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Short Communication

Synthesis of chiral fluorine-containing compounds via Pd-catalyzed asymmetrical allylations of dimethyl 2-fluoromalonate using sulfonamide-pyridine ligands

Min Zhang, Mingzhu Zhao, Purui Zheng, Hongbo Zhang, Xiaoming Zhao*

Shanghai Key Lab of Chemical Assessment and Sustainability, Department of Chemistry, Tongji University, 11239 Siping Road, Shanghai 200092, PR China

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ABSTRACT

Chiral *o*-aniline sulfoxides serving as chiral sulfurous source were synthesized, from which new sulfonamide-pyridine ligands were made in three-steps. These compounds proved to be efficient *S,N*-ligands for enantiocontrol of palladium-catalyzed allylic substitutions of dimethyl 2-fluoromalonate. The induced effect of the Pd/*S,N*-ligand catalyst on the enantioselectivity depends on the steric demand of the substituent on the sulfoxide moiety. This method provided the fluorine-containing allylic products with up to 94% *ee*.

1. Introduction

Asymmetric catalysis with transition metal complexes has been rapidly developing in synthetic chemistry. Chiral ligands play an essential role for the achievement of excellent stereoselectivity. In this regard, design and synthesis of novel effective ligands remain a big challenge [1]. Chiral sulfoxides were used as an auxiliary in asymmetric synthesis [2]. More recently, chiral sulfoxide ligands have attracted considerable attention for their utilization in asymmetric synthesis [3]. The sulfinyl group of such ligands is featured with both an intrinsic stereogenic center and binding site to transition metals. Therefore, it is reasoned that a structurally proper sulfoxide could possibly act as a sulfur ligand [4], which may offer sulfurous source for asymmetric catalysis. There were several examples focused on palladium (Pd)-catalyzed asymmetric allylations with using chiral sulfoxide ligands [5], which made from *tert*-butylsulfinyl group. [5g–j] To expand the chiral sources of sulfoxide ligands, a structural diversity of *o*-aniline sulfoxides has been envisioned, which may be synthesized according to our previous works (Scheme 1).

Fluorine-containing compounds are of great importance to pharmaceutical industry [6]. In particular, optically active monofluorinated compounds such as *Pharmacia, Clofarabin,* and *Difluprednate* are popular drugs [6d,7]. There are several methods reported for the synthesis of monofluorinated compounds [6a] however, transition metal-catalyzed asymmetrical allylic substitutions of fluorinated methylene derivatives are less disclosed [8], which could afford the monofluorinated allylic products. Herein we report the synthesis of new chiral sulfonamide-pyridine ligands stemmed from *o*-aniline sulfoxides and their application in Pd-catalyzed asymmetric allylic substitutions of dimethyl 2-fluoromalonate.

2. Results and discussion

We initially aimed at developing a method for the preparation of enantioenriched 2-allylthio-substituted aniline **3** on a large-scale (Scheme 1). This allylation reaction was carried out on a 4 mmol scale; and we found that the presence of a little water led to the reduction of the yield; and that the amount of iridium catalyst has an influence on this reaction. After avoiding the presence of water and reducing iridium catalyst from 2 mmol% to 1 mmol%, a large-scale synthetic method for **3** was developed on the basis of our previous work [9] (see: SI). The key intermediate **5** was prepared by a reduction of **3** with *o*-nitro benzenesulfonylhydrazide (NBSH) [10], following by an oxidation with *m*CPBA without loss of *ee* value (Scheme 1, see: SI).

As a result, two isomers (**5′** and **5**) were obtained and they can be separated by flash column chromatography. Among these isomers, the absolute configuration of **5b'** (R^1 = 3,5-*di*-$MeOC_6H_3$)

* Corresponding author.
E-mail address: xmzhao08@mail.tongji.edu.cn (X. Zhao).

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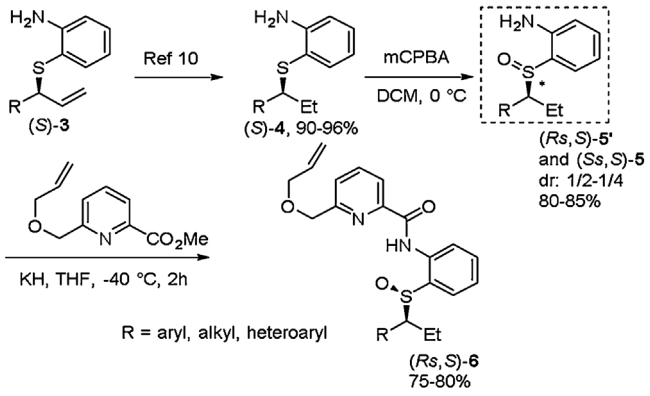

Scheme 1. Synthesis of new chiral sulfonamide-pyridine ligands **6**.

was established as (*Rs*,*S*) by its X-ray diffraction analysis (Fig. 1) [11]. Finally, the treatment of **5**, either (*Rs*,*S*)-**5** or (*Ss*,*R*)-**5′**, with potassium hydride (KH) at −40 °C, following by a reaction with methyl 6-((allyloxy)methyl)picolinate, gave the corresponding ligand **6** (Scheme 1 and Fig. 2) [12]. The 6-(allyloxymethyl) picolinamide, a substituent at 6-position of pyridine moiety, is optimal for these *N*,*S*-ligands, which were reported in our previous work [13]. We found that the *N*,*S*-ligands generated from *tert*-butylsulfinyl group are unsuitable for Pd-catalyzed asymmetrical allylations of 2-napthyl-substituted allylic acetate with dimethyl 2-fluoromalonate [13].

To evaluate the catalytic potential of the *S*,*N*-ligand **6**, a Pd-catalyzed reaction of (*E*)-1,3-bis(3-fluorophenyl)allyl acetate **7a** with dimethyl 2-fluoromalonate **8a** [14] was carried out (Table 1). In the presence of a catalyst [15] made from [Pd(C_3H_5)Cl_2] and (*Rs*,*S*)-**6b**, the reaction was performed in THF at room temperature without base and no allylic products were observed. When sodium hydride (NaH) was used as an additive, to our delight, the allylic product **9a** was formed in a 35% yield with 80% *ee*; a little amount of (*E*)-1,3-bis(3-fluorophenyl)prop-2-en-1-ol was observed as well (entry 1). Thus, a number of bases including potassium 2-methylpropan-2-olate (^{t}BuOK), K_3PO_4, LiCl, 1,8-diazabicyclo [5.4.0]undec-7-ene (DBU), CsF and *tetra*-butylammonium fluoride (TBAF) was further investigated, we found that Cs_2CO_3 led to a superior result, whereas K_3PO_4, ^{t}BuOK and CsF gave moderate to good *ee* (entries 2, 3 and 6). Both LiCl and DBU were unsuitable for the reaction (entries 4 and 5). TBAF led to the highest yield but with an acceptable *ee* (entry 7). Variation of solvents has a significant impact on this reaction (entries 8 – 10). Chiral ligands are essential for the enantiocontrol of palladium-catalyzed allylic substitutions [5]. Consequently, a variety of the chiral sulfonamide-pyridine ligands was further explored. For instance, (*Ss*,*R*)-**6a** containing a phenyl group gave a somewhat lower *ee* than that of (*Rs*,*S*)-**6b**, which contains a 3,5-*di*-methoxy group on the phenyl ring (entry 8). The different configuration of ligand (*Ss*,*R*)-**6a** and (*Rs*,*S*)-**6b** resulted in the opposite configuration of **9a** (entry 8 vs entry 11). (*Rs*,*S*)-**6c** bearing a furanyl group gave a little lower *ee* than that of (*Ss*,*R*)-**6a** although it is structurally similar to (*Ss*,*R*)-**6a** (entry 12). Interestingly, (*Rs*,*R*)-**6d** with the least steric substituent such as a methyl group gave rise to good *ee* (entry 13). (*Rs*,*R*)-**6f** bearing a pyridine ring was also examined and it led to a poor outcome (entry 14). These results suggested that both the steric demand and nature of the substituent in **6** have a great influence on the enantioselectivity of this reaction. Furthermore, both Josiphos [16] and Trost ligands [17] were examined under the optimized conditions; Josiphos ligand gave **9a** in racemic form with a 83% yield (entry 15). Trost ligand led to a moderate result (entry16). It is noted that only trace amount of **9a** was formed when the reaction was carried out at 0 °C. Change of the ratio of reactants has a considerable influence, for example, **9a** was obtained in an improved yield (80%) albeit with a lowering *ee* (70%) when the ratio of **7a**/**8a** in 3/1 was employed at room temperature.

Analysis of **7a** which was recovered upon the completion of the reaction by HPLC on a chiral stationary phase illustrated that it was racemic.

Having established the optimized reaction conditions presented in entry 8 of Table 1, the scope of a series of (*E*)-1,3-disubstituted allyl acetates **7** was examined (Table 2). The substrates **7a** and **b** with the 3-substituted group, which is an

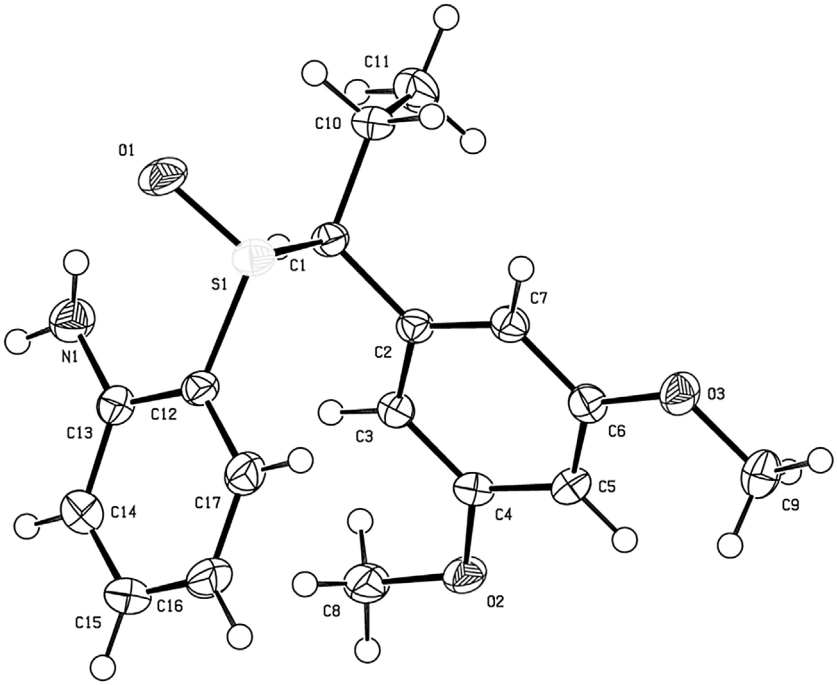

Fig. 1. X-ray structure of (*Rs*,*S*)-**5b'**.