不对称合成
Asymmetric Synthesis

第2次课

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2016年02月24日

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如何实现手性合成?

◆手性合成中的基本概念

◆对映体组成的测定方法

◆如何实现手性合成?

不对称合成

1.5 不对称合成的定义和描述

Asymmetric synthesis **refers to the conversion of an achiral starting material to a chiral product in a chiral environment.**

不对称合成是这样一个过程：在手性环境中，它将非（潜）手性单元转化成手性单元，使得产生不等量的立体异构体。

-Markwald,Morrison,Morsher

如何判断一个成功的不对称反应？

一个成功的不对称反应的标准是：(1) 高的对映体过量(ee%)；(2) 手性辅剂易于制备并能循环使用； (3) 可以制备得到*R*和*S*两种构型（双立体选择性）； (4) 最好是催化性的合成。

光学活性化合物 vs 光学纯化合物

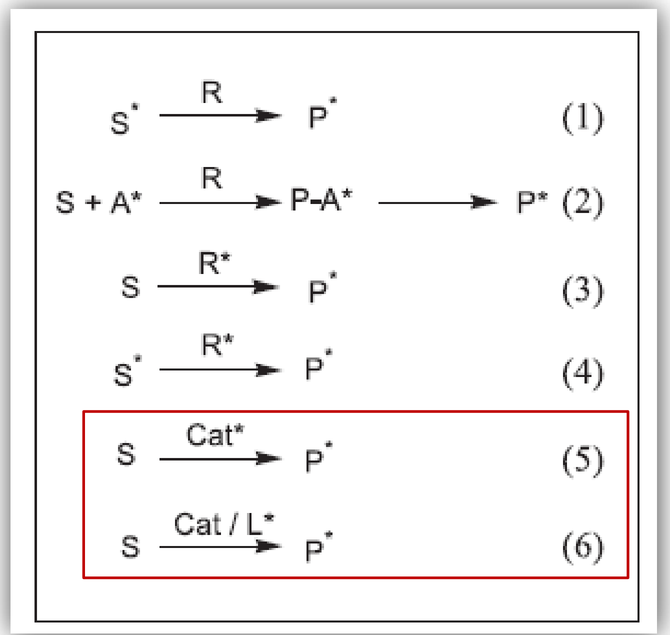
1.6 不对称合成（立体化学控制）总策略

1.6.1 “Chiron” Approaches （“手性子”途径）

(1) 20世纪70年代，外消旋体拆分-经典方法

(2) 天然手性化合物：氨基酸，酒石酸和乳酸，萜类，糖类和生物碱等(廉价手性原料和拆分试剂)

1.6.2 Acyclic Diastereoselective Approaches（开链非对映选择性途径）



（1）底物控制

（2）辅基控制反应

（3）试剂控制法

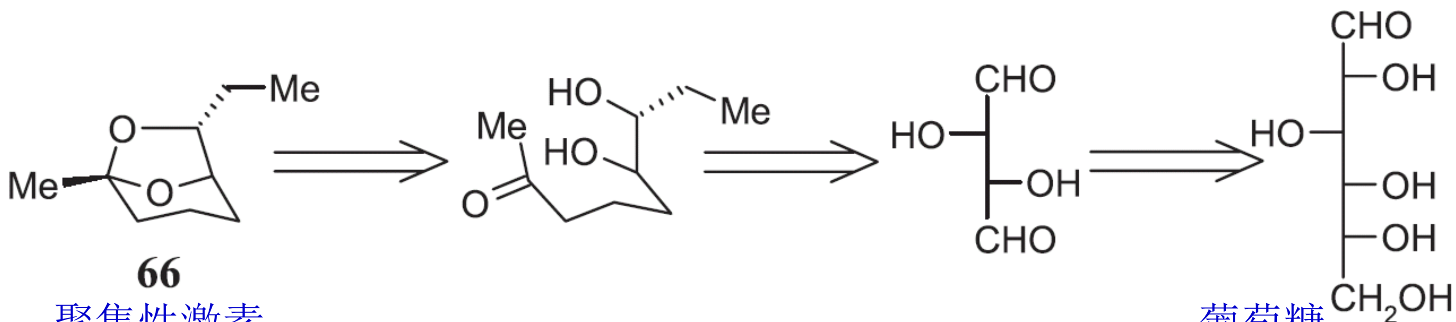
（4）双不对称合成反应

缺点：化学计量的对映体纯化合物

（5，6）不对称催化反应

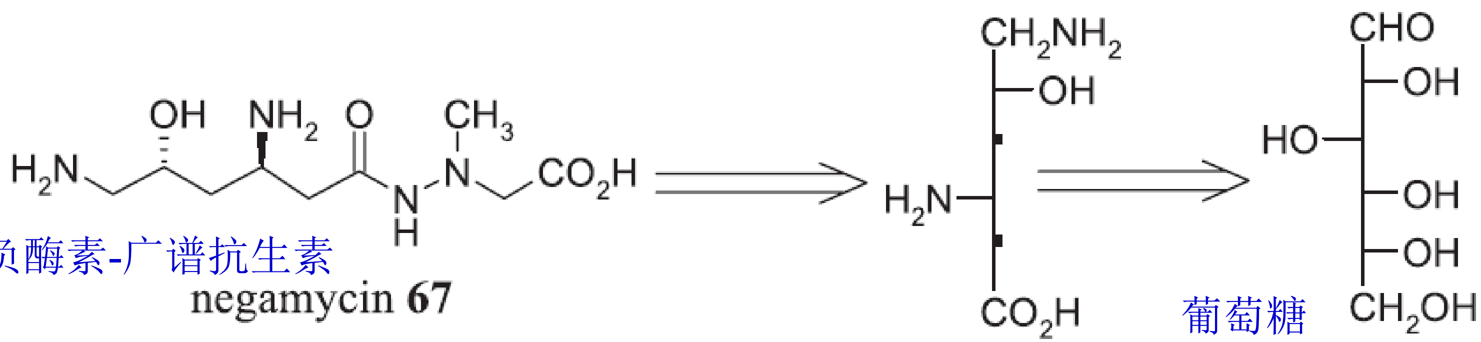
1.6 不对称合成（立体化学控制）总策略-举例

``Chiron" Approaches: Naturally occurring chiral compounds provide an enormous range and diversity of possible starting materials.



66
聚集性激素
葡萄糖

Retro synthesis of (+)-exo-brevicomin *J. Org. Chem.*, **1982**, *47*, 932.



负酶素-广谱抗生素
negamycin **67**
葡萄糖

Retro synthesis of negamycin(负霉素) .

``Chiron'' Approaches

ORGANIC LETTERS

2005
Vol. 7, No. 5
871−874

Lewis Acid Assisted Ring-Closing Metathesis of Chiral Diallylamines: An Efficient Approach to Enantiopure Pyrrolidine Derivatives

Qian Yang,[†] Wen-Jing Xiao,[*,†] and Zhengkun Yu[*,‡]

The Key Laboratory of Pesticide and Chemical Biology, Ministry of Education, College of Chemistry, Central China Normal University, 152 Luoyu Road, Wuhan, Hubei 430079, China, and Dalian Institute of Chemical Physics, Chinese Academy of Sciences, 457 Zhongshan Road, Dalian, Liaoning 116023, China

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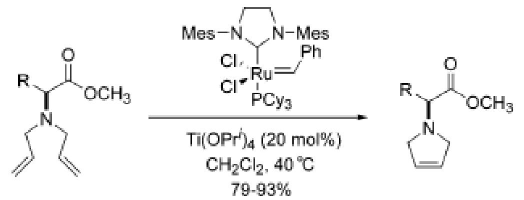
Received December 23, 2004

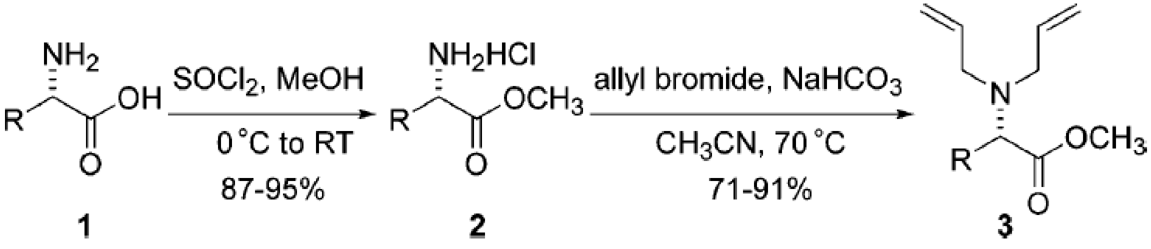
ABSTRACT



Lewis acid assisted ring-closing olefin metathesis (RCM) of chiral diallylamines, using the second generation RCM ruthenium-based catalyst, leads to enantiopure pyrrolidine derivatives in 79–93% yields under very mild conditions. The scope of the olefin metathesis has been expanded.

``Chiron'' Approaches

Scheme 1. Synthesis of Diallylamines



Yang, Q.; Xiao, W. J.; Yu, Z. *Org. Lett.* **2005,** *7*, 871.

``Chiron'' Approaches

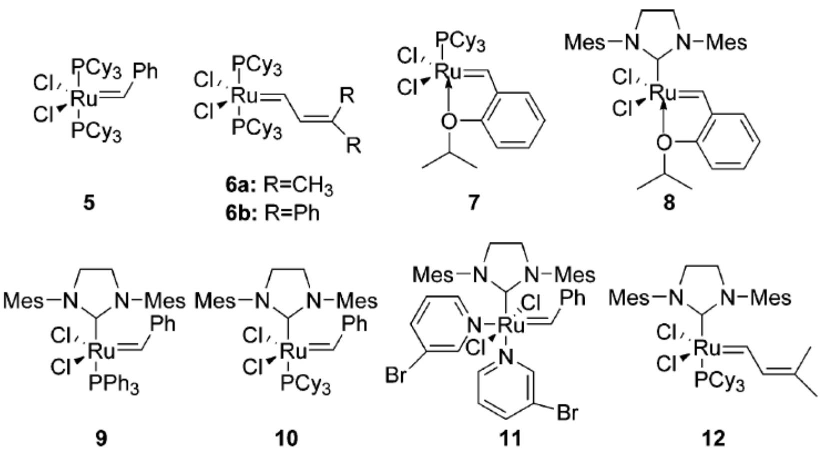
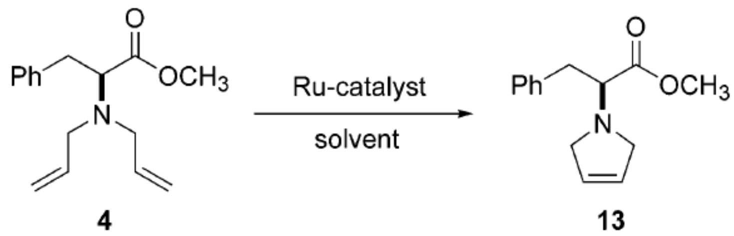


Figure 1. Ruthenium catalysts investigated.

钌卡宾催化剂

Table 1. Ru-Catalyzed RCM Reaction of **4**

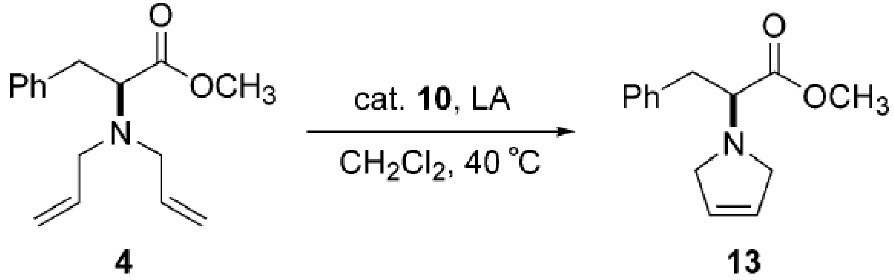


catalyst	solvent	temp (°C)	time (h)	yield of **13** (%)[a]
5 (5 mol %)	CH_2Cl_2	40	48	0
6a (5 mol %)	CH_2Cl_2	40	48	0
7 (5 mol %)	CH_2Cl_2	40	48	0
8 (5 mol %)	CH_2Cl_2	40	48	11
9 (5 mol %)	CH_2Cl_2	40	48	17
10 (5 mol %)	CH_2Cl_2	40	48	24
11 (5 mol %)	CH_2Cl_2	40	48	0
12 (5 mol %)	CH_2Cl_2	40	48	0
10 (15 mol %)	DCE[b]	80	36	27
10 (15 mol %)	toluene	110	12	19

[a] Isolated yield. [b] 1,2-Dichloroethane.

``Chiron'' Approaches

Table 2. RCM Reaction of **4** in the Presence of Lewis Acids[a]

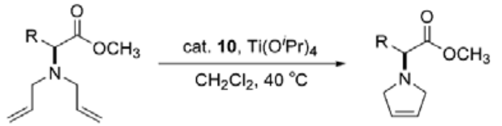


Lewis acid	amount (mol %)	time (h)	yield of **13** (%)
LiI	100	36	53
$AlCl_3$	100	2	0[b]
$La(OTf)_3$[c]	100	2	0[b]
$Ti(O^iPr)_4$	100	2	91
$Ti(O^iPr)_4$	50	5	82
$Ti(O^iPr)_4$	20	6	93

[a] Reaction conditions: **4** (2 mmol), **10** (0.1 mmol), LA (20−100 mol %), 40 °C, CH_2Cl_2 (20 mL). [b] Catalyst decomposed. [c] $La(OTf)_3$: lanthanum(III) trifluoromethanesulfonate.

``Chiron'' Approaches

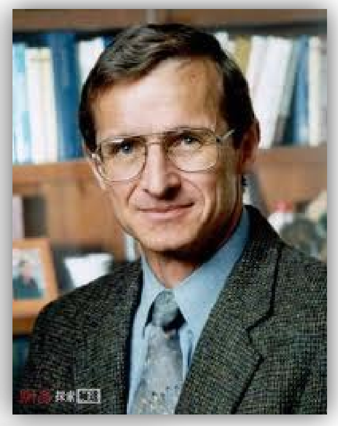
Table 3. Lewis Acid Assisted RCM Reactions[a]



Substrate	time (h)	Product	Yield (%)[b]
4	6	13	93
16	2	17	78[c]
18	4	19	91
20	8	21	82
22	13	23	79
24	4	25	79

[a] Reaction conditions: diallylamines (2 mmol), **10** (0.1 mmol), $Ti(O^iPr)_4$ (20 mol %), 40 °C, CH_2Cl_2 (20 mL), 2−13 h. [b] Isolated yield. [c] Isolated it by making its HCl salt.

2005年诺贝尔化学奖



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Monday, October 17, 2005

Douglass Taber
University of Delaware

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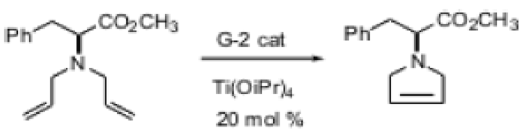
N-Heterocycle Construction by Alkene Metathesis

The first *N*-heterocycles prepared by alkene metathesis were simple five- and six-membered ring amides. Ring-closing metathesis of free amines is much more difficult. The diene **1**, for instance, gave only low yields of cyclization product. Wen-Jing Xiao of Central China Normal University and Zhengkun Yu of the Dalian Institute of Chemical Physics have shown (*Org. Lett.* 2005, *7*, 871. DOI) that precomplexation of 1 with the inexpensive $Ti(O\textit{i}Pr)_4$ ties up the amine, allowing for facile cyclization.



1 **2**

Diastereoselective Approaches

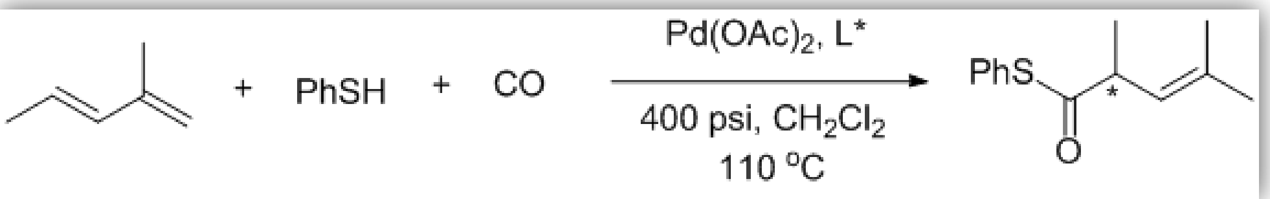
不对称催化反应

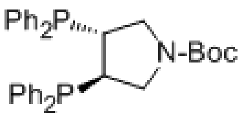
J. Org. Chem. **2001**, *66*, 6229−6233 **6229**

First Examples of Enantioselective Palladium-Catalyzed Thiocarbonylation of Prochiral 1,3-Conjugated Dienes with Thiols and Carbon Monoxide: Efficient Synthesis of Optically Active β,γ-Unsaturated Thiol Esters

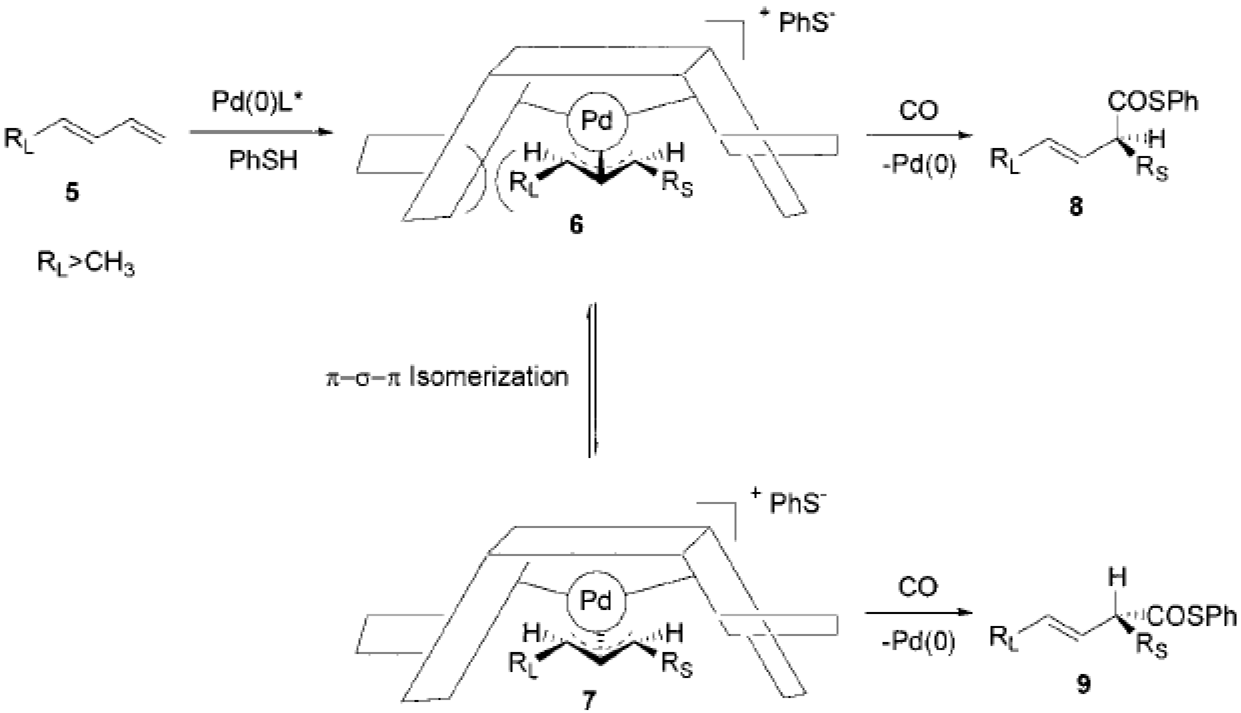
Wen-Jing Xiao and Howard Alper*

Diastereoselective Approaches



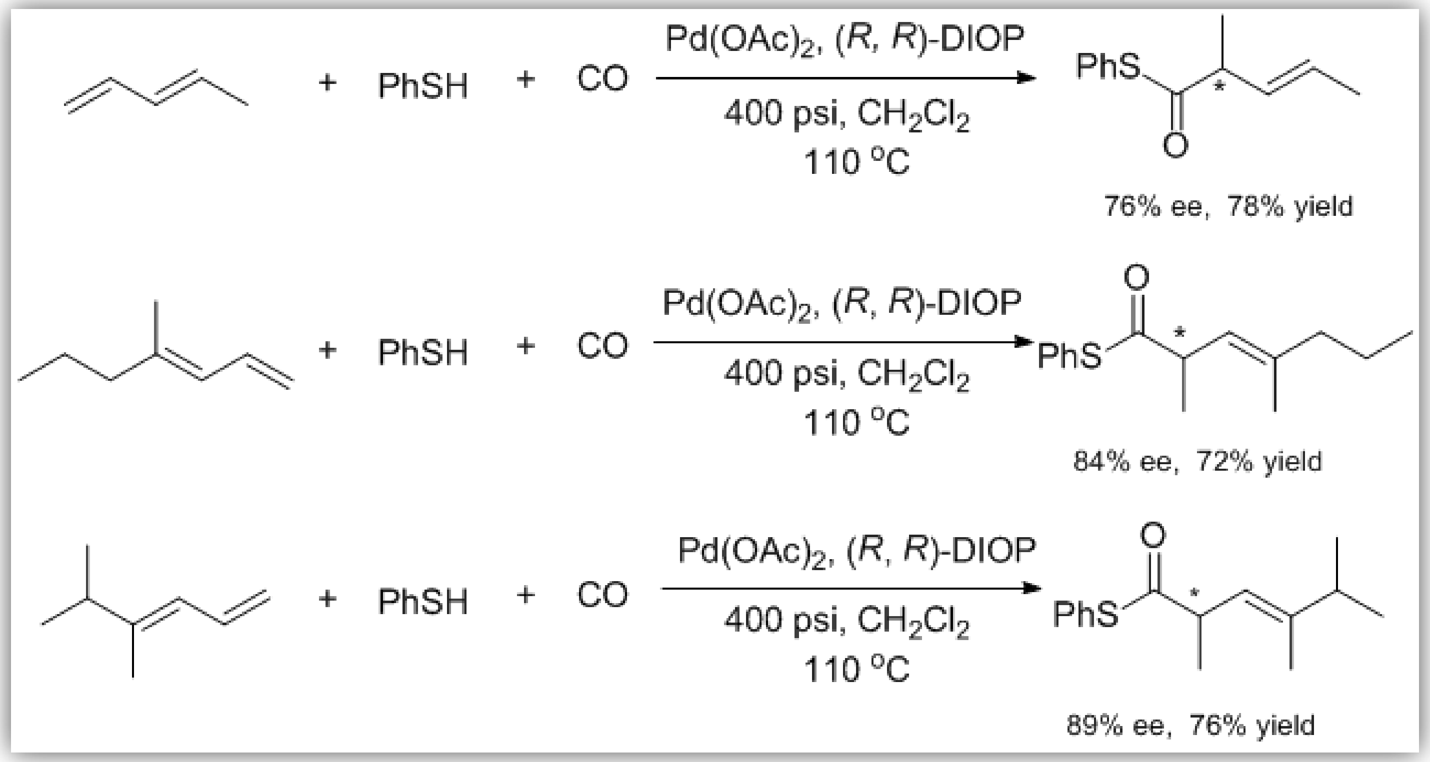
ligand	ee%	yield(%)
R-Tol-BINAP	47	77
R-BINAP	42	56
R-PROPHOS	17	53
S, S-BDPP	76	62
R, R-DIOP	89	71
	56	18

Diastereoselective Approaches



Diastereoselective Approaches

First Examples of Asymmetric Thiocarbonylation



Xiao, W.-J.; Alper, H. *J. Org. Chem*. **2001**, *66*, 6229.

Diastereoselective Approaches

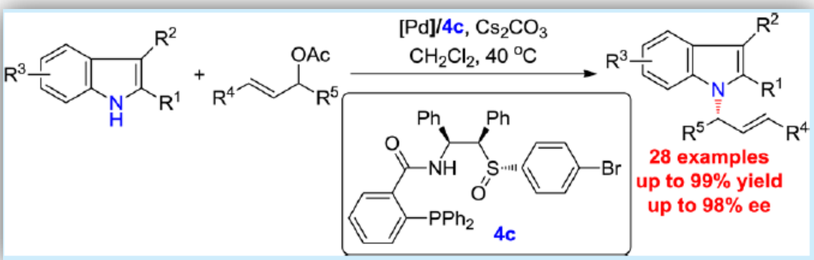
Organic LETTERS

Letter

pubs.acs.org/OrgLett

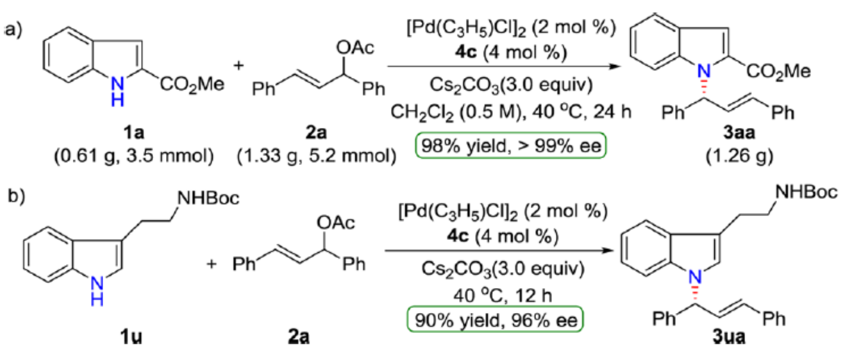
Enantioselective Direct Functionalization of Indoles by Pd/Sulfoxide-Phosphine-Catalyzed *N*-Allylic Alkylation

Li-Yan Chen,[†,§] Xiao-Ye Yu,[†,§] Jia-Rong Chen,[*,†] Bin Feng,[†] Hong Zhang,[†] Ying-Hua Qi,[†] and Wen-Jing Xiao[*,†,‡]



Chen, L.-Y.; Yu, X.-Y.; Chen, J.-R.; Feng, B.; Zhang, H.; Qi, Y.-H.; Xiao, W.-J. *Org. Lett*. **2015**, *17*, 1381-1384.

Scheme 5. Proof of the Synthetic Potential of the Method



Diastereoselective Approaches

Angewandte Communications

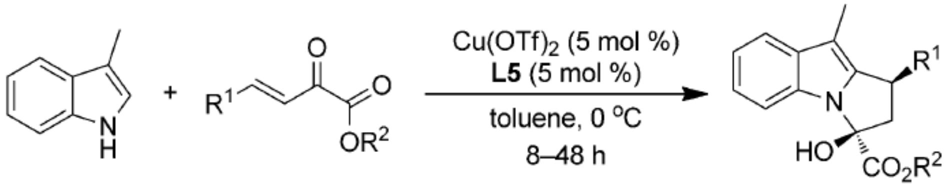
Indole Chemistry

DOI: 10.1002/anie.201209998

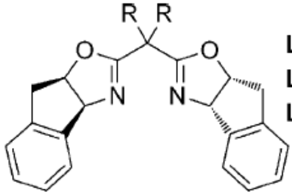
Highly Enantioselective Friedel–Crafts Alkylation/*N*-Hemiacetalization Cascade Reaction with Indoles**

Hong-Gang Cheng, Liang-Qiu Lu, Tao Wang, Qing-Qing Yang, Xiao-Peng Liu, Yang Li, Qiao-Hui Deng, Jia-Rong Chen, and Wen-Jing Xiao**

Table 2: Scope of the β,γ-unsaturated α-ketoesters.[a]



1a + **2** → **3**



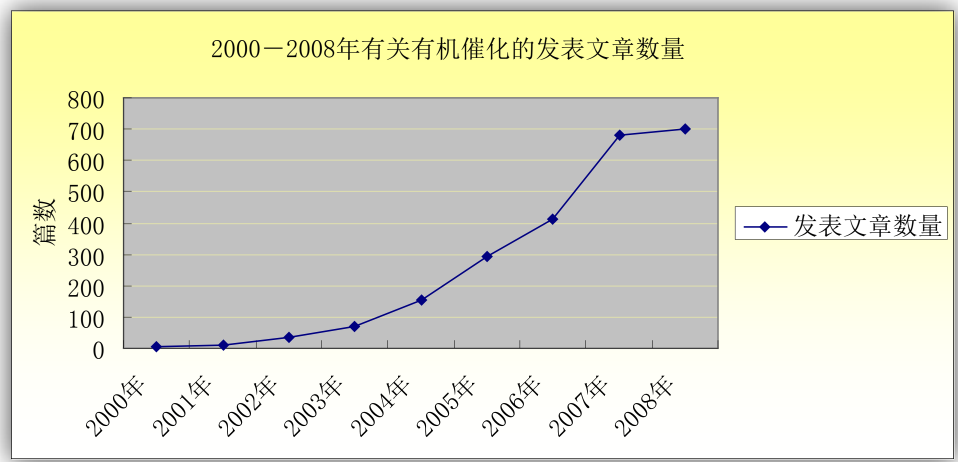
L3, R = Me
L4, R = C_2H_4
L5, R = H

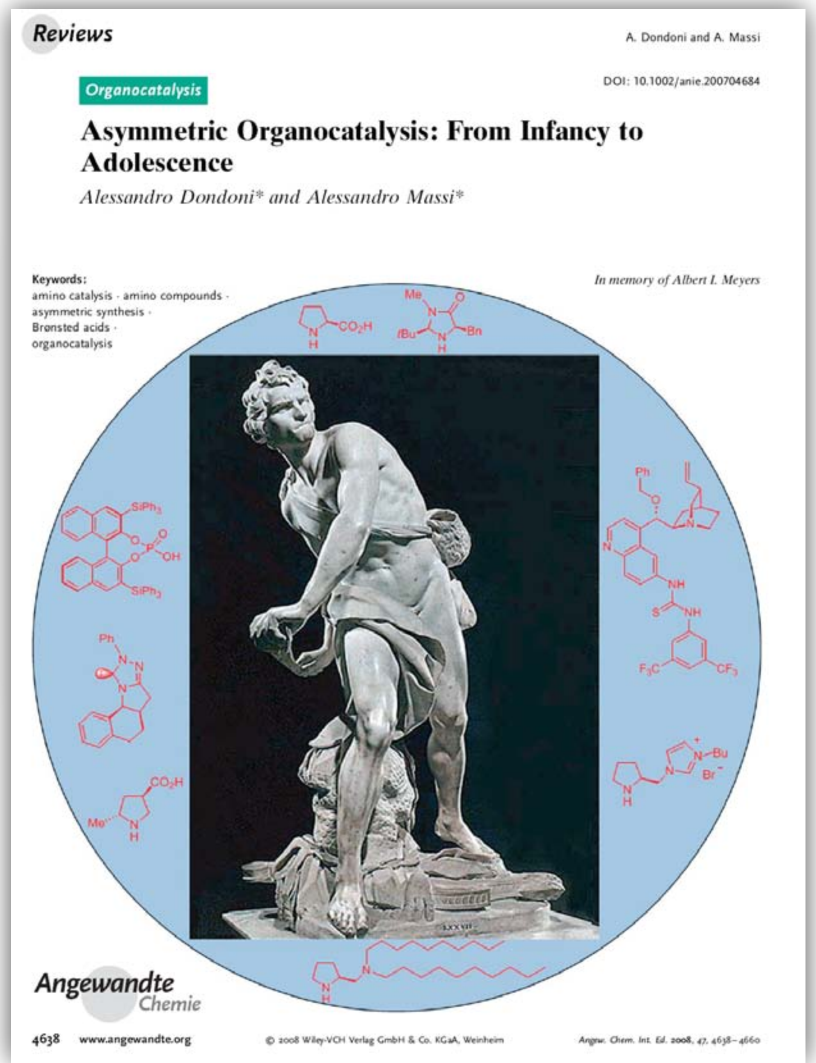
Entry	R^1, R^2	3	Yield [%][b]	d.r.[c]	*ee* [%][c]
1	Ph, Me (**2a**)	**3aa**	95	95:5	>99
2	Ph, Et (**2b**)	**3ab**	93	96:4	>99
3	Ph, Bn (**2c**)	**3ac**	92	95:5	>99
4	Ph, *i*Pr (**2d**)	**3ad**	93	96:4	>99
5	4-MeC_6H_4, Me (**2e**)	**3ae**	96	95:5	>99
6	4-$MeOC_6H_4$, Me (**2f**)	**3af**	95	96:4	>99
7	4-FC_6H_4, Me (**2g**)	**3ag**	95	95:5	>99

Angew. Chem. Int. Ed. **2013**, *52*, 3250.

Diastereoselective Approaches

不对称有机催化





DOI: 10.1002/anie.200704684

Organocatalysis

Asymmetric Organocatalysis: From Infancy to Adolescence

Alessandro Dondoni and Alessandro Massi**

Keywords:
amino catalysis · amino compounds · asymmetric synthesis · Brønsted acids · organocatalysis

In memory of Albert I. Meyers

Angewandte Chemie

Angew. Chem. Int. Ed. **2008**, *47*, 4638.

Diastereoselective Approaches

不对称催化反应 $S \xrightarrow{cat^*} P^*$

ORGANIC LETTERS

2005
Vol. 7, No. 20
4543−4545

Readily Tunable and Bifunctional L-Prolinamide Derivatives: Design and Application in the Direct Enantioselective Aldol Reactions

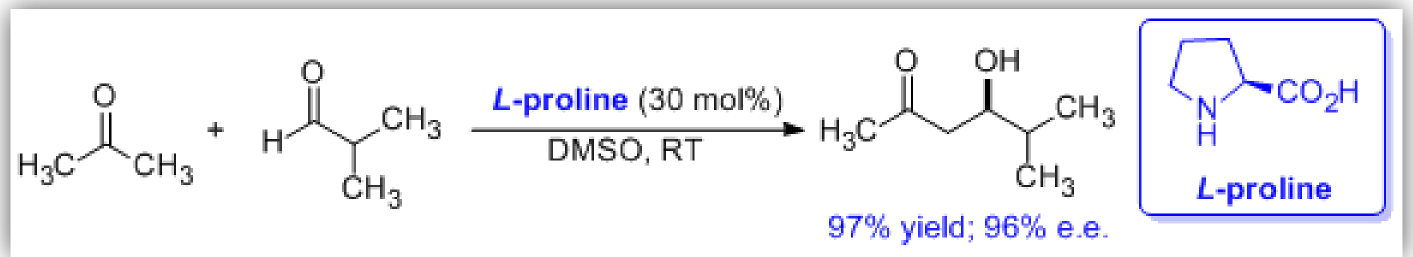
Jia-Rong Chen, Hai-Hua Lu, Xin-Yong Li, Lin Cheng, Jian Wan, and Wen-Jing Xiao*

The Key Laboratory of Pesticide & Chemical Biology, Ministry of Education, College of Chemistry, Central China Normal University, 152 Luoyu Road, Wuhan, Hubei 430079, China

wxiao@mail.ccnu.edu.cn

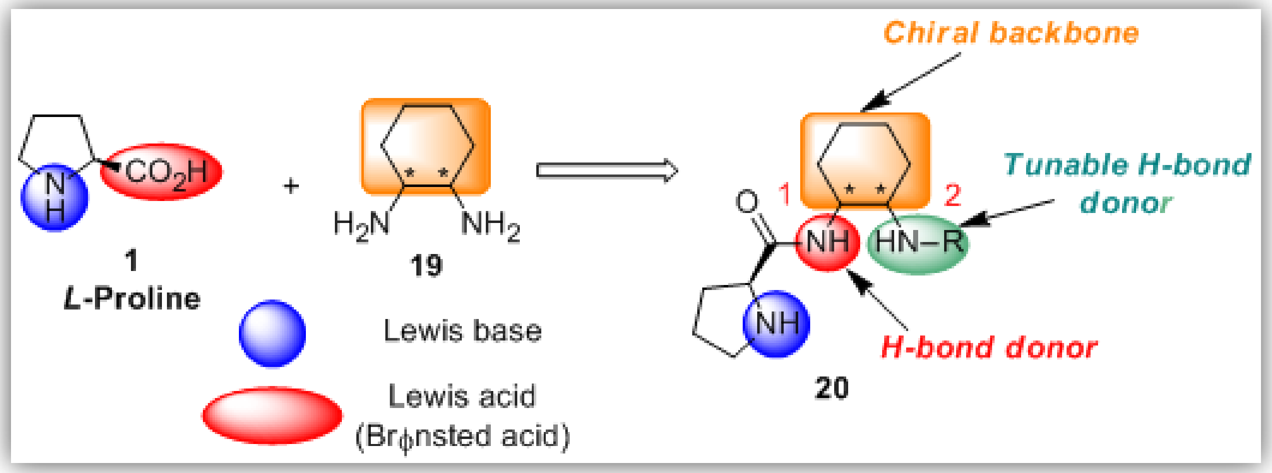
Diastereoselective Approaches

Modern organocatalysis



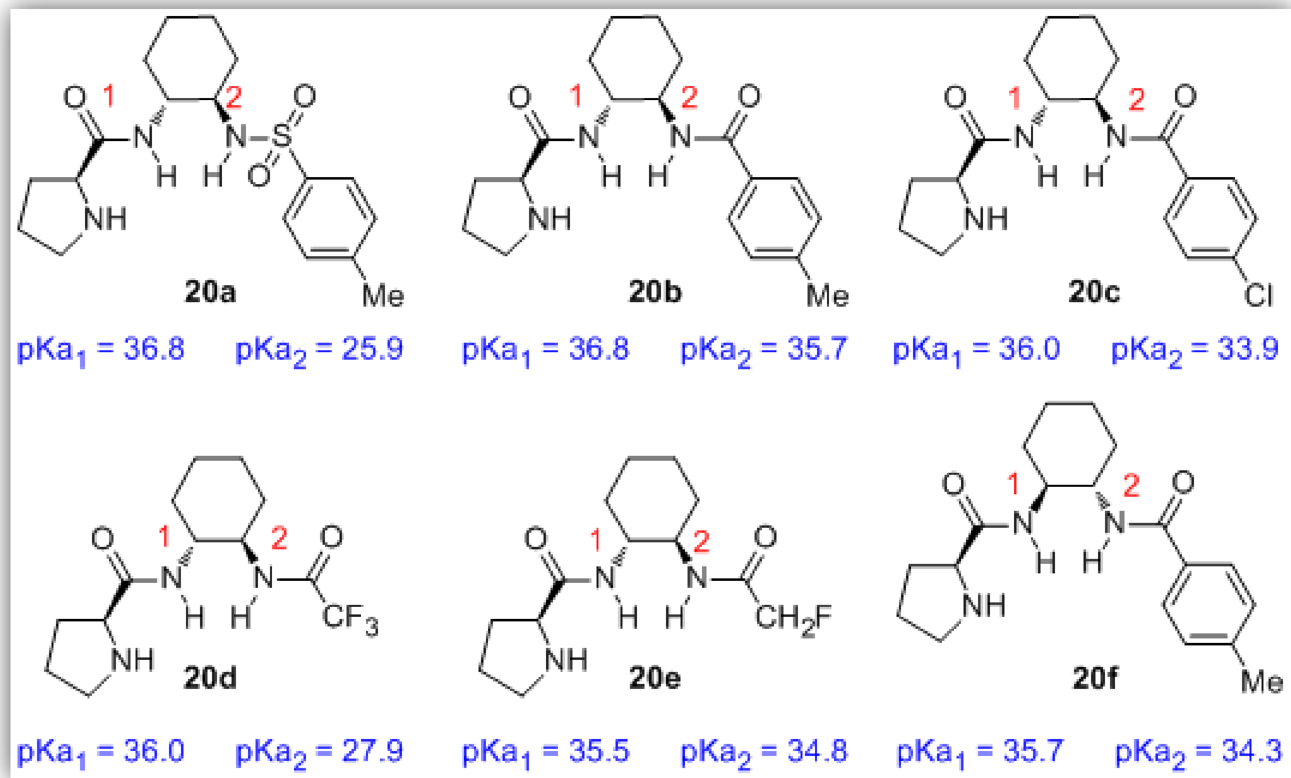
List, Lerner, Barbas, III, *J. Am. Chem. Soc.* **2000**, *122*, 2395.

催化剂设计思路

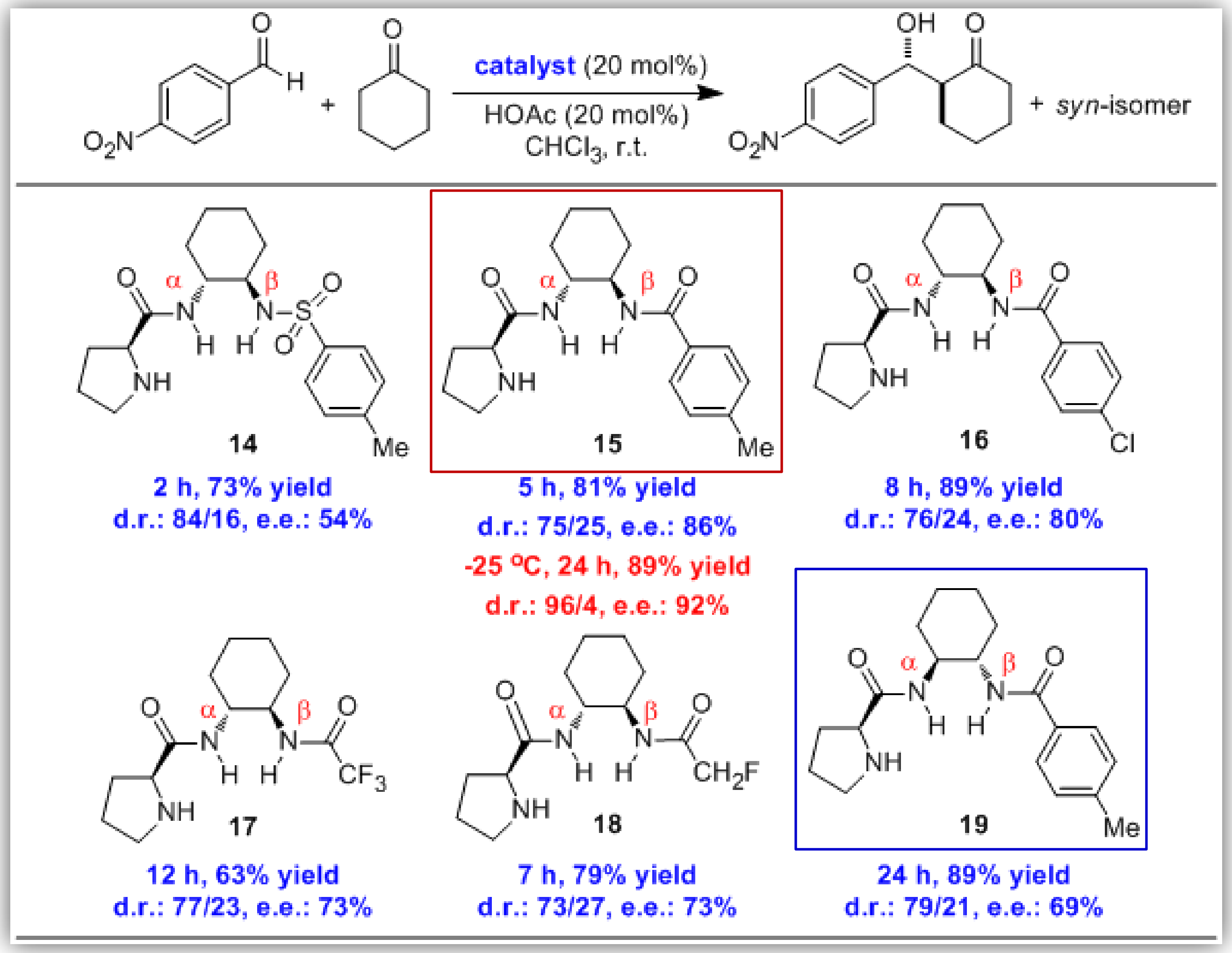


Diastereoselective Approaches

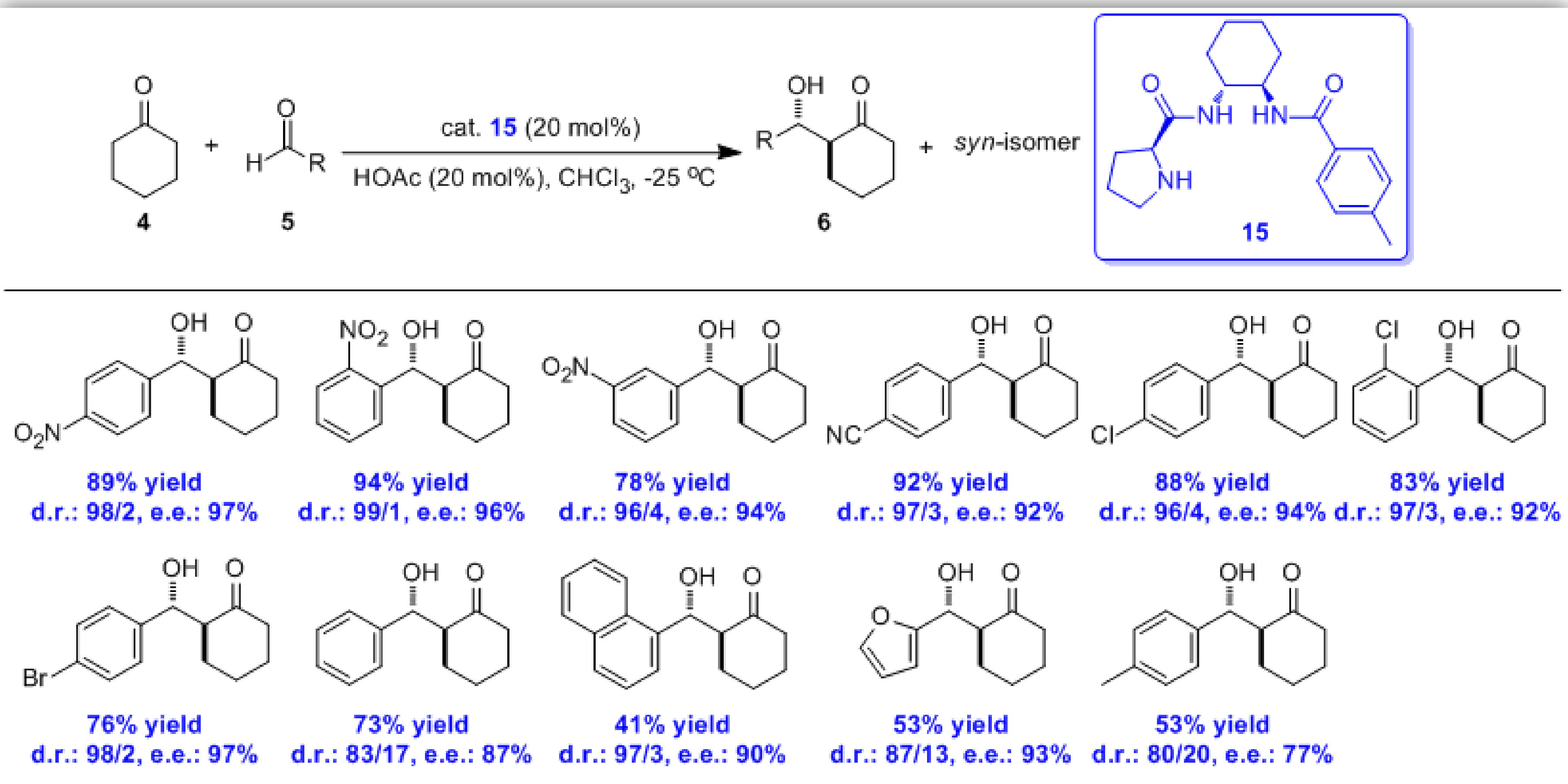
催化剂设计



Condition optimization

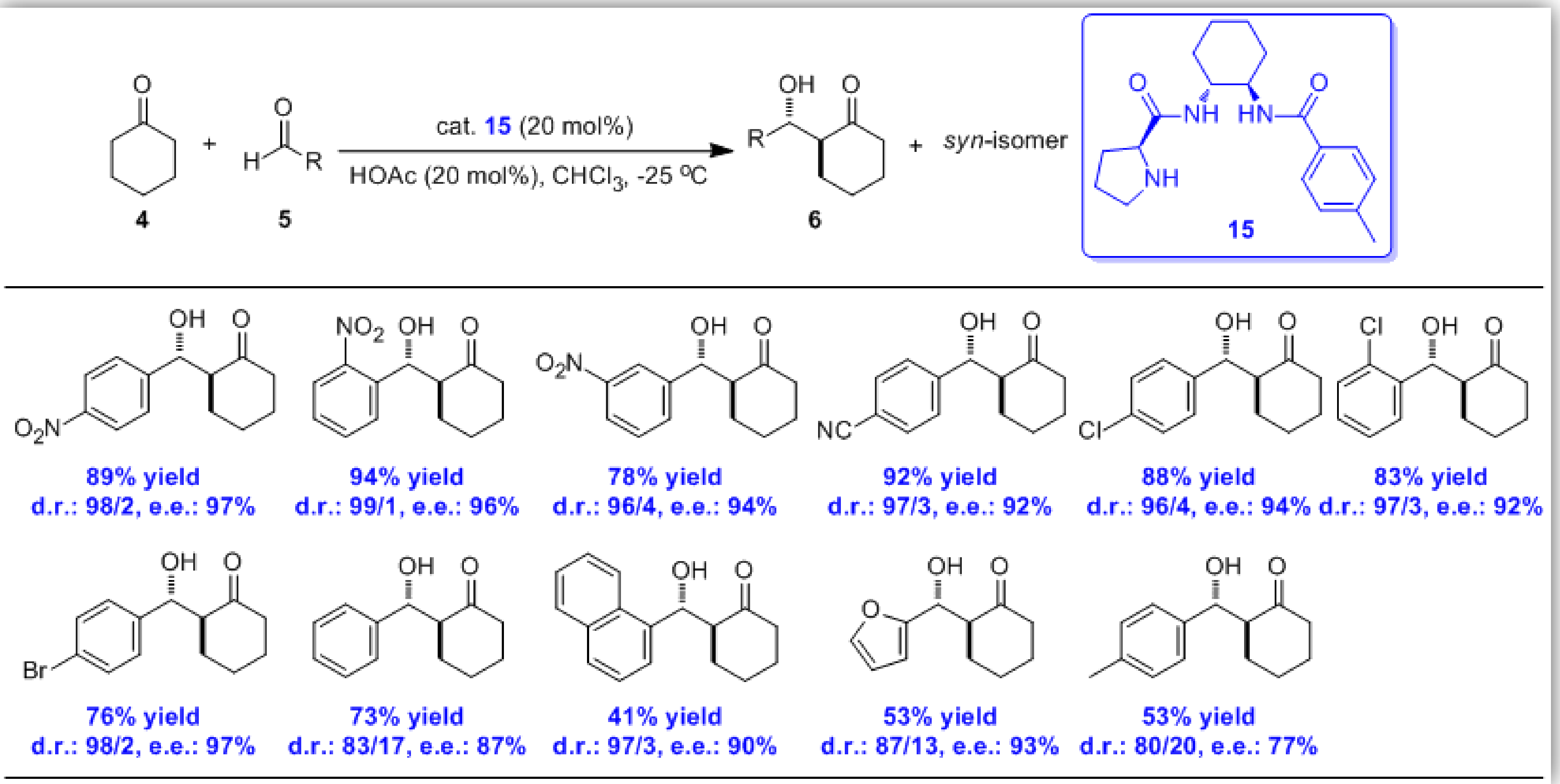


Conditions optimization



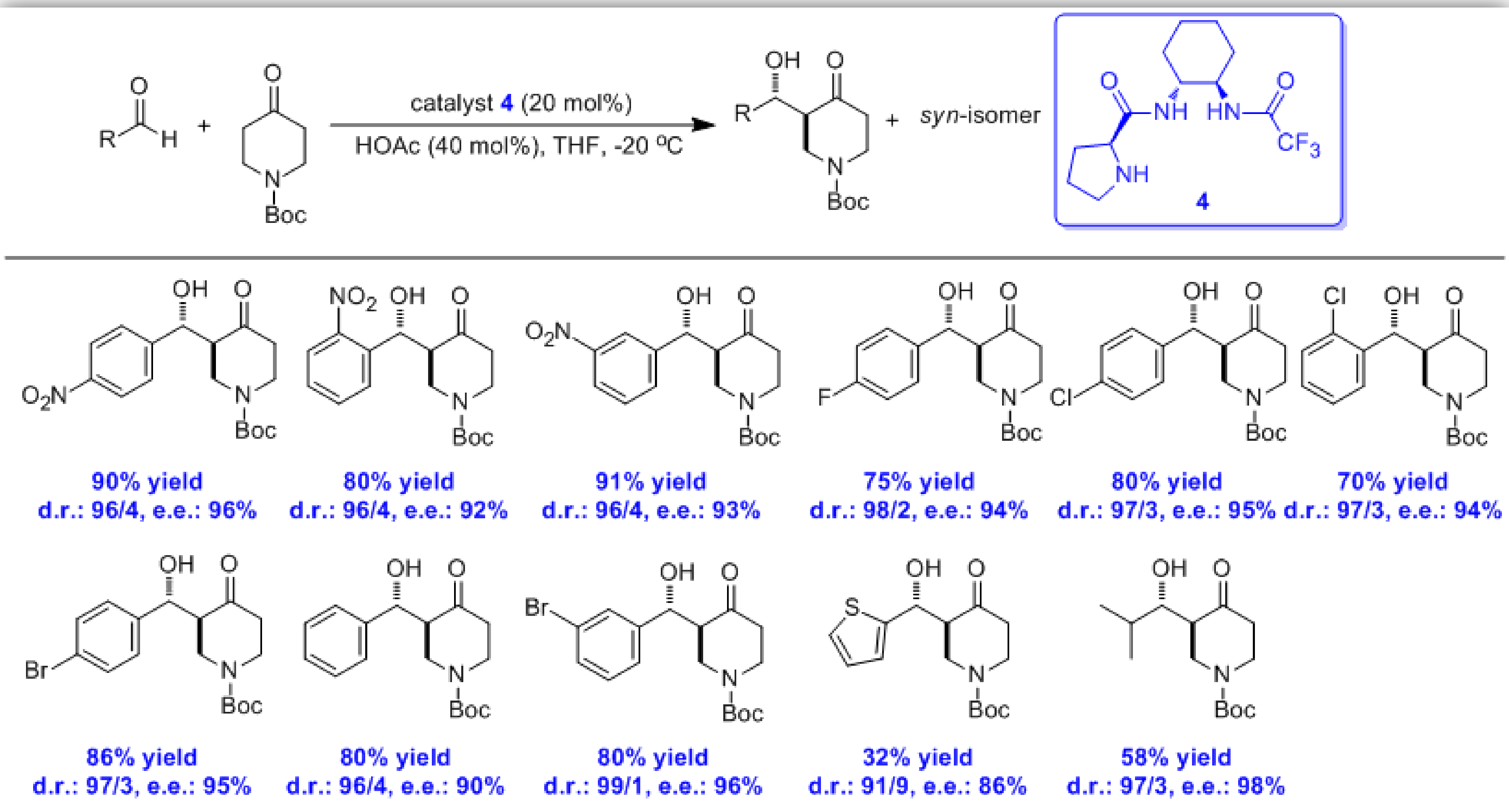
Chen, Lu, Li, Cheng, Wan, Xiao. *Org. Lett.* **2005**, *7*, 4543.
Huang, Chen, Li, Cao, Xiao. *Can. J. Chem.* **2007**, *85*, 208.

Diastereoselective Approaches



Chen, Lu, Li, Cheng, Wan, Xiao. *Org. Lett.* **2005**, *7*, 4543.
Huang, Chen, Li, Cao, Xiao. *Can. J. Chem.* **2007**, *85*, 208.

Diastereoselective Approaches



Chen, Li, Xing, Xiao. *J. Org. Chem.* **2006**, *71*, 8198.

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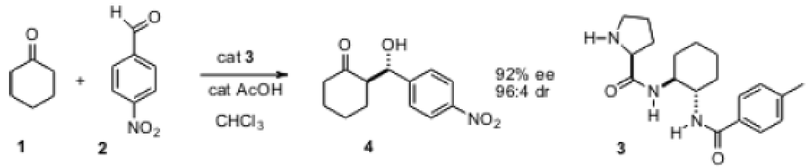
Wen-Jing Xiao of Central China Normal University in Wuhan has reported (*Org. Lett.* **2005**, *7*, 4543. DOI: 10.1021/ol0520323) that the *L*-prolinamide **3** is a particularly effective organocatalyst for this transformation.

Monday, August 21, 2006
Douglass Taber
University of Delaware

http://www.organic-chemistry.org/Highlights/2006/21August.shtm

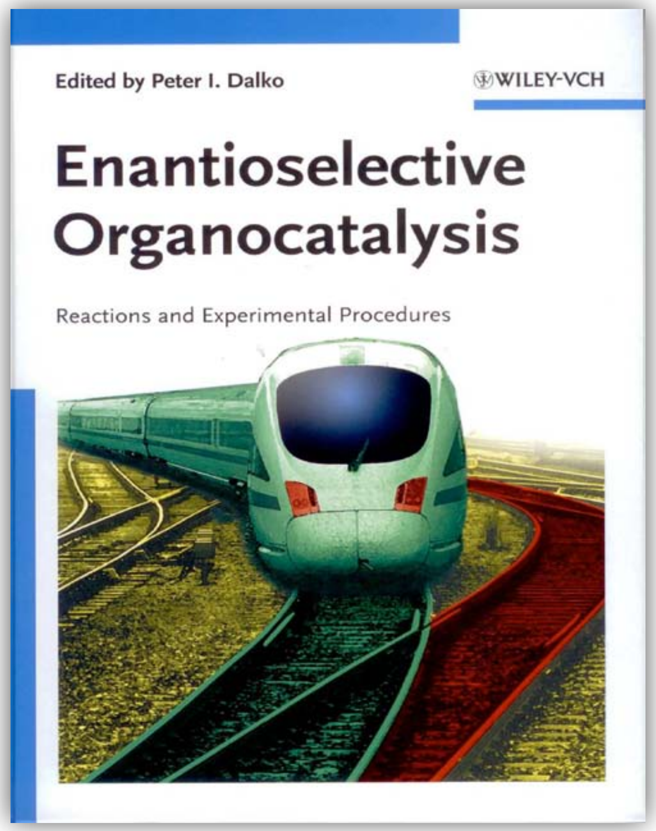
Organocatalytic Preparation of Enantiomerically-Pure Carbocycles

Enantiomerically-pure carbocycles can be prepared either *de novo*, or by desymmetrization of prochiral rings. A classic illustration of the latter approach is the condensation of cyclohexanone (**1**) with *p*-nitrobenzaldehyde (**2**). Wen-Jing Xiao of Central China Normal University in Wuhan has reported (*Org. Lett.* **2005**, *7*, 4543. DOI: 10.1021/ol0520323) that the L-prolinamide **3** is a particularly effective organocatalyst for this transformation.



Cyclohexenones such as **5** and **8** are also prochiral. Steven V. Ley of the University of Cambridge (*Chem. Commun.* **2005**, 5346. DOI: 10.1039/b511441a) and Keiji Maruoka of Kyoto University (*Org. Lett.* **2005**, *7*, 5143. DOI: 10.1021/ol0517170) independently developed organocatalysts that effect enantioselective conjugate addition of nitroalkanes. Nitromethane and primary and secondary nitroalkanes participated efficiently in the addition. Addition to acyclic enones also proceeded with high ee. Professor Ley has shown that quaternary centers can be formed with high ee, and Professor Maruoka has shown that the sidechain stereocenter is also controlled. Note that the primary nitro group of adducts such as **7** is readily converted into the nitrile or the carboxylic acid.

Comments



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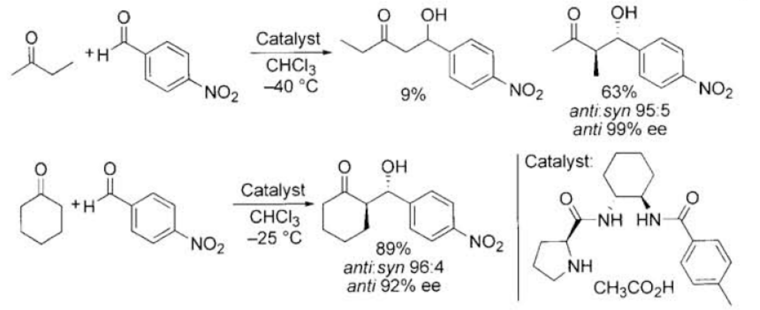
Chen, Lu, Li, Cheng, Wan, Xiao. *Org. Lett.* **2005**, *7*, 4543.

2.1 Aldol and Mannich-Type Reactions | 23



Scheme 2.2 Aldol reactions using a proline amide catalyst [13].

was improved using a proline amide derivative (Scheme 2.2) [13]. Proline-derived diamine-acid combination catalysts and O-protected-4-hydroxyproline derivatives also afforded good diastereo- and enantioselectivities for the aldol reactions of cyclopentanone in water [14, 15], as discussed later in this section. The aldol reactions of a series of ketone donors with chloral using a proline-derived tetrazole catalyst afforded the products with high enantioselectivities [16] (see below, later in this section).

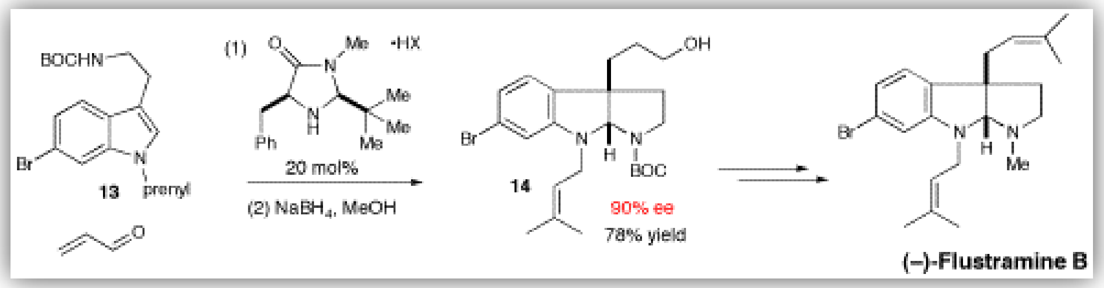
1.7 复杂天然产物的合成实例

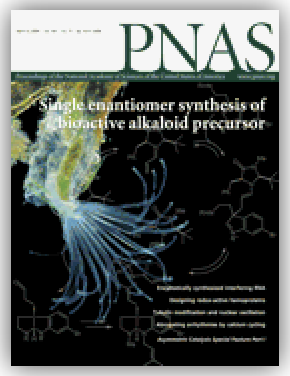
Enantioselective organocatalytic construction of pyrroloindolines by a cascade addition–cyclization strategy: Synthesis of (–)-flustramine B

Joel F. Austin, Sung-Gon Kim, Christopher J. Sinz, Wen-Jing Xiao, and David W. C. MacMillan*

Division of Chemistry and Chemical Engineering, California Institute of Technology, Pasadena, CA 91125

Edited by Jack Halpern, University of Chicago, Chicago, IL, and approved February 23, 2004 (received for review December 12, 2003)

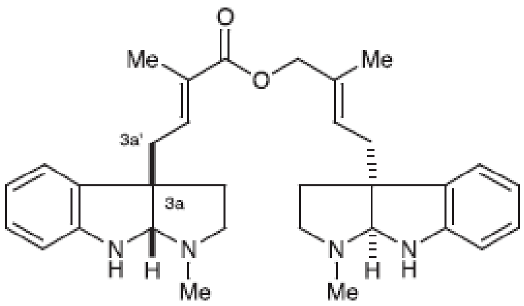




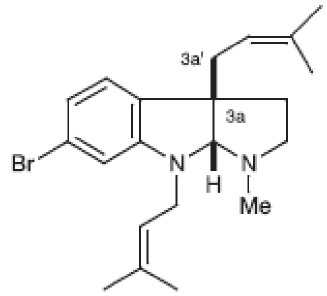
www.pnas.org

1.7 复杂天然产物的合成实例

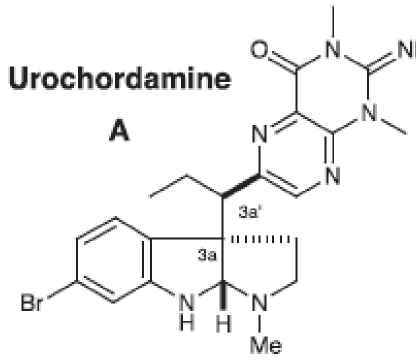
Representative pyrroloindoline natural isolates



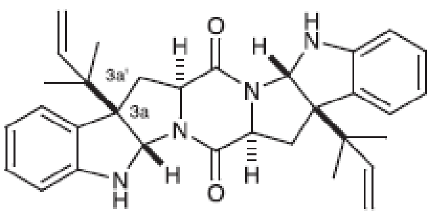
Pseudophrynamine A



(−)-Flustramine B

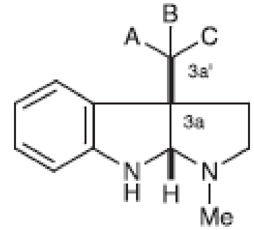


Urochordamine A



Amauromine

Challenges



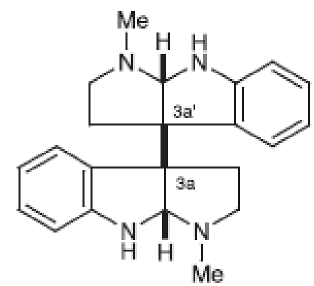
synthetic challenges

(1) Quaternary stereocenter C(3a)

(2) Diastereocontrol C(3a)–C(3a')

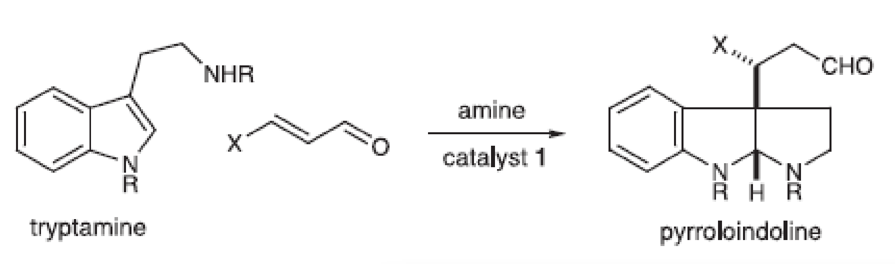
(3) Pyrroloindoline ring system

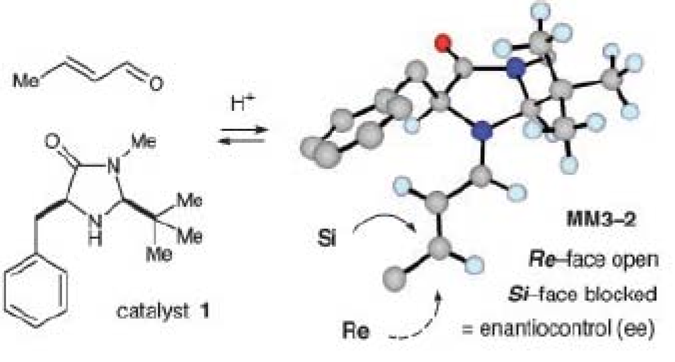
(4) Enantioselective Catalysis

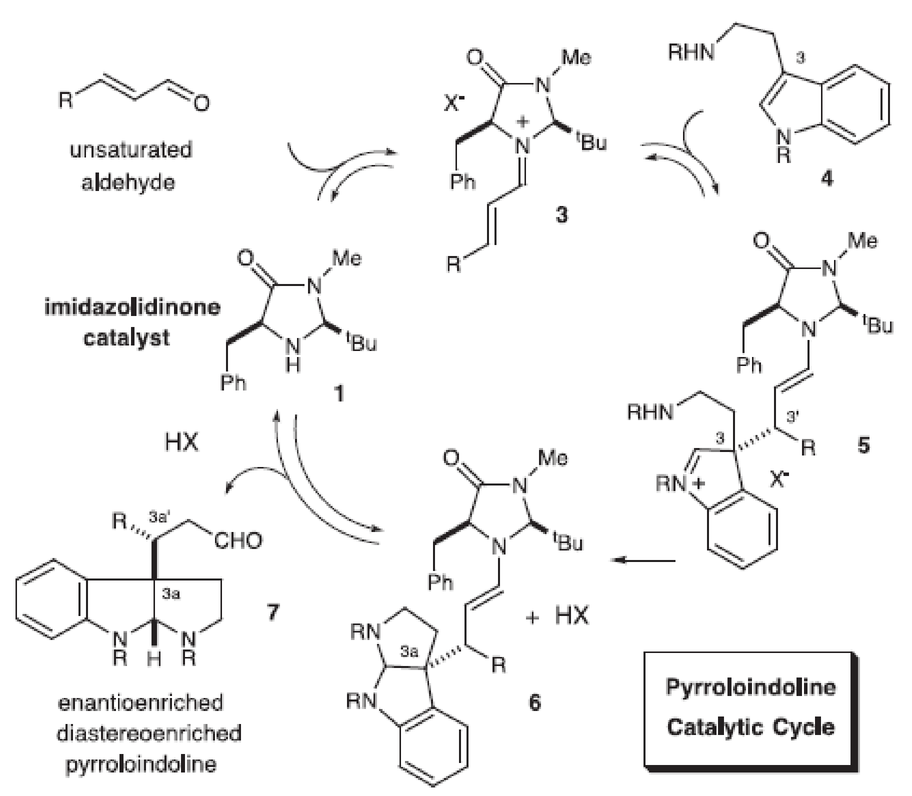


(−) Chimonanthine

关键步骤

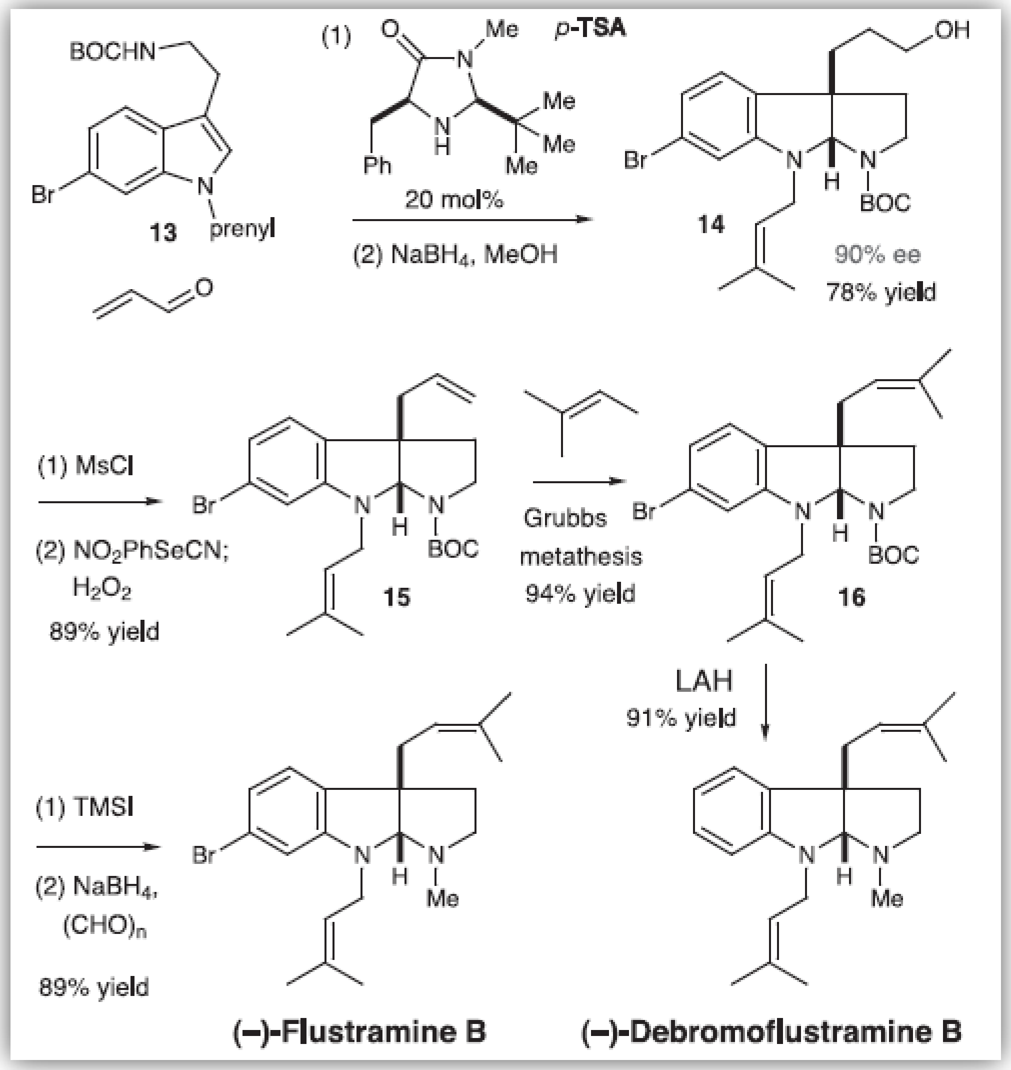




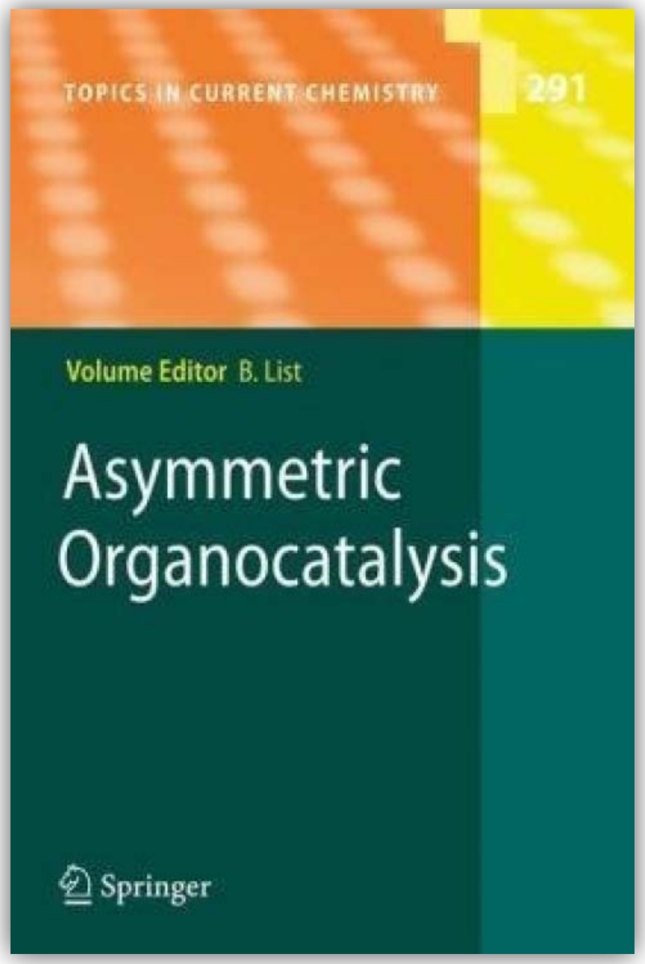


Proc. Natl. Acad. Sci. U. S. A. **2004**, *101*, 5482.

1.7 复杂天然产物的合成实例



复杂天然产物的合成实例



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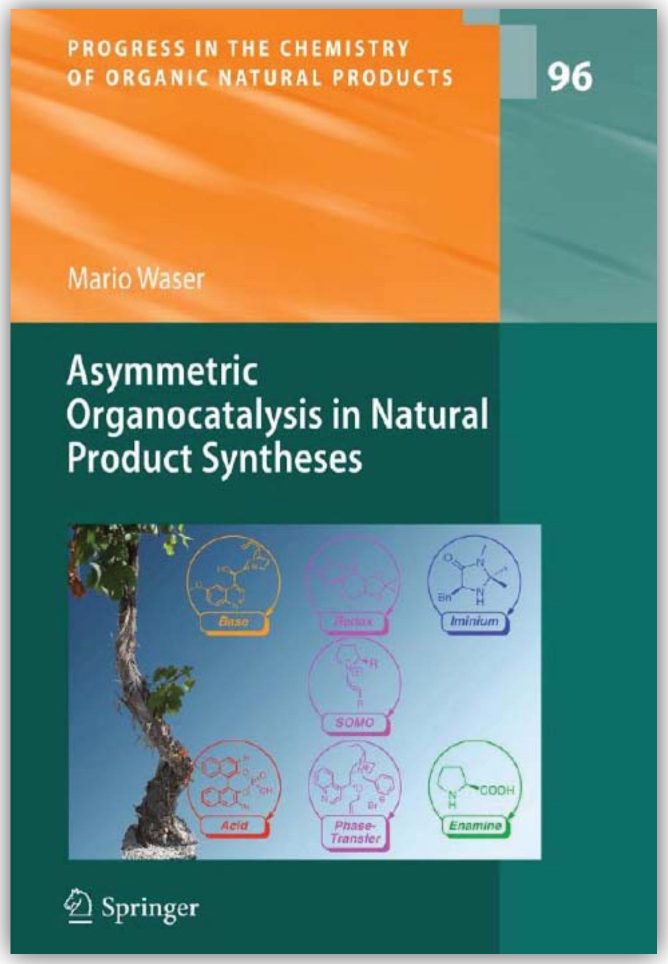

Mario Waser