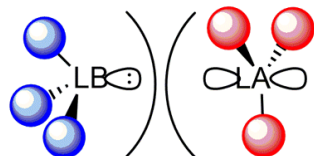


frustrated Lewis pair
(FLP)

Lewis base Lewis acid

“we have recently observed several systems in which sterically demanding phosphine donors and Lewis acids generate what we now coin ‘frustrated Lewis pairs’ (FLPs) in that this Lewis acid–base couple is sterically incapable of adduct formation, which opens alternate reaction pathways”

Stephan et al. *Dalton Trans.*, **2007**, 3407.

Overview

1. Background
2. Hydrogenation
3. Other reductive transformations
4. Cyclizations / C–C bond formation / C–H functionalization

“Nothing frustrating about frustrated lewis pairs”

“the chemistry of FLPs is certainly not a one-trick pony”

–Doug Stephan
Dalton Trans. **2012**, 41, 9015.



Prof. Douglas Stephan
@University of Toronto

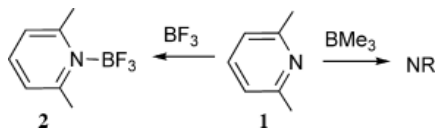
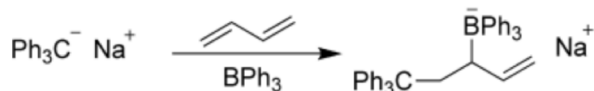
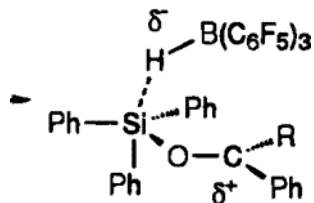
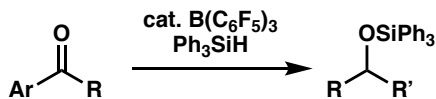
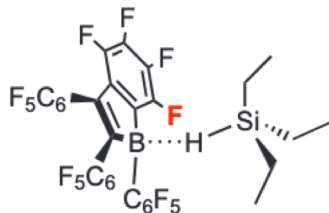
Good reviews (all by Stephan)

- *JACS* **2015**, 137, 10018.
- *Acc. Chem. Res.* **2015**, 48, 306.
- *Trends Chem.* **2019**, 1, 35.

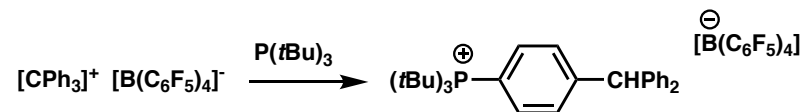
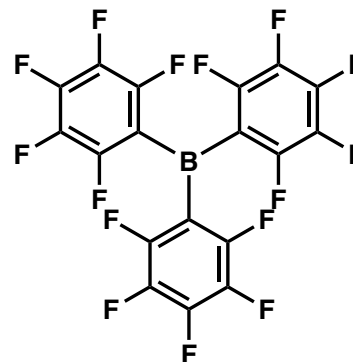
1923 – Concept of Lewis acid-base reactivity

with the formation of a classical donor-acceptor adduct

1942

Brown *JACS* **1942**, 64, 325.**1966 – “antagonistisches Paar”**Tochtermann *ACIE* **1966**, 5, 351.**1996 – Piers' hydrosilylation**Piers *JACS* **1996**, 118, 9440.

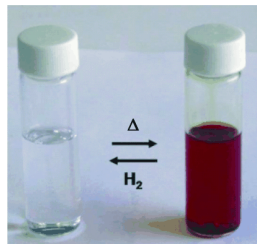
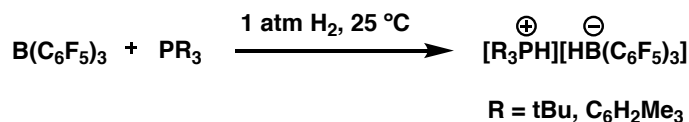
- obtained crystal structure of the borane-silane adduct

Piers *Nat. Chem.* **2014**, 6, 983.**2006 – phosphines and trityl cations**Stephan *Inorg. Chim. Acta.* **2006**, 359, 3066.the archetypical FLP Lewis acid: B(C₆F₅)₃

- Lewis acidity somewhere between BF₃ and BCl₃
- stable up to 270 °C
- magic balance of sterics and electronics

Proc. Chem. Soc. **1963**, 212.

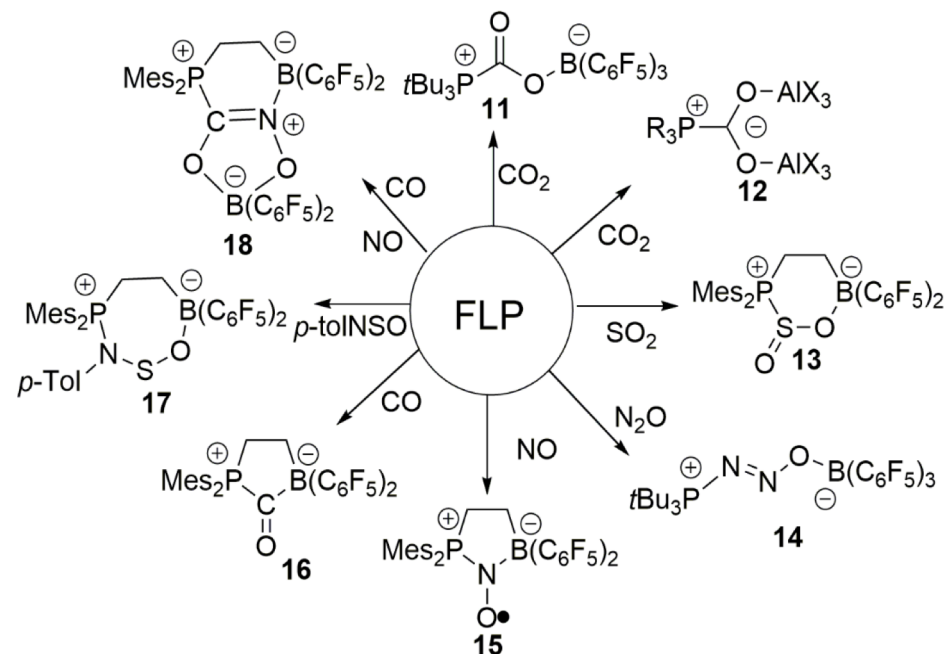
Pioneering work by Stephan

Stephan *Science* **2006**, 314, 1124.

sterics *and* electronics important: none of these could split H_2
 PMes_3 and BPh_3 , $\text{P}(\text{C}_6\text{F}_5)_3$ and $\text{B}(\text{C}_6\text{F}_5)_3$, PtBu_3 and BMes_3

Stephan *JACS* **2007**, 129, 1880.

Activation of other small molecules



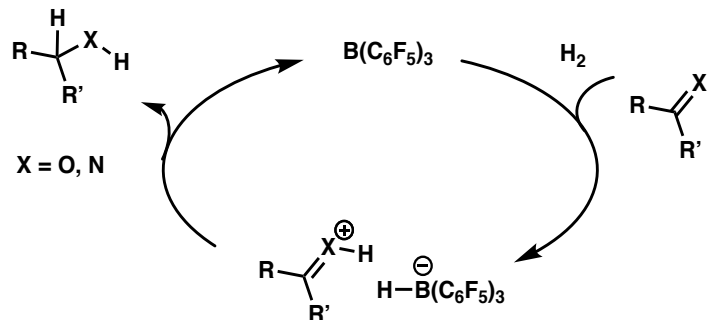
Diversity of FLP systems

P/B and P/N systems are most common, but many other combinations of LAs (Al, Zn, Se, Sn) and LBs (O, S, NHCs) exist

Continuum of reactivity

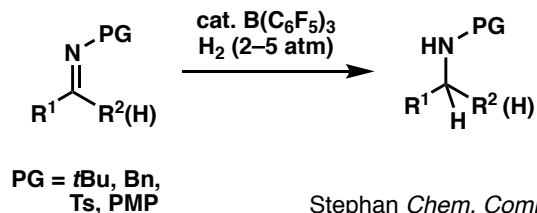
“thermally induced FLPs”: FLP-type transformations achieved using Lewis adducts exhibiting no “frustration” at the resting state, but have dynamic equilibria

Catalytic hydrogenations



- polar substrates: sequential proton and hydride delivery
- electron-rich substrates are reduced faster

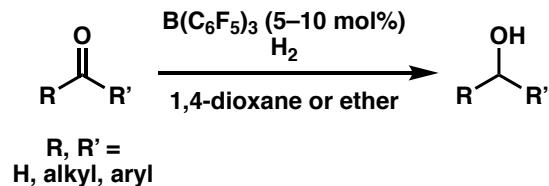
imines



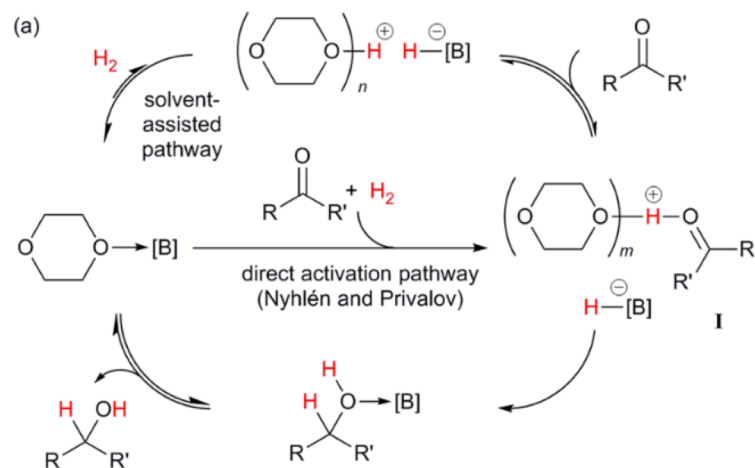
Stephan *Chem. Commun.* **2008**, 1701.
Klankermeyer *Chem. Commun.* **2008**, 2130.

- found that imine (with bulky PG) could itself act as both substrate and Lewis base
- the amine product itself is also a Lewis base
- quickly expanded to other polar functionalities like ketimines, nitriles, N-heterocycles, silyl enol ethers, enamines, etc.

ketones & aldehydes



have to overcome high oxophilicity of Lewis acid
(to avoid borinic esters)

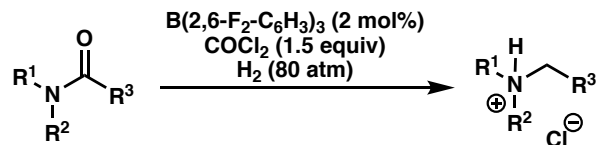


etheral solvent necessary for competitively binding to the LA
to facilitate product dissociation and catalytic turnover

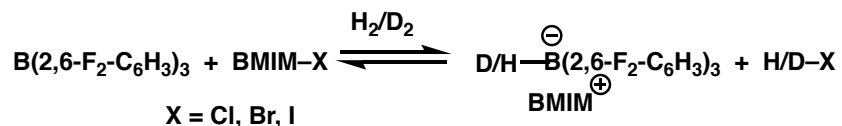
Stephan *JACS* **2014**, *136*, 15809; Ashley *JACS* **2014**, *136*, 15813.

Catalytic hydrogenations

amides

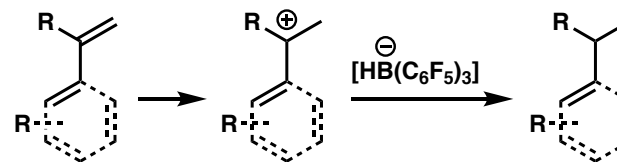


- generate chlorinium ion in situ
- selective for amide hydrogenation
- first example of using halide as the Lewis base
 - observed H₂/D₂ scrambling
- tolerant of hydride sensitive groups
- not tolerant of N-heterocycles

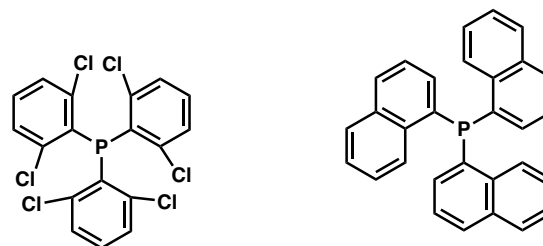
Grimme & Paradies *JACS* **2019**, *141*, 159.

alkenes

challenge for nonpolar substrates: need counteraction that is sufficiently acidic to protonate olefin



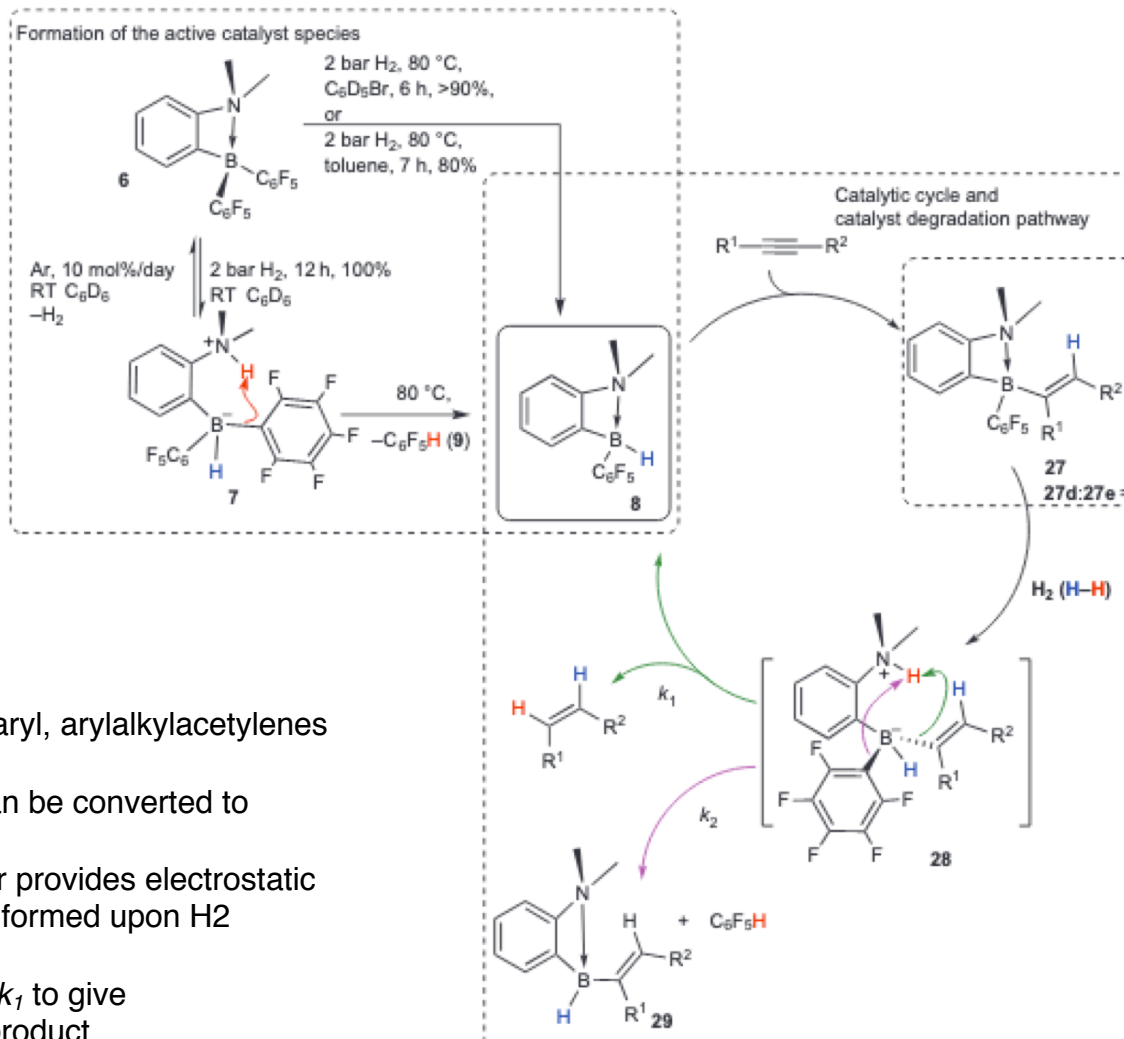
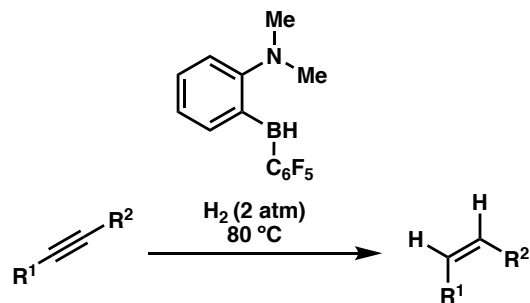
- using less nucleophilic phosphines
- need substrate to generate stabilized carbenium ion
- dimerization competitive with hydride transfer



Grimme, Paradies, and Stephan *ACIE* **2012**, *51*, 10164;
Grimme & Paradies *Chem. Sci.* **2013**, *4*, 2788.

Catalytic hydrogenations

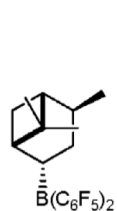
alkynes



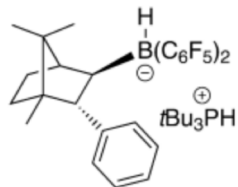
- impressive substrate scope: dialkyl, diaryl, arylalkylacetylenes in generally excellent yields
- terminal alkynes are unreactive, but can be converted to corresponding silylacetylenes
- computation suggests the phenyl linker provides electrostatic stabilization in the zwitterionic species formed upon H₂ cleavage
- tried to apply towards alkenes, but $k_2 > k_1$ to give protodeborylation of -C₆F₅ instead of product

Catalytic hydrogenations

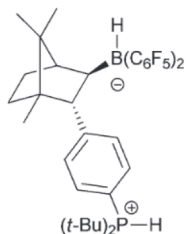
rendering it enantioselective



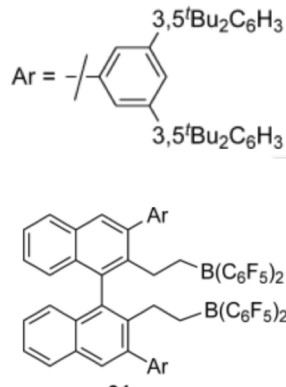
2008
unstable
1 example
13% ee



2010
relatively stable
80% ee



2012
recyclable!
70–76% ee



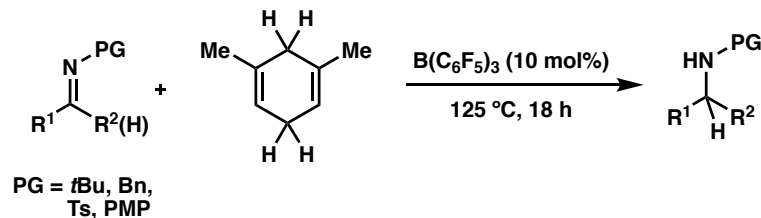
2013
generated in situ
74–89% ee

- obtained through hydroboration
- all examples are with bulky aryl imines

Klankermayer *Chem. Commun.* **2008**, 2130;
Klankermayer *ACIE* **2010**, 49, 9475;
Klankermayer *Dalton Trans.* **2012**, 41, 9026;
Du *JACS* **2013**, 135, 6810.

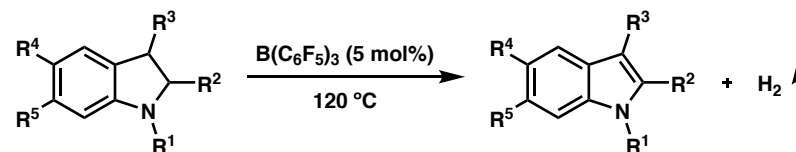
Transfer hydrogenation

can also use *i*Pr₂NH as source of H₂



Stephan *Organometallics* **2011**, 30, 4497; Oestreich *ACIE* **2015**, 54, 1965.

Dehydrogenation



B(C₆F₅)₃ acts as a hydride shuttle
pyridines, thiazoles, quinolines also viable

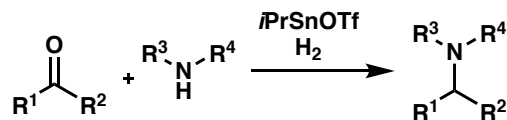
Paradies *ACIE* **2016**, 55, 12219; Kanai *ACIE* **2016**, 55, 12224.

reductive amination & water-tolerant FLPs

once H₂O is bonded to B(C₆F₅)₃ it has pKa of 8.4 (in MeCN)
resulting in an inactive hydroxytriarylborate anion

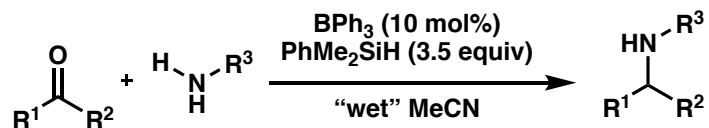
JACS **2000**, *122*, 10581.

- solution #1: use a heavier element for a softer LA
 - ex. using Sn for reductive amination (stoich. water byproduct)



Ashley *ACIE* **2016**, *55*, 14738.

- solution #2: tuning electronics

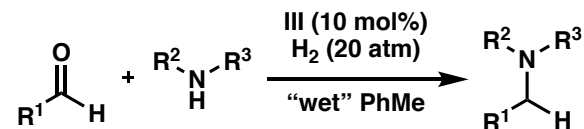
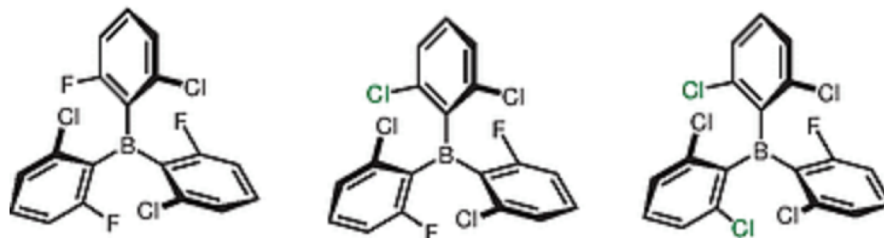


- less acidic BPh₃ lowers acidity of H₂O–BPh₃
- only tolerates alkylamines (arylamines are too basic)
- can't use H₂ as the reductant (too slow)

Ingleson *Chem. Eur. J.* **2017**, *23*, 2217.

- solution #3: tuning sterics

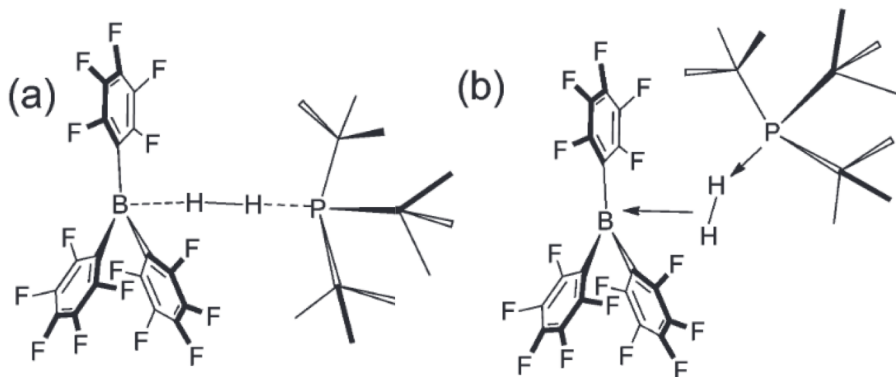
F–Cl exchange increases back-strain for a “spring-loaded system” to push back into sp² state



- tolerant of many FGs: esters, ethers, heteroatom containing rings
- aryl and alkylamine substrates (but not too bulky)

Soós *ACIE* **2017**, *56*, 9512.
see also: O'Hare *JACS* **2011**, *133*, 14727.

Mechanism of hydrogenation

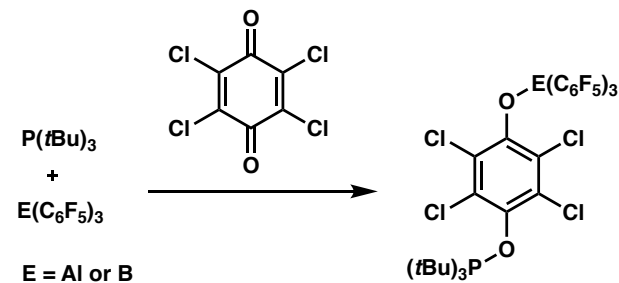


- “encounter complex”: associated form of the FLP through noncovalent interactions (0.5% preorganized states)
- reaction with H₂ is essentially bimolecular
- donation of H–H σ bond with the Lewis acid and donation of the Lewis base to the s* orbital
- approach of H₂ is controversial whether
 - a) linear, as Papai suggests there is polarization of H₂ by the electric field generated by the FLP
 - b) side-on, as Grimme suggests there is “side-on” H₂ σ donation to the B center with concurrent donation from P to the σ*orbital

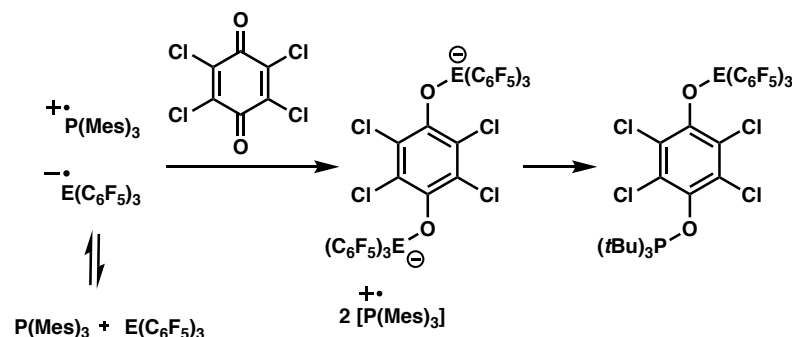
Papai *Chem. Commun.* **2008**, 3148.
 Grimme & Erker *ACIE* **2010**, 49, 1402.
 Papai *Dalton Trans.* **2012**, 41, 9023.
 Papai *JACS* **2013**, 135, 4425.
 Privalov *ChemPhysChem* **2014**, 15, 3714.

or is it homolytic??

- could a SET mechanism be in effect?



- P(tBu)₃/E(C₆F₅)₃ exhibits heterolytic cleavage
- no radical intermediates observed by EPR

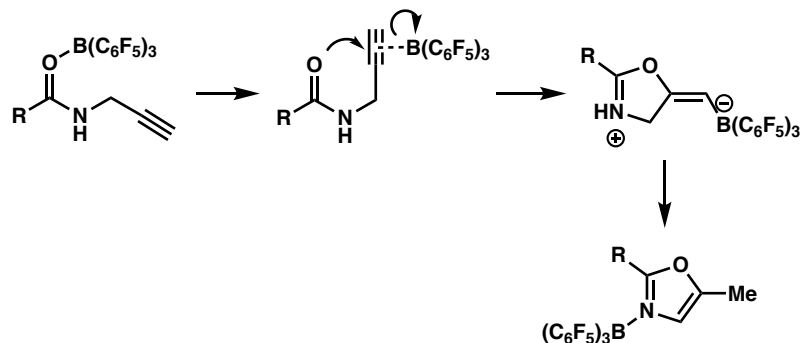


- P(Mes)₃/E(C₆F₅)₃ exhibits homolytic cleavage
- EPR signal consistent with MesP.+

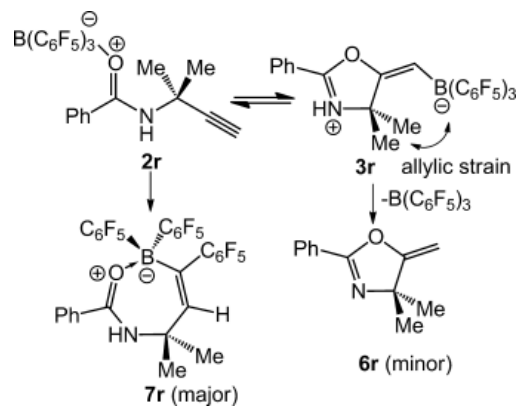
Stephan *Chem.* **2017**, 3, 259.

cyclization

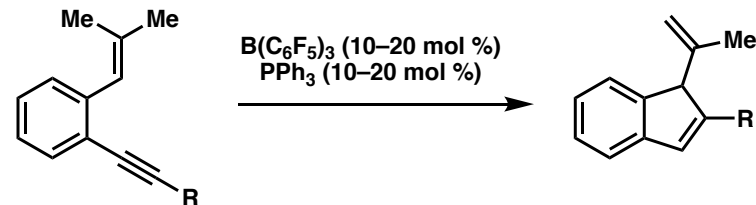
propargyl amides



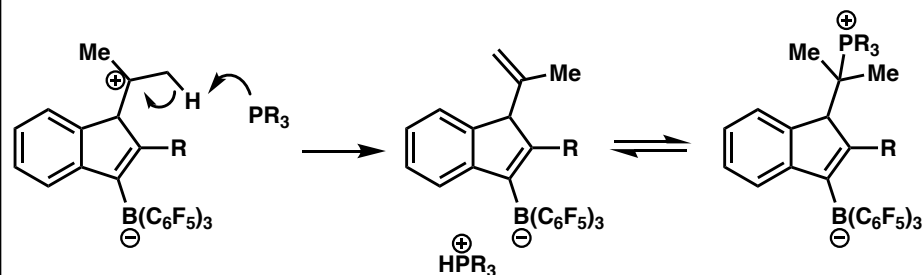
- 5-exo-dig cyclization
- unfortunately has to be stoichiometric
- when R = Ad then the oxazole could be formed in 83% yield after 10 days at 100 °C using 10 mol% $B(C_6F_5)_3$
- N–B dative bond too strong to render catalytic

Stephan *Chem. Eur. J.* **2013**, *19*, 11928.

key challenge: formation of stable onium borates precludes a desirable catalytic reaction



5-endo-dig cyclization/protodeborylation sequence
good yields (44-90%)

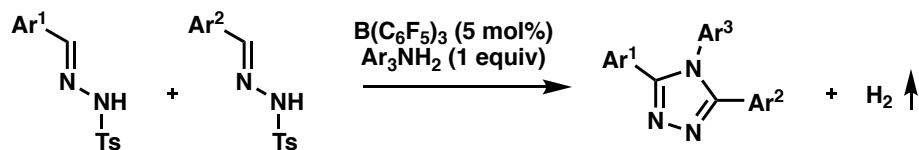


- protodeborylation is r.d.s
- PPh_3 is key to protodeborylation (more basic $PtBu_3$ did not undergo, stuck as phosphonium borate)
- first example of successful protodeborylation to turnover catalyst

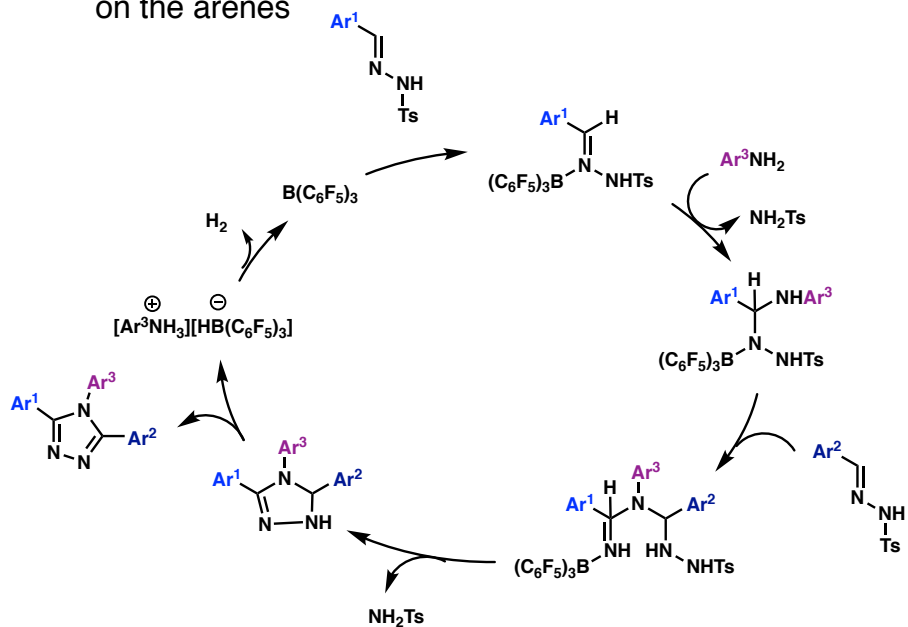
Grimme & Paradies *ACIE* **2016**, *55*, 4336.

cyclizations – catalytic

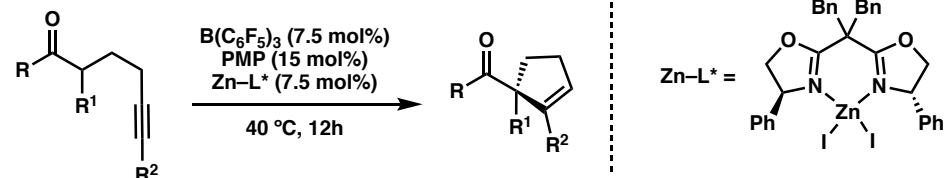
acceptor-less dehydrogenative cyclization



- symmetrical as well as asymmetrical 1,2,4-triazoles
- 70-80% yields
- for the asymmetric case, need to have differing electronics on the arenes

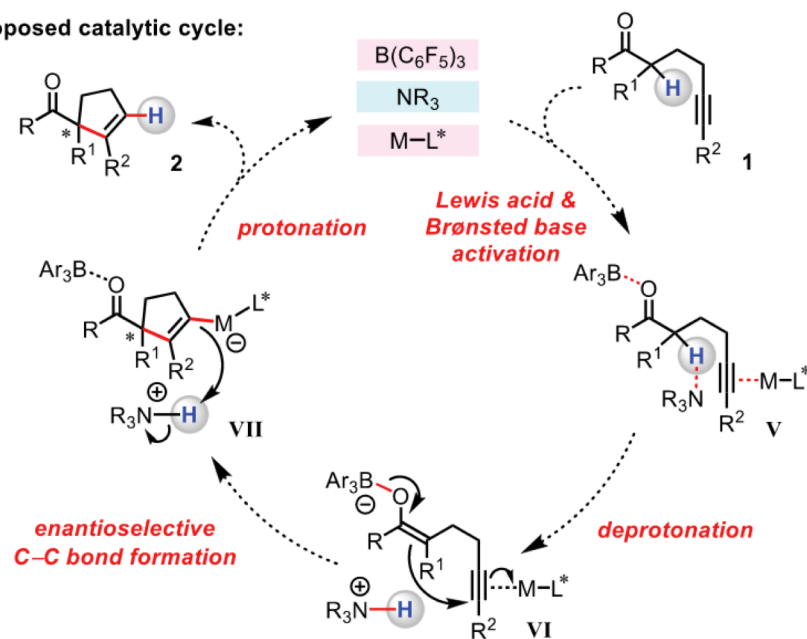
Koley & Maji *Chem. Sci.* **2019**, *10*, 7964.

enantioselective Conia-ene cyclization



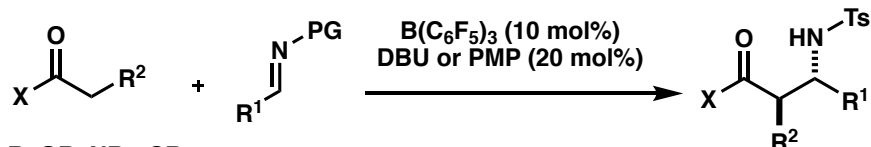
- two independent Lewis acid cocatalysts working in conjunction
- 18 examples, generally >90% yield and >85% ee
- aryl and alkylketones work well, scales up well

Proposed catalytic cycle:

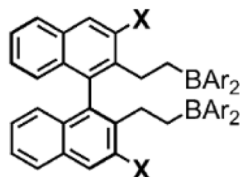
Wasa *JACS* **2019**, *141*, 4199.

C–C bond formation

Direct Mannich-type reaction

X = R, OR, NR₂, SR

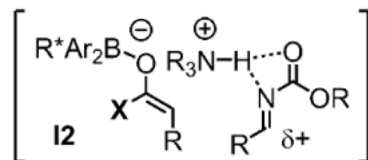
- good to excellent diastereoselectivities (*anti:syn* 5:1 up to >20:1)
- Cu(OTf)₂ as a cocatalyst activates less reactive imines for improve yields



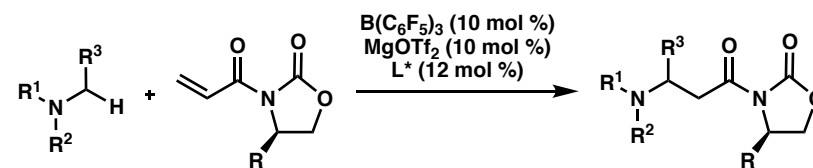
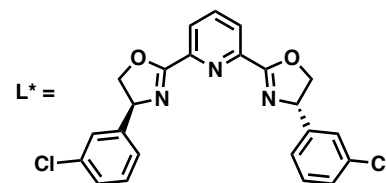
can be rendered enantioselective (>20:1 dr, >90% ee)

R^{*}BAr₂, Ar₂ = (C₆F₅)₂

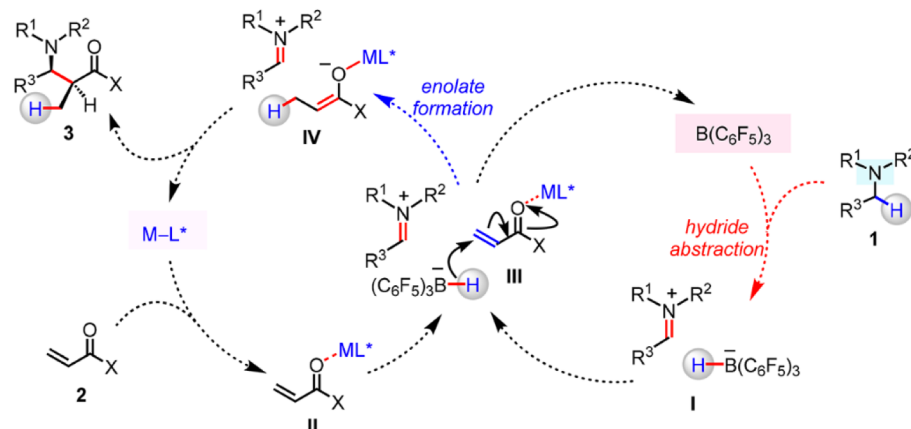
- better stereoselectivities with PG = Boc vs Ts, suggestive of a hydrogen-bonding interaction to aid stereoselective C–C bond formation

Wasa *ACIE* **2016**, *55*, 13877; *ACIE* **2017**, *56*, 13338.

C–H functionalization via cooperative catalysis

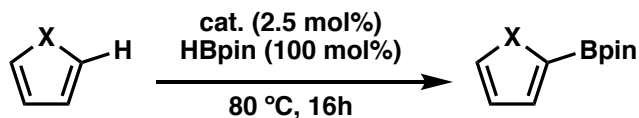


- okay diastereoselectivity (*anti:syn* 3:1 up to 7:1)
- excellent enantioselectivity (>99:1 er)
- isolate enantiomerically pure β amino acids

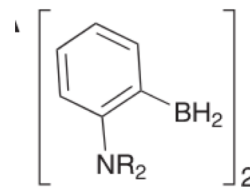
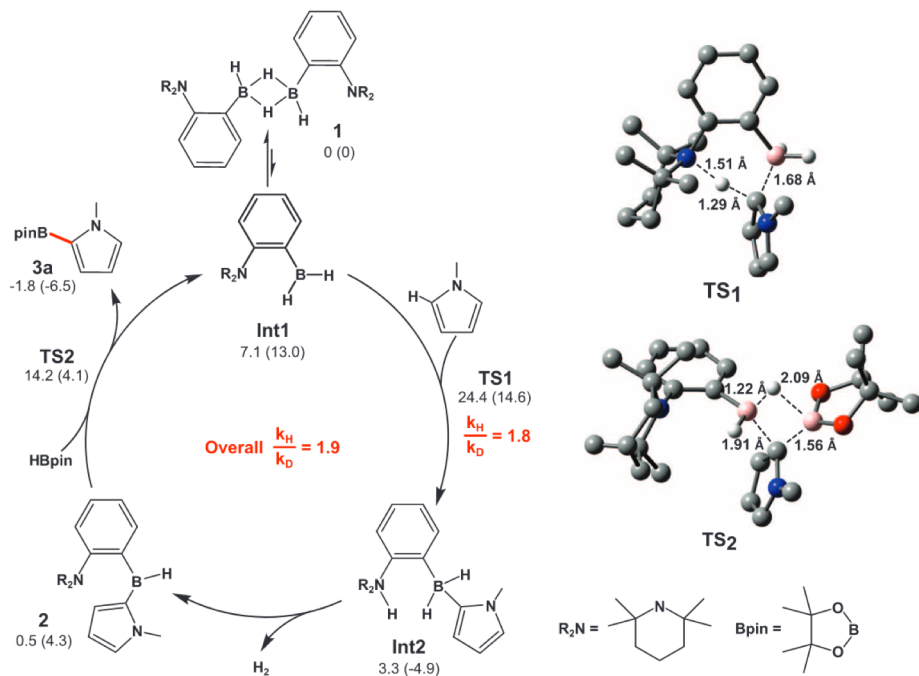
Wasa *JACS* **2018**, *140*, 10593.

sp² C–H borylation

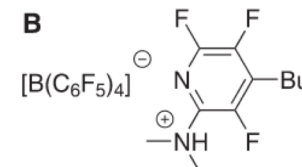
examples of sp, sp², and sp³ C–H insertions
promise for metal-free catalysis: elementary C–H insertion
and protonation steps can be incorporated into catalytic cycles



X = O, NR, S



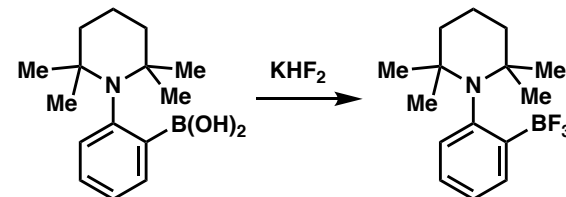
Fontaine 2015



Repo 2016

Repo et al. expanded scope
to arenes and alkenes

- limited scope: substrate must be electron rich but impressive yields (60–98%)
- HBCat and 9BBN perform with lower but still good yields
- electronics matter:
 - PG = TIPS/TMS give exclusively 3-borylation
 - PG = Bz gives 3:2 mixture of 3- to 2-borylation
 - PG = Boc inhibits reaction
- same regioselectivity as observed in Ir-cat. electrophilic borylations (favors more electron-rich 3 position)



air- and water-
stable precatalyst!

Fontaine *Science* 2015, 349, 513.
Pápai & Repo *JACS* 2016, 138, 4860.
Fontaine *JACS* 2017, 139, 14714.