New Strategies for Organocatalysis

IASOC 2006, Ischia, Italy, September 17th 2006



Benjamin List Max-Planck-Institut für Kohlenforschung Mülheim an der Ruhr Germany The ideal chemical process is that which a one-armed operator can perform by pouring the reactants into a bath tub and collecting the product from the drain hole.

-Sir John Cornforth

A Catalysis Dogma

Only Metal Complexes and Enzymes can be Asymmetric Catalysts.



"In a catalytic asymmetric reaction, a small amount of an enantiomerically pure catalyst, either an enzyme or a synthetic, soluble transition metal complex, is used to produce large quantities of an optically active compound from a precursor that may be chiral or achiral."

About Half of all Known Enzymes are Metal-Free

Metal-free Catalysis of the Direct Aldol Reaction in Nature

Class I Aldolases and Catalytic Antibodies



Shibasaki's Direct Asymmetric Aldol Reaction



Shibasaki et al., Angewandte Chemie 1997

Masakatsu Shibasaki

The Hajos-Parrish-Eder-Sauer-Wiechert Reaction





Enamine Mechanism? (Jung, Eschenmoser, Agami)



Wieland-Miescher-Ketone (71% ee)

Hajos, Parrish DE 2102623, July 29, 1971

Eder, Sauer, Wiechert DE 2014757, Oct. 7, 1971

The Proline-Catalyzed Direct Asymmetric Aldol Reaction



Mechanism of the Proline-Catalyzed Aldolization



The Enamine Catalysis Cycle



Other Electrophiles (X=Y)



Enamine Catalysis of Nucleophilic Substitution Reactions

-All previous reactions were nucleophilic additions. Alkylation is first example of a nucleophilic substitution.



Alkylation: Vignola, N.; List, B. *J. Am. Chem. Soc.* **2004**, *126*, 450-451. Chlorination: (a) Brochu, M. P.; Brown, S. P.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2004**, *126*, 4108-4109. (b) Halland, N.; Braunton, A.; Bachmann, S.; Marigo, M.; Jørgensen, K. A. *J. Am. Chem. Soc.* **2004**, *126*, 4790-4791. Fluorination: (c) Beeson, T. D.; MacMillan, D. W. C.; *J. Am. Chem. Soc.* **2005**, *127*, 8826-8828. (d) Steiner, D. D.; Mase, N.; Barbas, C. F., III. *Angew. Chem. Int. Ed.* **2005**, *44*, 3706-3710. (e) Marigo, M.; Fielenbach, D.; Braunton, A.; Kjærsgaard, A.; Jørgensen, K. A. *Angew. Chem. Int. Ed.* **2005**, *44*, 3703-3706. (f) Enders, D.; Hüttl, M. R. M. *Synlett* **2005**, 991-993. Bromination, Iodination: Bertelsen, S.; Halland, N.; Bachmann, S.; Marigo, M.; Braunton, A.; Jørgensen, K. A. *Chem. Comm.* **2005**, 4821-4823. Sulfenylation: Marigo, M.; Wabnitz, T. C.; Fielenbach, D.; Jørgensen, K. A. *Angew. Chem., Int. Ed.* **2005**, *44*, 794.

The First Proline-Catalyzed Asymmetric Mannich-Reaction



Proline-Catalyzed Mannich-Reaction of Aldehydes





Y. Hayashi et al. Angew. Int. 2003, 3677.

70%, dr >95:5, 96% ee

Proline-Catalyzed Mannich-Reaction of Aldehydes



Barbas et al. JACS 2002, 1866.

Anti-Selective Mannich-Reaction of Aldehydes



			catalyst	time			
	R1	R ²	(mol %)	(h)	% yield ^b	anti/syn ^c	% ee ^d
	Me	Et	1	0.5	93	13/1	>99
Γf	Me	Et	0.2	22	82	11/1	97
	Bu	Et	1	4	93	>20/1	99
	Bu	Et	0.5	8	92	>20/1	97
Н	Bn	Et	1	4	92	11/1	>99
	<i>i</i> -Pr	Et	2	0.5	93	>20/1	>99
	t-Bu	Et	5	16	42	>20/1	>99
	<i>i</i> -Pr	allyl	2	0.5	99	16/1	>99
	<i>i</i> -Pr	t-Bu	2	0.5	99	16/1	>99



NH'

Maruoka et al. JACS 2005, 16408.



Would be a powerful reaction for the synthesis of $\beta^{2,3}$ -amino acids



Product precipitates from the reaction mixture!



rac-Proline, rt

(S)-Proline, 0°C



For one example with a ketone, see: Enders et al. Synthesis 2006, 2155





95%, >99:1 er, >99:1 dr

$$[\alpha]_D^{20}$$
 (HCI-salt) = +4.7 (*c* 0.91, H₂O)
lit.⁵ $[\alpha]_D^{25}$ (HCI-salt) = +1.7 (*c* 1.06, H₂O)

Enamine Catalysis



Enantioselective Specific Brønsted Acid Organocatalysis





Akiyama et al. Angew. Chem. Int. Ed. 2004, 1566.





Terada et al. JACS 2004, 5356





In Nature: Pictet-Spenglerases



No chemical direct, catalytic asymmetric Pictet-Spengler reactions have been described



In Chemistry: Acyl-Iminium Ion Pictet-Spengler Reaction



Jacobsen et al. JACS 2004, 10558.













3,3'-bis-(2,4,6-tris-isopropylphenyl)-1,1-binaphthyl hydrogen phosphate (*TRIP*)

With Jayasree and Abdul Seayad JACS 2006, 1086-1087.

Brønsted Acid-Catalyzed Reductive Amination



Brønsted Acid-Catalyst Screening





Hoffmann, Seayad Angew. Int. 2005, 7424.



Rüping et al. *OL* **2005**, 3781;

Extension to Aldehydes



Dynamic Kinetic Resolution







Sebastian Hoffmann, Marcello Nicoletti



Hydrogenation in Nature



Concept of an Organocatalytic Conjugate Reduction of α , β -Unsaturated Aldehydes



A Metal-Free Transfer Hydrogenation of α , β -Unsaturated Aldehydes





Jung Woon Yang

List et al. *Angew. Int.* **2004**, 6660. (Highlighted in *Nature, Angew.*, and *C&EN*)

Organocatalytic Conjugate Reduction of α , β -Unsaturated Aldehydes

-A Metal-Free Catalytic Asymmetric Transfer Hydrogenation





Developing a new Strategy for Asymmetric Catalysis



Asymmetric Brønsted Acid Catalysis

Asymmetric, Counteranion-Directed Catalysis

Asymmetric Brønsted acid catalysis may be a special case of a far more general catalysis strategy: Asymmetric, Counteranion-Directed Catalysis (ACDC)

Asymmetric, Counteranion Directed Catalysis: Previous Attempts



Other attempts by A. Nelson and A. Pfaltz



Asymmetric, Counteranion-Directed Catalysis: Application to Iminium Catalysis







Asymmetric, Counteranion-Directed Catalysis: Results





Asymmetric, Counteranion-Directed Catalysis: Citral



Asymmetric, Counteranion-Directed Catalysis: Ketone Substrates









<30%, <57:43 er



40%, 75:25 er



Asymmetric, Counteranion-Directed Catalysis: Ketone Substrates

	Catalyst-Cation	-Anion	Conv. [%]	er	
CO2Et Catalyst salt (20 mol%)	⁺ NH ₃	CF ₃ COO	23	75:25	
H 1,4-dioxane, H 60°C, 48 h	i-Pr CO₂ <i>t</i> -Bu	CF ₃ COO ⁻	66	77:23	
	⁺ NH₃ [±] t-Bu CO₂t-Bu	CF ₃ COO ⁻	72	76:24	
i_Dr	[⁺] NH ₃ [¯] <i>t-</i> Bu ⊂CO ₂ Me	CF₃COO [−]	42	64:36	
<i>i</i> -Pr	⁺ NH₃ <i>i-</i> Pr ́CO₂ <i>t</i> -Bu		25	87:13	in Bu ₂ O
$P = H_3 N CO_2 t$ -Bu	⁺ №H ₃ <i>i-</i> Pr CO ₂ <i>t-</i> Bu	R = Ph R = 2,4,6-(<i>i</i> -Pr) ₃ C ₆ H ₂	14	95:5	
<i>i</i> -Pr <i>i</i> -Pr	<i>i</i> -Pr CO ₂ <i>t</i> -Bu	$R = 2,4,6-(i-Pr)_3C_6H_2$	81	97:3	in Bu ₂ O
<i>i</i> -Pr	[†] NH₃ └────────────────────────────────────	$R = 2,4,6-(i-Pr)_3C_6H_2$	66	74:26	
<i>ì</i> -Pr	H ⁺ R	$R = 2,4,6-(i-Pr)_3C_6H_2$	5	40:60	in Bu ₂ O
	⁺ NH ₃ [¯] <i>i</i> -Pr ∕⊂CO ₂ <i>t</i> -Bu	$z = 2,4,6-(i-Pr)_3C_6H_2$ (S)-Enantiomer	45	58:42	in Bu ₂ O

Highly Enantioselective Transferhydrogenation of Enones



Acknowledgement

Peter Pojarliev Chris Castello Wolfgang Notz Harry Martin James Turner Jon McDunn Linh Hoang David Goldsheft Chandrakala Pidathala

Nicola Vignola

Arno Döhring Maria Hechavarria Fonseca Sebastian Hoffmann Jung Woon Yang Jayasree Seayad Abdul Seayad Inge Sander Ramon Rios Torres David Monge Fernández Lidia Ozores Viturro Michael Stadler



Nolwenn Martin Sonja Mayer Hendrik van Thienen Kathrin Wobser Xingwang Wang Jian Zhou Daniela Kampen Subhas Chandra Pan Marcello Nicoletti Xiaoguang Li Xu Cheng Corrina Reisinger Roba Moumne



The National Institutes of Health

Saltigo Wacker Novartis Merck Sanofi-Aventis

Alexander von Humboldt-Stiftung DFG Max-Planck-Gesellschaft Fonds der Chemischen Industrie

> Ken Houk Walter Thiel







The Scripps Research Institute





Max-Planck-Institut für Kohlenforschung



