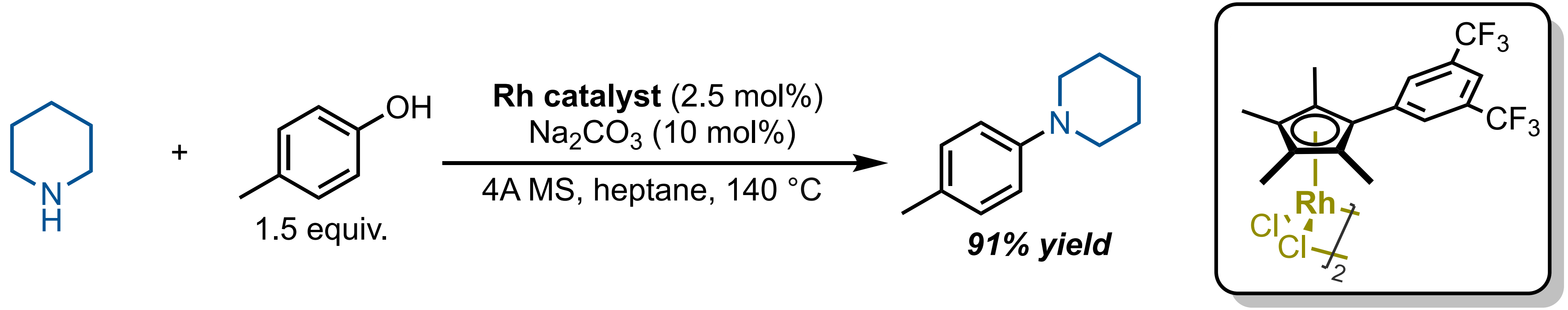


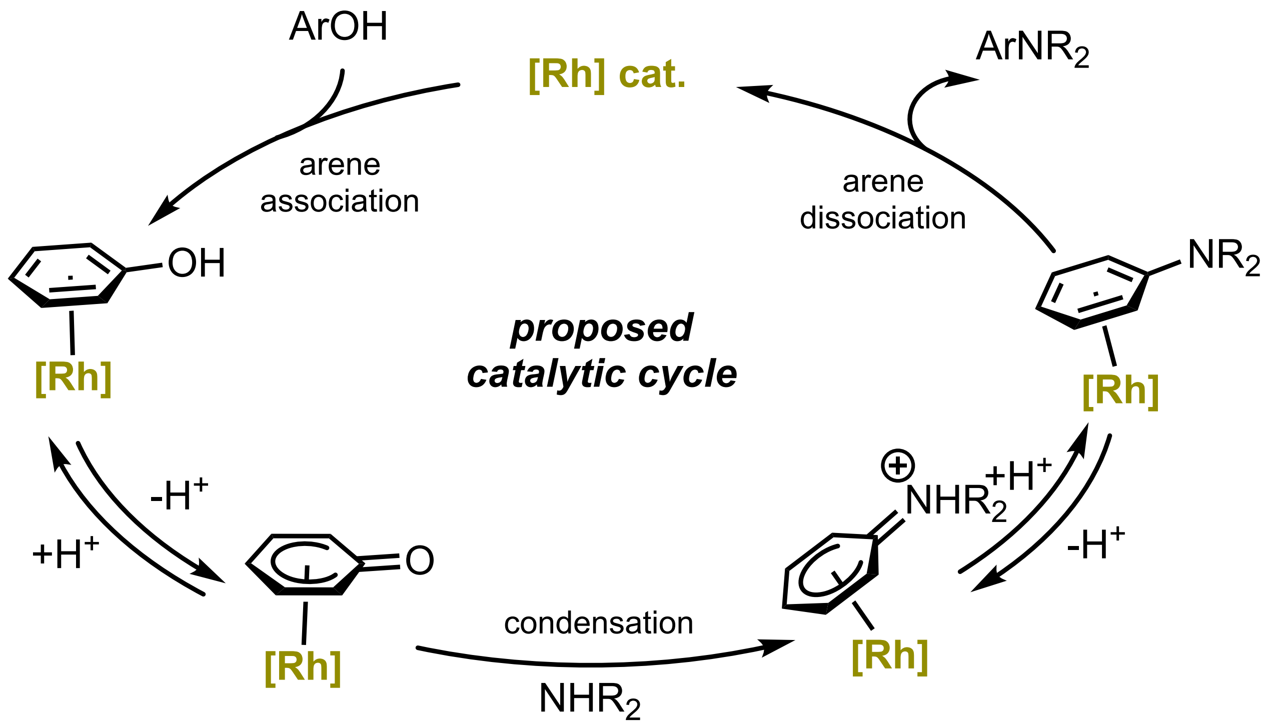




Chen, K.; Kang, Q.-K.; Li, Y.; Wu, W.-Q.; Zhu, H.; Shi, H. *J. Am. Chem. Soc.* **2022**, *144* (3), 1144–1151.

Rh(III)-Catalyzed Amination of Phenols

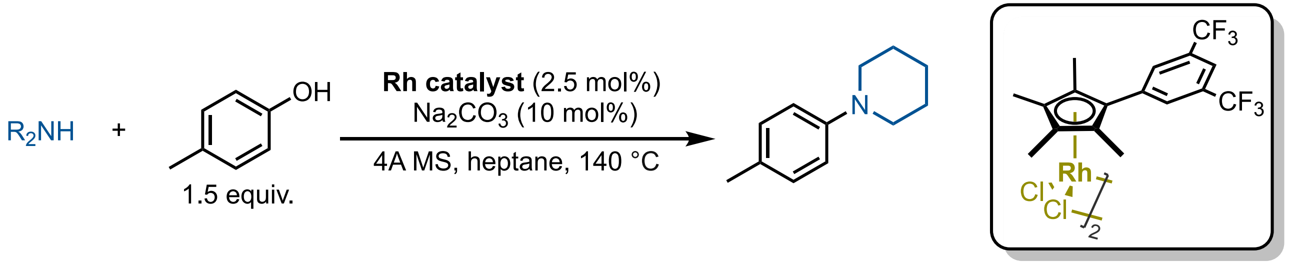


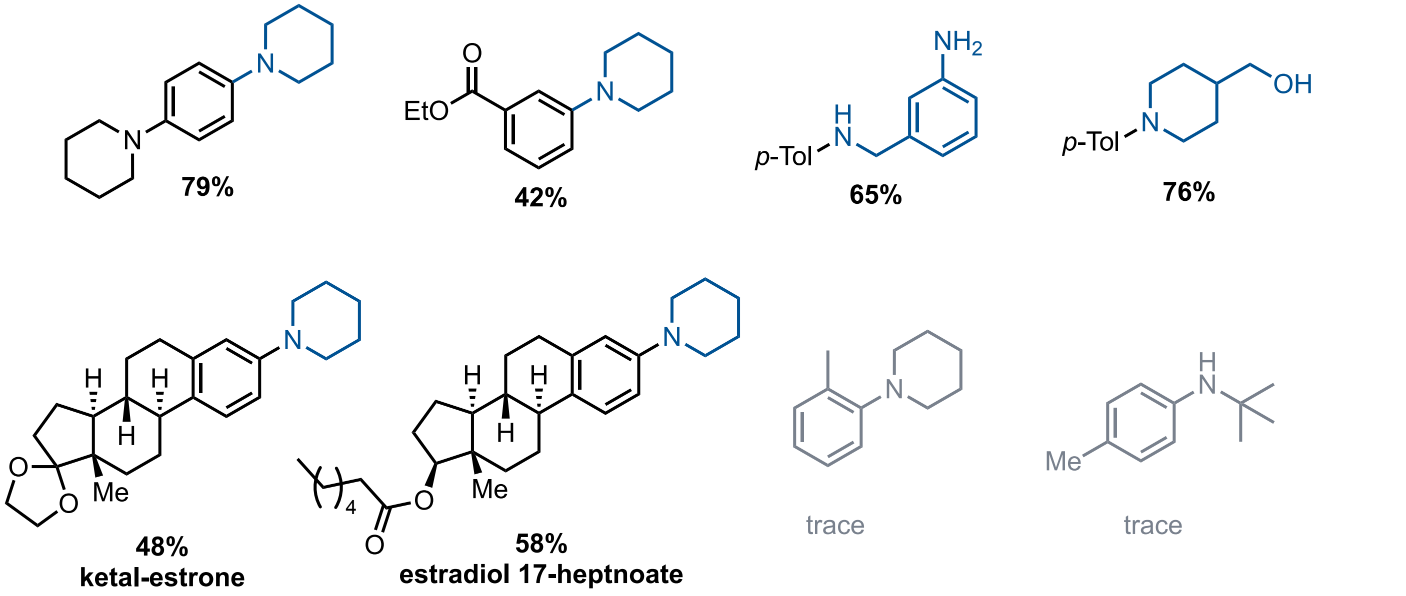


1. *π-Coordination*
2. *Formation of η⁵-phenoxo complex*
3. *Carbonyl−amine condensation*
4. *Formation of η⁶-aniline complex*
5. *Arene exchange*

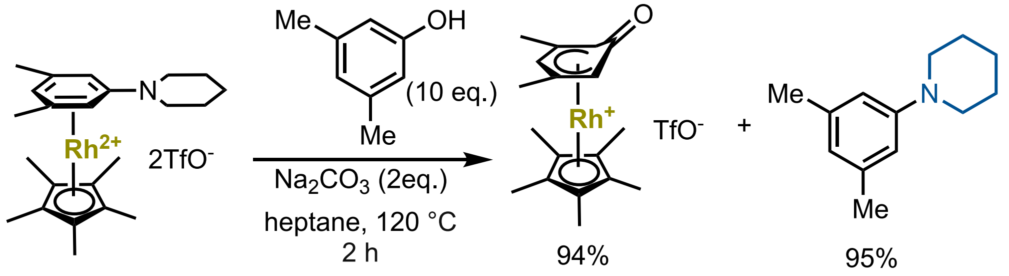
Chen, K.; Kang, Q.-K.; Li, Y.; Wu, W.-Q.; Zhu, H.; Shi, H. *J. Am. Chem. Soc.* **2022**, *144* (3), 1144–1151.

Rh(III)-Catalyzed Amination of Phenols

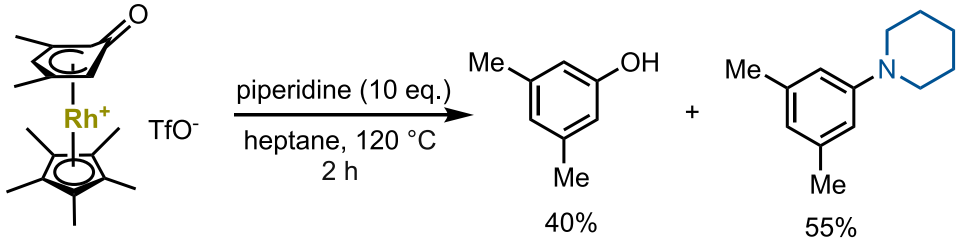




arene exchange test



aniline formation test



A more rigorous validation of their proposed reaction mechanism is necessary

kinetic studies
rate constant determination
inhibitory effect of water

But this does not detract from the significance of this study as a milestone

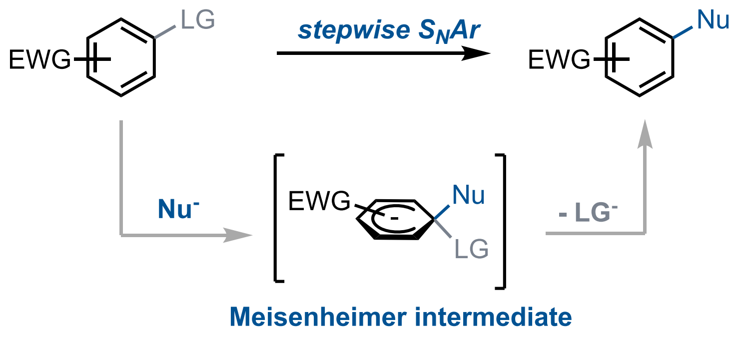
Chen, K.; Kang, Q.-K.; Li, Y.; Wu, W.-Q.; Zhu, H.; Shi, H. *J. Am. Chem. Soc.* **2022**, *144* (3), 1144–1151.

Outline

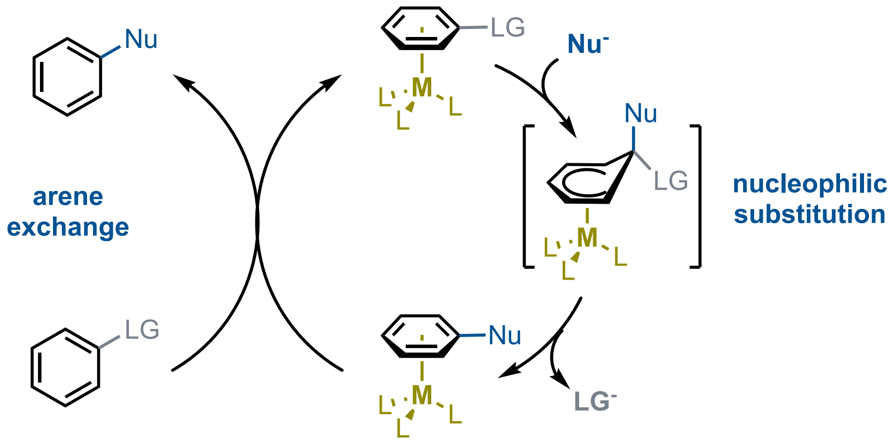
- Historical perspective into Lewis π-Acid Activated S_NAr Reactions
- Lewis π-Acid Catalyzed S_NAr Reactions of Aryl Halides
- Lewis π-Acid Catalyzed S_NAr Reactions of Phenol
- **Summary and Perspective**

Summary

- Limitation of Traditional S_NAr: the reaction substrates are restricted to electron-deficient arenes because the formation of Meisenheimer intermediate requires stabilization of EWGs.



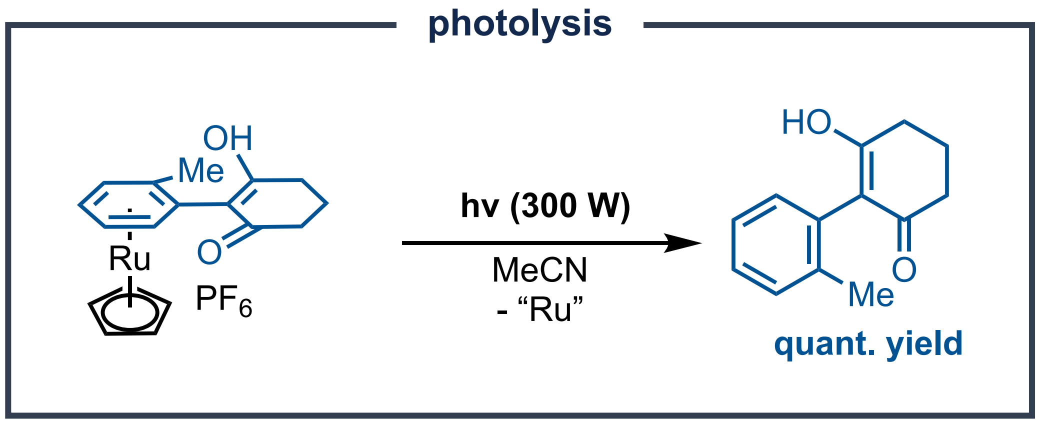
- Lewis π-Acid Activated S_NAr provide a solution to electron-neutral or electron-rich arenes. However, It is relatively easy to coordinate the arene with the metal, but removing the metal afterwards is far more challenging. Therefore, rapid Lewis arene exchange is the key process to achieve catalytic S_NAr



- Several catalytic methods utilizing Ru and Rh have been successfully developed for SNAr reactions involving both aryl halides and phenols. However, high temperatures are required in all cases.

Perspective

- **Rate constant benchmark**
  - For the existing reactions, all conditions are more or less different, making it difficult to compare the reaction rates of arene exchange and nucleophilic substitution under a unified standard.
  - Select a benchmark reaction for each type to compare the reaction rates of arene exchange and nucleophilic substitution with different ligands, allowing for a direct evaluation of ligand performance.
- **Milder arene exchange: visible-light mediated arene exchange**
  - Under the current conditions, high temperatures are required in all cases.
  - Tuning ligands on transition metals can adjust the energy required for excitation, enabling arene exchange under visible-light irradiation.
- **Atropselective synthesis**
  - Enantioinduction is likely to occur during nucleophilic substitution, enabling atroposelective synthesis, as S_NAr reactions of electron-neutral arenes only proceed with coordination to transition metals.



Further Reading

Minireview | Open Access

As Nice as π: Aromatic Reactions Activated by π-Coordination to Transition Metals

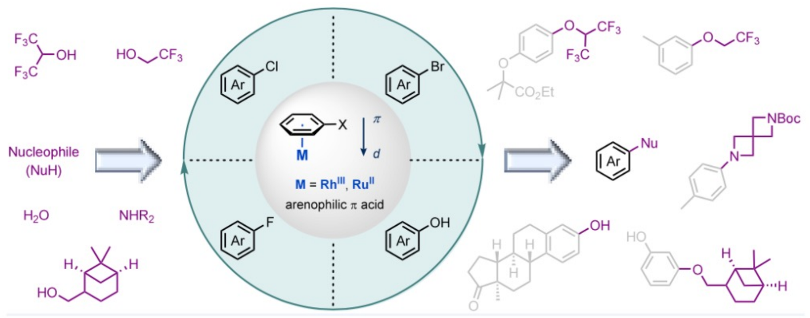
Luke J. Williams, Dr. Yunas Bhonoah, Dr. Luke A. Wilkinson, Dr. James W. Walton

First published: 19 November 2020 | https://doi.org/10.1002/chem.202004621 | Citations: 23

SECTIONS   PDF   TOOLS   SHARE

26. Nucleophilic Aromatic Substitution of Halobenzenes and Phenols with Catalysis by Arenophilic π Acids

https://pubs.acs.org/doi/10.1021/acs.accounts.4c00327



Home > Transition Metal Arene π-Complexes in Organic Synthesis and Catalysis > Chapter

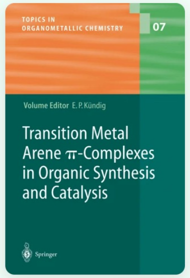
Introduction

Chapter

pp 1–2 | Cite this chapter

Access provided by University of Illinois Urbana-Champaign Library

Download book PDF



Transition Metal Arene π-Complexes in Organic Synthesis and Catalysis

PERSPECTIVE

View Article Online
View Journal | View Issue

Check for updates

Cite this: *Dalton Trans.*, 2024, **53**, 18819

Strategies for arene dissociation from transition metal η^6-arene complexes

Brett Akana-Schneider, † Yahui Guo, † Bryan Parnitzke and Joseph Derosa *

Received 24th August 2024,
Accepted 7th October 2024

DOI: 10.1039/d4dt02408g

rsc.li/dalton

Transition metal η^6-arene complexes have unique properties that facilitate a variety of arene substitution reactions, rendering π-activation a powerful approach for arene functionalization. For decades, these complexes have been studied in the context of coordination chemistry and synthetic methodology *via* stoichiometric reactivity; one central challenge in expanding the utility of arene functionalization *via* transition-metal-π-activation is the dissociation of the arene product that remains bound to the transition metal. In this perspective, we highlight representative strategies and methods for the removal and/or exchange of arenes from such complexes. Recent studies that implement these strategies toward catalytic processes are discussed, along with remaining challenges in this area.

Questions?