anti-Markovnikov Hydroamination of Alkenes Catalyzed by a Two-Component Organic Photoredox System: Direct Access to Phenethylamine Derivatives

1

Tien M. Nguyen, Namita Manohar, and David A. Nicewicz.

Angew. Chem. Int. Ed., 2014, ASAP, April 24th Web

(University of North Carolina at Chapel Hill)

A. Manos-Turvey,
Wipf Group Current Literature
May 10th, 2014

Anti-Markovnikov Hydroamination

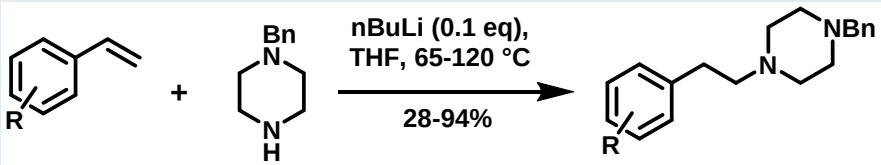
- In 1993, *anti*-Markovnikov Hydroamination was highlighted as one of the top 10 challenges for catalysis

  - repulsion of nitrogen by the olefin must be overcome
  - regioselectivity can be difficult to control

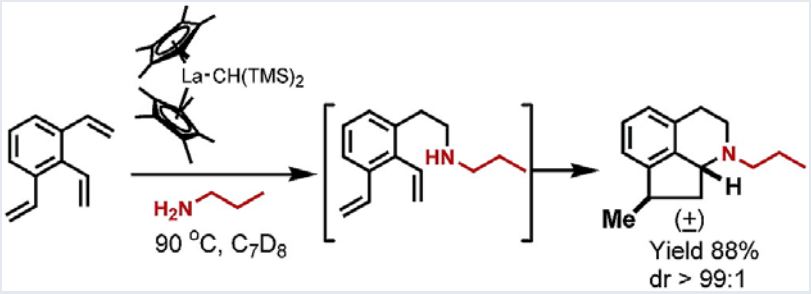
J. Haggins, *Chem. Eng. News*, **1993**, *71*, 23-27

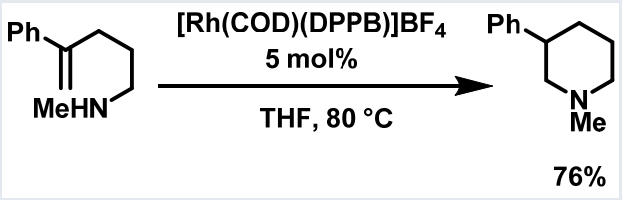
Some Literature Examples

- Alkali-base catalysed amine activation



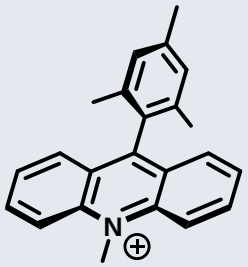
- Organolanthanide/Titanium/Iridium or Rhodium/Ruthenium catalysed





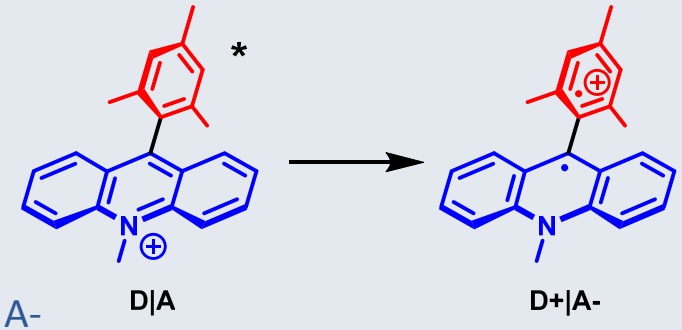
K. Kumar, D. Michalik,….H. Böttcher, M. Beller, *Chem. Eur. J*, **2004**, *10*, 746-757
J-S. Rya, G.Y. Li, T.J. Marks, *JACS*, **2003**, *125*, 12584-12605
A. Takemija, J.F. Hartwig, *JACS*, **2006**, *128*, 6042-6043

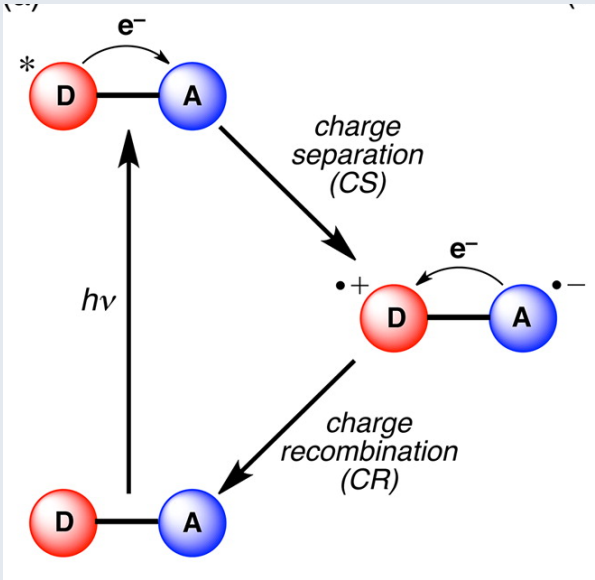
The 9-Mesityl-10-methylacridinium Ion

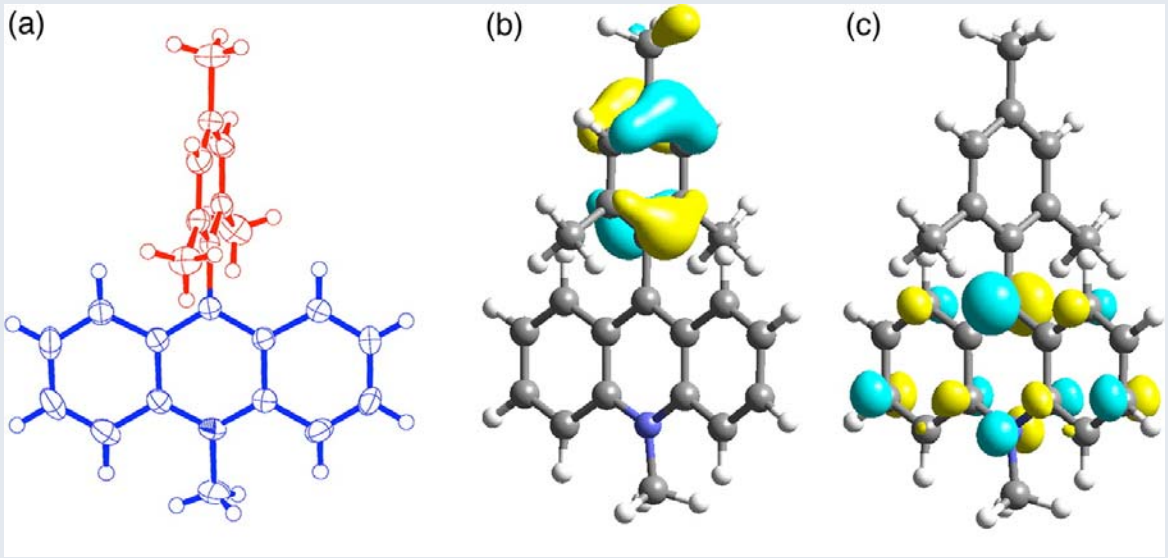


- Donor = mesitylene portion
- Acceptor = acridinium ion

- Reorganisation energy is very small
  - charge remains the same from D|A to D+|A-



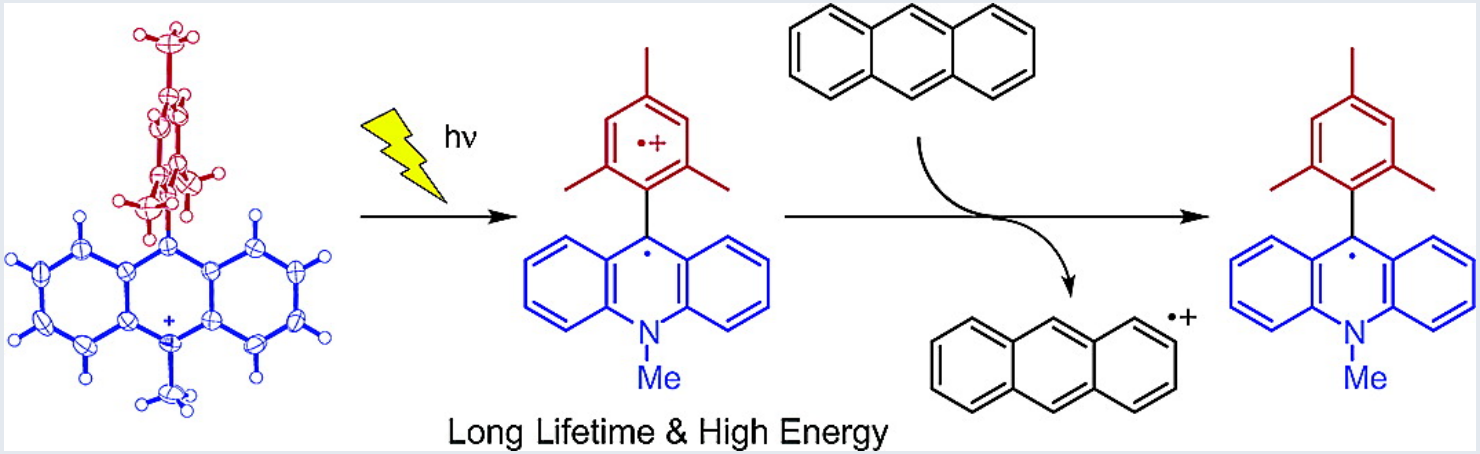




S. Fukuzumi, H. Kotani, K. Ohkubo, S. Ogo, N.V. Tkachenko, H. Lemmetyinen, *JACS*, **2004**, *126*, 1600-1601
S. Fukuzumi, K. Ohkubo, T. Suenobu, *Acc. Chem. Res.*, ASAP, DOI: 10.1021/ar400200u

The 9-Mesityl-10-methylacridinium Ion

- absorbs in the visible region (450 nm)
  - upon photoexcitation it reaches a long lived electron transfer (ET) state

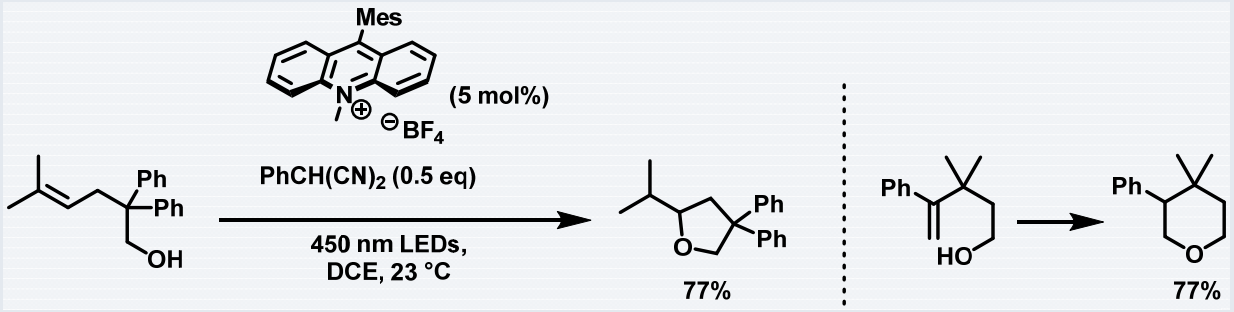


  - 2 h at 203 K and higher energy transfer state (Acr^{+}-Mes = 2.37 eV)

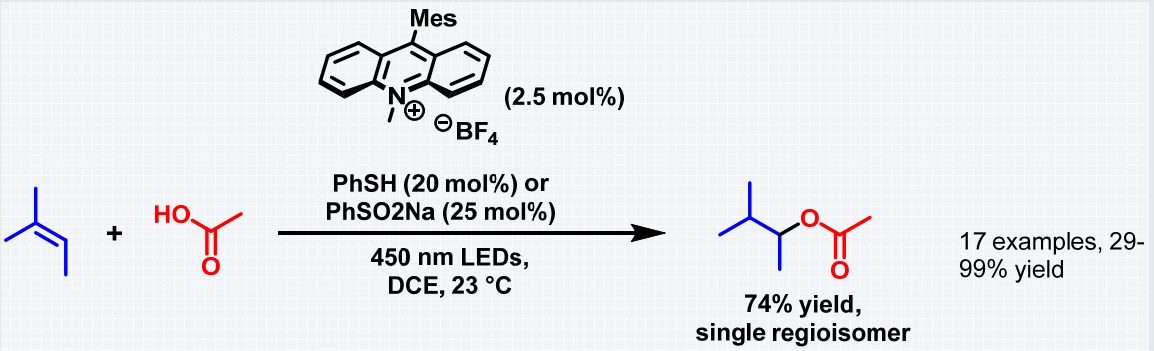
S. Fukuzumi, H. Kotani, K. Ohkubo, S. Ogo, N.V. Tkachenko, H. Lemmetyinen, *JACS*, **2004**, *126*, 1600-1601

Nicewicz and Anti-Markovnikov Reactions

- *Anti*-Markovnikov Alkenol Hydroalkoxylation
  - cyclic ether formation with complete regioselectivity through intramolecular hydroalkoxylation



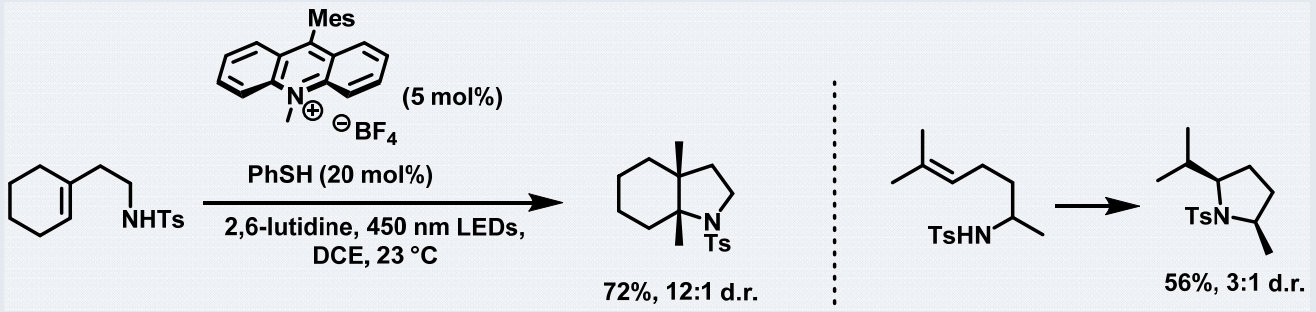
- *Anti*-Markovnikov Alkene Hydroacetoxylation
  - use of oxidisable *E*-olefins to react with a variety of carboxylic acids regioselectively



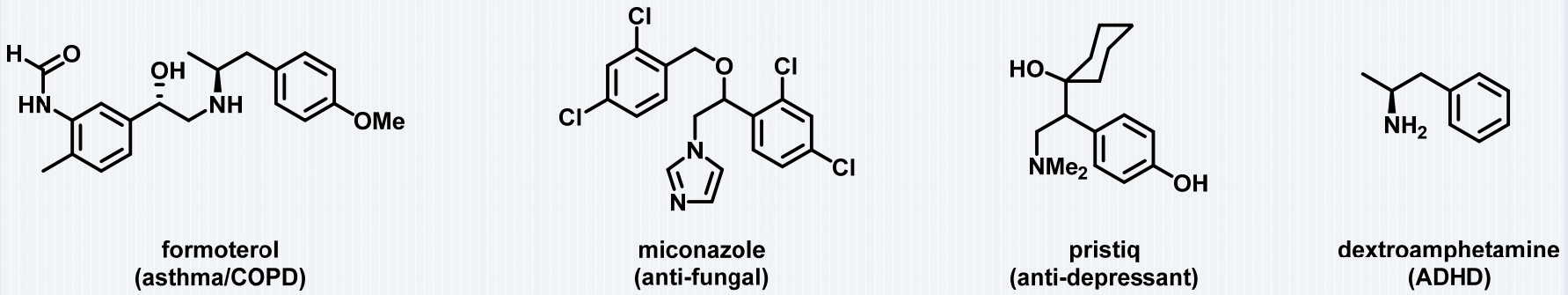
D.S. Hamilton, D.A. Nicewicz, *JACS*, **2012**, *134*, 18577-18580
A.J. Perkowski, D.A. Nicewicz, *JACS*, **2013**, *135*, 10334-10337

Nicewicz and *Anti*-Markovnikov Reactions

- *Anti*-Markovnikov Intramolecular Hydroamination
  - achieve the formation of nitrogen containing heterocycles regioselectively



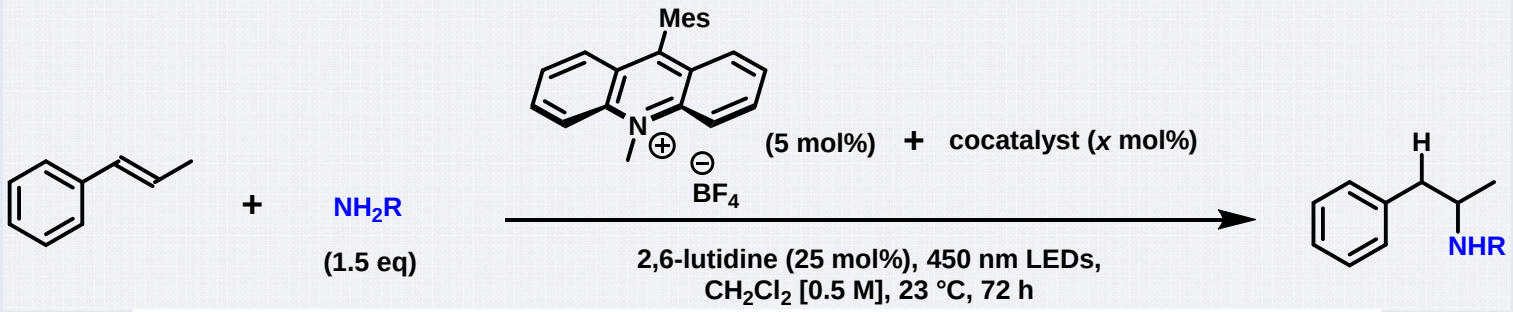
- **Expansion to intermolecular *anti*-Markovnikov hydroamination of alkenes**
- Focus upon β-methylstyrenes as phenethylamine derivatives are an important motif in biologically active molecules



T.M. Nguyen, D.A. Nicewicz, *JACS*, **2013**, *135*, 9588-9591
D.A. Nicewicz, T.M. Nguyen, *ACS Catal.*, **2014**, *4*, 355-360

Optimization of Reaction Conditions

8

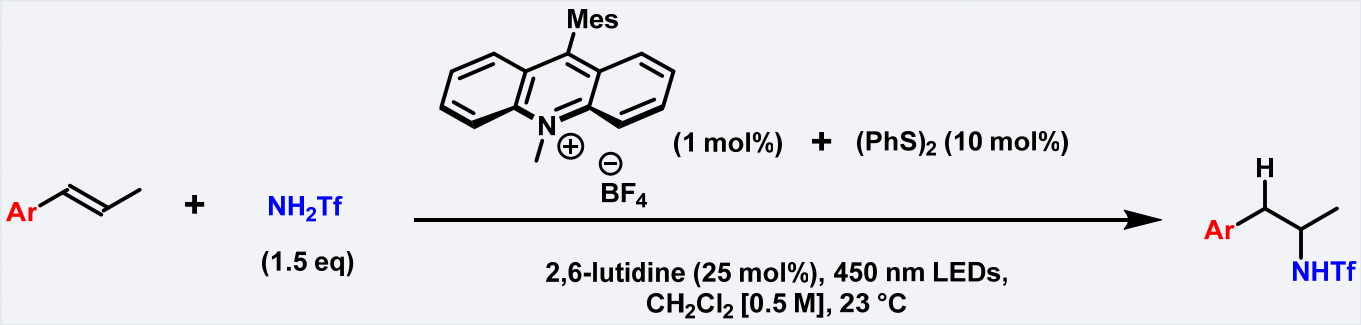


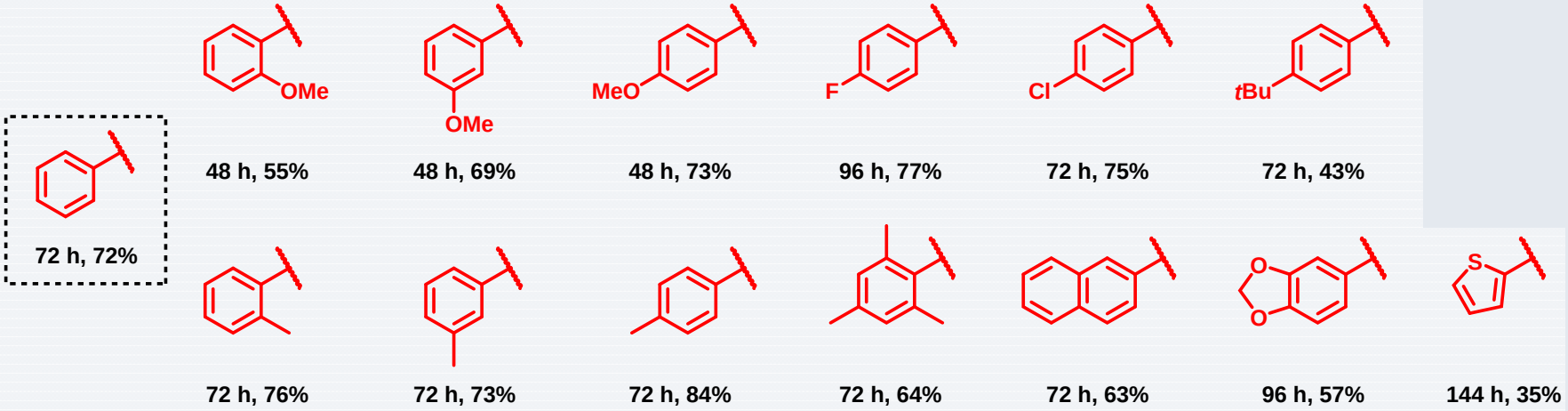
Entry	R	Cocatalyst	mol %	Yield [%][b]
1	Tf	thiophenol	20	87
2	Tf	2,6-dimethylthiophenol	20	80
3	Tf	4-nitrothiophenol	20	58
4	Tf	phenyl disulfide	20	78
5	Tf	–	0	< 5
6	Tf	phenyl disulfide	5	35
7	Tf	phenyl disulfide	10	89
8	Tf	phenyl disulfide	100	40
9	Boc	phenyl disulfide	10	8
10	Ts	phenyl disulfide	10	< 5
11	Ns	phenyl disulfide	10	< 5

All reactions irradiated with a 15 W 450 nm LED flood lamp and run on a 0.2 mmol scale.
Yields determined by 1H NMR spectroscopy using $[(H_3C)_3Si]_2O$ as an internal standard

Scope of Reaction with Styrenyl Substrates

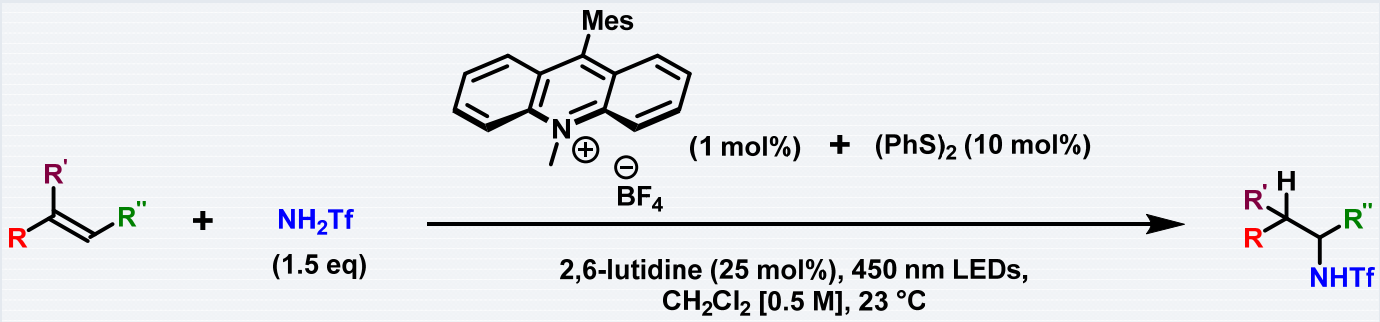
9

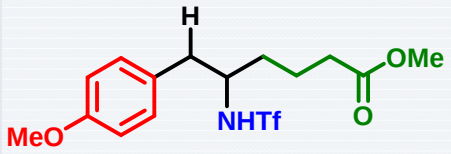




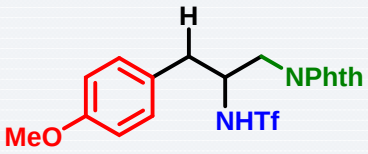
All reactions irradiated with a 15 W 450 nm LED flood lamp and yields of isolated products (average of two trials).

Scope of Reaction with Different Alkenes

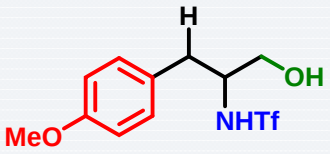




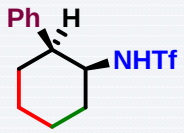
96 h, 58%



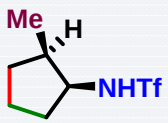
48 h, 67%



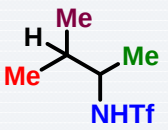
96 h, 70%



96 h, 50%, 2.5:1 d.r.



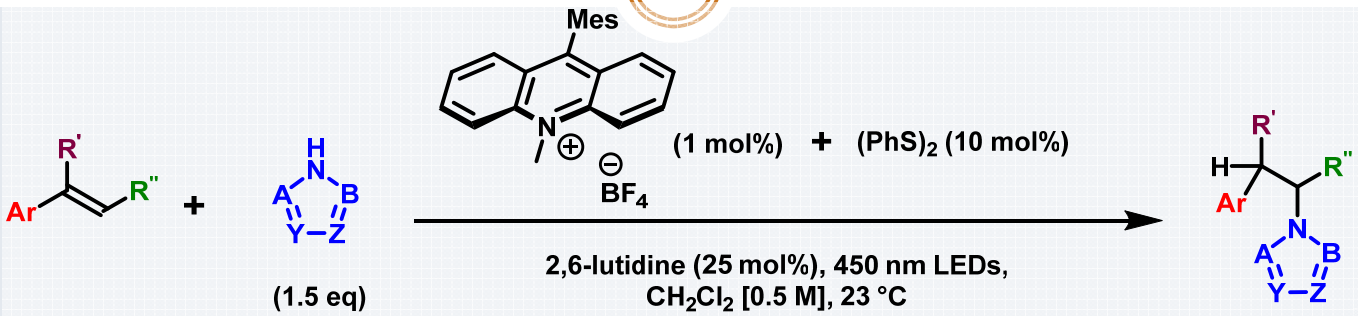
96 h, 85%, 2.3:1 d.r.

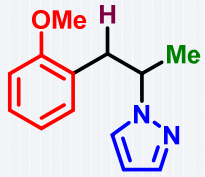


96 h, 72%
(3 eq of 2-methyl-2-butene)

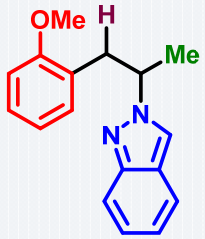
All reactions irradiated with a 15 W 450 nm LED flood lamp and yields of isolated products (average of two trials).

Scope of Reaction with Heterocyclic Amines

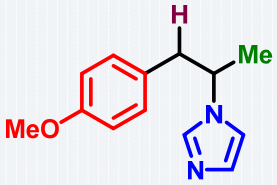




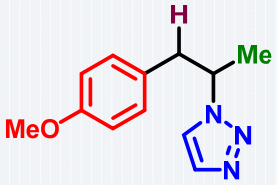
96 h, 83%



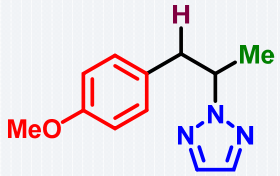
96 h, 57%



96 h, 50%
(3 eq imidazole)

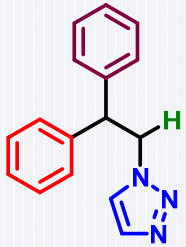


Major

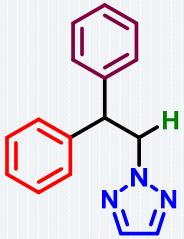


Minor

96 h, 80%, 2:1 (N1/N2)

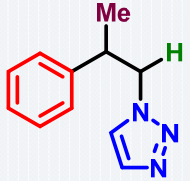


Major

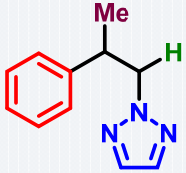


Minor

X h, 81%, 4:1
(N1/N2)



Major

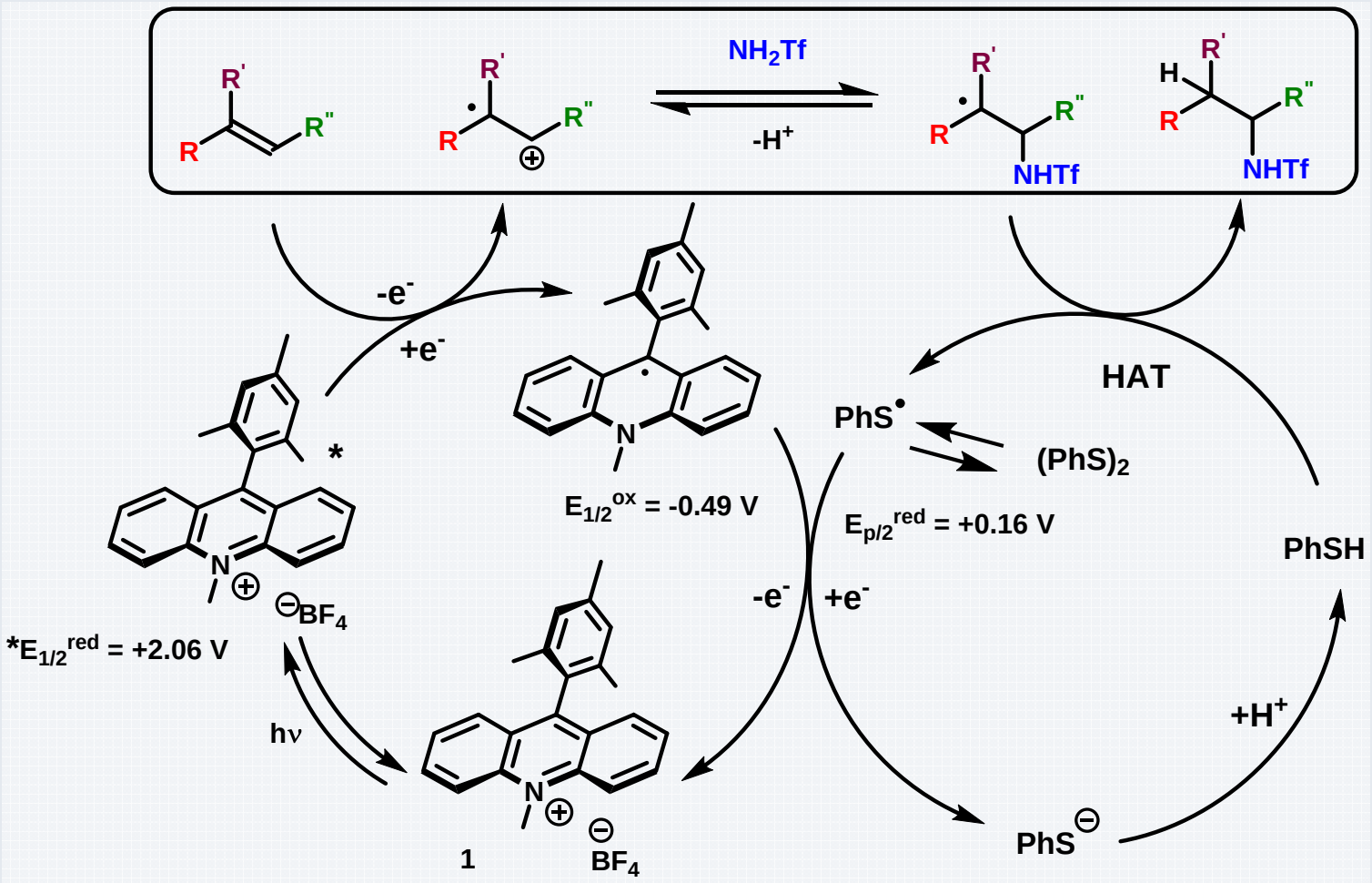


Minor

72 h, 41%, 1.9:1 (N1/N2)

All reactions irradiated with a 15 W 450 nm LED flood lamp and yields of isolated products (average of two trials).

Proposed Reaction Mechanism



Conclusions

- Successfully demonstrated the use of an acridinium catalyst in intermolecular *anti*-Markovnikov hydroamination reactions
  - trisubstituted aliphatic alkenes and α- and β-substituted styrenes with various functional groups appear to be tolerated
  - the amine nucleophiles employed are triflylamide or heterocyclic amines
  - all carried out at rt
- Diastereoselectivity needs to be probed
- Interesting to see further extensions of this work on further substrates and additional reactions apart from hydroamination