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Enantioselective β-hydroxy thioesters formation via decarboxylative aldol reactions of malonic acid half thioesters with aldehydes promoted by chloramphenicol derived sulfonamides[1]

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ABSTRACT

A highly enantioselective synthesis of chiral β-hydroxy thioesters that uses a decarboxylative aldol reaction of malonic acid half thioesters and aldehydes catalyzed by a chloramphenicol base-derived bifunctional organocatalyst is reported. The resulting chiral β-hydroxy thioesters were obtained in high yields (up to 82%) with good to excellent enantioselectivities (up to 94% ee). The synthetic application of the methodology is illustrated by the asymmetric synthesis of the selective serotonin reuptake inhibitor dapoxetine.

1. Introduction

Chiral β-hydroxy thioesters[2] are important synthetic building blocks in many pharmaceuticals and natural products, including erythromycin (**1**), oxytetracycline (**2**), triamcinolone diacetate (**3**), tephrosin (**4**), atorvastatin (**5**) and fluoxetine (**6**). In the past two decades, tremendous efforts have been devoted to the construction of this class of β-hydroxy thioester motifs using a highly enantioselective catalytic approach. For example, Ikariya and co-workers[3] reported work on the asymmetric synthesis of β-hydroxy thioesters using an asymmetric Mukaiyama aldol reaction catalyzed by a BINOL-Ti complex. Subsequently, Shair[4] and Cozzi[5] and their co-workers independently investigated a direct aldol reaction with malonic acid half thioesters (MAHTs) using a chiral Cu/bis(oxazoline) catalyst to give the corresponding β-hydroxy thioesters; this method required the use of metal catalysts. Recently, Shibata[6] disclosed a metal-free decarboxylative addition reaction of MAHTs with isatins for the synthesis of β-hydroxy thioesters that is catalyzed by cinchona-derived squaramide. Most importantly, when using cinchona-based bifunctional thioureas or sulfonamides as catalysts, the groups of Song[7] and Wennemers[8] obtained β-hydroxy thioesters with up to 96% and 99% ee, respectively. Despite considerable progress, however, the inaccessibility and high cost of the catalysts used in these protocols limits their use in industrial applications. The ultimate goal of developing a practical and highly effective catalytic system remains elusive for the construction of chiral β-hydroxy thioester scaffolds using the asymmetric decarboxylative aldol reaction.

Chloramphenicol base is a byproduct of chloramphenicol production and an important chiral scaffold. Many homogeneous catalysts based on this structural motif have been reported and used in a wide variety of efficient enantioselective and non-enantioselective asymmetric reactions. These reactions have been applied to many pharmaceuticals and natural products, including the asymmetric ring opening of prochiral cyclic anhydrides, asymmetric transfer hydrogenation/dynamic kinetic resolution of α-amino-β-ketoesters, and catalytic enantioselective aldol reactions of α,β-unsaturated aldehydes with diketenes (Scheme 1).

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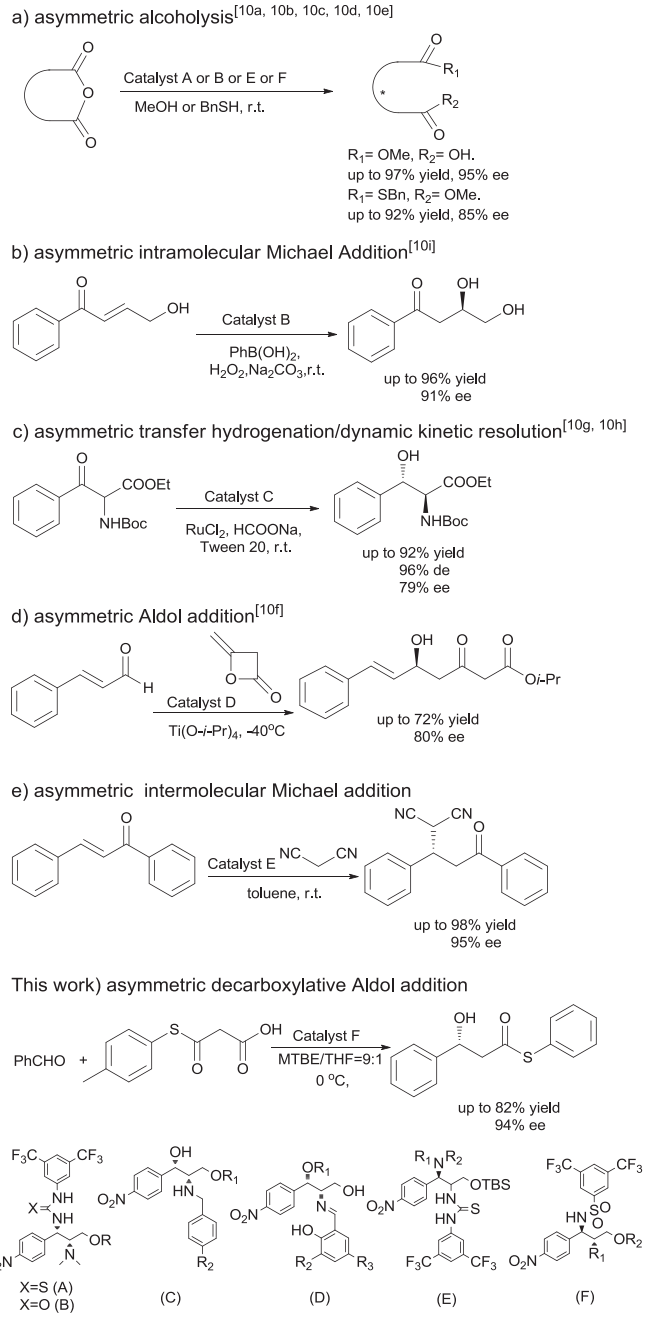

Scheme 1. Various asymmetric reactions catalyzed by our chloramphenicol derived catalysts.

Continuing our work[9] on the development of organocatalysts and their applications in asymmetric synthesis, we herein report the highly efficient enantioselective synthesis of β-hydroxy thio-esters from MAHTs and aldehydes using our chiral chloram-phenicol derived sulfonamide catalysts in a decarboxylative aldol reaction.

2. Results/discussion

We commenced our evaluation of the catalytic ability of chiral chloramphenicol derived sulfonamide catalysts **10a**-**10g, 11**–**14** by using thioester **8a** and aldehyde **7a** as model substrates for the decarboxylative aldol reaction. In the presence of organo-catalysts **10a**-**10g, 11**–**14** and using MTBE/THF = 9:1 as the solvent, desired product **9a** was obtained in good to excellent yields and poor to high ee values (Table 1, entries 1–11). In terms of both isolated yield and ee, the best result was obtained with catalyst **10g**.

With this preliminary result in hand, we investigated further parameters that may affect the efficiency of this transformation, including solvent (entries 1–6, Table 2), catalyst loading (entries 7–9) and temperature (entries 10–11). MTBE/THF (9:1) was the best solvent system among those that we screened. The catalyst loading had a marked effect on the reaction, with 50 mol% organocatalyst giving the best balance in terms of isolated yields and ee values. The reaction temperature had a considerable impact on the reaction rate, isolated yield and ee value. The aldol reaction proceeded slowly in very low yield and enantio-selectivity when it was carried out at −10 °C (entry 11). When the temperature was increased to 0 °C(entry 8), the reaction gave a 76% yield with 88% ee. A slight acceleration in the reaction rate and ee value was observed in the presence of 4 Å molecular sieves (entry 13, Table 2). We therefore decided to run the aldol reaction at 0 °C, with 50 mol% of the catalyst and 4 Å molecular sieves in MTBE/THF (9:1).

A series of β-hydroxy thioesters was obtained from a variety of aldehydes and MAHTs with the aim of extending the scope of the methodology under the optimized conditions. As shown in Scheme 2, we found that electron-rich thioesters **9a** and **9b** give high yields (80%, 73%) and excellent ee values (90%, 90%). Electron-deficient thioesters afforded products with ee values lower than 84%. In general, electron-donating groups at the ortho, para or meta positions of the phenyl ring of the aldehydes (**9f**-**k**) enable the decarboxylative aldol reaction to proceed effectively in high yield (70%–76%) and excellent enantiomeric excess(90%–94% ee). The enantiomeric excess decreases when strongly electron-withdrawing groups, such as *p*-nitro and *p*-cyano groups, are attached to the phenyl ring of the aldehyde. In addition, weakly electron-withdrawing groups are tolerated on the phenyl ring of the aldehyde under the optimized conditions, providing desired products **9o**-**q** with 88%–90% ee. The electron-withdrawing *p*-bromo group at the 2-positon of the aldehyde had the biggest influence on the aldol reaction, and led to very low enantioselectivities (70% ee). The reaction of 1-naphthaldehyde afforded product **9l** in high yield (70%) with excellent enantioselectivity (90% ee) (see Fig. 1).

Considering the mechanism reported previously by the groups of Song[7] and Wennemers,[8] we propose the mechanism shown in Fig. 2. The tertiary amine of the chloramphenicol base forms two hydrogen-bonds with the MAHTs because of its basicity. The sulfonamide group acts as a hydrogen-bond donor and activates the aldehyde. Intermediate **I** is converted to complex **II** as a result of the orientation determined by the three hydrogen-bonds. The β-hydroxy thioester product is generated from **9′**, which results from the decarboxylation of intermediate **II**. Importantly, only CO_2 is generated as a byproduct in this decarboxylative aldol reaction.

We demonstrate the value of our methodology by carrying out the asymmetric synthesis of (+)-dapoxetine, a selective serotonin reuptake inhibitor, from primary alkyl substrates in very few steps. The reduction of chiral β-hydroxy thioester **9a** with $LiBH_4$, which was prepared in situ from KBH_4 and anhydrous LiCl in THF at 70 °C, provided (R)-1-phenylpropane-1,3-diol **15** in 85% yield. The 1,3-diol smoothly underwent hydroxyl tosylation with TsCl to form (R)-3-hydroxy-3-phenyl-propyl-4-methylbenzenesulfonate(**16**), which then successfully underwent nucleophilic substitution with 1-naphthol in the presence of K_2CO_3 to afford (R)-3-(naphthalen-1-yloxy)-1- pheny lpropan-1-ol(**17**) in excellent yield. The (S)-3-(naphthalen-1-yloxy)-1-phenylpropan-1-amine(**18**) was formed by electro-philic substitution, azidated, and reduced of the *O*-mesylated derivative (**17**). Finally, (+)-dapoxetine **19** was generated in 68% yield by refluxing with aqueous formaldehyde solution and formic acid for 10 h (Scheme 3).