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Synthesis of axially chiral 1,8-diarylnaphthalene ligands and application in asymmetric catalysis: an intriguing fluorine effect

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ABSTRACT

A fluorinated and a non-fluorinated axially chiral 1,8-diarylnaphthalene ligand have been synthesized through an Ullmann and Suzuki coupling reaction based strategy. A practical methodology for the successful chiral resolution of the newly synthesized catechol based moiety is presented. We also disclose the preliminary application of these axially chiral molecules as ligands in asymmetric transformation reactions.

1. Introduction

The 1,8-diaryl substituted naphthalene scaffold possesses interesting properties due to the unique orientation of the two-aryl moieties in a parallel-stacked geometry. Molecules of this type have consequently found applications in the study of π–π interactions,[1–10] parallel displaced aromatic π-interactions,[11] through-space spin–spin coupling[12] and in studies of the through-space control of the kinetic decay of *ortho*-quinonoid intermediates.[13] Chemical sensors based on this scaffold have been developed as fluorescence based detectors of dicarboxylic acids,[14] for the enantioselective CD analysis of chiral amino alcohols,[15] as an intramolecular excimer emitting compound,[16] as well as stereodynamic chemosensors.[17,18]

Catechols are important in biological settings where they are ubiquitous in siderophores that control iron absorption; they also have high affinity for metal ions in high oxidation states or with high charge/radius ratios.[19] Some catechol siderophores even undergo chiral recognition during enzymatic reactions as part of the iron transport pathway.[20]

In asymmetric catalysis, axially chiral ligands hold a unique place among privileged ligand structures such as BINOL, BINAP and their derivatives.[21,22] In spite of the many potential uses mentioned, the application of 1,8-diarylnaphthalene based scaffolds as ligands in asymmetric catalysis is relatively unexplored.[23,24]

The development of new ligand scaffolds remains important in modern synthetic organic chemistry in order to increase the scope and efficiency of catalytic asymmetric reactions. While known privileged ligands have a wide range of applications in asymmetric catalysis,[25] new ligands must be designed and tested in order to escape the confines defined by the reactivity profiles of existing ligands. Herein we report a short and efficient synthesis of a new type of axially chiral 1,8-diarylnaphthalene based catechol ligand with both fluorinated and non-fluorinated substituents. The enantiomers were resolved using chiral pool based techniques. These compounds should be of interest, both as chiral ligands for asymmetric catalysis as well as chiral detector systems and charge transfer complexes. We also report an application in the asymmetric Mukaiyama aldol reaction in which the perfluorinated ligand **2** shows higher enantioselectivity than the non-fluorinated ligand **1**.[26,27]

2. Results and discussion

Herein, we report the preparation of two ligands; ligand **1** with an electron rich benzene ring and ligand **2** with five strongly electron withdrawing fluorine groups and an inverted quadrupole (Fig. 1). We hypothesized that these effects might result in differences in reactivity and chiral induction. The aryl groups are in a parallel-stacked geometry, but can rotate around the aryl–naphthalene

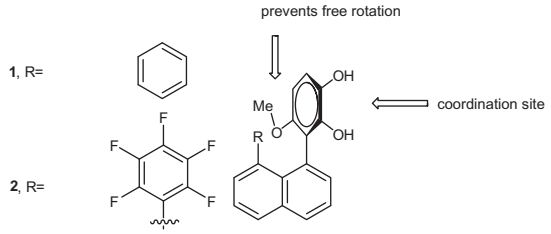

Figure 1. Design of axially chiral molecules **1** and **2**.

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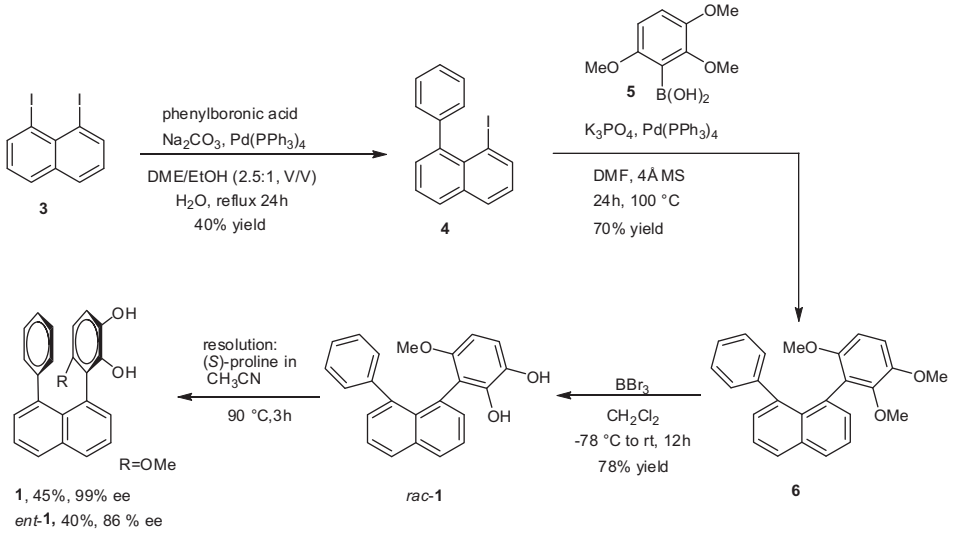
bond depending on the strength of parallel-stacked π–π interactions. In the neighbouring catechol aryl group, a methoxy group was incorporated into the design in order to prevent free rotation around the aryl-naphthyl C–C bond. The catechol would serve the double function of preventing free rotation as well being a metal coordination site for detector or catalytic applications.

Our synthesis of **1** started from 1,8-diiodonaphthalene **3**.[28] Suzuki coupling of **3** and phenylboronic acid gave the mono arylated product **4** in 40% yield (Scheme 1). This is presumably due to the known propensity of the second iodine to react more rapidly than the first[29] leading to 1,8-diphenylnaphthalene as a by-product. Indeed, a second Suzuki coupling using trimethoxy boronic acid **5** afforded **6** in 70% yield. Selective deprotection of the methylated catechol functionality was achieved in 78% yield using BBr_3 to give the chiral racemic catechol *rac*-**1**.

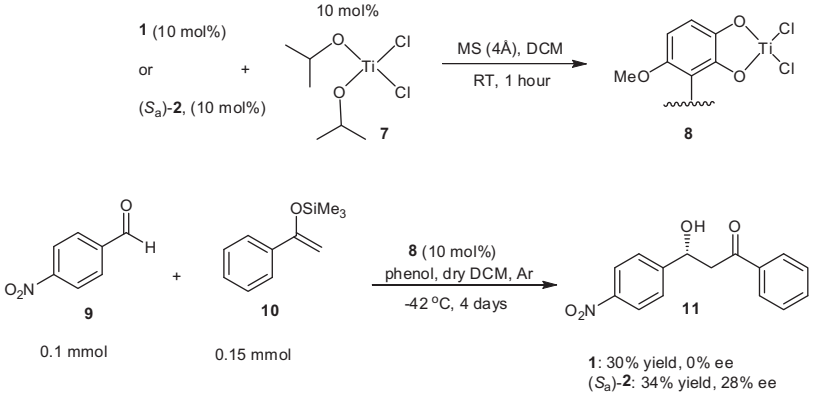
Resolution of *rac*-**1** was achieved via chiral recognition by (*S*)-proline in acetonitrile at 90 °C.[30] *Rac*-**1** and (*S*)-proline were added to acetonitrile in equimolar amounts and refluxed for 3 h. Upon cooling to room temperature, the inclusion complex precipitated from solution as a white solid precipitated from the solution. The precipitate was hydrolysed in a mixture of ethyl acetate and water, after which crystallization from toluene furnished ligand **1** in 45% yield and with >99% ee. The enantiomer ***ent*-1** was recovered from the mother liquor in 40% yield and with 86% ee.

Unfortunately, the inclusion complex of **1** with (*S*)-proline was not amenable to X-ray analysis. However, the complex was characterized by NMR.

In order to investigate the applicability of ligand **1** in asymmetric catalysis, we performed an asymmetric Mukaiyama aldol reaction (Scheme 2). A titanium complex of ligand **1** was generated in situ. Ligand **1** was dissolved in dry dichloromethane, after which molecular sieves (4 Å) were added followed by freshly prepared diisopropoxide-titanium(IV) dichloride **7**. Upon the addition of **7**, the reaction mixture turned red, which indicated complex formation with **1**. The putative complex **8** was left for one hour and then phenol and aldehyde were added. The reaction mixture was cooled to −42 °C and then silyl enol ether was added. After 4 days reaction, product **11** was isolated in 30% yield, with the mass balance being unreacted starting material. Disappointingly, the aldol product was isolated as a racemic mixture. We hypothesized that the lack of stereochemical induction from the ligand might be due to too many degrees of freedom in the catalyst–aldehyde complex. Taking note of the recent finding that fluorine, when appropriately situated in a chiral catalyst, might have a positive effect on the chiral induction,[31] we prepared fluorinated ligand **2** (Fig. 1 and Scheme 3). In this ligand, the fluorines are situated in such an orientation that they might interact orthogonally with the titanium-complexed aldehyde through polar interactions as



Scheme 1. Synthesis of the axially chiral catechol **1** and ***ent*-1**.



Scheme 2. Asymmetric catalytic Mukaiyama aldol reaction using **1** and **2**.