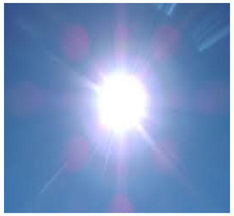


Sustainable Catalysis –
Concepts and Applications

Magnus Rueping

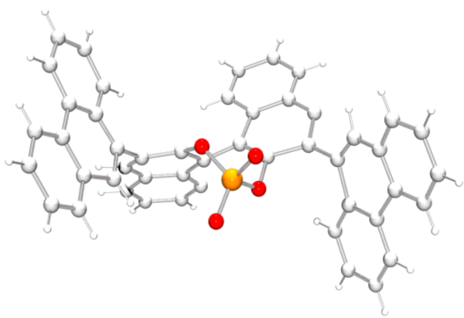
IASOC - 2018

جامعة الملك عبدالله
للعلوم والتقنية
King Abdullah University of
Science and Technology
KAUST Catalysis Center

RWTH AACHEN

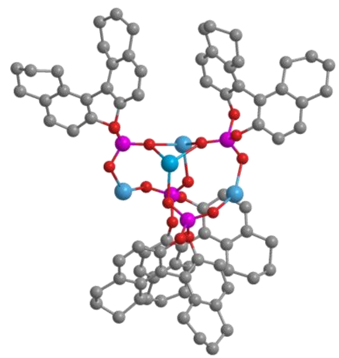
Current Research Topics

Metal-free Catalysis - Organocatalysis



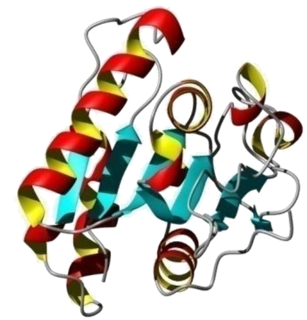
Covalent and Non-covalent Activation

Metal Catalysis

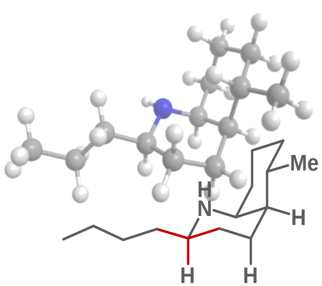


C-H Activation, Direct C-C Bond Formation

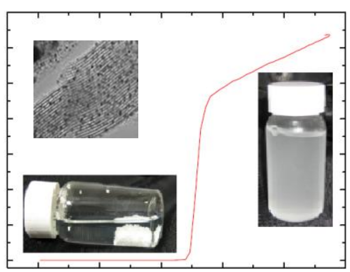
Enzyme Catalysis



Reduction and Oxidation Reactions

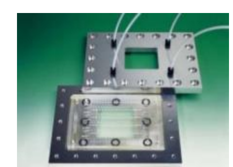


Natural Products
Bioactive Substances



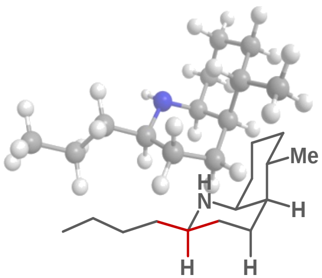
Smart Functional Materials
Surfaces/Polymers

Photocatalysis
Heterogenous/
Homogeneous

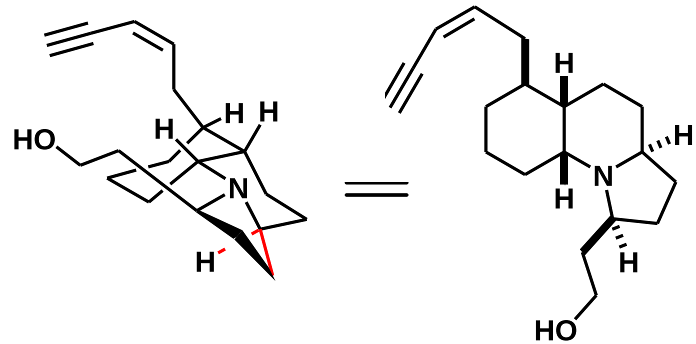


Reaction & Separation Technologies

New Reaction Development



Natural Products
Bioactive Substances



(+)-Gephyrotoxin

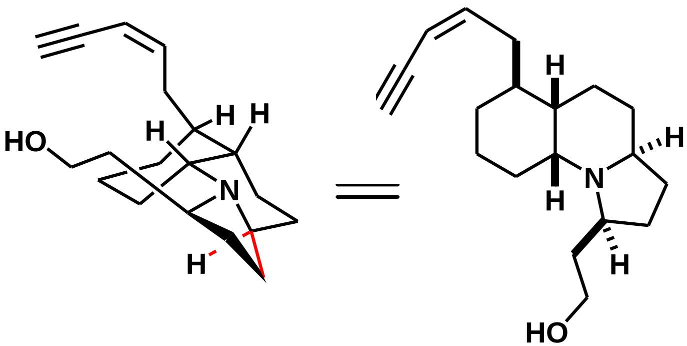
Natural Product Inspired

Methodology Development

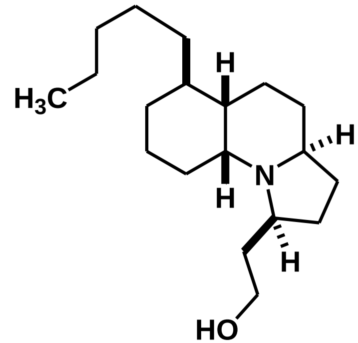
Muscarinic acetylcholine receptor antagonist and shows neurological activities

Potential use:
motion sickness, gastrointestinal spasms
renal spasms, irritable bowel syndrome

Natural Product Synthesis – Case Study Gephyrotoxin



(+)-Gephyrotoxin



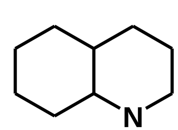
Perhydrogephyrotoxin

dentrobates histrionicus

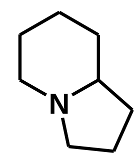
Dendrobatidae alkaloids:

Isolation (1974): 15 mg from 3200 frogs

Isolation/elucidation: (X-ray):
Daly, J.W. *Helv. Chim. Acta.* 1977, *60*, 1128



decahydroquinoline



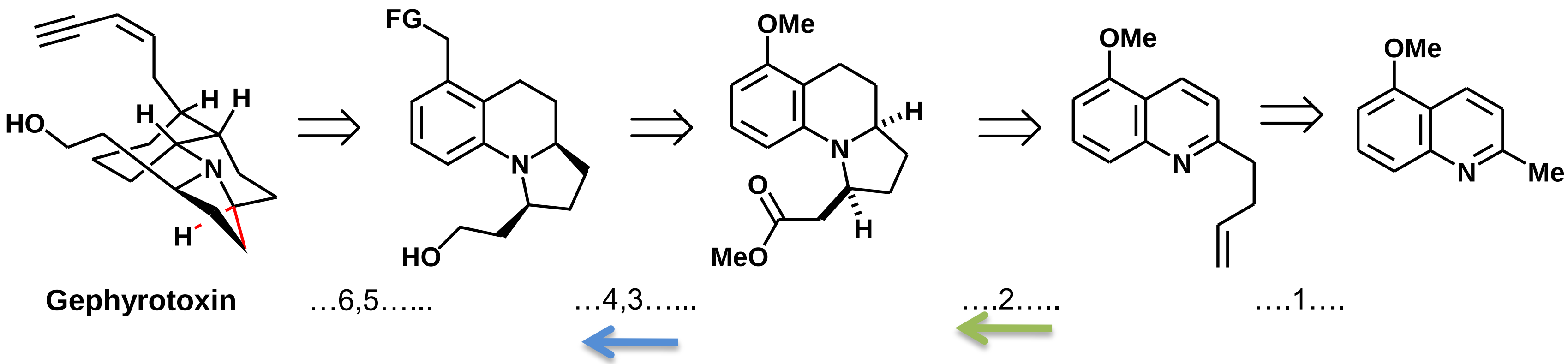
indolizindine

Syntheses:
Kishi, Y. *J. Am. Chem. Soc.* 1980, *102*, 7154
Overman, L. *J. Am. Chem. Soc.* 1983, *105*, 5373
Hart, D. *J. Am. Chem. Soc.* 1983, *105*, 1255
and several formal syntheses

Perhydrogephyrotoxin Syntheses:
Overman, L. *J. Am. Chem. Soc.* 1980, *102*, 1454
Hart, D. *J. Org. Chem.* 1981, *46*, 3576

Natural Product Synthesis – Case Study Gephyrotoxin

Combining metal- and organocatalysis



Hydrogenation of quinolines

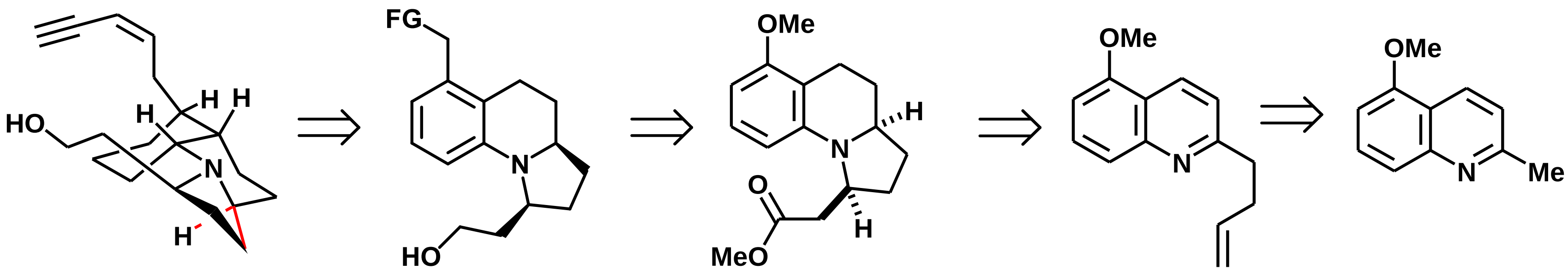
Organocatalytic multi-component reaction

Dealkoxylative C-C cross coupling

Natural Product Inspired Methodology Development

Natural Product Synthesis – Case Study Gephyrotoxin

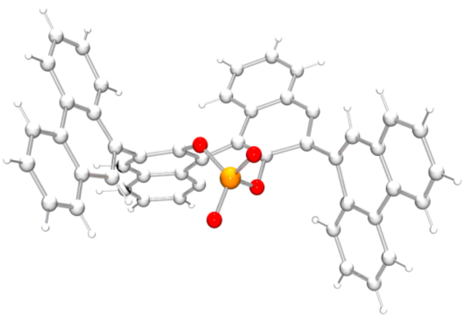
Combining metal- and organocatalysis



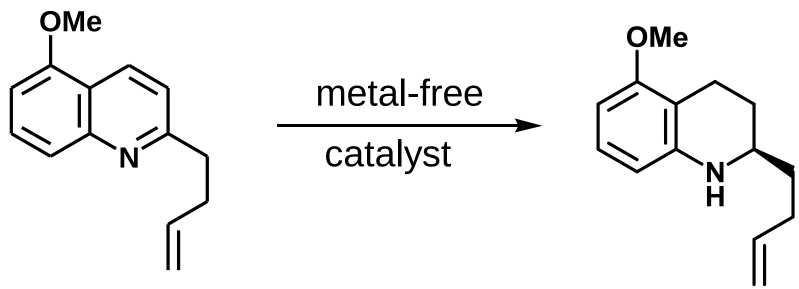
Gephyrotoxin …6,5…... …4,3…... ….2….. ….1….

Biomimetic Organocatalysis

Metal-free Catalysis - Organocatalysis



Non-Covalent Activation



Biomimetic Metal-free Hydrogenation

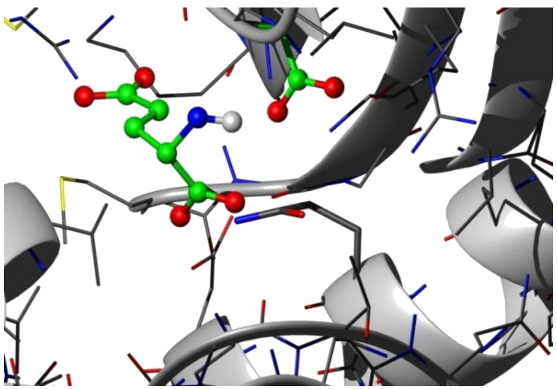
E. Sugiono, C. Azap, T. Theissmann, M.R.

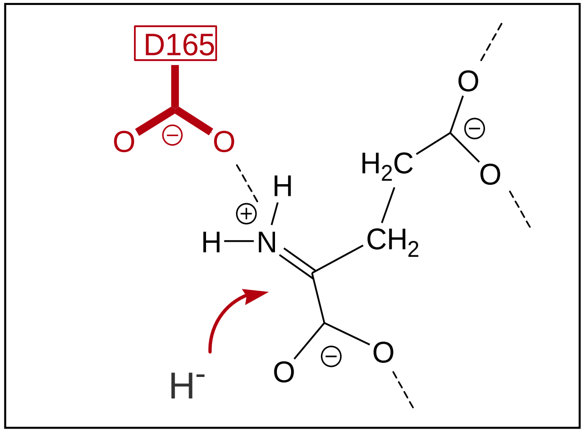
Aminations in Nature

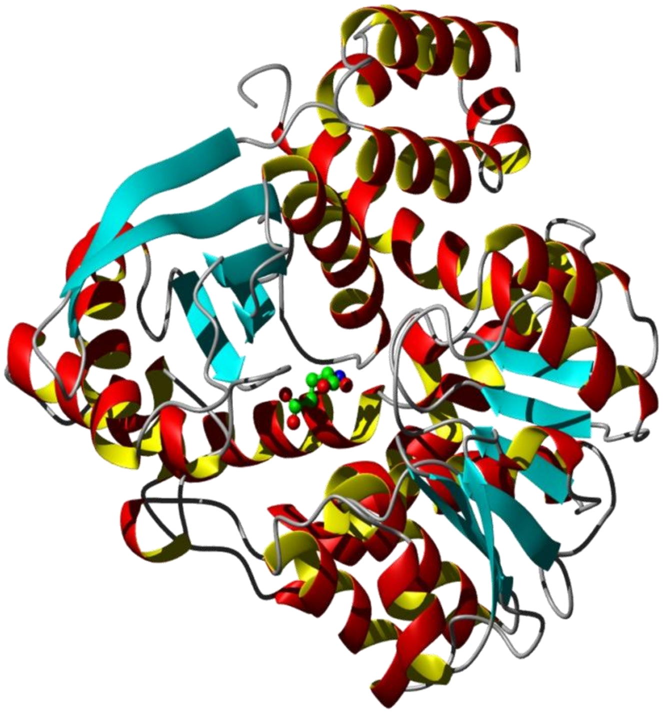
Routes of Ammonia Assimilation into Amino Acids

Glutamate Dehydrogenase (GDH)

2-ketoglutarate + NH_3 + NAD(P)H $\rightleftharpoons$ glutamate + $NAD(P)^+$



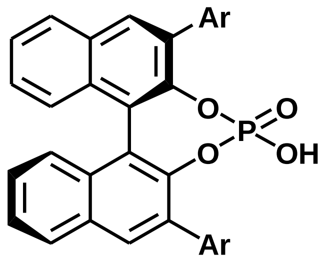




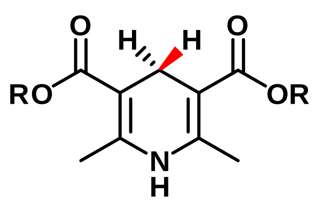
- **Aspartate-165 is essential for catalytic activity**

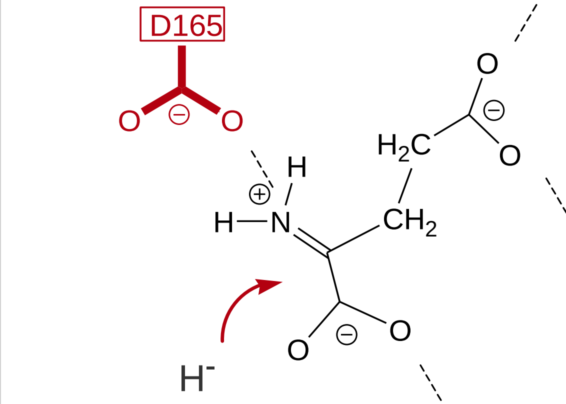
Brønsted Acid Catalyzed Transfer Hydrogenation

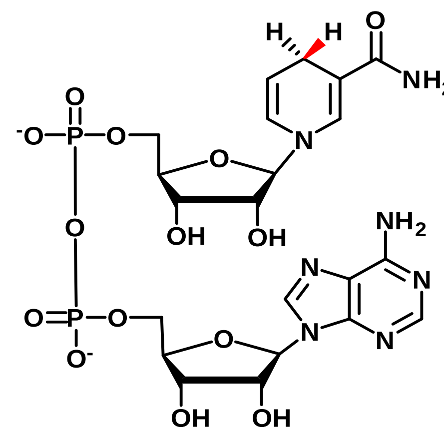
Brønsted Acids



Hydrogen Sources







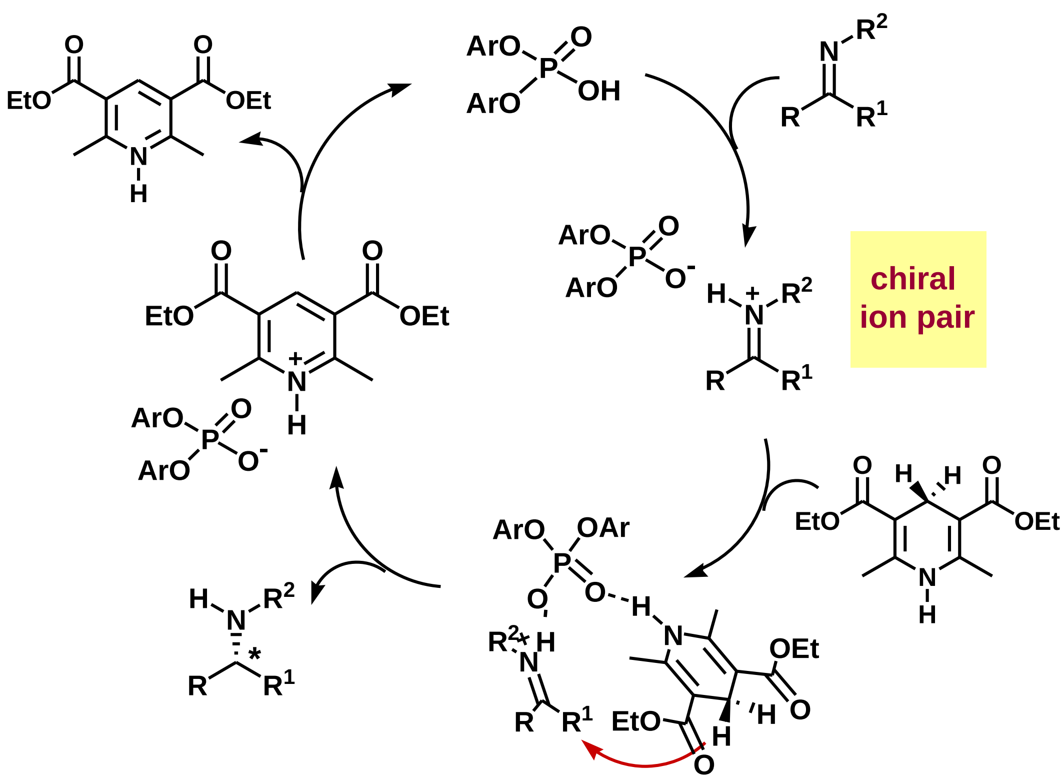
NADH
Nature's "H-"

See also: List, MacMillan, You, Gong and over 40 other groups

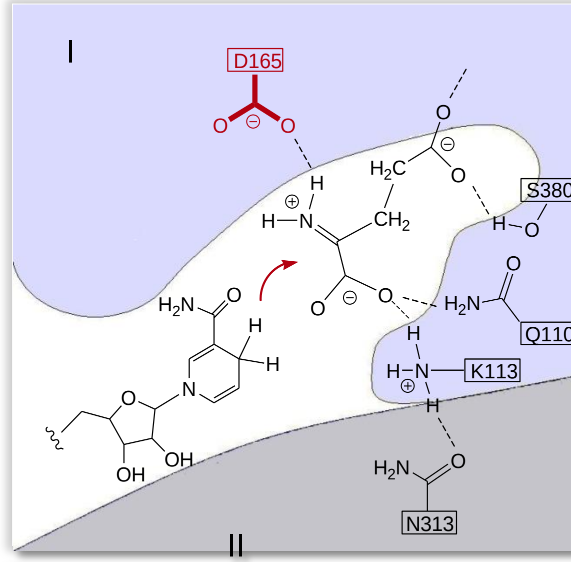
D. Mauzerall, F.H. Westheimer, *J. Am. Chem. Soc.* 1955, 77, 226 Studies on the hydride transfer from Hantzsch esters

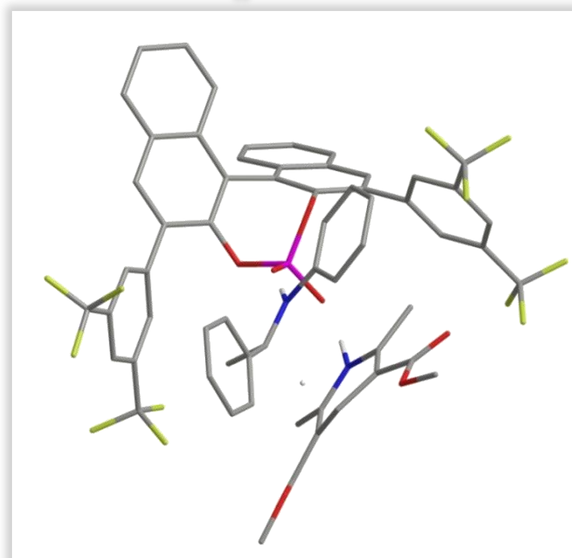
Plausible Mechanism

Catalytic Cycle



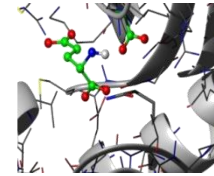
bifunctional activation

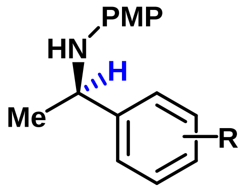




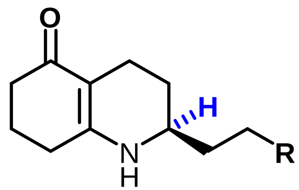
E. Sugiono, C. Azap, T. Theissmann Org. Lett. *7*, 3781-3783

Biomimetic Brønsted Acid Catalyzed Reductions

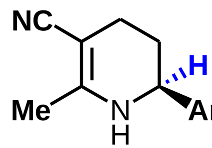




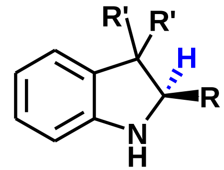
89-94% ee



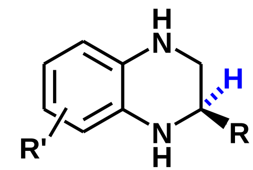
87-92% ee



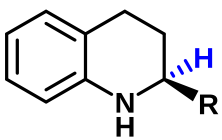
91-99% ee



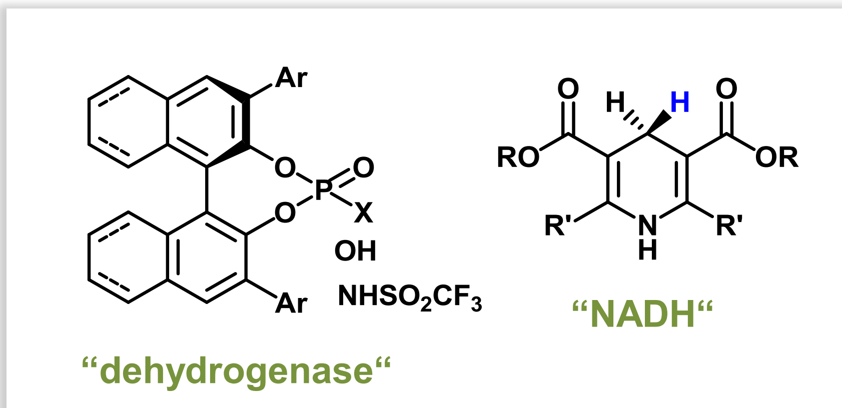
91-99% ee

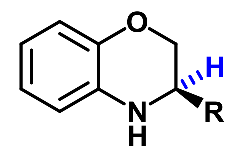


82-96% ee

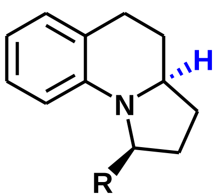


87-99% ee

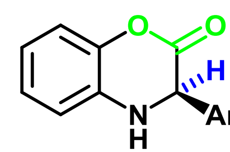




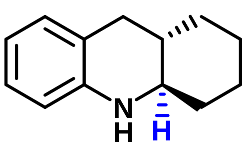
96-99% ee



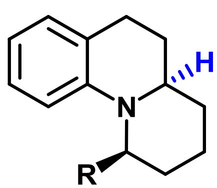
85-91% ee



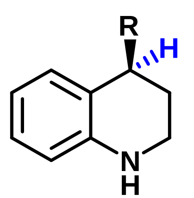
90-99% ee



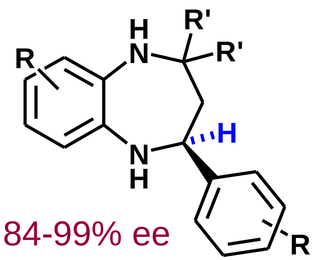
95% ee



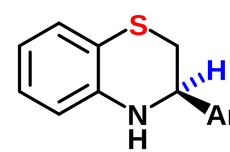
85-97% ee



75-91% ee



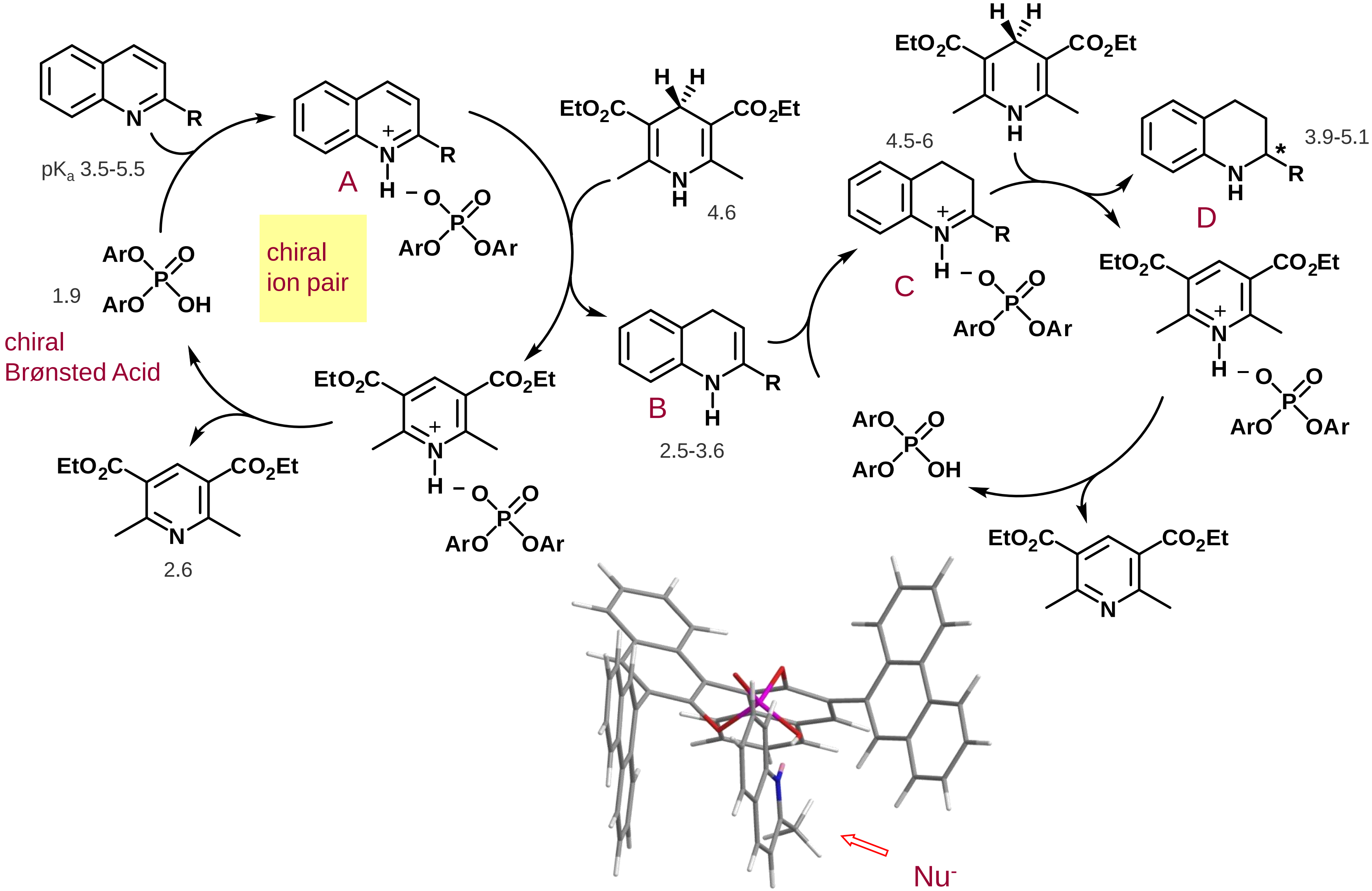
84-99% ee



88-99% ee

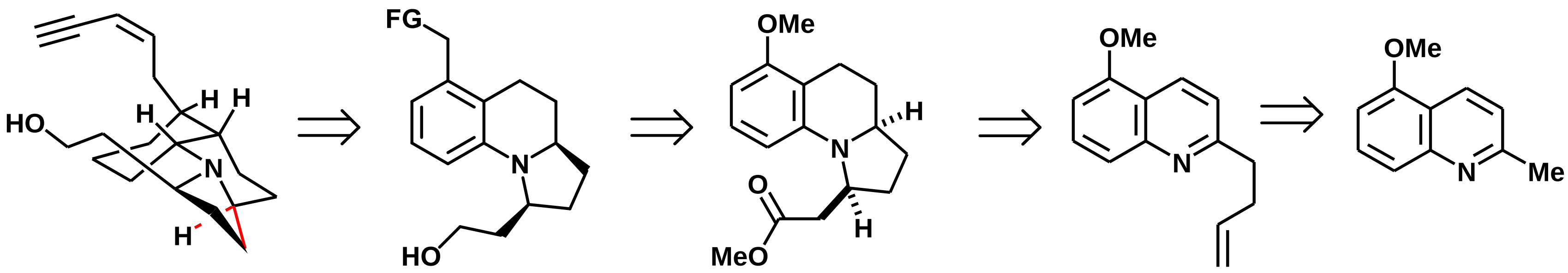
ACIE 45, 3683; *ACIE* 45, 6751; *ACIE* 46, 4562; *ACIE* 47, 5836; *ACIE* 48, 7556; *Chem. E. J* 16, 2688; *Chem. Sci.* 1, 473

Mechanism of the Brønsted Acid Catalyzed Cascade Reduction

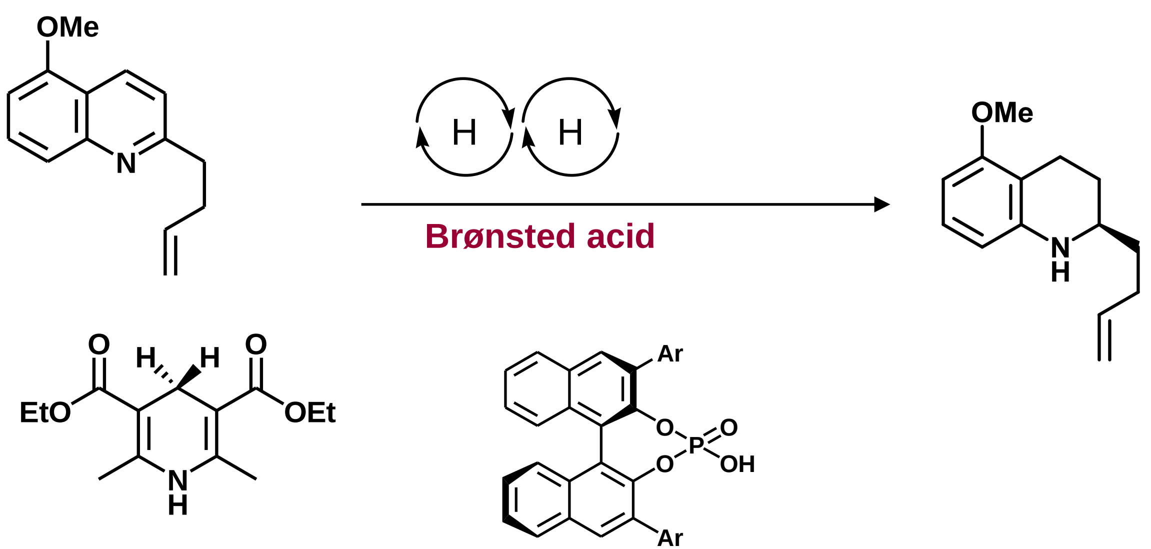


Natural Product Synthesis – Case Study Gephyrotoxin

Combining metal- and organocatalysis

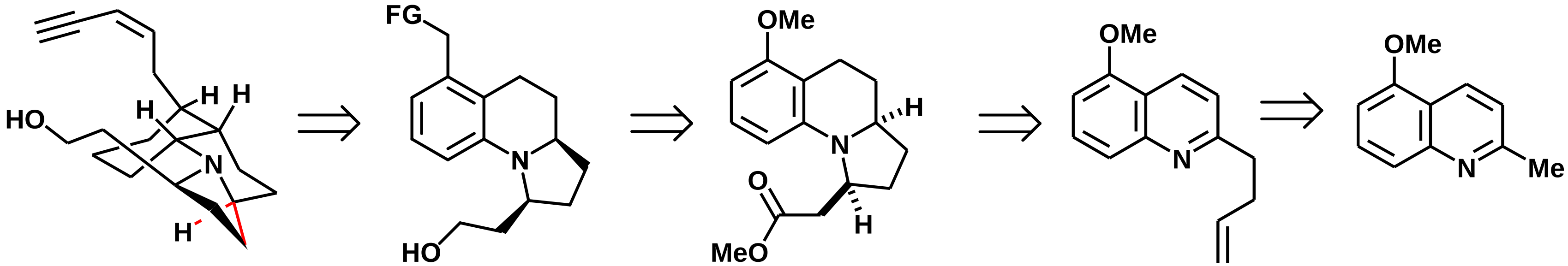


Gephyrotoxin …6,5…... …4,3…... ….2….. ….1….

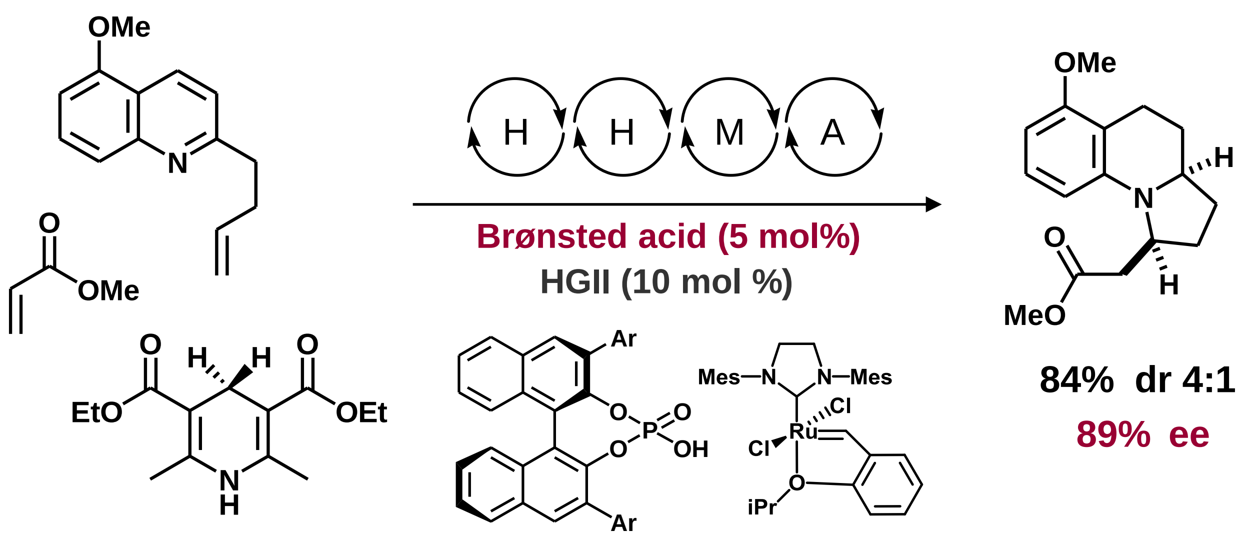


Natural Product Synthesis – Case Study Gephyrotoxin

Combining metal- and organocatalysis



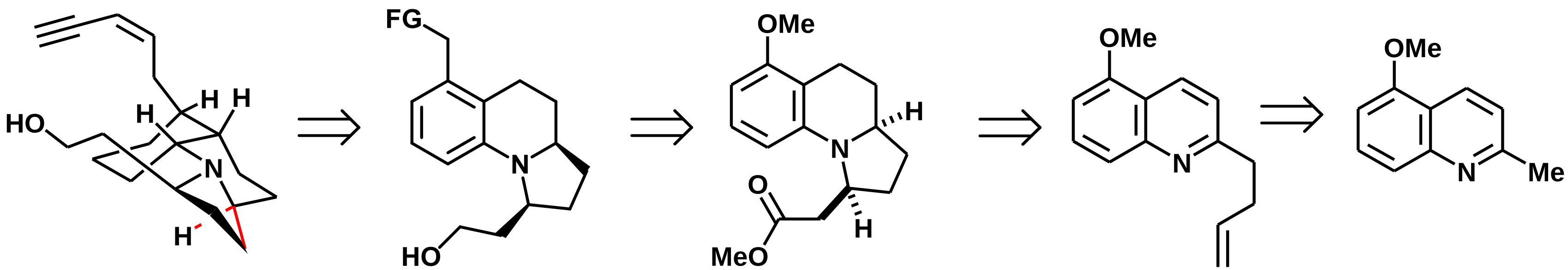
Gephyrotoxin …6,5….. …4,3….. ….2….. ….1….



2 catalysts – 3 components

Natural Product Synthesis – Case Study Gephyrotoxin

Combining metal- and organocatalysis



Gephyrotoxin …6,5….. …4,3….. ….2…. ….1….

Asymmetric dearomatization / hydrogenation

Natural Product

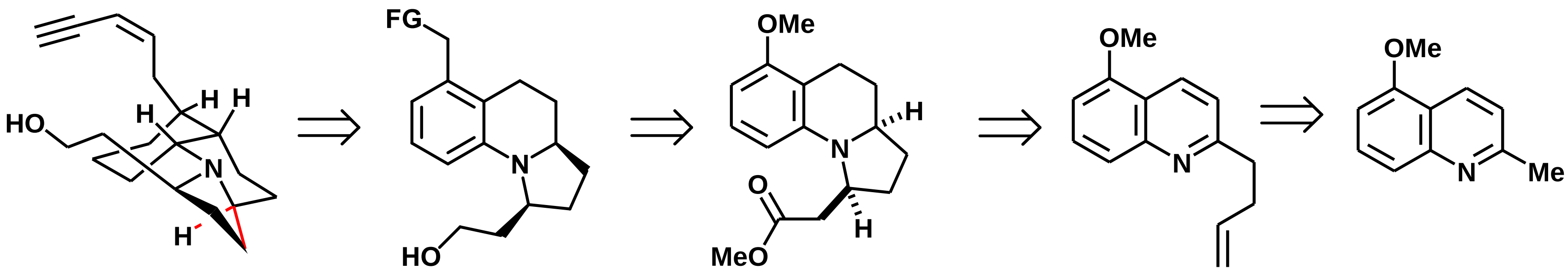
Inspired

Methodology

Development

Natural Product Synthesis – Case Study Gephyrotoxin

Combining metal- and organocatalysis



Gephyrotoxin …6,5…... …4,3…... ….2…. ….1….

Asymmetric dearomatization / hydrogenation

Dealkoxylative C-C cross coupling

Natural Product

Inspired

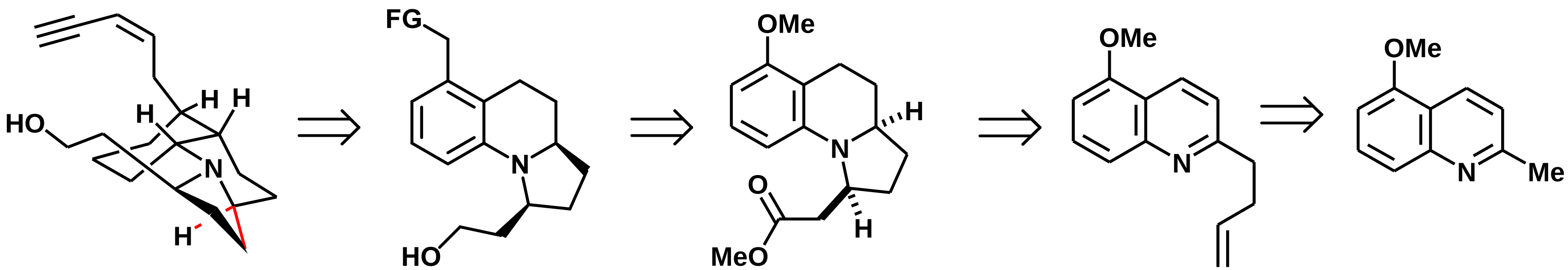
Methodology

Development

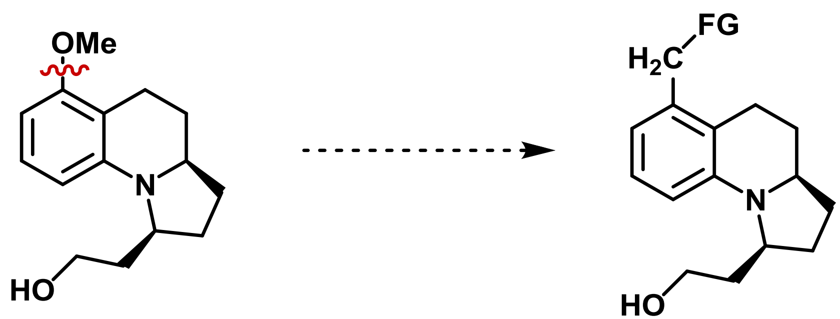
Lukas Hubener, Matthias Leiendecker

Natural Product Synthesis – Case Study Gephyrotoxin

Combining metal- and organocatalysis

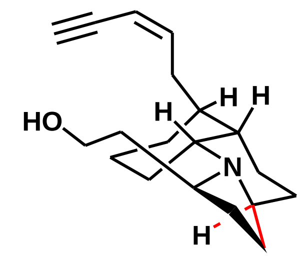


Gephyrotoxin …6,5….. …4,3….. ….2…. ….1….



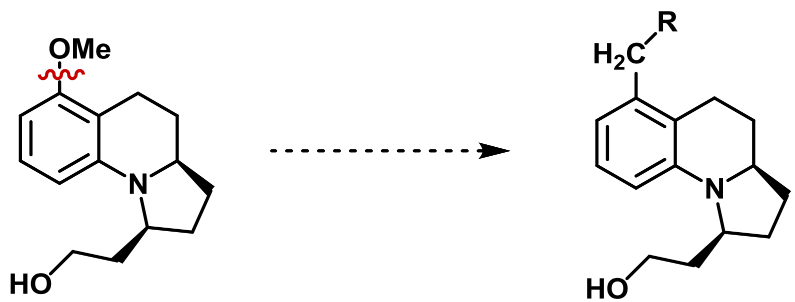
direct replacement of a MeO-Group by alkyl group ?

Lukas Hubener, Matthias Leiendecker



Natural Product Synthesis – Case Study Gephyrotoxin

Combining metal- and organocatalysis



direct replacement of a MeO-Group by alkyl group ?

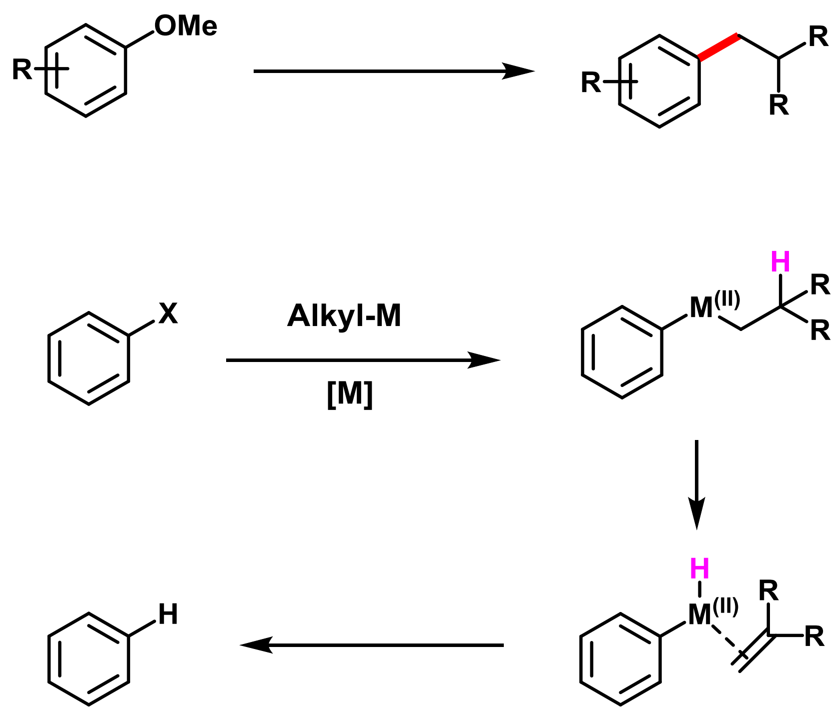
ArI > ArBr = ArOTf >> ArCl = ArOTs >> ArOMe

Ph—I	Ph—Br	Ph—Cl	Ph—OMe
65 kcal/mol	**81 kcal/mol**	**96 kcal/mol**	**102 kcal/mol**

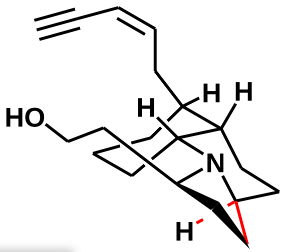
M. Leiendecker, C.-C. Hsiao, L. Guo, N. Alandini, M.R. *ACIE, 53*, 12912

Natural Product Synthesis – Case Study Gephyrotoxin

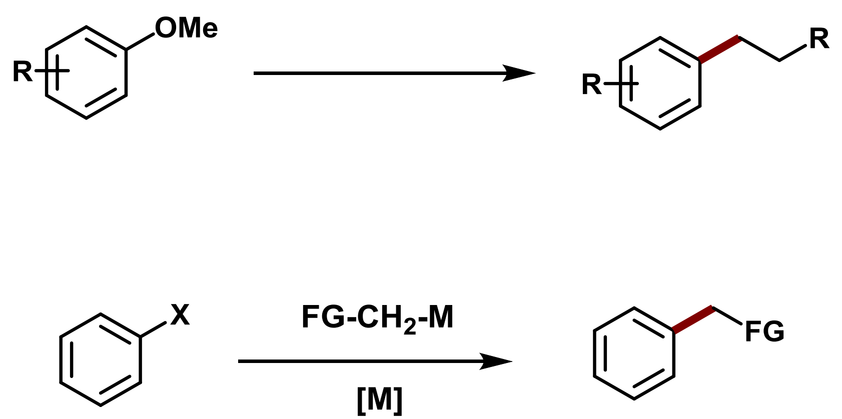
Direct replacement of a MeO-Group by a long chain alkyl group



Natural Product Synthesis – Case Study Gephyrotoxin



Direct replacement of a MeO-Group by a long chain alkyl group



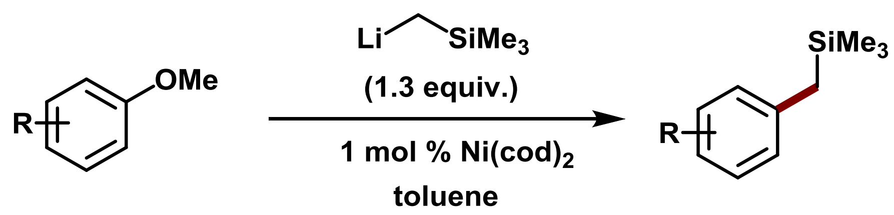
Recent overview: Nickel catalyzed C-O bond cleavage: Garg, Percec *Chem. Rev*. 2011, 111, 1346; R. Martin, *Chem. Soc. Rev.* 2014, *43*, 8081-8097, M. Tobiso, N. Chatani*, Acc. Chem.Res.* 2015, *48* , 1717-1726; Z. Shi, Homogeneous Catalysis for Unreactive Bond Activation

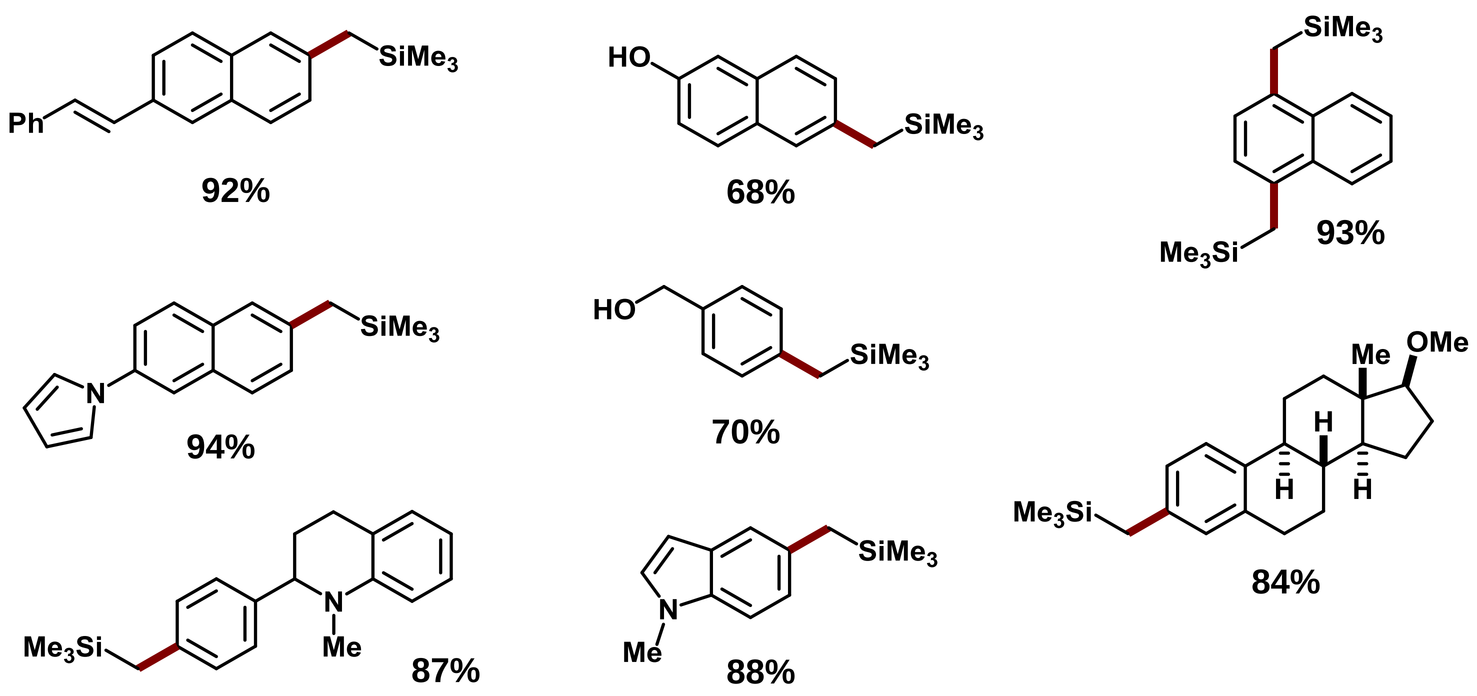
Wenkert, Dankwardt, Kakiuchi, Chatani, Tobiso, Shi, Martin, Nicasio/Prieto, Uchiyama, Snieckus, Itami, Garg, Hartwig, Han, Feringa, Jarvo, Wang,….

M. Leiendecker, C.-C. Hsiao, L. Guo, N. Alandini, M.R. *ACIE 53*, 12912

Natural Product Synthesis – Case Study Gephyrotoxin

Direct replacement of a MeO-Group by a functionalized nucleophile



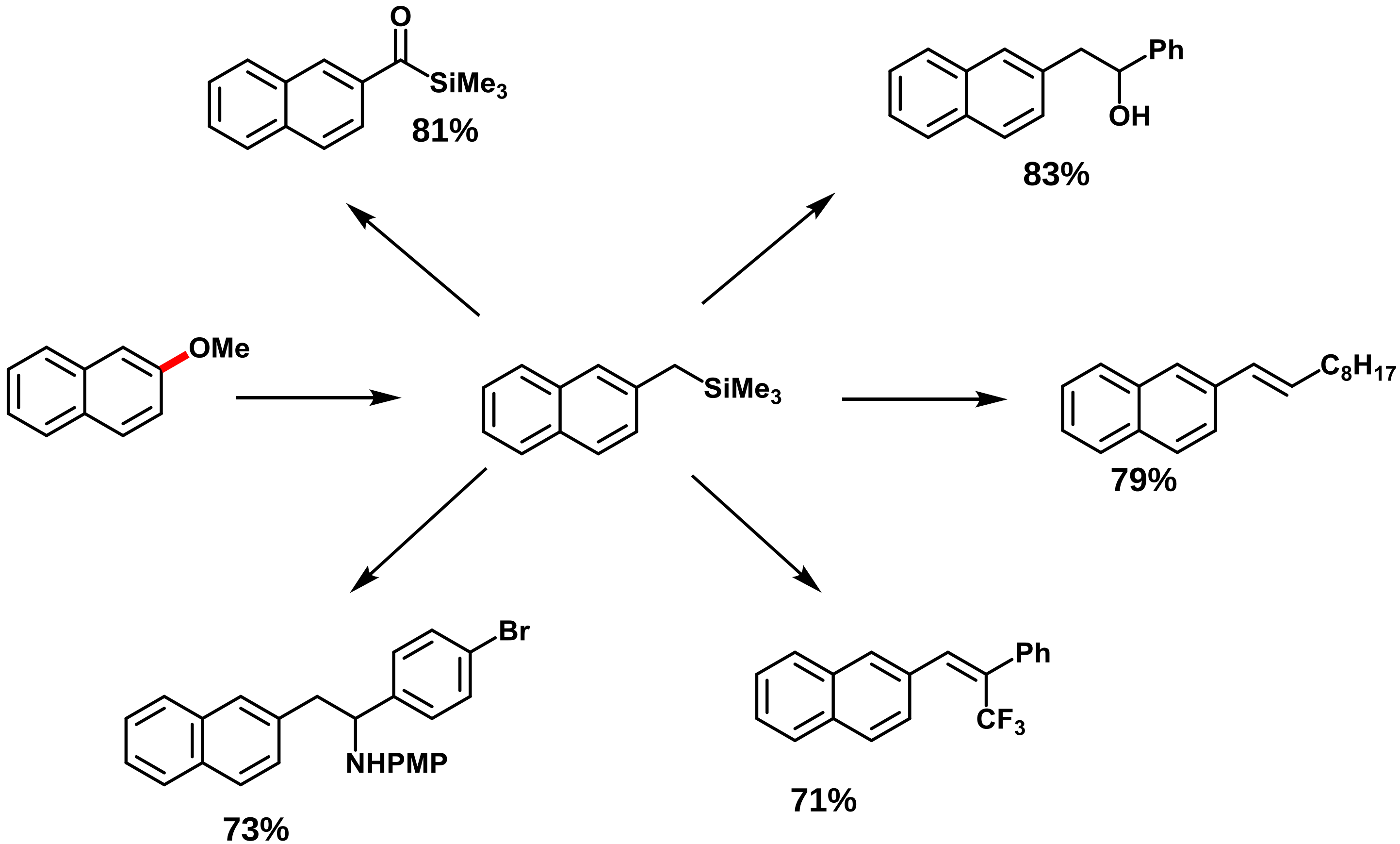


M. Leiendecker, C.-C. Hsiao, L. Guo, N. Alandini, M.R. *ACIE 53*, 12912

Natural Product Synthesis – Case Study Gephyrotoxin

Direct replacement of a MeO-Group by a functionlized nucleophile

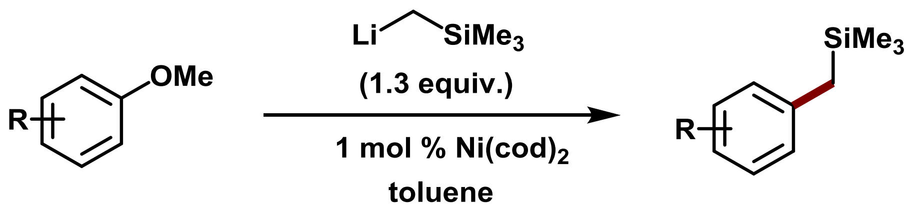
One pot operations

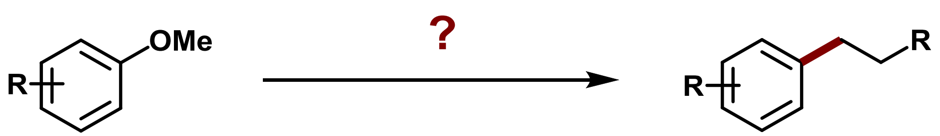


M. Leiendecker, C.-C. Hsiao, L. Guo, N. Alandini, M.R. *ACIE, 53*, 12912

Natural Product Synthesis – Case Study Gephyrotoxin

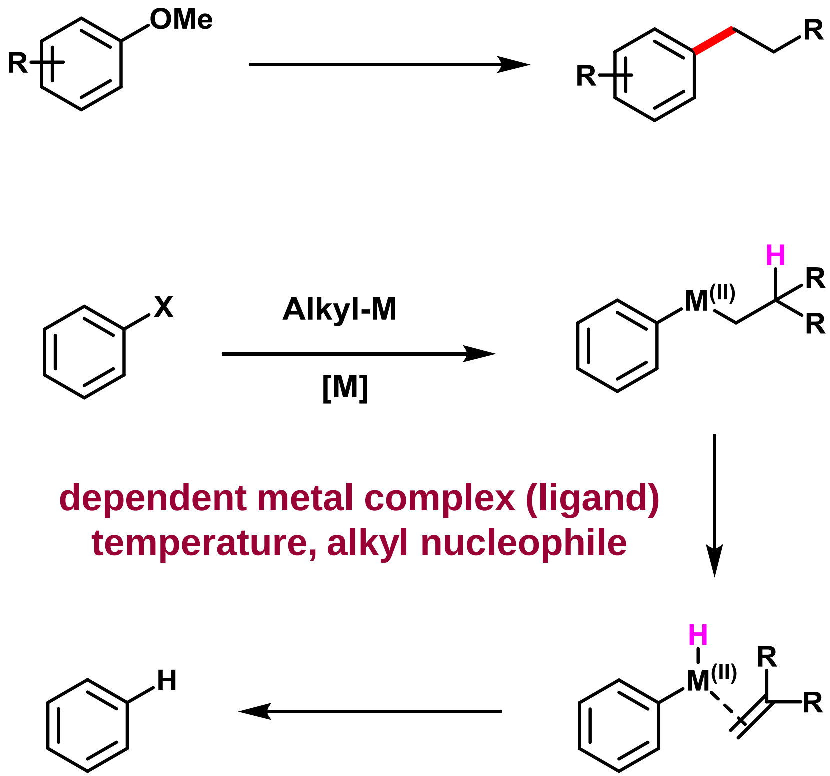
Direct replacement of a MeO-Group by a functionalized nucleophile





Natural Product Synthesis – Case Study Gephyrotoxin

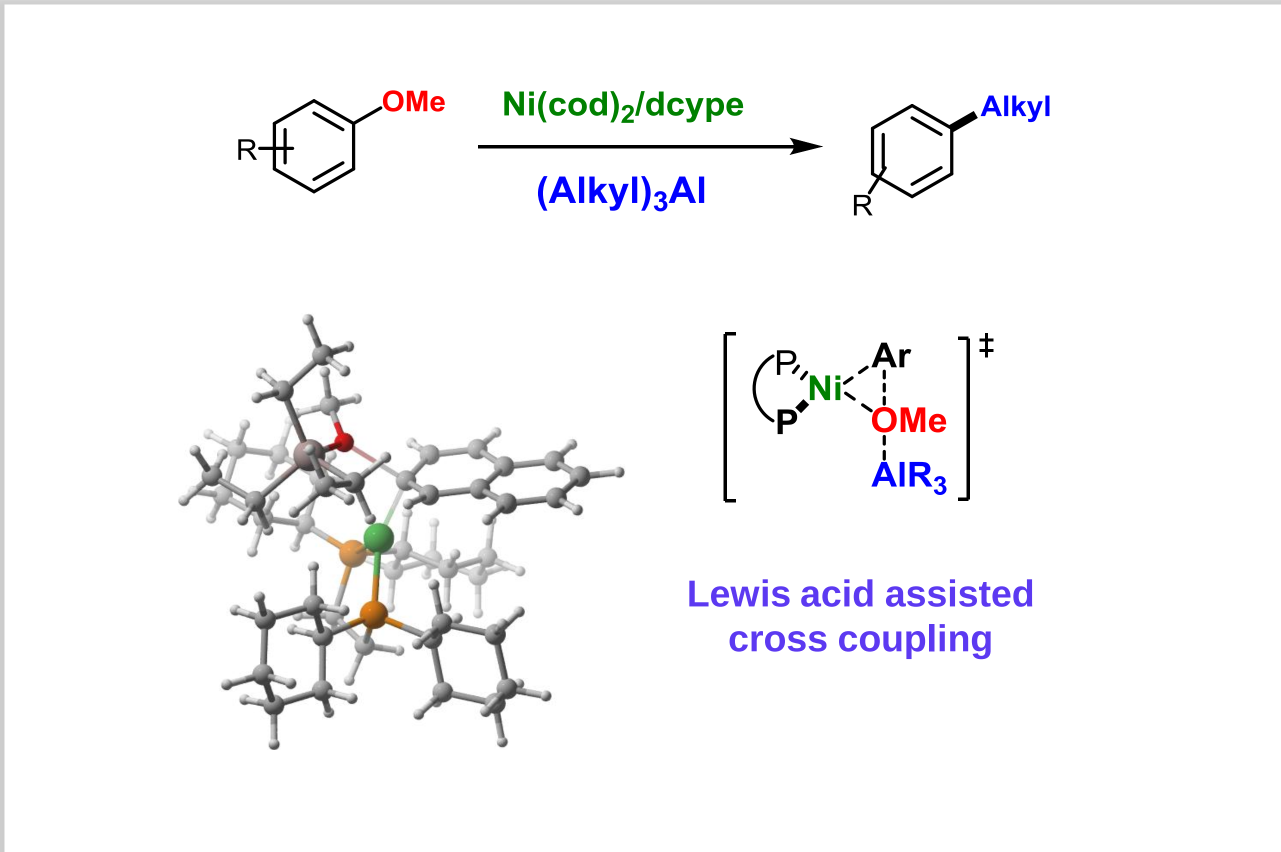
Direct replacement of a MeO-Group by a long chain alkyl group



Xiangqian Liu, C.-C. Hsiao, M. Leiendecker, Lin Guo, F. Schoenebeck, M.R. *ACIE*, *55,* 6093

Natural Product Synthesis – Case Study Gephyrotoxin

Direct replacement of a MeO-Group by a long chain alkyl group

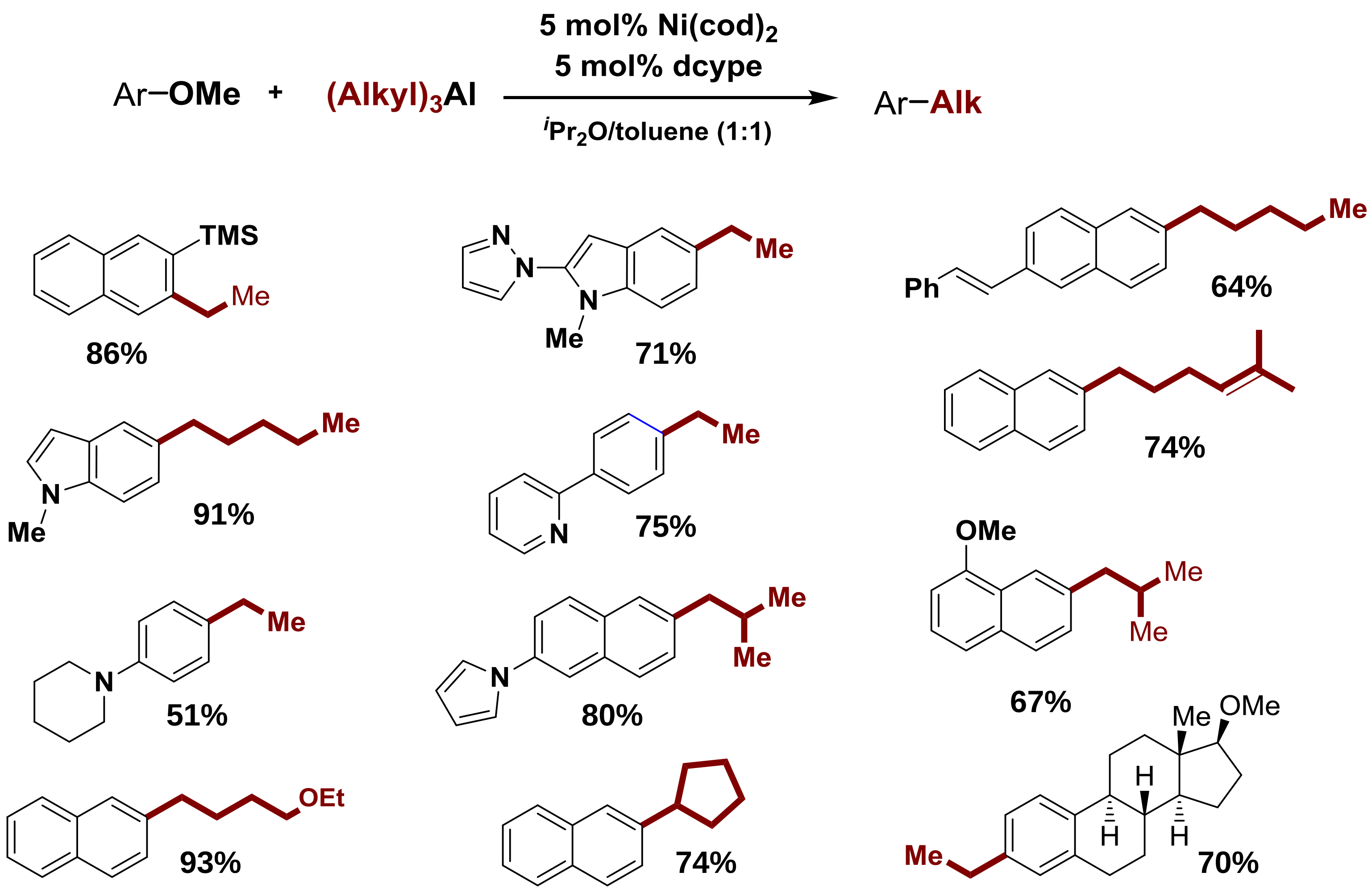


Use of AlR_3 in cross couplings: Nakamura, Knochel, Beletskaya, Chatani, Tobisu, Schmalz …

$AlMe_3$ in CO-Me exchange: Tobisu, Chatani*, Chem. Lett.* 2015, 44, 1729

Natural Product Synthesis – Case Study Gephyrotoxin

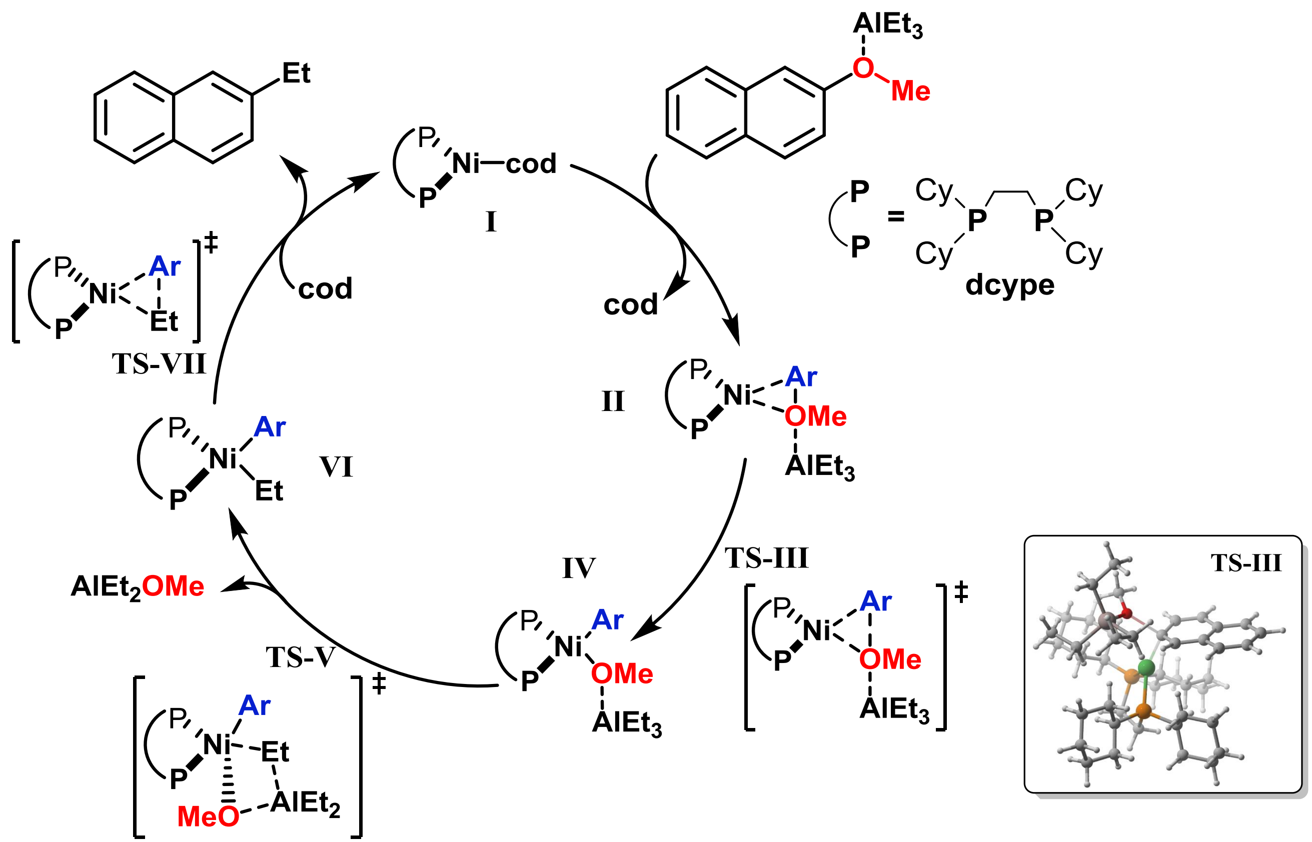
Direct replacement of a MeO-Group by Lewis acid assisted cross coupling



Xiangqian Liu, C.-C. Hsiao, M. Leiendecker, Lin Guo, F. Schoenebeck, M.R. *ACIE*, *55,* 6093

Natural Product Synthesis – Case Study Gephyrotoxin

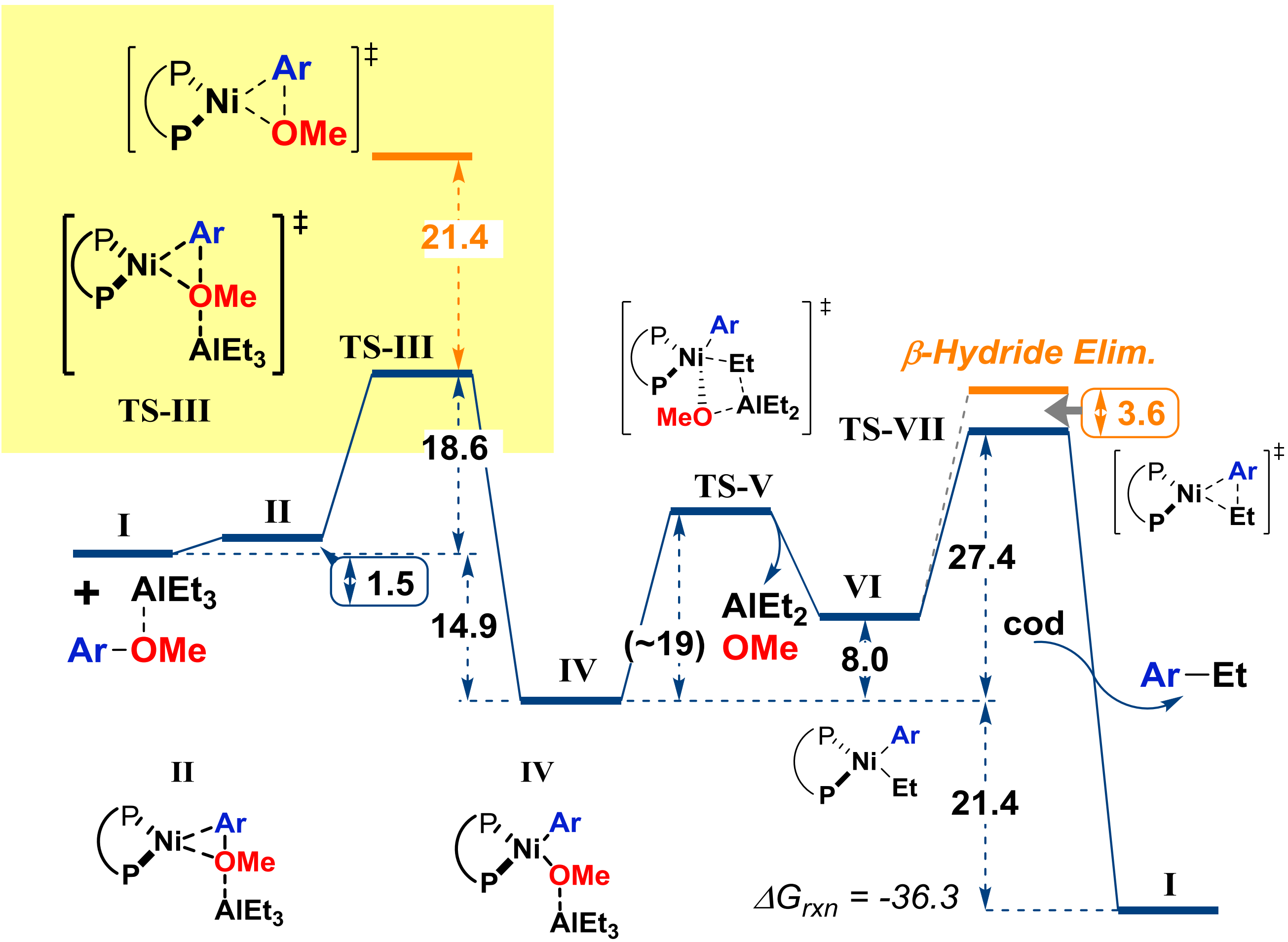
Proposed Mechanism based on experiments and DFT calculations



Xiangqian Liu, C.-C. Hsiao, M. Leiendecker, Lin Guo, F. Schoenebeck, M.R. *ACIE*, *55,* 6093

Natural Product Synthesis – Case Study Gephyrotoxin

Proposed Mechanism based on experiments and DFT calculations



Xiangqian Liu, C.-C. Hsiao, M. Leiendecker, Lin Guo, F. Schoenebeck, M.R. *ACIE*, *55,* 6093

Natural Product Synthesis – Case Study Gephyrotoxin

Direct replacement of a MeO-Group by Lewis acid assisted cross coupling

$$\text{Ar–OMe} + (\text{Alkyl})_3\text{Al} \xrightarrow[{}^{i}\text{Pr}_2\text{O/toluene (1:1)}]{\text{5 mol\% Ni(cod)}_2,\ \text{5 mol\% dcype}} \text{Ar–Alk}$$

$$\text{Ar–OMe} + (\text{Alkyl})_x\text{Y} \xrightarrow{\text{catalyst}} \text{Ar–Alk}$$

?

- broader substrate scope
- readily accessible and more stable nucleophiles

Natural Product Synthesis – Case Study Gephyrotoxin

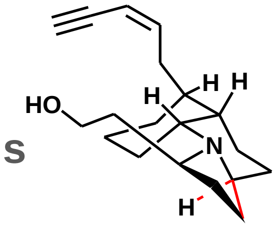
Direct replacement of a MeO-Group by Lewis acid assisted cross coupling

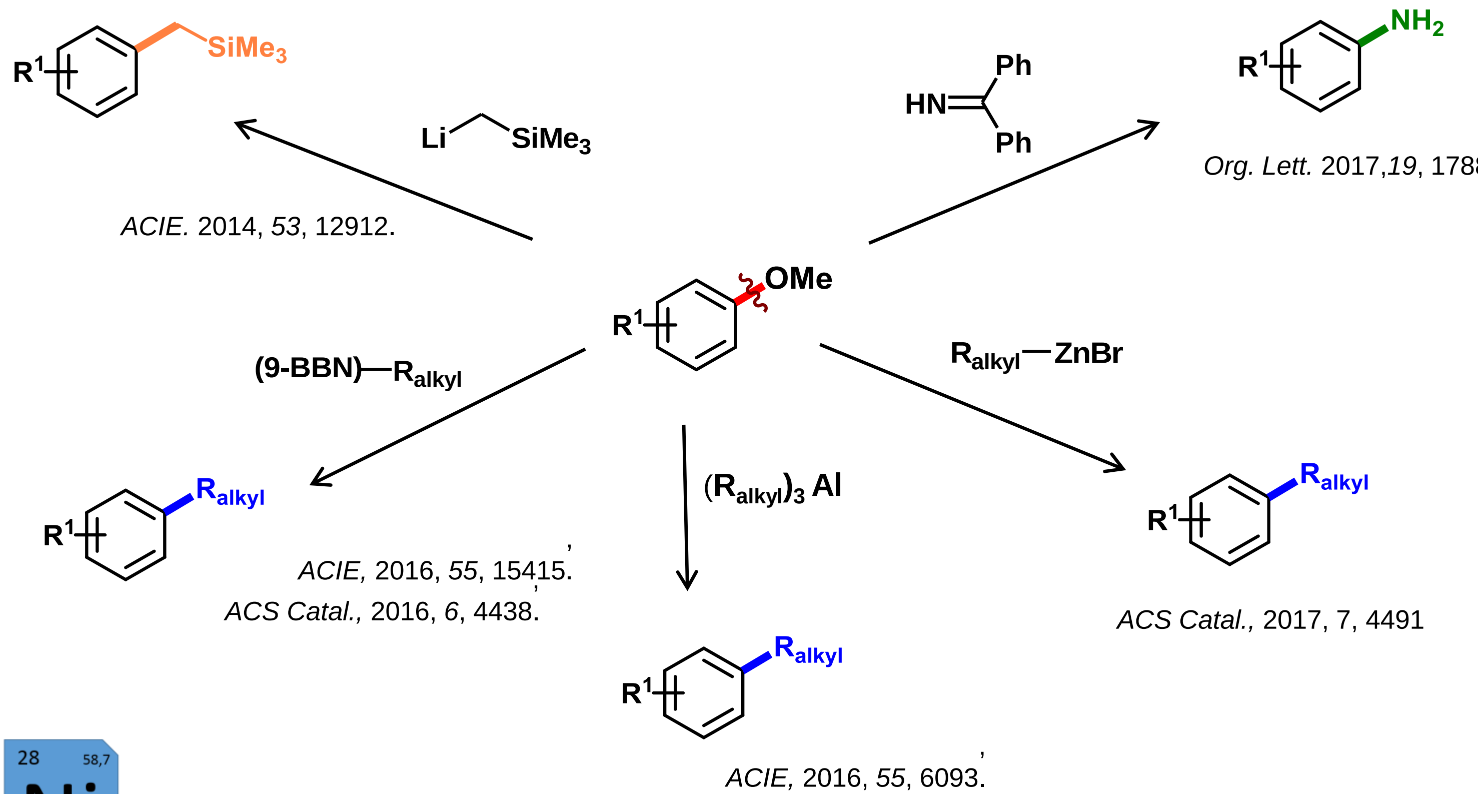
$$\mathrm{Ar{-}\mathbf{OMe}} + \mathbf{B(Alkyl)_n} \xrightarrow{\text{catalyst}} \mathrm{Ar{-}\mathbf{Alk}}$$

- **readily accessible and more stable nucleophiles**

Recent reaction developments in homogeneous metal catalysis

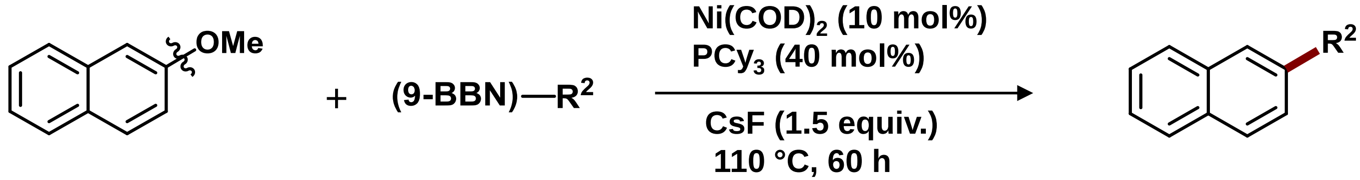
C-OMe Bond activations – dealkoxylative Nickel catalyzed cross-couplings

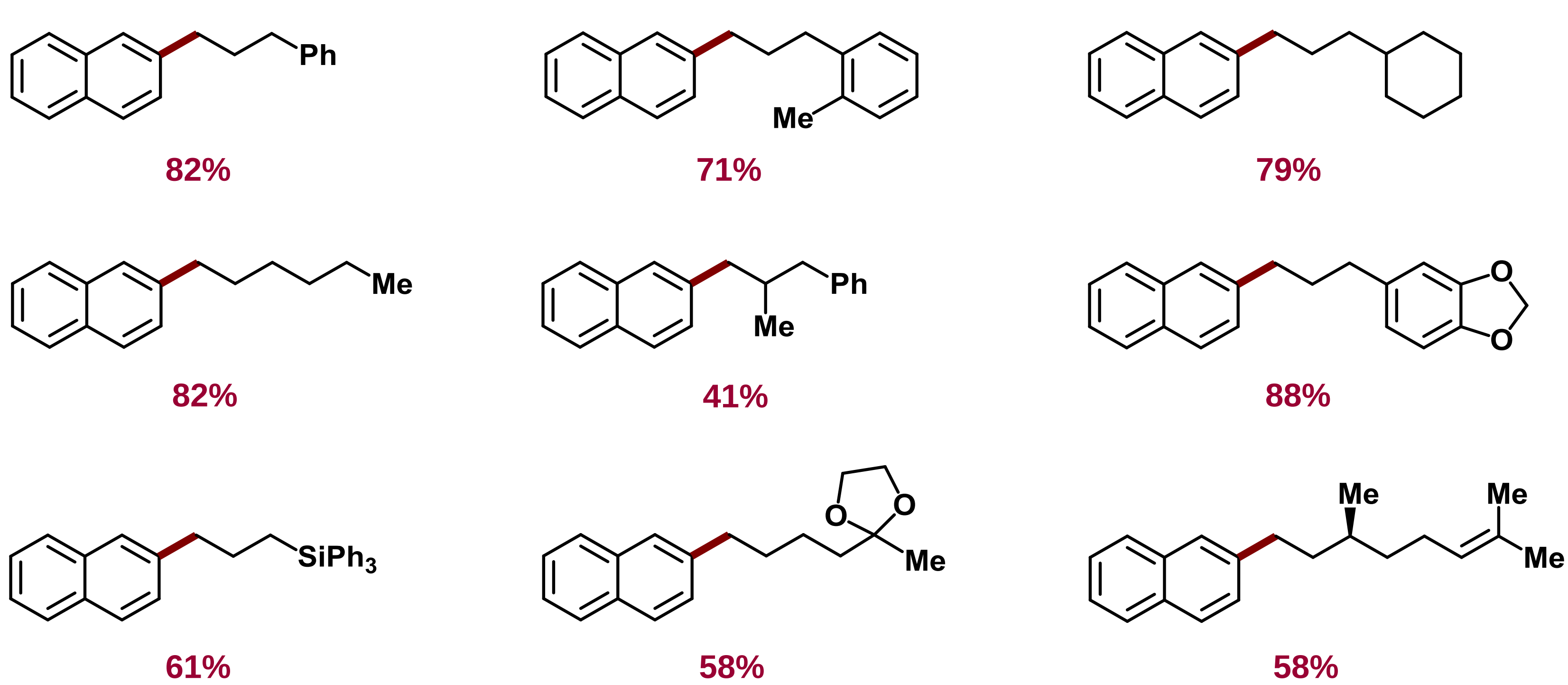




Catalytic Dealkoxylating C_{sp2}-C_{sp3} Cross Coupling Reactions

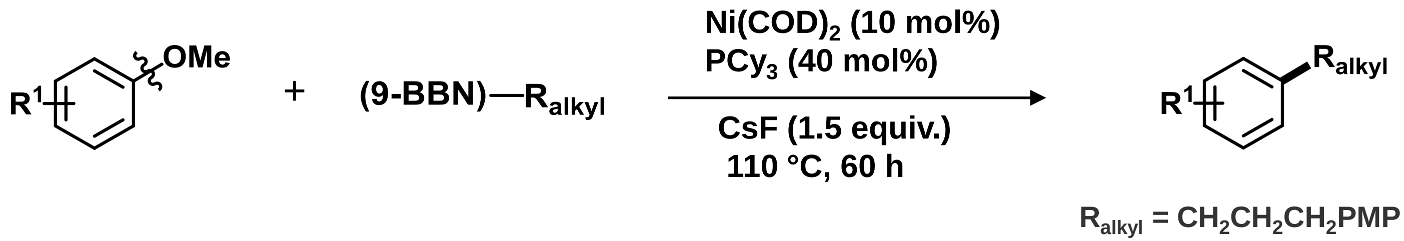
Ni-Catalyzed Alkoxy-Alkyl Interconversion with Alkylboranes

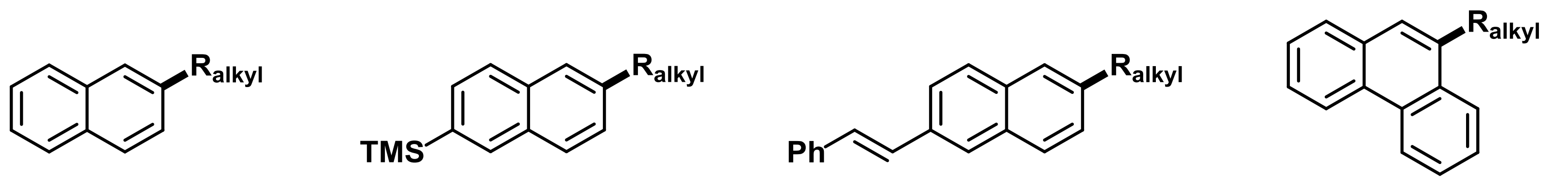




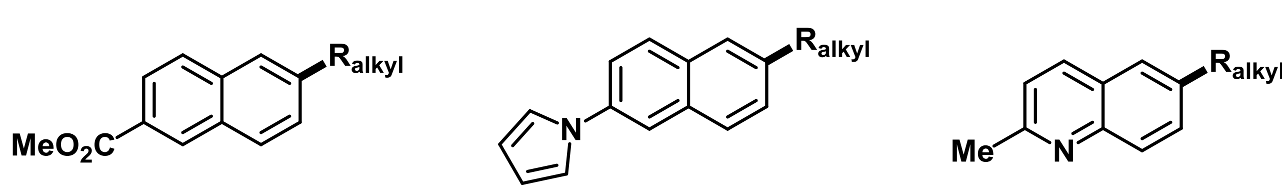
Catalytic Dealkoxylating C_{sp2}-C_{sp3} Cross Coupling Reactions

Ni-Catalyzed Alkoxy-Alkyl Interconversion with Alkylboranes





93% 75% 90% 92%



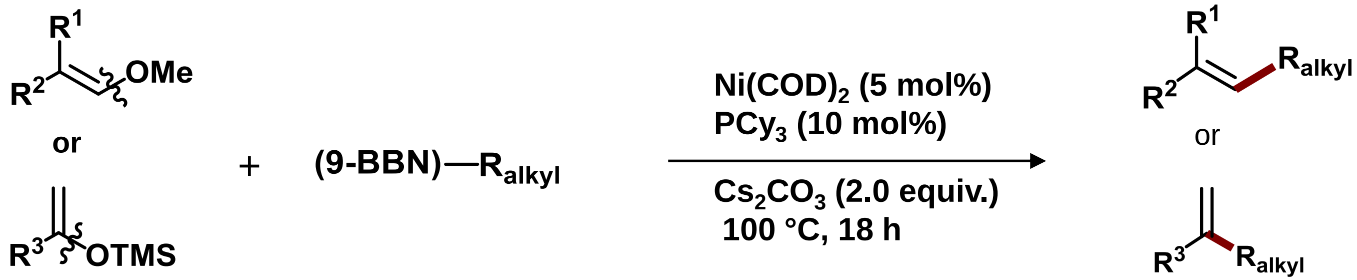
69% 63% 77% 62%

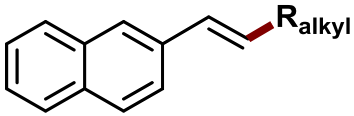
ArOMe-alkylation with Grignard reagents: M. Tobisu, T. Takahira, T. Morioka, N. Chatani, *JACS*, 2016, 138, 6711

L. Guo, X. Liu, C. Baumann, MR ACIE, 55,15415

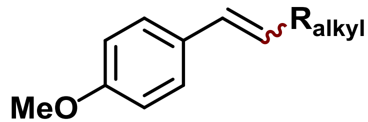
Catalytic Dealkoxylating C_{sp2}-C_{sp3} Cross Coupling Reactions

Ni-Catalyzed Alkoxy-Alkyl Interconversion with Alkylboranes

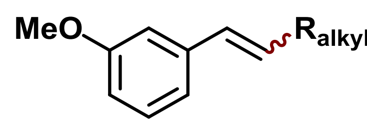




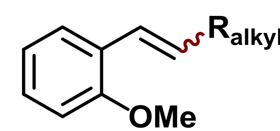
92%



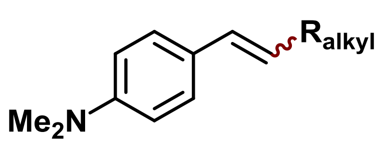
95%, E:Z > 10:1



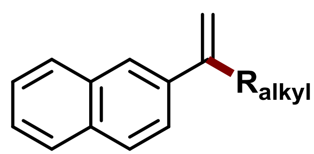
89%, E:Z > 10:1



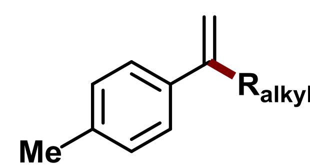
49%, E:Z > 10:1



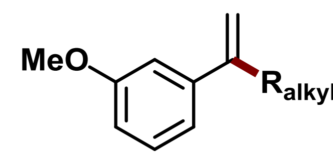
81%, E:Z > 10:1



79%



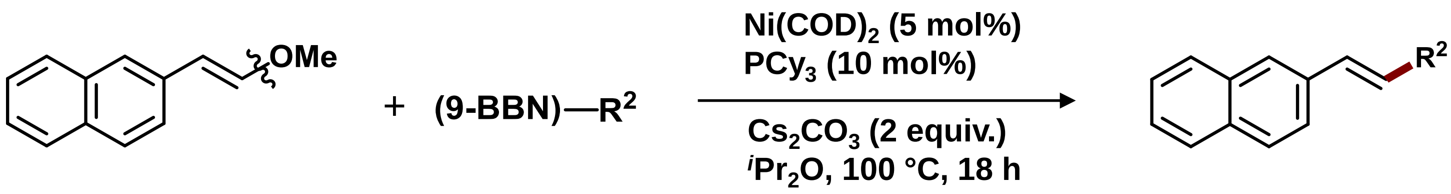
75%

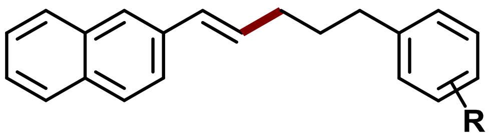


56%

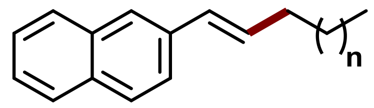
Catalytic Dealkoxylating C_{sp2}-C_{sp3} Cross Coupling Reactions

Ni-Catalyzed Alkoxy-Alkyl Interconversion with Alkylboranes

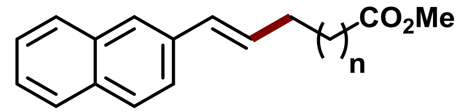




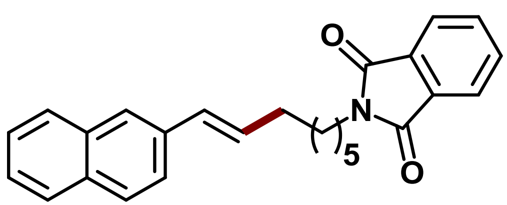
R = H: 85%
R = 4-F: 77%
R = 3,4-OMe: 90%



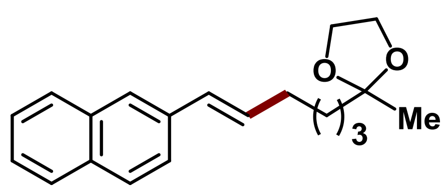
n = 6: 75%
n = 12: 84%



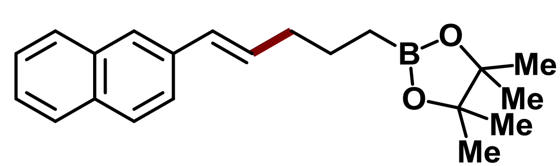
n = 4: 75%
n = 9: 85%



94%



89%

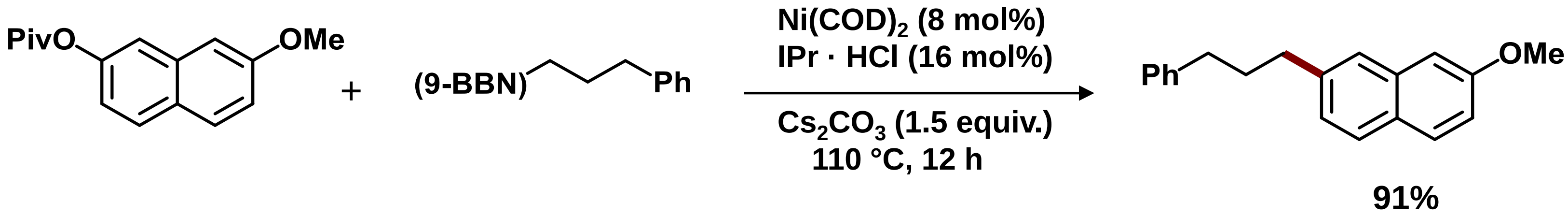


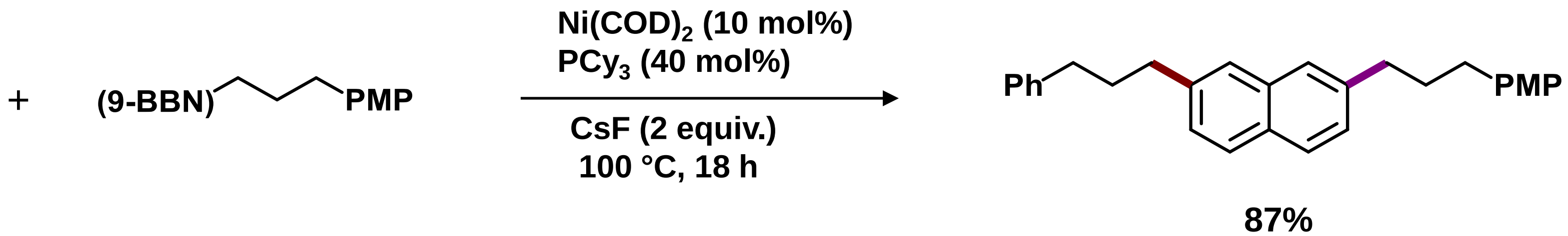
86%

L. Guo, X. Liu, C. Baumann, MR ACIE, 55,15415

Catalytic Dealkoxylating C_{sp2}-C_{sp3} Cross Coupling Reactions

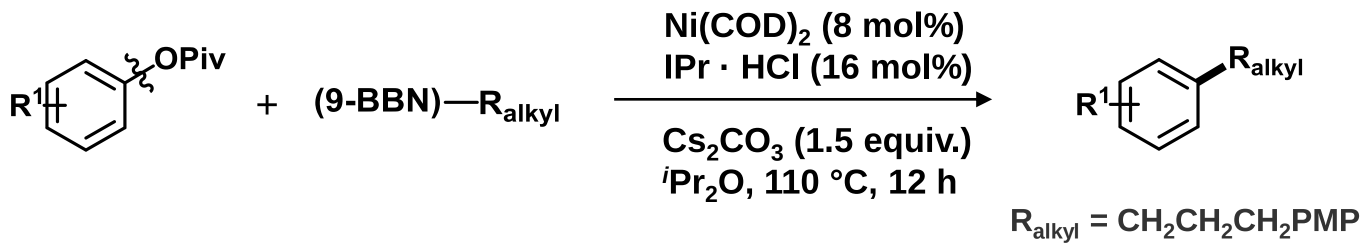
Ni-Catalyzed Sequential Alkylation with Alkylboranes

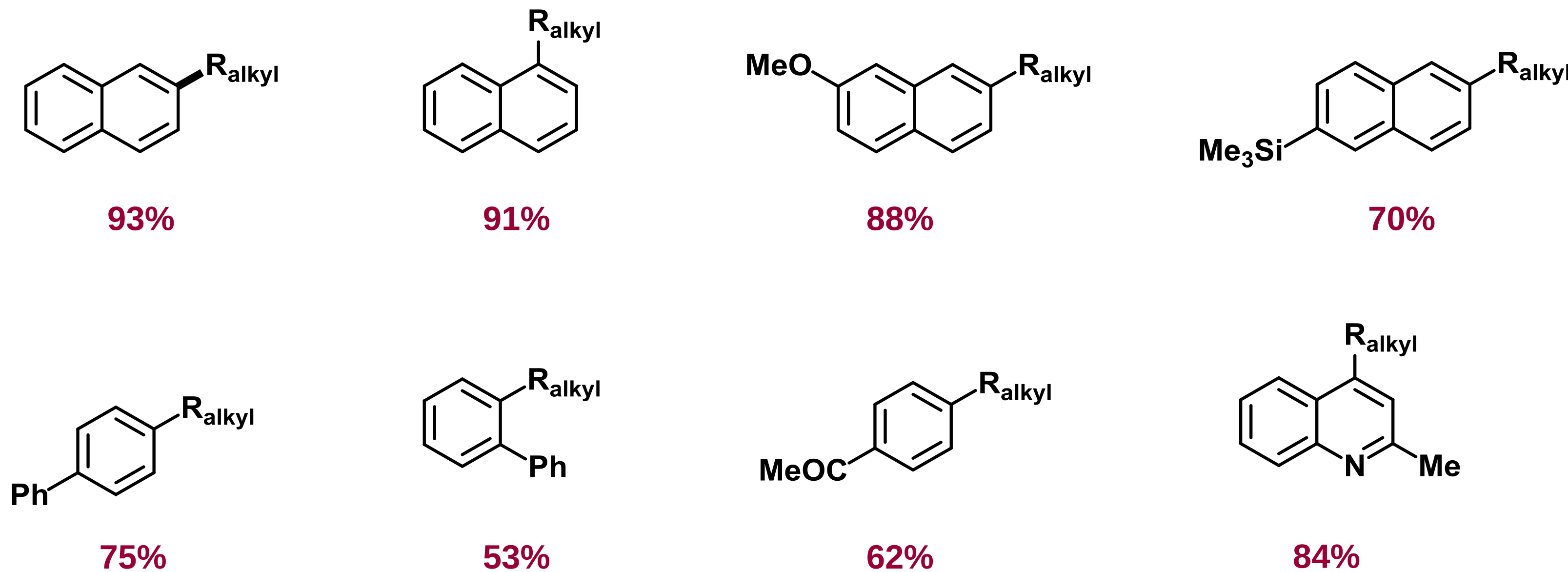




Catalytic Dealkoxylating C_{sp2}-C_{sp3} Cross Coupling Reactions

Ni-Catalyzed Alkylation with Alkylboranes

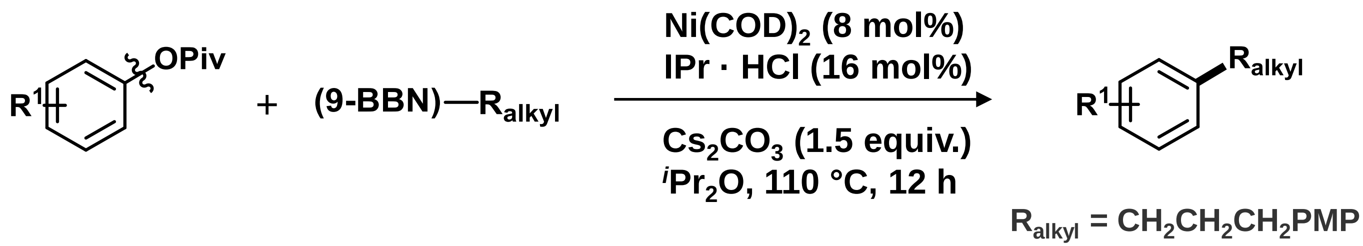


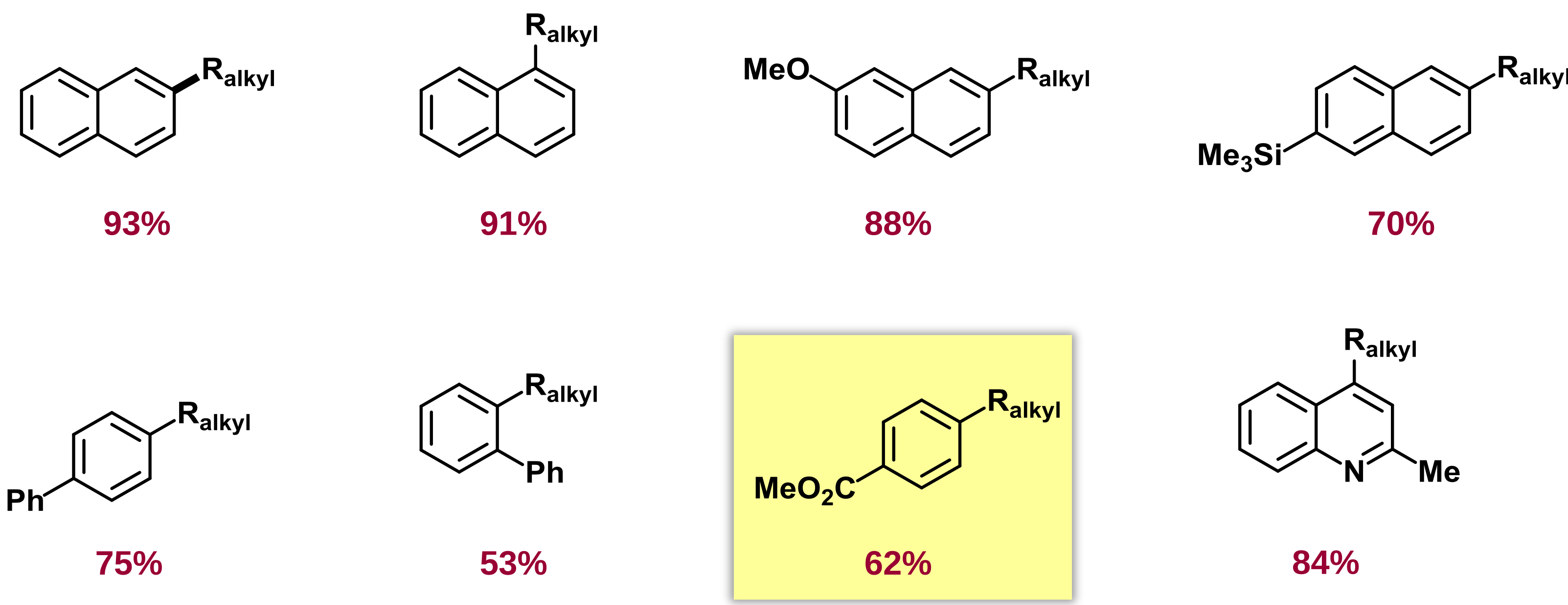


L. Guo, C.-C. Hsiao, H. Yue, X. Liu, M. Rueping, *ACS Cat.,* 2016, *6*, 4438

Catalytic Dealkoxylating C_{sp2}-C_{sp3} Cross Coupling Reactions

Ni-Catalyzed Alkylation with Alkylboranes



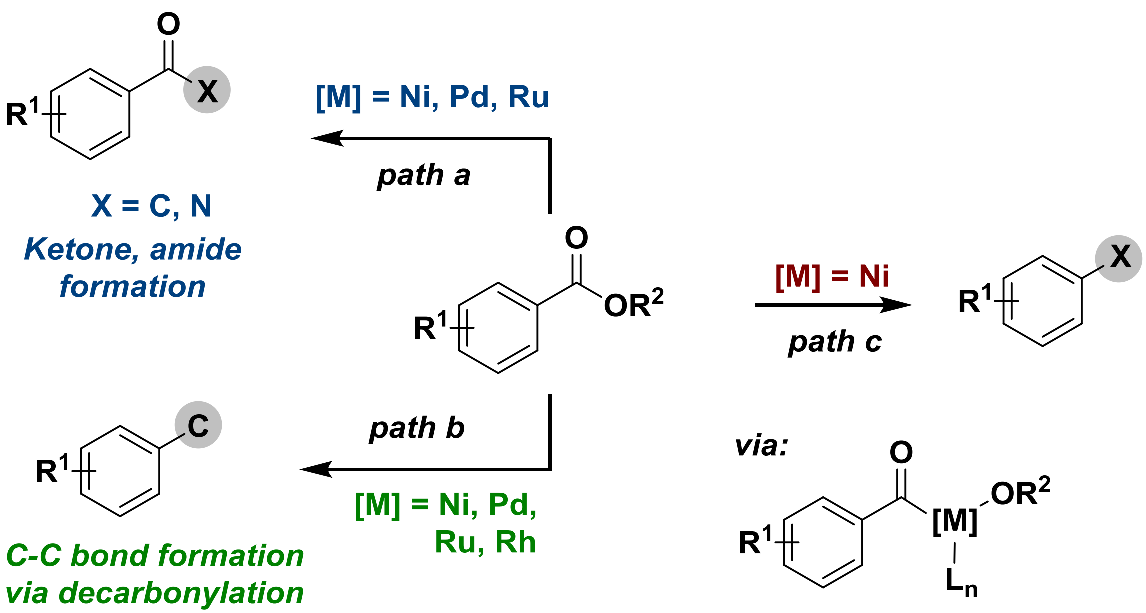


Decarbonylation observed

L. Guo, C.-C. Hsiao, H. Yue, X. Liu, M. Rueping, *ACS Cat.,* 2016, *6*, 4438

Catalytic Decarbonylative Cross Coupling Reactions

Ni-Catalyzed Decarbonylative Catalysis



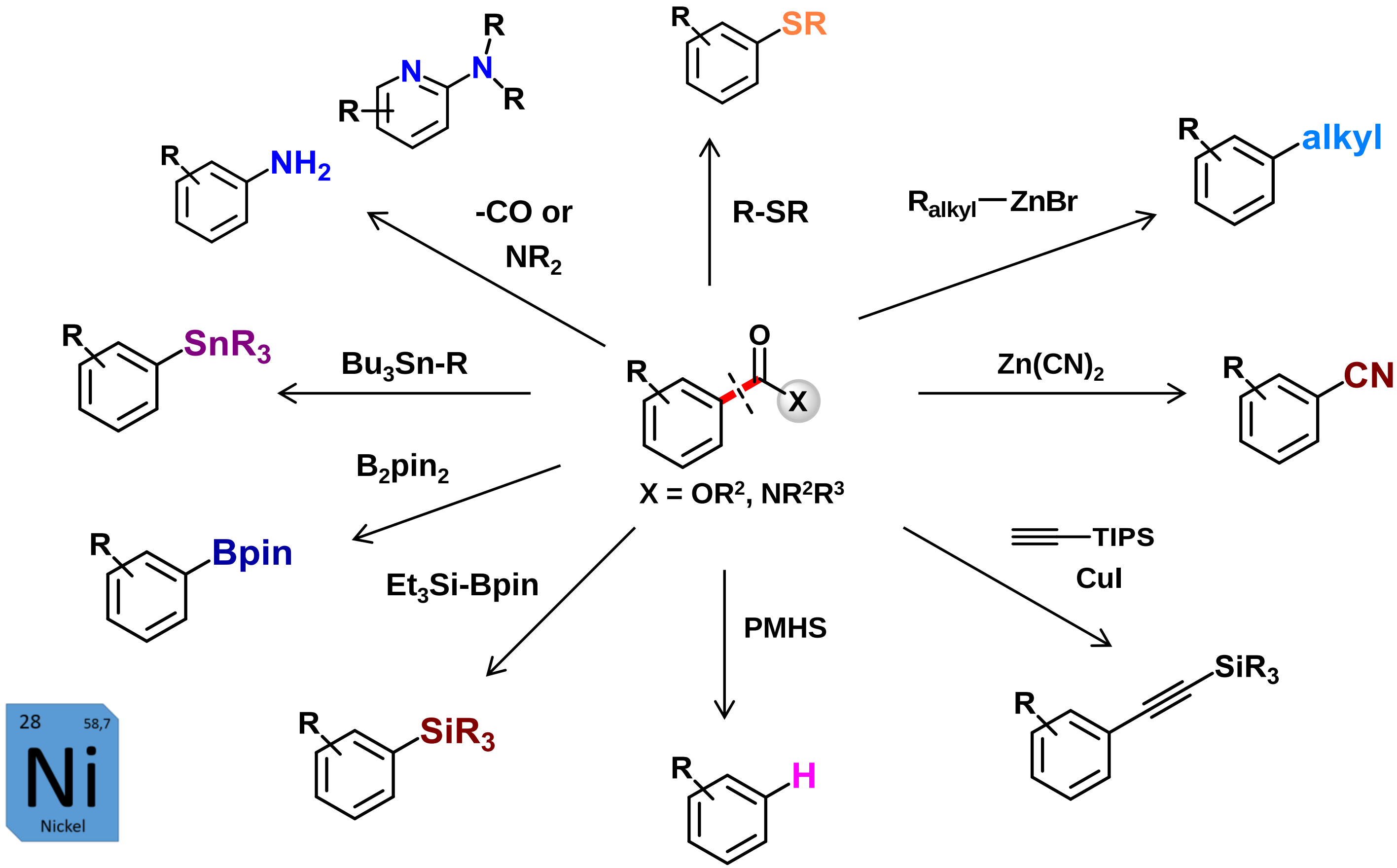
First example: T. Yamamoto, J. Ishizu, T. Kohara, S. Komiya, A. Yamamoto, *JACS,* **1980**, *102*, 3758
Representative examples for Ketones from esters: H. Tatamidani, F. Kakiuchi, N. Chatani, *Org. Lett.* **2004**, *6*, 3597; H. Tatamidani, K. Yokota, F. Kakiuchi, N. Chatani, *J. Org. Chem.* **2004**, *69*, 5615
Amides from esters: L. Hie, N. F. F. Nathel, X. Hong, Y. F. Yang, K. N. Houk, N. K. Garg, *ACIE* **2016**, *55*, 2810
Biaryls and alkynes from esters: K. Amaike, K. Muto, J. Yamaguchi, K. Itami, JACS, **2012**,*134*,13573; K. Muto, J. Yamaguchi, D. G. Musaev, K. Itami, *Nat. Commun*. **2015**, *6,* 7508

Recent reaction developments in nickel catalyzed functional group interconversion

C-O; C-N and C-C Bond activations – decarbonylative transformations

decarbonylative C-Het bond formations

decarbonylative C-C bond formations



Acc. Chem. Res. **2018,** *51*, 1185, *JACS* **2018**, *140*, 3724; *CEJ* **2018**, 24, 3608; *Org. Lett*. **2018**, *20*, 385; *Org. Lett.* **2017**, *19*, 4255; *ACIE* **2017**, *56,* 4282; *Chem. Eur. J.* **2016**, *22,* 16787; *ACIE.* **2016**, *55*, 11810, *ACIE* **2017**, *56,* 3972; *CEJ.* **2017**, *23,* 11771