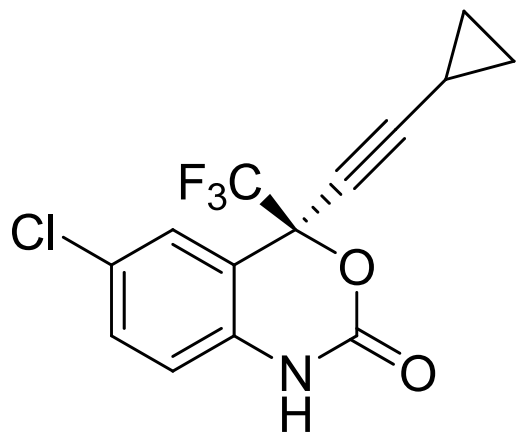
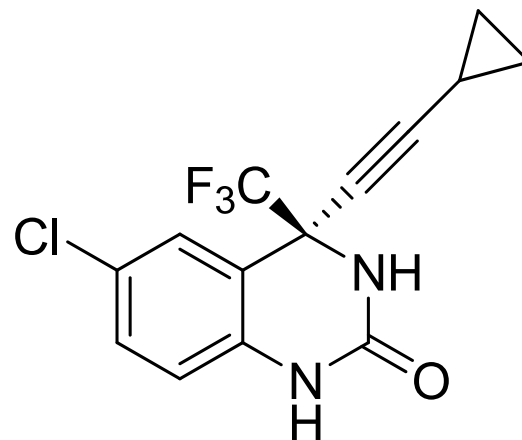


Industrial Scale Asymmetric Synthesis of Anti-HIV Drug Efavirenz and its analogues DPC 961

--A good and worth-analyzing case of asymmetric catalysis on industrial scale application into the formation of carbon-carbon bond



Efavirenz(依法韦恩茨)
(SUSTIVA™)



DPC 961

By C. Shen

Classic asymmetric catalysis on industrial scale

Ti(IV)-(+)-DIPT 烯丙醇的不对称环氧化 普萘洛尔

Ti(IV)-(S,S)-DET 硫醚的不对称氧化 (S)-Omeprazole (Astra Zeneca)

Ir-xylyphos 通过亚胺氢化合成异丙甲草胺(Solvias AG)

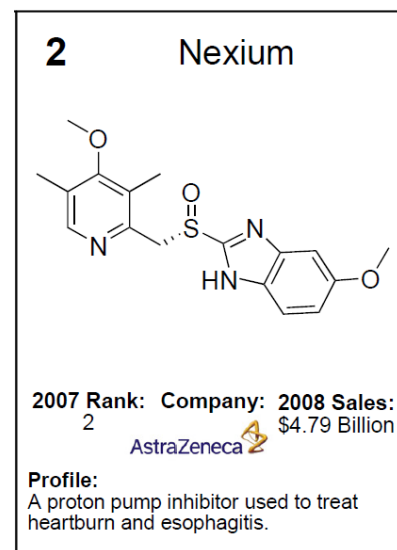
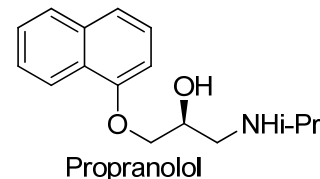
Ru-BIPHEP (通过烯丙醇的不对称氢化合成生育酚) (Hoffmann-La Roche)

Co()-手性salen 前手性环氧氯丙烷的Jacobsen水解动力学拆分(Rhodia)

Ru(I)-DuPhos 不对称氢化 (Dowphama)

Josiphos (Solvias AG)

SEGPHOS(Takasago Corp.)



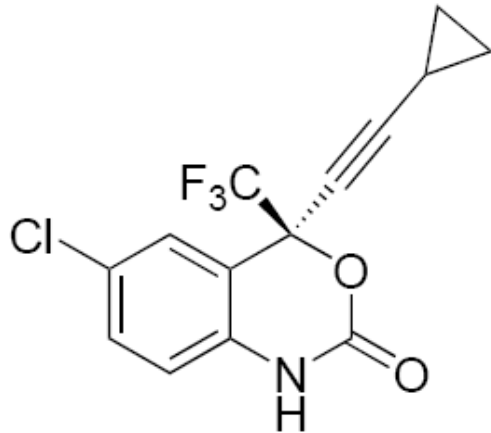
以上这些著名的应用实例仅限于氢化还原、氧化和环氧化或环氧化物开环等几个方面

不对称催化形成碳碳键的工业规模应用尚未得到广泛发展

Top200 Pharmaceutical Products by Worldwide Sales in 2008

180

Sustiva



2007 Rank: 157 Company: Bristol-Myers Squibb 2008 Sales: \$0.17 Billion



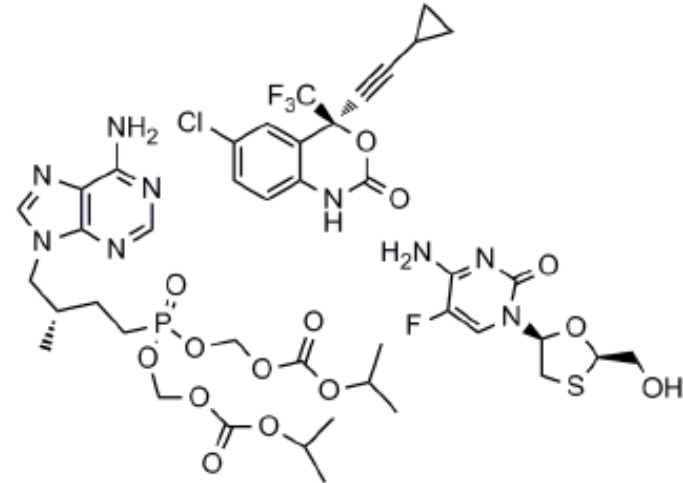
Profile:

A non-nucleoside reverse transcriptase inhibitor used to treat HIV.

66

ATRIPLA

(Tenofovir & Emtricitabine & Efavirenz)



\$1591 Million
HIV ANTIVIRALS

Top200 Brand Name Drugs by Retail Dollars in 2008

Brief introduction of Efaviren and DCP 961

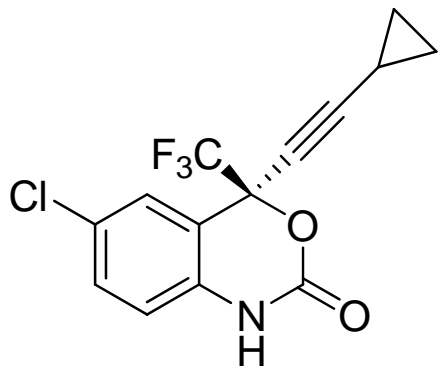
抗AIDS药物主要针对HIV复制过程的关键酶-HIV逆转录酶(HIV RT)及HIV蛋白酶(HIV PT),前者又分为NRTI(核苷类HIV RT抑制药)和NNRTI (非核苷类HIV RT抑制药)

Efaviren: NNRTI

优点：抑制HIV复制活性强，每日只需服药一次，耐药性发展慢，患者耐受好

DPC 961:第二代NNRTI，已经过二期临床试验，比Efaviren活性更高，对第一代NNRTI产生耐药性的菌株均有活性，药物半衰期更长。

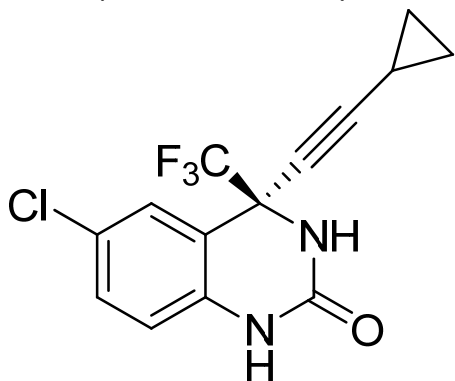
两种药物的对映体均无活性



Efavirenz(依法韦恩茨)
(SUSTIVA™)

Merck, DuPont Pharmaceuticals Company
Angew. Chem. Int. Ed. **1999**, 38,711-713
J. Org. Chem. **1998**, 63, 8536-8543

特点：简洁而有效的方法，已用于大规模生产



DCP 961

DuPont Pharmaceuticals Company
(2001年DuPont Pharmaceuticals Company被Bristol-Myers Squibb
收购)

J. Med. Chem. **2000**, 43, 2019-2030

特点：通过手性HPLC制备柱分离对映异构体

DuPont Pharmaceuticals Company

Tetrahedron Letters, **2000**, 41, 3015-3019

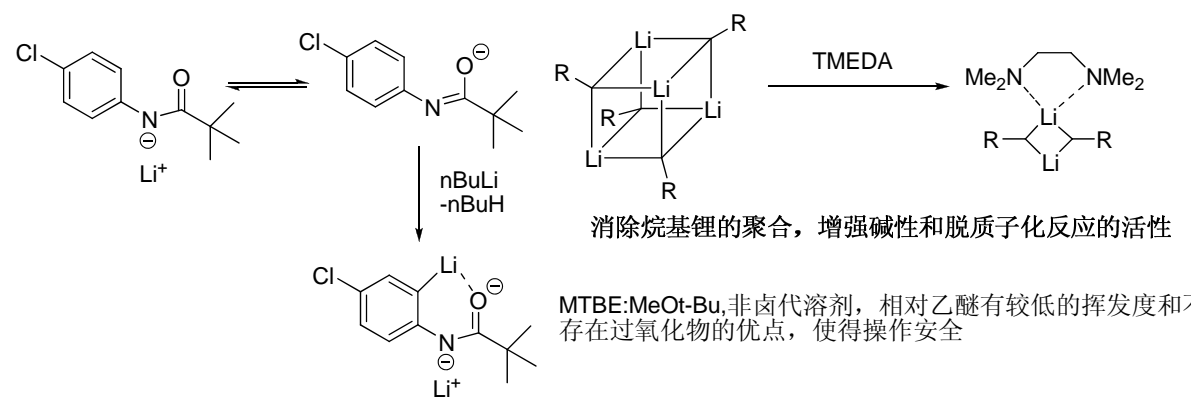
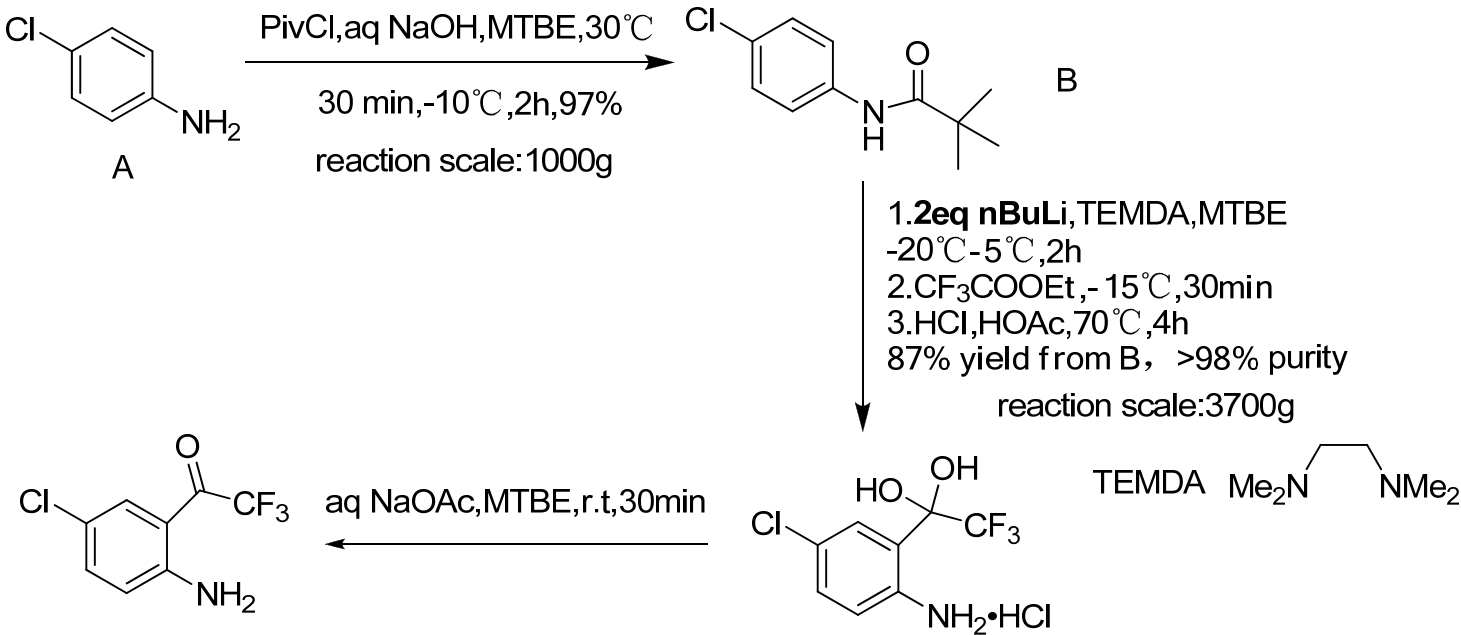
特点：在底物中引入手性辅基来构筑手性叔碳

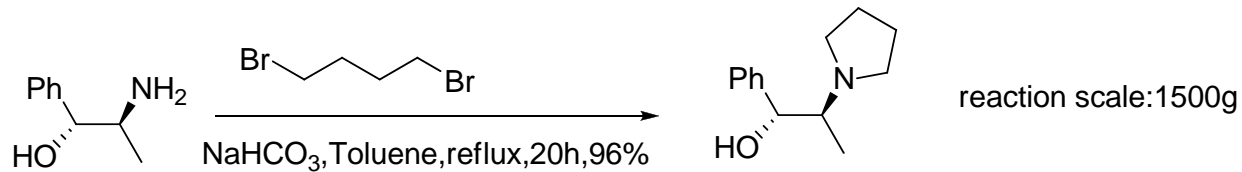
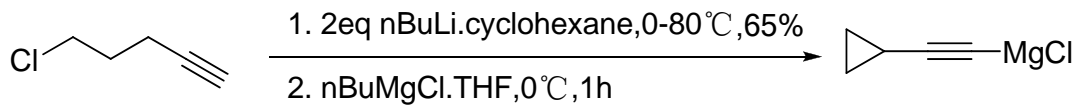
Bristol-Myers Squibb

J. Org. Chem. **2003**, 68, 754-761

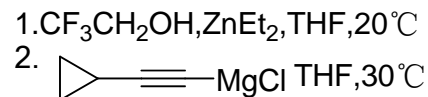
特点：通过手性试剂茨烷酰氯来拆分

Classic industrial scale synthesis strategy for Efavirenz

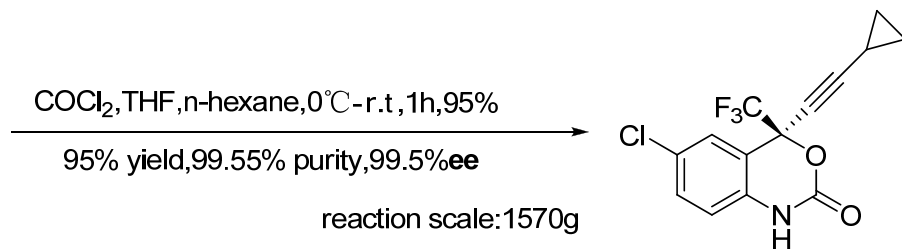
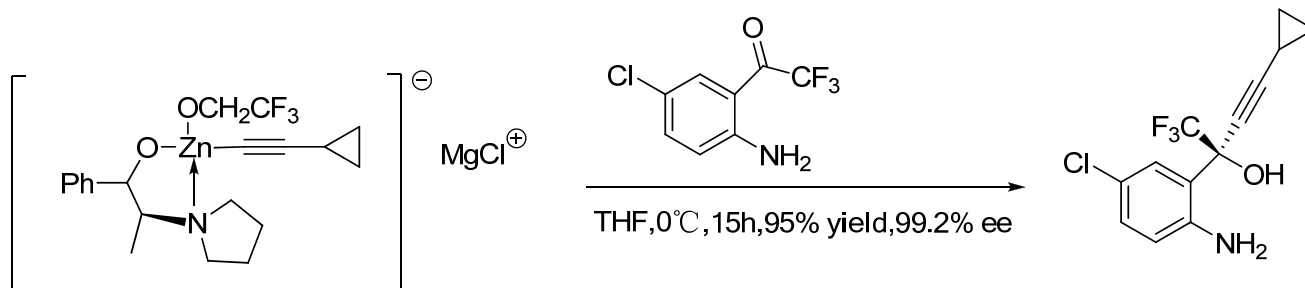
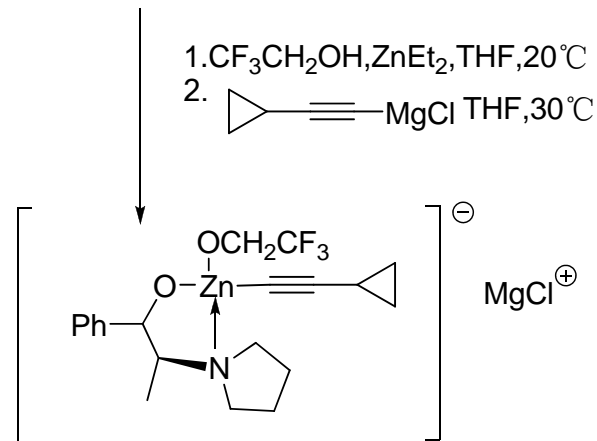




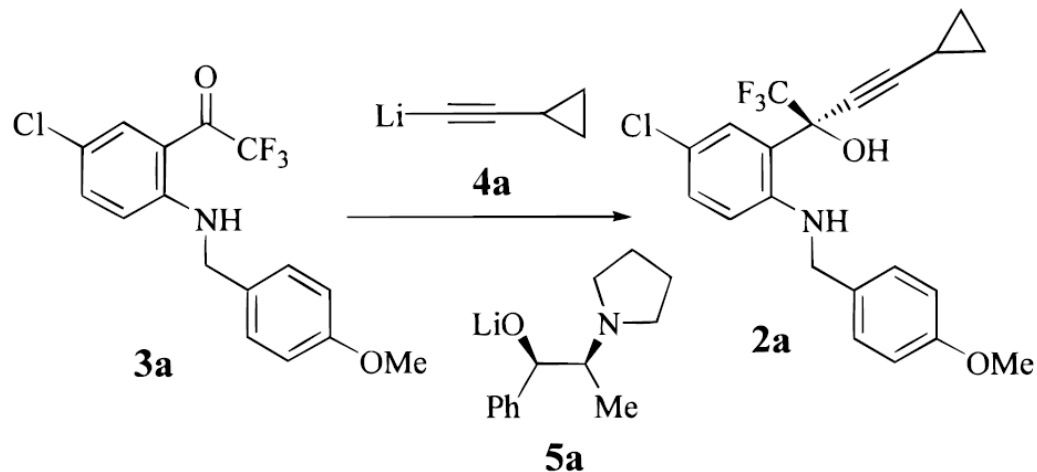
伪麻黄碱



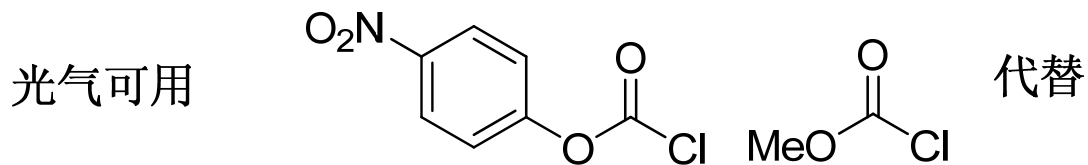
手性配体通过加入柠檬酸可回收重复利用9次



开发这个策略的研究小组的早期工作

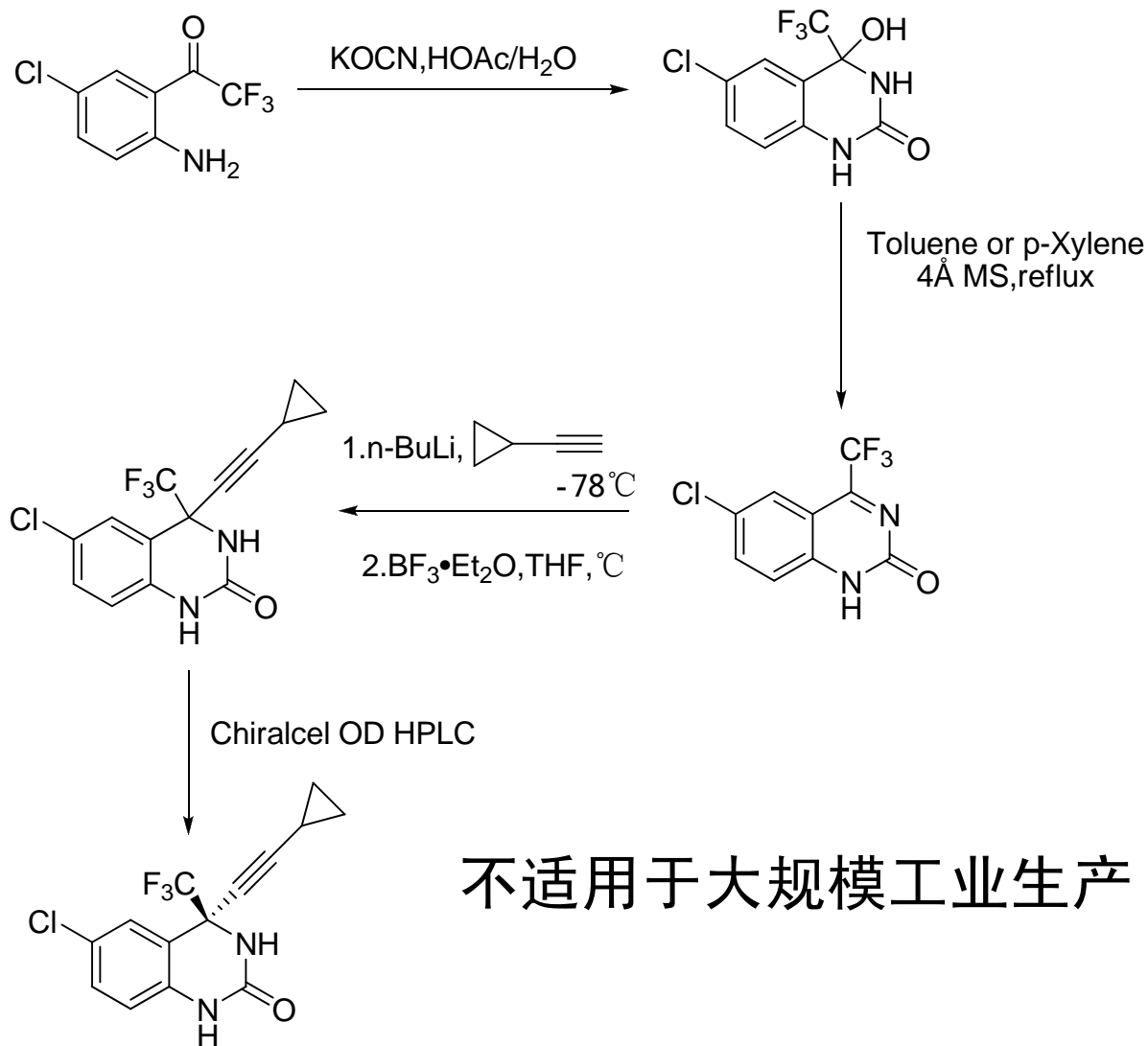


PMB作为PG是必须的。然而PMB的去除需要等当量的CAN或者DDQ这类氧化剂，而且反应必须在 -60°C 下进行才能保证高的ee值



高效的对映选择性工业合成Efavirenz的方法。这个合成策略提供了一种从4-氯苯胺通过5步以75%产率合成分析纯Efavirenz的方法。优点：非卤代溶剂的使用、废料只有惰性无机盐、室温反应、不必引入PG、重要副产物回收

通过Chiral HPLC制备柱



不适用于大规模工业生产

在底物中引入手性辅基

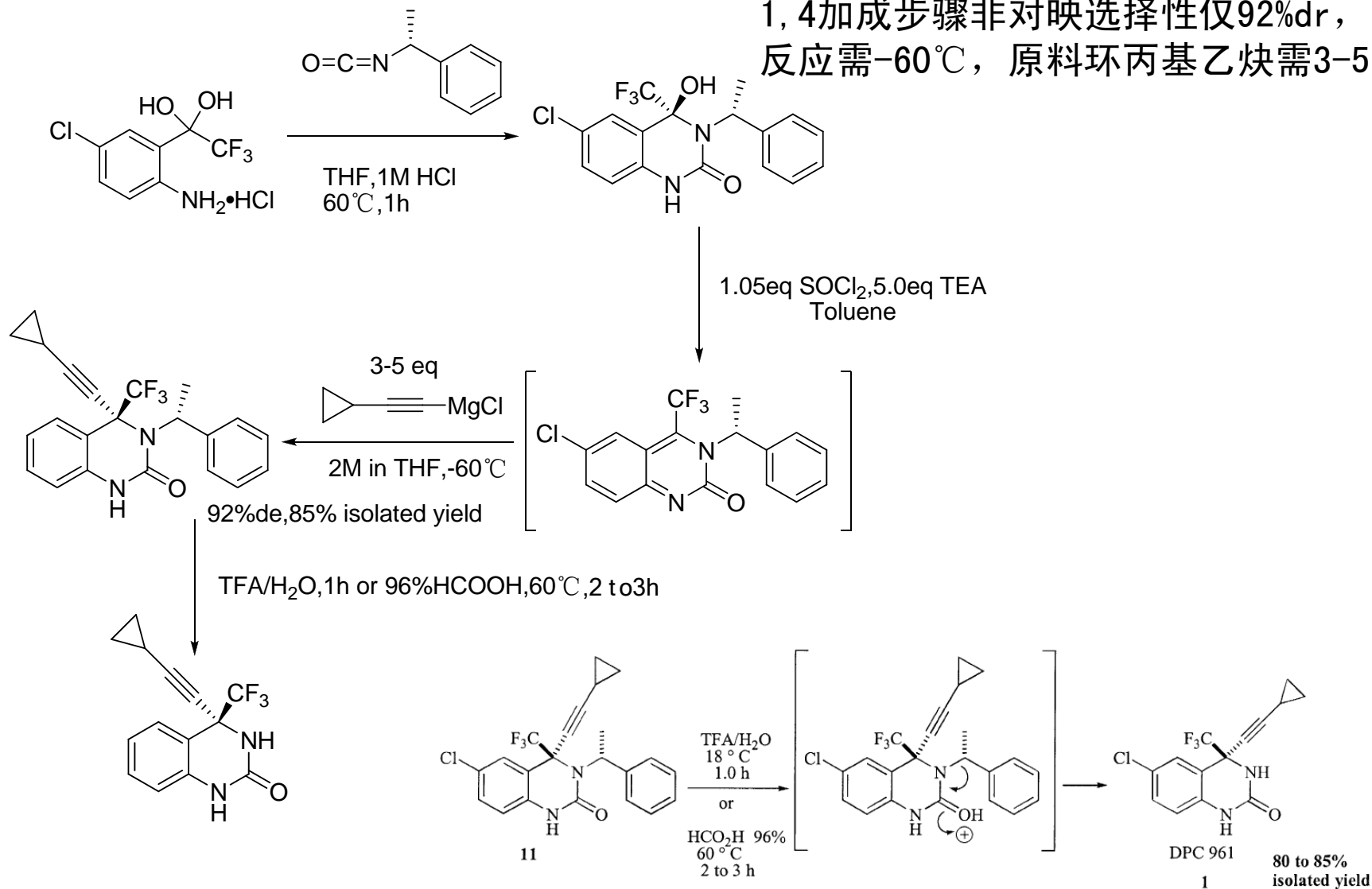
缺点:

辅基的大量制备

需将辅基接上底物和从底物中切断

1,4加成分步骤非对映选择性仅92%dr,

反应需 -60°C , 原料环丙基乙炔需3-5 eq



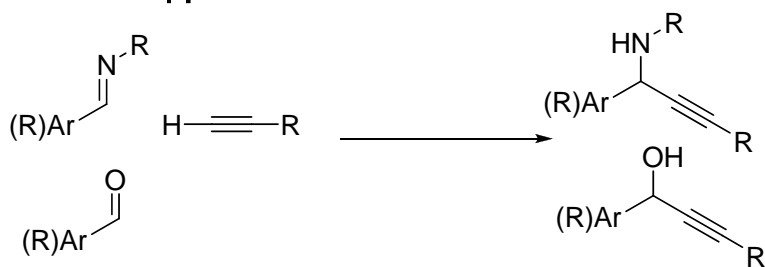
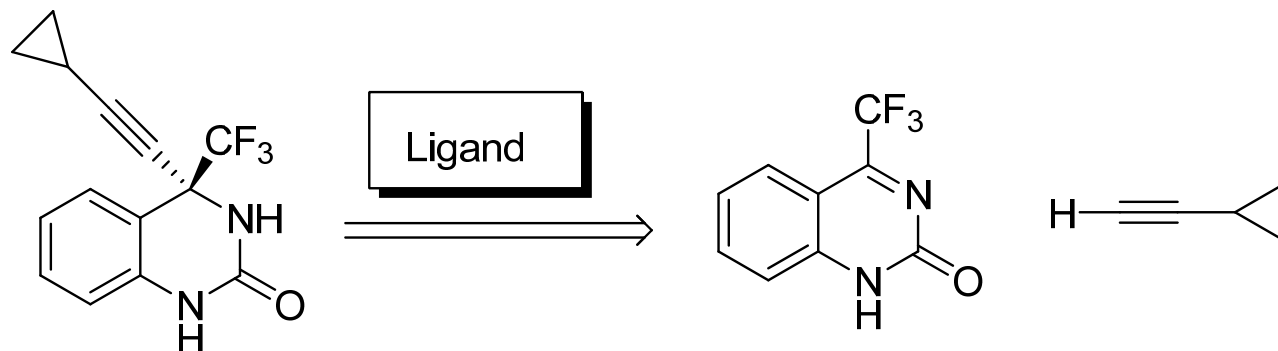
手性试剂茨烷酰氯拆分工艺



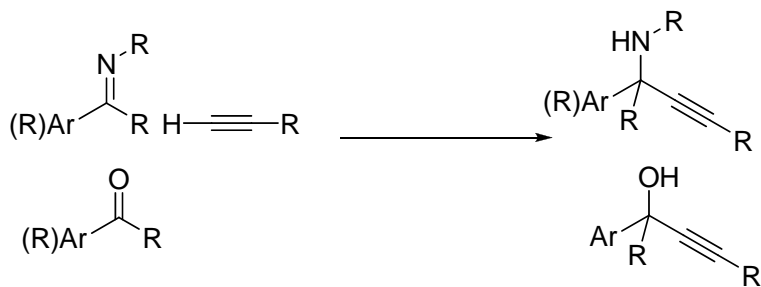
拆分效率太低，需多次重结晶得到大于99: 1的选择性
需要用到CAN来脱PMB

最高效的方法：不对称催化的方法构建分子中的叔碳手性中心

端炔对酮亚胺的催化不对称加成



已经有了很大的进展

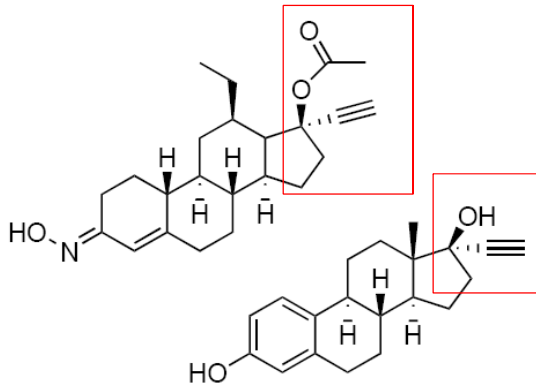


两个反应都有巨大的实用价值

?

Top 200 Brand Name Drugs by Retail Dollars in 2008

103 Ortho TriCyclen Lo



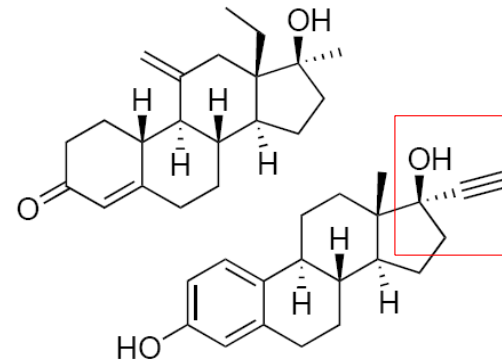
2007 Rank: 101 **Company:** *Johnson & Johnson* **2008 Sales:** \$0.35 Billion

Johnson & Johnson

Profile:

An estrogen and progestin combination used as birth control.

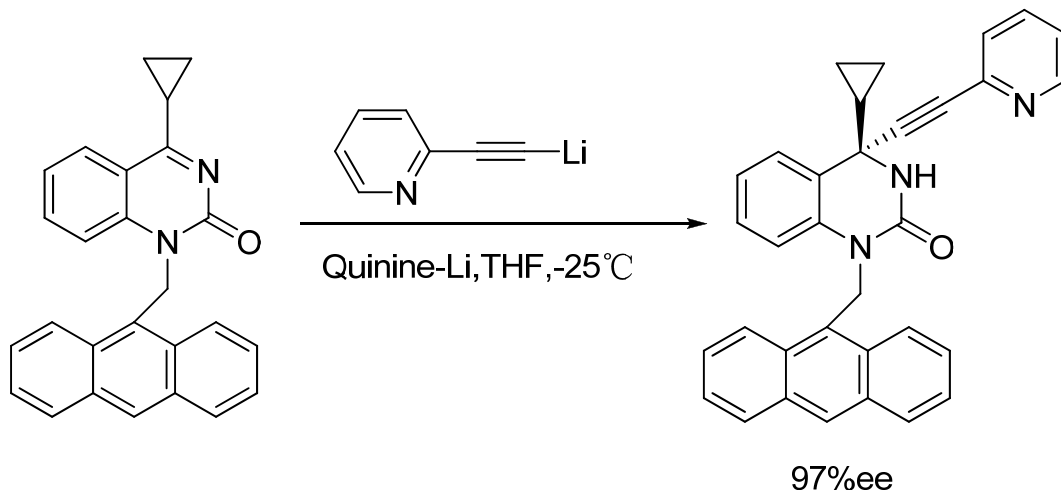
124 NuvaRing



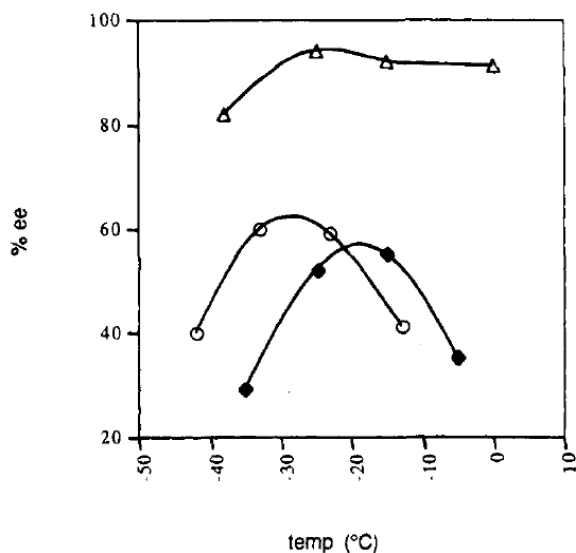
2007 Rank: 137 **Company:**  **2008 Sales:** \$0.27 Billion

Profile:

An estrogen and progestin combination used as birth control.



Merck, *J. Org. Chem.* **1995**, 60, 1590-1594

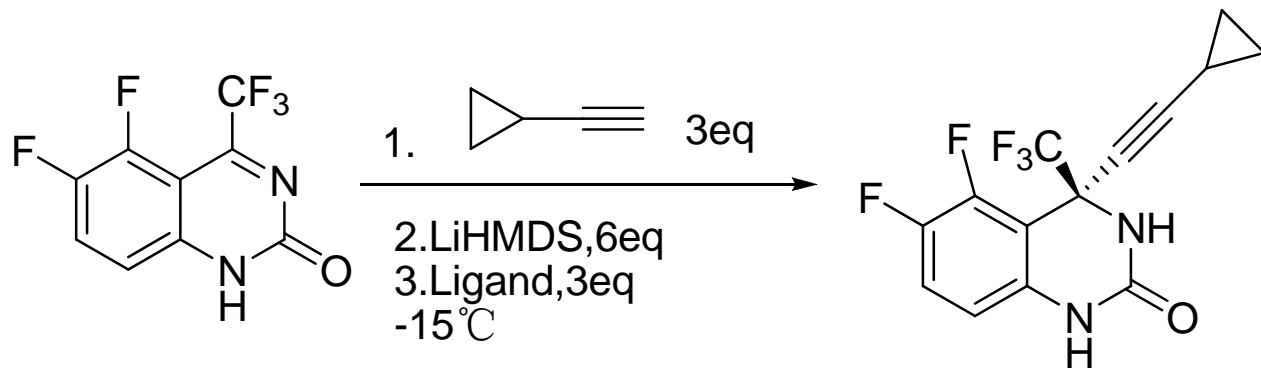


不利于工业化生产:

1. 对温度要求严格
2. 炔和配体奎宁均需1.5 eq
3. 反应分步进行: 先将端炔和quinine在 -45°C 锂化后再进行加成反应。

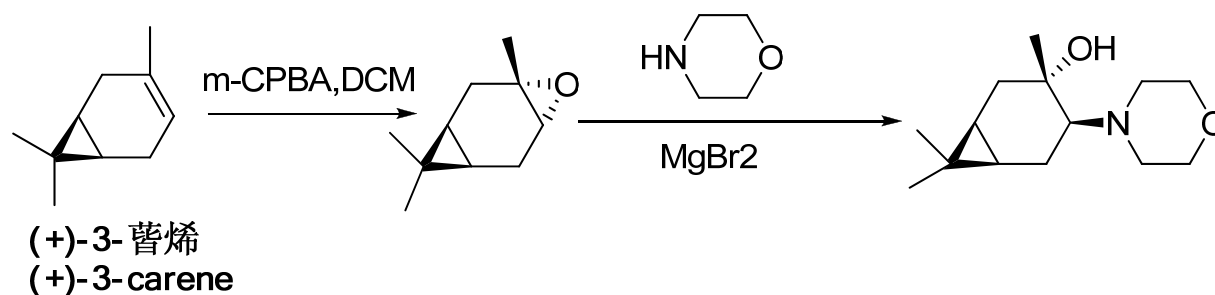
Figure 1. Temperature effect on enantioselectivity of quinine-mediated addition of 2-ethynylpyridine to **1a** (♦) and **1g** (Δ) (0.15 M acetylide, 0.16 M quinine alkoxide), and to **1e** (○) (0.11 M acetylide, 0.12 M quinine alkoxide).

DuPont, Org. Lett. 2000,2, 3119-3121



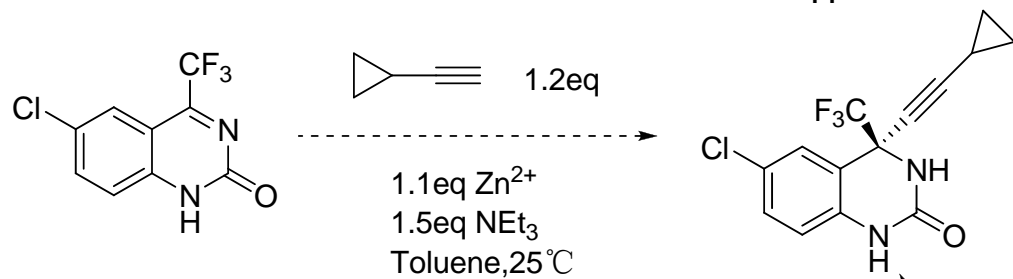
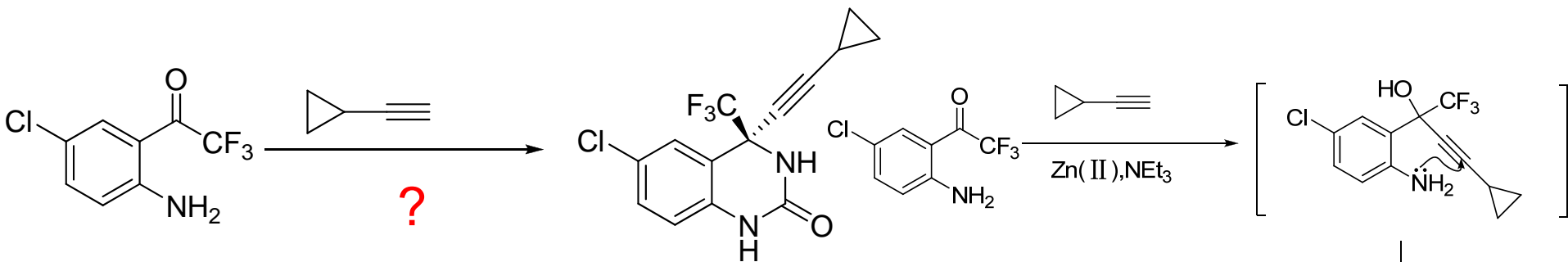
炔和配体均需3eq
使用大大过量的强碱
配体昂贵

85% yield, 99.6ee%



An Efficient Chiral Moderator Prepared from **Inexpensive** (+)-3-Carene: Synthesis of the HIV-1 Non-Nucleoside Reverse Transcriptase Inhibitor DPC 963

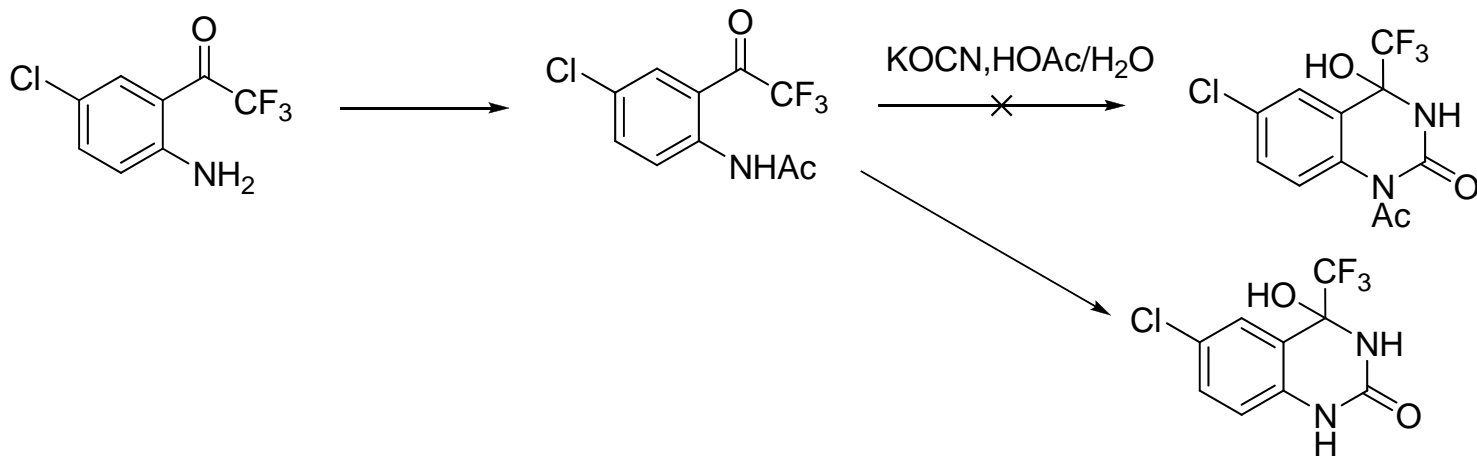
(+)-3-carene in Sigma-Aldrich: 473RMB/1g

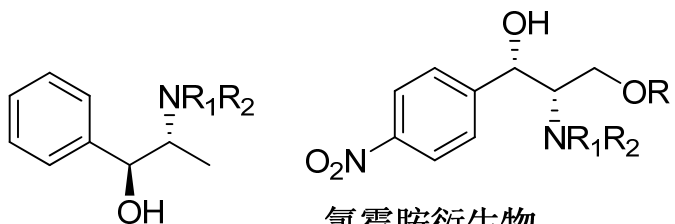
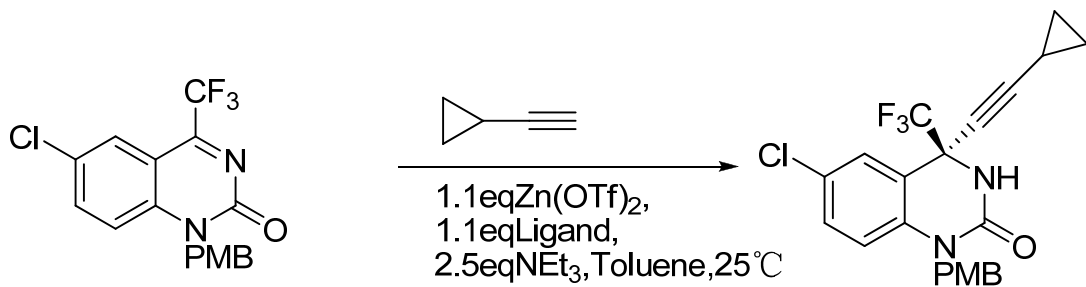
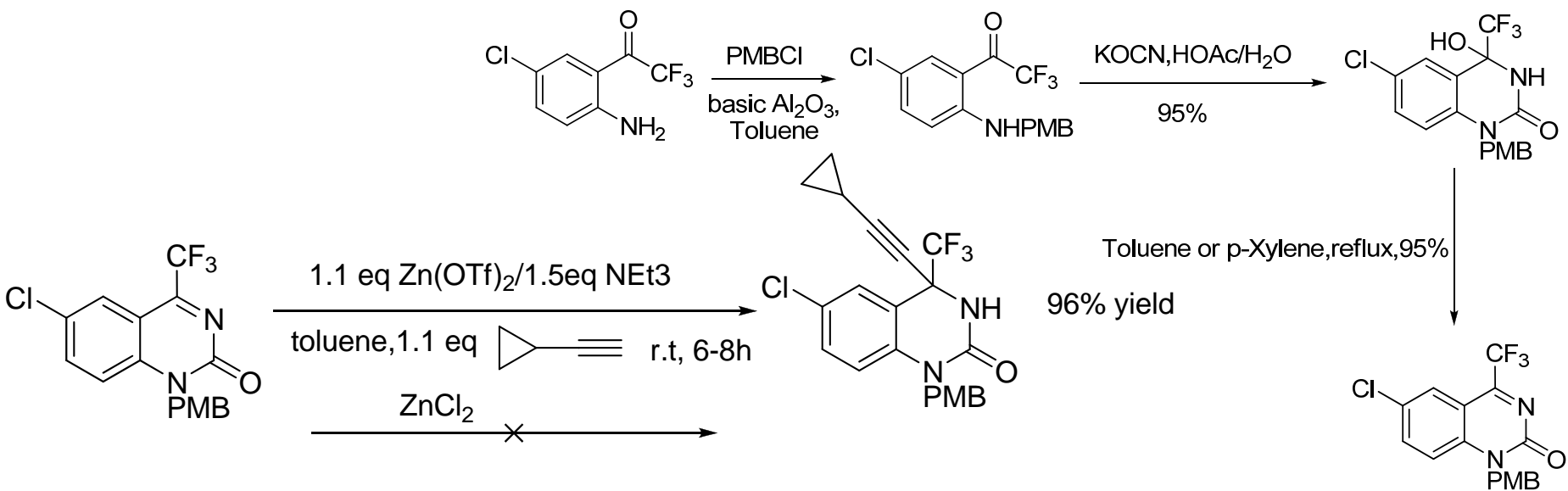


First: ZnCl₂/Zn(OTf)₂ mix with NEt₃
 Second: add cyclopropylacetylene and react for 1-2 h
 Finally: add the ketimine
 Result: **no reaction**

has acidity, need -PG

C1CC1C#C-Zn Not only a **Nu**, but also a **base**

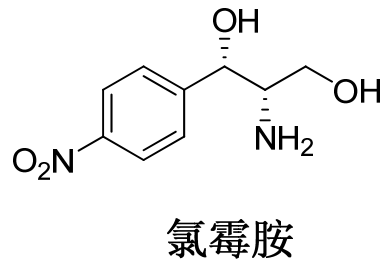
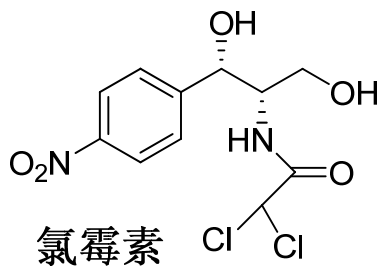




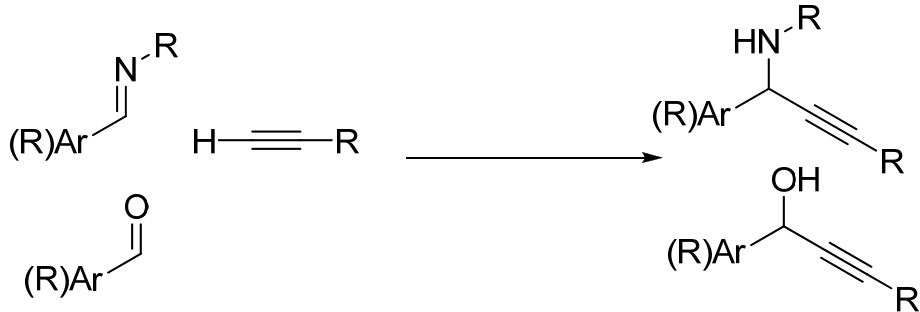
R1=Me; R2=Me
 R1=Me; R2=Bn

R1=Me; R2=Me; R3=TBDMS
 R1=Me; R2=Bn; R3=Tr
 R1=Me; R2=Me; R3=t-Bu
 R1=Me; R2=Bn; R3=Tr

具体工艺：室温下锌盐与Ligand及NEt₃在toluene中搅拌1h后加入环丙基乙炔再搅拌2，加入底物亚胺，室温搅拌反应10h完成反应
 分离过程：0℃下6N HCl淬灭反应，搅拌1h,体系分相配体进入水相产物留在toluene中，6M HCl洗涤甲苯将配体全部转入水相，加碱中和回收配体，蒸去甲苯获得产物。

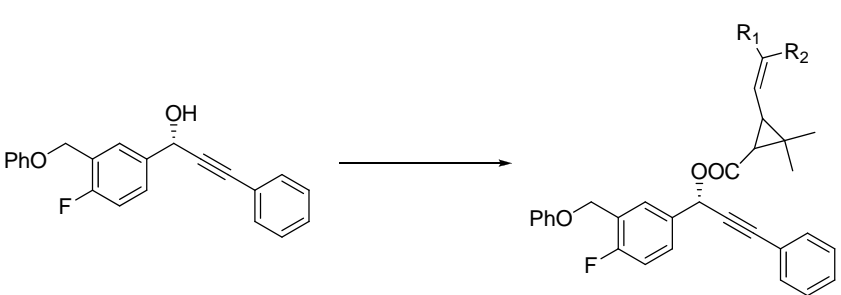


氯霉素胺为拆分法制备氯霉素工艺中的无效对映异构体，200RMB/1KG，制备配体的原料廉价易得通过几步简单反应衍生即可得，能方便回收配体酸溶碱析，产物分离简单，此合成策略有工业化大量生产的可能



Top 200 Generic
Drugs by Retail
Dollars in 2006

Top 200 Generic
Drugs by Retail
Dollar in 2007



37 Quinapril

2005 Rank: 31 **Brand Name:** Accupril **2006 Sales:** \$238.5 Million

Profile:
An ACE inhibitor used to treat hypertension and heart failure.

9 Lisinopril

2005 Rank: 6 **Brand Name:** Prinivil, Zestril **2006 Sales:** \$727.3 Million

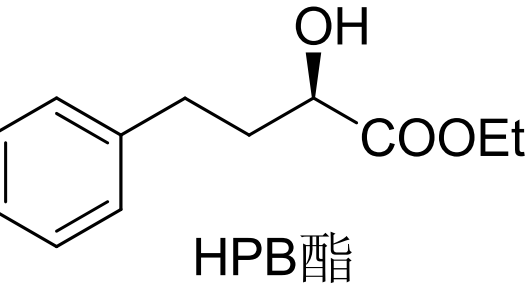
Profile:
An ACE inhibitor used to treat hypertension.

68 Enalapril

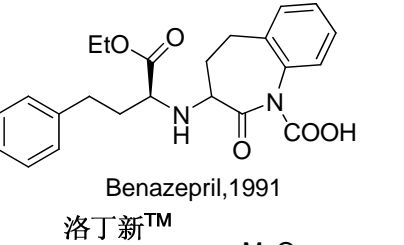
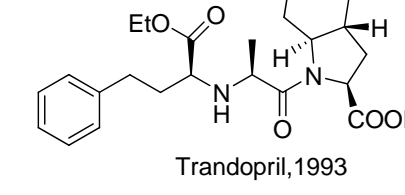
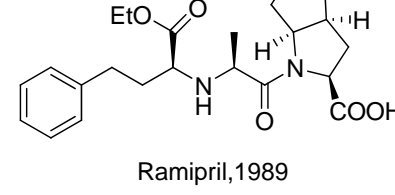
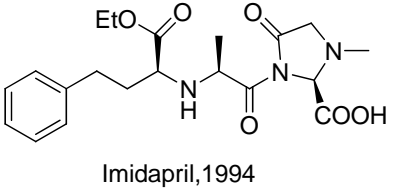
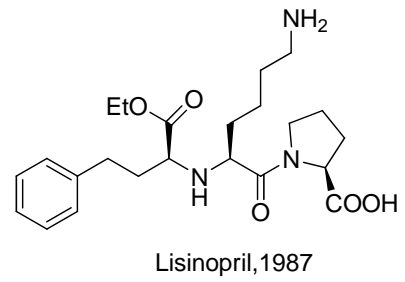
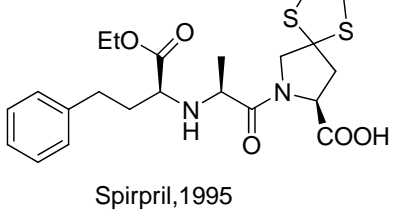
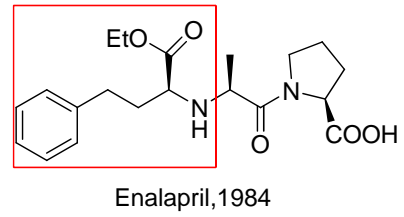
2006 Rank: 54 **Brand Name:** Vasotec **2007 Sales:** \$168.9 Million

Profile:
An ACE inhibitor used to treat hypertension and heart failure.

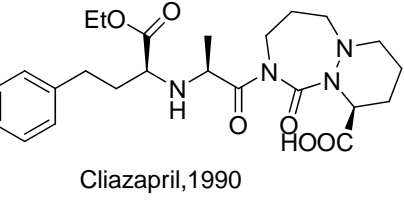
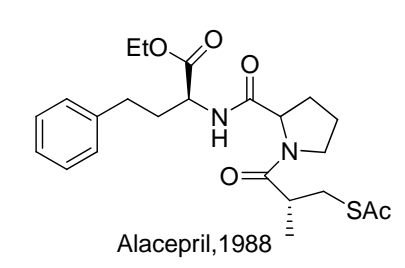
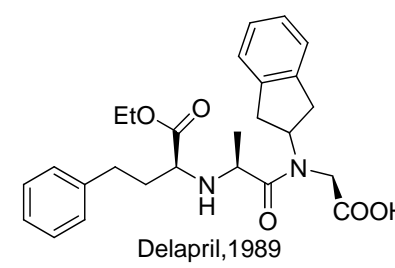
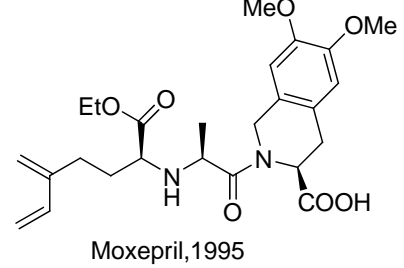
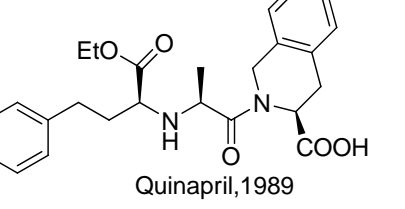
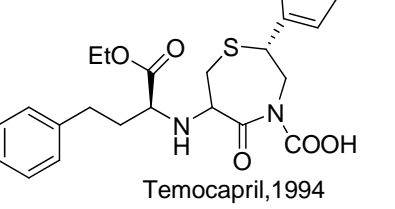
ACE inhibitor(血管紧张素转化酶抑制剂): 治疗高血压等心脑血管疾病和糖尿病



Solvias AG
Novartis Phama
Ciba-Geigy



洛丁新™



策略1: 消旋化还原后拆分

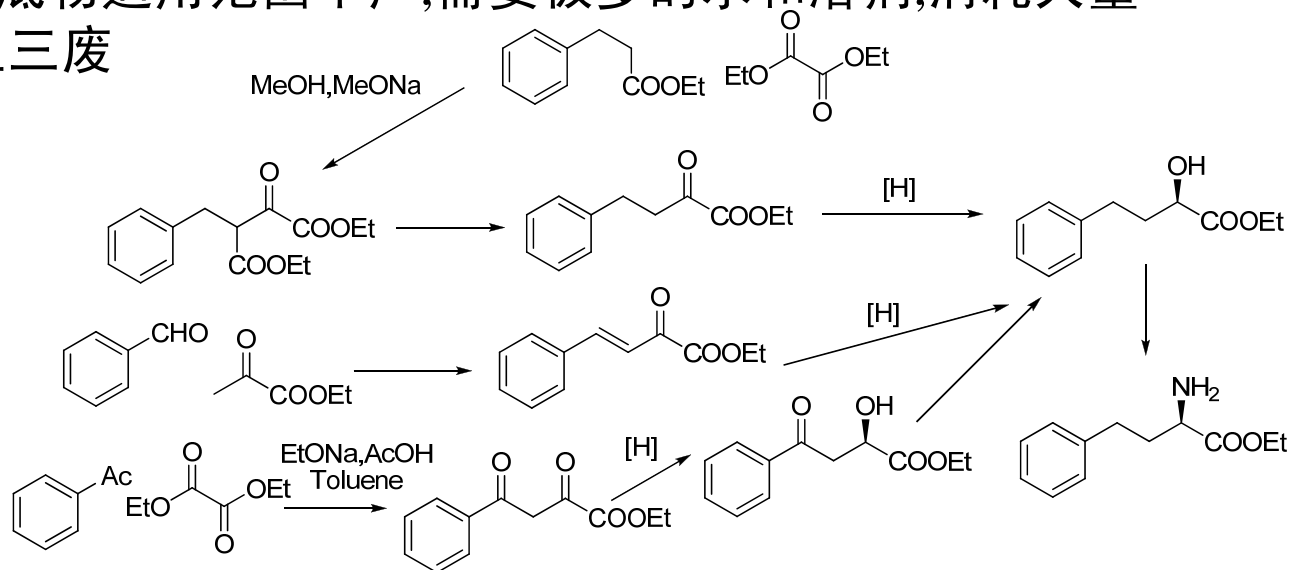
拆分方法: 使用酶的动力学拆分比如脂肪酶; 与手性胺成盐结晶拆分

策略2: 生物合成: 使用甲酸或甲酸盐作还原剂, 生物酶/微生物比如D-乳酸脱氢酶/普通变形杆菌催化还原前手性酮。

Org. Lett., 2008,10, 2155-2158;

Adv. Synth. Catal, 2008, 350, 426-430

反应对底物纯度敏感, 底物适用范围不广, 需要极多的水和溶剂, 消耗大量的盐配制缓冲溶液, 产生三废



策略3: 酮酯、二酮酯的还原

Pt-Al₂O₃, 金鸡纳碱

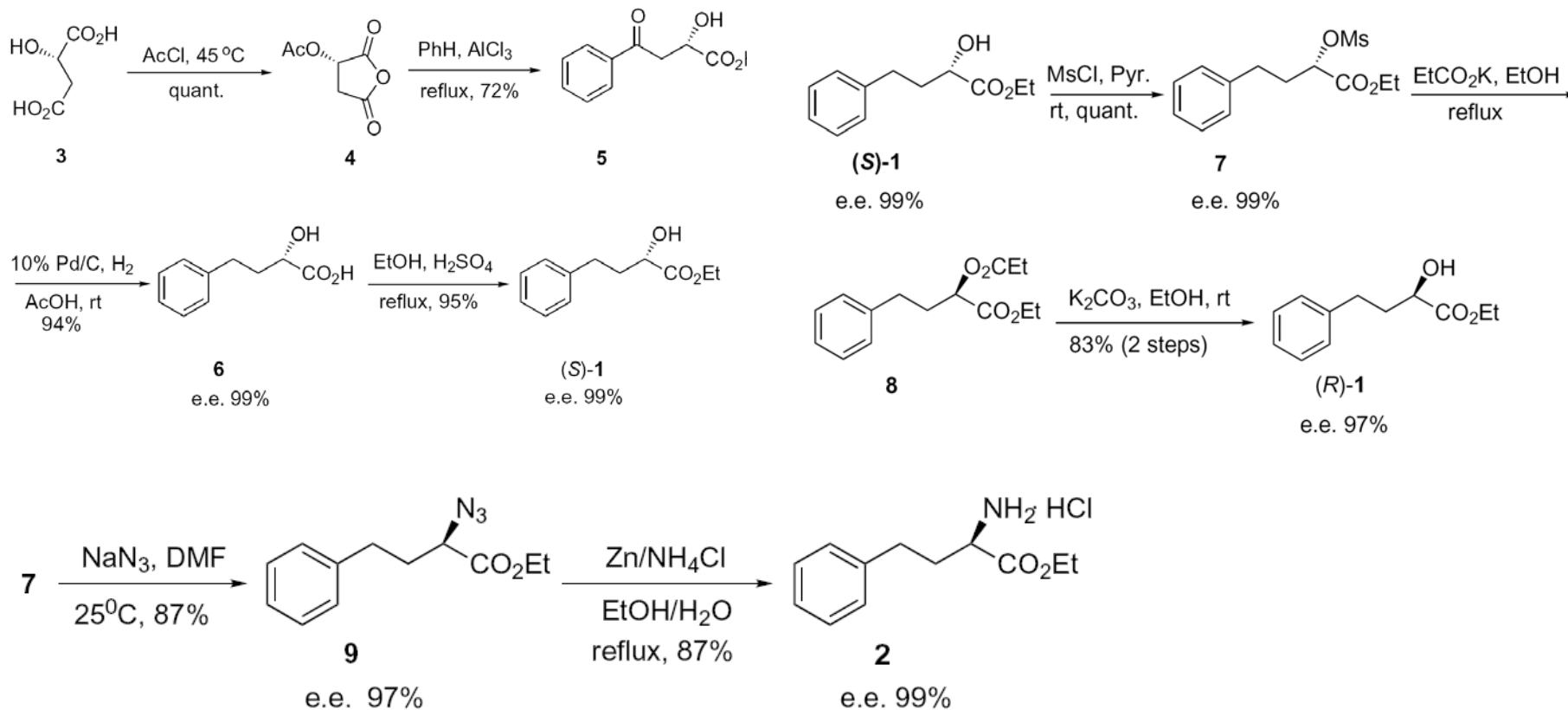
Ru Tune-Phos: *J. Org. Chem.*, 2008,73, 1143-1146

Ru Tol-SEGPHOS: *J. Org. Chem.*, 2008,73, 7209-7212

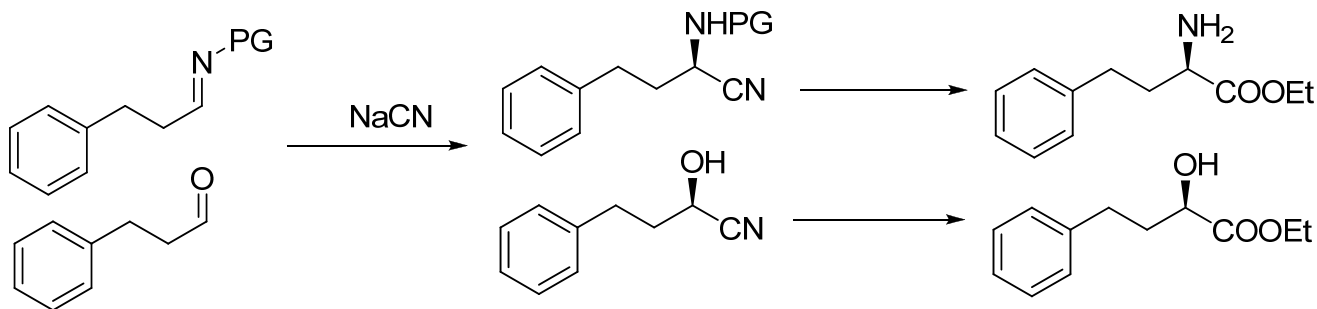
Tetrahedron: Asymmetry, 2009,20, 2033-2037

氢化原理合成路线长, 配体用量、贵金属的使用, 反应条件和速率

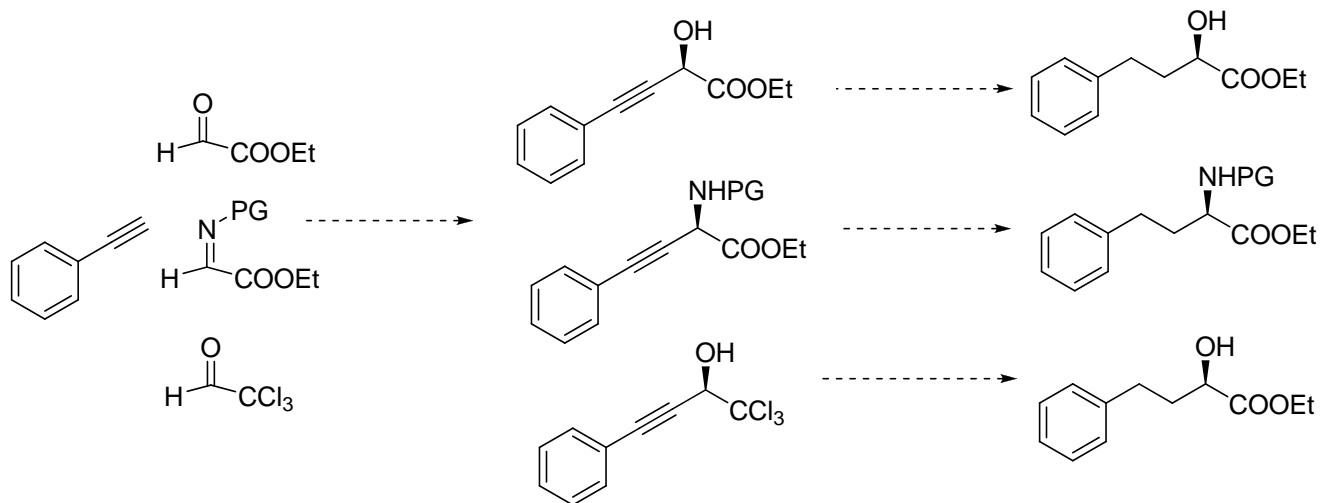
策略4: 手性源合成 例如: 从苹果酸衍生物为起始原料合成。反应规模
Tetrahedron Asymmetry 2001,12,1583



策略5: Strecker反应合成

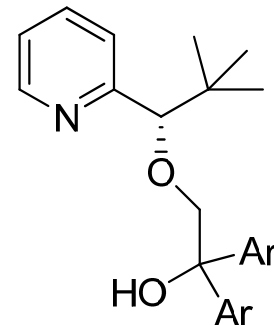
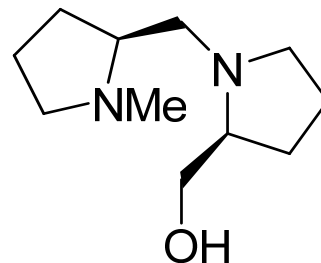
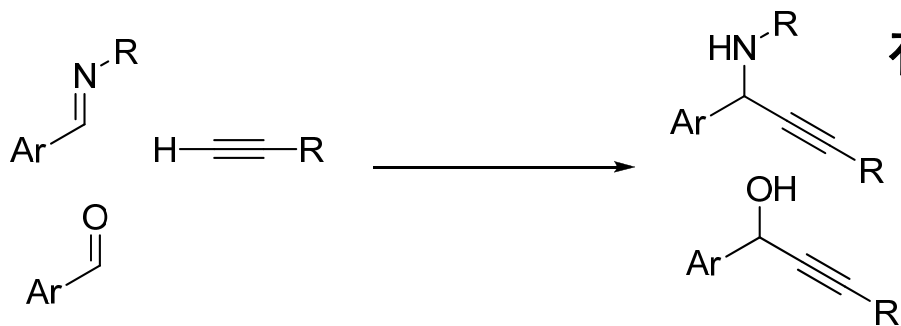


策略6:



简洁高效，高的原子利用率

有关这两个反应研究开发的相关文献



第一例醛和酮的不对称炔基化反应 Mukaiyama T., *Chem. Letter*, 1979,447

炔锂，条件太苛刻-123℃

Soai K., *J. Chem. Soc. Perkin. Trans*, 1990,1,137 配体:(-)-N-烷基麻黄碱 5% eq，二炔基锌试剂，条件稍微温和

Corey E J., *J. Am. Chem. Soc.*, **1994**,116,6457 手性噁唑啉硼试剂 ee up to 97%
硼试剂现场制备，操作不便，炔基锡试剂

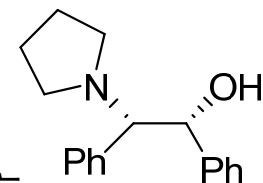
Hoshino, *Tetrahedron Asymmetry*, **1994**,1901 第一例二乙基锌与端炔生成炔锌试剂
直接参与醛的炔化反应，分步反应，室温进行
以上反应均需先制备金属炔试剂，再进行加成

Li Z, *Synthesis*, **1999**,1453 使用二乙基锌，不用分步先制备炔金属试剂，ee不高—
85%ee，底物有限—仅限芳醛

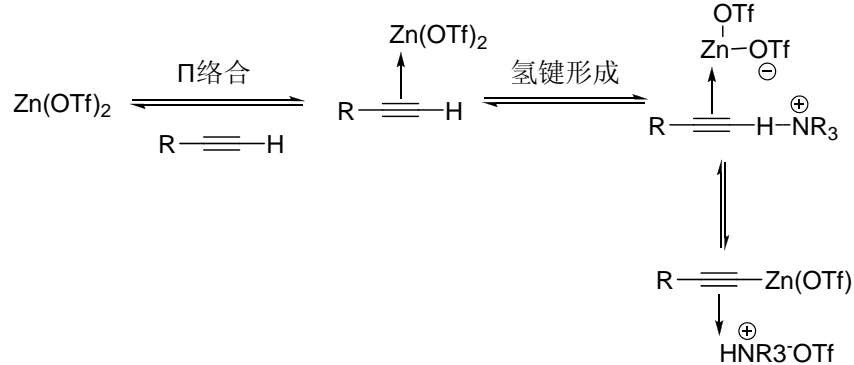
Carreira E., *J. Am. Chem. Soc.*, **2000**,122,1806; *Org. Lett.*, **2002**,4,1855; *J. Am. Chem. Soc.*, **2001**,1223,9687 配体:(+)-N-甲基麻黄碱 **突破性的进展**

三乙胺和在Zn(OTf)₂的存在，配体与端炔直接络合后对醛加成，简化了反应操作，条件非常温和，不需严格无水无氧；提高温度实现催化反应

不足：对芳香醛底物效果不好

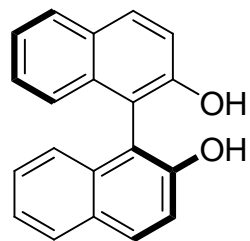
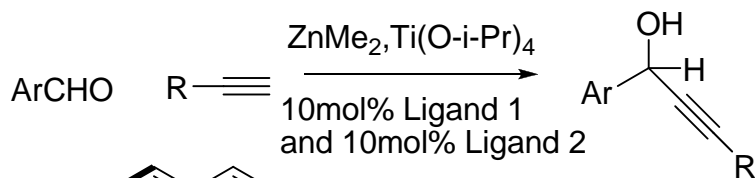
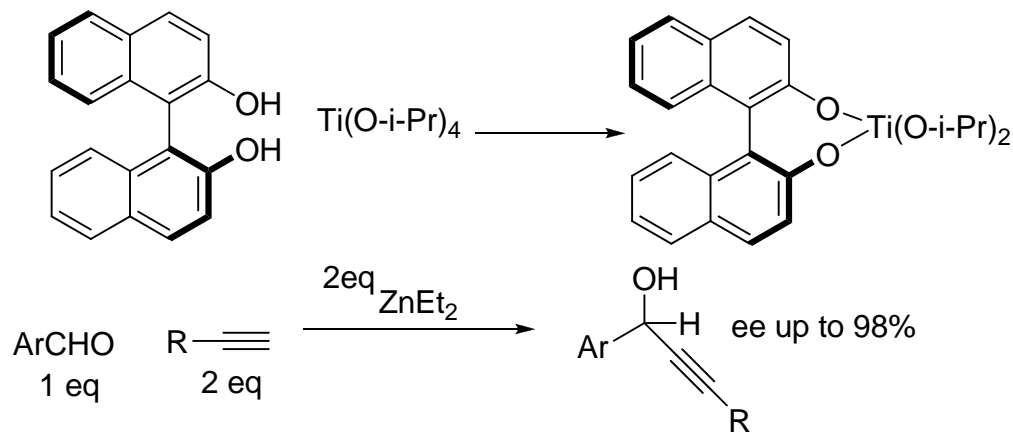


机理:



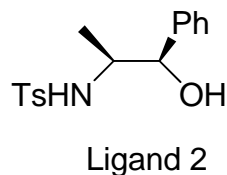
弥补Carreira的不足

Pu, *Org. Lett.*, 2002, 4, 4143; *Org. Lett.*, 2002, 4, 1855



Ligand 1

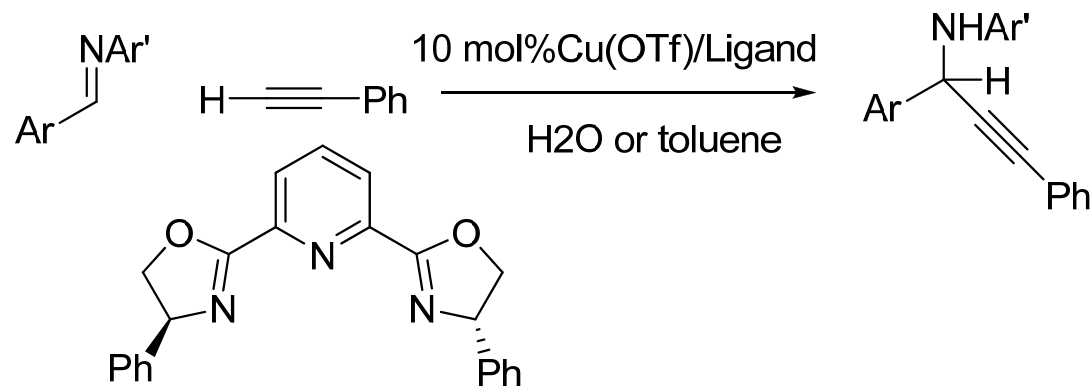
self-assemble



Ligand 2

Chan A. S. C., *J. Am. Chem. Soc.*, 2002, 124, 12636

端炔对碳氮双键直接加成研究不多，亚胺活性不如醛



2002年才有突破

Li C-J, *J. Am. Chem. Soc.*, 2002, 124, 5638

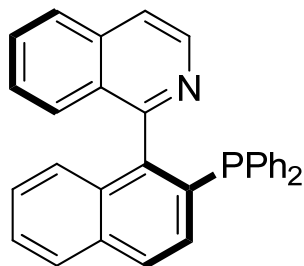
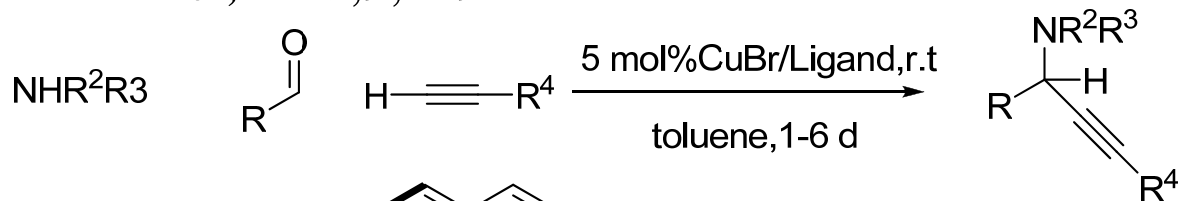
2002年, Knochel

Angew. Chem. Int. Ed., 2003, 42, 5763

Angew. Chem. Int. Ed., 2002, 41, 2535

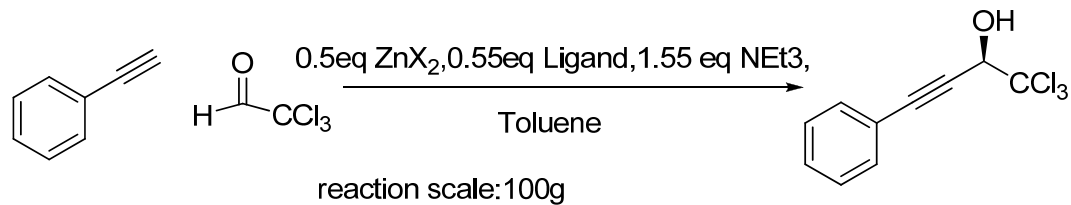
Chem. Eur. J., 2003, 9, 2797

改进：一锅法分步反应，不分离亚胺
PNAS, 2004, 101, 5749–5754



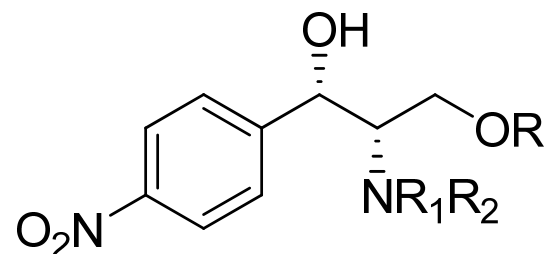
底物适用广泛、N上PG易于脱去后进一步转化为重要炔丙胺化合物

Adv. Synth. Catal. 2004, 346, 669 -674

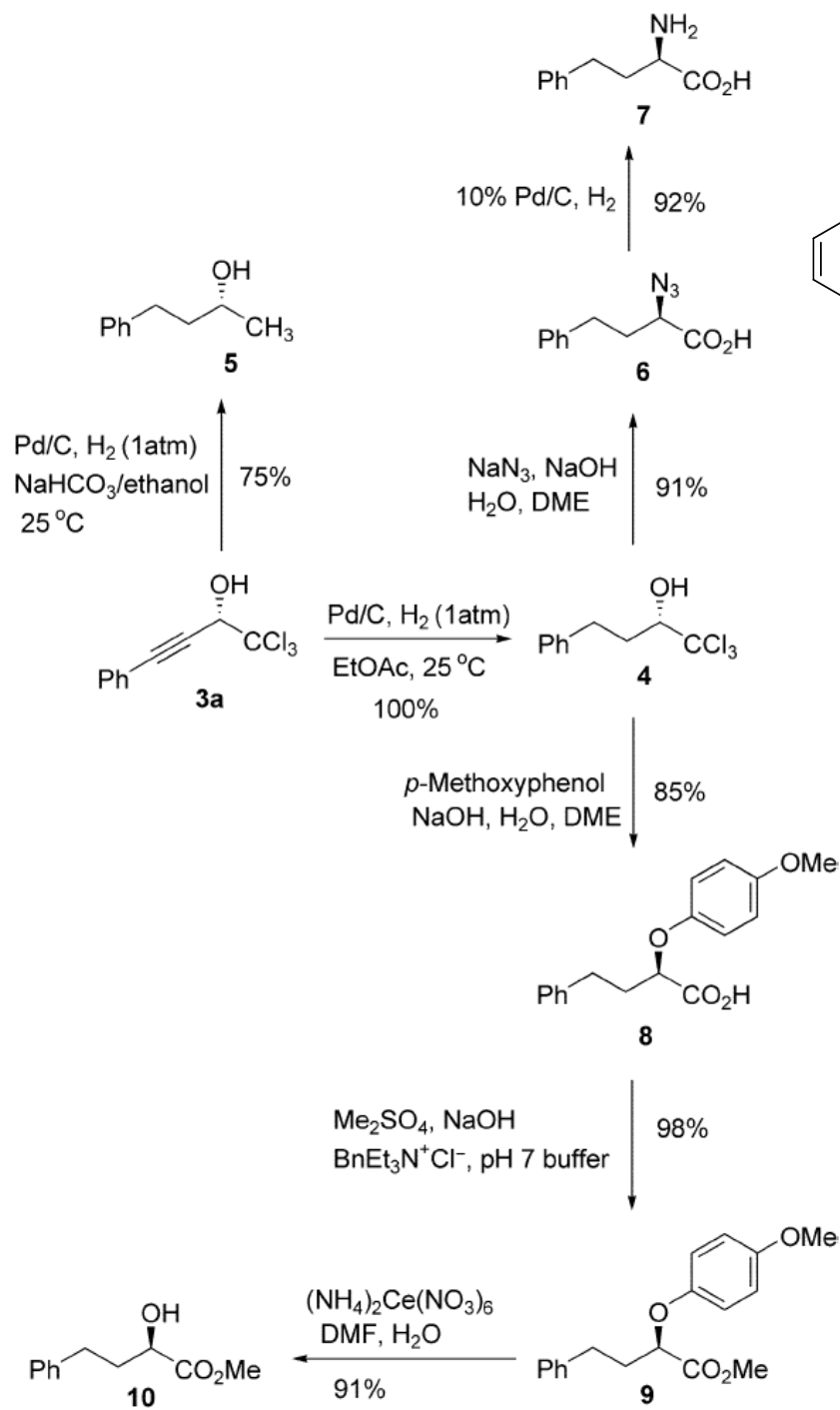


已在中科合臣通过放大试验

三氯甲醛工业原料，水合三氯甲醛就是一种安眠药的成分。工业品进行简单蒸馏后可直接使用，放置数月不影响反应



氯霉胺衍生物



总结:

不对称催化形成碳碳键的工业化

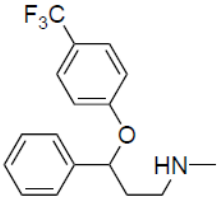
1. 与其他策略相比有明显的优势或能很大弥补其他策略的不足
2. 原料因素的考虑，价格、纯度及提纯的方法、用量、原子经济性
3. 高效的配体，低的用量
4. 如果无法有效降低配体用量，配体的合成必须简洁高效（一般1至3步）可以方便回收（水相中酸溶碱析/固载使用），原料廉价易得
5. 反应条件温和，Lewis酸（低毒）、温度、溶剂（绿色环保——不易挥发、不易形成过氧化物）
6. 反应的后处理简单适合工业上的生产操作习惯

Fluoxetine(氟西汀)、Tomoxetine(托莫西汀)、Nisoxetine(尼索西汀)、
Duloxetine(度洛西汀)

抗抑郁药物

Top 200 Generic Drugs by Retail Dollars in 2006

21 Fluoxetine

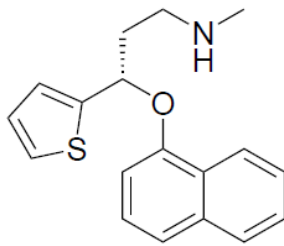


2005 Rank: 11 **Brand Name:** Prozac **2006 Sales:** \$439.8 Million

Profile:
A selective serotonin reuptake inhibitor used to treat depression and OCD.

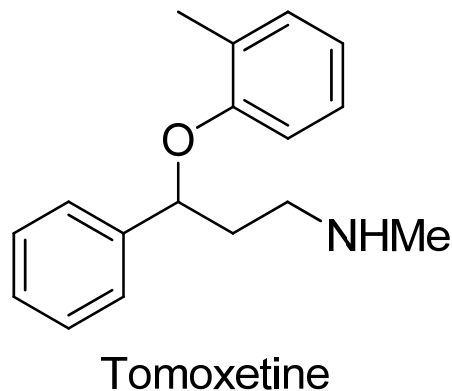
由于不同对映体体内代谢过程的不同以及各自药物活性的差异，同时还考虑到近年来制备光学纯药物的重要性，把这些药物制备成单一异构体已成当务之急
有研究表明（R）-氟西汀药效更快，副作用更小

35 Cymbalta



2005 Rank: 61 **Company:** Eli Lilly **2006 Sales:** \$1.08 Billion

Profile:
A serotonin and norepinephrine reuptake inhibitor used to treat depression.



Top200 brand name drug by retail dollar in2006

1988年起文献报道了12条不同的不对称合成路线

1988年 H.C. Brown

1988年 Shapless

1989年 E. J. Corey

1991年 Achiwa

1994年 D. Mitchell

1995年 D. Mitchell

1997年 Agbossou

2001年 Miles

2002年 Kumar

2002年 Sudalai

2002年 Barry Trost

2005年 Zhao G.

酶/化学拆分

不对称氢化

不对称双羟化

不对称动力学拆分

不对称羰基—烯反应

CBS不对称还原

不对称环氧化

烯丙基取代反应

手性原料出发的反应

Eli Lilly工业合成的方法