Frustrated Lewis Pairs: From Concept to Catalysis

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Concett

Classical Lewis acid-base chemistry

Lewis acid (electron acceptor) + Lewis base (electron donor) → Lewis acid-base adduct (donor-acceptor bond formation)

For almost 100 years, the combination of electron acceptors (Lewis acids) and electron donors (Lewis bases) has been known to give Lewis acid-base adducts that incorporate donor-acceptor bonds.

Frustrated Lewis pair chemistry

Lewis acid + Lewis base → Frustrated Lewis pair (sterically inhibited bond formation)

Research over the past decade has shown that the introduction of steric demands or a dissociative equilibrium provides access to free donors and acceptors, allowing them to interact with a third molecule and leading to distinct reactivity.

Discovery Timeline

1923
Definition of Lewis acids and bases by Gilbert Lewis

Propagation of use in organic chemistry
The acid/base reaction for the formation of adducts

1942
Effect of steric hindrance within adduct noticed by Brown

JACS, 1942, 64, 325

1959
Wittig, Benz and then Tochtermann noticed similar anomalies


1978-1990
Gutmann published his analysis of the interaction of Lewis acids and bases

Discovery Timeline

1996
Piers reported first metal-free hydrosilylation of aromatic ketones

\[ \text{R}^1\text{O} + \text{R}^2\text{SiH} \xrightarrow{\text{B(C₆F₅)}_3} \text{R}^1\text{OSiPh₃} \]

*JACS, 1996, 118, 9440*

2006
Stephan Douglas encounters same phenomena as Brown
The first reversible, metal-free hydrogen activation

\[ \text{Mes}_2\text{P} + \text{B(C₆F₅)}_2 \xrightarrow{\text{H}_2, \text{r.t.}} \text{Mes}_2\text{P} \xrightarrow{-\text{H}_2, 150 \, ^\circ \text{C}} \text{Mes}_2\text{PH} \]

*Science, 2006, 314, 1124*

2007
Stephan formalizes the concept (*Frustrated Lewis Pairs*)

*ACIE, 2007, 46, 4968*

2007
Erker reported activation of dihydrogen by intramolecular FLPs:

\[ \text{Mes}_2\text{P} \xrightarrow{\text{H}_2, \text{r.t.}} \text{pentane} \xrightarrow{\text{H}_2, \text{r.t.}} \text{Mes}_2\text{P} \]

2018
Over the past decades rapid and great progress have been made in the filed of FLPs chemistry.

Representative players in the field

Prof Douglas W. Stephan
Ph.D 1980 (University of Western Ontario)
Postdoc 1980-1982 (Harvard, R.H. Holm)

*University of Windsor*
University Professor 2002-2007
Department Head 2003-2006
Professor 1992-2002
Associate Professor 1985-1992
Assistant Professor 1982-1985

*University of Toronto*
Professor 2008-present

Prof Gerhard Erker

Studied chemistry 1966 - 1970 (Universities Köln and Bochum)
Dr. rer. nat. 1973 (Univ. Bochum, W. R. Roth)
Postdoctoral Fellow 1974 - 75 (Princeton University, M. Jones, Jr.)
Habilitation 1981 (Univ. Bochum, Organic Chemistry)
Heisenberg-Fellow 1984 - 1985 (Max-Planck-Institut für Kohlenforschung, Mülheim)
Professor 1985 - 1990 (C3, Univ. Würzburg, Organic Chemistry)
Professor 1990 - 2015 (C4/W3, WWU Münster, Organic Chemistry)
Senior Professor 2015 - present (WWU Münster, Organic Chemistry)
To date, which aspects of applications on Frustrated Lewis Pairs have been concerned?

a. Activation of H₂ and catalytic hydrogenation
b. Small-molecule activation (CO; CO₂, SO₂, N₂O, NO etc.)
c. Organic molecule activation (alkene, alkynes, silanes, C-H bonds etc.)


This presentation will mainly focus on homogeneous catalysis and synthesis application based on Frustrated Lewis Pairs.

1. Hydrogenation

1.1 Seminal work by Stephan (H₂ activation by FLPs)

1.2 Catalytic Hydrogenation (amines)

Science, 2006, 314, 1124
1.3 Catalytic Hydrogenation (Ketone)

Ketone $\xrightarrow{\text{B(C_6F_5)_3 (5 mol%)}}$ Alcohol

$\xrightarrow{\text{Ether or Dioxane}}$ 60 atm H$_2$, 70 °C, 12 h

$\xrightarrow{\text{Et\text{O\text{--O\text{--O}}\text{--O}}} \text{Et}}$ B(C$_6$F$_5$)$_3$

$\xrightarrow{\text{Et\text{O\text{--O\text{--O}}\text{--O}}} \text{Et}}$ B(C$_6$F$_5$)$_3$

$\xrightarrow{\text{OH}}$ R'R'

$\xrightarrow{\text{R\text{--R'}}}$ R'R'


1.4 Catalytic Hydrogenation (Olefin)

$\xrightarrow{\text{R'}}$ B(C$_6$F$_5$)$_3$ (5 mol%)

$\xrightarrow{\text{(C$_6$F$_5$)$_3$Ph$_2$P}}$ R'

Unactivated olefin

ACIE, 2012, 51, 10164

Hydrogenation of electron-poor alkene or allene, see:

ACIE, 2012, 51, 12367; ACIE, 2013, 52, 5876

1.5 Catalytic Hydrogenation (Alkynes)

$\xrightarrow{\text{H$_2$, 80 °C}}$ - C$_6$F$_5$H

Nat. Chem. 2013, 5, 718.

1.6 Catalytic Hydrogenation (Heterocycles)

$\xrightarrow{\text{B(C$_6$F$_5$)$_3$}}$ X = CH, N

Y = CH$_2$, N

A = S, NH

B = N, NH

CC, 2010, 46, 4884; IC, 2011, 50, 12338; CEJ, 2012, 18, 574

Hydrogenation of electron-poor heterocycle, see:

ACIE, 2012, 51, 10164; ACIE, 2013, 52, 5876

BCF

Hydrogen

Activation

Hydride

Addition

Isomerization

or

BCF

H$_2$
2. FLP catalyzed asymmetric hydrogenation

2.1 Substrate-controlled selectivity

In 2010, the first example of chiral substrate induced asymmetric hydrogenation catalyzed by a FLP catalyst was reported by Soós and co-workers.

\[
\begin{align*}
\text{B(C}_6\text{F}_5)_2 (\text{Mes}) + \text{N}_2 \text{N} & \xrightarrow{\text{H}_2 (4 \text{ atm}) \ 24 \text{ h}} \text{BH(C}_6\text{F}_5)_2 (\text{Mes}) \text{H} \text{N} \text{N} \\
\text{1} & \xrightarrow{3 (20 \text{ mol})} \text{2} \xrightarrow{\text{H}_2 (4 \text{ atm}) \ C_6\text{H}_6 \ r.t. \ 6 \text{ d}} \text{3}
\end{align*}
\]

D-carvone \( \text{ACIE, 2010, 49, 6559} \)

In 2011, Stephan et al. reported a highly diastereoselective catalytic hydrogenation of opticallypure ketimines using 10–20 mol % B(C6F5)3 as a catalyst.

Chiral imines \( \xrightarrow{\text{B(C}_6\text{F}_5)_3 \ \text{H}_2 \ \text{Toluene}} \) Chiral amines

80 \degree C

\[
\text{HN} \text{N} \text{N} \\
\text{Ph} \ 7a, 21 \text{% de} \\
\text{Cy} \ 7b, 39 \text{% de} \\
\text{Cy} \ 7c, 39 \text{% de} \\
\text{Cy} \ 7d, 68 \text{% de}
\]

115 \degree C

\[
\text{NH}_{\text{Bn}} \\
\text{NHP} \text{h} \ 7e, 99 \text{% de} \\
\text{NH}_{\text{Bn}} \ 7f, 99 \text{% de} \\
\text{PhH} \text{N} \ 7g, 99 \text{% de} \\
\text{BnHN} \ 7h, 99 \text{% de}
\]

\( \text{CC, 2011, 5729–5731.} \)

2.2 Chiral FLP catalyst controlled selectivity

In 2008, Chen and Klankermayer reported the first chiral FLP-catalyzed asymmetric hydrogenation of imine.

\[
\begin{align*}
\text{HN} \text{N} \text{Ph} & \xrightarrow{11 (5 \text{ mol})} \text{HN} \text{N} \text{Ph} \\
\text{Ph} & \xrightarrow{\text{H}_2 (20 \text{ atm}) \ \text{Toluene, 65 \degree C}} \text{Ph} \\
\text{C}_6\text{F}_5 & \xrightarrow{\text{Cc}, 2008, 2130–2131.}
\end{align*}
\]

11 from (+)-a-pinene

catalyst derived from (1R)-(+)-(camphor)

In 2011, Repo and co-workers designed a novel class of chiral intramolecular ansa-aminoborates.

\[
\begin{align*}
\text{Amine} \xrightarrow{\text{H}_2} \text{Amine} \\
\text{B(C}_6\text{F}_5)_2 \xrightarrow{100 \% \text{ Conv.} \ 35 \% \text{ ee}} \text{B(C}_6\text{F}_5)_2 \\
\text{HN} \text{N} \text{Ph} \\
\text{Ph} \ 100 \% \text{ Conv.} \ 37 \% \text{ ee}
\end{align*}
\]

\( \text{ASC, 2011, 353, 2093} \)
In 2011, Stephan and co-workers employed (S,S)-diop and B(C₆F₅)₃ as an intermolecular FLP catalyst for the asymmetric hydrogenation of ketimine 9a to result in a promising 25% ee.

In 2013, Du et al. developed an elegant strategy for preparation of chiral borane catalyst.

The use of terminal olefins ensured the optical purity of boranes by the hydroboration with Piers borane and avoided to produce diastereoisomers for the case of internal olefins.
2. Activation of hydrosilane and transformations

In 1996, Piers et al. reported the first metal-free hydrosilation of ketones.

In 2008, Oestreich et al. obtained proof of an $S_{N}2$-Si transition state employing a stereogenic silane as a stereochemical probe.

In 2013, Fujimoto et al. performed mechanism study by DFT.

In 2014, Piers et al. obtained crucial X-ray crystallography structure of borane-silane adduct and demonstrates conclusively the role of this species in metal-free ‘frustrated-Lewis-pair’ hydrosilylation reactions.
2. Activation of hydrosilane and transformations

In 2014, Chang et al. reported silylative reduction of Quinolines.

\[
\text{N} + \text{Et}_2\text{SiH}_2 + \text{B(C}_6\text{F}_5)_3 \text{ (1 mol\%)} + \text{R} \rightarrow \text{Et}_2\text{HSi} + \text{N} \text{R}^{1-40 \text{ equiv}} \text{CHCl}_3, 6-24 \text{ h} \text{, r.t.-100 \degree C}
\]

31-94\% yield

In 2012, Klankermayer et al. reported the first chiral FLP-catalyzed silylative reduction of imines.

\[
\text{N}^+ \text{R}^1 \rightarrow \text{N}^+ \text{R}^2 \text{1) Catalyst/PhMe}_2\text{SiH} \rightarrow \text{N}^+ \text{R}^2 \text{2) hydrolysis} \text{, C}_{\text{EJ}}, 2012, 18, 5184
\]

33-90\% yield

81-87\% ee

In 2012, Mewald and Oestreich demonstrated an axially chiral C_{6}F_{5}-substituted borane. With this catalyst, a phenyl-substituted imine could be reduced to amine with low to moderate ee value.

\[
\text{N} \text{R} \rightarrow \text{N} \text{H} \rightarrow \text{N} \text{H} \text{ after hydrolysis}
\]

up to 62\% ee

Besides these, silylative reduction of pyridines, imines, amides and nitriles also have been reported.

see: JACS, 2013, 135, 17537; CC, 2014, 50, 9349; JACS, 2015, 137, 15176; JOC, 2015, 80, 7281; CC, 2016, 52, 12195; OBC, 2016, 14, 5774.

2. Activation of hydrosilane and transformations

In 2016, Du et al. reported chiral FLPs-catalyzed highly enantioselective hydrosilylations of 1,2-dicarbonyl compounds. (great progress)

\[
\begin{align*}
&\text{Ar} \quad \text{Ar} \\
&\text{O} \quad \text{O} \\
&\text{1} \hspace{1cm} \text{2} \\
&\text{PhMe}_3\text{SiH (3.0 equiv) tolune, 60 °C, 5 h} \\
&\text{Py-HF, hexane, r.t., 0.5 h} \\
&\text{1 Chiral diyne 2a (5 mol%) HB(C_6F_5)_2 (10 mol%) Cy}_3\text{P (3d) (10 mol%)} \\
&\text{58-92% yield 88->99% ee}
\end{align*}
\]

94% conv, 99% ee

11% conv, 56% ee

JACS, 2016, 138, 810.

In 2016, Oestreicher et al. realized the first asymmetric piers hydrosilylation. (simple ketone)

\[
\begin{align*}
&\text{Ar} \quad \text{Me} \\
&\text{Ph} \\
&\text{B} \quad \text{C}_6\text{F}_5 \\
&\text{1.2 mol%} \\
&\text{PhSiH}_3 (3.0 equiv) neat, r.t. \\
&\text{R}_1 \quad \text{R}_2 \\
&\text{OH} \\
&\text{24-87% yield 14-99% ee}
\end{align*}
\]

JACS, 2016, 138, 6940.

3. Activation of borane and transformations

In 2015, Wang et al. reported 1,4-Hydroboration of Pyridines via FLP

The reduction of unsubstituted pyridine with FLPs has not been achieved. This could be due to the lack of steric protection around the nitrogen atom of pyridine, which can coordinate to the Lewis acid of FLPs and deactivate the catalysts.

\[
\begin{align*}
&\text{ArF}_2\text{BF} \quad \text{MeMgBr} \\
&\text{tolune/Et}_2\text{O 25 °C} \\
&\text{ArF}_2\text{BMe} + 1 \\
&\text{ArF} = \text{3-F} \quad \text{CF}_3 \\
&\text{F}_3\text{C} \\
&\text{F}_3\text{C} \\
&\text{F}_3\text{C} \\
&\text{F}_3\text{C} \\
&\text{F}_3\text{C}
\end{align*}
\]

JACS, 2015, 137, 4910.

In 2017, Oestreicher and Melen reported borylative reduction of imine, respectively.

\[
\begin{align*}
&\text{N} \quad \text{R}^3 \\
&\text{R}_1 \quad \text{R}_2 \\
&\text{1 (10 mol%) HBPin (1.0 eq.)} \\
&\text{C}_6\text{D}_6 \text{or toluene 25 °C, 16 h} \\
&\text{40-93% yield}
\end{align*}
\]

OM, 2017, 36, 2381; CEJ, 2017, 23, 10997
4. Activation of C-H bond and transformations

4.1 Examples on stoichiometric C-H bonds activation

In 2009, Stephan et al. reported the stoichiometric cleavage of a terminal Csp-H bond by a mixture of P(tBu)_3 and B(C_6F_5)_3.

\[
\text{B(C}_6\text{F}_5\text{)}_3 + \text{Base} + \underset{\text{R}}{\text{H}} \rightarrow \left[ \frac{\text{Base-H}}{\text{B(C}_6\text{F}_5\text{)}_3} \right]
\]

**Base** = tBu_3P, PhNMe_2, 2,6-lutidine, 2,2,6,6-tetramethylpiperidine

*C(Sp^3)-H bond*

\[
\begin{array}{c}
\text{Ph} \\
\text{Ph} \\
\text{Ph} \\
\text{Ph}
\end{array} 
\rightarrow 
\begin{array}{c}
\text{Ph} \\
\text{Ph} \\
\text{Ph} \\
\text{Ph}
\end{array} + 2\text{[B(C}_6\text{F}_5\text{)}_4]
\]

**JACS, 2015, 137, 7298**

4.2 FLP-catalyzed C-H bonds activation and borylation

In 2015, Fontaine et al. reported C-H bond borylation of heteroarenes via FLP catalysis. It represents the first example of FLP-catalyzed C-H bond activation.

\[
\text{E = NR; S; O}
\]

**JACS, 2016, 138, 4860**

**JACS, 2017, 139, 14714**

**Science 2015, 349, 513**
5. Other catalytic transformation

5.1 Hydroamination

In 2013, Stephan et al. reported Frustrated Lewis Pair catalyzed hydroamination of terminal alkynes

\[
\begin{align*}
\text{PhNH} + \text{R'\text{-}C\equiv C\text{-}R} & \xrightarrow{\text{B(C}_6\text{F}_5)_3 (10 \text{ mol\%})} \text{R-NH} - \text{R'} \\
\text{[PhCCB(C}_6\text{F}_5)_3] \quad & \text{1} \\
\end{align*}
\]

52-84% yield

5.2 Difunctionalization of Alkenes

In 2016, Czekelius et al. reported perfluoroalkylation of alkenes by Frustrated Lewis Pairs

\[
\begin{align*}
\text{B(C}_6\text{F}_5)_3 & + \text{P}^t\text{Bu}_3 \xrightarrow{\text{R}_t\text{-I (4)}} \text{Bu}^+\text{Bu}^+ \quad \text{[C}_6\text{F}_5\text{C}_6\text{F}_5] \\
\text{CH}_2\text{Cl}_2, \text{r.t.} & \text{3} \\
\end{align*}
\]

<table>
<thead>
<tr>
<th>Entry</th>
<th>R_t-I</th>
<th>Time</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>F_3C—I (4a)</td>
<td>20 min</td>
<td>65</td>
</tr>
<tr>
<td>2</td>
<td>C_4F_9—I (4b)</td>
<td>24 h</td>
<td>62</td>
</tr>
<tr>
<td>3</td>
<td>C_6F_17—I (4c)</td>
<td>24 h</td>
<td>54</td>
</tr>
<tr>
<td>4</td>
<td>C_4F_9—C—CF_3 (4d)</td>
<td>20 min</td>
<td>85</td>
</tr>
<tr>
<td>5</td>
<td>C_6F_11—I (4e)</td>
<td>60 min</td>
<td>75</td>
</tr>
<tr>
<td>6</td>
<td>C_6F_5CF_2—I (4f)</td>
<td>30 min</td>
<td>70</td>
</tr>
</tbody>
</table>

Catalytic C-H bond functionalization

Functionalization of carbon carbon multiple bonds

Asymmetric catalytic transformation

Catalytic usage of CO_2, CO etc.