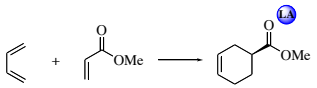
ISCHIA ADVANCED SCHOOL OF ORGANIC CHEMISTRY

Dual Activation in Enantioselective Synthesis of Cyanohydrins

Christina Moberg

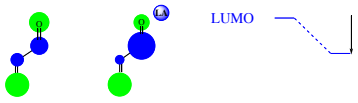
Lewis acid activation

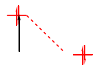
Lewis base activation

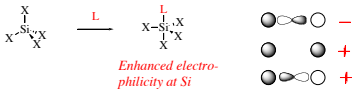


"Lewis base catalysis is the process by which an electron-pair donor increases the rate of a given reaction by interacting with an acceptor atom in one of the reagents or substrates. The binding event may enhance either the electrophilic or nucleophilic character of the bound species. Furthermore, the Lewis base should not be consumed or altered during the course of the reaction - a hallmark of any catalytic process."

S.E. Denmark and G. L. Beutner, *Angew. Chem. Int. Ed.* **2008**, *47*, 1560.

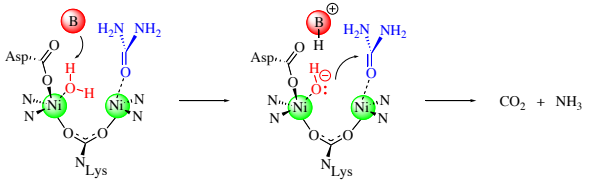






Enhanced electrophilicity at Si

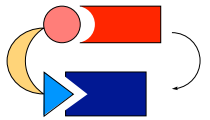
Biocatalysis



rate enhancement: 10^{14}

Synthetic systems

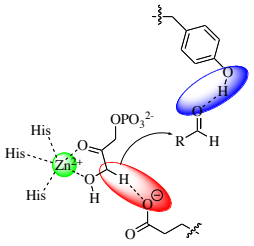
Lewis or Brønsted base



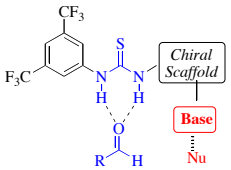
Lewis acid

Shibasaki, M.; Kanai, M. *Chem. Pharm. Bull.* **2001**, *49*, 511-525
Kanemasa, S.; Ito, K. *Eur. J. Org. Chem.* **2004**, 4741-4753
Ma, J.-A.; Cahard, D. *Angew. Chem. Int. Ed.* **2004**, 43, 4566-4583
Kanai, M.; Kato, N.; Ichikawa, E.; Shibasaki, M. *Synlett* **2005**, 1491-1508

Enzyme catalysis

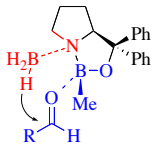


Organocatalysis

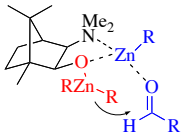


Early examples

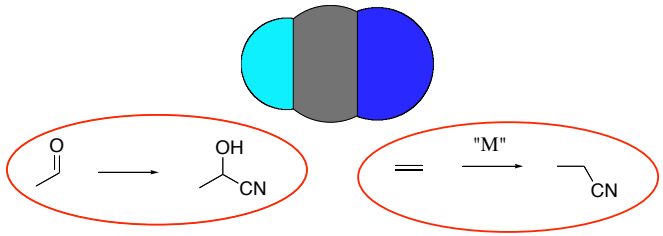
Corey's oxazaborolidine



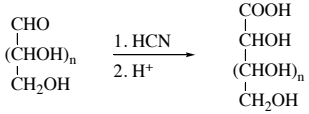
Noyori's dialkylzinc



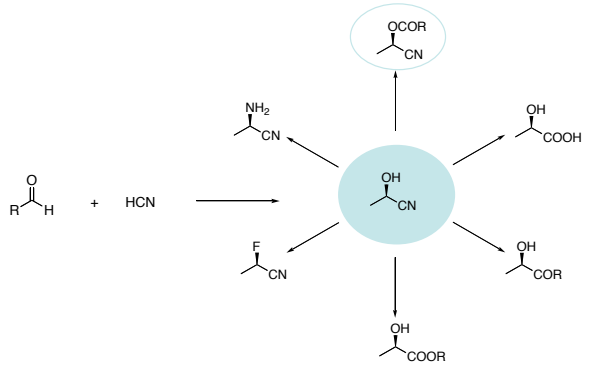
HCN



Carbohydrate elongation



The adiponitrile process



- *HCN first prepared in 1782 by C. W. Scheele*
- *Versatile synthetic route to cyanohydrins known for more than 100 years*
- *First asymmetric cyanation made by Rosenthaler in 1908*
- *Metal catalysts affording highly enantioenriched products known today*

Carl Wilhelm Scheele
(1742-1786)

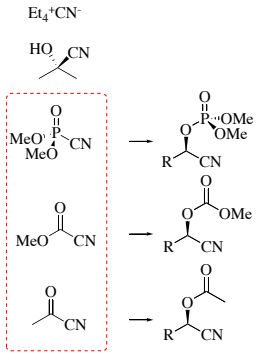
Mowry, D. T., *Chem. Rev.* **1948**, *42*, 189
Rosenthaler, L., *Biochem. Z.* **1908**, *14*, 238
North, M., *Tetrahedron: Asymmetry*, **2003**, *14*, 147
Brunel, J.-M.; Holmes, I. P. *Angew. Chem. Int. Ed.* **2004**, *43*, 2752

TMSCN as cyanide source

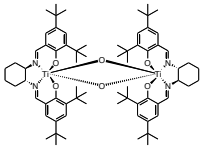
+ Easy to handle in lab
+ TMS-protected cyanohydrins prepared directly,
+ prevents racemization:

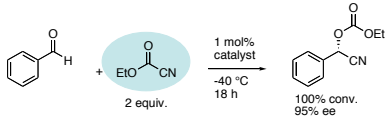
- Labile
- Expensive
- Volatile, highly toxic and flammable

Other sources



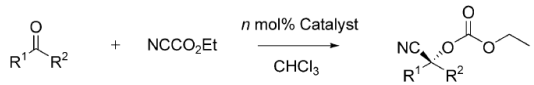
Lewis acid catalysis-Ti-salen catalyst





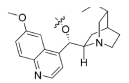
Belokon, Y. N; Blacker, A. J.; Clutterbuck, L. A.; North, M. *Org. Lett.*, **2003**, *5*, 4505

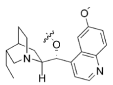
Base Catalysed Additons to Ketones

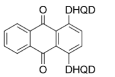


Natural and modified cinchona alkaloids

Several days reaction times


DHQD


DHQ

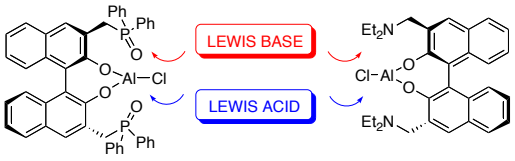


$(DHQD)_2AQN$

DHQD-PHN

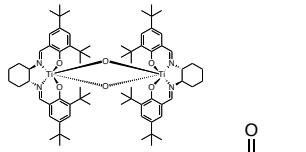
S.-K. Tian, L. Deng, *J. Am. Chem. Soc.* **2001**, *123*, 6195-6196

Dual Activation



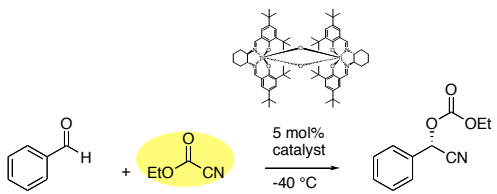
Y. Hamashima, D. Sawada, M. Kanai, M. Shibasaki, *J. Am. Chem. Soc.* **1999**, *121*, 2641

J. Casas, A. Baeza, J. M. Sansano, C. Nájera, J. M. Saá, *Tetrahedron: Asymmetry* **2003**, *14*, 197

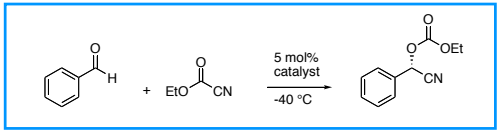


18 h

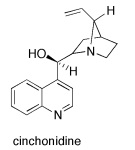
Will Lewis Acid - Lewis Base Catalysis increase the reactivity?

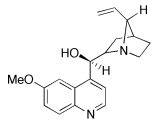


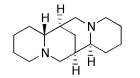
Base	*time (h)*	*yield*	*ee (%)*
-	18	100	95
Et_3N, 10%	3	97	92



Base	time(h)	yield	ee(%)
DMAP	7	99	93
DABCO	7	90	90
Et_3N	3	97	92
EtN^iPr_2	3	96	89
Cinchonidine	4	98	94
Quinine	4	93	93
Sparteine	3	98	78

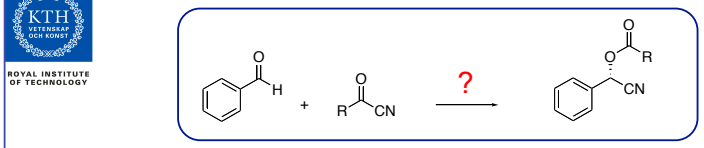

cinchonidine

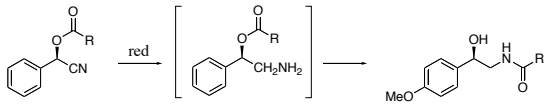

quinine

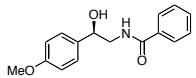

sparteine

Aldehyde	time (h)	yield isolated	ee (%)
Benzaldehyde	4	95	92
Pivalaldehyde	6	81	73
Valeraldehyde	6	78	87
p-MeO-benzaldehyde	7	79	94
p-Cl-benzaldehyde	3	90	92
t-cinnemaldehyde	7	97	94

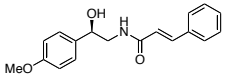
(*R*,*R*)-Salen-Ti + Et_3N -40 °C





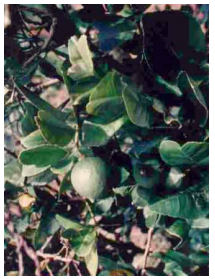


(*R*)-tembamide



(*R*)-aegeline

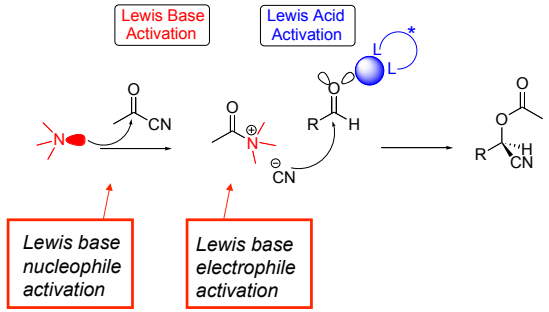
traditional indian medicines with hypoglycemic activity

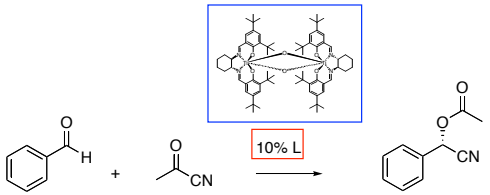


Aegle marmelos

L. Veum, S. R. M. Pereira, J. C. van der Waal, U. Hanefeld, *Eur. J. Org. Chem.* **2006**, 1664-1671.

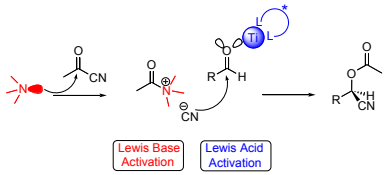
Dual Activation





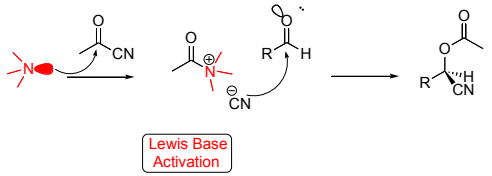
L	*time (h)*	*yield*	*ee (%)*	
-	24	0	-	
DABCO	9	67	92	
Et_3N	8	96	94	
Sparteine	8	93	65	
Cinchonidine	9	78	96	
Sparteine	8	96	-67	(*ent*-complex)
Cinchonidine	9	75	-92	(*ent*-complex)

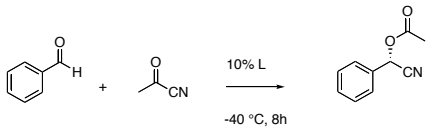
S. Lundgren, E. Wingstrand, M. Penhoat, C. Moberg, *J. Am. Chem. Soc.* **2005**, *127*



Aldehyde	*time (h)*	*yield isolated (%)*	*ee (%)*
Benzaldehyde	10	89	94
Pivalaldehyde	6	84	76
Valeraldehyde	6	89	90
p-Me-benzaldehyde	10	90	96
p-MeO-benzaldehyde	12	72	94
p-Cl-benzaldehyde	8	89	95
(*E*)-cinnemaldehyde	12	64	93

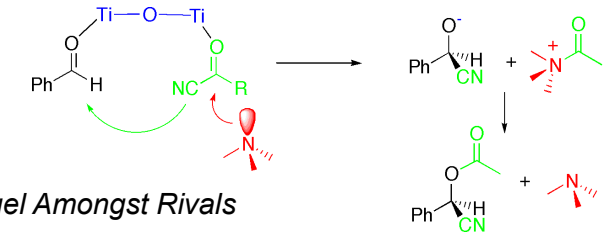
S. Lundgren, E. Wingstrand, M. Penhoat, C. Moberg, *J. Am. Chem. Soc*. **2005**, *127*, 11592-11593.



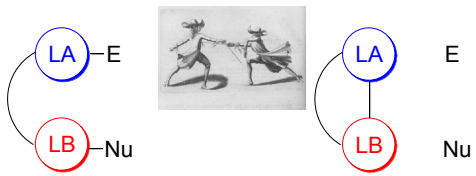


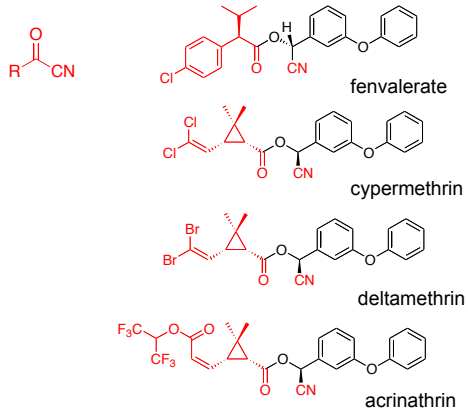
L	*yield*	*ee (%)*
DABCO	<1	-
Et_3N	13	-
Sparteine	23	0
Cinchonidine	9	40

Dual Activation

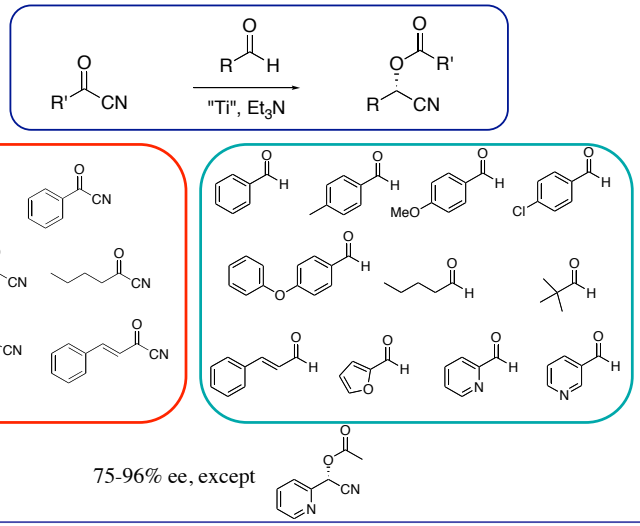


A Duel Amongst Rivals



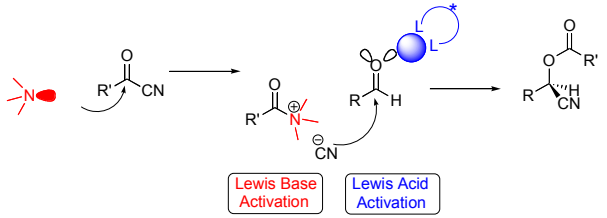


Results



75-96% ee, except

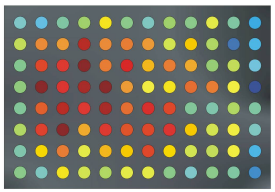
Dual Activation



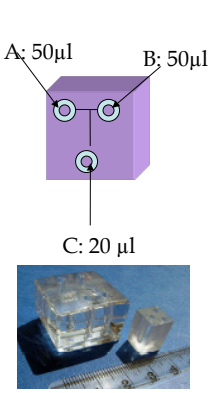
High Throughput Screening

- *Increase reactivity of the system*
- *Increase selectivty of the system*

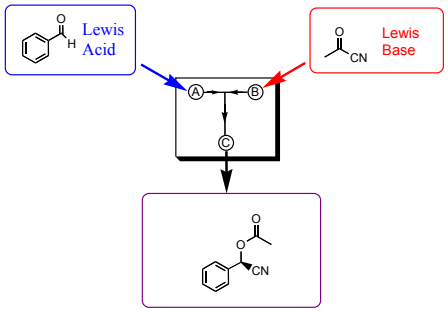
Lewis Bases



Lewis Acids



S Haswell, Hull

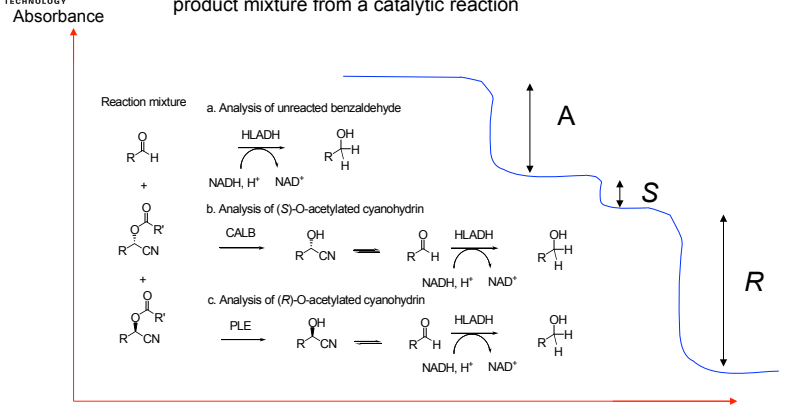


Channel dimensions of
100*50 µm
Flow: 1 µl/ min
Pressure driven flow

Up to 92% conversion and 80% ee

Enzymatic method for determining enantiomeric excess

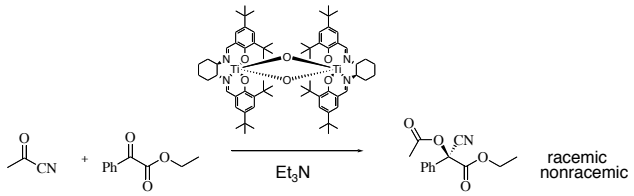
Principle: Selectively process one of the enantiomers of a product mixture from a catalytic reaction



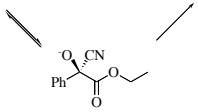
A. Hamberg, S. Lundgren, M. Penhoat, C. Moberg, K. Hult, *J. Am. Chem. Soc.* **2006**, *128*, 2234-2235

ROYAL INSTITUTE OF TECHNOLOGY

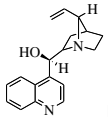
Additons to Ketones



Activated by MeOH



racemic



Dynamic kinetic resolution

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Conclusion

Lewis acid-Lewis base activation is efficient in cyanations of aldehydes with acetyl cyanide and cyanoformate, providing O-functionalized highly enantioenriched cyanohydrins in high yields with perfect atom economy. The conversions and enantioselectivities can be idetermined by an enzymatic high throughput method.