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Direct enantioseparation of diarylmethylamines with an *ortho*-hydroxy group via diastereomeric salt formation and their application to the enantioselective addition reaction of diethylzinc

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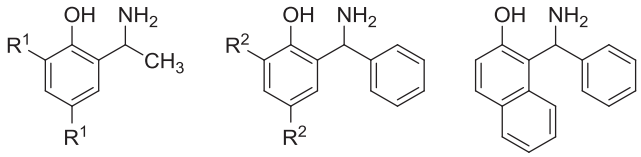
ABSTRACT

Two chiral diarylmethylamines with a phenolic hydroxy group at their *ortho* positions (**1c** and **1d**) were synthesized, and their direct enantioseparation via diastereomeric salt formation was investigated. Crystallographic analyses of the diastereomeric salts involving **1c** were conducted: water molecules incorporated in the space played an important role in chiral recognition. Enantiopure **1** were applied for the enantioselective addition of diethylzinc to benzaldehyde. Ligand (*R*)-**1d** afforded the product in very high yield (96%) and enantiopurity (92% ee). Not only the phenyl group on the stereogenic center of (*R*)-**1d** but also its bulky *tert*-butyl group is important for chiral induction.

1. Introduction

Enantiopure aminoalcohols are important chiral building blocks, which have been widely applied as chiral ligands,[1] organocatalysts,[2] and resolving agents for carboxylic acids.[3] Thus far, various enantiopure aliphatic aminoalcohols have been reported as they are predominantly derivatized from naturally occurring chiral sources.[4] In contrast, enantiopure *ortho*-(aminomethyl)phenols (*o*-APs), which represent a category of 1,3-aminoalcohols with a phenolic hydroxy group, have not been extensively examined. Because of their rigid backbone and the acidic hydroxy group, *o*-APs are unique, potential candidates for asymmetric reactions[5] and models for proton-coupled electron transfer.[6] In addition, *o*-AP is a substructure of salan compounds, which are extensively investigated as powerful ligands.[7]

Previously, we have reported the synthesis and enantioseparation of 2-(1-aminoethyl)phenols (**1a** and **1b**), which are chiral *o*-APs with a simple structure based on 1-phenylethylamine.[8] Resolution of enantiomers via diastereomeric salt formation with an acidic resolving agent is one of the most useful methods for preparing enantiopure amines.[9] Despite the intramolecular hydrogen bond between an amino group and an *ortho*-hydroxy group in the native form of **1**, salt formation is possible for several carboxylic acids, and the hydroxy group plays an important role in chiral recognition by the formation of OH ⋯ O and CH ⋯ O hydrogen bonds.[8]



1a: R^1 = H
1b: R^1 = ^{t}Bu

1c: R^2 = H
1d: R^2 = ^{t}Bu

Betti base

For systematically investigating chiral *o*-APs, herein, we focused on *o*-APs with two phenyl groups on the stereogenic center. Such a diarylmethylamine skeleton is an important substructure found in biologically active compounds.[10] In addition, the Betti base, a type of an *o*-AP based on a diarylmethylamine, is well known to be applied for asymmetric synthesis as well as a chiral auxiliary.[11] This suggests that other *o*-APs based on diarylmethylamine are potentially useful as chiral auxiliaries. As the initial target diarylmethylamine-based simple *o*-APs, 2-[amino(phenyl)methyl]

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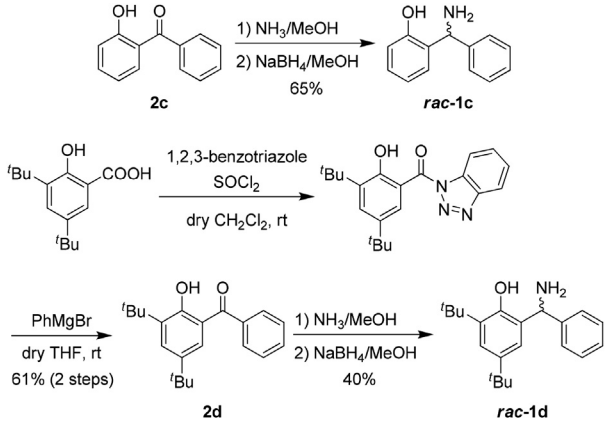
phenols (**1c** and **1d**), were selected, where a methyl group on the stereogenic centers of **1a** and **1b** is replaced by a phenyl group. The sterically demanding phenyl groups of **1c** is expected to enhance molecular recognition ability, as well as the bulky *tert*-butyl groups of **1d** contribute to high chiral induction ability. Herein, **1c** and **1d** were synthesized, followed by their direct enantioseparation via diastereomeric salt formation to obtain their enantiopure forms. The mechanism of chiral recognition was discussed on the basis of X-ray crystallographic analysis of their less-soluble salts; finally, their potential as a chiral ligand was demonstrated for the asymmetric addition of Et_2Zn to benzaldehyde.

2. Results and discussion

2.1. Synthesis of racemic substrates (*rac*-1c and *rac*-1d) and resolution of their enantiomers

For accessing enantiopure **1c** and **1d**, we first synthesized their racemic forms, followed by resolution of their enantiomers via diastereomeric salt formation. Although asymmetric hydrogenation transfer of the corresponding imine has been reported to afford enantio-enriched **1c**, a chiral Brönsted acid catalyst with a complicated structure is necessary, and **1c** is not obtained in an enantiopure form.[12] Scheme 1 shows the synthesis of *rac*-**1c** and *rac*-**1d**, where the one-pot reductive amination of the corresponding ketones **2** was adopted.[8] Ketone **2d** was prepared from 3,5-di-*tert*-butylsalicylic acid by amidation, followed by the Grignard reaction according to a previously published study.[13] The yields were moderate probably caused by the steric hindrance around the carbonyl group, and the products were characterized by ^{1}H NMR, ^{13}C NMR, IR spectra, and elemental analysis.



Scheme 1. Synthesis of *rac*-**1c** and *rac*-**1d**.

Fig. 1 shows the X-ray crystallographic structure of *rac*-**1d** after its recrystallization from EtOH. Both enantiomers of **1d** were crystallized together in the $Pna2_1$ space group, and an intramolecular hydrogen bond was observed between the hydroxy hydrogen atom and the nitrogen atom (the N ⋯ O distance was as short as 2.65 Å, and the O–H ⋯ N angle was 151°), which was also observed for *rac*-**1b**.[8]

Fig. 2 shows the eight commercially available acidic resolving agents **3**–**10**, which were used for testing the enantioseparation of *rac*-**1c** and *rac*-**1d**. Equimolar amounts of racemic *o*-AP and each resolving agent were mixed and recrystallized from an aqueous ethanol solution (Table 1). Among the tested resolving agents, L-mandelic acid (**3**), L-pyroglutamic acid (**5**), and (+)-10-camphorsulfonic acid (**7**) did not afford crystalline salts with both

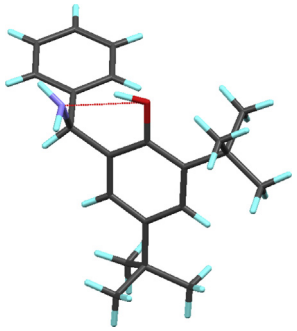


Fig. 1. Crystal structure of *rac*-**1d**. Dotted line represents the hydrogen bond.

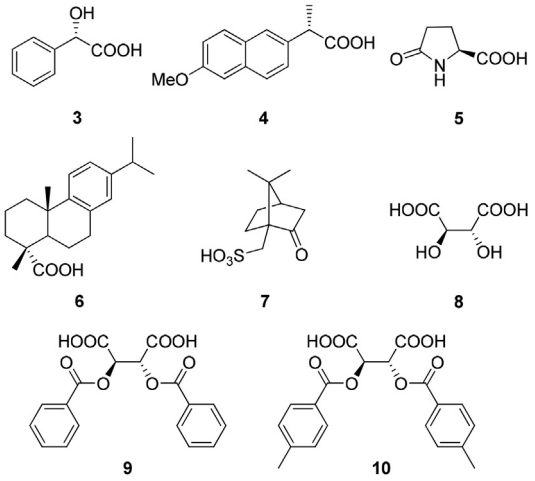


Fig. 2. Acidic resolving agents used in this study.

1c and **1d**, probably because these resolving agents have lower molecular weight, or are not significantly functionalized. On the other hand, highly functionalized L-tartaric acid (**8**) afforded a crystalline salt with **1c**; however, it did not exhibit any ability for chiral recognition. For the resolution of *rac*-**1c**, (*S*)-naproxen (**4**), dehydroabietic acid (**6**), and dibenzoyl-L-tartaric acid (**9**) afforded moderate efficiencies. Two former acids afforded (*R*)-**1c** salt as a less-soluble salt; on the other hand, antipode (*S*)-**1c** was preferentially deposited by salt formation with **9**. To our surprise, di-(*p*-toluoyl)-L-tartaric acid (**10**), which is structurally related to **9**, afforded a crystalline salt with **1c** but resulted in only a racemic form. Although **9** and **10** are divalent carboxylic acids, the molar ratio of **1c** and **9**/**10** in the precipitated solid was 1:1, as estimated from ^{1}H NMR analysis.

In contrast, *rac*-**1d** was separated with good efficiencies by **9** or **10**, while others were not useful. During the resolution of *rac*-**1d**, some insoluble material (**11**) was obtained, which was produced by the bimolecular condensation of *rac*-**1d** at refluxing temperature. Fig. S1 shows the X-ray crystallographic structure of **11**. Scheme 2 shows the plausible reaction mechanism, and such a reaction previously reported for simple 2-(aminomethyl)phenol has been found to proceed via an *ortho*-quinone methide intermediate.[14] After insoluble **11** was filtered, from ^{1}H NMR analysis, the composition ratio of **1d** and **9** in the precipitated solid was approximately **1d**:**9**=3:2. The IR spectra and powder X-ray diffraction patterns were compared; **1d** or **9** was not found to be included in the precipitate, and a new solid phase was produced (Fig. S2). The molar amount of **9** was less than that of **1d** probably because **9** is a divalent carboxylic acid, and a part of the carboxyl groups is not ionized.