Calcium Compounds In Catalysis

David J. P. Kornfilt

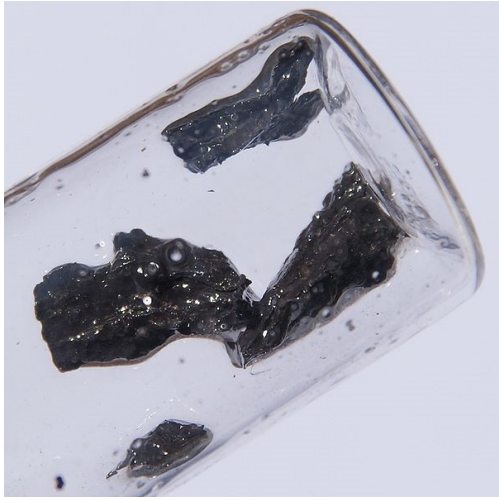
3/15/2011

Welcome- to Group 2

Mg

Ca

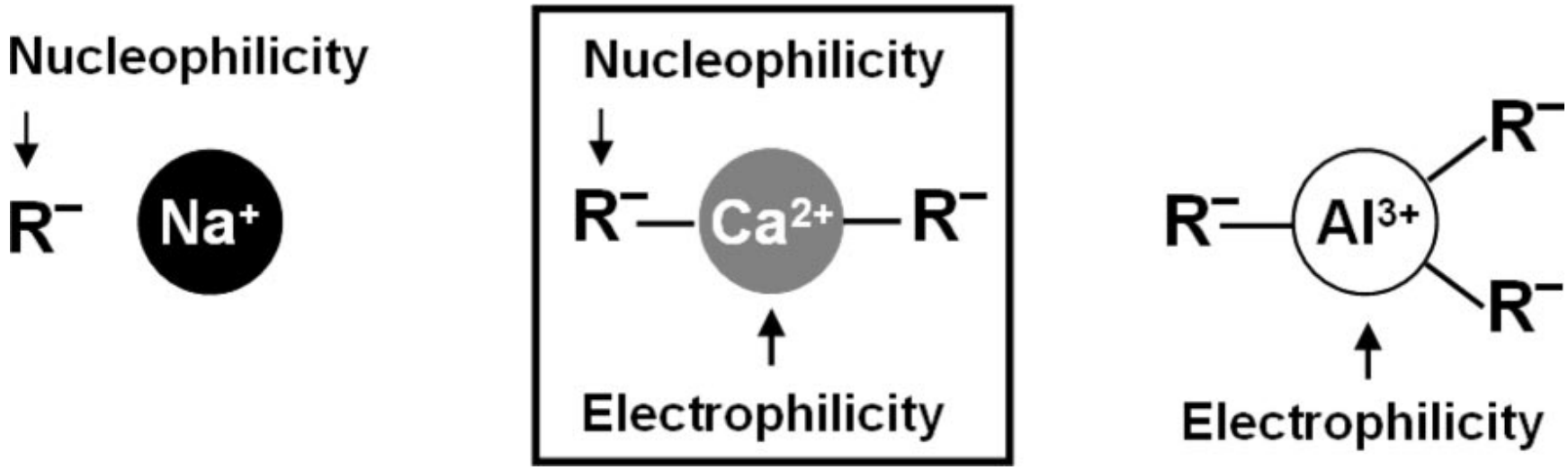
Ba



Sr

http://en.wikipedia.org

Organocalcium Overview



Harder, S.; *Chem. Rev.* **2010,** *110,* 3852–3876

Advantages of Calcium

- Abundant : 3.4 % of Earth's crust (one of the cheapest commerically available metals, <$4/kg)
- Non-toxic: Human tolerance of Ca is high (≈1 g/day is considered safe)
- Associated environmental hazards are low: easily convertible to limestone ($CaCO_3$)and slaked lime ($Ca(OH)_2$) for disposal

Harder, S.; *Chem. Rev.* **2010,** *110,* 3852–3876
Westerhausen , M.; *Z. Anorg. Allg. Chem.* **2009, *635*,** 1332

The Challenges of Organocalcium Compounds

- Increased ionic character compared to Grignard reagents: Wurtz couplings, ether cleavage
- Fast Schlenk Equilibria: Heteroleptic calcium compounds are not always stable
- Large coordination numbers of calcium leads to insoluble aggregates
- Low reactivity of Ca metal, compared to very high reactivity of C-Ca bonds

Harder, S.; *Chem. Rev.* **2010,** *110,* 3852–3876

Preparation of Organocalcium Reagents

1) Direct route from metal

$$Ca + ArI \longrightarrow ArCaI \quad (a)$$

$$Ca + 2\,(Me_3Si)_2NH \longrightarrow Ca[N(SiMe_3)_2]_2 + H_2 \quad (b)$$

$$Ca + Sn[N(SiMe_3)_2]_2 \longrightarrow Ca[N(SiMe_3)_2]_2 + Sn \quad (c)$$

$$Ca + COT \longrightarrow Ca^{2+}\,COT^{2-} \quad (d)$$

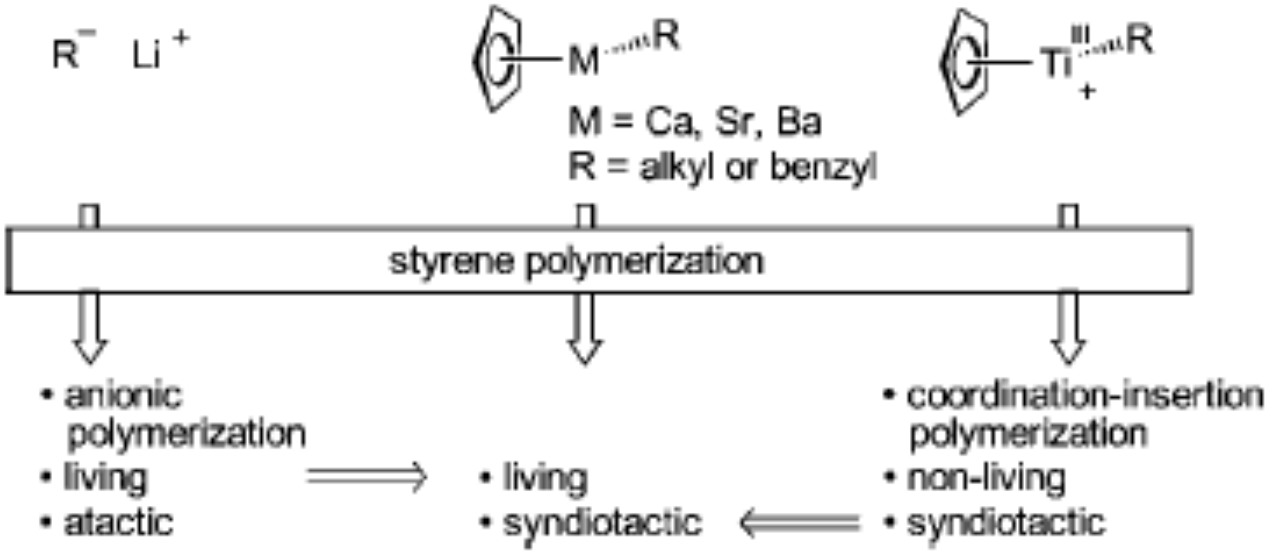
Harder, S.; *Chem. Rev.* **2010,** *110,* 3852–3876

Historical Use of Calcium Catalysis

- Union Carbide-type Calcocene Catalyst

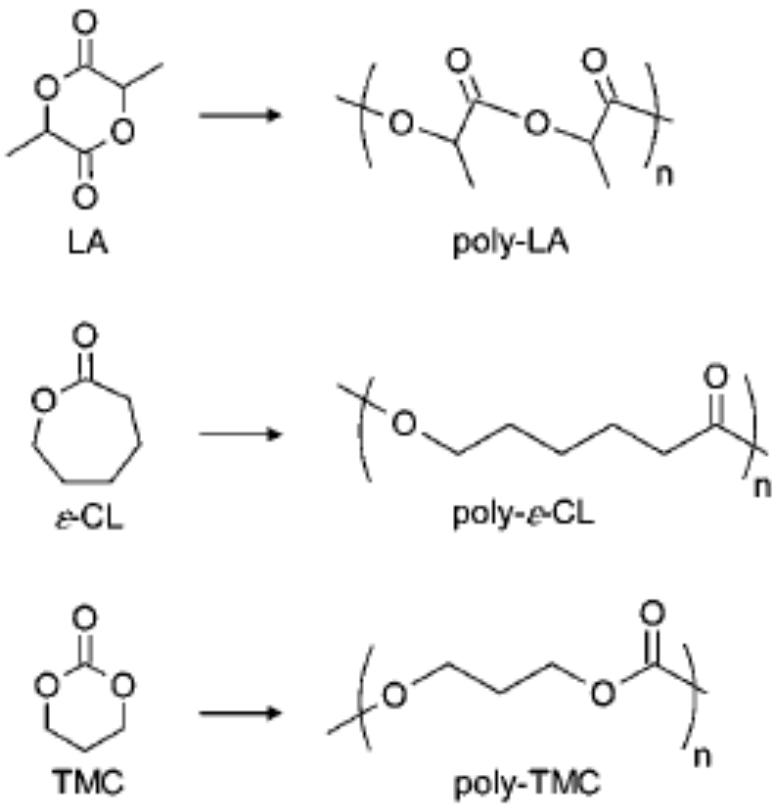
(heterogenous, poorly defined)

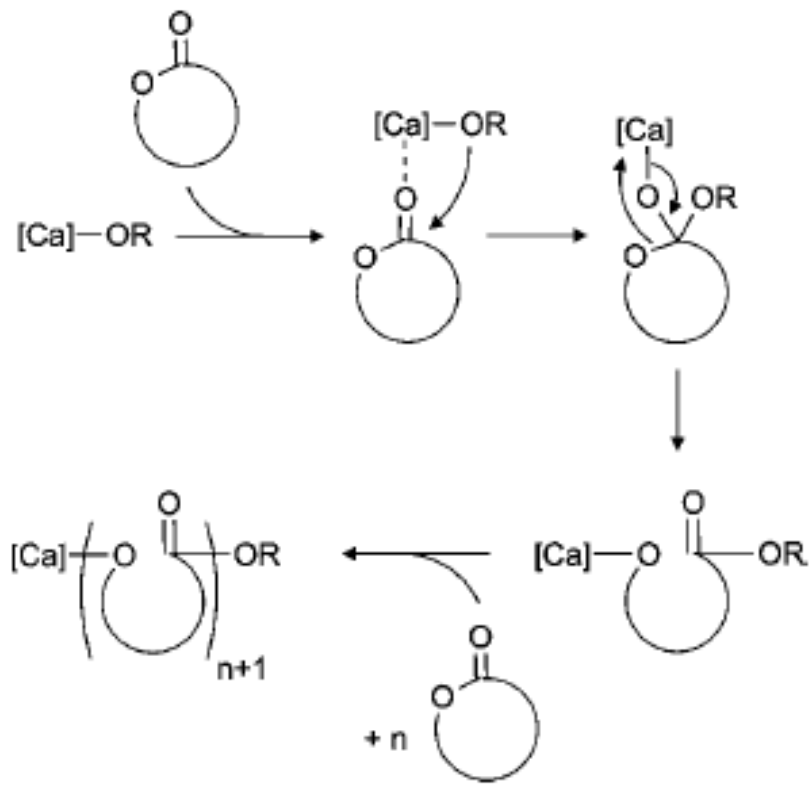
- Used as a polymerization Catalyst



Harder, S.; *Chem. Rev.* **2010,** *110,* 3852–3876

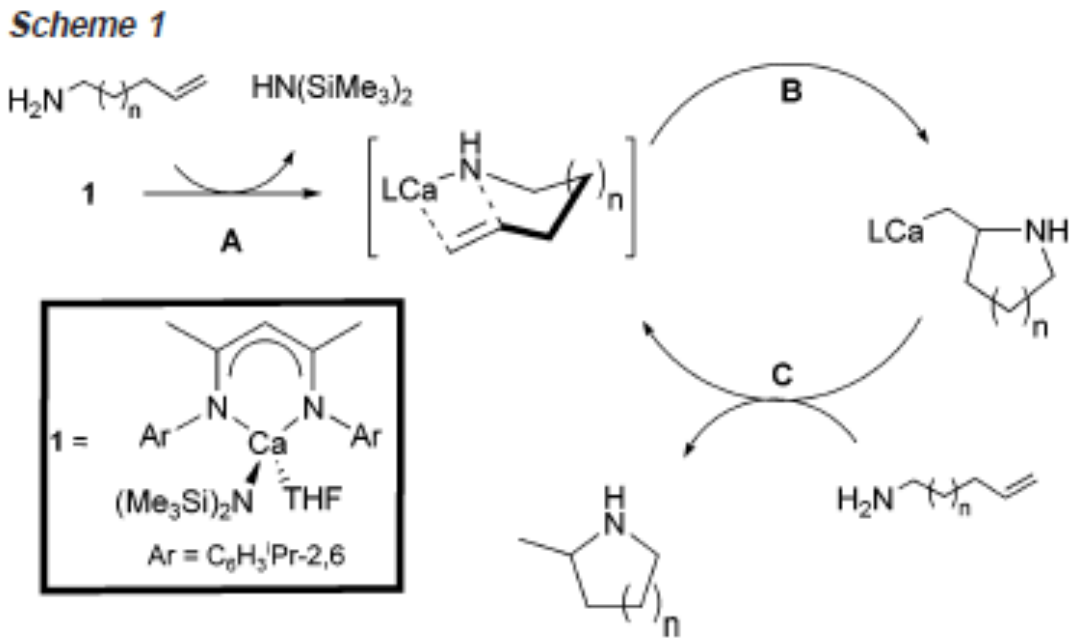
Modern Calcium Polymerisations





Harder, S.; *Chem. Rev.* **2010,** *110,* 3852–3876

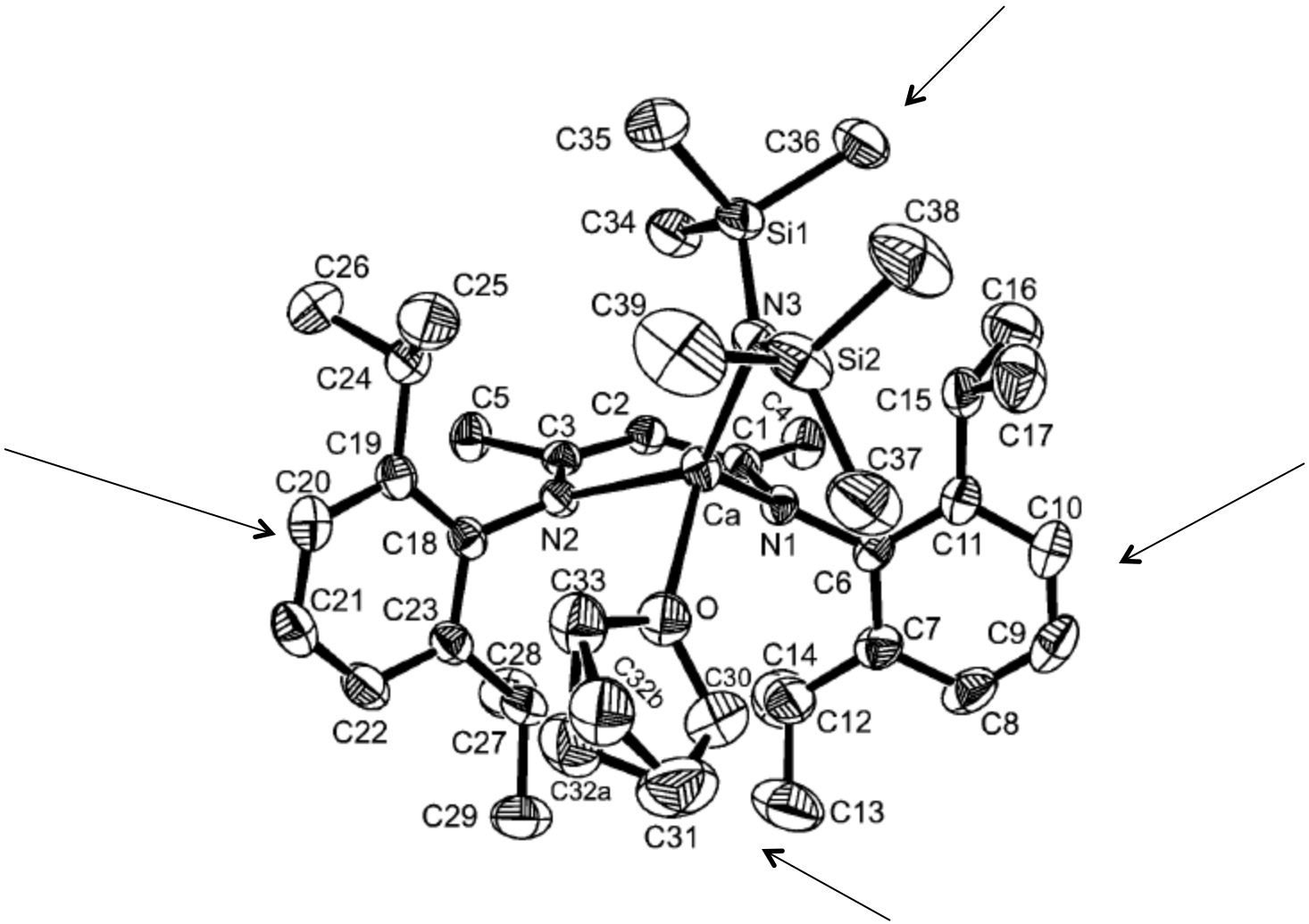
Genesis : New Forms of Reactivity



- >99% conv. In 15 min. using 10 mol% catalyst for 1-aminopentenes
- Forcing conditions required for 1-aminohexenes
- Formation of homoleptic $[Ca(ArNacNacAr)]_2$ detected in solution

Crimmin, M.R.; Casely, I. J.; Hill, S. M.; *J. Am. Chem. Soc.* **2005,** *127***,** 2042-2043

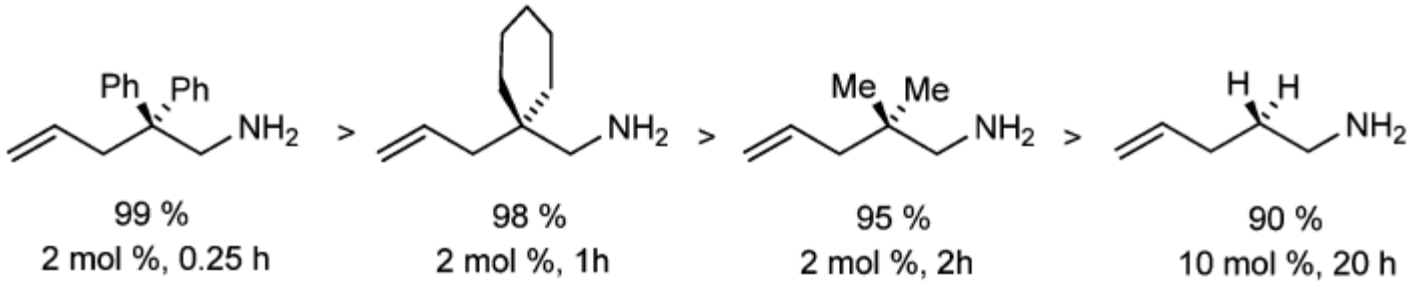
[DIPPNacNacCaHMDS]THF



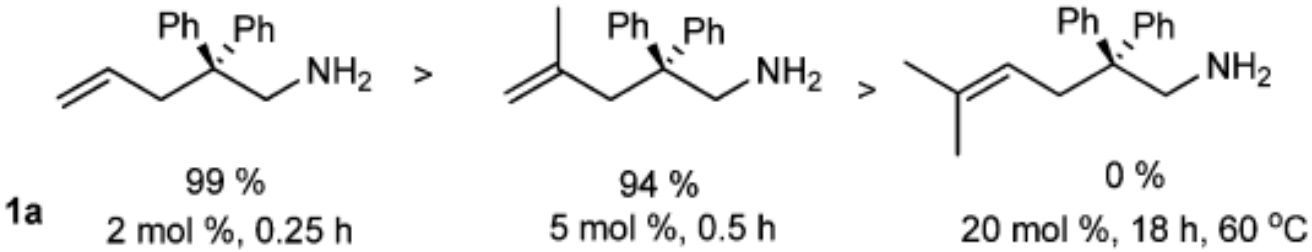
Chisholm, M. H.; Gallucci, J.; Phomphrai, K.; *Chem. Comm.* **2003,** 48-49

Reactivity Trends in Substrates

Reactivity trend of chain substitution



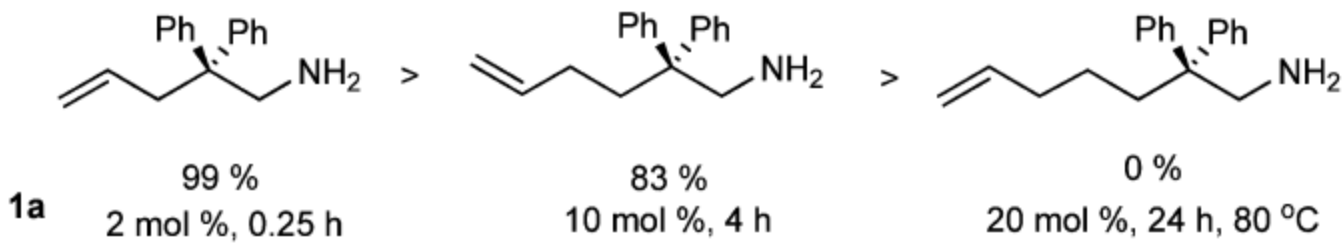
Reactivity trend of alkene substitution



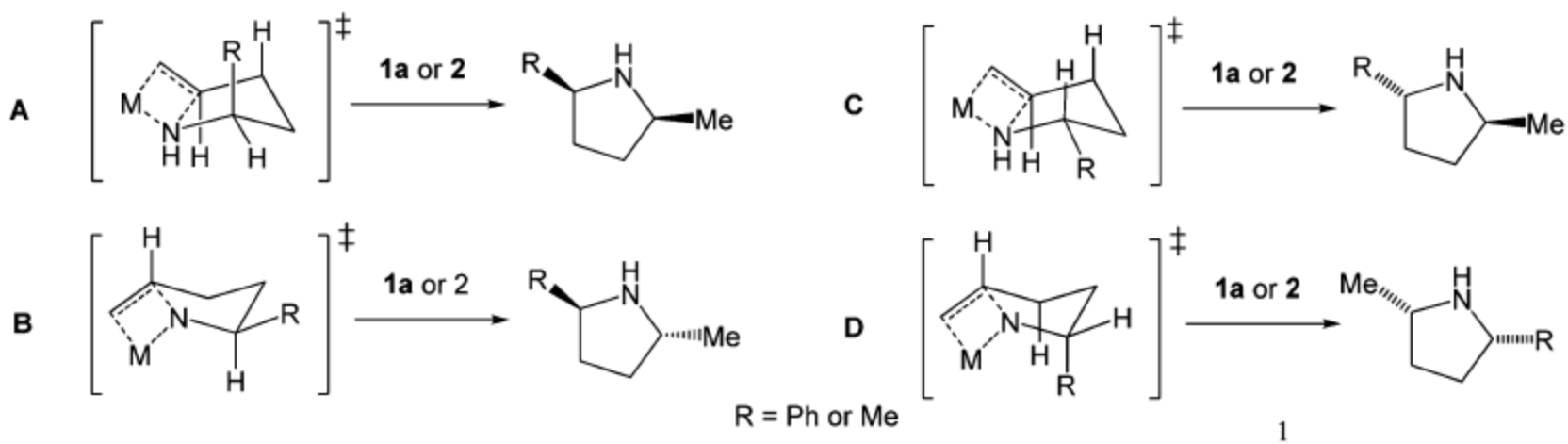
Crimmin, M.R.; Arrowsmith, M.; Barrett, A. G. M.; Casely, I. J.; Hill, S. M.; Procopiou *J. Am. Chem. Soc.* **2009,** *131***,** 9670-9685

Reactivity Trends in Substrates

Reactivity trend of chain length



Observed diastereoselectivity

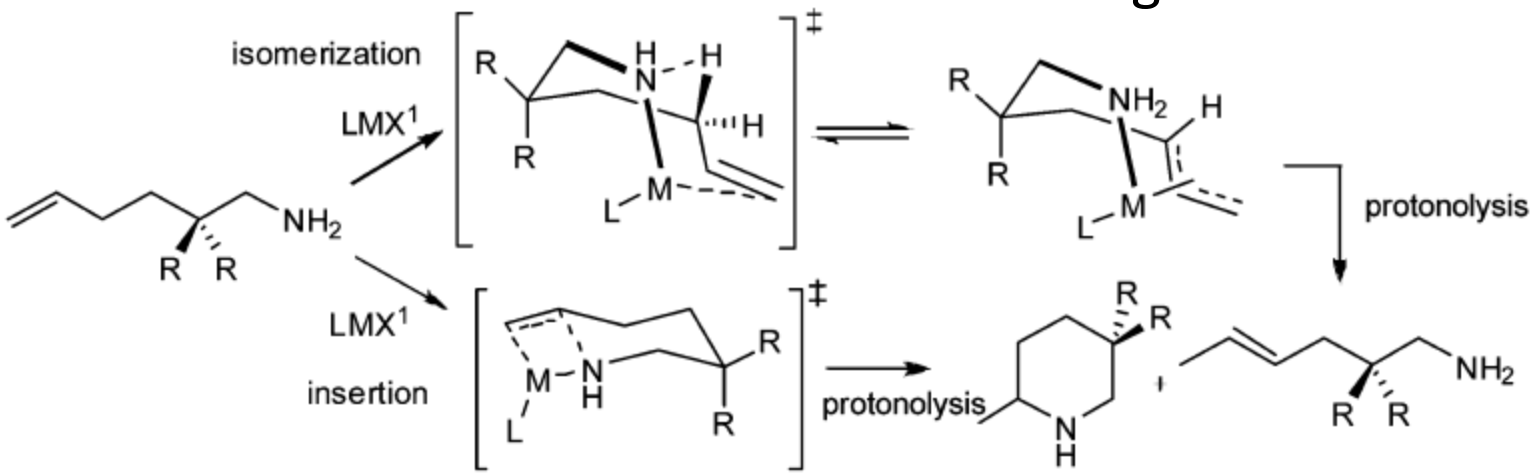


R=	Ph	Me
	95	89
	:	:
	5	11

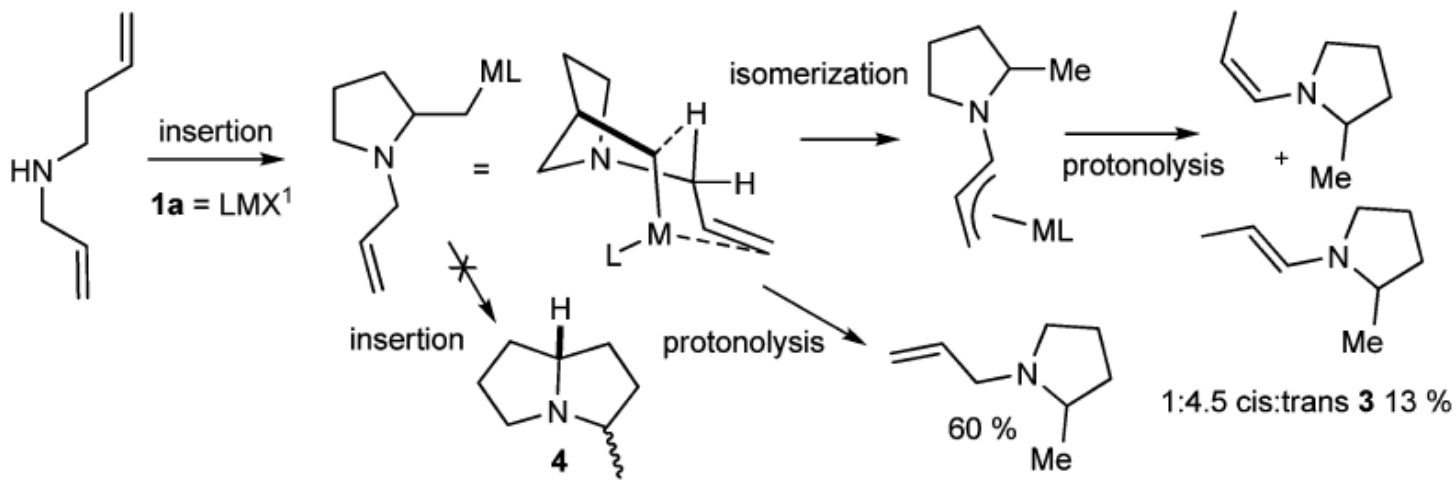
Crimmin, M.R.; Arrowsmith, M.; Barrett, A. G. M.; Casely, I. J.; Hill, S. M.; Procopiou *J. Am. Chem. Soc.* **2009,** *131***,** 9670-9685

Fate of Long-Lived Intermediates

Isomerization of terminal alkenes for long chains

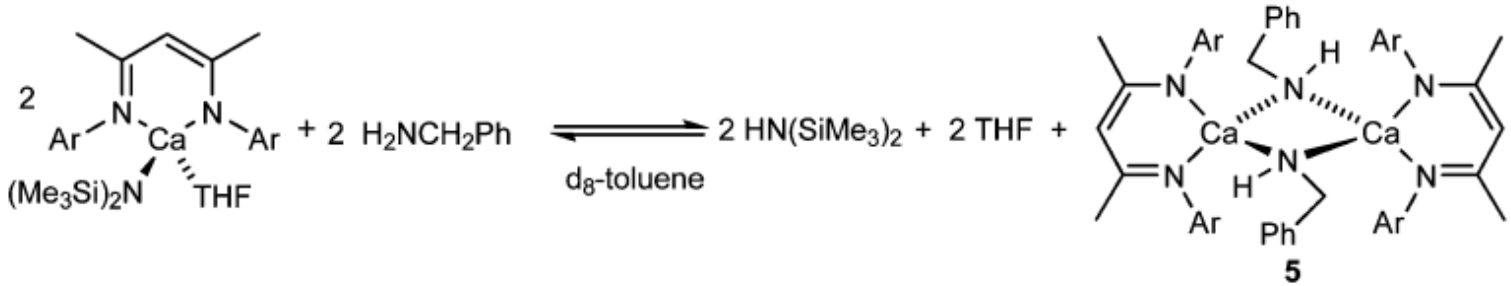


Isomerization of terminal alkenes for diolefins



Crimmin, M.R.; Arrowsmith, M.; Barrett, A. G. M.; Casely, I. J.; Hill, S. M.; Procopiou *J. Am. Chem. Soc.* **2009,** *131***,** 9670-9685

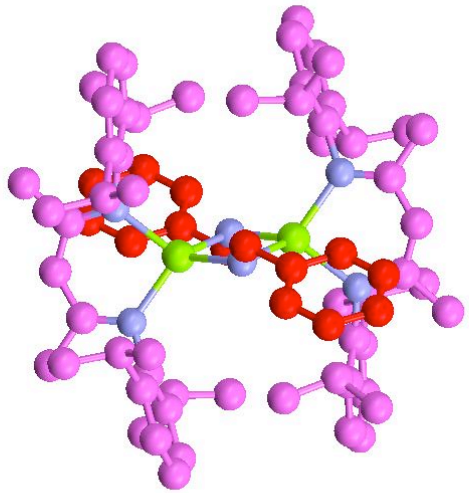
Reaction With Primary Amines

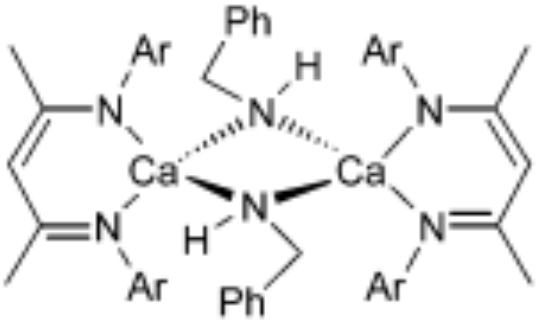


Crimmin, M.R.; Arrowsmith, M.; Barrett, A. G. M.; Casely, I. J.; Hill, S. M.; Procopiou *J. Am. Chem. Soc.* **2009,** *131***,** 9670-9685

Barrett, A.G.M.; Casely, I. J.; Crimmin, M. R.; Hill, M. S.; Lachs, J.R.; Mahon, M. F.; Procopiou P. A.**;** *Inorg. Chem.*, **2009**, *48,* 4445-4453

Bis-benzylamine adduct



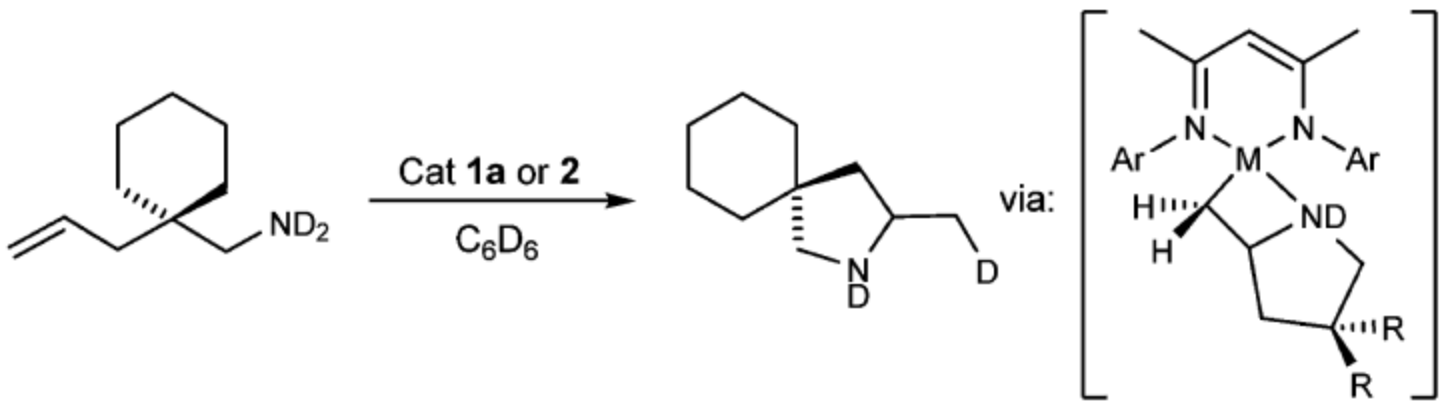


8

Barrett, A.G.M.; Casely, I. J.; Crimmin, M. R.; Hill, M. S.; Lachs, J.R.; Mahon, M. F.; Procopiou P. A.**;** *Inorg. Chem.*, **2009**, *48,* 4445-4453

Investigating Mechanistic Steps

Deuteration Studies

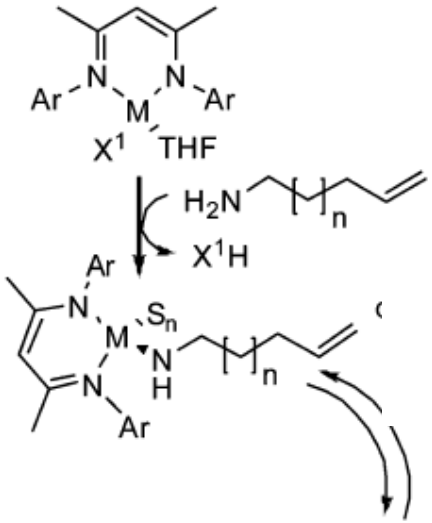


Further kinetic studies could not be undertaken with Ca catalyst due to reversible initiation.

Mg analog showed equal inhibition by substrate and product such that rate was determined by $[S]_0$

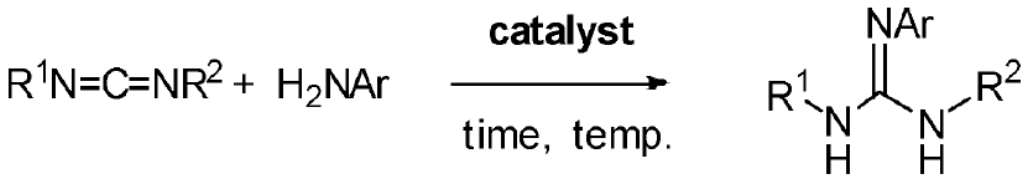
Crimmin, M.R.; Arrowsmith, M.; Barrett, A. G. M.; Casely, I. J.; Hill, S. M.; Procopiou *J. Am. Chem. Soc.* **2009,** *131***,** 9670-9685

Overall Catalytic Cycle for Hydroamination by Group 2 Metals

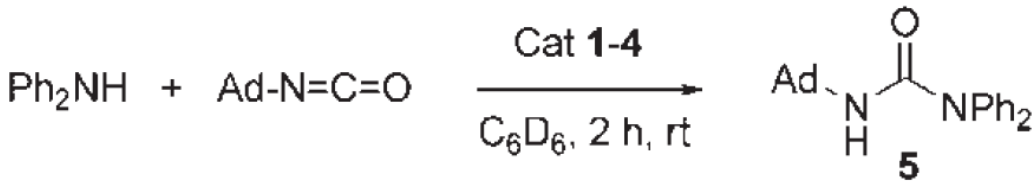


Crimmin, M.R.; Arrowsmith, M.; Barrett, A. G. M.; Casely, I. J.; Hill, S. M.; Procopiou *J. Am. Chem. Soc.* **2009,** *131***,** 9670-9685

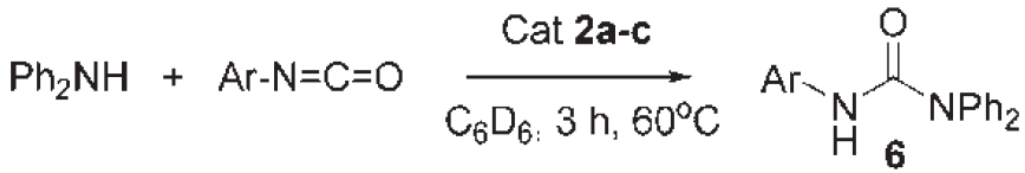
Hydroamination of C=N bonds



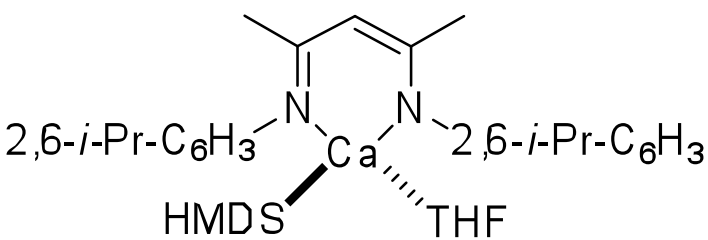
Cat. **2** (2-4 mol %)
0.1-72 h
37-91% yield



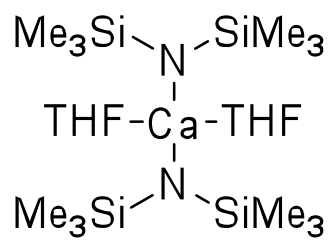
Stalls at 86%



Stalls at 62%



1

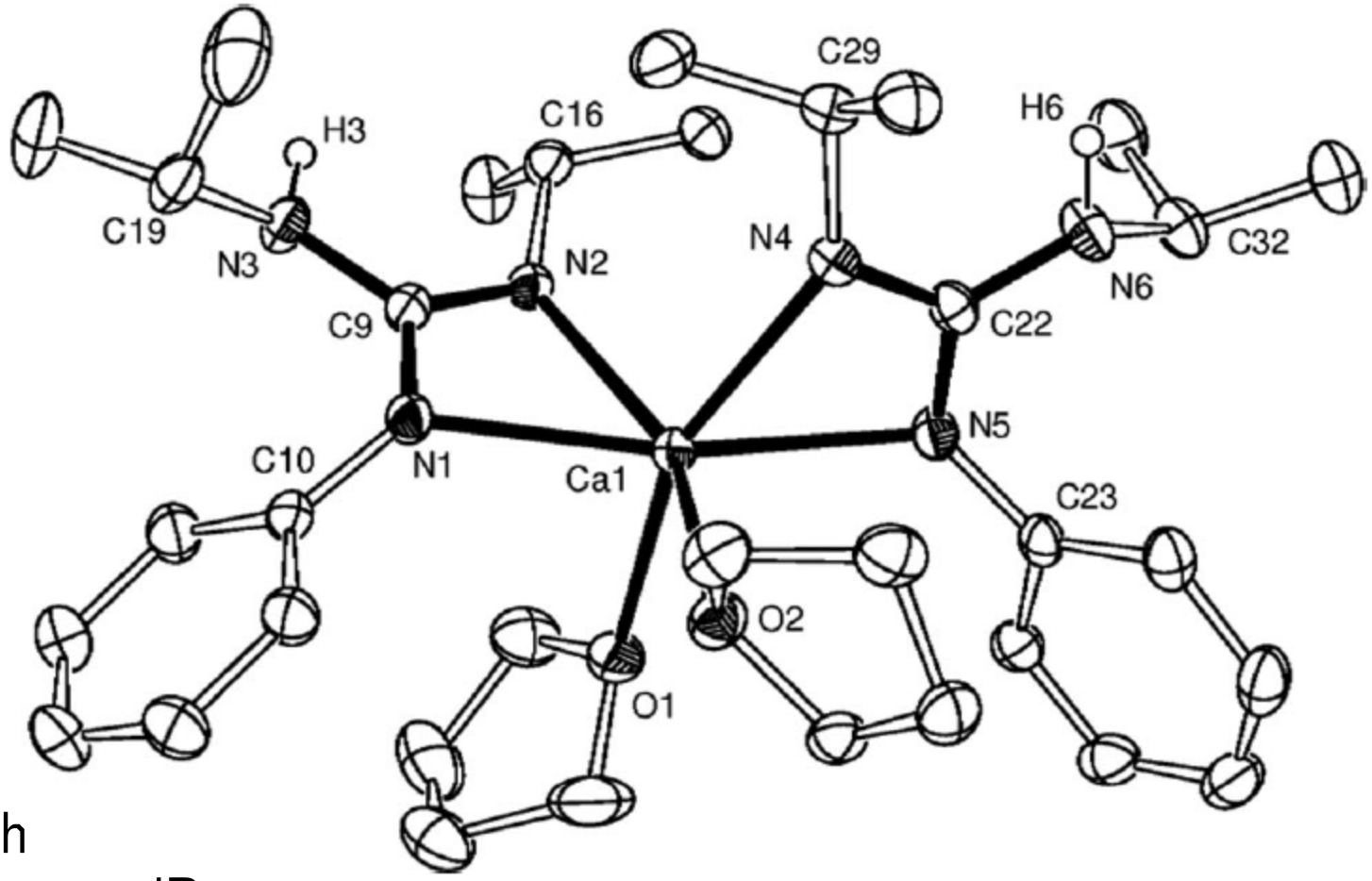


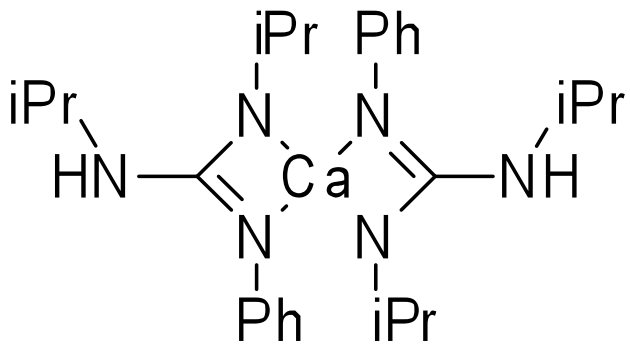
2

Barrett, A.G.M.; Boorman, T.C.; Crimmin, M. R.; Hill,S. M.;* Kociok-Köhn, G.; Procopiou, P. A. *Chem. Comm.,* **2008**, 5206-5208

Lachs, J. R.; Barrett, A.G.M.*; Crimmin, M. R.; Kociok-Köhn, G.; Hill, M.S.*;Mahon, M. F.; Procopiou, P. A.; *Eur. J. Inorg. Chem.,* **2008**, 4173-4179

Crystal Structure of Homoleptic Guanidine

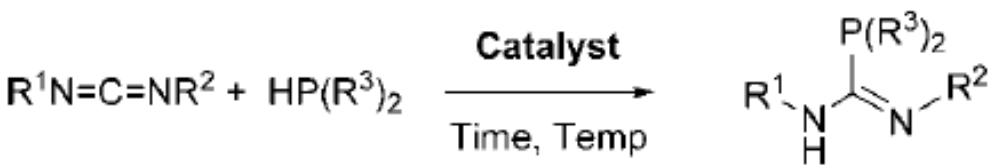




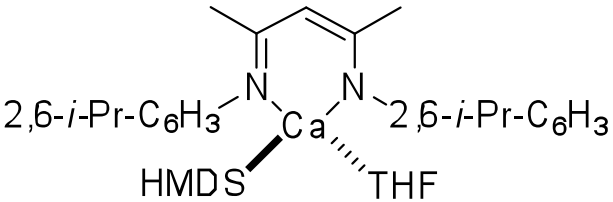
Product inhibition prevents full conversion

Lachs, J. R.; Barrett, A.G.M.*; Crimmin, M. R.; Kociok-Köhn, G.; Hill, M.S.*;Mahon, M. F.; Procopiou, P. A.; *Eur. J. Inorg. Chem.,* **2008**, 4173-4179

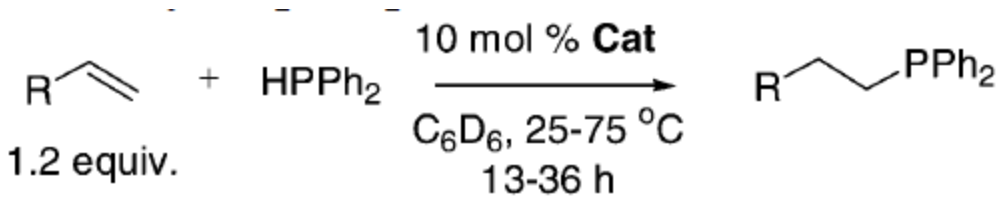
Hydrophosphination



$Ca(HMDS)_2(THF)_2$



1-2h, 25 °C, >95% conversion, Limited in scope

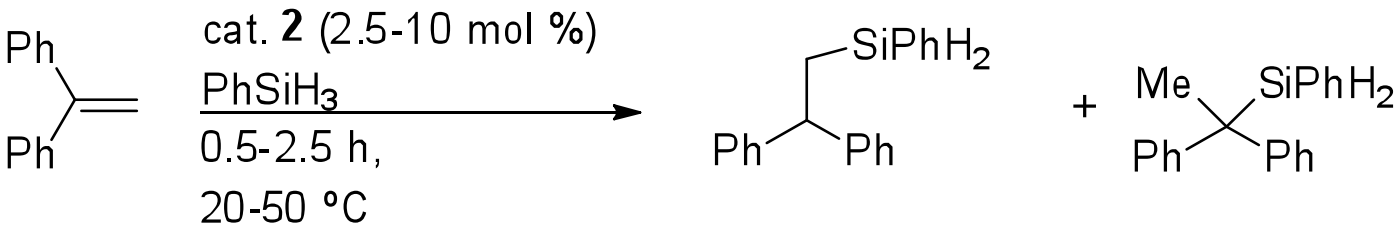


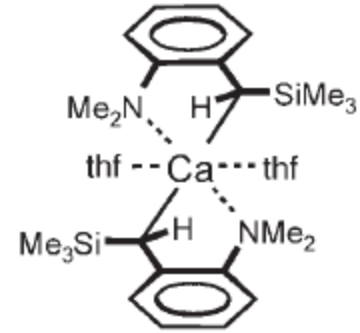
Only works for conjugated olefins (styrene, butadiene derivatives)

Crimmin, M.R.; Barrett, A. G. M.*; Hill, M. S.*; Hitchcock, P. B.; Procopiou, P. A.; *Organometallics* **2007,** *26,* 2953-2956
Crimmin, M.R.; Barrett, A. G. M.*; Hill, M. S.*; Hitchcock, P. B.; Procopiou, P. A.; *Organometallics* **2008,** *27,* 497-499

Hydrosilylation

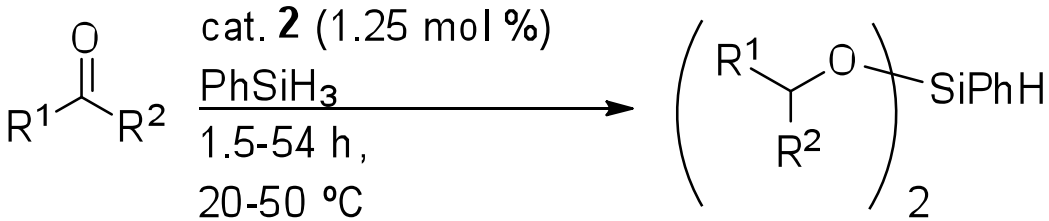
Constitutional Selectivity is strongly solvent dependant:





2

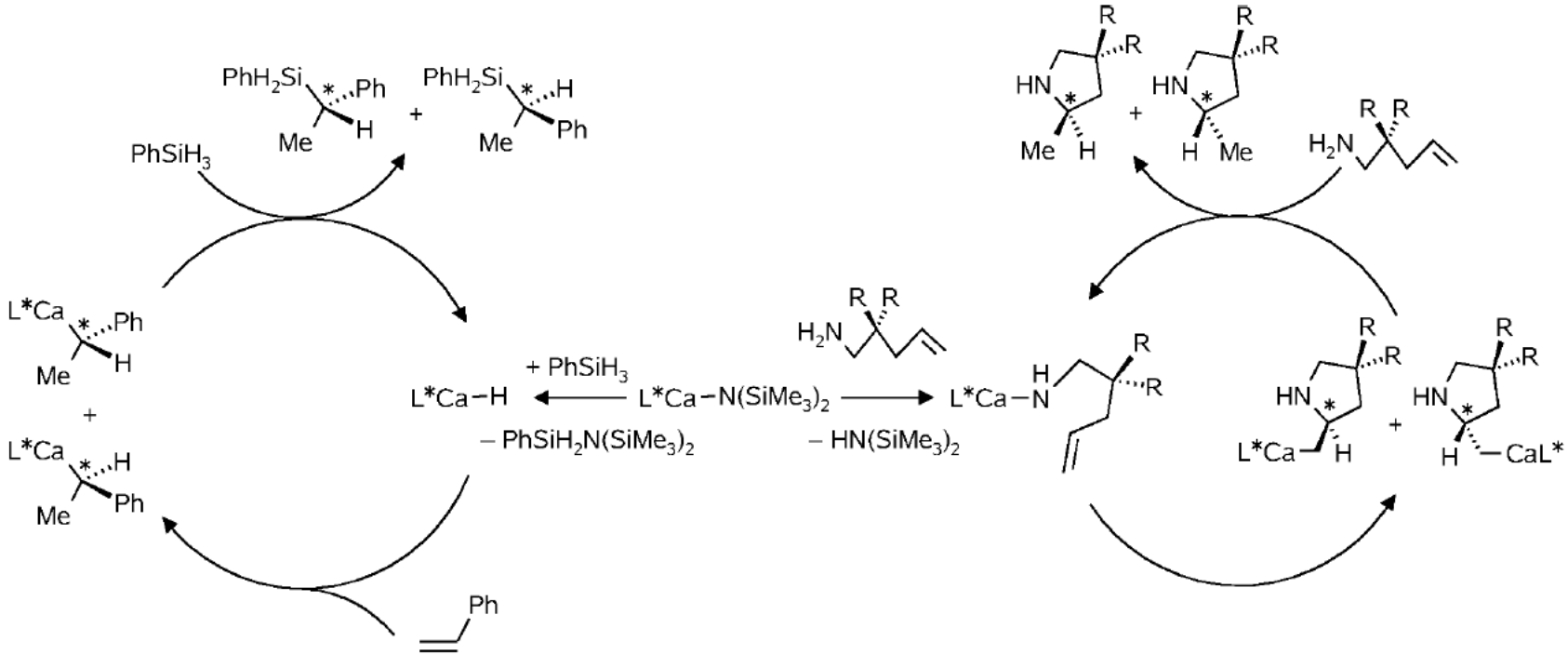
Benzene :	0	100
Diethylether	25	75
THF	100	0

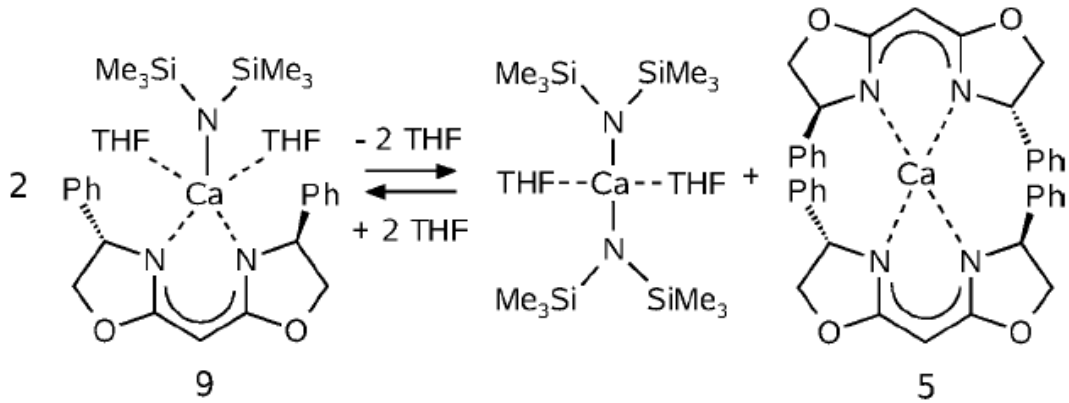


<5% enolization
>95% yield

Spielmann, J.; Harder, S.; *Eur. J. Inorg. Chem.*, **2008**, 1480-1486
Buch F.; Brettar J.; Harder S.; *Angew. Chem. Int. Ed.*; **2006**, *45*, 2741-2745

Progress towards Enantioselective Calcium catalysis

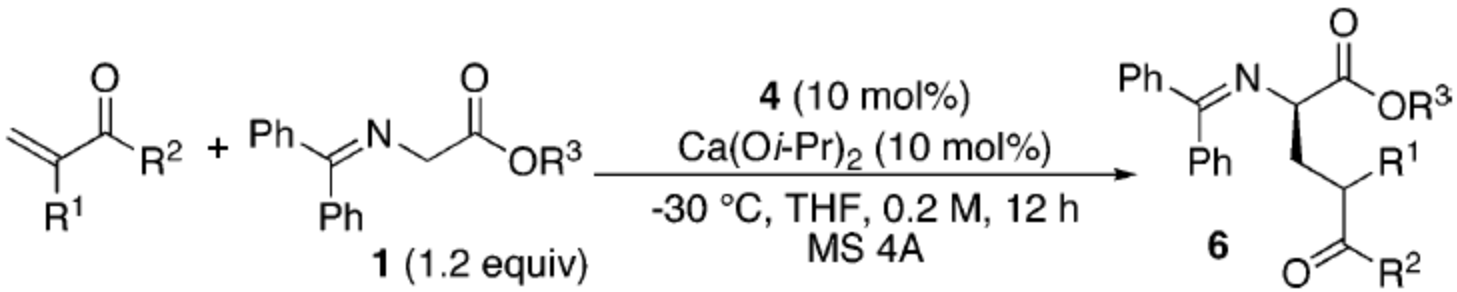




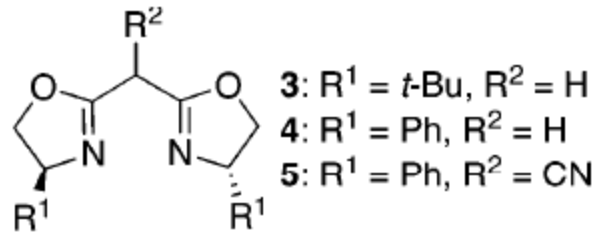
<55:45 e.r. in either case

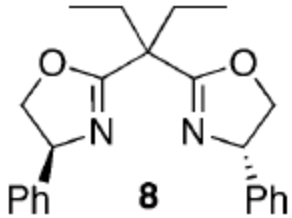
Buch F.; Harder, S.;*Z. Naturforsch.;* **2008**, *63b,* 169-177

Conjugate Addition Mediated by Organocalcium Catalysts



78-99% ee, 1:1-10:1 d.r.
R^3=*t*-Bu works best

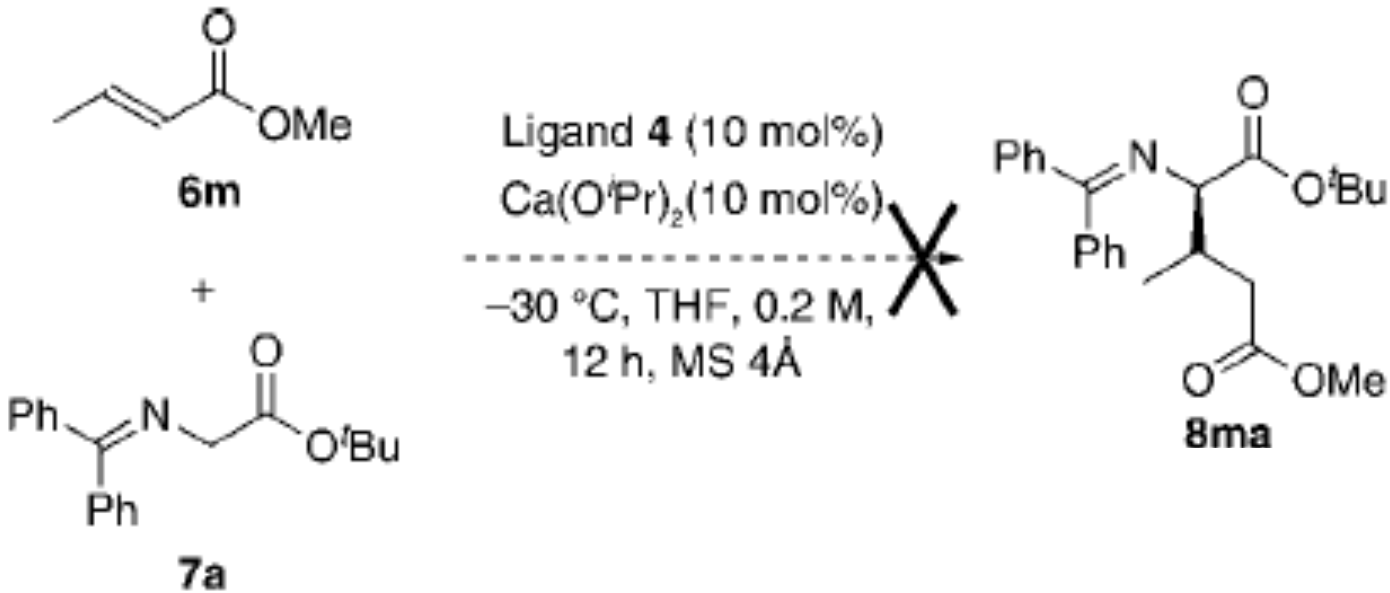




Ligand **8** gave 31% yield and 50:50 e.r.
(88% yield, 97:3 e.r. for **4**)

Saito, S.; Tsubogo T.; Kobayashi, S.; *J. Am. Chem. Soc.;* **2007**, *129,* 5364-5365

Group Question



Product IR [cm^{-1}] 3650, 3368, 3305, 3059, 2975, 2932, 2877, 2360, 1959, 1733, 1661, 1598, 1492, 1449, 1391, 1367, 1343, 1263,1158, 1080, 1030.

^{1}H NMR ($CDCl_3$) δ 7.8-7.1 (m, 10H), 3.68 (d, 1H, *J = 6.4 Hz),* 3.47 (br, 1H), 3.30 (m, 4H), 2.67 (ddq, 1H, *J = 8.4, 6.8, 6.4 Hz),* 1.51 (s, 9H), 1.05 (d,3H, *J = 6.8 Hz*).

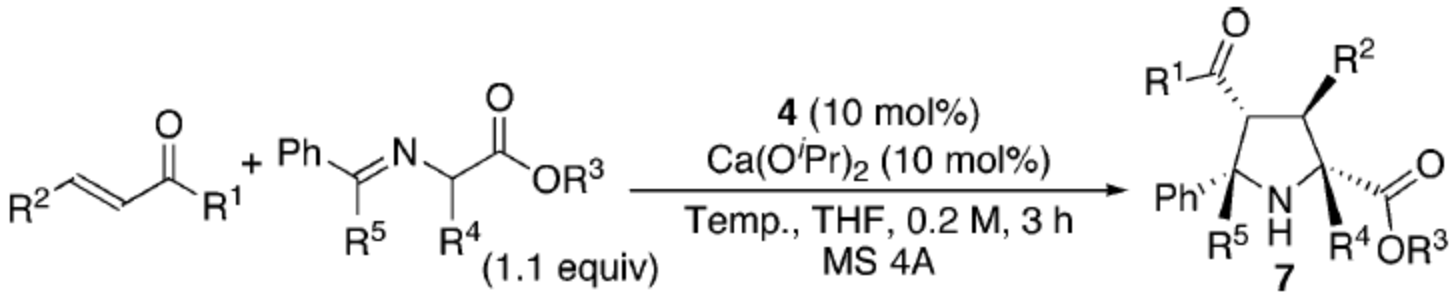
^{13}C NMR (CDCl3) δ 173.5, 172.3, 146.4, 145.3, 132.4, 130.0, 128.3, 127.9, 126.9, 126.5, 81.4, 74.6, 66.4, 62.7, 51.4, 44.8, 28.1, 18.2.

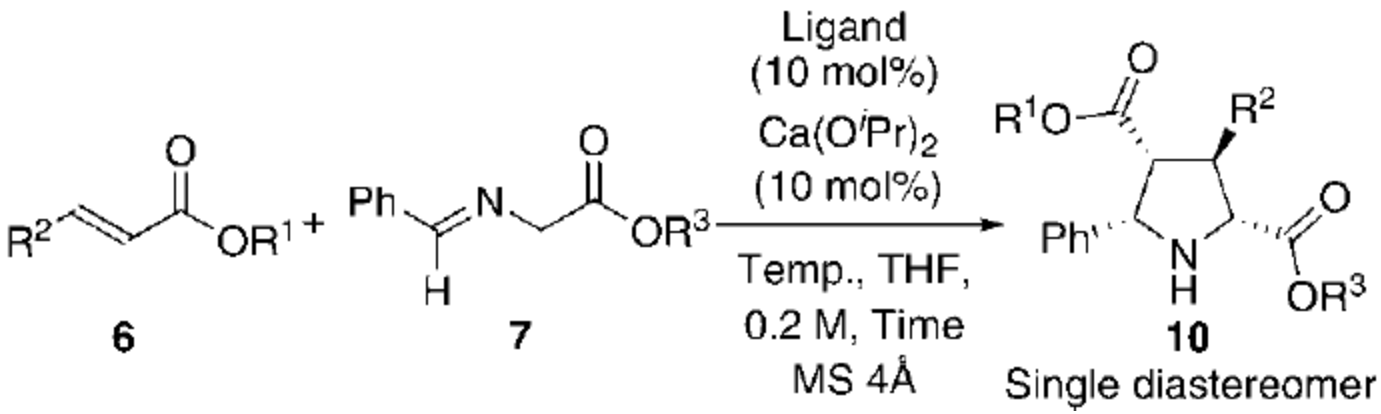
ESI-HRMS (m/z) calcd. for $C_{24}H_{30}NO_4$ ((M+H)+): 396.2169; found: 396.2187.

Saito, S.; Tsubogo T.; Kobayashi, S.; *J. Am. Chem. Soc.;* **2007**, *129,* 5364-5365

Tsubogo T.; Saito, S.; Seki, K; Yamashita, Y.; Kobayashi, S.; *J. Am. Chem. Soc.;* **2008**, *130,* 13321-13332

Crotonates Afford Different Products

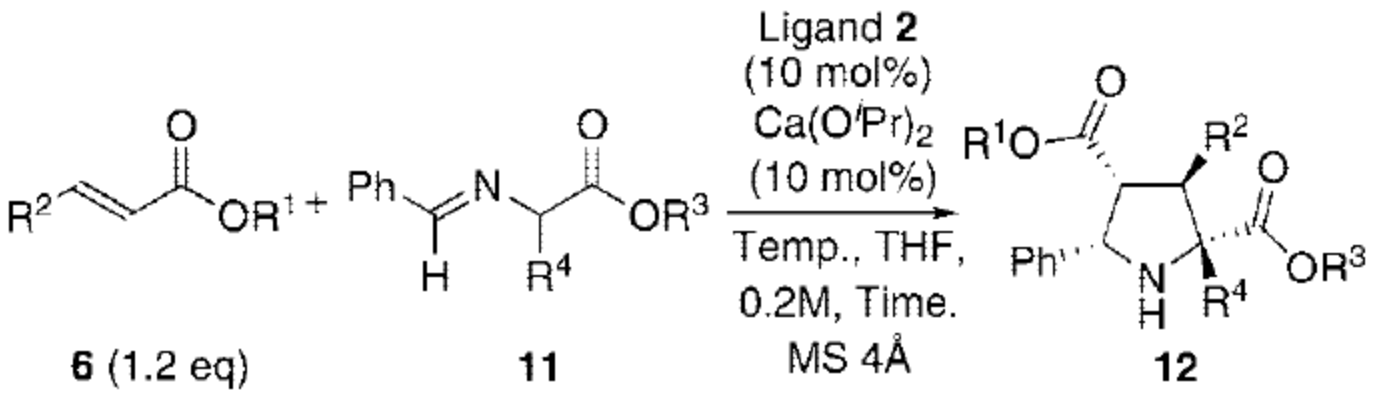




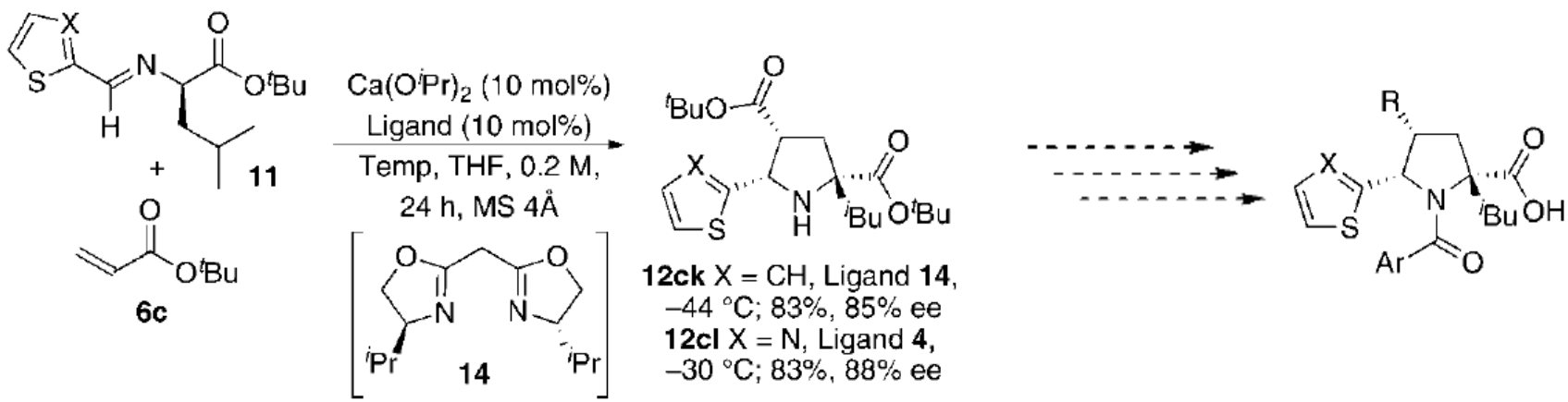
Temp. -30 – 10 ^{o}C, time 3-12 h. Ar group can also be varied

Tsubogo T.; Saito, S.; Seki, K; Yamashita, Y.; Kobayashi, S.; *J. Am. Chem. Soc.;* **2008**, *130,* 13321-13332

Formation of Contiguous Tertiary Centers

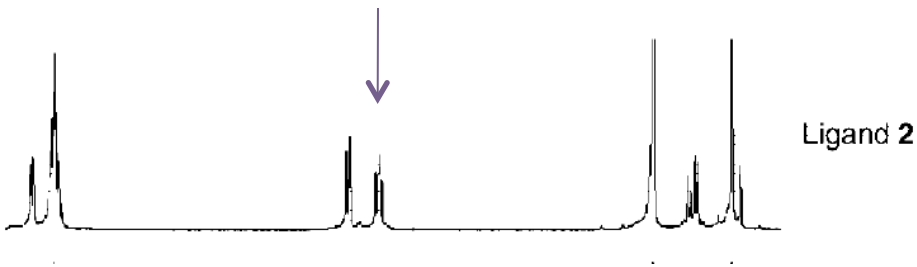


T = -30 – 10 °C
t = 3 - 72h



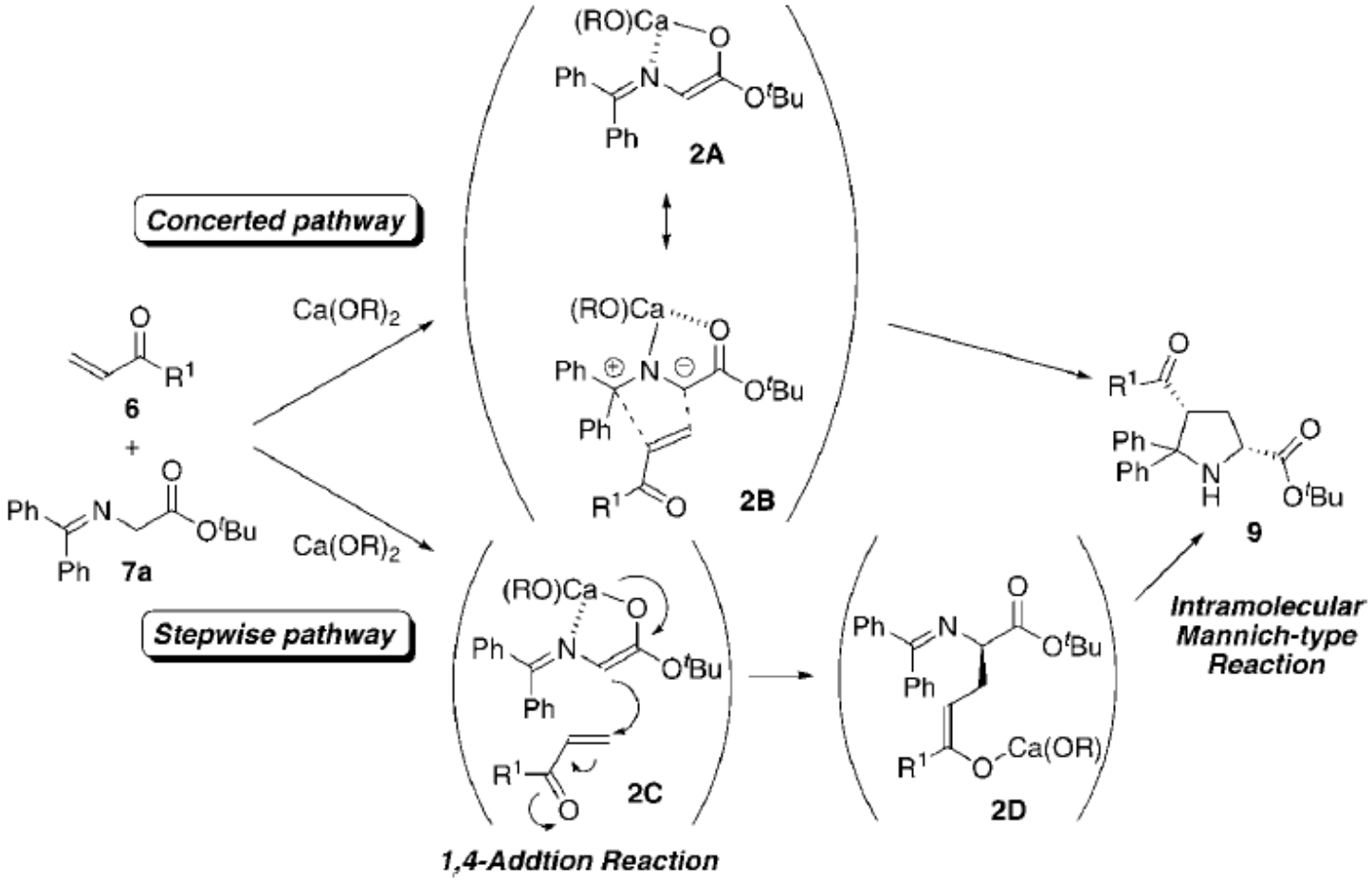
Tsubogo T.; Saito, S.; Seki, K; Yamashita, Y.; Kobayashi, S.; *J. Am. Chem. Soc.;* **2008**, *130,* 13321-13332

Determination of the active catalytic species



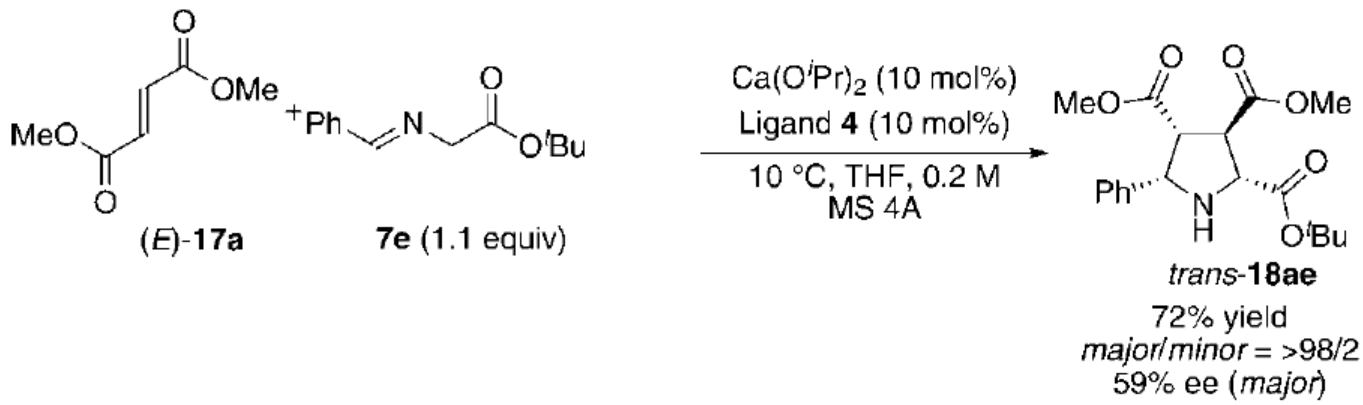
Tsubogo T.; Saito, S.; Seki, K; Yamashita, Y.; Kobayashi, S.; *J. Am. Chem. Soc.;* **2008**, *130,* 13321-13332

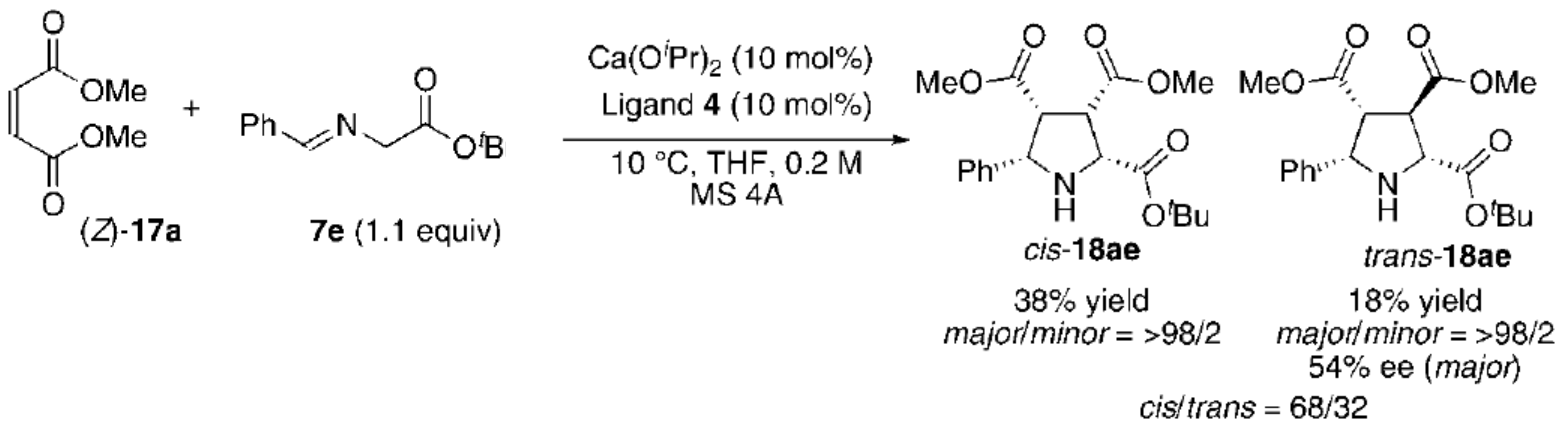
Two Possible Pathways Towards the [3+2] Cycloaddition Product



Tsubogo T.; Saito, S.; Seki, K; Yamashita, Y.; Kobayashi, S.; *J. Am. Chem. Soc.;* **2008**, *130,* 13321-13332

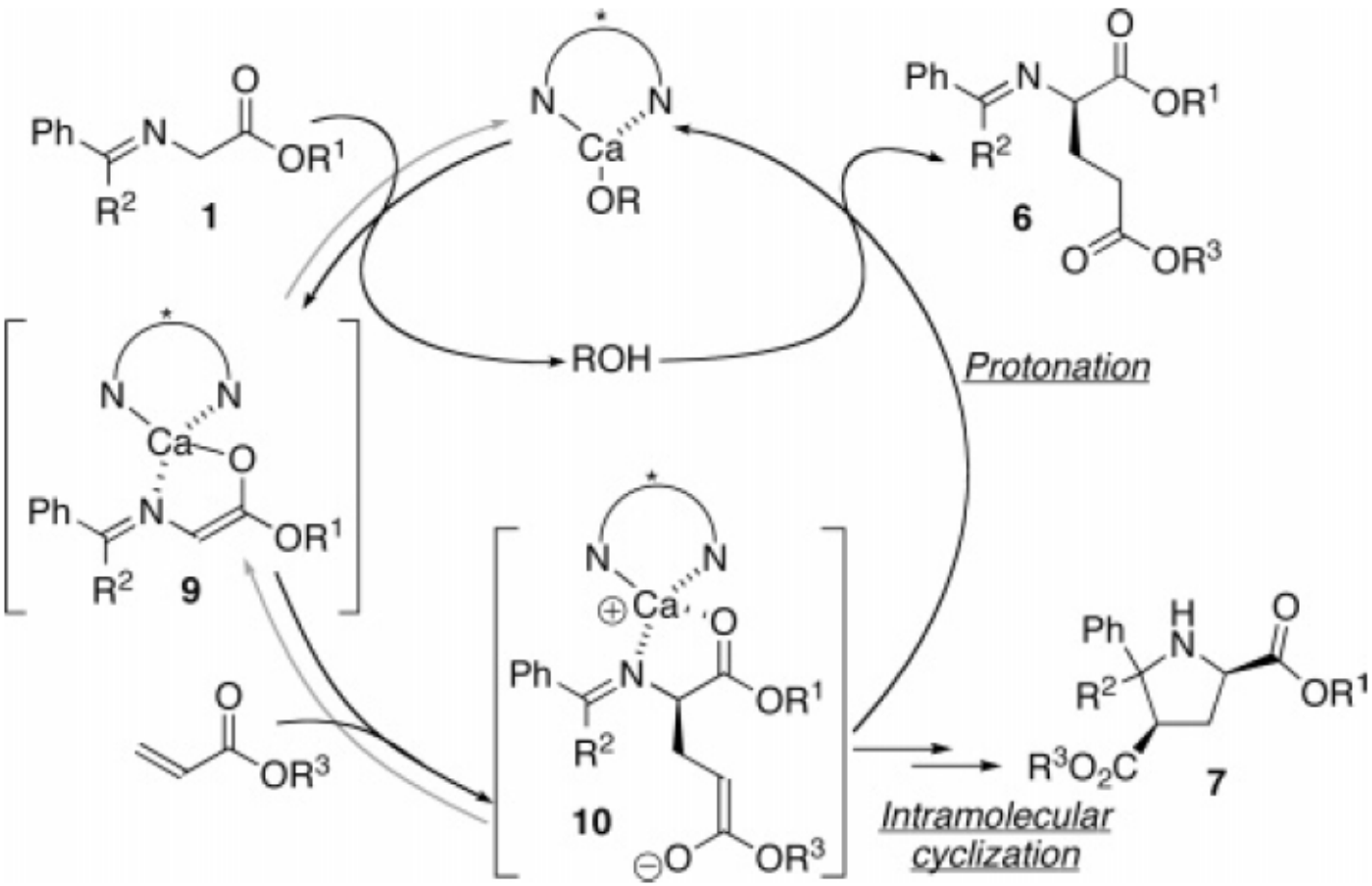
Stepwise Pathway Operative





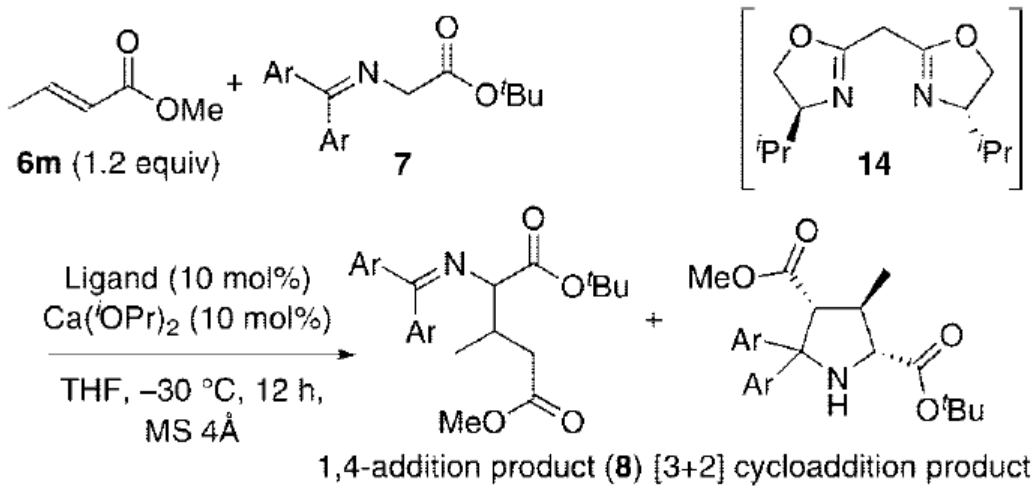
Tsubogo T.; Saito, S.; Seki, K; Yamashita, Y.; Kobayashi, S.; *J. Am. Chem. Soc.;* **2008**, *130,* 13321-13332

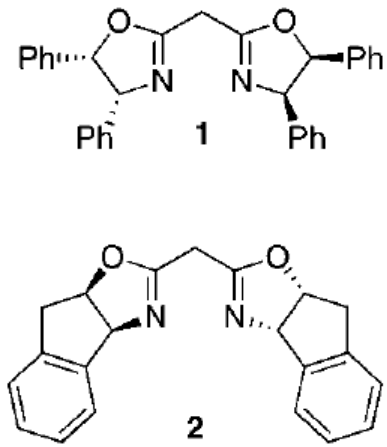
Overall Mechanistic Cycle



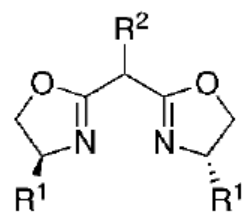
Tsubogo T.; Saito, S.; Seki, K; Yamashita, Y.; Kobayashi, S.; *J. Am. Chem. Soc.;* **2008**, *130,* 13321-13332

Isomer Ratio Influenced by Ligand Size





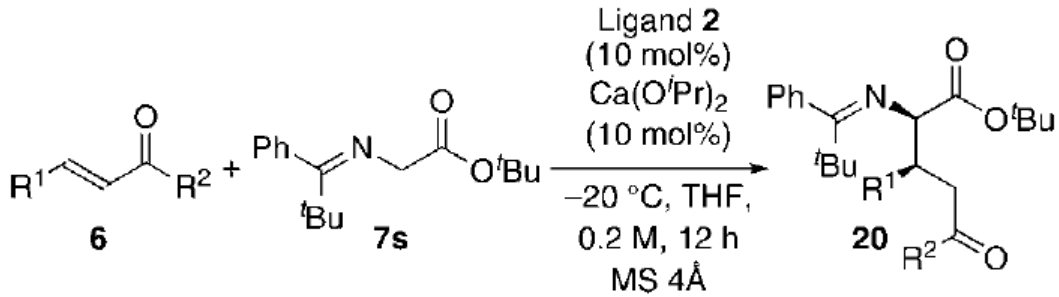
entry	Ar	ligand	yield (%)	8/9[a]	ee (%)
1	Ph	none	34	62/38	
2	Ph	**2**	95	**9mc** only	99
→ 3	Ph	**4**	99	**9mc** only	>99
4	Ph	**14**	quant[b]	18/82	98[c]
→ 5	p-$MeOC_6H_4$	**4**	90	18/82	96/98



3: R^1 = ^{t}Bu, R^2 = H
4: R^1 = Ph, R^2 = H
5: R^1 = Ph, R^2 = CN

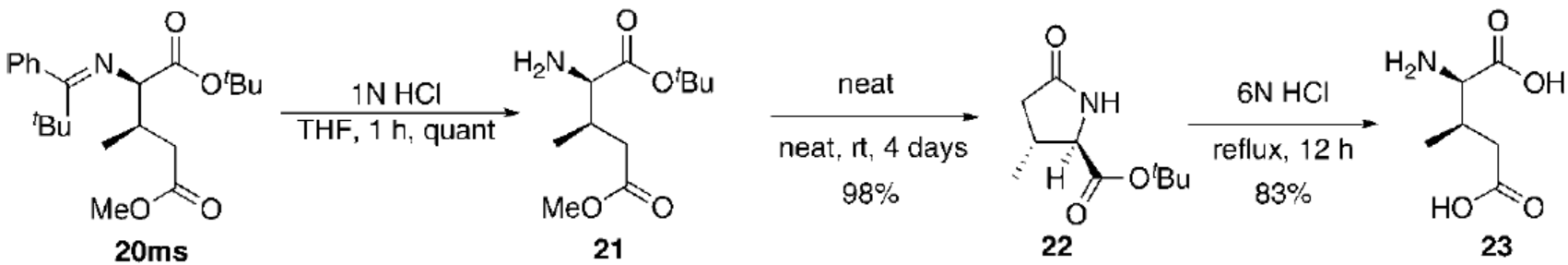
Tsubogo T.; Saito, S.; Seki, K; Yamashita, Y.; Kobayashi, S.; *J. Am. Chem. Soc.;* **2008**, *130,* 13321-13332

Preferential Formation of the 1,4-Adduct



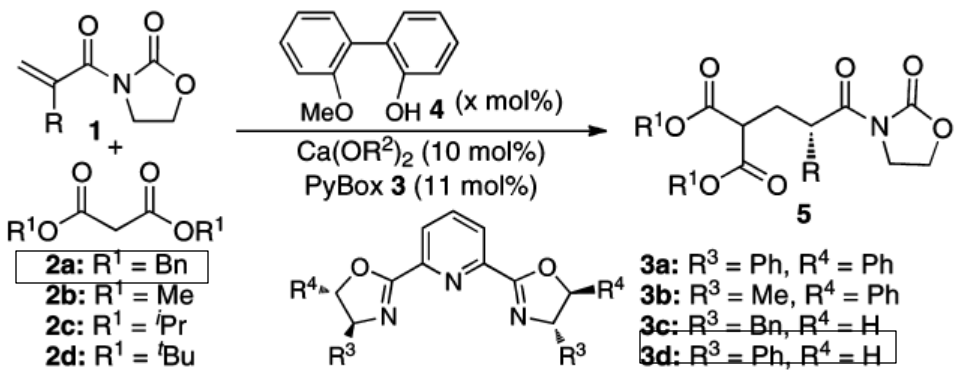
>99:1 d.r., >95:5 e.r. for R^1= alkyl

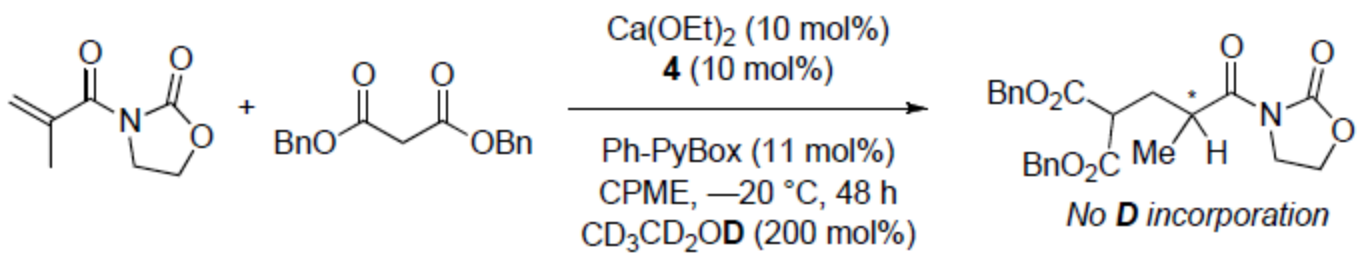
Acid additives failed to give exclusively 1,4-adduct

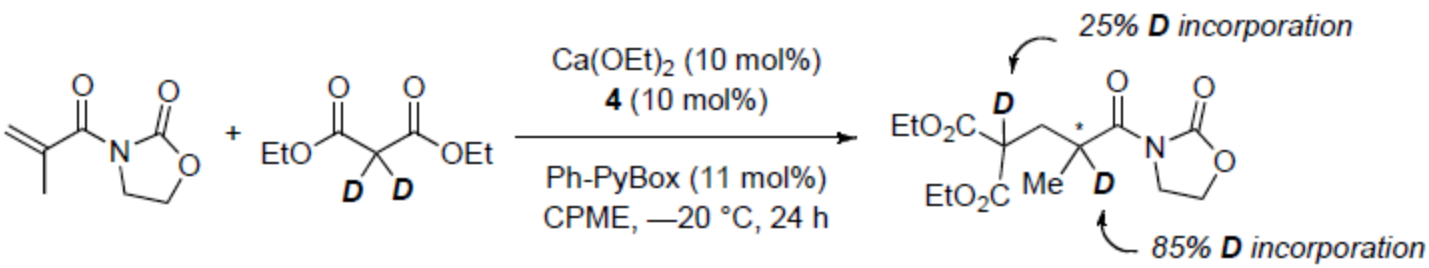


Tsubogo T.; Saito, S.; Seki, K; Yamashita, Y.; Kobayashi, S.; *J. Am. Chem. Soc.;* **2008**, *130,* 13321-13332

Observation Leads to New Chemistry

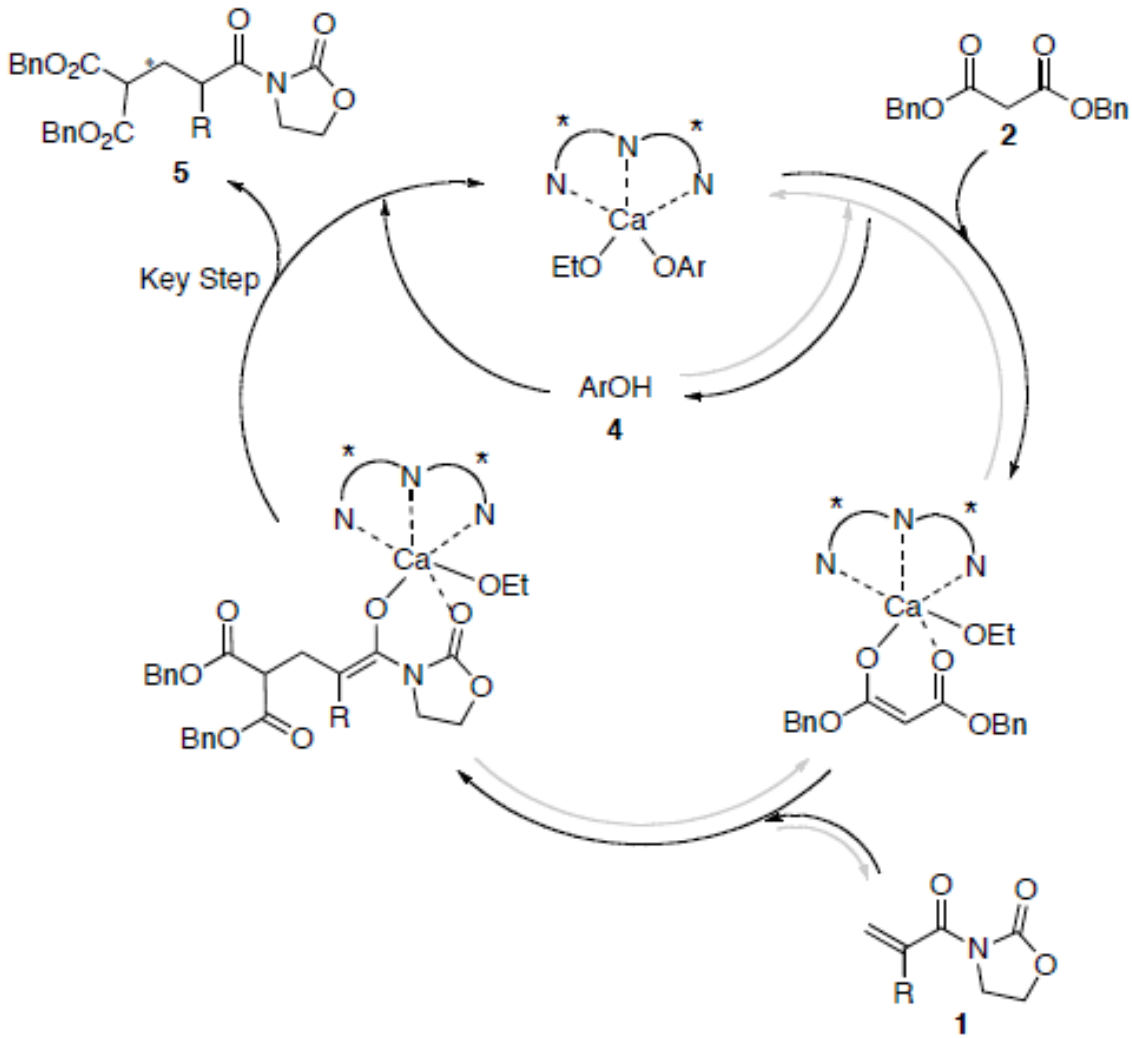






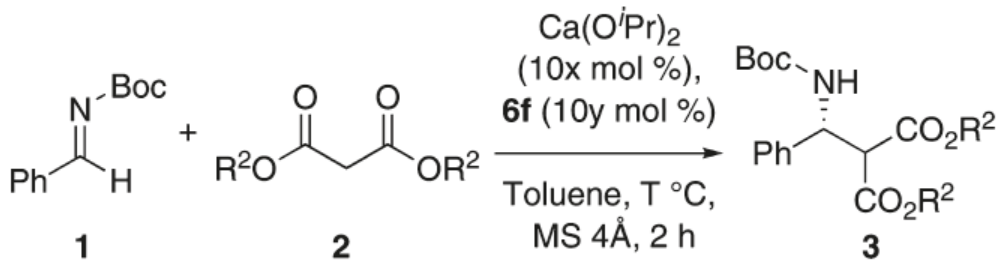
Poission T.; Yamashito Y.; Kobayashi, S.; *J. Am. Chem. Soc.;* **2010**, *132,* 7890-7892

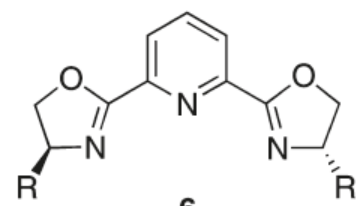
Protonation as the Slow Step



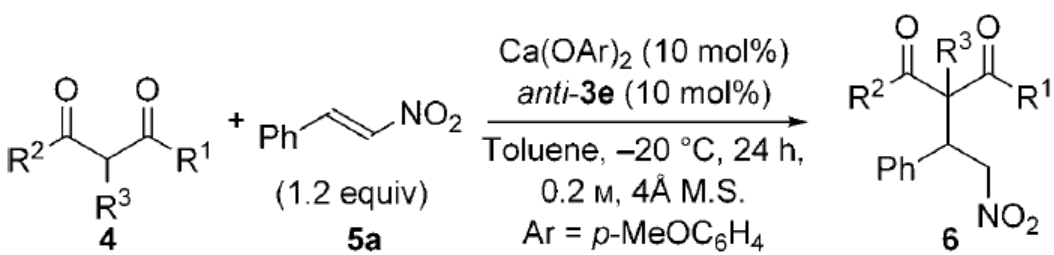
Poission T.; Yamashito Y.; Kobayashi, S.; *J. Am. Chem. Soc.;* **2010**, *132,* 7890-7892

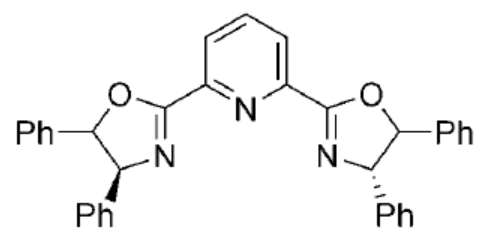
Other Conjugate Additions





6a R = ^{i}Pr
6b R = ^{i}Bu
6c R = ^{s}Bu
6d R = Me
6e R = Ph
6f R = Bn

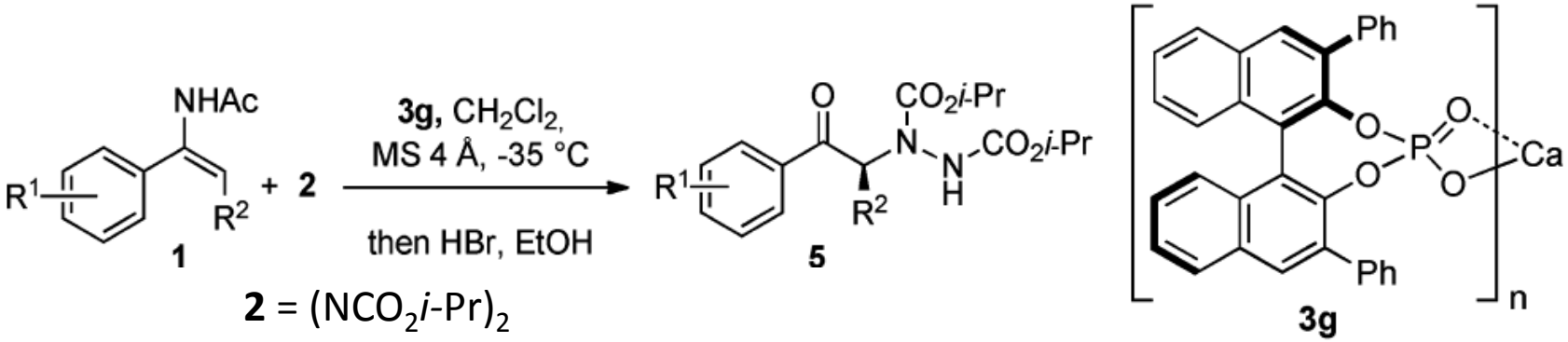




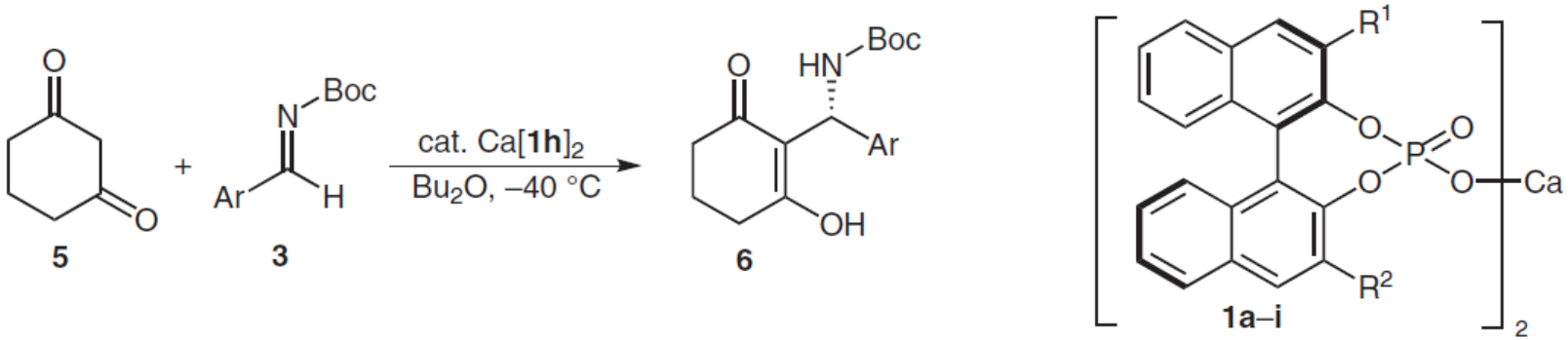
syn-**3e**
anti-**3e**

Poisson, T.; Tsubogo, T.; Yamashita, Y.; Kobayashi, S.; *J. Org. Chem.* **2010**, *75*, 963–965
Van Nguyeh, H.; Matsubara, R.; Kobayashi, S.; *Angew. Chem. Int. Ed*. **2009**, *48*, 9117 –9120

1,4-Additions Mediated By Chiral Phosphate Salts of Calcium



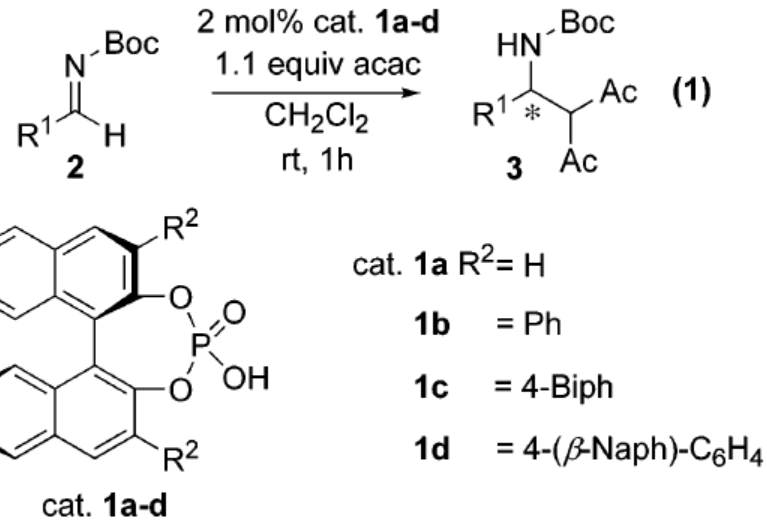
2 = $(NCO_2i\text{-}Pr)_2$



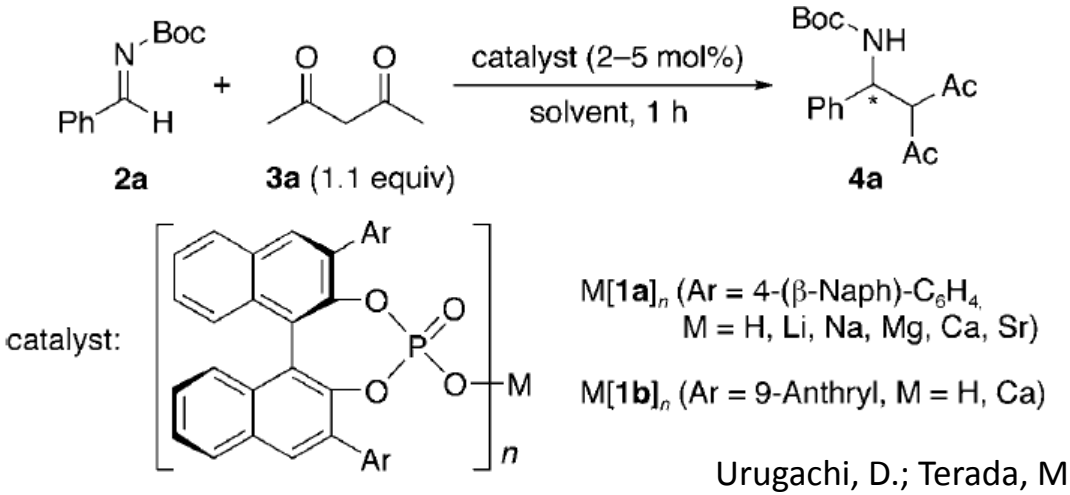
Ca[**1h**]$_2$: $R^1 = R^2 = 2,4,6\text{-}(i\text{-}Pr)_3C_6H_2$

Drouet, F.; Lalli, C.; Liu, H.; Masson, G.; Zhu, J.; *Org. Lett.*, **2011**, *13*, 94-97
Rueping, M.; Bootwicha, T.; Sugiono, E.; *Synlett*, **2011**, 323-326

Contradicting Reports Regarding BINOL-phosphoric acids



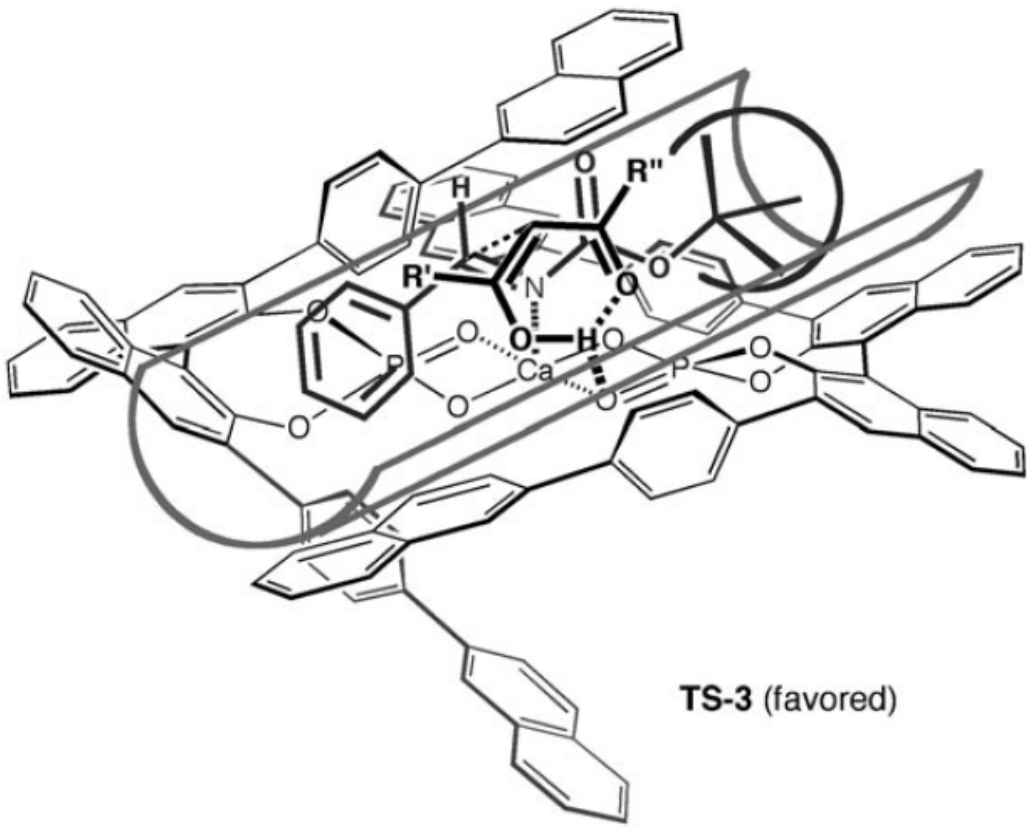
Terada:
Chiral Phosphoric Acids
>95:5 e.r. (*R*)



Ishihara:
Acid-washed Chiral Phosphoric Acids 63:37 (*S*)
Ca-Salt of **1a** 96:4 (*R*)

Urugachi, D.; Terada, M.; *J. Am. Chem. Soc.*, **2004,** 126, 5356-5357
Hatano, M.; Moriyama, K.; Maki , T.; Ishihara, K.; *Angew. Chem. Int. Ed*. **2010**, *49*, 3823 –3826

A Potential Basis for Stereoinduction



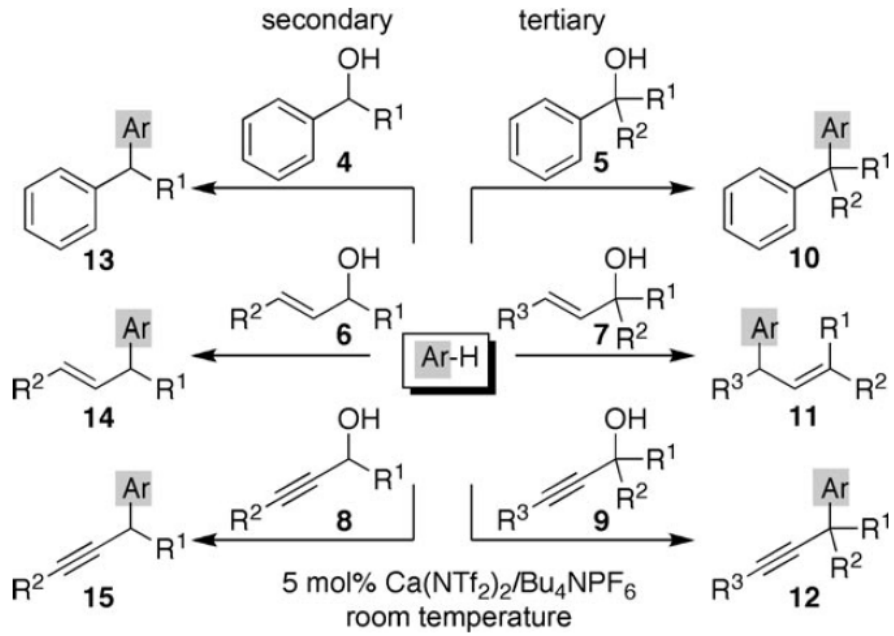
Broad peak at 0.05 ppm observed for salt, upon addition of imine new peak at 4.55ppm.

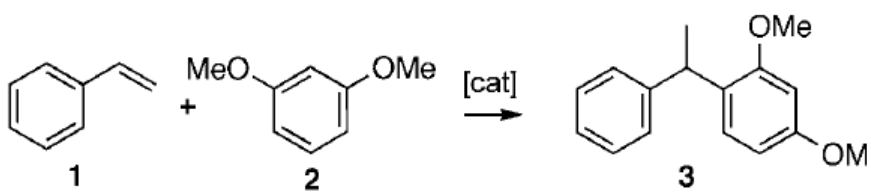
Mononuclear complex likely.

Half-pipe-like transition state forces enolate onto *re*-face of imine.

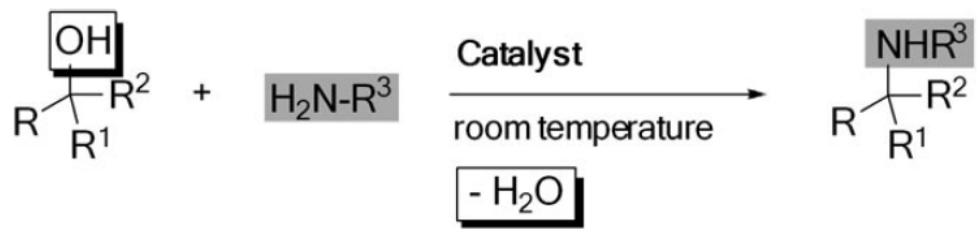
Hatano, M.; Moriyama, K.; Maki , T.; Ishihara, K.; *Angew. Chem. Int. Ed*. **2010**, *49*, 3823 –3826

Reactions Catalyzed by Lewis Acidic Calcium





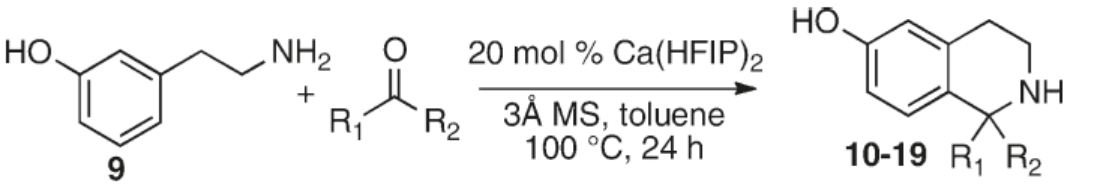
2.5 % $Ca(NTf)_2$, Bu_4NPF_6
0.5-12 h, 65-95%



Activated (allylic, propargylic, benzylic) alcohols
Broad scope in amine

Bisek, N.; Niggemann, M.; *Chem. Eur. J.* **2010**, *16*, 11246 – 11249
Niggemann, M.; Meel, M. J.; *Angew. Chem. Int. Ed.* **2010**, *49*, 3684 –3687
Haubenreisser, S.; Niggemann, M.; *Adv. Synth. Catal*. **2011**, *353*, 469 – 474

Reactions Catalyzed by Lewis Acidic Calcium

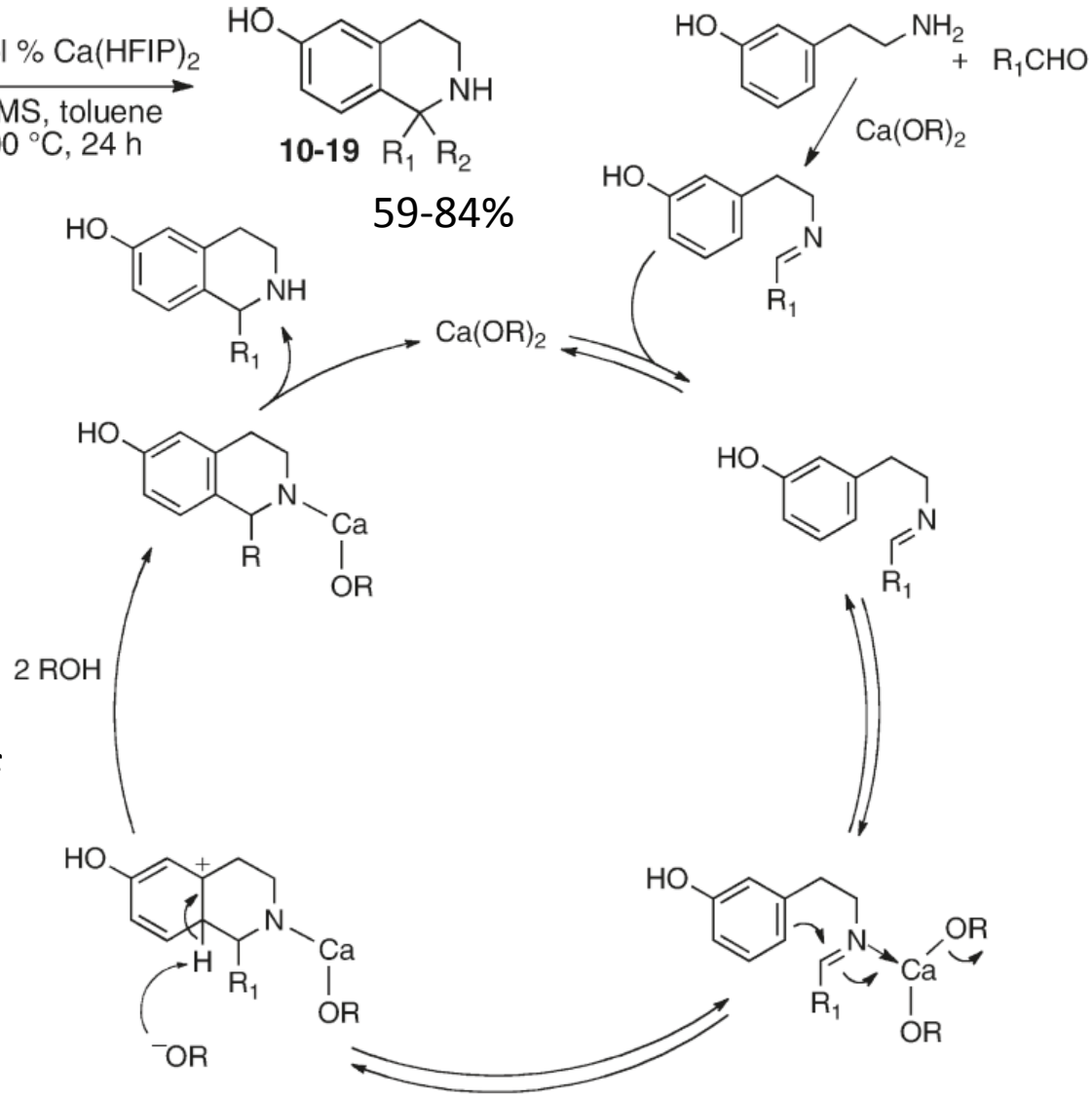


59-84%

Only electron rich arenes were used

Aldehydes can be used and are very reactive (Room Temp.)

Increasing e⁻ density of arene allows for conversion at lower temperatures.



Eynden, M. V. J.; Kunchithapatham, K.; Stambuli, J. P.; *J. Org. Chem.* **2010**, *75*, 8542–8549

Conclusions

- Calcium catalysis is governed by the strong Lewis acidity of the Ca center, as well as the carbanionic character of C-Ca bonds.
- Organocalcium reagents are highly labile due to the ionic C-Ca bond.
- Schlenk equilibria prevents the isolation and characterization of well-defined catalytic intermediates, as well as presenting challenges regarding the preparation and use of heteroleptic Ca species.
- Insolubility of Ca salts confounds kinetic analysis.
- Enantioselectivity has been achieved through the use of bulky, strongly chelating ligands that disfavor the formation of CaL_2.
- Calcium chemistry has so far been limited in general applicability.

A Few Lessons to Take Home

- Organocalcium reagents are vastly different than their organomagnesium cousins.
- The calcium reagent in solution is most likely not what you think it is.
- Strongly chelating ligands are necessary for mononuclear (and hence reproducible) catalysis.
- When using phosphoric acids, acid wash your product.

Barrett, A. G. M.; Crimmin, M. R.; Hill M. S.; Procopiou, P. A.; *Proc. R. Soc. A* **2010** *466,* 927-963
Yamashita, Y.; Kobayashi, S.; *Acc. Chem. Res.*, **2011**, *44*, 58-71
Harder, S.; *Chem. Rev.* **2010,** *110,* 3852–3876