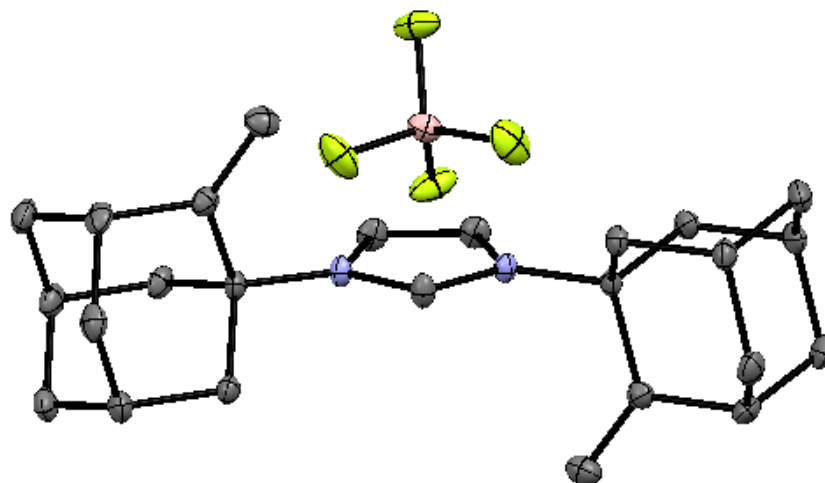


NHC-derivatives based on 1-amino-2-substituted-adamantane

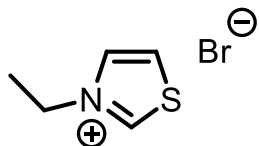
Radim Hrdina

Seminar
AG Schreiner



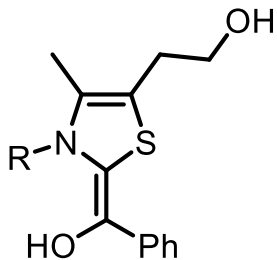
3.5.2019

History of NHC derivatives



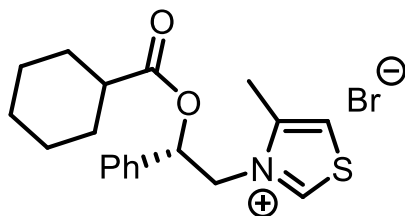
1943 T. Ukai, R. Tanaka, T. Dokawa

„For the title we ask Fumito- Thiazolium derivatives as catalysts for benzoin condensation“
J. Pharm. Soc. Jpn. **1943**, 63, 296.



1958 Breslow

On the Mechanism of Thiamine Action. Evidence from Studies on Model Systems *J. Am. Chem. Soc.* **1958**, 80, 3719.

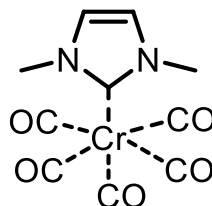


1966 J. C. Sheehan, D. H. Hunneman

Homogeneous Asymmetric Catalysis,
J. Am. Chem. Soc. **1966**, 3666.

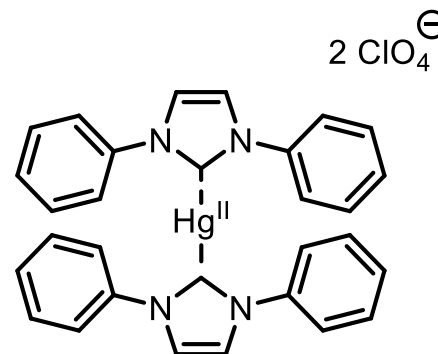
1968 K. Öfele

1,3-Dimethyl-4-Imidazolinylden-(2)-Pentacarbonylchrom ein neuer Übergangsmetall-Carben-Komplex,
J. Organometal. Chem. **1968**, 12, 42.



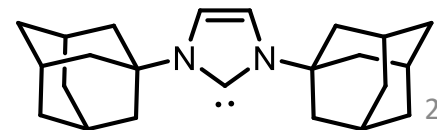
1968 H. W. Wanzlick, H. J. Schönherr

Direkt-Synthese eines Quecksilbersalz-Carben-Komplexes,
Angew. Chem. 1968, 180, 4.



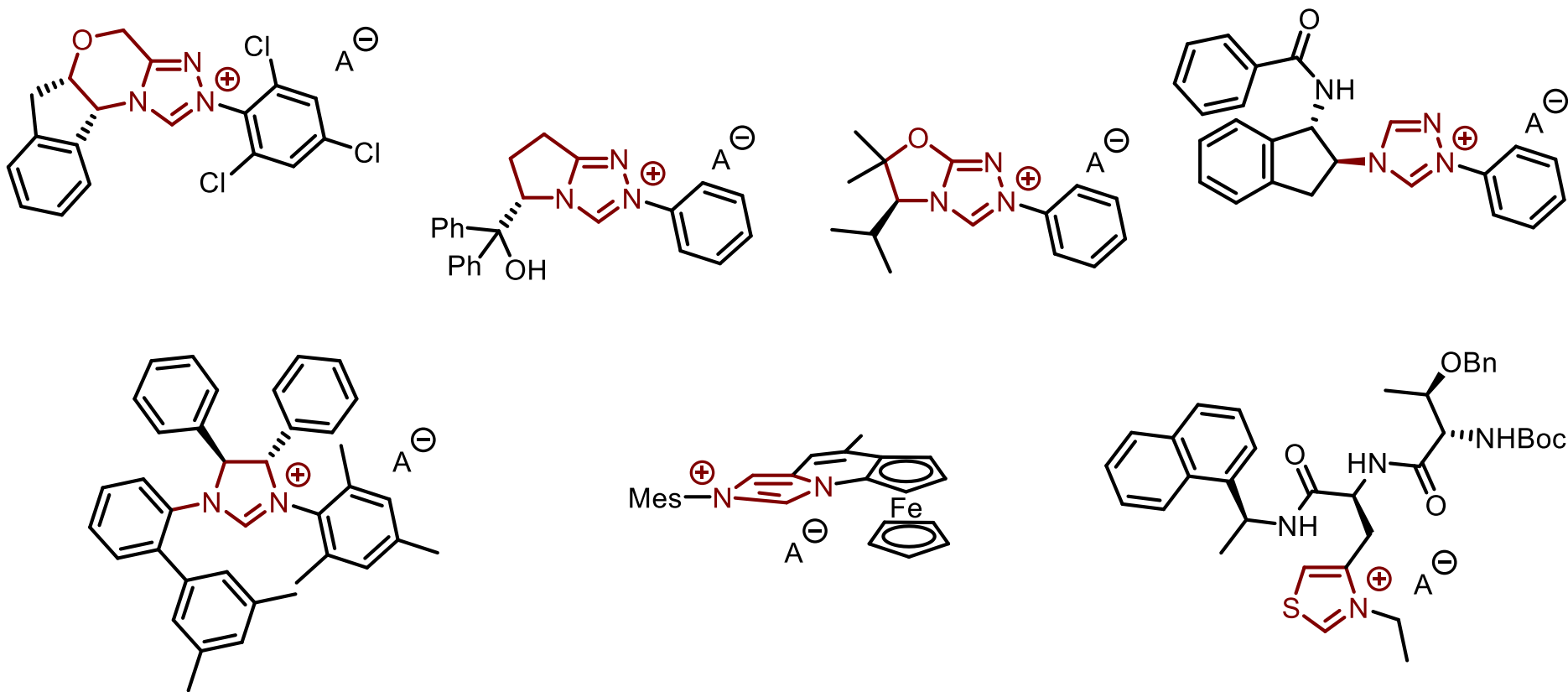
1991 A. J. Arduengo III, R. L. Harlow, M. Kline

A Stable Crystalline Carbene, *J. Am. Chem. Soc.* **1991**, 113, 363.



NHC derivatives in organocatalysis

1. As Organocatalysts in Umpolung Catalysis and Nucleophilic Catalysis



Gehrke, S.; Holloczki, O., Are There Carbenes in *N*-Heterocyclic Carbene Organocatalysis? *Angew. Chem. Int. Ed.* **2017**, 56, 16395.

Flanigan, D. M.; Romanov-Michailidis, F.; White, N. A.; Rovis, T., Organocatalytic Reactions Enabled by *N*-Heterocyclic Carbenes. *Chem. Rev.* **2015**, 115, 9307.

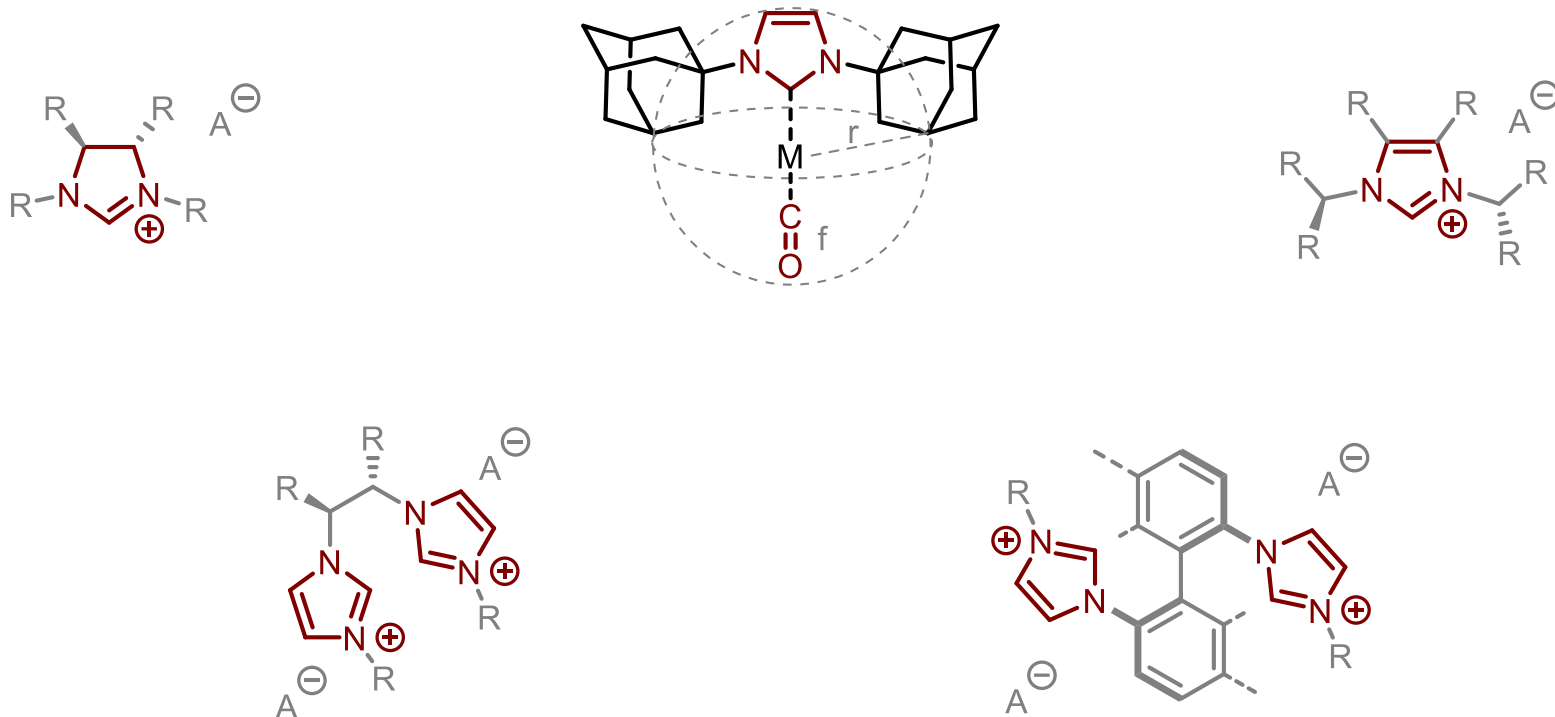
Hopkinson, M. N.; Richter, C.; Schedler, M.; Glorius, F., An overview of *N*-heterocyclic carbenes. *Nature* **2014**, 510, 485.

Enders, D.; Niemeier, O.; Henseler, A., Organocatalysis by *N*-heterocyclic, carbenes. *Chem. Rev.* **2007**, 107, 5606.

NHC transition metal complexes

2. As ligands for metal-based catalysts

Ligand description (sterics and electronics)

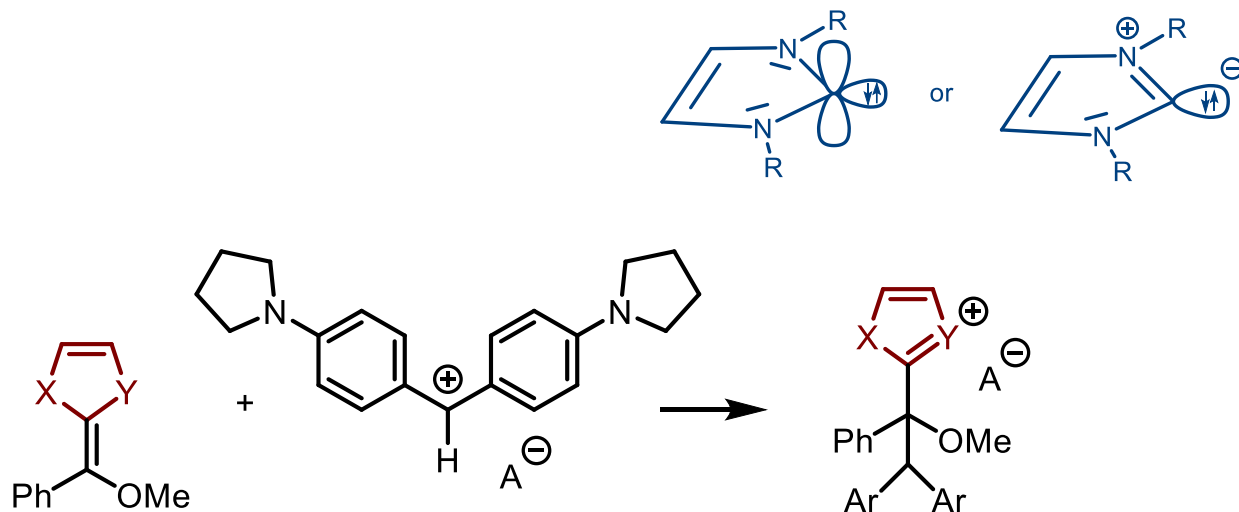
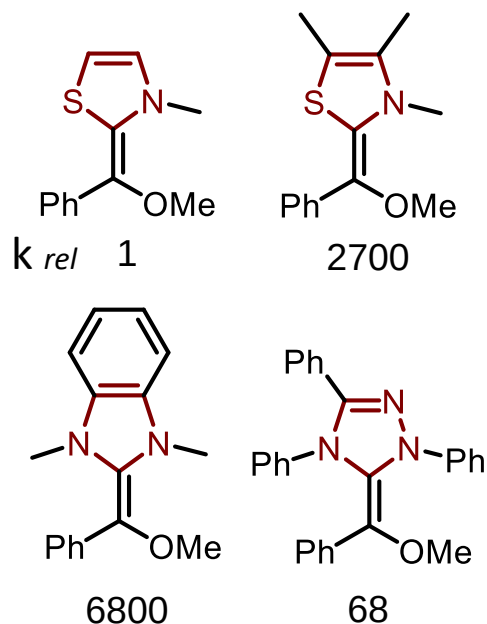


Janssen-Müller, D.; Schlepphorst, C.; Glorius, F., Privileged chiral *N*-heterocyclic carbene ligands for asymmetric transition-metal catalysis. *Chem. Soc. Rev.* **2017**, 46, 4845.

Wang, F. J.; Liu, L. J.; Wang, W. F.; Li, S. K.; Shi, M., Chiral NHC-metal-based asymmetric catalysis. *Coord. Chem. Rev.* **2012**, 256, 804.

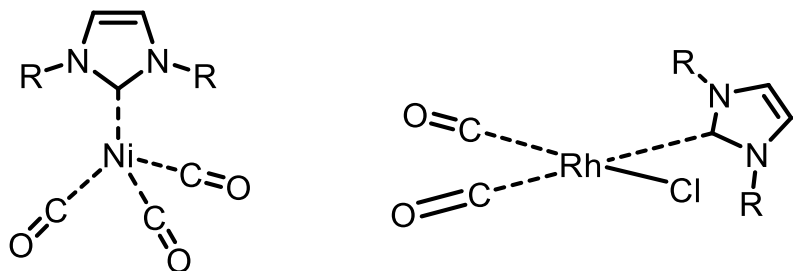
Characterisation of NHC's

1. As organocatalysts



Maji, B.; Mayr, H. Structures and Reactivities of O-Methylated Breslow Intermediates. *Angew. Chem. Int. Ed.* **2012**, 51, 10408.

2. As ligands

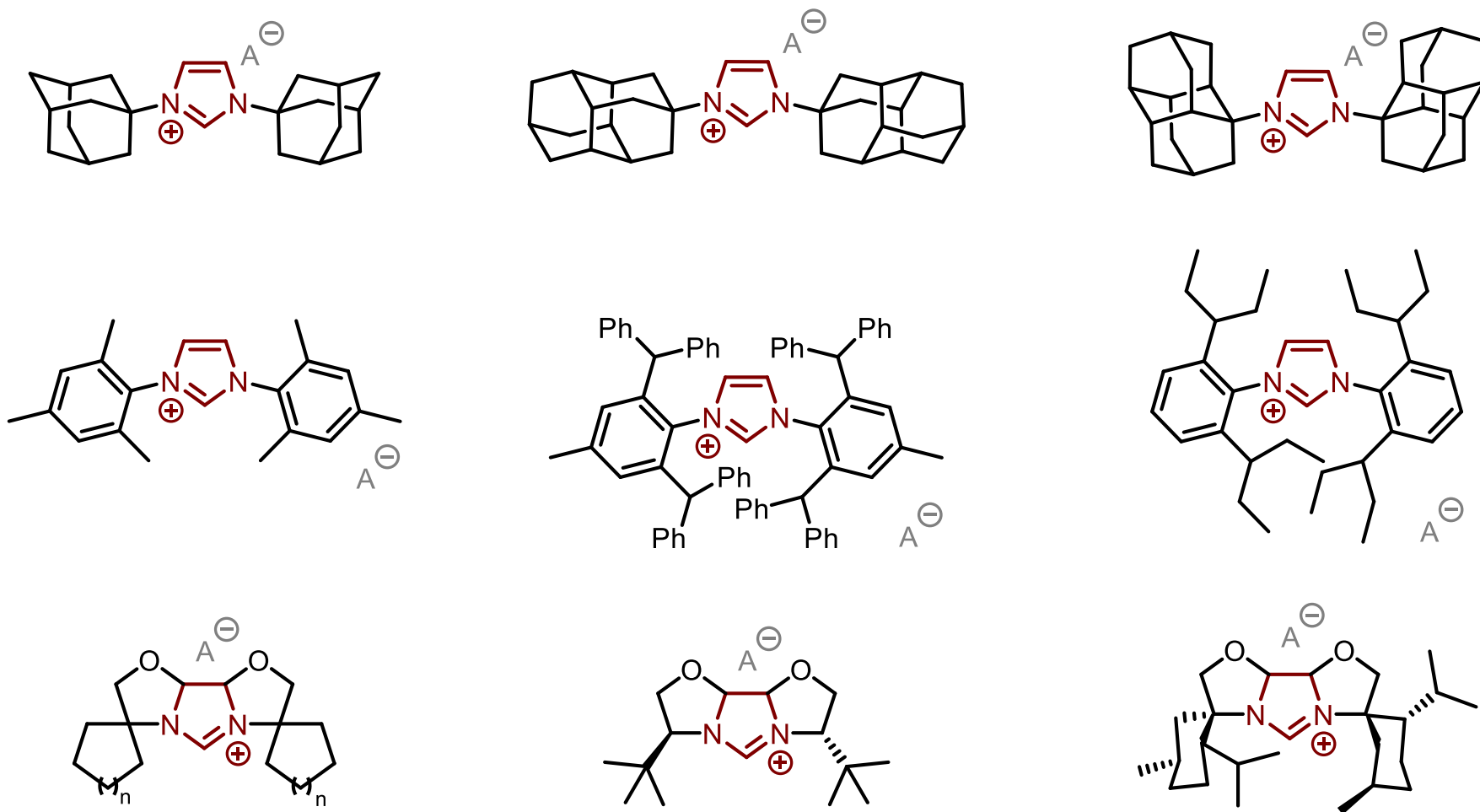


Better the ligand is sigma donor
Or worse pi acceptor is then the stretching frequency of CO in the metal complex is lower

Huynh, H. V., Electronic Properties of N-Heterocyclic Carbenes and Their Experimental Determination. *Chem. Rev.* **2018**, 118, 9457.

Tolman, C. A. Electron Donor-Acceptor Properties of Phosphorus Ligands. Substituent Additivity, *J. Am. Chem. Soc.* **1970**, 92, 2953.

Bulky NHC derivatives

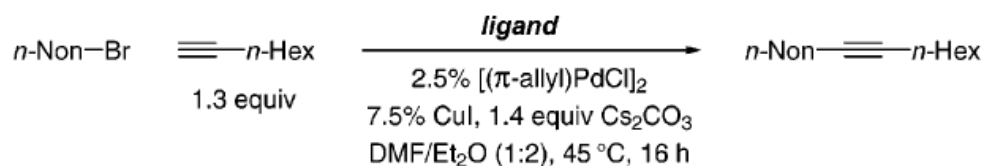
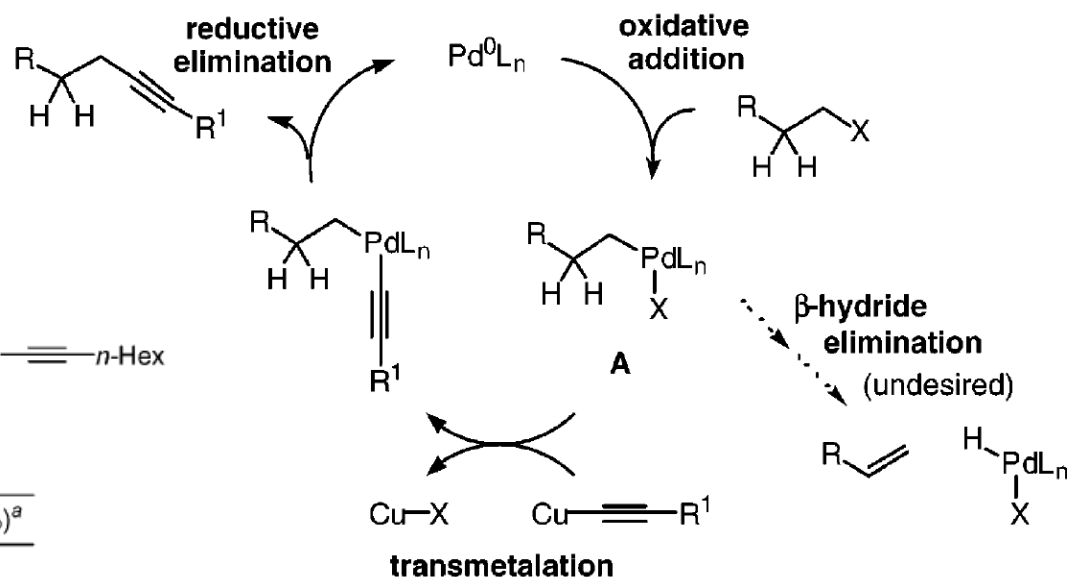
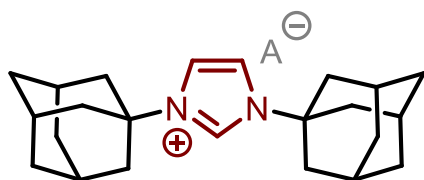


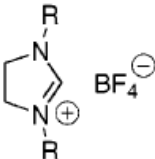
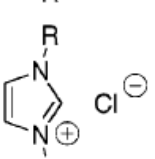
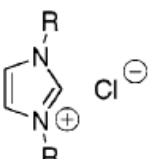
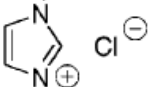
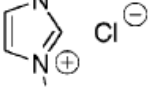
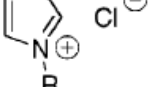
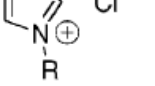
Richter, H.; Schwertfeger, H.; Schreiner, P. R.; Frohlich, R.; Glorius, F., Thieme Chemistry Journal Awardees - Where are They Now? Synthesis of Diamantane-Derived *N*-Heterocyclic Carbenes and Applications in Catalysis. *Synlett* **2009**, 193.

Izquierdo, F.; Manzini, S.; Nolan, S. P., The use of the sterically demanding IPr* and related ligands in catalysis. *Chem. Comm.* **2014**, 50, 14926.

Bulky NHC derivatives in catalysis

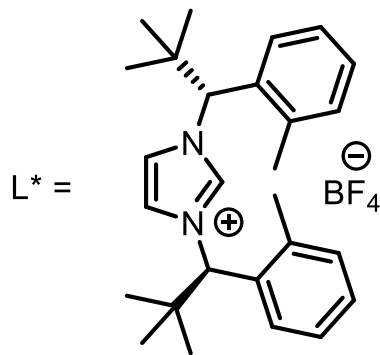
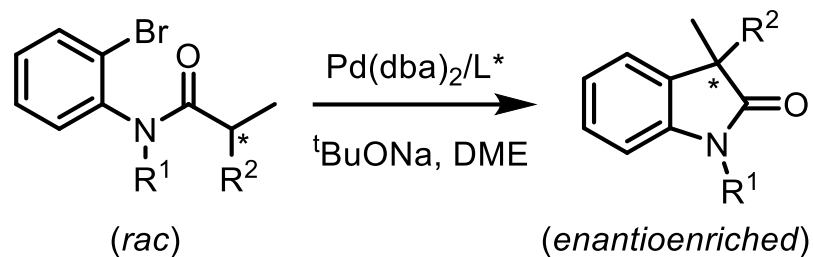
The First Applications of Carbene Ligands in Cross-Couplings of Alkyl Electrophiles: Sonogashira Reactions of Unactivated Alkyl Bromides and Iodides



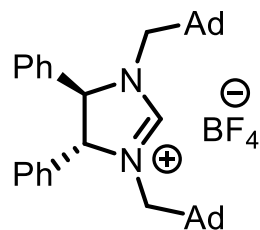
entry	ligand	yield (%) ^a
1	10% PPh_3	<5
2	10% PCy_3	<5
3	10% $\text{P}(t\text{-Bu})_2\text{Me}$	<5
4	10% $\text{PCy}(1\text{-pyrrolidinyl})_2$	<5
5		<5
6		58
7		67
8		81
9		80
10		<5
11		<5

„Because the transmetalating agent in the Sonogashira reaction is generated in situ in low concentration, we anticipate that the development of an effective catalyst (that avoids hydride elimination) for this coupling process may be of particular interest.“

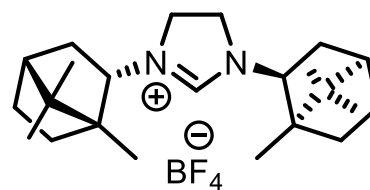
Chiral bulky NHC derivatives in catalysis



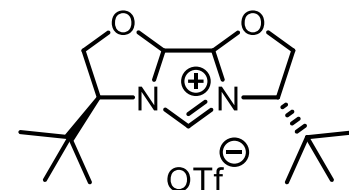
99%, 94% ee



62%, 62% ee

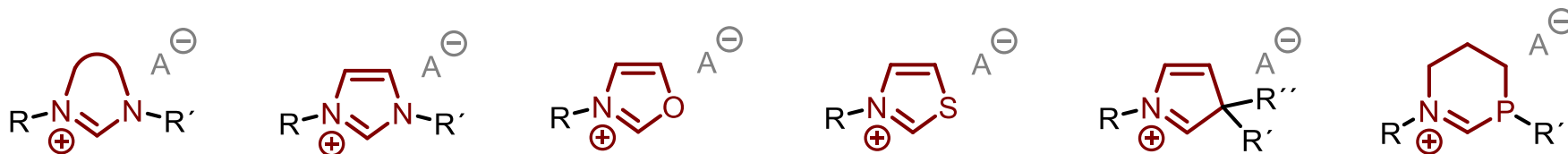


74%, 57% ee

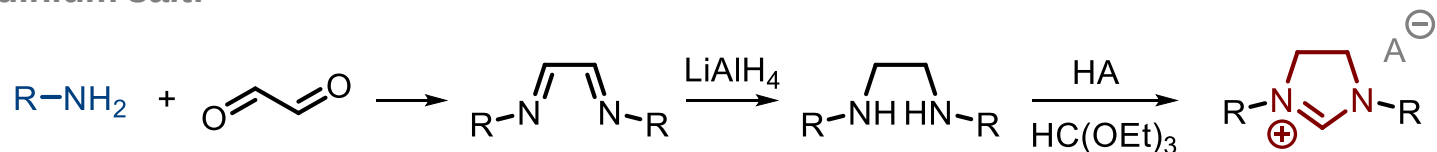


94%, 43% ee

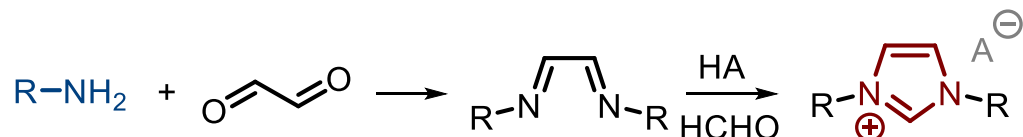
Preparation of the precursors (heterocyclic salts)



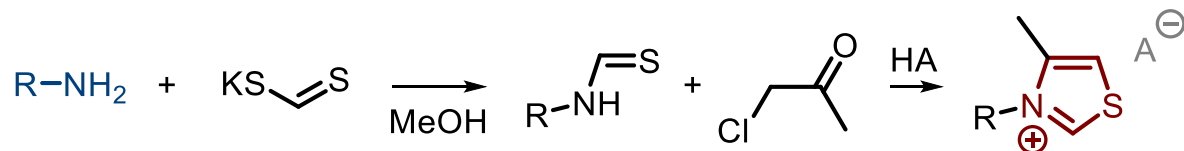
Formamidineum salt:



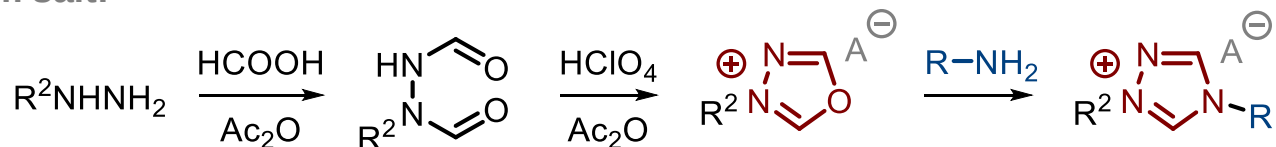
Imidazolium salt:



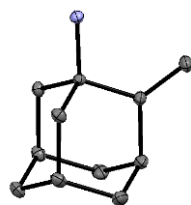
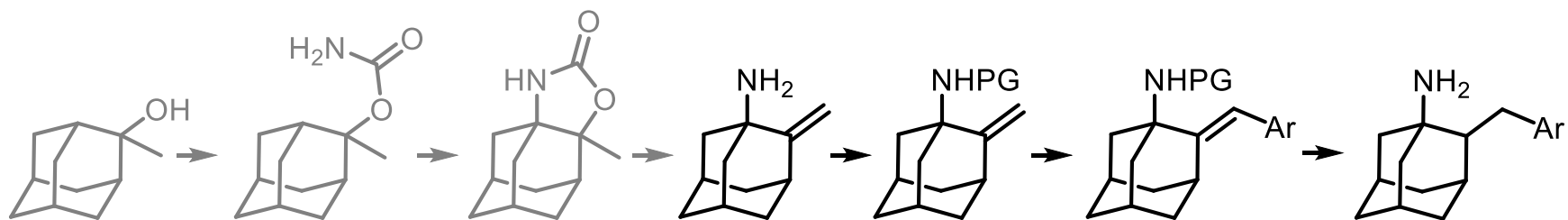
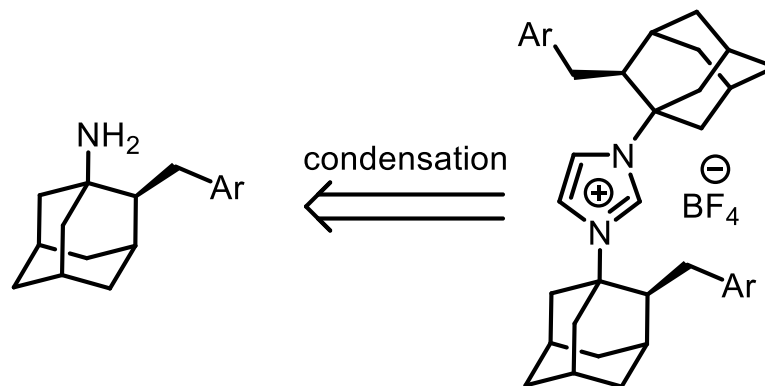
Thiazolium salt:



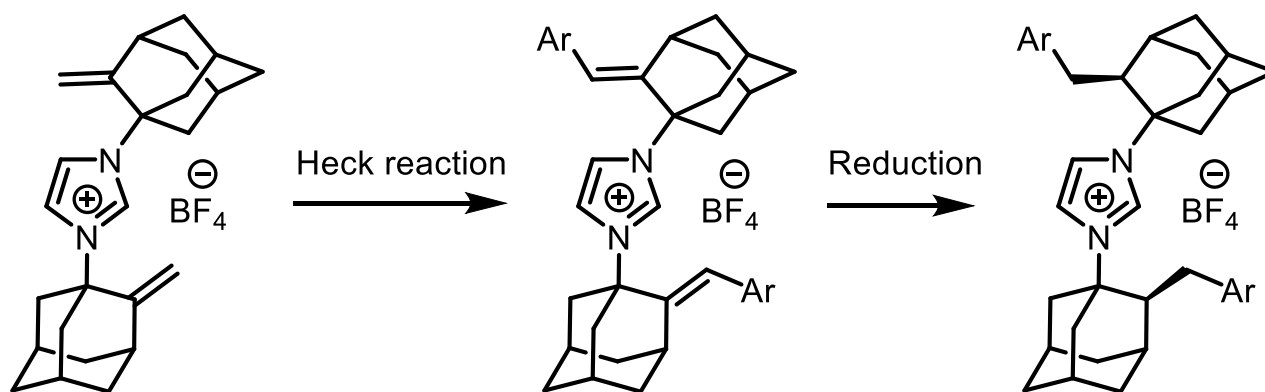
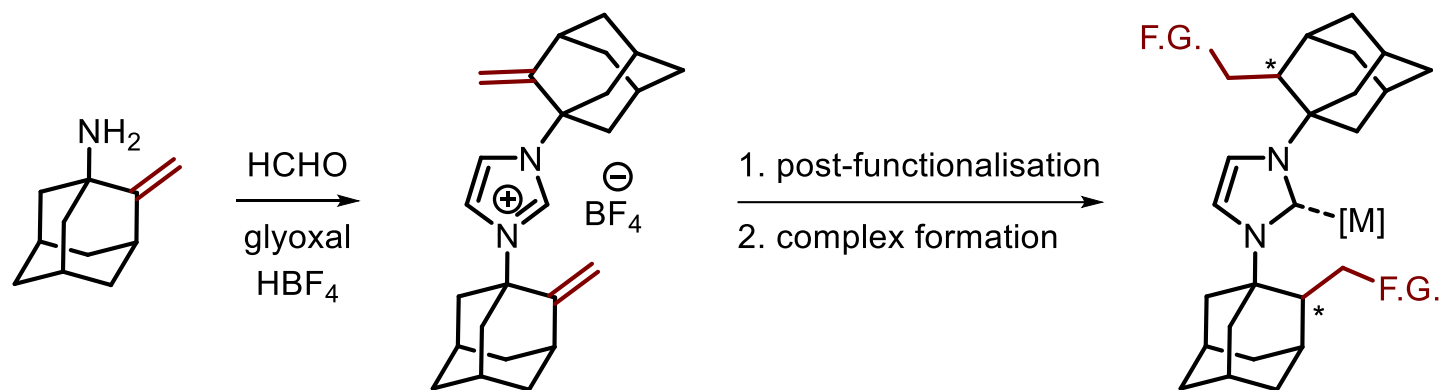
Triazolium salt:



The plan

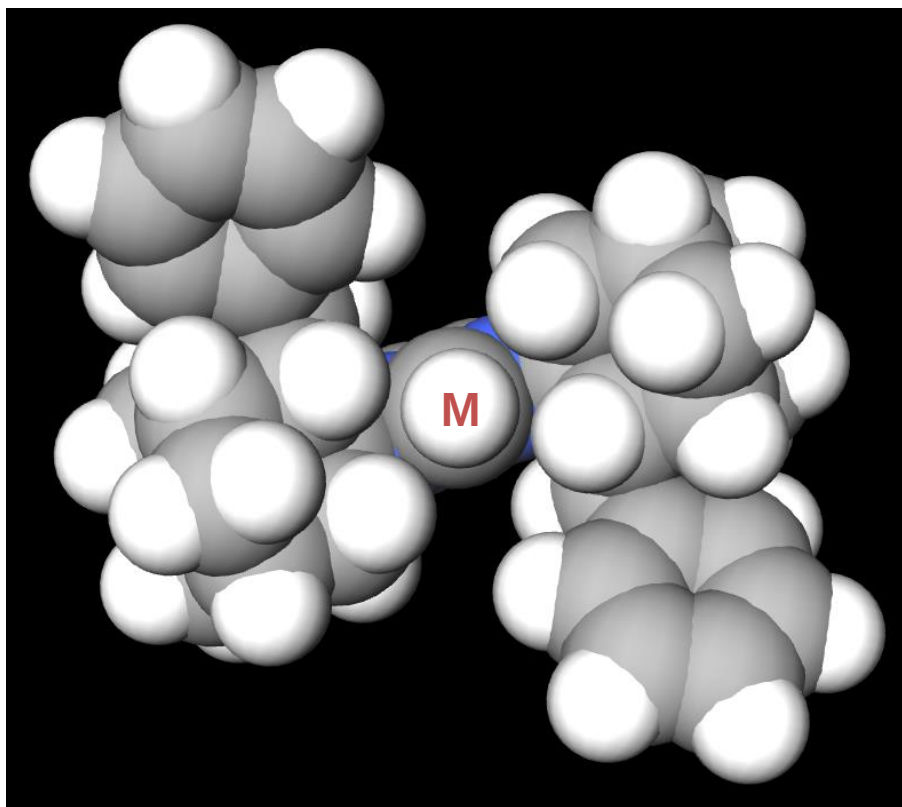
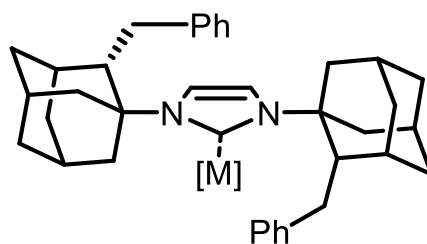


The plan



Reductive Heck reaction

Desired properties of the compound



Synthetic approaches to 1,2-disubstituted adamantane derivatives

1. Through the construction of the adamantane framework

1.1 Protoadamantane route

1.2 Noradamantane route

1.3 Bicycloalkane route

1.4 Total synthesis

1.5 Diamondoids (separately presented)



2. Through the directed C–H functionalization of the adamantane framework

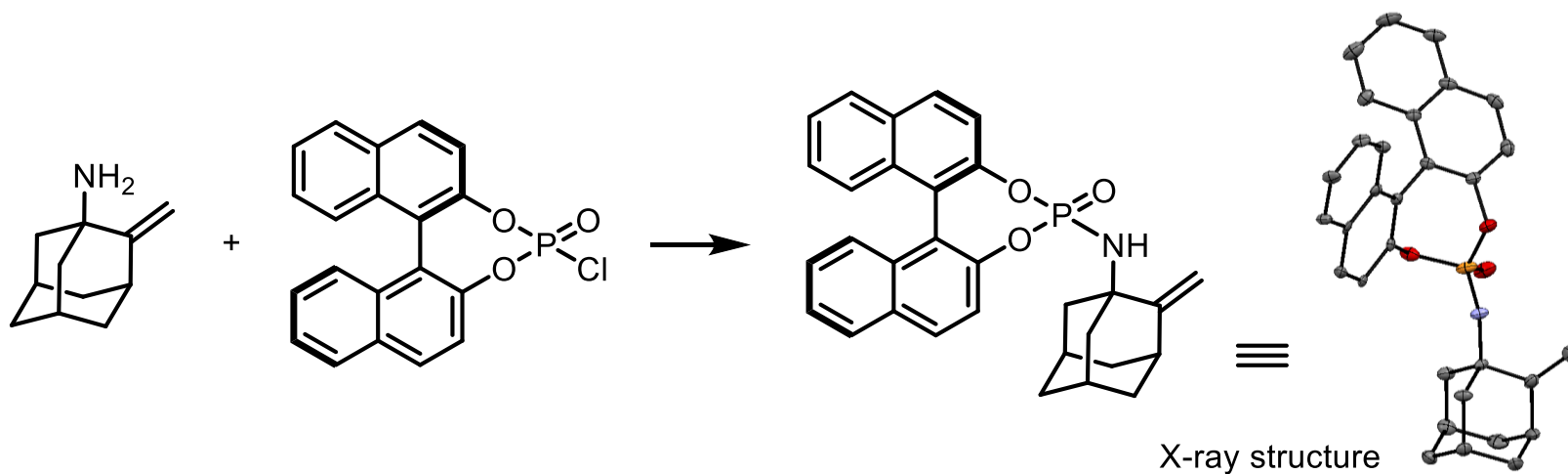
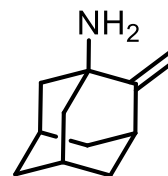
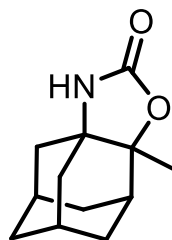
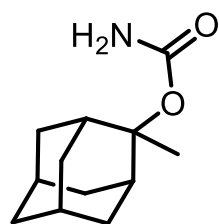
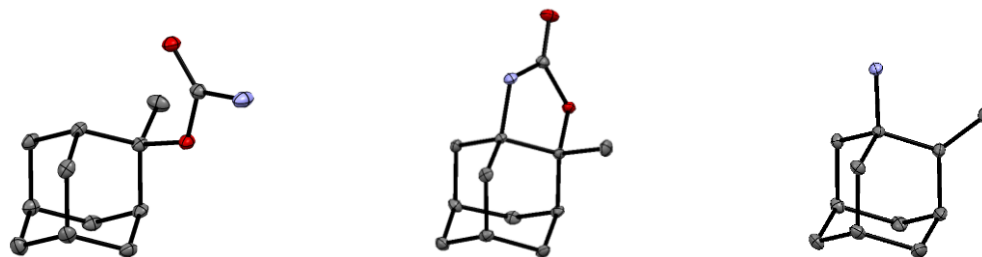
2.1 Insertion reactions of electrophilic organic species

2.2 Hydrogen radical abstraction reactions

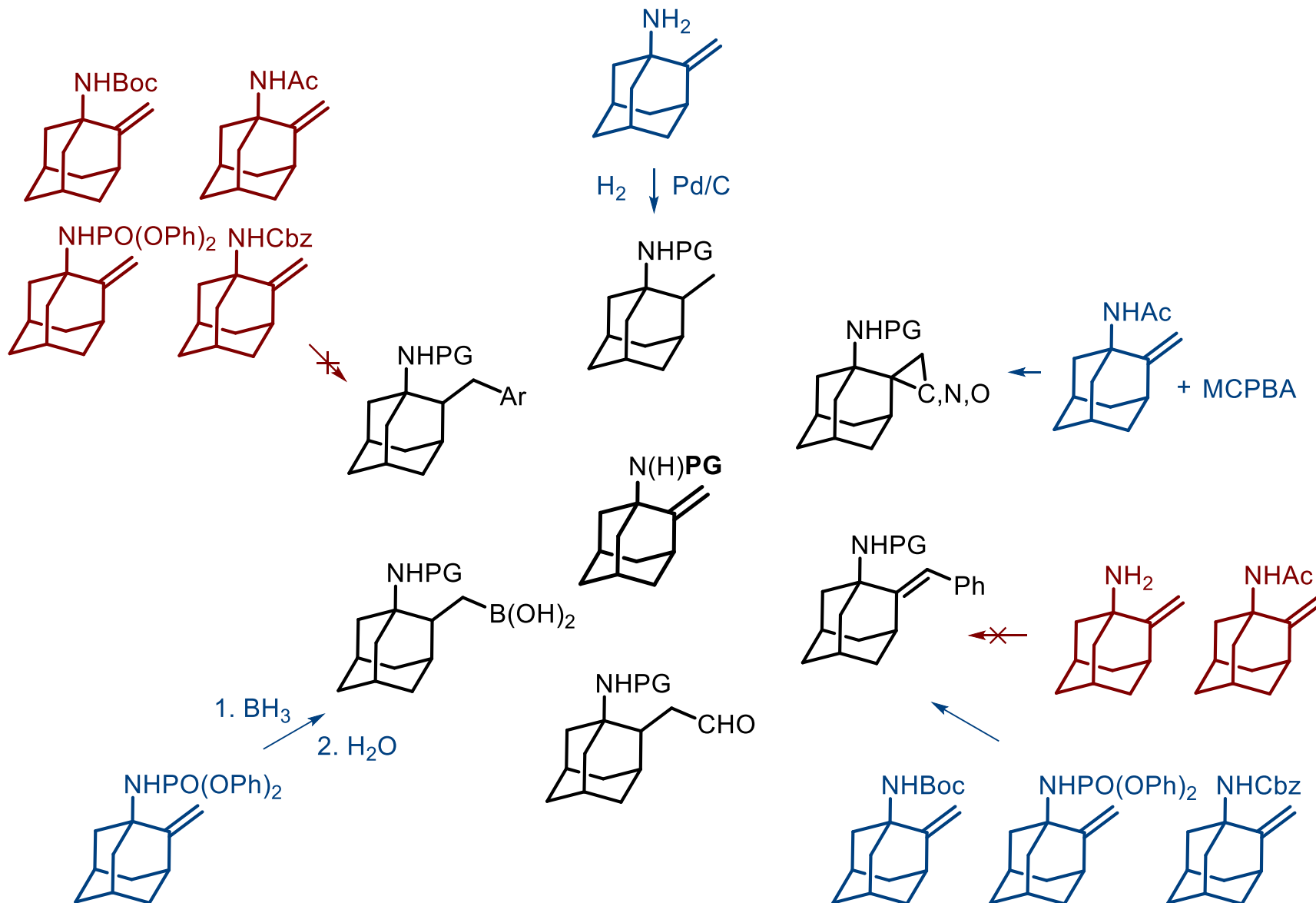
2.3 Carbometalations (C–H activation with transition metals)

2.4 Hydride shift

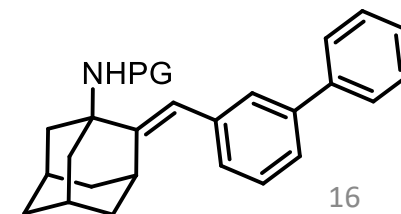
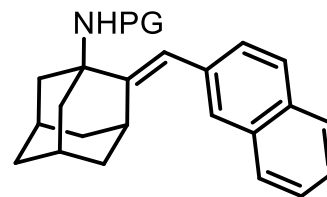
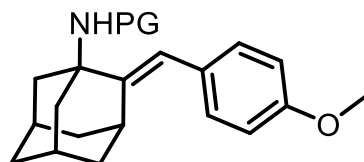
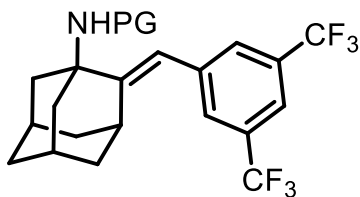
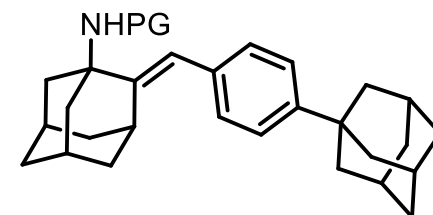
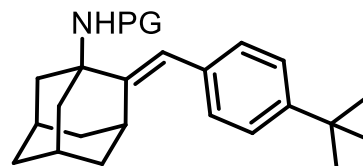
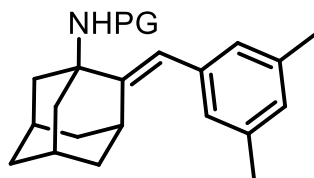
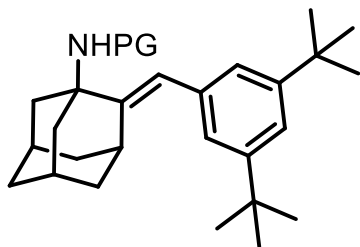
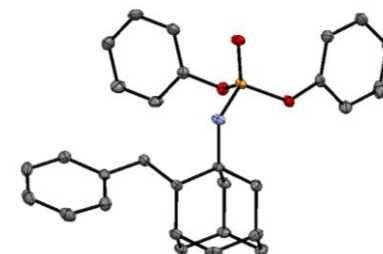
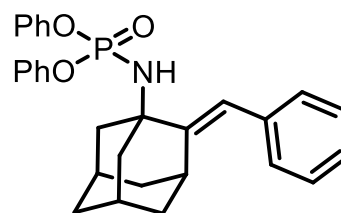
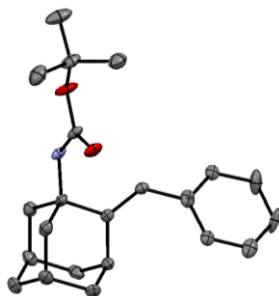
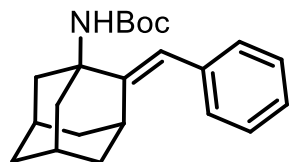
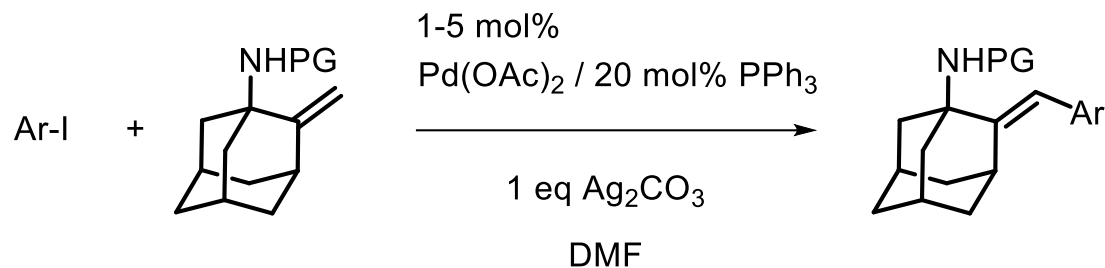
Synthesis of the advanced intermediate



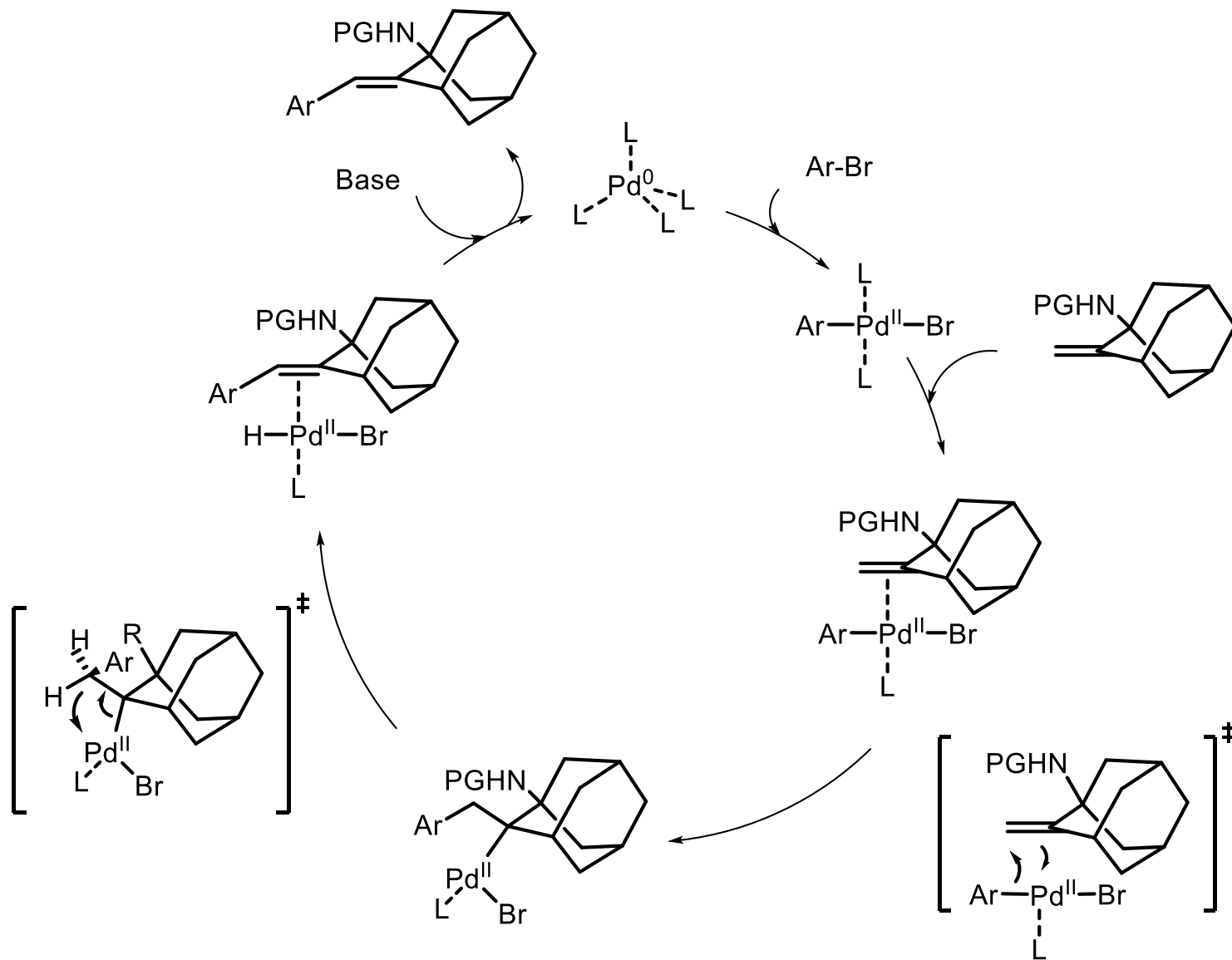
Reactions with the advanced intermediate

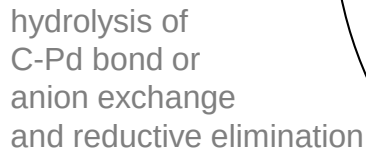


Heck reaction with non-coordinating protecting group

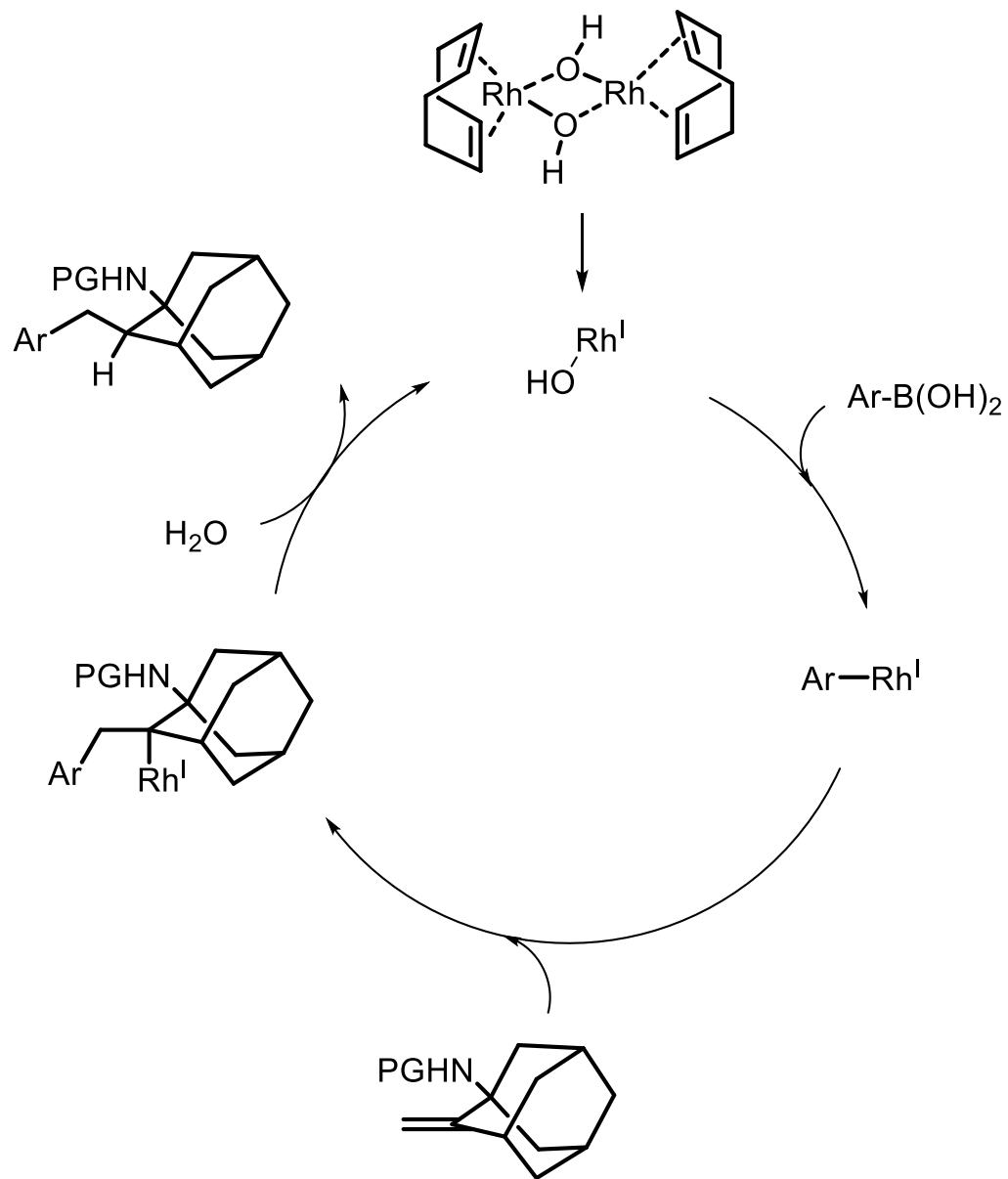


Heck reaction

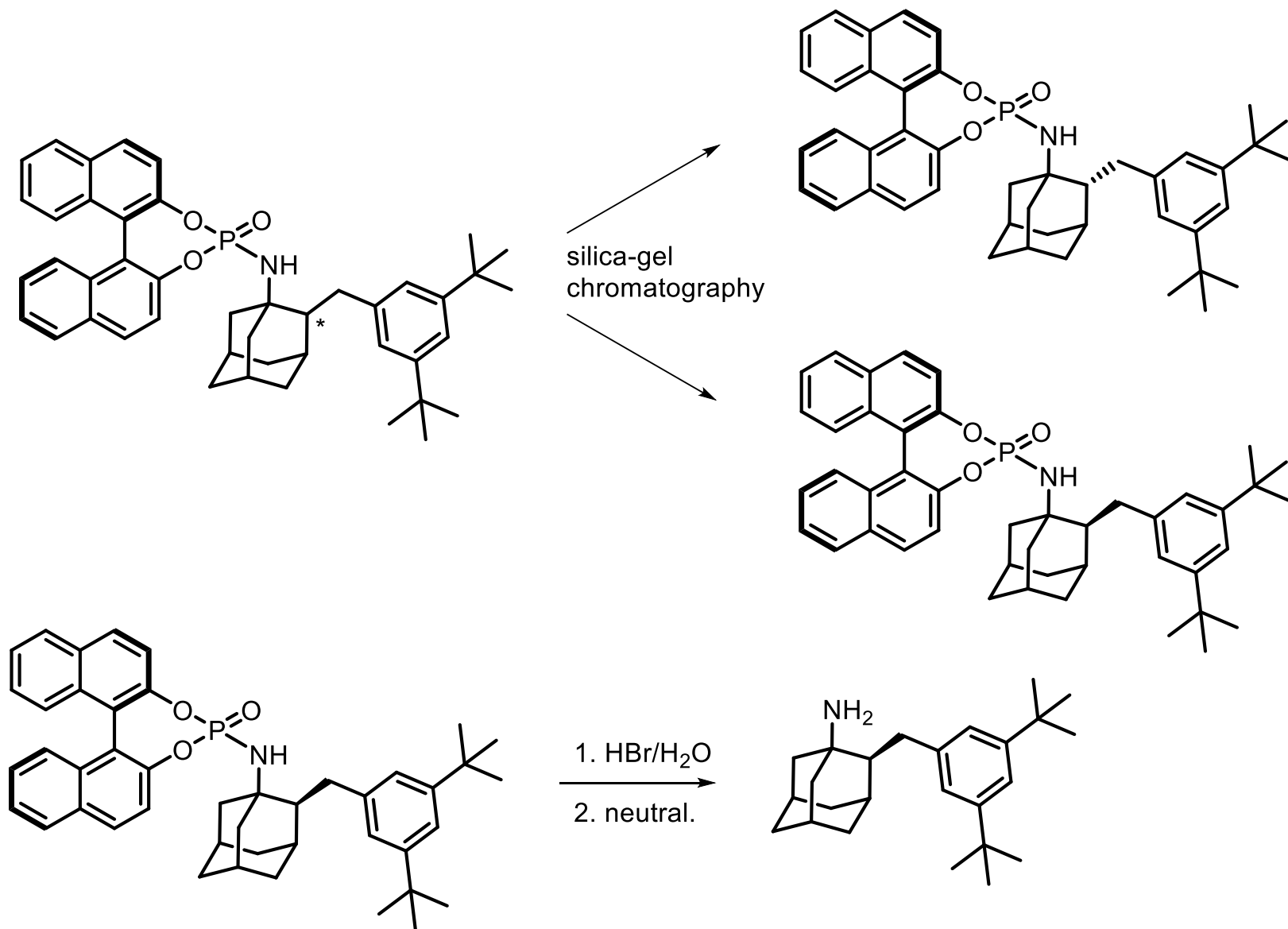




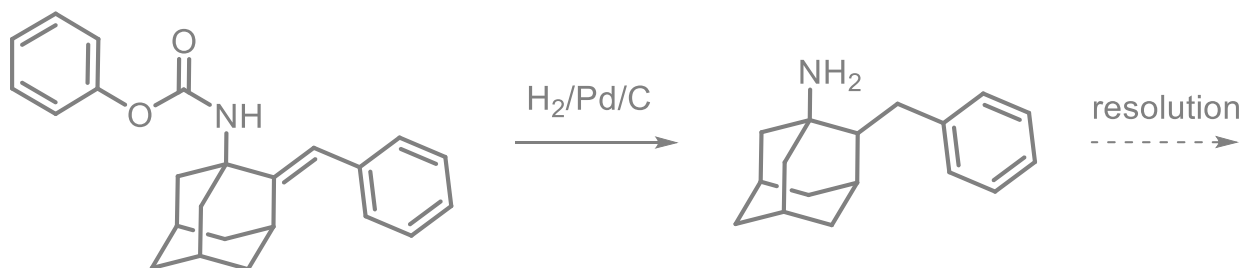
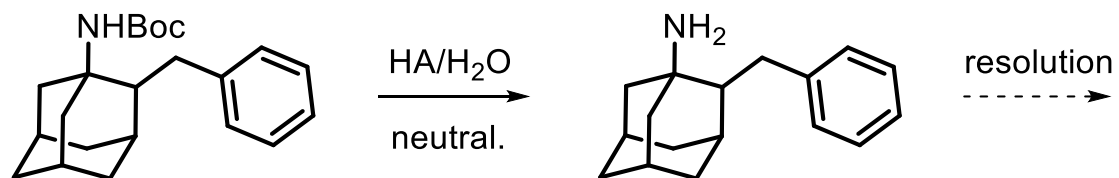
Hydroarylation with boronic acids



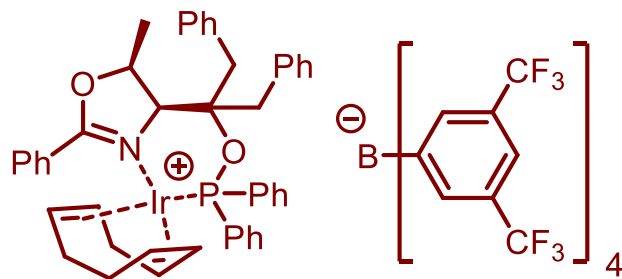
Resolution and cleavage



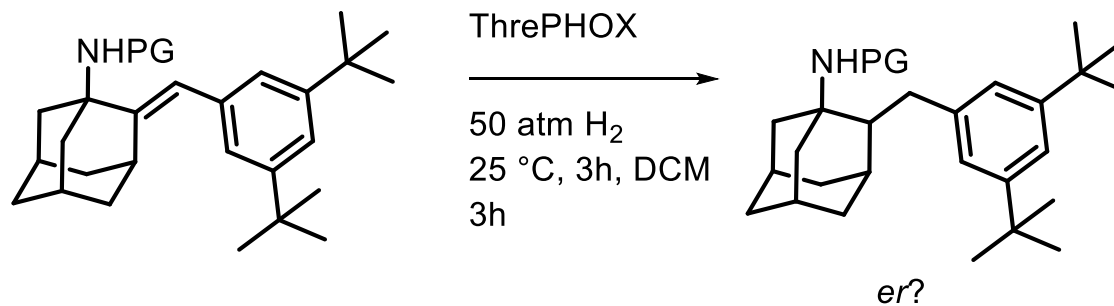
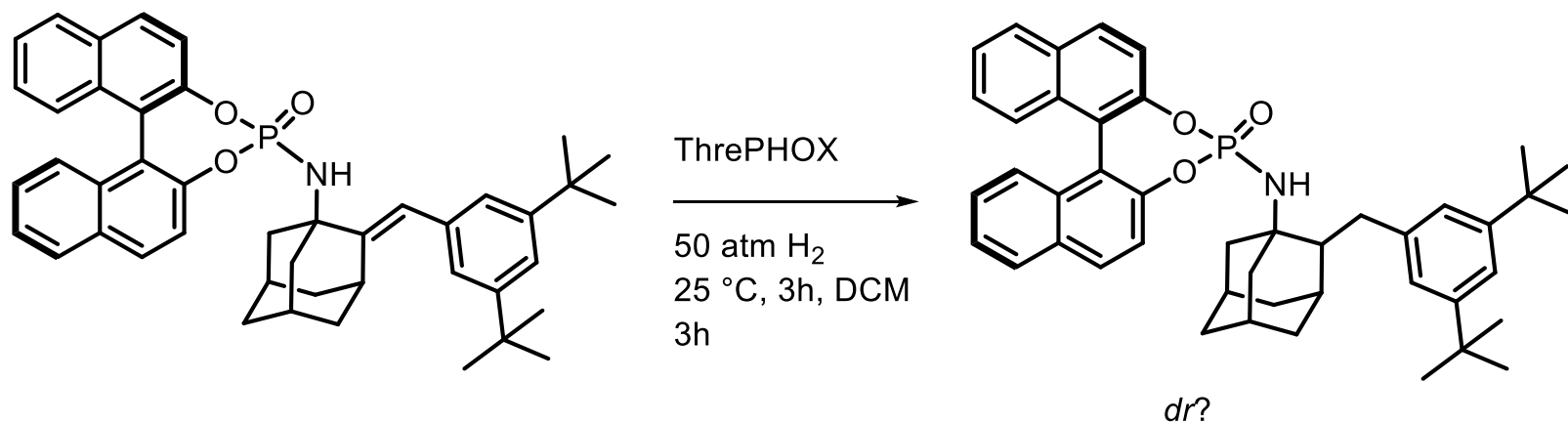
Cleavage and resolution



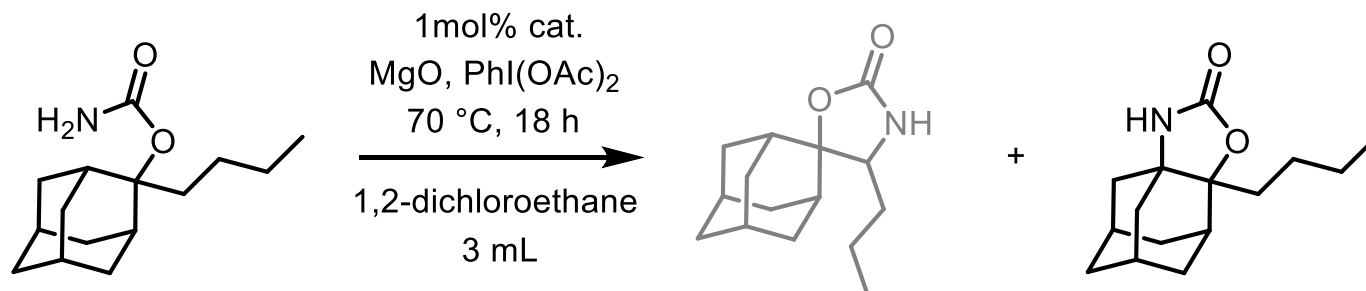
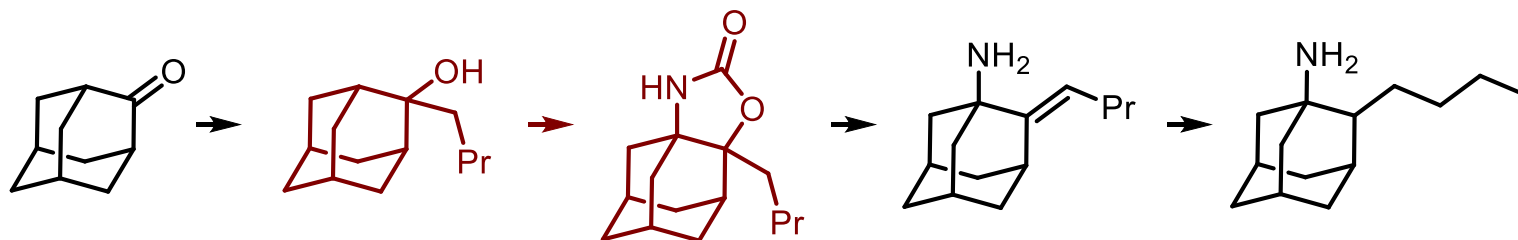
Enantioselective reduction with Pfaltz's catalysts



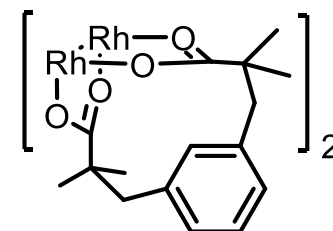
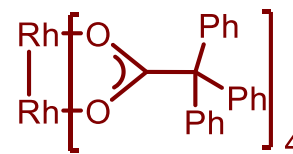
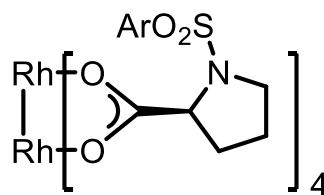
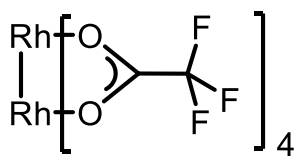
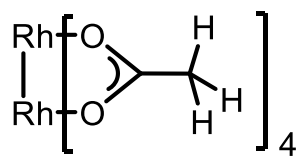
commercial as *ThrePHOX*



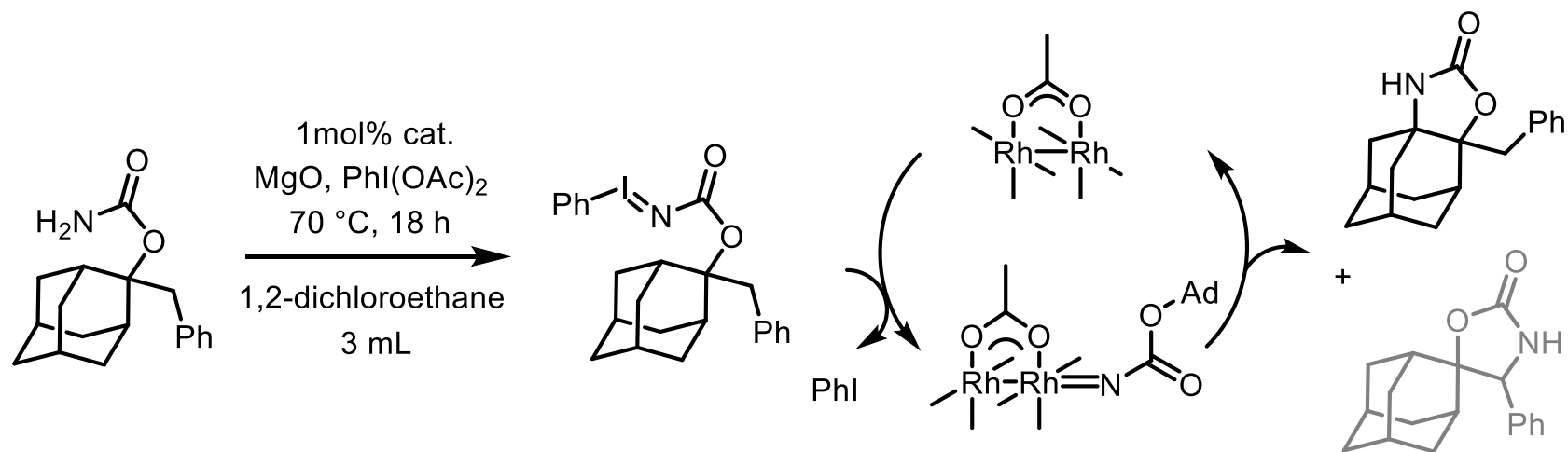
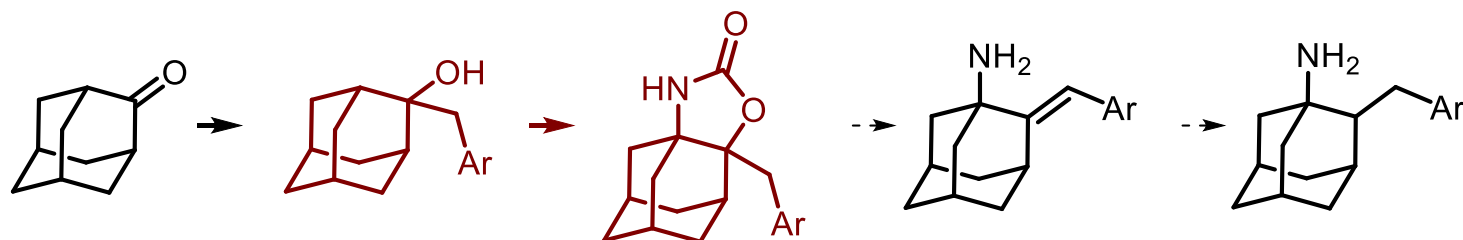
How to make derivative with aliphatic chain?



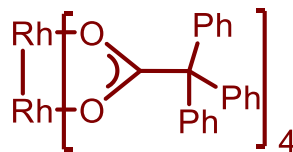
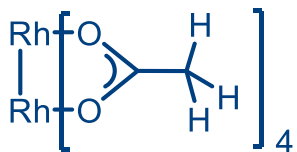
1 : 1



Can the synthesis be shorter for the original target?

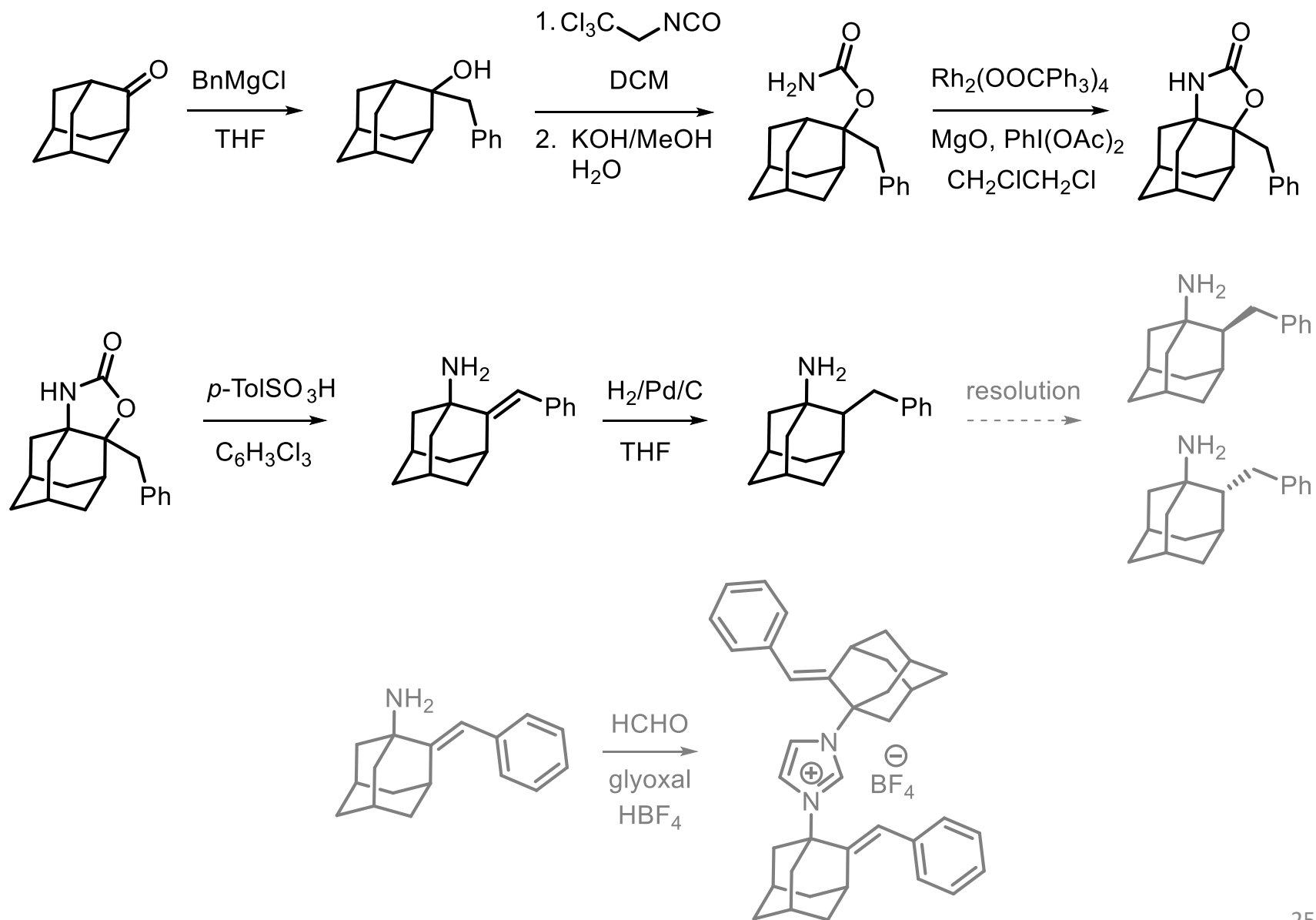


gives 2 : 1 ratio of products



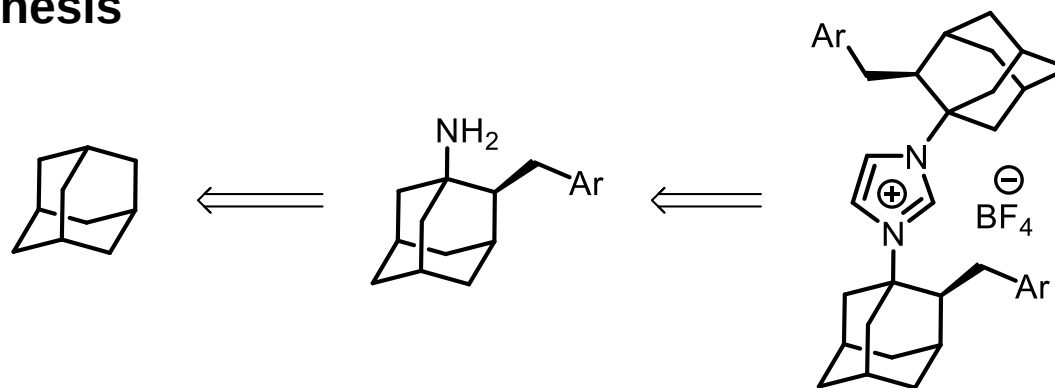
gives 1 : 0.85 ratio of products

It can

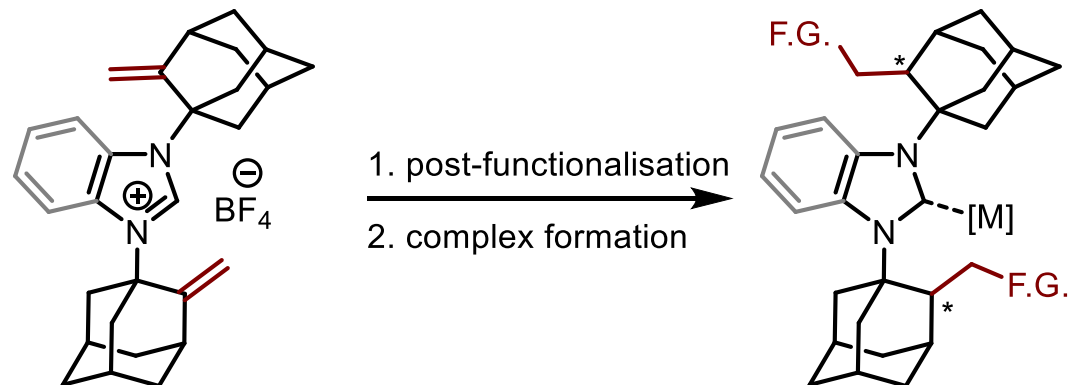


The goal

Any short synthesis



Any reaction that works



Acknowledgement

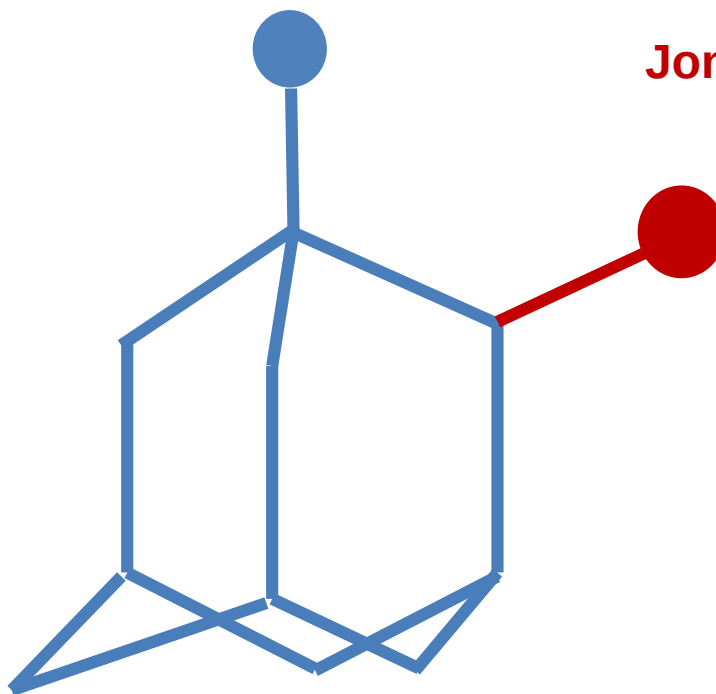
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