Practical Olefin Hydroamination with Nitroarenes

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Presented by Alexander Chatterley
30th of May 2015

The Baran Group

- Professor Phil Baran is based at The Scripps Research Institute in La Jolla, California, USA.

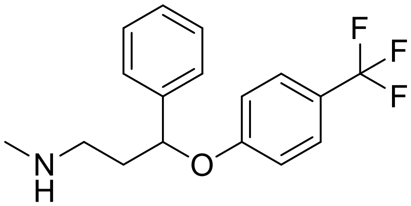
- Graduated from New York University in 1997. Undertook a PhD at Scripps (Nicolaou) 2001. He was then appointed a Post doctoral fellow at Harvard (Corey) 2001-2003. Following this he was made Assistant Professor at Scripps June 2003 aged 26.

- Group comprises of 39 members: 18 post doctoral associates and 19 grad students.

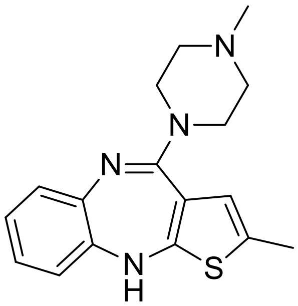
- Research areas are total synthesis and methodology.

Why are forming C-N bonds important?

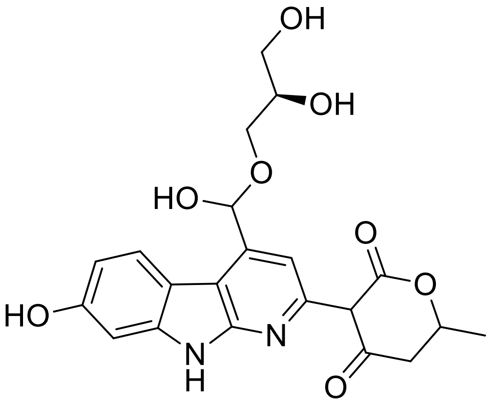
- Almost ubiquitous in both nature and pharmaceutical compounds.



Fluoxetine
(Prozac)



Olanzapine
(Zyprexa)

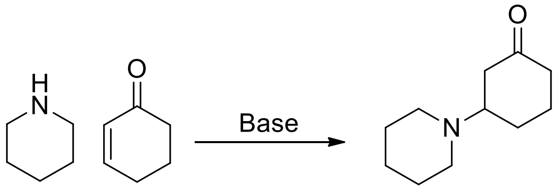


Mescengricin

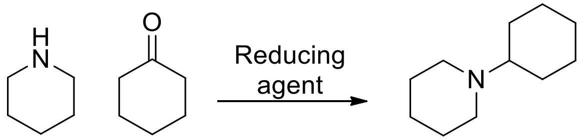
Without the ability to form these bonds synthetic chemistry would be extremely limited.

Current C-N bond forming methodology

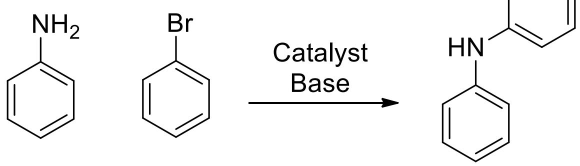
- Conjugate addition



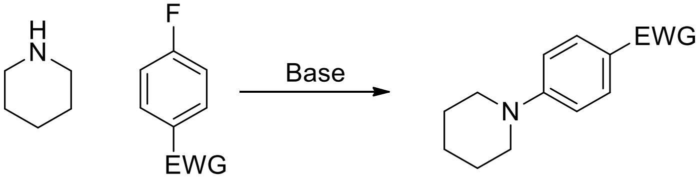
- Reductive amination



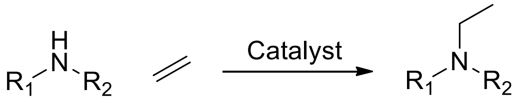
- Buchwald-Hartwig



- Alkylation

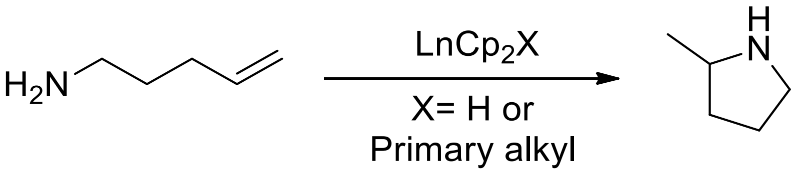


- Hydroamination



Hydroamination

- Dates back to late 80’s where T. J. Marks observed intramolecular cyclisation using a lanthanide metalloferrocene.

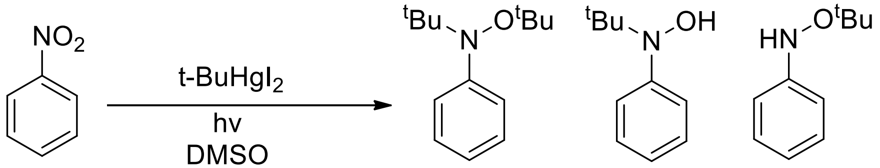


- To date many examples using both metals and organo-catalysis have been published.

T. J. Marks, M. R. Gagné. J. Am. Chem Soc. 1989. 4108.

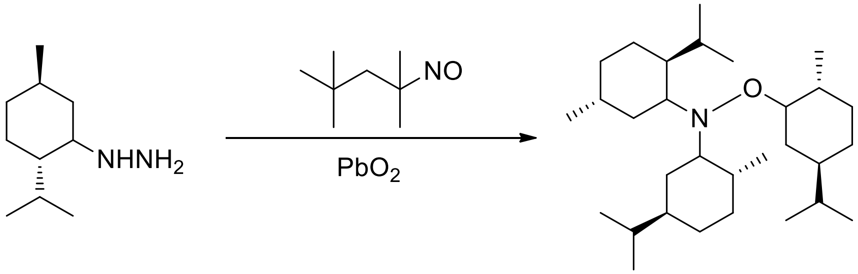
Inspirational transformations

- Russell and Yao demonstrated *tert*-butyl radicals could add to nitro- and nitrosoarenes to generate N- and N,O-alkylated adducts.

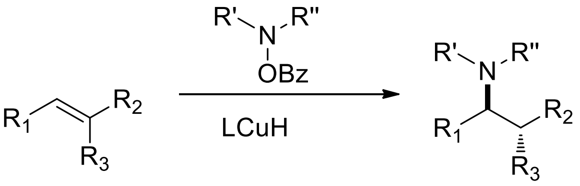


as well as other products

- Corey and Gross demonstrated radicals react with nitro compounds to form hindered amines.



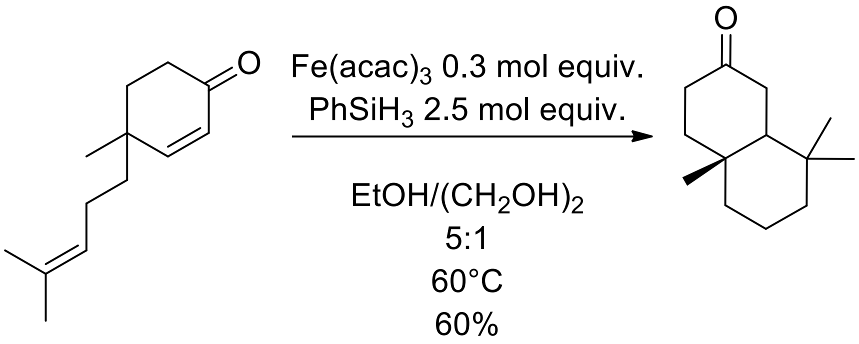
- Buchwald demonstrated the coupling of hydroxylamines and alkenes utilising a copper catalyst.



G. A. Russell, C. Yao. Heteroatom Chem. 1993. 433. E. J. Corey, A. W. Gross. J. Org. Chem. 1985. 5391.
S. Zhu, N. Niljianskul, S. L. Buchwald. J. Am. Chem. Soc. 2013. 15746.

Inspiration from within the group

Previously Baran *et al.* had demonstrated that it is possible to cross couple olefins via alkyl radical intermediates.



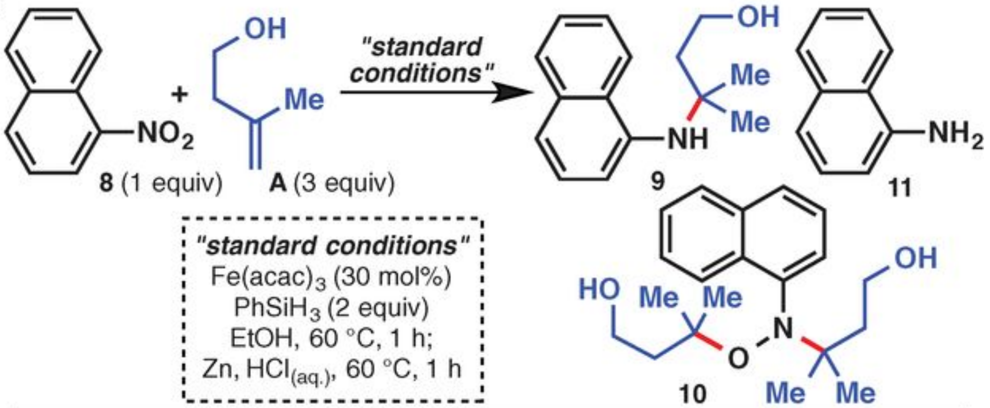
They then applied these conditions to the coupling of nitronaphthalene with isoprenyl alcohol.

J. C. Lo, Y. Yabe, P. S. Baran, J. Am. Chem. Soc. 2014. 136. 1304

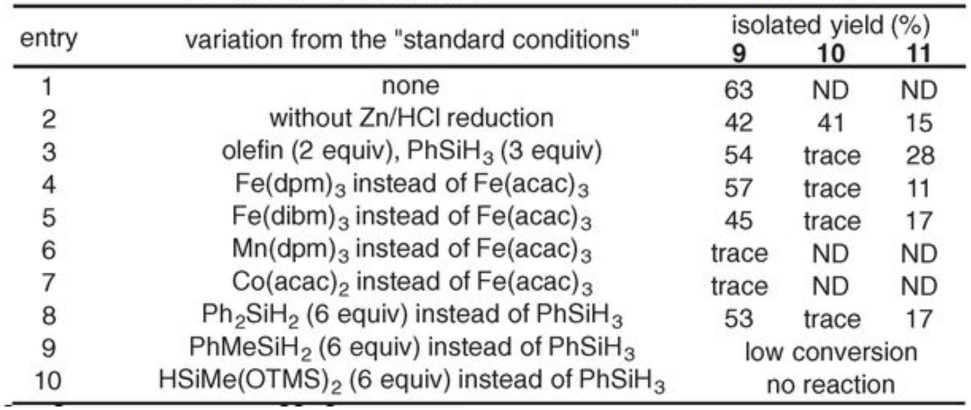
The first attempt

They applied the aforementioned conditions to the coupling of nitronaphthalene with isoprenyl alcohol. To their delight it worked on the first attempt!

Optimisation studies indicated that iron was unique in its ability to catalyse this reaction and that $PhSiH_3$ proved to be the best reductant.

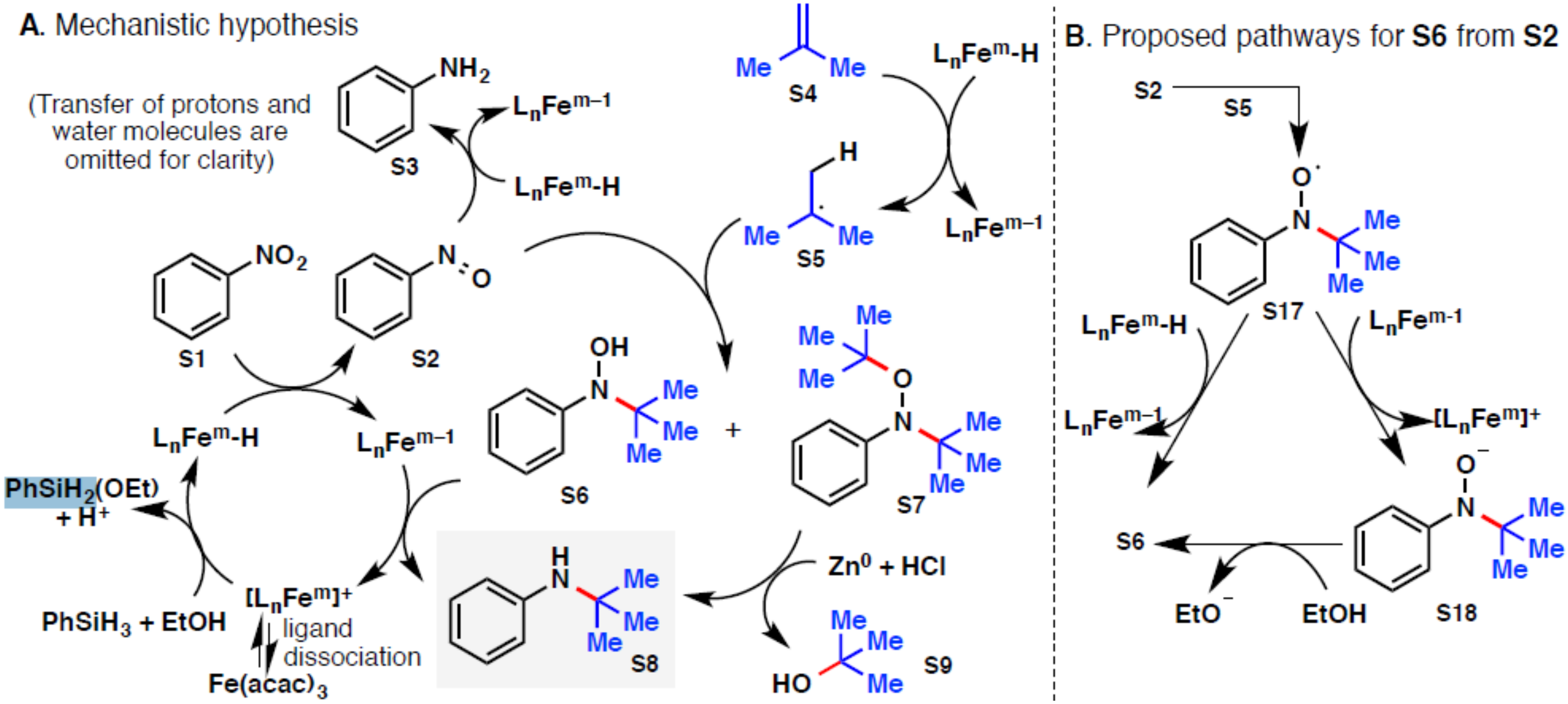


"standard conditions"
$Fe(acac)_3$ (30 mol%)
$PhSiH_3$ (2 equiv)
EtOH, 60 °C, 1 h;
Zn, $HCl_{(aq.)}$, 60 °C, 1 h

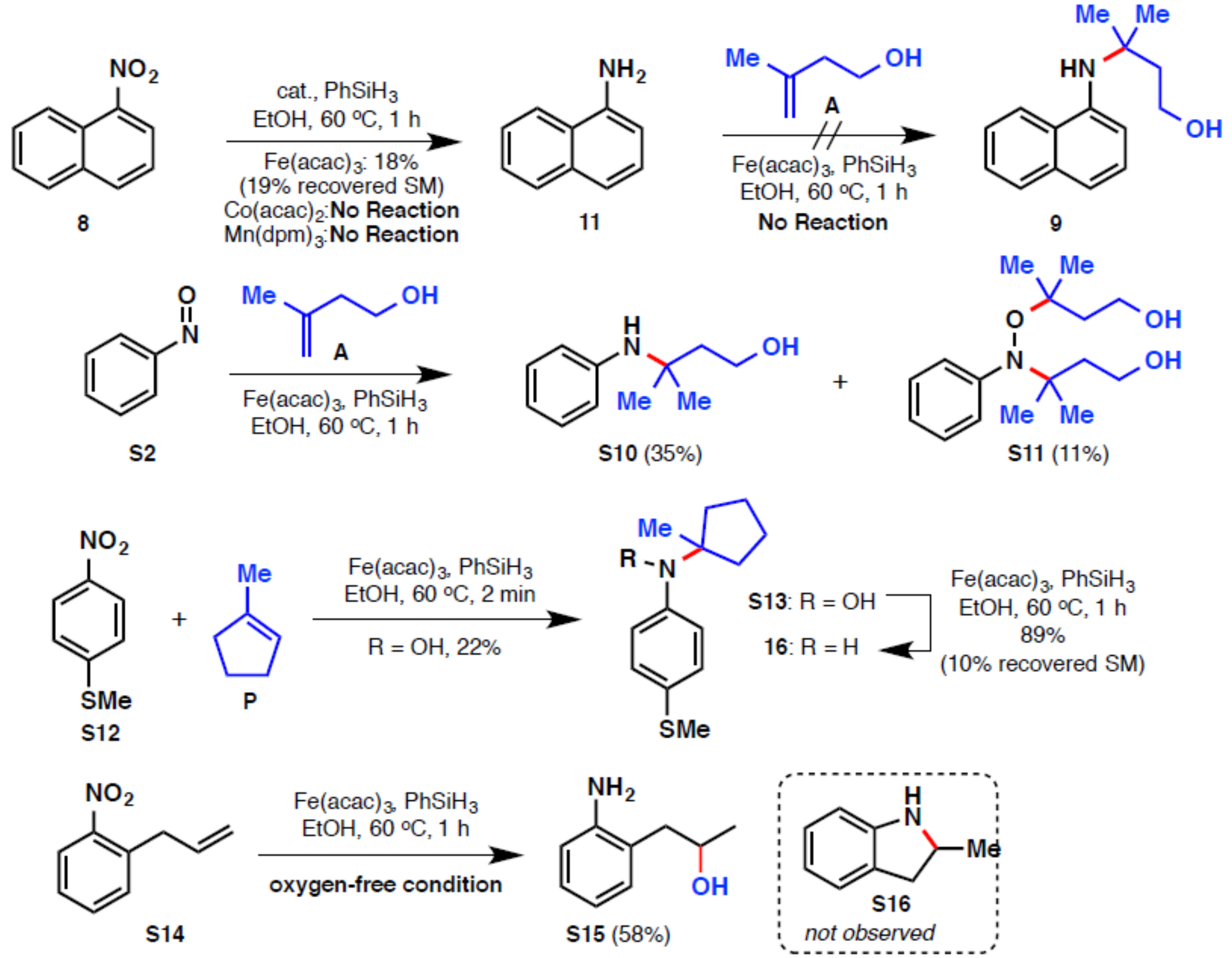


entry	variation from the "standard conditions"	isolated yield (%) 9	10	11
1	none	63	ND	ND
2	without Zn/HCl reduction	42	41	15
3	olefin (2 equiv), $PhSiH_3$ (3 equiv)	54	trace	28
4	$Fe(dpm)_3$ instead of $Fe(acac)_3$	57	trace	11
5	$Fe(dibm)_3$ instead of $Fe(acac)_3$	45	trace	17
6	$Mn(dpm)_3$ instead of $Fe(acac)_3$	trace	ND	ND
7	$Co(acac)_2$ instead of $Fe(acac)_3$	trace	ND	ND
8	Ph_2SiH_2 (6 equiv) instead of $PhSiH_3$	53	trace	17
9	$PhMeSiH_2$ (6 equiv) instead of $PhSiH_3$	low conversion		
10	$HSiMe(OTMS)_2$ (6 equiv) instead of $PhSiH_3$	no reaction		

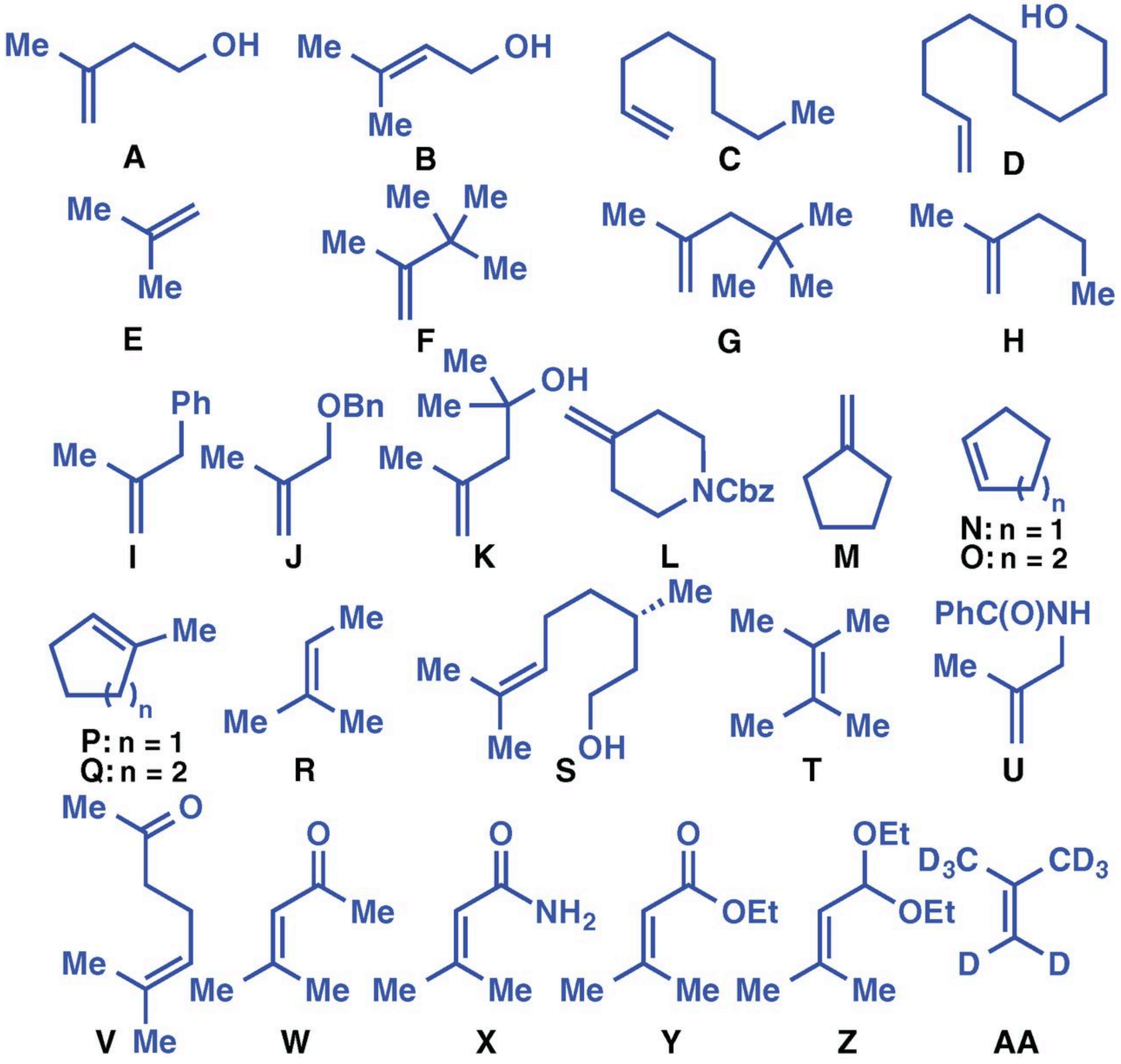
Postulated mechanism

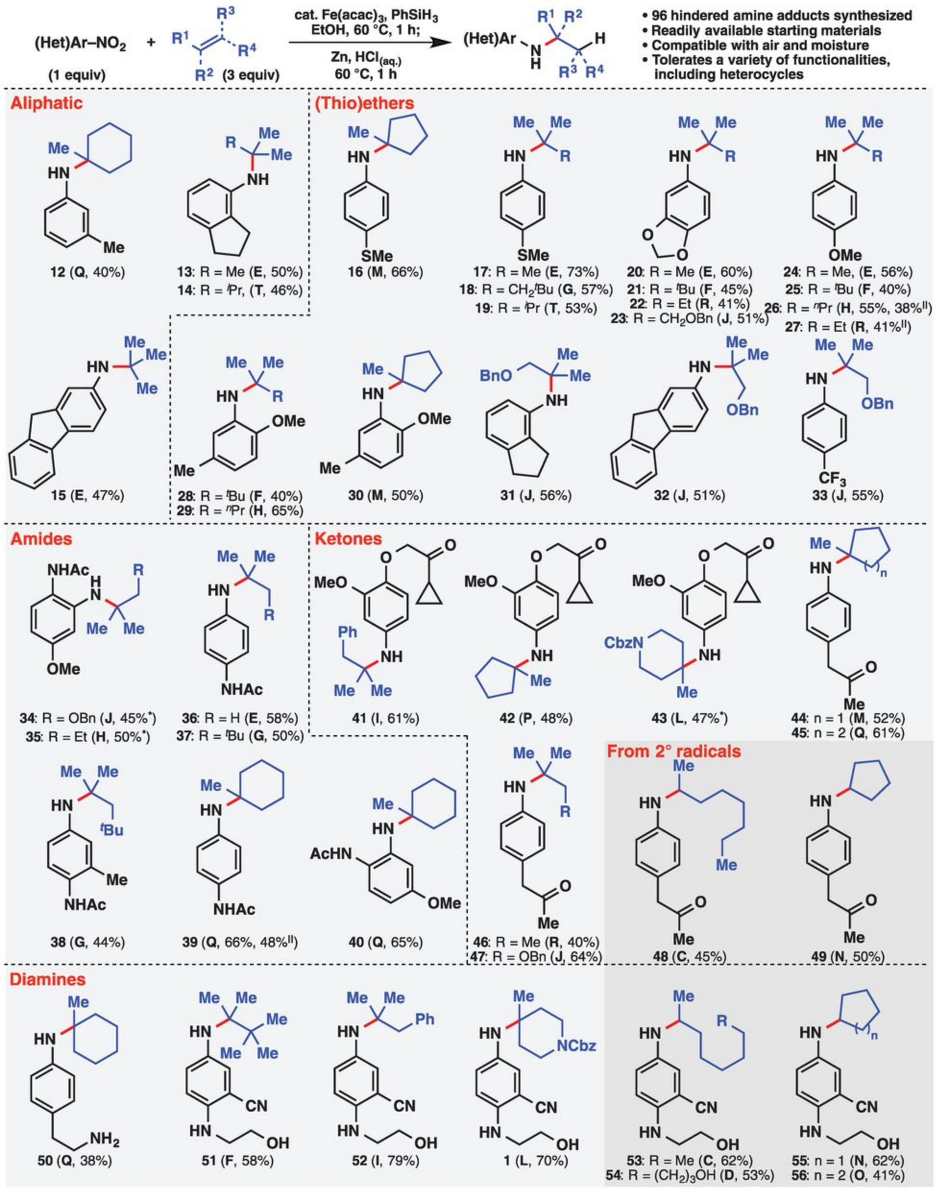


Control reactions

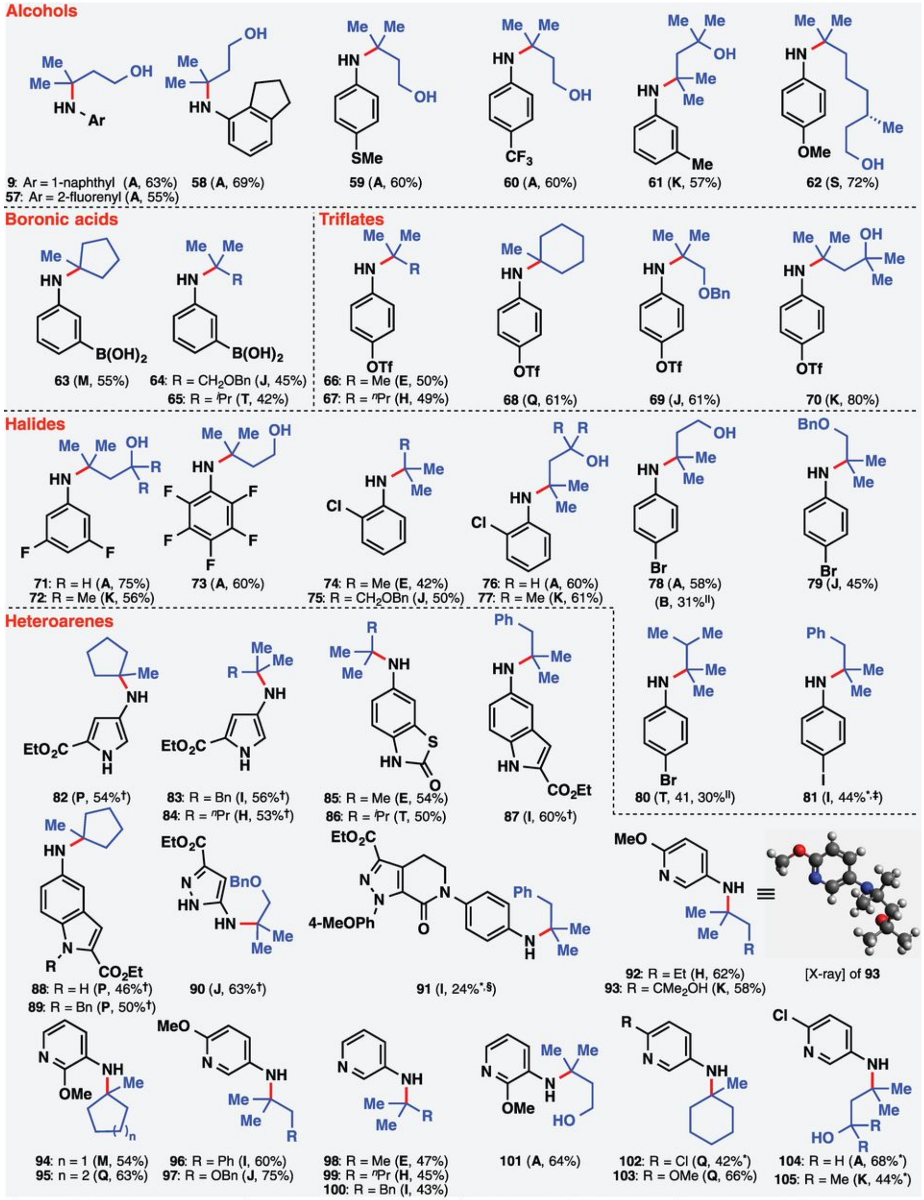


Substrate scope





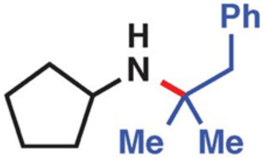
*Without Zn/HCl reduction procedure. †Olefin (5 equiv), PhSiH$_3$ (3 equiv). ‡Olefin (2 equiv), PhSiH$_3$ (3 equiv). §Olefin (2 equiv), PhSiH$_3$ (2 equiv). ‖Performed on decagram scale with no additional optimization.



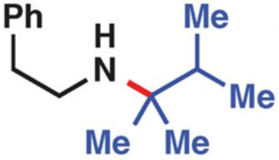
*Without Zn/HCl reduction procedure. †Olefin (5 equiv), PhSiH$_3$ (3 equiv). ‡Olefin (2 equiv), PhSiH$_3$ (3 equiv). §Olefin (2 equiv), PhSiH$_3$ (2 equiv). ‖Performed on decagram scale with no additional optimization.

Limitations of this methodology

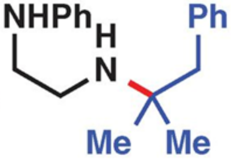
- Poor yields observed with nitroalkanes.



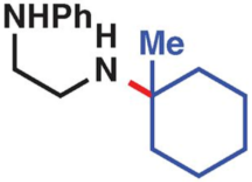
127 (I, 24%)



128 (T, 20%)



129 (I, 21%)



130 (Q, 25%)

- Phenols and thiophenols not tolerated.

- 2-Nitropyridines and Substitued styrenes are low yielding.

- Nitro-imidazoles produce a complex mixture.

- Multiple equivlents of olefin are required.

Future research possibilites?

There is no commentary on future work within the paper, however, some ideas are:

- Optimise conditions to produce good yields with nitro alkanes.
- Decrease the amount of olefin required.
- Develop a stereoselective method.
- Explore olefins with a greater steric bulk at the site of radical formation.

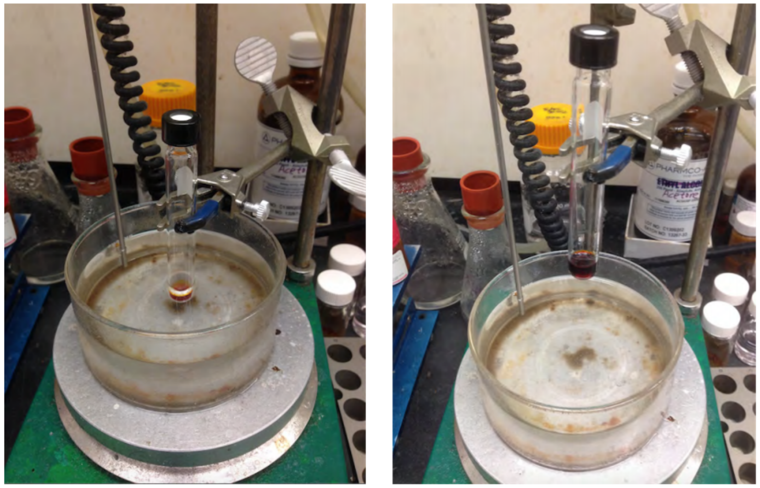


Fig. S4. Left: The reaction mixture was heated at 60 °C for 1 h;
Right: The reaction mixture after 1 h.

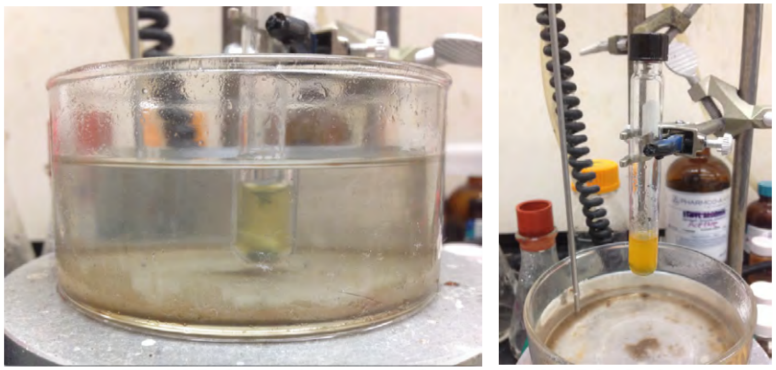


Fig. S6. Left: Reaction mixture after stirred at 60 °C for 5 min;
Right: Reaction mixture after stirred at 60 °C for 1 h.

Fig. S7. Left: Filtering the reaction mixture through Celite® and washing with EtOAc;
Right: Extraction with EtOAc after neutralized with sat. $NaHCO_3$ (aq).

Conclusion

Radical hydroamination with nitro-aromatics represents a novel and useful tool in the synthetic organic chemists toolbox.

It posses good to average yields across a wide range of substrates with few drawbacks and posses scope for further improvement.

Questions?