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Practical synthesis of four different pseudoenantiomeric organocatalysts with both *cis*- and *trans*-substituted 1,2-cis-cyclohexanediamine structures from a common intermediate

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ABSTRACT

A new and convenient approach has been deviced for the practical synthesis of structurally robust, four different pseudoenantiomeric amino Tf-amido organocatalysts with the unique *cis*- and *trans*-substituted 1,2-cis-cyclohexanediamine structures. These pseudoenantiomeric organocatalysts are easily prepared by the Diels-Alder strategy of 2-phenyl-1,3-butadiene and maleic anhydride, and their chemical behavior was investigated by their application to asymmetric aldol synthesis for the practical synthesis of both enantiomeric aldols.

1. Introduction

The chiral phenomenon plays an crucially important role not only in nature but also in pharmaceutical, agrochemical and other chemical industries.[1] A variety of compounds associated with living organisms are chiral, and enantiomers of such compounds may possess distinctly different biological activity. Those include DNA, enzymes, hormones, antibodies, etc. Thus, the biology is quite sensitive to the chirality, and the biological activity of drugs depends on which enantiomer is used. In fact, in pharmaceutical industries, about half of the drugs currently in use are known to be chiral products, and its number is steadily increasing.[2] Accordingly, it is important to synthesize both enantiomeric products, and to promote the chiral separation and analysis of racemic drugs in pharmaceutical industries as well as in clinical use in order to eliminate the unwanted enantiomer from the preparation. The most traditional way for obtaining both enantiomeric products is the proper use of both enantiomeric catalysts,[3–6] although the preparation of both enantiomeric catalysts in a separate manner is often time-consuming. In a practical viewpoint, the use of two different pseudoenantiomeric catalysts derived from the common chiral compounds or intermediates seems to be more convenient for the synthesis of both enantiomeric products. In this context, we are interested in the design of new pseudoenantiomeric organocatalysts from the common chiral source for efficient asymmetric transformations. Indeed, we previously reported the facile synthesis of two different pseudoenantiomeric organocatalysts **2** and **3** from the common chiral compound **1** with the unique *cis*-diamine structure via 3-step sequence (Scheme 1).[7] The synthetic application of these pseudoenantiomeric organocatalysts **2** and **3** is illustrated by asymmetric aldol reaction of cyclohexanone and *p*-nitrobenzaldehyde **4a**, leading to both enantiomeric aldol products, *anti*-**5a** and *anti*-**6a**, respectively.[8,9]

2. Results and discussion

Although this asymmetric strategy is highly practical, there still

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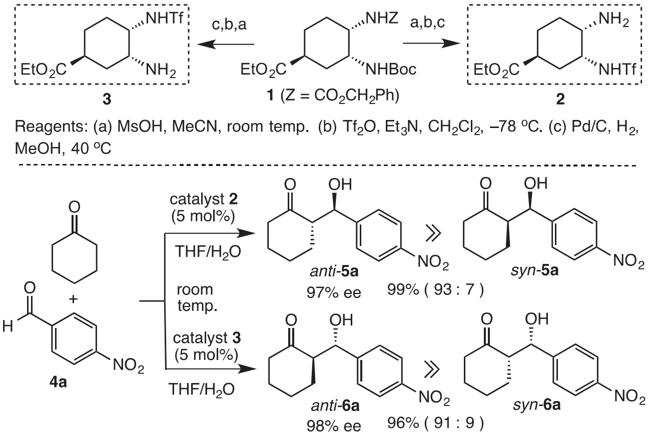
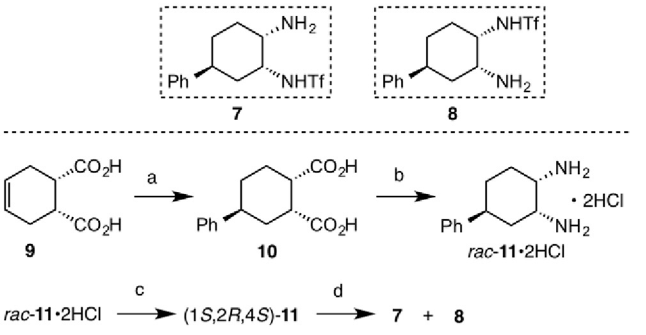


Reagents: (a) MsOH, MeCN, room temp. (b) Tf_2O, Et_3N, CH_2Cl_2, –78 °C. (c) Pd/C, H_2, MeOH, 40 °C

Scheme 1. Synthesis of two different pseudoenantiomeric organocatalysts **2** and **3**, and the application to asymmetric aldol synthesis.

needs some improvements on the design of pseudoenantiomeric organocatalysts **2** and **3**. Namely, the common chiral source **1** is not commercially available, and the synthesis of **1** generally requires some more steps from an easily available starting material.[10] In addition, the ester functionality in **1** is labile under acidic or basic conditions. Apparently, more robust pseudoenantiomeric organocatalysts of type **7** and **8** would be desirable for the wide variety of asymmetric transformations (Scheme 2). Accordingly, pseudoenantiomeric organocatalysts **7** and **8** can be prepared from commercially available *cis*-4-cyclohexene-1,2-dicarboxylic acid **9** in 4-step sequence as shown in Scheme 2. Thus, the Friedel-Crafts alkylation of *cis*-4-cyclohexene-1,2-dicarboxylic acid **9** in benzene furnished 4-phenyl-1,2-cyclohexanedicarboxylic acid **10** in 81% yield.[11] The Curtius rearrangement of diacid **10** afforded **11** as hydrogen chloride salt.[12] This racemic salt was then resolved with optically pure (*S*,*S*)-benzoyltartaric acid to furnish optically pure (1*S*,2*R*,4*S*)-**11**.[13] Mono-triflation of (1*S*,2*R*,4*S*)-**11** gave a mixture of amino Tf-amido organocatalysts **7** and **8**, which were easily separated by column chromatography to furnish optically pure **7** and **8**.[14]

We then compared the reactivity and selectivity of robust organocatalysts **7** and **8** in comparison with the original organocatalysts **2** and **3** in asymmetric aldol reaction of cyclohexanone with substituted benzaldehyde derivatives as shown in Table 1.[15,16]

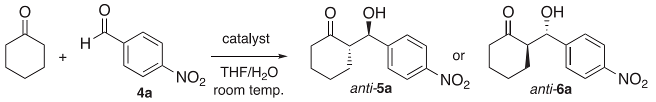
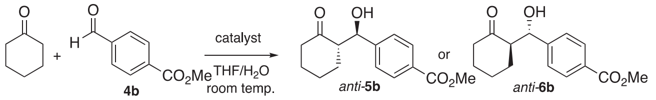
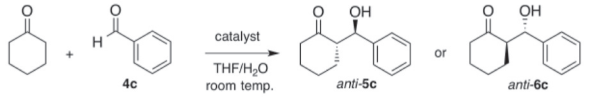


Reagents and conditions: (a) (i) benzene, $AlCl_3$, 50 °C; (ii) 6 M HCl aq., room temp. (b) (i) DPPA, Et_3N, THF, room temp.; (ii) toluene, reflux then 6 M HCl aq. (c) (i) NaOH, H_2O, room temp.; (ii) (*S*,*S*)-DBTA, MeOH, EtOH, room temp.; (iii) 2 M NaOH aq., CH_2Cl_2, room temp.; (d) TfCl, Et_3N, CH_2Cl_2, room temp.

Scheme 2. Synthetic route of two different, robust pseudoenantiomeric organocatalysts **7** and **8** from *cis*-4-cyclohexene-1,2-dicarboxylic acid **9**.

Table 1

Asymmetric direct aldol reaction of cyclohexanone and substituted benzaldehydes catalyzed by pseudoenantiomeric organocatalysts **2**, **3**, **7**, **8**, **12** or **13**.[a]

entry	catalyst	major aldol	% yield[b]	anti/syn ratio[c]	% ee[d]
					
1	**2**	*anti*-**5a**	99	93: 7	97
2	**3**	*anti*-**6a**	96	91: 9	98
3[e]	**7**	*anti*-**5a**	96	81: 19	95
4	**8**	*anti*-**6a**	96[f]	93: 7	99
5	**12**	*anti*-**5a**	94[f]	91: 9	99
6	**13**	*anti*-**6a**	48[e]	52: 48	67
					
7	**2**	*anti*-**5b**	99	89: 11	93
8	**3**	*anti*-**6b**	96	85: 15	94
9[e]	**7**	*anti*-**5b**	95	82: 18	93
10	**8**	*anti*-**6b**	97[f]	93: 7	99
11	**12**	*anti*-**5b**	95[f]	90: 10	99
12	**13**	*anti*-**6b**	46	51: 49	54
					
13	**2**	*anti*-**5c**	53[g]	96: 4	98
14	**3**	*anti*-**6c**	27[g]	89: 11	76
15[e]	**7**	*anti*-**5c**	42[g]	81: 19	83
16	**8**	*anti*-**6c**	61[f,g]	94: 6	98
17	**12**	*anti*-**5c**	66[f,g]	91: 9	98
18	**13**	*anti*-**6c**	20[g]	51: 49	58

[a] Unless otherwise specified, asymmetric direct aldol reaction of cyclohexanone and substituted benzaldehyde in the presence of 5 mol% of catalyst **2**, **3**, **7**, **8**, **12** or **13** at room temperature for three days.

[b] Isolated yield.

[c] The *anti*/*syn* ratio was determined by ^1H NMR analysis.

[d] Enantiopurity of *anti*-aldol products was determined by HPLC analysis using a chiral column [DAICEL Chiralpak AD-H and AS-H] with hexane-isopropanol as solvent.

[e] DMSO/H_2O was used as solvent.

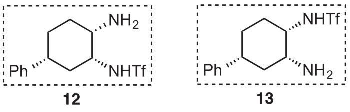
[f] Reaction for one day.

[g] The reaction was not complete under the standard conditions.

With three different benzaldehyde substrates, there is a general tendency among four different pseudoenantiomeric organocatalysts **2**, **3**, **7**, and **8**. In the asymmetric aldol synthesis of *anti*-**5**, the robust organocatalyst **7** exhibited lower reactivity and selectivity (both *trans*- and enantioselectivity) than **2** (entries 3, 9, 15 vs. 1, 7, 13), while pseudoenantiomeric organocatalyst **8** showed better reactivity and selectivity than **3** (entries 4, 10, 16 vs. 2, 8, 14).

So far, we studied the reactivity and selectivity of *trans*-substituted 1,2-cis-diamine-derived organocatalysts **2**, **3**, **7**, and **8**. However, we are also interested in the chemical behavior of the corresponding *cis*-substituted 1,2-cis-diamine-derived organocatalysts **12** and **13** (Scheme 3).

The intermediary 4-phenyl-4-cyclohexene-1,2-cis-dicarboxylic



Scheme 3. Robust *cis*-substituted pseudoenantiomeric organocatalysts **12** and **13**.

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