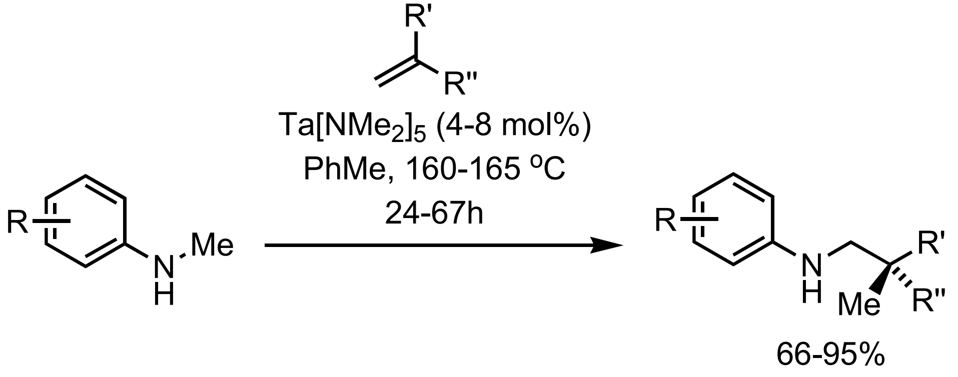
Direct, Catalytic Hydroaminoalkylation of Unactivated Olefins with *N*-Alkyl Arylamines

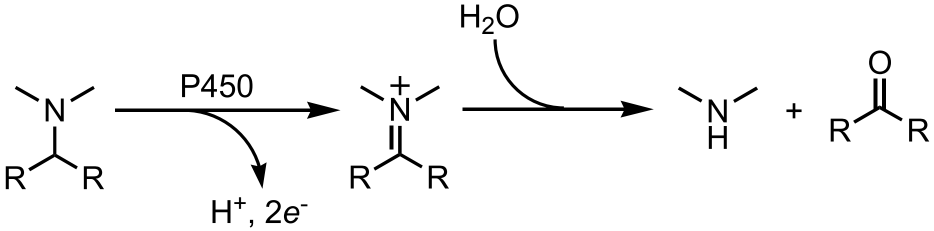


S. B. Herzon and J. F. Hartwig, *J. Am. Chem. Soc.*, ASAP

DOI: 10.1021/ja0718366

Biological Activation of CH Bonds

- Cytochrome P450, a family of over 60 enzymes, participates in a variety of cellular redox processes



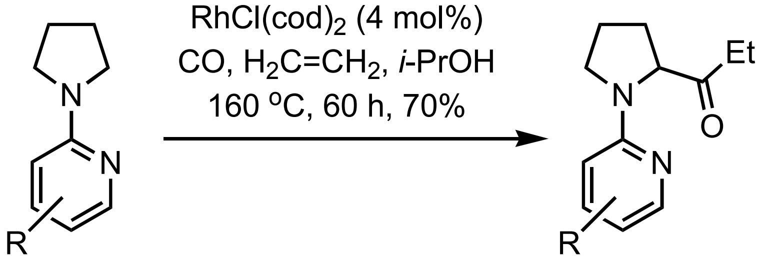
- Ability of P450 to transform endogeous and foreign compounds has a tremendous impact on the metabolism of drugs

For recent studies on the metabolism of cyclopropylamines, see:
Cerny, Hanzlik *J. Am. Chem. Soc.* **2006**, *128*, 3346

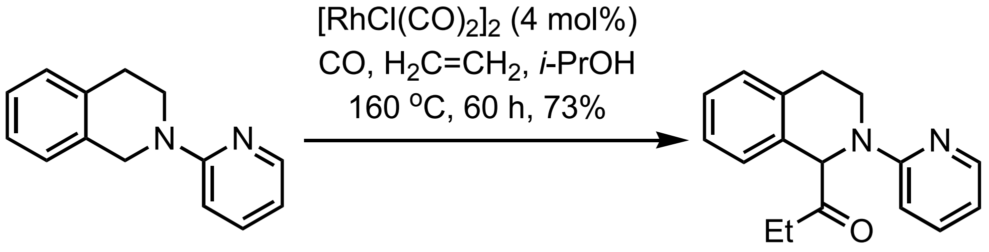
- Many efforts have been focused on developing a catalytic system mimicking activity of P450. Metals such as Pd(0), Ru(II), Cu(I) are successful candidates for the catalytic activation of CH bonds.

Activation of sp^3 CH Bonds Adjacent to Nitrogen

- Catalytic carbonylation via pyridine-directed activation of pyrrolidine has been achieved using Rh(I) catalysts



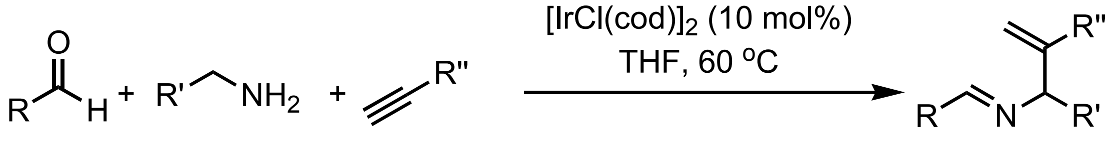
R =		
H,	40 h,	68%
3-Me,	60 h,	73%
4-Me,	60 h,	73%
5-Me,	40 h,	84%
6-Me,	60 h,	12%
5-CF_3,	60 h,	15%



Murai et al. *J. Am. Chem. Soc.* **2000**, *122*, 12882

Doye *Angew. Chem. Int. Ed.* **2001**, *40*, 3351

- Similarly, imines are viable substrates in Ir(I) promoted 3 component coupling with alkynes



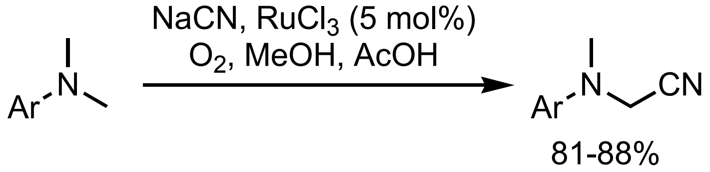
R, R', R'' = *n*-Pr, *i*-Pr, *n*-Bu,
i-Bu, *s*-Bu, Hex

45-74%

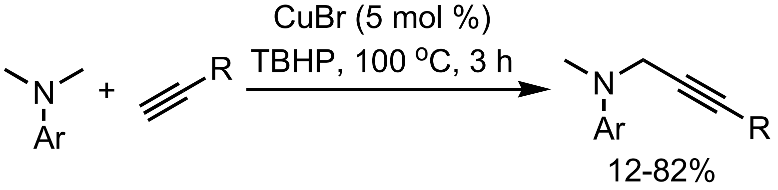
Ishii et al. *Angew. Chem. Int. Ed.* **2001**, *40*, 2534

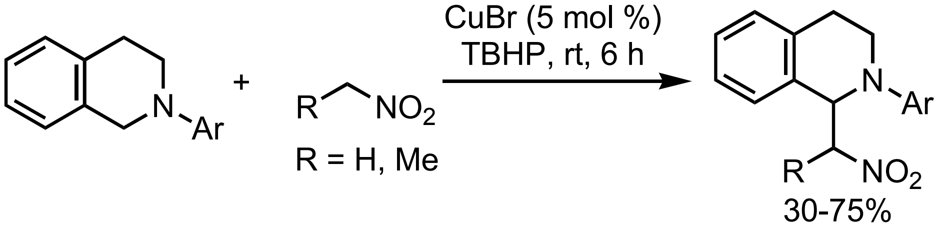
Activation of sp^3 CH Bonds Adjacent to Nitrogen

Aerobic oxidation of alkyl amines using $RuCl_3$ has been successfully applied to dimethyl aryl amines



Murahashi et al. *J. Am. Chem. Soc.* **2003**, *125*, 15312

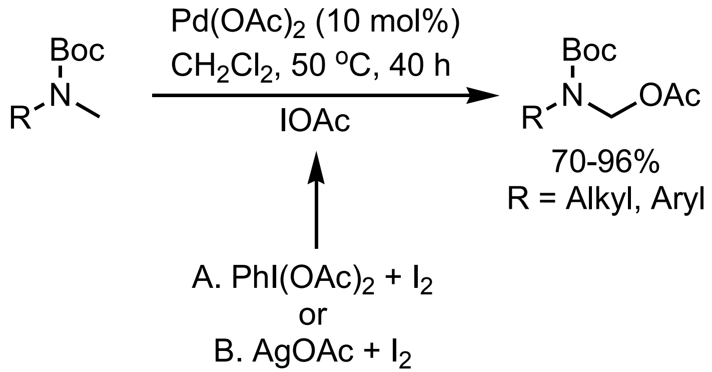




Similarly, Li showed that CuBr can catalyze oxidative coupling of amines in the presence of TBHP

Li, Li *J. Am. Chem. Soc.* **2004**, *126*, 11810
Li, Li *J. Am. Chem. Soc.* **2004**, *126*, 3672

Activation of sp^3 CH Bonds Adjacent to Nitrogen

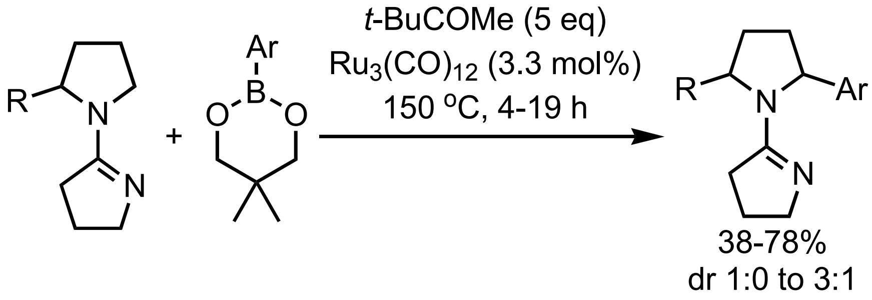


Nitrogen protecting groups are commonly applied as directing moieties in Pd-promoted CH activations

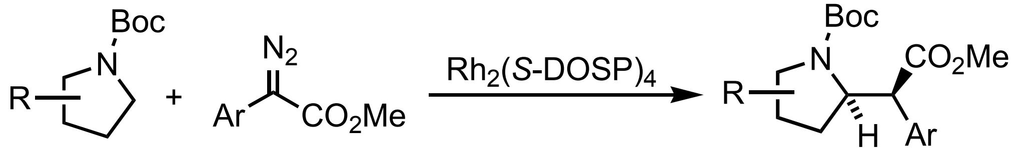
Yu et al.
Org. Lett. **2006**, *8*, 3387

Imine-directed coupling of boronic esters was carried out in the presence of reducing agent (ketone) in good yields amd modest selectivities

Pastine, Gibkov, Sames
J. Am. Chem. Soc. **2006**, *128*, 14220

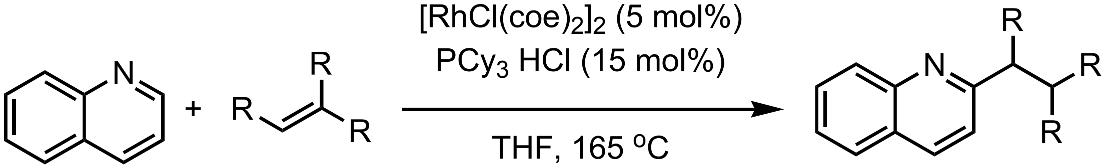


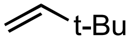
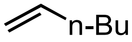
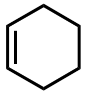
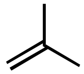
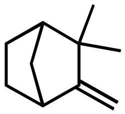
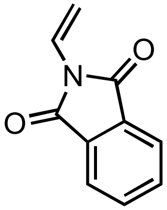
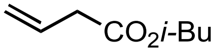
A conceptually different approach was applied by Davis - catalytic CH insertion into CH bonds afforded pyrrolidines and piperidines in high chemoslectivities, de's, and ee's.



Davis et al. *J. Am. Chem. Soc.* **2003**, *125*, 64620

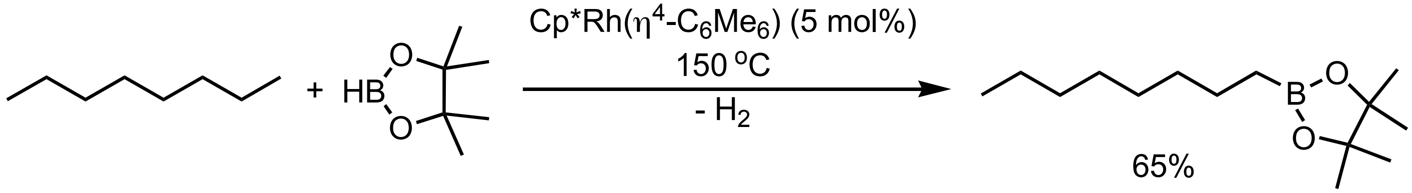
Activation of sp^3 CH Bonds Adjacent to Nitrogen



entry	alkene	time (h)	Yield (%)
1		9.5	98
2		9.5	80 (linear) 14 (branched)
3		9.5	96
4		19	91
5		19	90
6		3.5	53
7		16	53
8		14	57

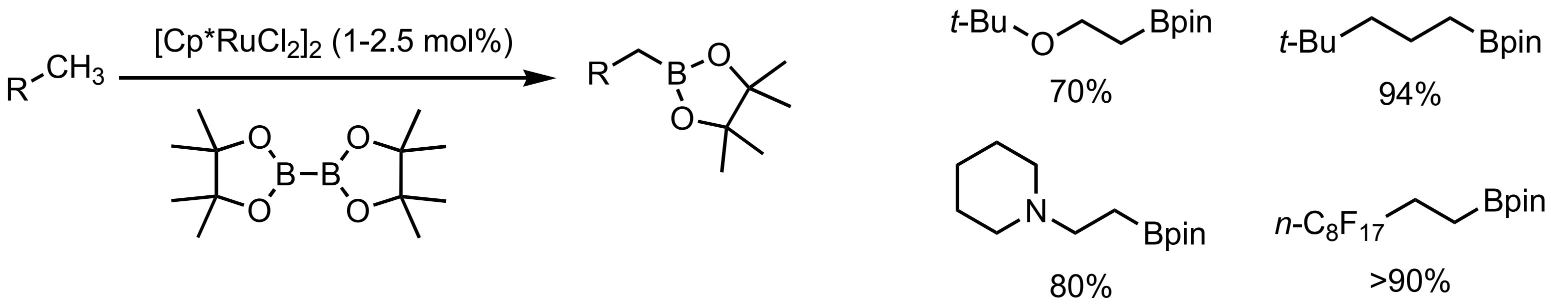
Lewis, Bergman, Ellman *J. Am. Chem. Soc.* **2007**, *127*, 5332

CH activation in the Hartwig Group

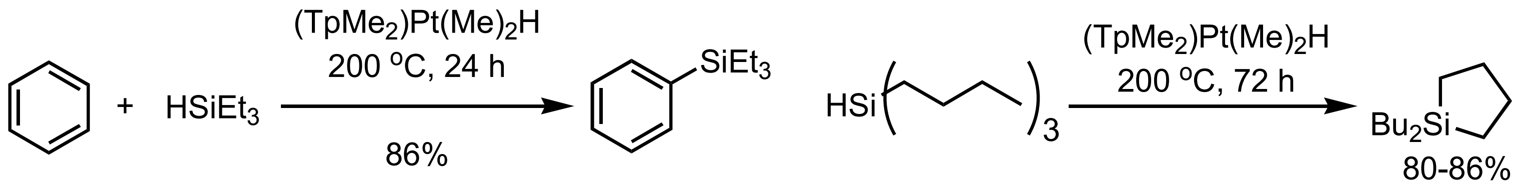


Hartwig et al. *Science* **2000**, *287*, 1995

Hartwig et al. *J. Am. Chem. Soc.* **2004**, *126*, 15443



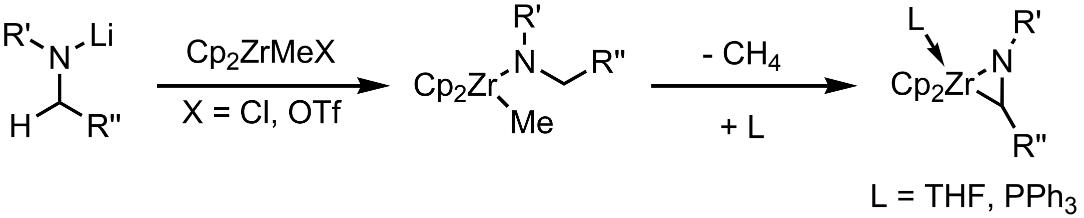
Hartwig et al. *J. Am. Chem. Soc.* **2006**, *128*, 13684



Tsukada, Hartwig *J. Am. Chem. Soc.* **2005**, *127*, 5022

Zirconaaziridines

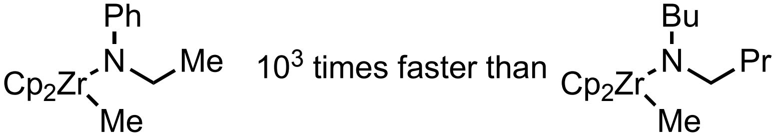
- Many metal η^2-imine complexes of early TM and lanthanides are known



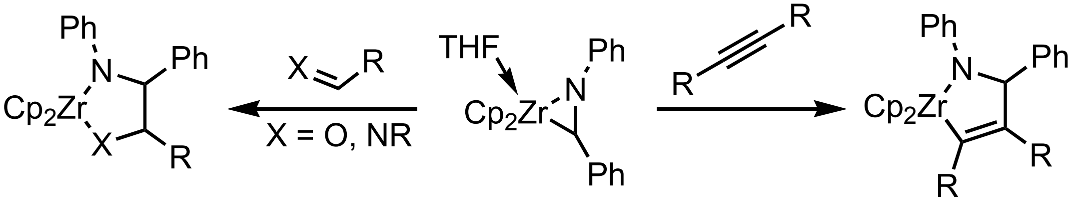
Buchwald et al. *J. Am. Chem. Soc.* **1989**, *111*, 4486

Cumming et al. *Top. Curr. Chem.* **2005**, *10*, 1

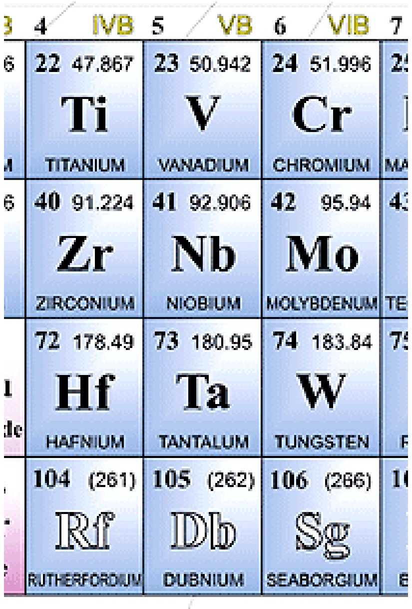
- Rate of methane elimination is dependent on nitrogen substitution ("availability of nitrogen lone pair")



- Unlike η^{1}-complexes, metallaaziridines undergo typical d^0 Ti/Zr (IV) reactions - insertion of multiple bonds and coupling reactions

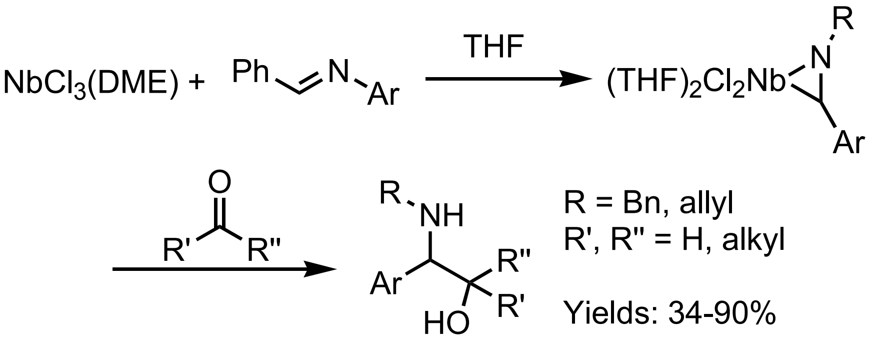


Group 5 Metals



4 IVB	5 VB	6 VIB
22 47.867 Ti TITANIUM	23 50.942 V VANADIUM	24 51.996 Cr CHROMIUM
40 91.224 Zr ZIRCONIUM	41 92.906 Nb NIOBIUM	42 95.94 Mo MOLYBDENUM
72 178.49 Hf HAFNIUM	73 180.95 Ta TANTALUM	74 183.84 W TUNGSTEN
104 (261) Rf RUTHERFORDIUM	105 (262) Db DUBNIUM	106 (266) Sg SEABORGIUM

- Stoichiometric reactions of η^2-complexes with aldehydes and ketones have been described (umpolung)

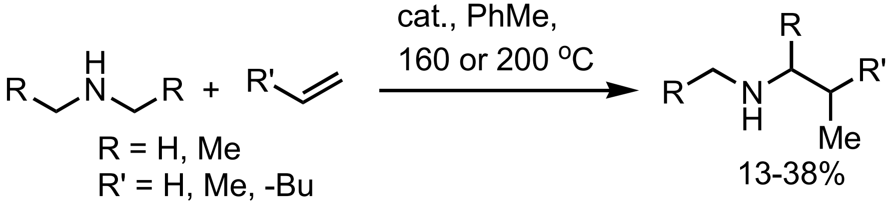


R = Bn, allyl
R', R'' = H, alkyl

Yields: 34-90%

Roskamp, Pedersen *J. Am. Chem. Soc.* **1987**, *109*, 6551

- $M(NMe_2)_5$, M = Nb, Ta have been shown to catalyze alkylation of alkene in low yields



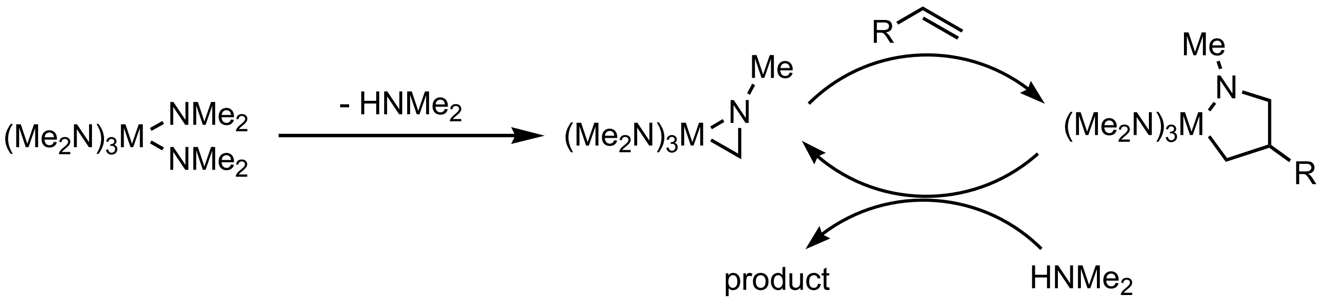
R = H, Me
R' = H, Me, -Bu

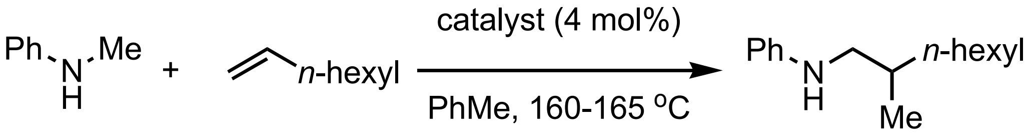
13-38%

Cleric, Maspero *Synthesis* **1980**, 305

Nugent, Ovenall, Holmes *Organometallics* **1983**, *2*, 161

Title Paper - Experiment Design and Initial Studies



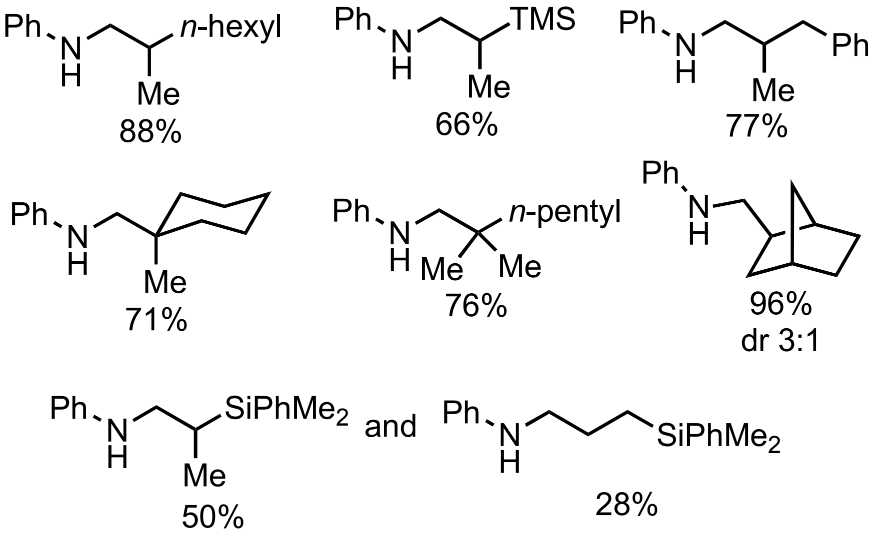


entry	catalyst precursor	% yield		
		1.3 h	5.1 h	24 h
1	$Ta[NMe_2]_5$	32	60	96
2	$Ta[NEt_2]_5$	23	41	66
3	$Nb[NMe_2]_5$	20	29	35
4	$Cp_2Zr[NMe_2]_2$	0.6	1.2	3
5	$Zr[NMe_2]_4$	0	0	0.1
6	none	0	0	0

Title Paper - Reaction Scope

Typically, high selectivity was observed although some olefins give a mixture of linear and branched isomers

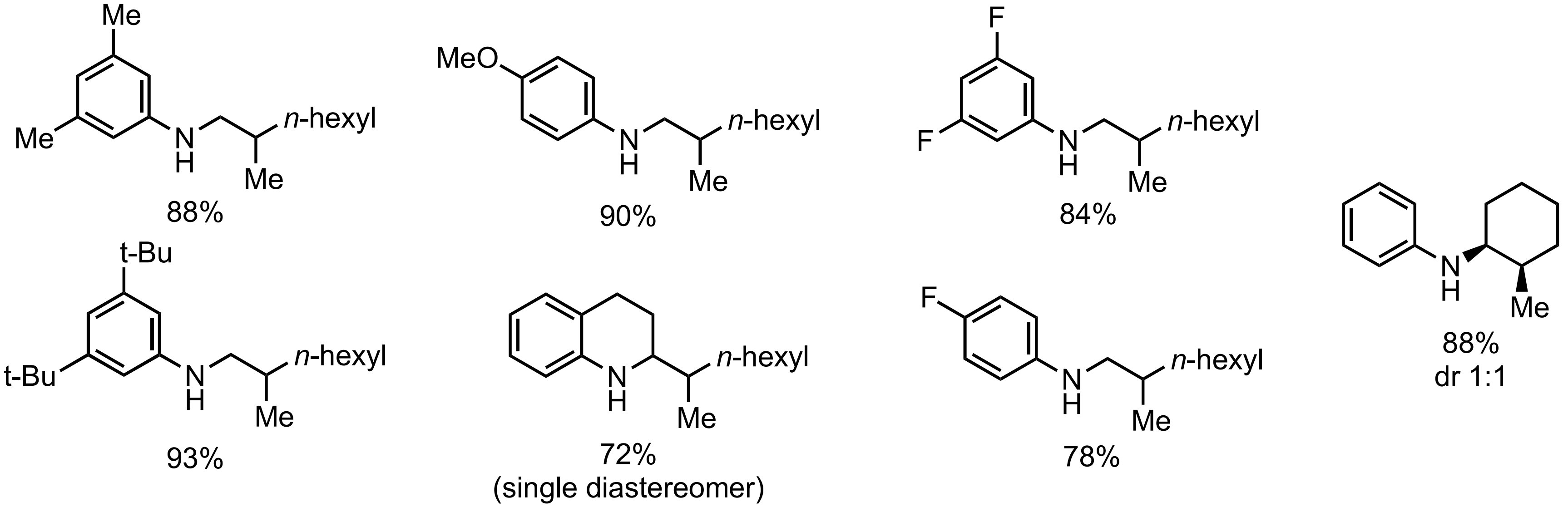
Only aromatic rings with *m*- and *p*-substituents were shown to undergo hydroaminoalkylation



88%, 66%, 77%

71%, 76%, 96% dr 3:1

50% and 28%



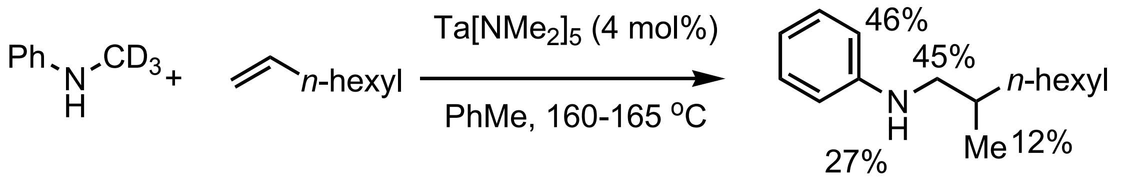
88%, 90%, 84%

93%, 72% (single diastereomer), 78%

88% dr 1:1

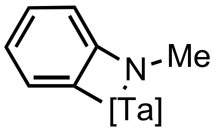
Title Paper - Mechanistic Proposal

- Exchange of aromatic protons occurs most likely faster than the insertion reaction

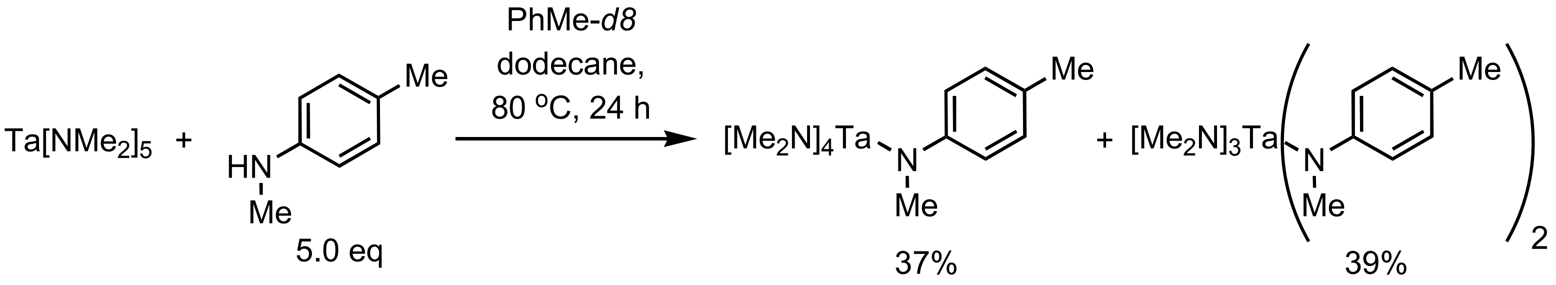


at 25% conversion:
15% D in *ortho* position

Arene activation via



- Ligand exchange



with 25 eq of toluidine,
1:1 ratio

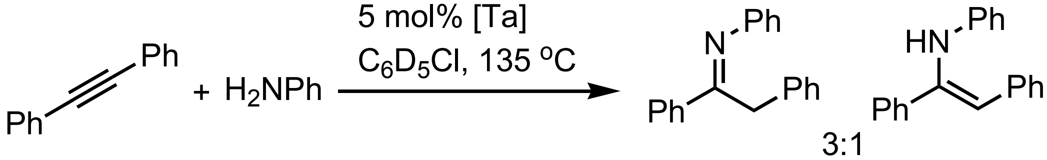
Reactivity of Tantalum Complexes

- Primary amines form imido complexes with tantalum

$$Ta(NMe_2)_5 + t\text{-}BuNH_2 \longrightarrow (NMe_2)_3Ta{=}Nt\text{-}Bu + 2\ NHMe_2$$

Nugent, Harlow *J. Chem. Soc. Chem. Comm.* **1978**, 579,

- Neutral Ta complexes have been shown to catalyze hydroamination reactions of anilines and alkynes



entry	alkene	time (h)	yield (%)
1	$Bn_3Ta{=}NCMe_3$	30	>95
2	$[BnTa{=}NCMe_3]^+$	8	>95
3	$Np_3Ta{=}CMe_3$	12	>95
4	$(Et_2N)_3Ta{=}NCMe_3$	30	>95
5	$Ta(NMe_2)_5$	30	>95
6	$Cl_3Ta{=}NCMe_3$	30	NR

Anderson, Arnold, Bergman *Org. Lett.* **2004**, *6*, 2519

Summary and Future Prospective

- Catalytic hydroaminoalkylation of alkenes using Ta proceeded in high yields and appreciable selectivities
- Although electronic properties of amine control the selectivity, typical directing groups (e.g. pyridyl, iminoyl, carbamoyl) are not necessary

What needs to be done

- Improve reaction conditions and scope
- More mechanistic data is needed to explain the selectivity as well as reactivity of Ta complexes