

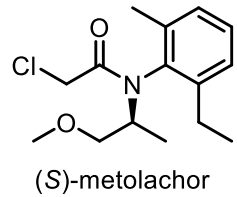
Acid-mediated hydroaminomethylation

Gitlina Anastasia

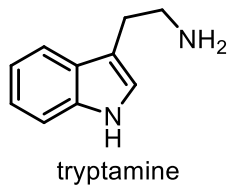
PhD student, LCS, Prof. Kay Severin

Amines

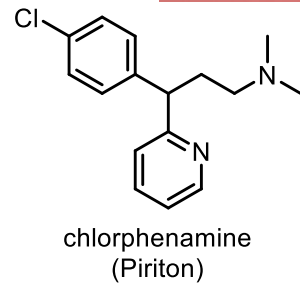
Agrochemicals



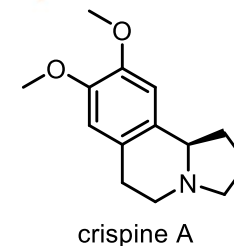
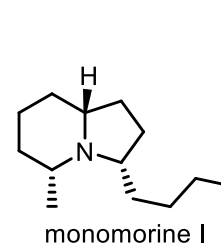
Food-additives



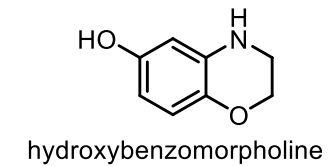
Pharmaceuticals



Natural products



Cosmetics



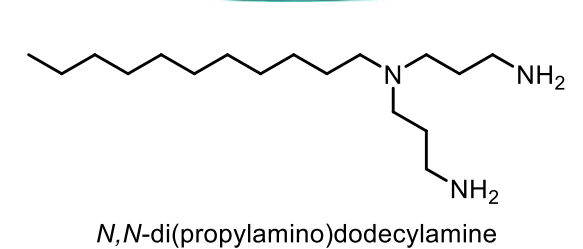
Lubricants

Antiseptics

Textiles

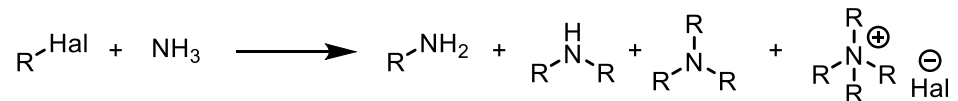
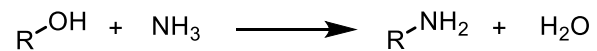
Solvents

Detergents



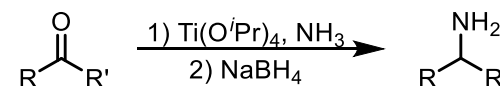
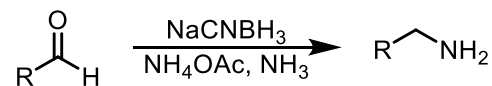
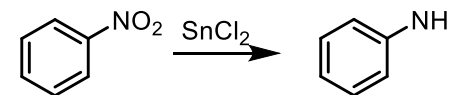
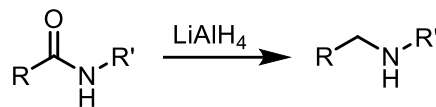
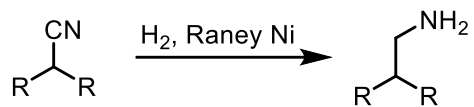
Summary of amines synthesis

Classical S_N2 reactions:

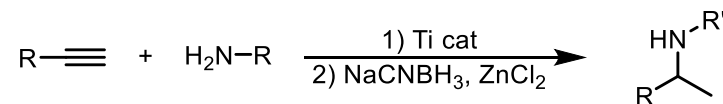
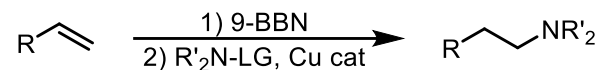


+ Gabriele synthesis
+ Delépine reaction
+ Mitsunobu reaction

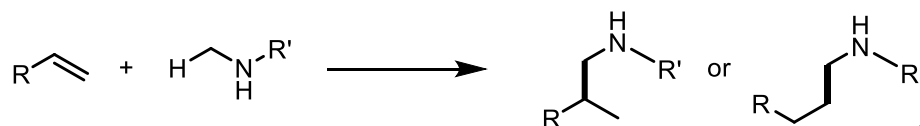
Reductive routes:



Hydroamination:

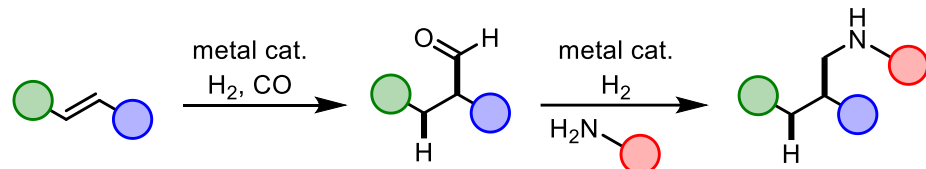


Hydroaminomethylation (HAM):

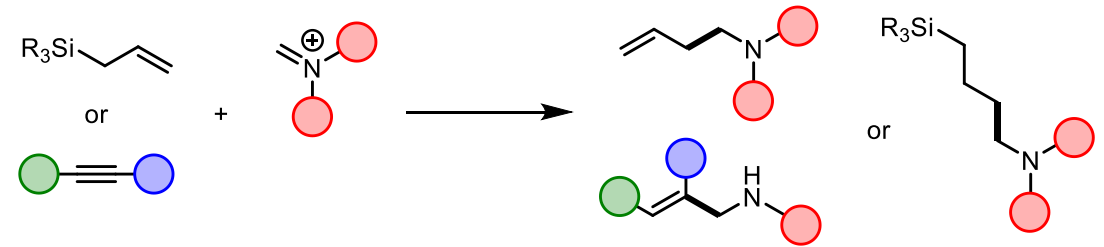


HAM methods

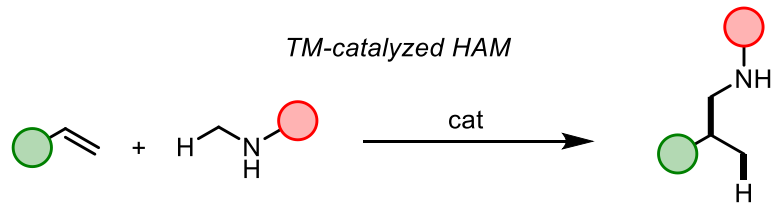
Tandem HAM via hydroformylation



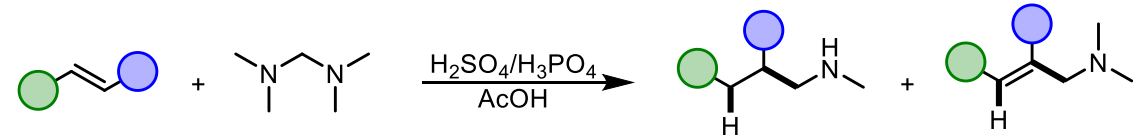
HAM with iminium salts



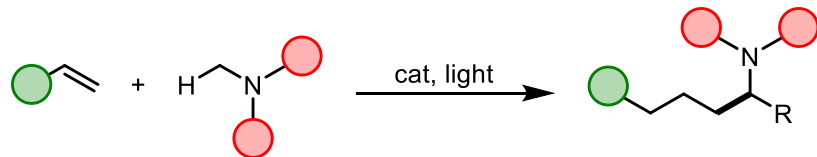
TM-catalyzed HAM



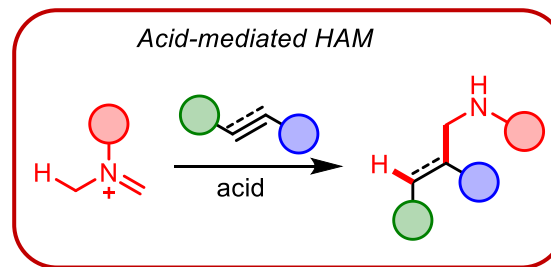
HAM with aminals



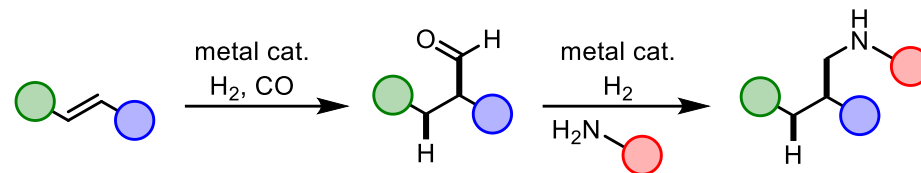
Photoredox HAM



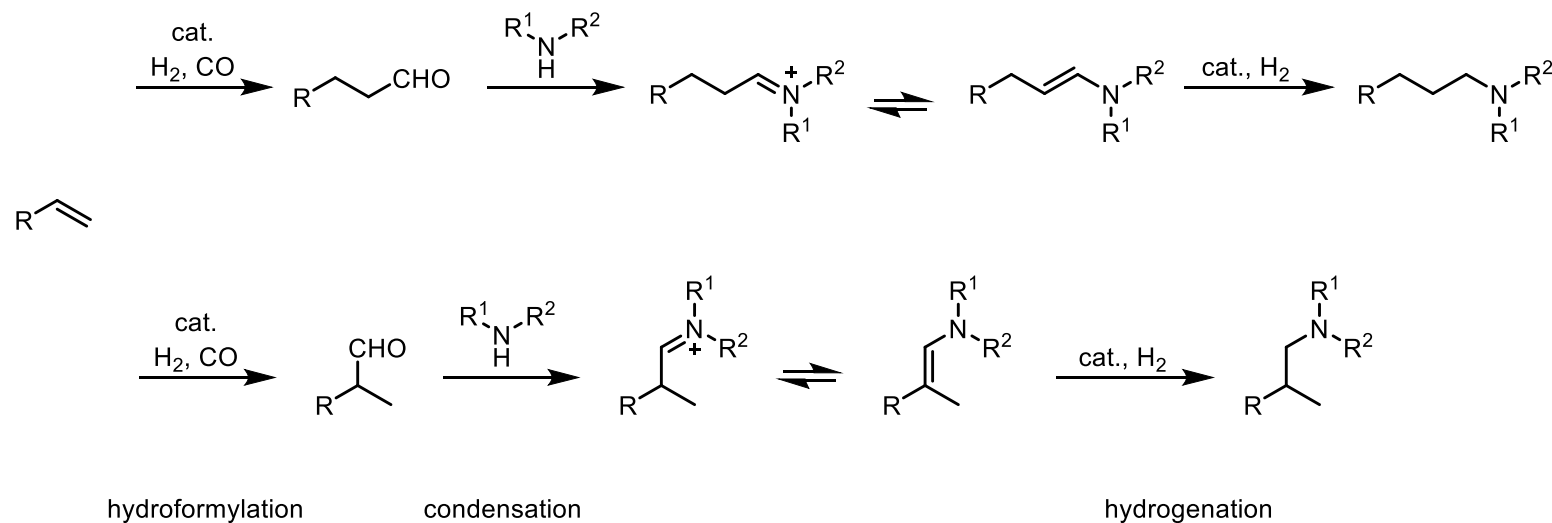
Acid-mediated HAM



Tandem HAM *via* hydroformylation

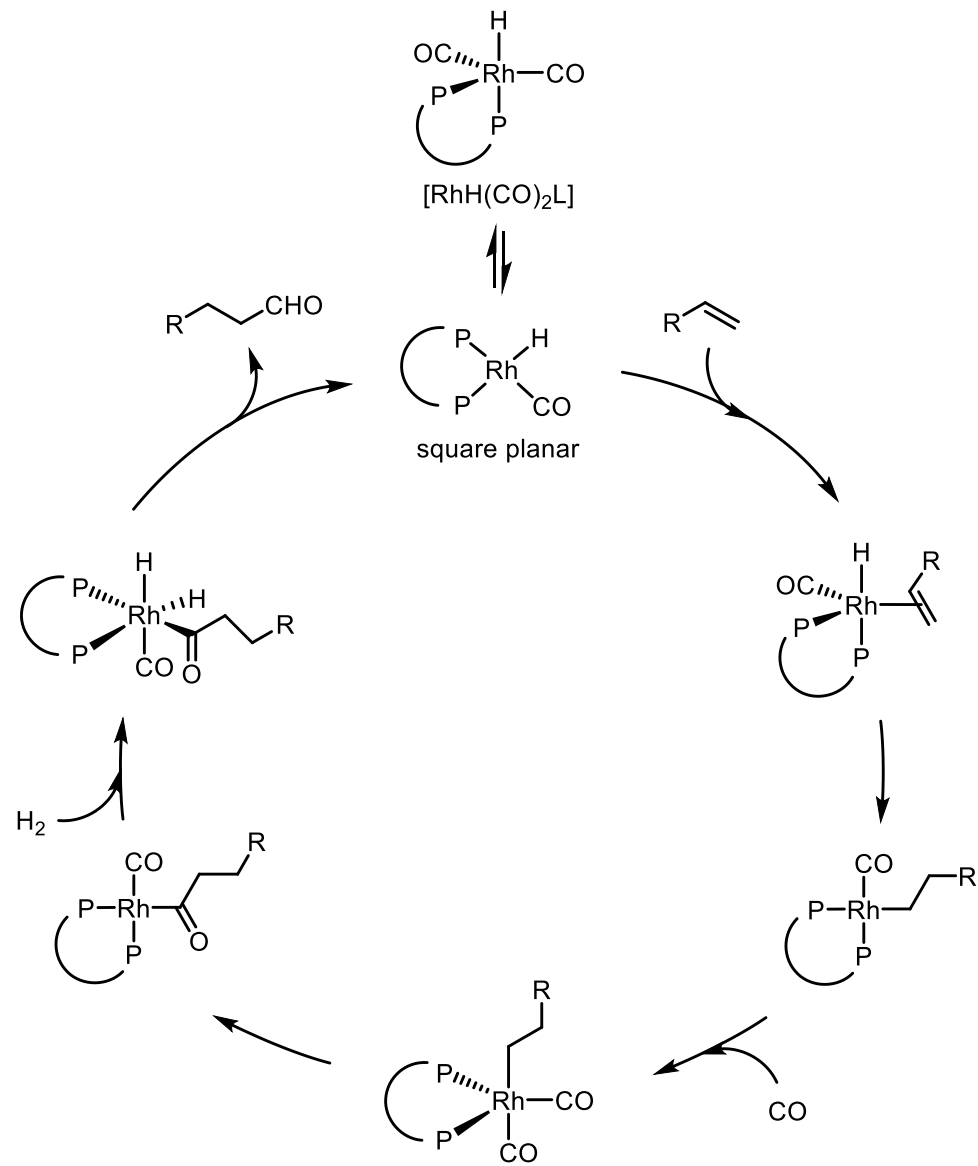


Kaiser et al., *Angew. Chem. In. Ed.*, **2019**, 58, 14639

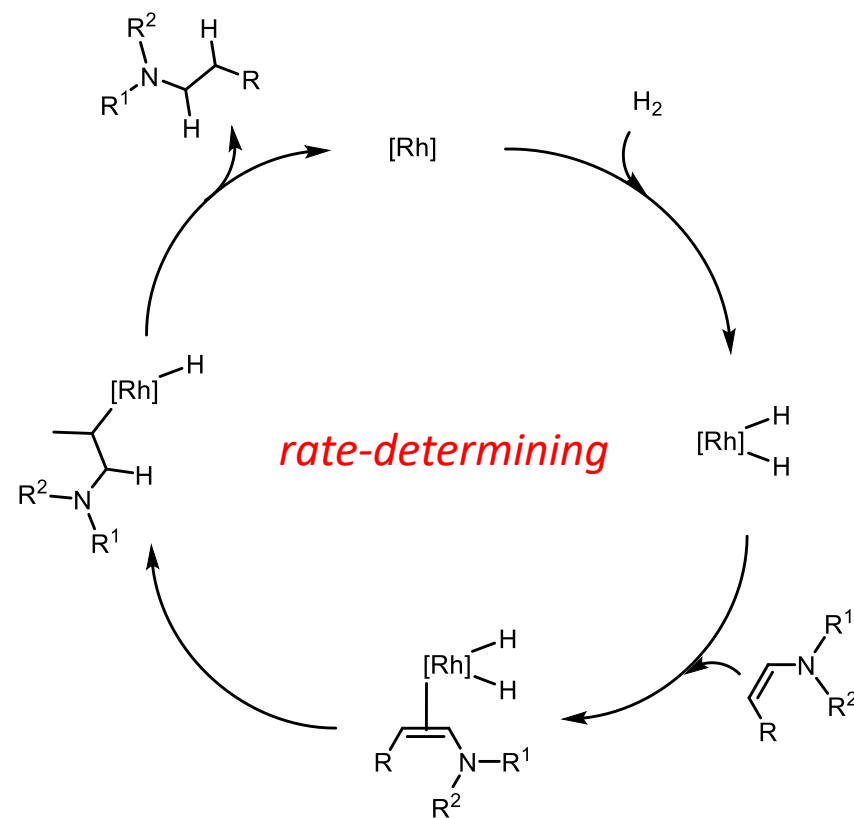


Kalck et al., *Chem. Rev.*, **2018**, 118, 3861

Catalytic cycle of hydroformylation step



Catalytic cycle of hydrogenation step

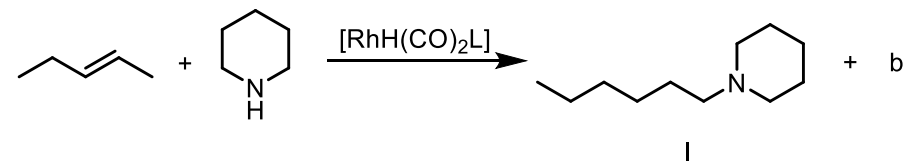
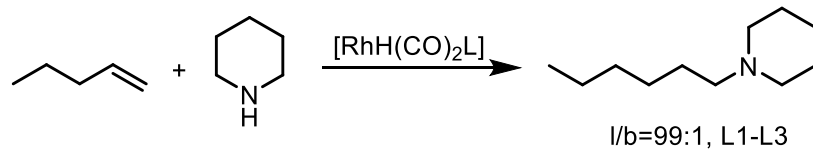
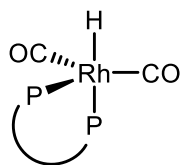


General conditions:

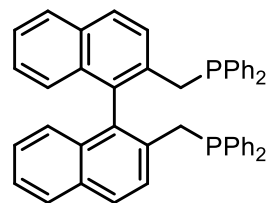
90 to 130 °C, 30 to 60 bar

CO/H₂ (1:1 to 1:5)

30 min to 72 h

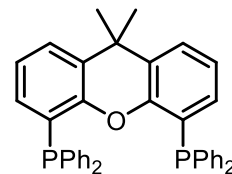
HAM reaction of terminal and internal alkenes**Unmodified catalysts:**Rh₂O₃[Ru₃(CO)₁₂][Rh(acac)(CO)₂][Rh₂(μ-Cl)₂(COD)₂]**Ligand-decorated catalysts:**[RhH(CO)₂L]

L =



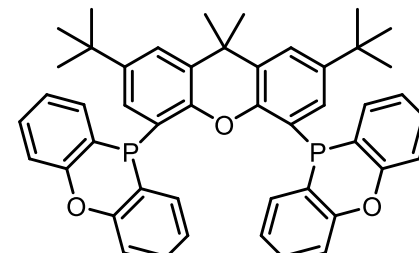
L1, 120°

yield (I) 6%, I/b=99:1



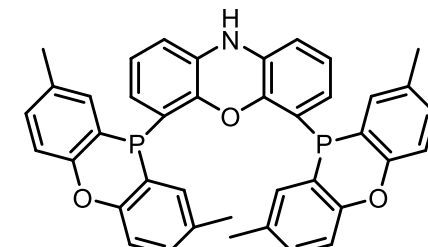
L2, 111°

yield (I) quant, I/b=93:7



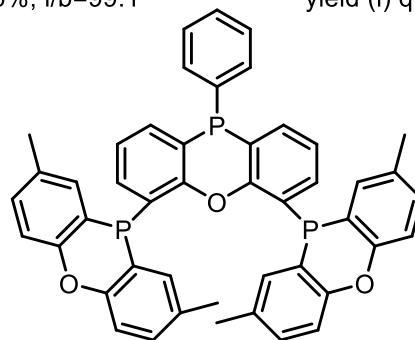
L3, 123°

yield (I) 67%, I/b=73:27



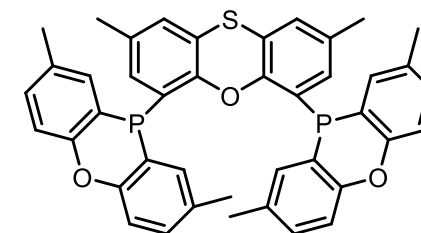
L4, 125°

yield (I) 56%, I/b=73:27



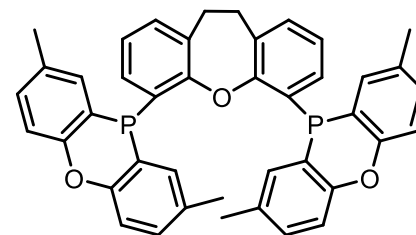
L5, 131°

yield (I) 40%, I/b=51:49



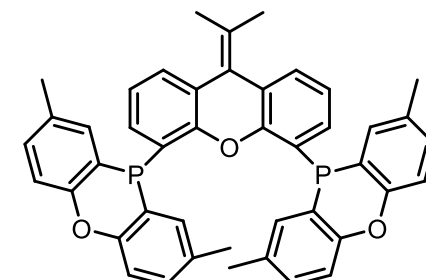
L6, 113°

yield (I) 43%, I/b=45:55



L7, 106°

yield (I) 15%, I/b=20:80



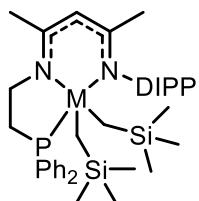
L8, 114°

yield (I) 67%, I/b=68:32

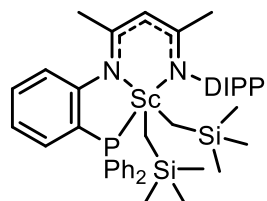
Metal-catalyzed HAM of alkenes

Recent catalytic systems:

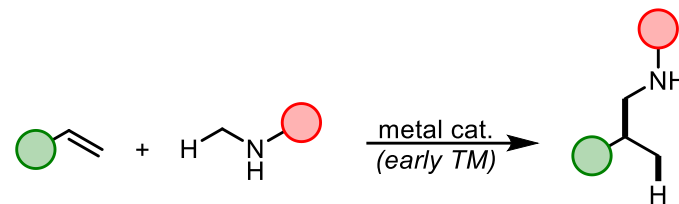
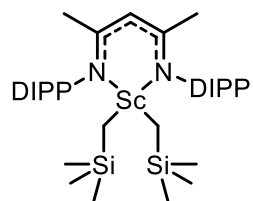
3 group



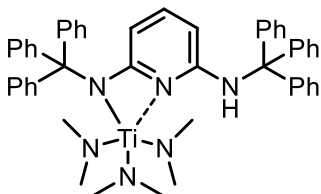
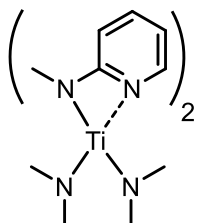
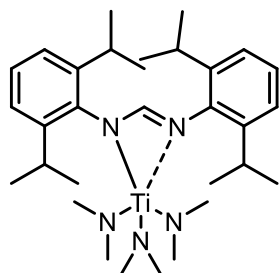
M = Sc, Y



Gao et al, *Org. Chem. Front.*, **2018**, 5, 59

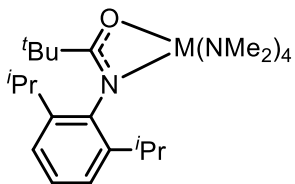


4 group

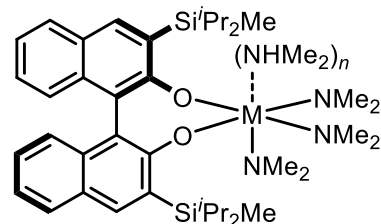
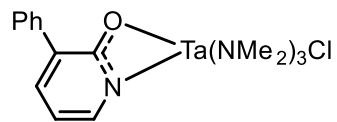


Lehning et al, *Chem. Eur. J.*, **2017**, 23, 4197
Bielefeld et al, *Angew. Chem. Int. Ed.*, **2017**, 56, 15155

5 group



M = Nb, Ta



M = Ta, n = 1
M = Nb, n = 0

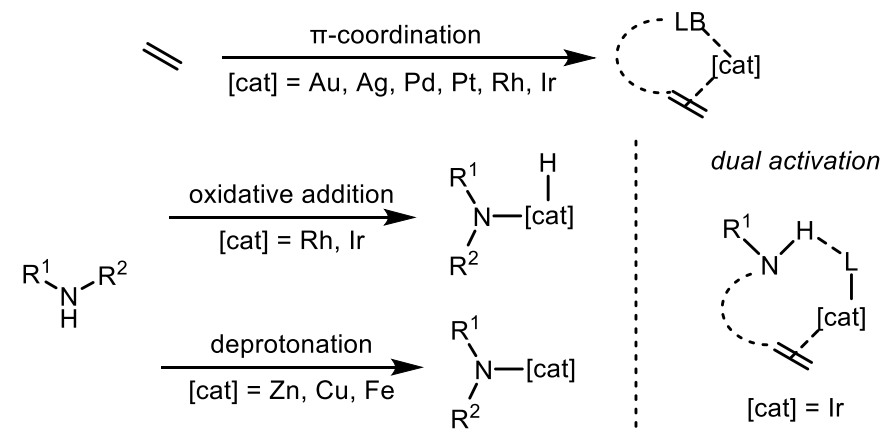
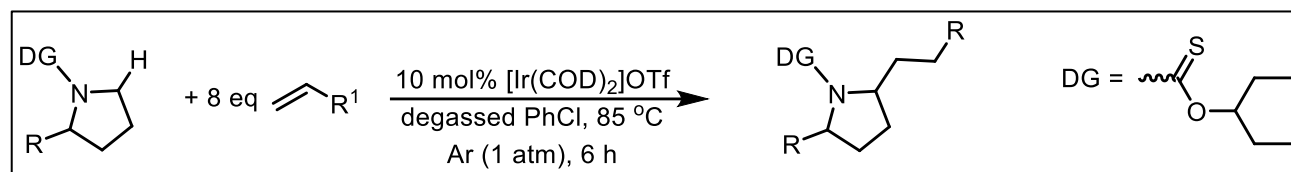
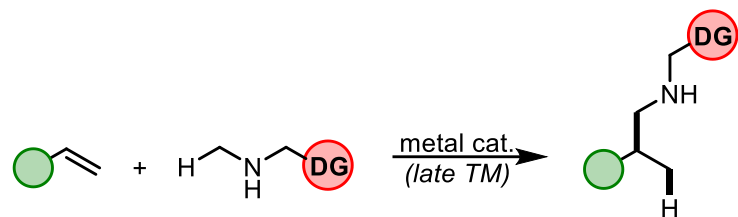
Lauzon et al, *ACS Catal.*, **2017**, 7, 5921

Chong et al, *J. Am. Chem. Soc.*, **2014**, 136, 10898

Reznichenko et al, *J. Am. Chem. Soc.*, **2012**, 134, 3300

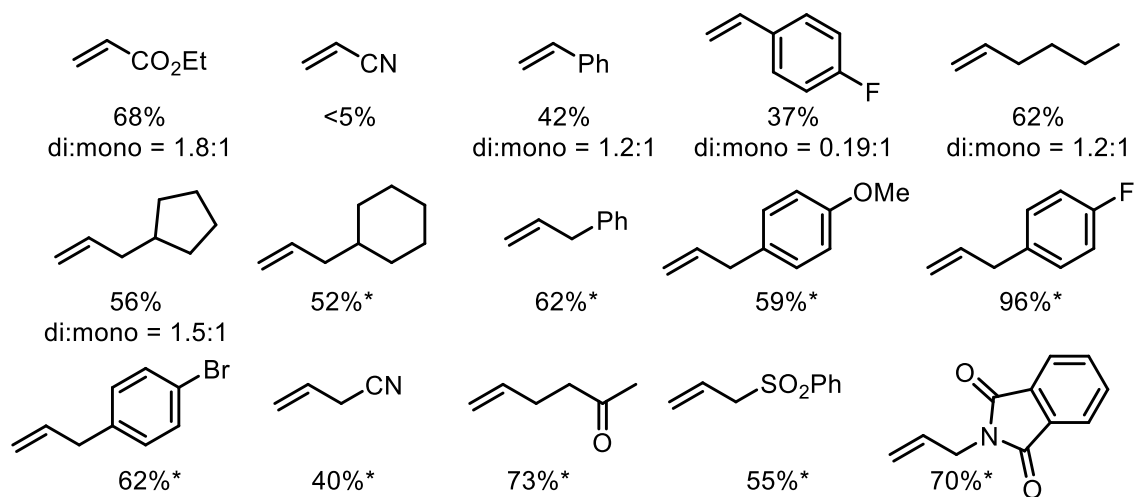
Overall:

- + 1^o, 2^o, 3^o amines
- + activated and nonactivated alkenes
- + moderate to good yields
- terminal alkenes
- double HAM
- mixture of linear and branched products
- moderate FG tolerance
- air sensitivity



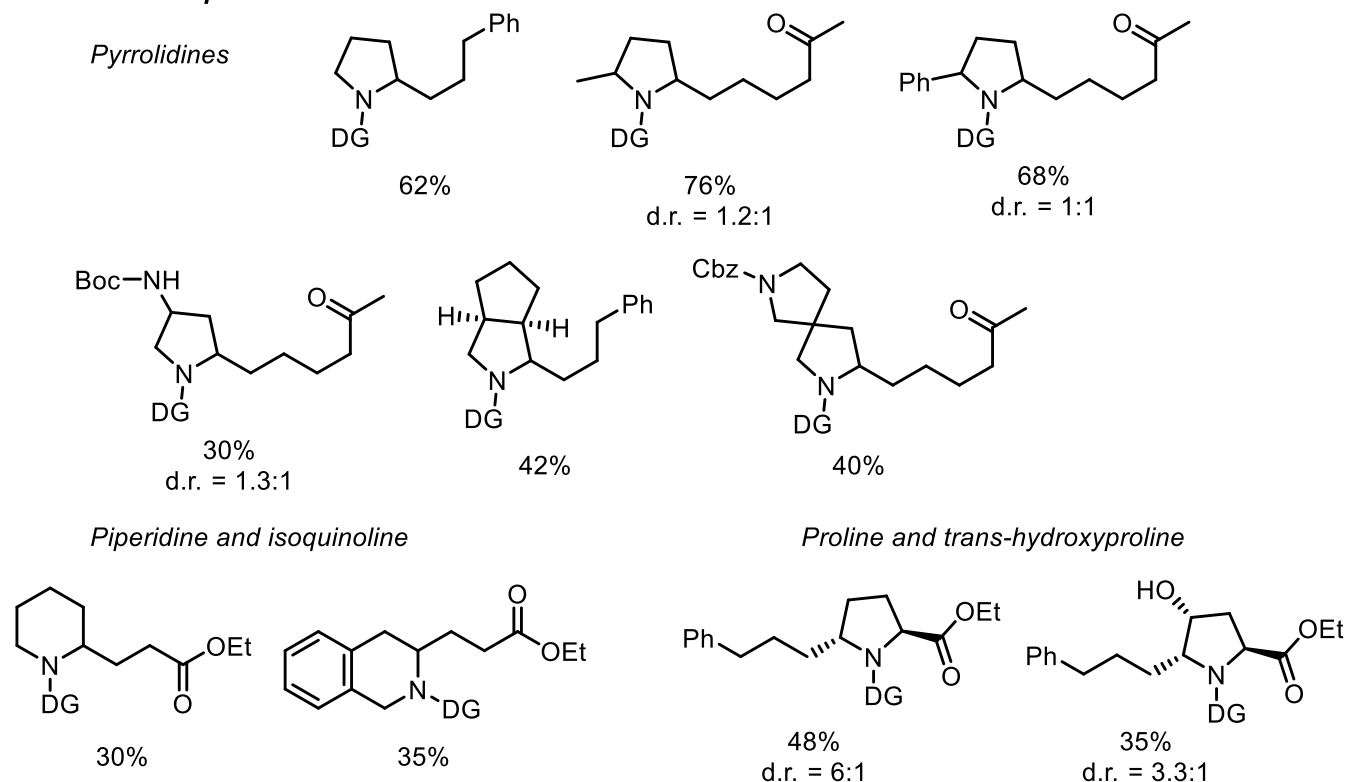
Bernoud *et al*, *Catal. Sci. Technol.*, **2015**, 5, 2017

Olefins scope, R = H

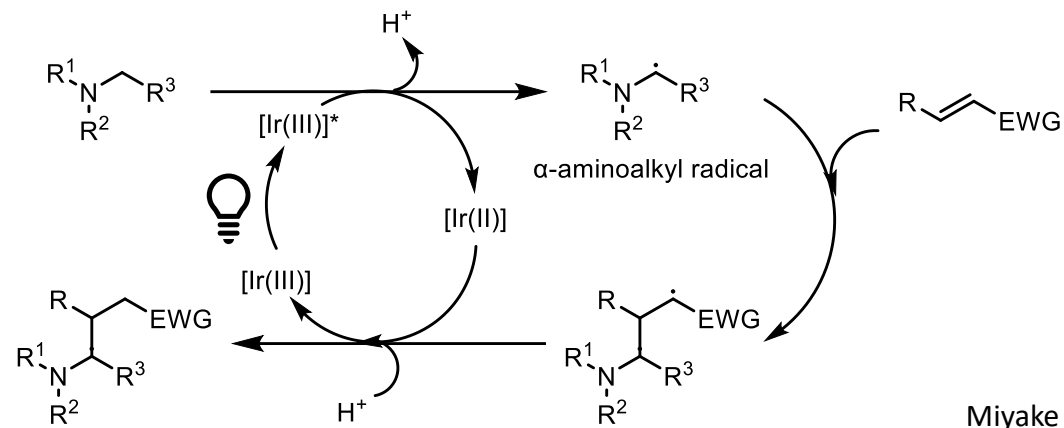


*only dialkylated products (d.r. > 20:1) were obtained for these substrates

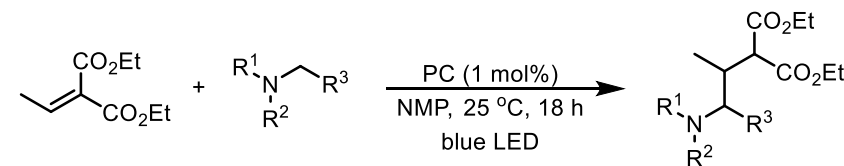
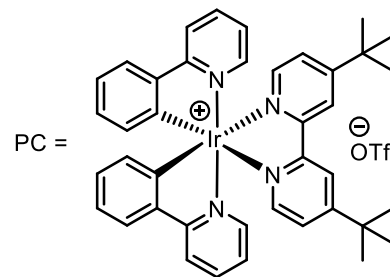
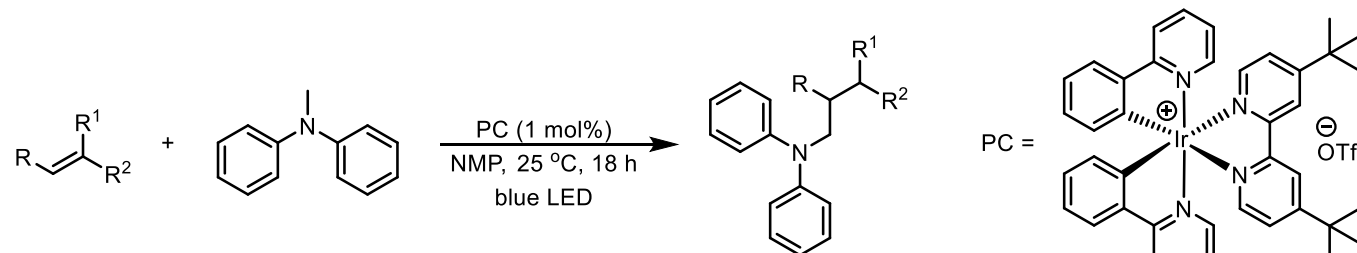
Amines scope



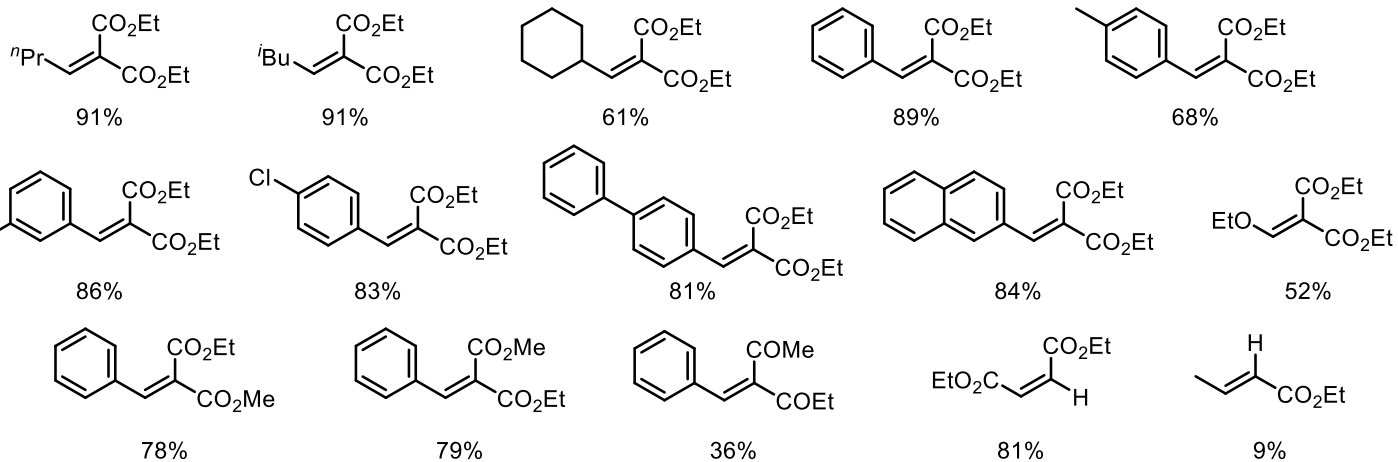
Photocatalytic approach to HAM



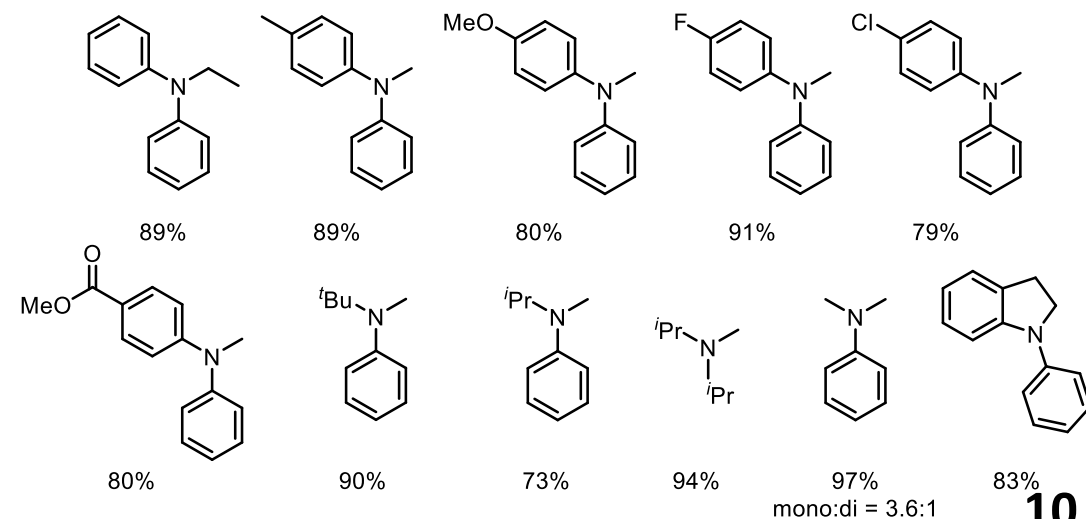
Miyake *et al*, *J. Am. Chem. Soc.*, **2012**, 134, 3338



Olefins scope



Amines scope



Pros vs Cons of metal-catalyzed methods of HAM of alkenes



one-pot
atom economy
orthogonal/autotandem catalysis
high yields*
high chemo-, regio-, enantioselectivity*
good functional group tolerance*

**if catalyst is well-designed*



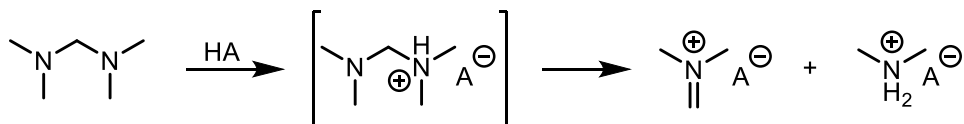
moderate yields in general
catalyst design
catalyst-based substrate design
early TM incompatible with air conditions
limited olefins scope (nonactivated, terminal)
selectivity restrictions
double alkylation
metal or oxidant additives in principle



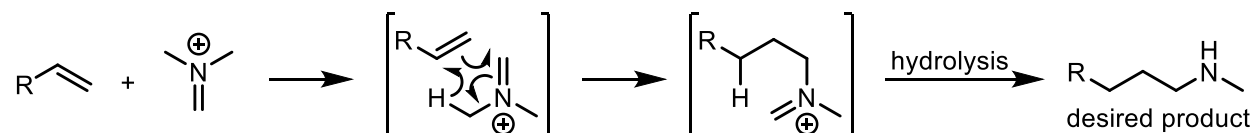
metal-free?
activated π -systems?

Acid-mediated HAM with amins

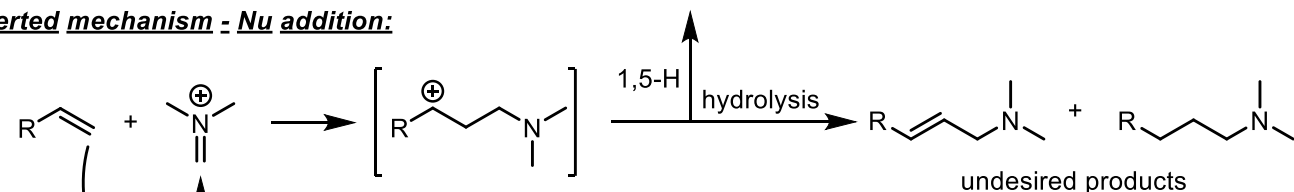
Formation of iminium salts - cleavage of amins with mineral acid:



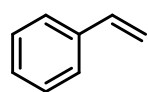
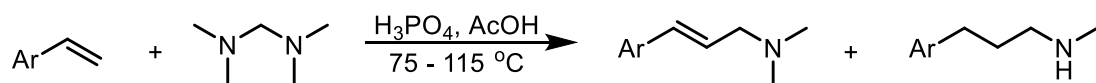
Concerted mechanism - ene reaction:



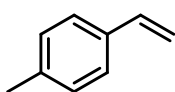
Unconcerted mechanism - Nu addition:



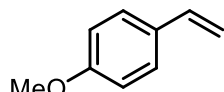
Aryl olefins



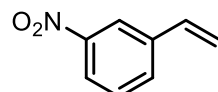
70%, 2:98



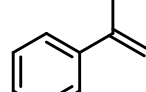
68%, 10:90



70%, 80:20

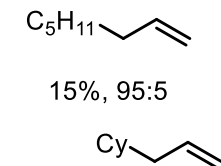
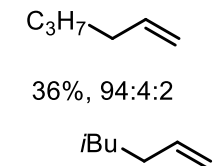
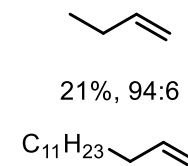
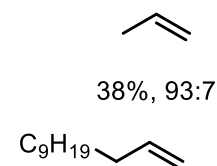
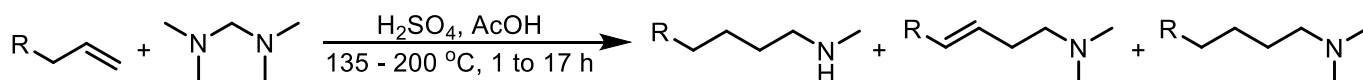


5%, 14:86



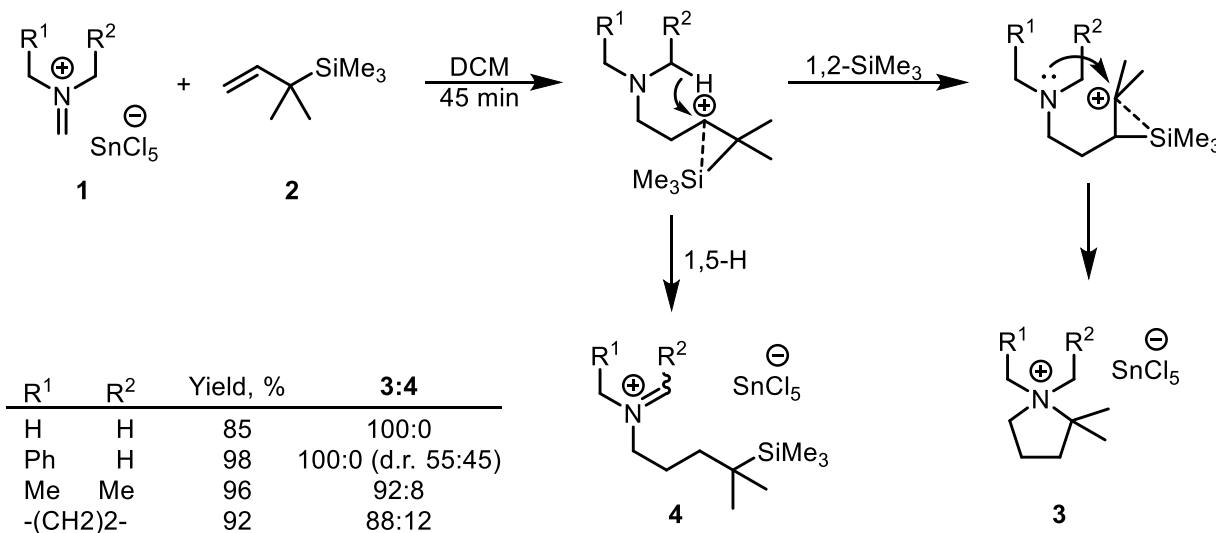
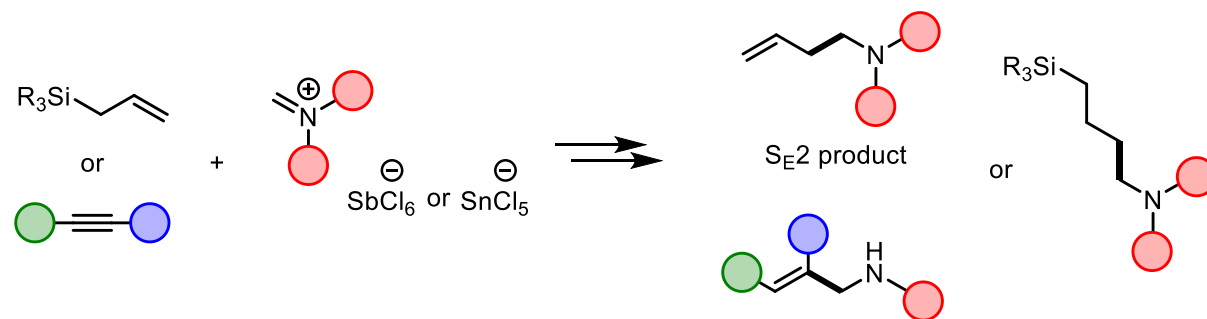
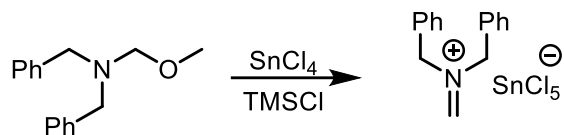
72%, 79:21

Nonconjugated olefins



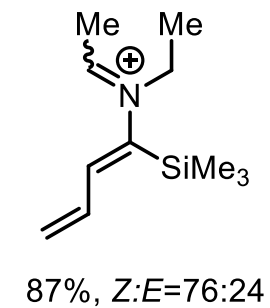
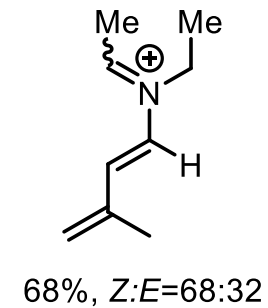
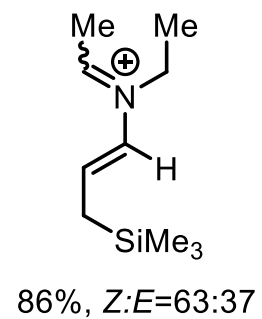
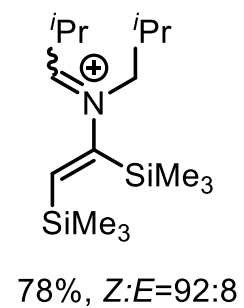
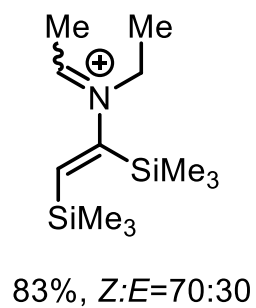
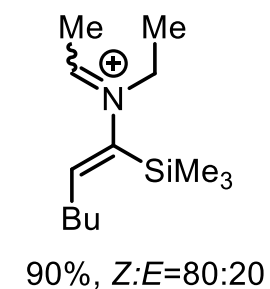
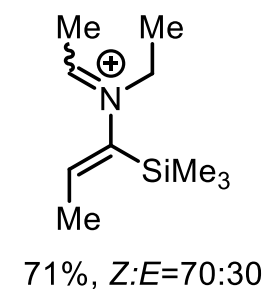
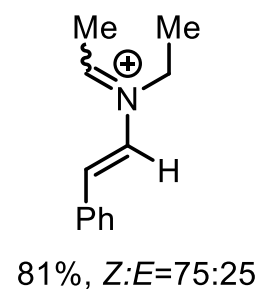
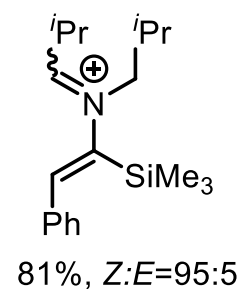
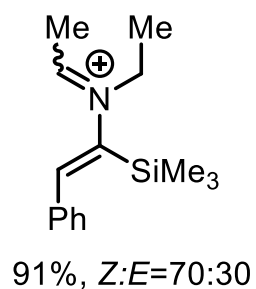
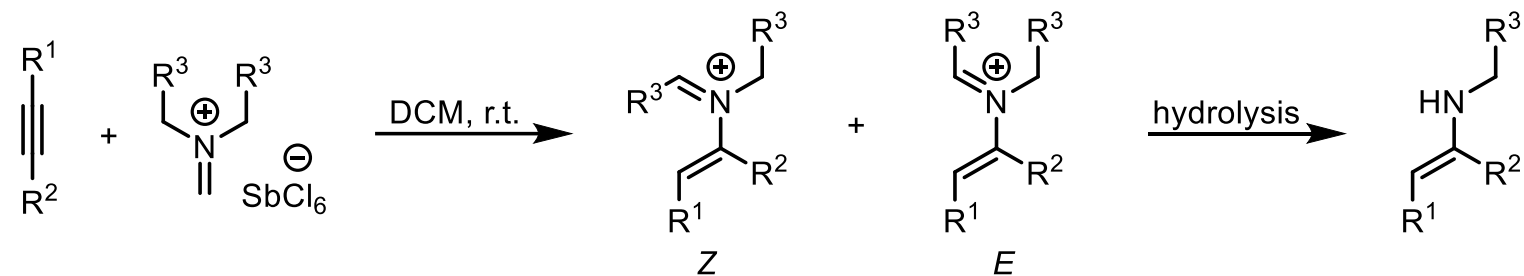
HAM of activated substrates with N,O-acetals

Formation of iminium salts - cleavage of N,O-acetals with Lewis acids:



- β -silyl effect
- poor chemoselectivity
- poor regioselectivity
- only activated alkenes

R ¹	R ²	Yield, %	3:4
H	H	85	100:0
Ph	H	98	100:0 (d.r. 55:45)
Me	Me	96	92:8
-(CH ₂) ₂ -		92	88:12

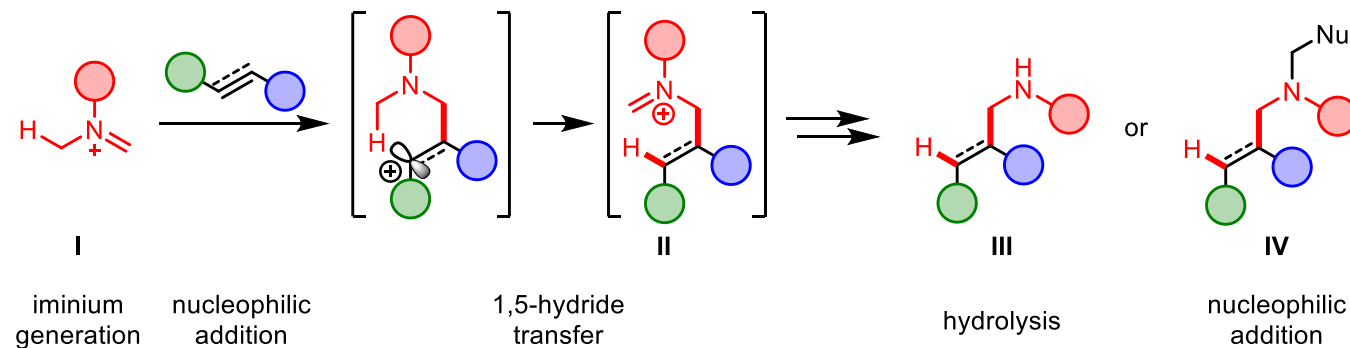


Acid-mediated HAM

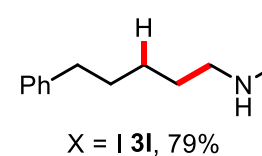
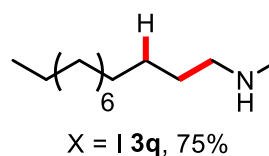
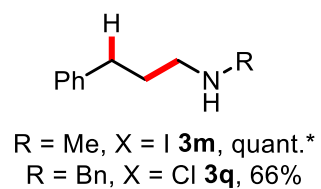
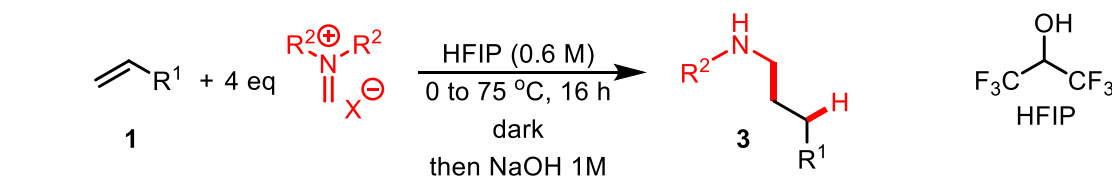


Prof. Nuno Maulide
University of Vienna

The concept

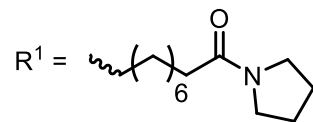
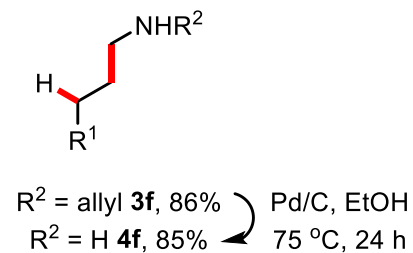
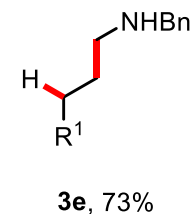
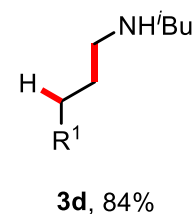
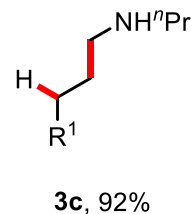
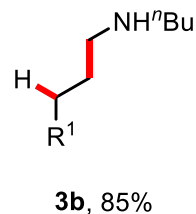
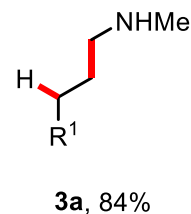
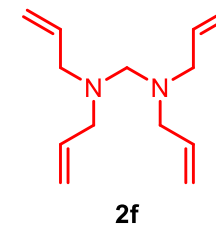
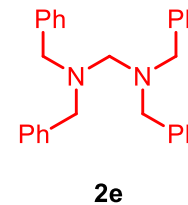
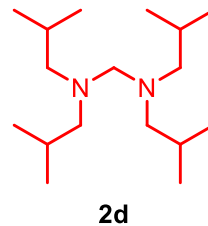
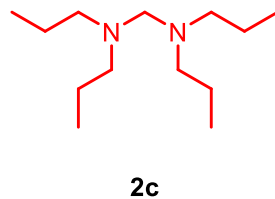
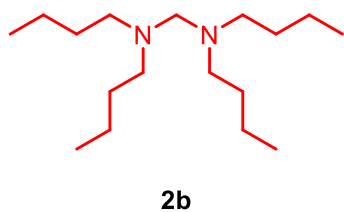
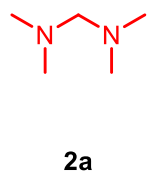
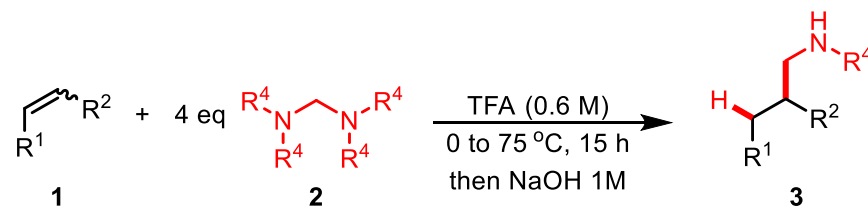


First steps



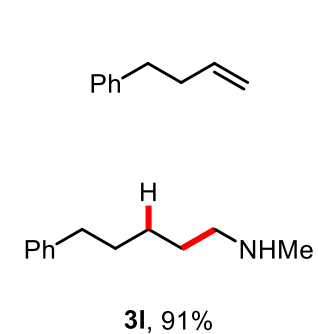
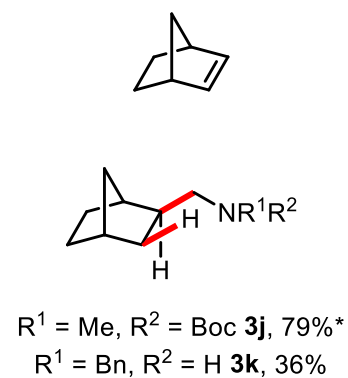
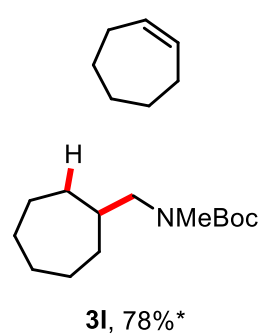
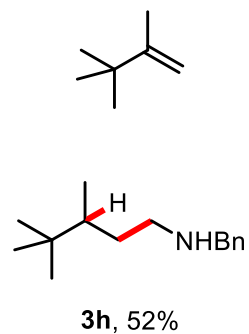
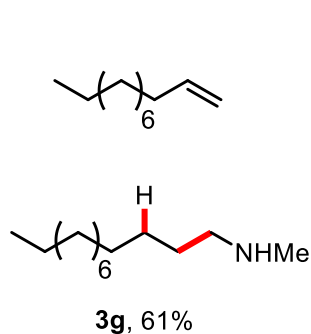
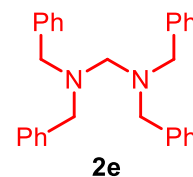
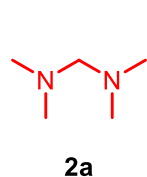
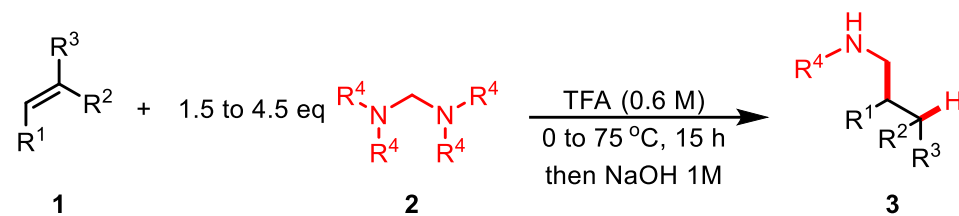
unsuccessful substrates:
internal alkenes, alkynes

Aminals scope

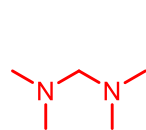
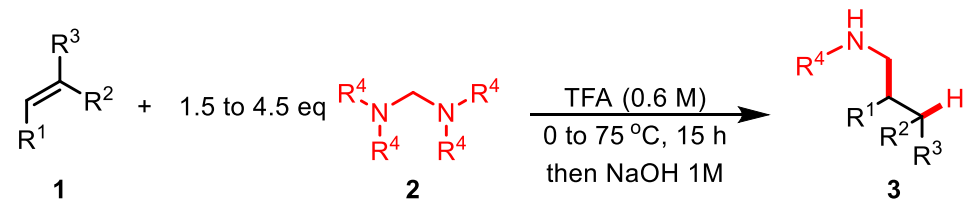


$\xrightarrow[\text{75 }^\circ\text{C, 24 h}]{\text{Pd/C, EtOH}}$

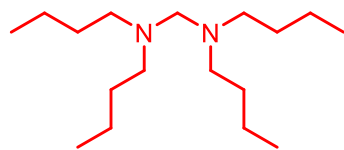
Olefins scope



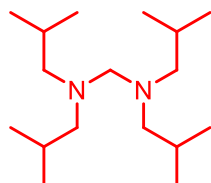
*Yield after acylative protection with Boc₂O to facilitate isolation



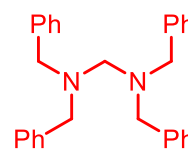
2a



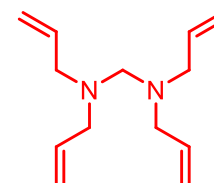
2b



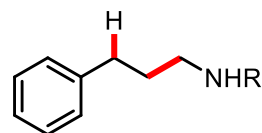
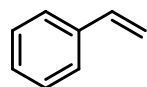
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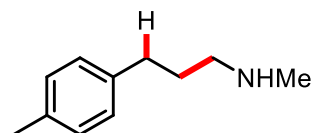
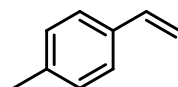
2e



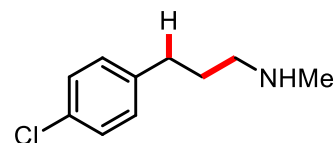
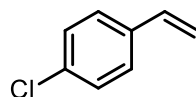
2f



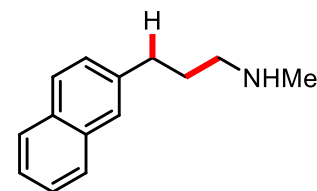
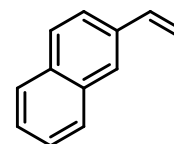
R = Me **3m**, 82%
(86% on 50 mmol)



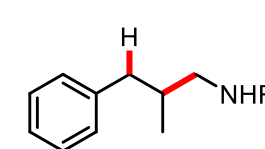
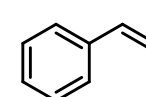
3n, 85%



3o, 86%



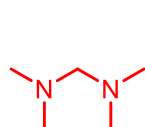
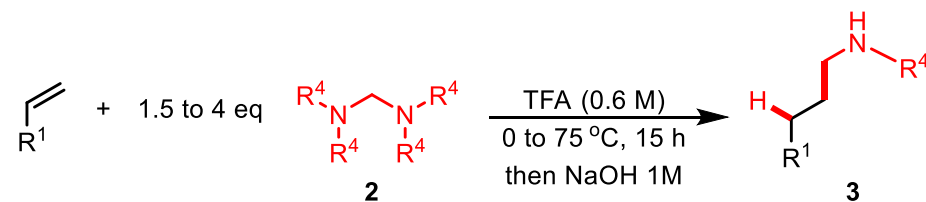
3p, 55%



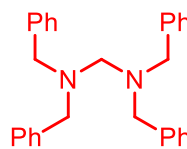
R = *i*Bu **3t**,
61% from *cis*- and 60% from *trans*-
R = Me **3u**,
39% from *cis*-

R = Bn **3q**, 42%
R = *n*Bu **3r**, 86%
R = allyl **3s**, 69%

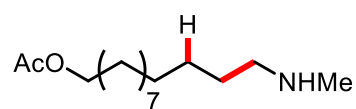
Functional group tolerance



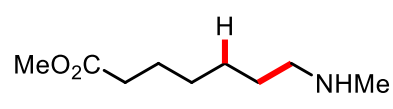
2a



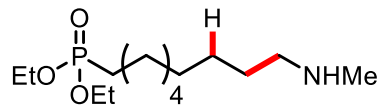
2e



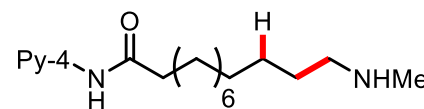
3v, 93%



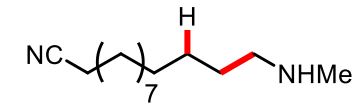
3w, 64%



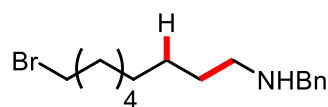
3x, 80%



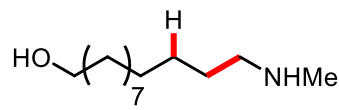
3y, 72%



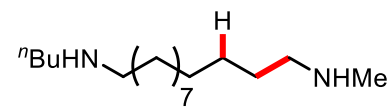
3z, 84%



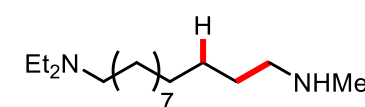
3aa, 40%



3ab, 82%
(71% on 20 mmol)

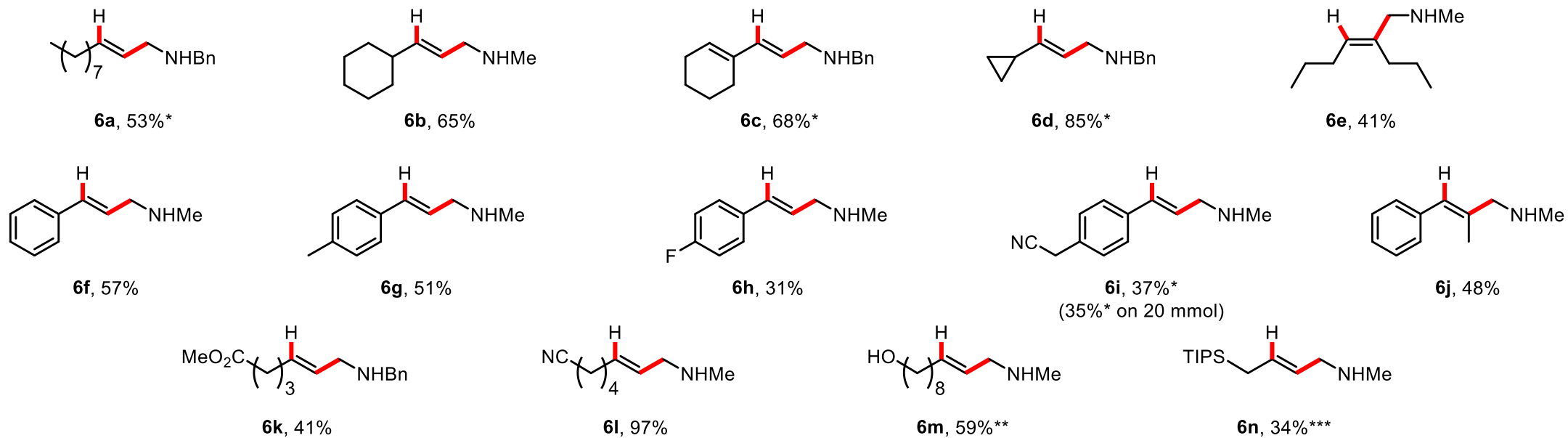
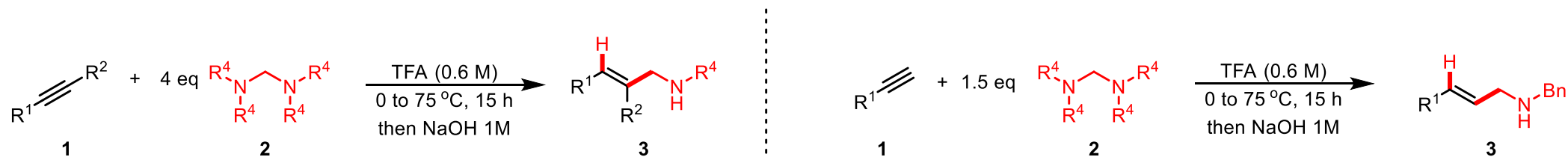


3ac, 60%



3ad, 75%

Alkynes scope

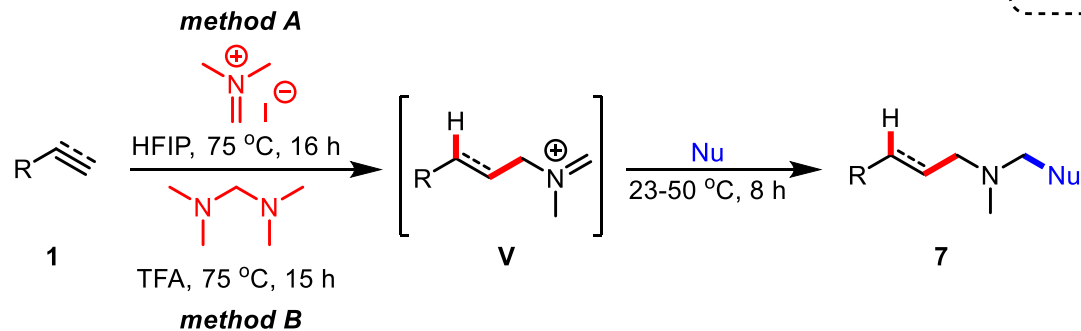
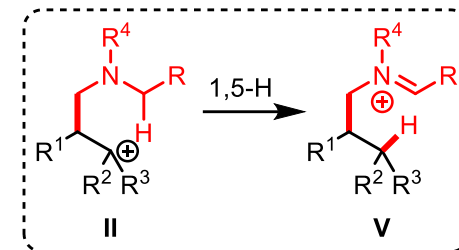


*DCE used as co-solvent

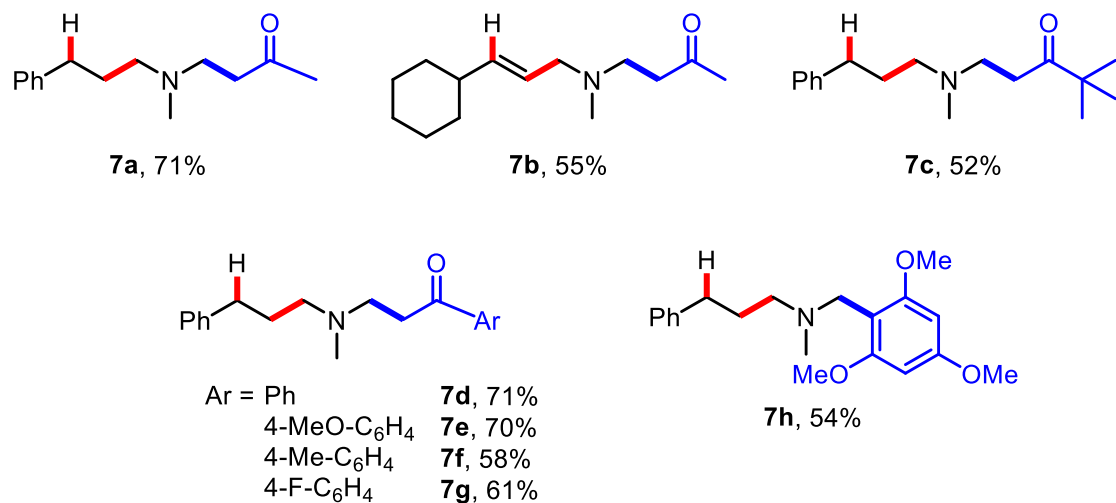
**Reaction was run for 5 h

***Reaction was run at room temperature

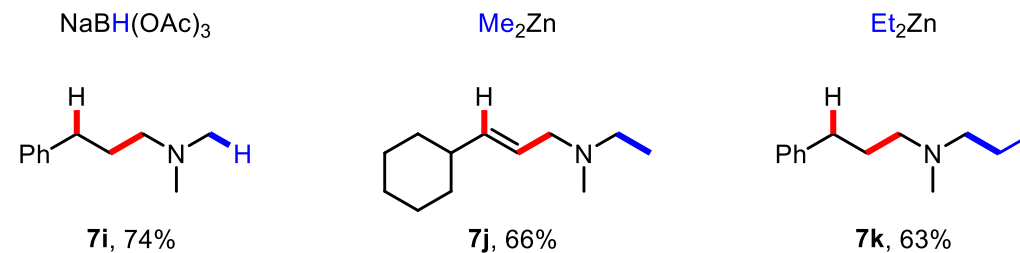
Domino functionalization



following method B, in TFA

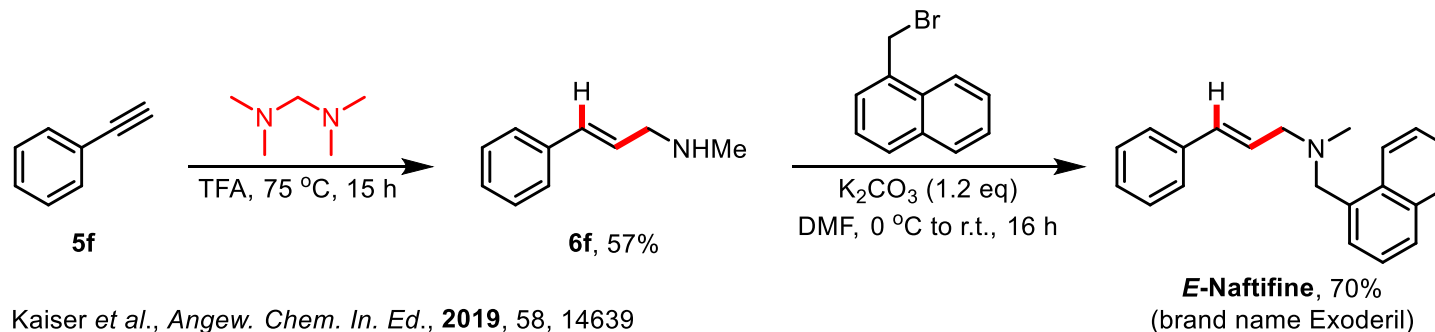


following method A, in HFIP

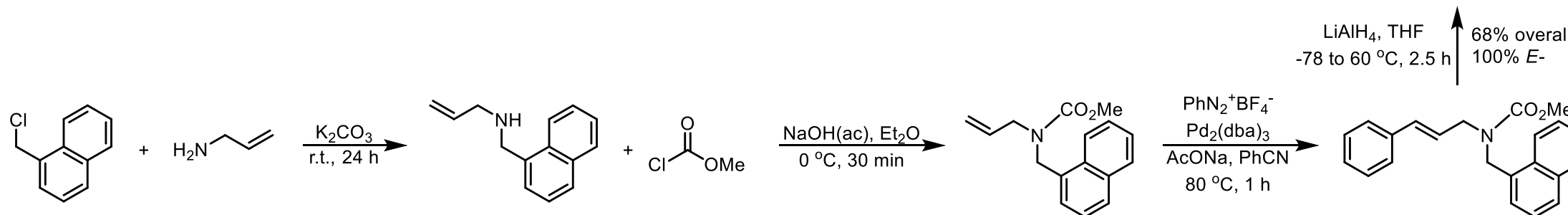
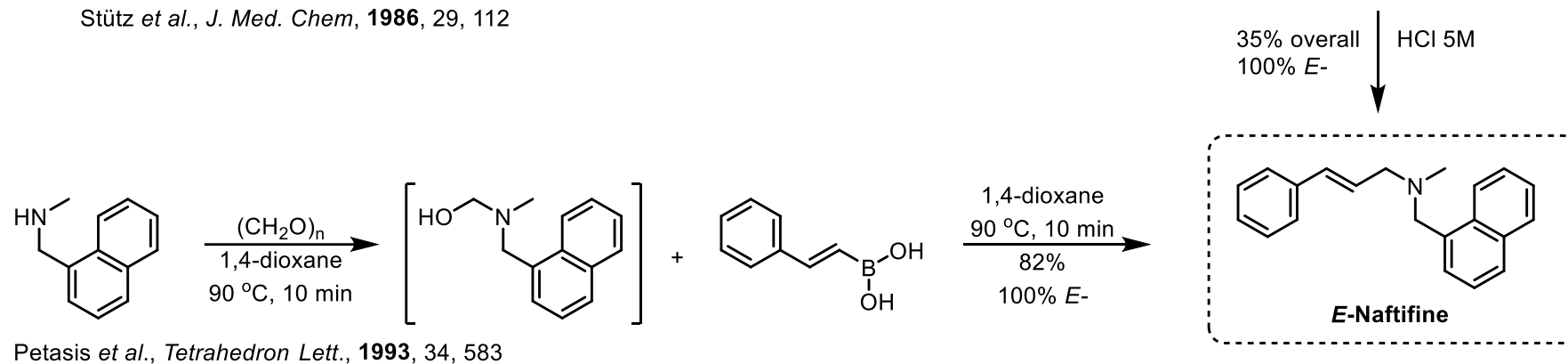
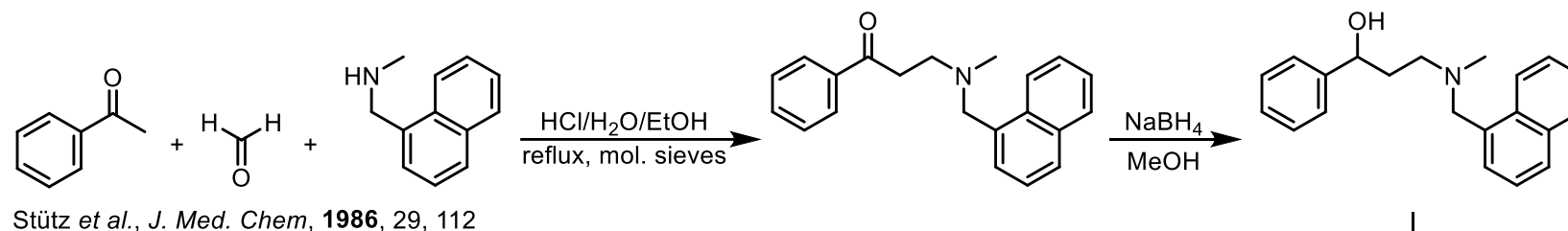


Pharmaceutical products synthesis

This work:

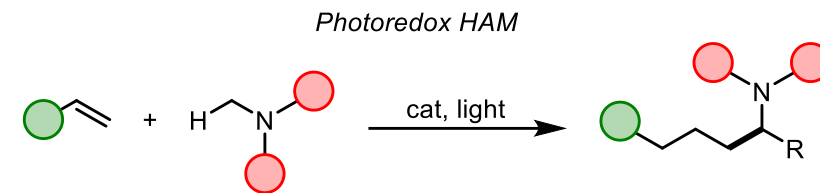


Previous works:

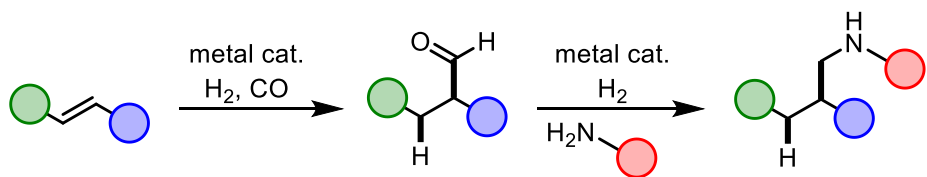


Conclusion

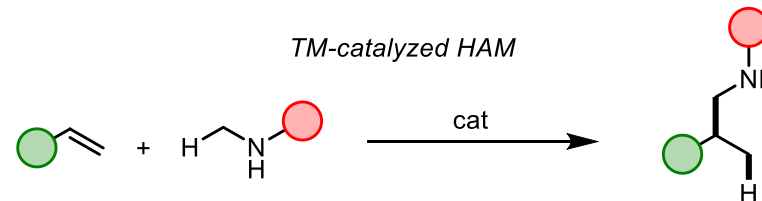
- lots of limited TM-catalyzed HAM methods



Tandem HAM via hydroformylation

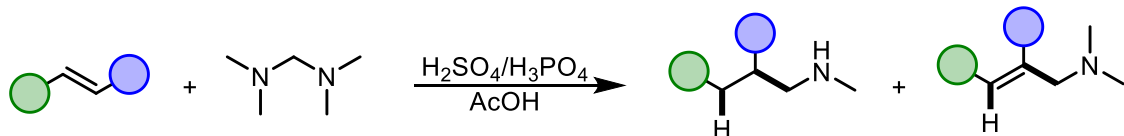


TM-catalyzed HAM

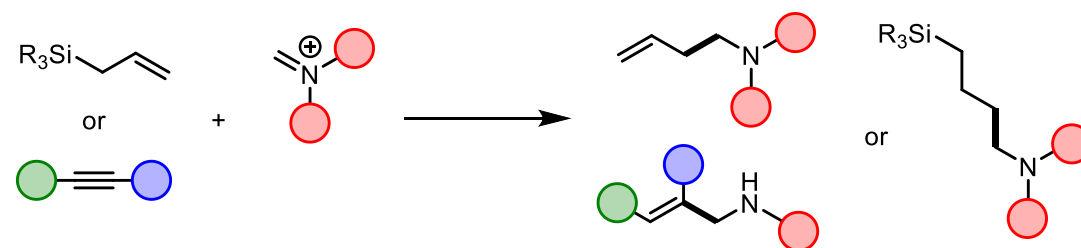


- number of limited metal-free HAM procedures

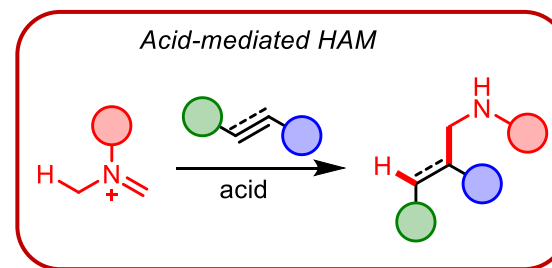
HAM with amins



HAM with iminium salts



- one general acid-mediated HAM method



References

Reviews

1. Urrutigoity, Tandem hydroaminomethylation reaction to synthesize amines from alkenes *Chem. Rev.*, **2018**, 118, 3833.
2. Agbossou-Niedercorn, Recent metal-catalysed asymmetric hydroamination of alkenes *Journal of Organometallic Chemistry*, **2017**, 847, 13.
3. Boutevin, Biobased amines: from synthesis to polymers; present and future *Chem. Rev.*, **2016**, 116, 14181.
4. Kustov, Catalytic hydroamination of unsaturated hydrocarbons *Top. Catal.*, **2016**, 59, 1196.
5. Hannedouche, Recent advances in metal free- and late transition metal-catalyzed hydroamination of unactivated alkenes *Catal. Sci. Technol.*, **2015**, 5, 2017.
6. Gooßen, Late transition metal-catalyzed hydroamination and hydroamidation *Chem. Rev.*, **2015**, 115, 2596.
7. Müller, Hydroamination: direct addition of amines to alkenes and alkynes *Chem. Rev.*, **2008**, 108, 3795.

Articles

1. Maulide, A general acid-mediated hydroaminomethylation of unactivated alkenes and alkynes *Angew. Chem. Int. Ed.*, **2019**, 58, 14639.
2. Zacchino, Design of two alternative routes for the synthesis of naftifine and analogues as potential antifungal agents *Molecules* **2018**, 23, 520.
3. Xu, Scandium-catalyzed C(sp³)-H alkylation of N,N-dimethyl anilines with alkenes *Org. Chem. Front.*, **2018**, 5, 59.
4. Doye, Hydroaminoalkylation of allylsilanes and a one-pot procedure for the synthesis of 1,5-benzoazasilepines *Chem. Eur. J.*, **2017**, 23, 4197.

5. Doye, Dimethylamine as a substrate in hydroaminoalkylation reactions *Angew. Chem. Int. Ed.*, **2017**, 56, 15155.
6. Schafer, Amidate complexes of tantalum and niobium for the hydroaminoalkylation of unactivated alkenes **2017**, *ACS Catal.*, 7, 5921.
7. Yu, Practical alkoxythiocarbonyl auxiliaries for iridium(I)-catalyzed C–H alkylation of azacycles *Angew. Chem. Int. Ed.*, **2017**, 56, 10530.
8. Schafer, 2-pyridonate tantalum complexes for the intermolecular hydroaminoalkylation of sterically demanding alkenes *J. Am. Chem. Soc.*, **2014**, 136, 10898.
9. Nishibayashi, Visible-light-mediated utilization of α -aminoalkyl radical: addition to electron-deficient alkenes using photoredox catalysts *J. Am. Chem. Soc.*, **2012**, 134, 3338.
10. Correia, Substrate-directable Heck reactions with arenediazonium salts. The regio- and stereoselective arylation of allylamine derivatives and application in the synthesis of naftifine and abamines *J. Org. Chem.* **2011**, 76, 7737.
11. Leeuwen, Influence of the bite angle on the hydroformylation of internal olefins to linear aldehydes *Organometallics*, **2003**, 22, 5358.
12. Mayr, Synthesis of allylamines from alkynes and iminium ions *Synthesis*, **2003**, 12, 1790.
13. Mayr, Ene reactions of alkynes for the stereoselective synthesis of allylamines *Angew. Chem. Int. Ed. Engl.*, **1997** 36, 143.
14. Mayr, Reactions of allylsilanes with iminium salts: ene reactions with inverse electron demand *J. Org. Chem.*, **1996**, 61, 5823.
15. Mayr, A novel pentaannulation reaction of iminium ions *Liebigs Ann./Recueil*, **1996**, 333.
16. Petasis, The boronic acid Mannich reaction: a new method for the synthesis of geometrically pure allylamines *Tetrahedron Letters*, **1993**, 34 (4), 583.
17. Stütz, Synthesis and structure-activity relationships of naftifine-related allylamine antimycotics *J. Med. Chem.*, **1986**, 29, 112.
18. Cohen, Onopchenko, Competing hydride transfer and ene reactions in the aminoalkylation of 1-alkenes with *N,N*-dimethylmethyleniminium ions. A literature correction *J. Org. Chem.*, **1983**, 48, 4531.

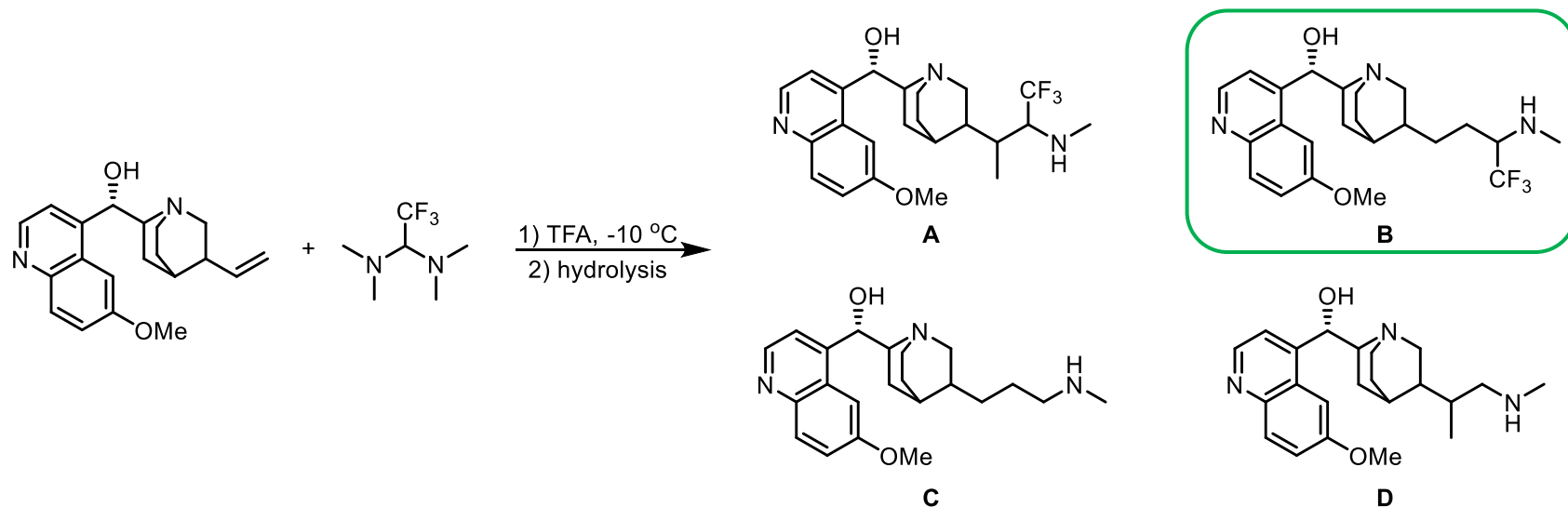
Thank you for your kind attention!

Question + Exercise

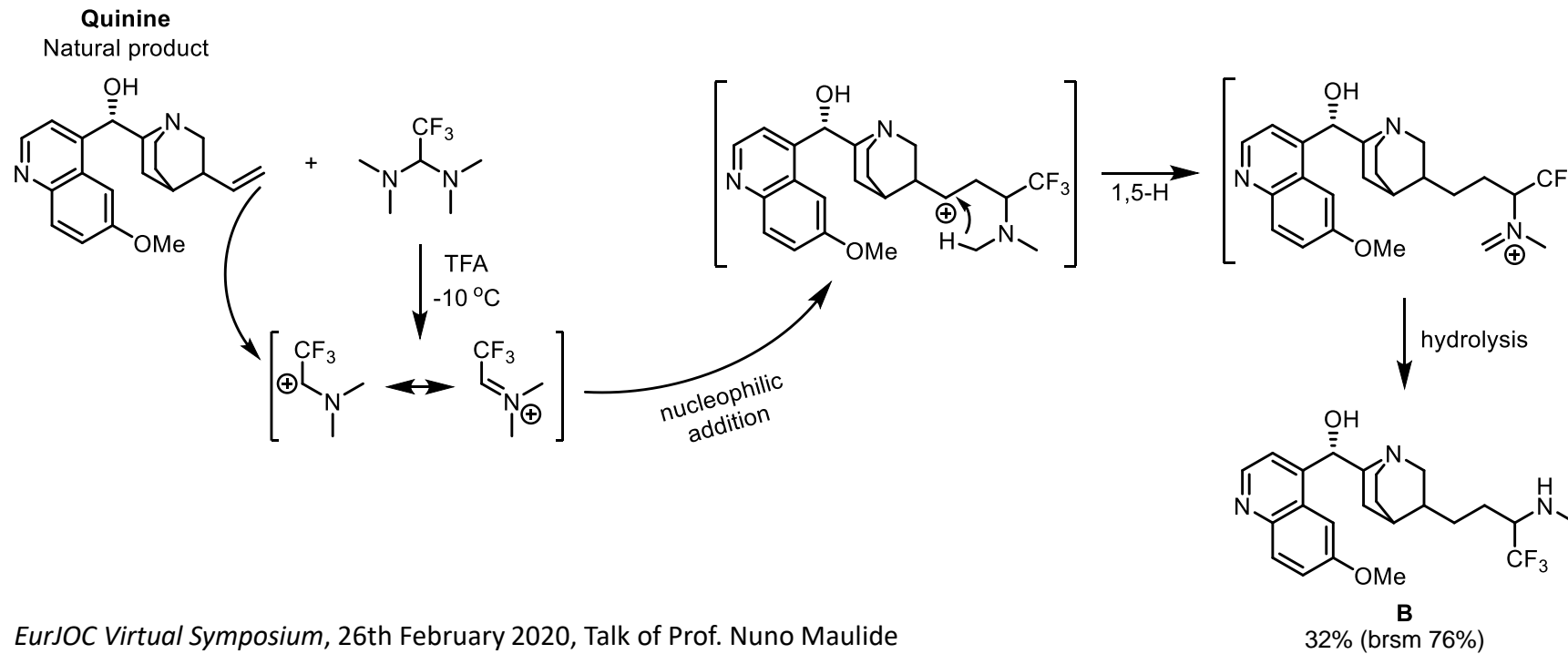
- Do you have any ideas regarding the choice of TFA in the work of Prof. Maulide group?

"...we suspect the solvating properties of TFA, as well as the low nucleophilicity and low basicity of the corresponding conjugate base play important roles in dictating the reaction outcome by facilitating the hydride transfer event."

- Choose the product of HAM



Exercise



EurJOC Virtual Symposium, 26th February 2020, Talk of Prof. Nuno Maulide

Additional slide – mechanistic studies of acid-mediated hydroaminomethylation

