手性伯胺催化剂用于顺式选择性的不对称 Cross-Aldol 反应

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摘要: 基于酸碱作用, 将手性伯胺与质子酸原位结合制得有机小分子催化剂, 并用于醛与醛的不对称 Cross-aldol 反应. 与一般手性仲胺催化剂不同, 该类伯胺催化剂得到的是顺式选择性构型的 Cross-aldol 产物, 其产率达 90%, 顺反比和 ee 值分别为 9:1 和 90%. 相比而言, 采用简单易得的 (1*S*,2*S*)-(+)-环己二胺即可得到较高选择性的顺式产物.

关键词: 手性伯胺; 有机催化; 不对称催化; Cross-aldol 反应

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Chiral Primary Amine Organocatalysts for *Syn*-selective Asymmetric Cross-Aldol ReactionsGAO Qiang^{1,2}, LIU Yan¹, LU Shengmei¹, LI Can^{1,*}¹State Key Laboratory of Catalysis, Dalian Institute of Chemical Physics, Chinese Academy of Sciences, Dalian 116023, Liaoning, China²Graduate University of Chinese Academy of Sciences, Beijing 100049, China

Abstract: Based on the “acid-base” interaction strategy, organocatalysts for the asymmetric cross-aldol reaction were synthesized by the in situ combination of chiral primary amines with protonic acids. Unlike general secondary amine catalysts that give *anti*-selective products, as-prepared primary amine catalysts can give *syn*-selective cross-aldol products with high yield and high selectivity (up to 90% yield, 90:10 *syn/anti* ratio, 90% ee). Compared with the complex synthesis of the reported catalysts, the primary amine catalyst that gave the best results was easily prepared using commercial available (1*S*,2*S*)-(+)-cyclohexanediamine.

Key words: chiral primary amine; organocatalysis; asymmetric catalysis; cross-aldol reaction

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Aldol 反应是有机化学中最重要的 C-C 键形成反应之一^[1,2]. 自 2000 年 List 等^[3]发现 L-脯氨酸催化的分子间不对称直接 Aldol 反应以来, 有机小分子催化的不对称 Aldol 反应已成为合成手性 β -羟基化合物最重要、最有效的工具^[4,5]. 其中, 醛与醛的不对称 Cross-aldol 反应可用于合成手性 α -取代的 β -羟

基醛, 因而广泛应用于多丙酸酯和多乙酸酯等手性化合物的合成.

2002 年 Northrup 等^[6]直接以 L-脯氨酸为催化剂, 首次实现醛之间的不对称 Cross-aldol 反应, 此后文献报道的 Cross-aldol 反应产物构型主要以反式为主^[7]. Kano 等^[8,9]采用轴手性的胺-磺酰胺催化

顺式选择性 Cross-aldol 反应, 得到高的区域选择性和对映体选择性, 但催化剂合成比较复杂. 最近, Li 等^[10]采用手性二胺-布朗特酸结合的催化剂, 同样可得到较好的顺式选择性, 但催化剂前体手性二胺的合成同样比较复杂, 而且底物适用范围有限. 此前, 他们还将该类催化剂用于顺式选择性的酮与醛的 Aldol 反应, 取得了很好的效果^[11]. 基于酸碱作用, 本文采用简单方法制备了手性伯胺-质子酸催化剂, 并将其用于醛之间的顺式选择性不对称 Cross-aldol 反应.

脯氨酸及伯胺催化 Cross-aldol 反应的区域选择性控制机理如图式 1 所示. 与文献 [12] 类似, 根据机理 (I), 在 L-脯氨酸催化的 Cross-aldol 反应中, 反式烯胺过渡态 (*E*-enamine TS) 优先诱导生成反式构型, 脯氨酸的羧基基团提供氢键稳定反应过渡态. 而在本文为伯胺催化的 Cross-aldol 反应推测的机理 (II) 中, 顺式烯胺过渡态 (*Z*-enamine TS) 优先生成的是顺式构型, 且过渡态中两个 N-H··O 氢键能稳定顺式烯胺过渡态. 基于上述假设的过渡态模型, 本文筛选了伯胺催化剂 **1**~**7**, 期望实现顺式选择性的 Cross-aldol 反应 (见图式 2).

催化剂经手性伯胺和质子酸在二氯甲烷中原位制备后蒸去溶剂所得, 再用于丙醛与邻氯苯甲醛的 Cross-aldol 反应中. 催化反应过程如下: 向带磨口的反应试管中加入 0.1 mmol 手性伯胺, 依次加入 1

Mechanism (I):

Mechanism (II):

图式 1 假设的机理: (I) 脯氨酸及衍生物催化的反式 Aldol 反应过渡态; (II) 伯胺催化的反式 Aldol 反应过渡态

Scheme 1. Proposed mechanisms. (I) *Anti*-aldol transition state (TS) favored when using proline and its derivatives; (II) *Syn*-aldol TS favored when using primary amines.

图式 2 用于不对称 Cross-aldol 反应的手性伯胺

Scheme 2. Chiral primary amines for the asymmetric cross-aldol reaction.

ml 二氯甲烷, 1 mmol 邻氯苯甲醛, 搅拌溶解, 再加入三氟乙酸 (TFA, 0.2 mmol), 搅拌 0.5 h 后, 减压旋干溶剂, 将反应试管置于 0 °C 冷浴中, 加入反应物丙醛 0.36 ml, 反应时间 72 h. 反应完成后, 0 °C 冷浴情况下加入 4 ml 甲醇, 缓慢加入 400 mg 硼氢化钠还原 1 h, 饱和硫酸钠溶液淬灭反应, 二氯甲烷萃取, 减压蒸去有机溶剂, 粗产品用制备薄层色谱 (TLC) 分离 (石油醚: 乙酸乙酯 = 3:1). 手性伯胺和所有的 aldol 产物均为已知化合物^[10,13]. 反应结果列于表 1. 反应产物 **10** 的核磁数据如下. ¹H NMR (400 MHz, CDCl₃): δ 0.84~0.89 (3H, m), 2.09~2.14 (1H, m), 2.58 (2H, br), 3.68~3.79 (2H, m), 5.31 (1H, d, *J* = 7.2 Hz), 7.20~7.25

表 1 手性伯胺催化剂用于丙醛和邻氯苯甲醛的模型 Cross-Aldol 反应

Table 1 Chiral primary amine catalysts for the cross-aldol reaction of propanal and 2-chlorobenzaldehyde

Entry	Primary amine	Yield ^a (%)	<i>Syn/Anti</i> ^b	ee ^b (%)
1	1	79	82:18	79
2	2	73	76:24	-65
3 ^c	3	—	—	—
4 ^c	4	—	—	—
5	5	80	75:25	-55
6	6	83	78:22	27
7	7	87	74:26	29

Reaction conditions: in situ prepared catalysts with 0.1 mmol primary amine and 0.2 mmol trifluoroacetic acid (TFA), 1 mmol 2-chlorobenzaldehyde, 0.36 ml propanal, 0 °C, 72 h.

^aIsolated yield. ^bDetermined by chiral phase HPLC after conversion to the monobenzoylester. ^cNo obvious aldol product was detected.

(1H, m), 7.30~7.34 (2H, m), 7.56~7.58 (1 H, d, $J = 7.6$ Hz); 其 ee 值在装配有 Chiralpak AS-H 手性色谱柱的高效液相色谱上测定 (正己烷:异丙醇 = 99:1, 流速 1.2 ml/min, $\lambda = 254$ nm, 主要的对映体保留时间 $t_r = 19.0$ min, 次要的对映体保留时间 $t_r = 28$ min)^[13]. 由表可见, 以伯胺为催化剂时, 确实能得到顺式产物, 这与机理分析一致. 当以联萘胺 **3** 为伯胺催化反应时, 通过 TLC 点板检测, 发现副反应较为严重; 而使用 2-苯乙胺 **4** 作为伯胺时, 几乎没有反应发生, 可归因于该催化剂不能像其它手性二胺一样提供额外的氢键来稳定反应过渡态以活化底物醛 (见图式 1 中机理 (II)). 而采用 (1*S*, 2*S*)-(+)-环己二胺 **1** 为催化剂时, 产物收率、区域选择性和手性选择性最高, 分别为 79%, 82:18 和 79%. 另外, 该催化剂简单易得, 所以下文均以 (1*S*, 2*S*)-(+)-环己二胺为催化剂来进一步优化反应条件.

通过分析反应模型, 发现 NH_3^+ 和羰基之间的氢键在顺式选择性的 Cross-aldol 反应中起着非常重要的作用. 因此, 本文以酸性不同的 TFA、三氟甲磺酸 (TfOH)、醋酸 (HOAc)、磷钨酸 ($\text{H}_3\text{PW}_{12}\text{O}_{40}$) 和手性的 L-樟脑磺酸 (L-CSA) 为质子酸, 与环己二胺结合制得催化剂, 用于上述反应中, 结果见表 2. 由表可见, 当使用酸性较强的 TfOH 时, 反应结果最好. 同时, 本文通过调变伯胺 **1** 与 TfOH 不同比例后发现, 当催化剂胺与酸的比例为 1:1.5 时, 产物收率为 90%, 顺反比和 ee 值分别为 90:10 和 90% (表 2, 实验 7).

表 2 (1*S*, 2*S*)-(+)-环己二胺 **1** 与不同质子酸结合的催化剂催化反应条件的优化

Table 2 Optimization of the reaction conditions for primary amine **1** with different protonic acid additives

Entry	Additive	Yield ^a (%)	Syn/Anti ^b	ee ^b (%)
1	0.2 mmol TFA	73	82:18	79
2	0.2 mmol TfOH	80	85:15	90
3	0.2 mmol HOAc	69	68:32	38
4	0.067 mmol $\text{H}_3\text{PW}_{12}\text{O}_{40}$	75	69:31	64
5	0.2 mmol L-CSA	60	84:16	40
6	0.1 mmol TfOH	70	77:23	85
7	0.15 mmol TfOH	90	90:10	90

Reaction conditions: in situ prepared catalysts with 0.1 mmol primary amine **1** and the corresponding protonic acid additives, 1 mmol 2-chlorobenzaldehyde, 0.36 ml propanal, 0 °C, 72 h.

^aIsolated yield. ^bDetermined by chiral phase HPLC after conversion to the monobenzoyl ester.

表 3 反应底物的扩展

Table 3 Substrate scope of the cross-aldol reaction

Entry	R ¹	R ²	Time (h)	Yield ^a (%)	Syn/Anti ^b	ee ^b (%)
1	Me	4-NO ₂	36	71	63:37	72
2	Me	3-NO ₂	36	78	56:44	70
3	Me	2-NO ₂	36	67	64:36	76
4 ^c	Me	4-F	80	69	61:39	72
5 ^c	Me	4-Cl	80	60	68:32	80
6 ^d	Et	2-Cl	72	—	—	—
7 ^d	<i>i</i> -Pr	2-Cl	72	—	—	—

Reaction conditions: in situ synthesized catalysts with 0.1 mmol primary amine **1** and 0.15 mmol TfOH, 1 mmol aromatic aldehyde, 0.36 ml propanal, 0 °C.

^aIsolated yield. ^bDetermined by chiral phase HPLC. ^cDetermined by chiral phase HPLC after conversion to the monobenzoyl ester. ^dNo obvious aldol product was detected.

在上述优化的反应条件下, 本文对底物范围进行了扩展, 结果见表 3. 可以看出, 对于不同的芳香醛与丙醛反应, 均能得到顺式构型占优的产物, 尽管效果不如模型反应, 但该催化剂对吸电子和斥电子基的芳香醛均能得到较高的产率和手性选择性 (表 3, 实验 1~5). 然而当位阻较大的正丁醛和异戊醛用于与对硝基苯甲醛的 Aldol 反应时, 几乎没有活性 (实验 6 和 7), 具体原因尚不清楚^[10].

综上所述, 本文通过简单的商业易得的手性伯胺, 与质子酸结合制得的催化剂, 能有效地催化不对称 Cross-aldol 反应, 产物顺反比和 ee 值最高可分别达 90:10 和 90%, 与仲胺催化剂不同, 该催化剂得到的产物主要是顺式的. 这为设计合成不同区域选择性的催化剂和理解反应机理提供了一种新的思路.

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英 译 文 English Text

The aldol reaction is one of the most important carbon-carbon bond forming reactions in organic chemistry [1,2]. Since the pioneering work on the L-proline catalyzed asymmetric direct aldol reaction was reported by List et al. in 2000 [3], organocatalytic aldol reactions have become the most powerful and versatile tools to synthesize optically active β -hydroxy compounds [4,5]. Among these aldol reactions, asymmetric cross-aldol reactions of aldehydes can provide an attractive strategy for the construction of chiral α -substituted β -hydroxy aldehydes, which are important synthons in the synthesis of polypropionate and polyacetate products.

In 2002, Northrup et al. [6] reported the first asymmetric cross-aldol reaction of aldehydes using proline as a catalyst. Since then, a variety of organocatalysts have been designed and synthesized for this kind of cross-aldol reaction and the products are mainly *anti*-selective [7]. Recently, Kano et al. [8,9] reported *syn*-selective cross-aldol reactions that were catalyzed by axially chiral amino sulfonamide with high diastereoselectivity and enantioselectivity, however, the synthetic routes to obtain the catalyst are too convoluted. During our data collection for this paper, Li et al. [10] reported *syn*-selective cross-aldol reactions with good enantioselectivity that were catalyzed by chiral primary-tertiary diamine-Brønsted acid salts, however, the substrate scope and enantioselectivities were limited. Excellent *syn*-selectivities and enantioselectivities have previously been obtained while these catalysts have been used to catalyze the aldol reaction between aliphatic ketones and aromatic aldehydes [11]. Herein, we report the asymmetric *syn*-selective cross-aldol reaction of aldehydes (up to 90% yield, 90:10 *syn/anti* ratio, 90% ee), using easily prepared primary amine catalysts.

Diastereoselectivity control in these reactions depends on finding an appropriate catalyst based on a reasonable analy-

sis of the reaction mechanism. Similar to the previously proposed mechanism [12], mechanism (I) for the proline catalytic cross-aldol reaction (Scheme 1) shows that the *E*-enamine transition state (TS) is the main factor that determines *anti*-selectivity in this reaction, and the carboxylic acid group of L-proline provides a hydrogen bond to stabilize the TS. However, the mechanism (II), we proposed for the primary amines catalyzed cross-aldol reaction, shows that *syn*-selectivity could be reasoned by the *Z*-enamine TS, and the N-H $\cdots$ O hydrogen bonds are assumed to stabilize the *Z*-enamine TS. Based on this model, various primary amines **1**–**7** were screened for the *syn*-selective asymmetric cross-aldol reaction (Scheme 2).

The cross-aldol reaction of propanal and 2-chlorobenzaldehyde was selected as a model reaction. The catalysts were prepared in-situ by stirring 0.1 mmol primary amine and 0.2 mmol trifluoroacetic acid (TFA) in CH_2Cl_2 for 0.5 h. After evaporating the solvent under reduced pressure, the residues obtained were used directly as catalysts for the reaction. All the aldol reaction products are known compounds [10,13]. The reaction results are listed in Table 1. ^1H NMR of the aldol products **10**: ^1H NMR (400 MHz, CDCl_3): δ 0.84–0.89 (3H, m), 2.09–2.14 (1H, m), 2.58 (2H, brs), 3.68–3.79 (2H, m), 5.31 (1H, d, $J = 7.2$ Hz), 7.20–7.25 (1H, m), 7.30–7.34 (2H, m), 7.56–7.58 (1H, d, $J = 7.6$ Hz); Enantiomeric excess was determined by HPLC with a Chiralpak AS-H column (*n*-hexane:2-propanol = 99:1, $\lambda = 254$ nm, 1.2 mL/min; major enantiomer $t_r = 19.0$ min, minor enantiomer $t_r = 28$ min, after conversion to the monobenzoyl ester [13]. Except for the primary amine catalysts **3** and **4** which gave trace amounts of the product (entries 3 and 4), all the other primary amine catalysts gave *syn*-selective cross-aldol products in accordance with the proposed mechanism (II). Using primary amine **3**, many side reactions were found by TLC detection. No products were found when using primary amine **4** and this may be attributed to the lack of hydrogen bonds that would stabilize the TS as proposed in mechanism (II). The best diastereoselectivity and enantioselectivity (82:18 *syn/anti* ratio, 79% ee) were achieved in the model reaction when using **1** [(1*S*,2*S*)-(+)-cyclohexanediamine] as the catalyst (entry 1). The commercially available (1*S*,2*S*)-(+)-cyclohexanediamine was then chosen as the primary amine to optimize the reaction conditions.

From the transition state model, the hydrogen-bond between NH_3^+ and the carbonyl group plays an important role in the *syn*-selectivity of the cross-aldol reaction of aldehydes. The strength of the hydrogen bond is dependent on the acidity of the additives. Therefore, different acid additives such as TFA, triflic acid (TfOH), acetic acid (HOAc), $\text{H}_3\text{PW}_{12}\text{O}_{40}$, and chiral camphorsulfonic acid (L-CSA) were screened in our work (Table 2). Higher yields, diastereoselectivities, and enantioselectivities (80% yield, 85:15 *syn/anti*, 90% ee) were

obtained when using TfOH (Table 2, entry 2 vs entries 1, 3–5). After that, different ratios of (1*S*,2*S*)-(+)-cyclohexanediamine to TfOH were also investigated (entries 6 and 7). The best result was a 90% yield, 90:10 *syn/anti*, and 90% ee for the 1:1.5 ratio (entry 7 vs entries 2 and 6).

Under the optimized conditions (Table 2, entry 7), the scope of the substrates in the cross-aldol reactions was expanded to a series of aldehyde donors and aromatic aldehyde acceptors (Table 3). In all these cases, *syn*-selective cross-aldol products were obtained and moderate diastereoselectivities as well as good enantioselectivities characterized the cross-aldol reactions of propanal with the other aromatic aldehydes. Unfortunately, no desired cross-aldol products were obtained when *n*-butyraldehyde and 3-methyl butanal

were used as aldehyde donors and the mechanism for this phenomenon remains unclear [10].

In summary, primary amine organocatalysts based on our proposed mechanism for catalyst design efficiently catalyzed the *syn*-selective cross-aldol reaction of aldehydes with up to 90% yield, 90:10 *syn/anti*, and 90% ee. Compared with the complex synthesis of the reported catalysts, we present primary amine catalysts prepared from commercially available (1*S*,2*S*)-(+)-cyclohexanediamine. This paper may offer a new method to design catalysts for different selectivities in various reactions.

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