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A new class of C_2 chiral photodimer ligands for catalytic enantioselective diethylzinc addition to arylaldehydes

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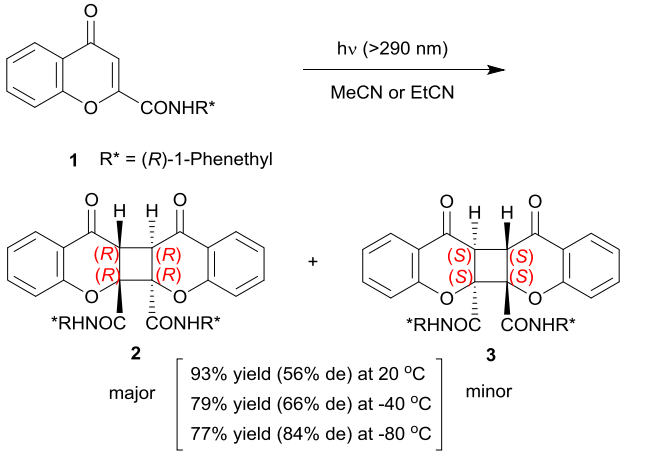
ABSTRACT

A new class of C_2 chiral materials was easily prepared by the photodimerization reaction of (*R*)-*N*-phenethyl-2-chromonecarboxamide followed by recrystallization. Reduction of the photodimer gave the corresponding alcohol stereoselectively. Both C_2 chiral materials worked effectively as ligands for enantioselective ethylation of arylaldehydes using diethylzinc.

1. Introduction

Many C_2–symmetric chiral materials have been utilized for several kinds of asymmetric syntheses as useful organic catalysts or ligands of organometallics.[1] However, most of these chiral materials are cumbersome to prepare and are expensive even if commercially available. Considering the challenging new structural motifs, we conceived of a convenient synthesis of C_2 chiral materials that may spark the creative endeavors of many synthetic organic chemists.

Recently, we reported a convenient method to construct C_2 chiral scaffolds by the diastereoselective photodimerization reaction of chromone-2-carboxamides possessing a chiral substituent on the nitrogen atom as shown in Scheme 1.[2] The reaction provided high product selectivity and stereochemistry, and the predominant dimerization products had easily modifiable carbonyl and amide groups.[3] Here, we utilized the C_2 chiral photodimers as ligands for catalytic asymmetric synthesis of secondary alcohols using diethylzinc as a typical model reaction.[4]



Scheme 1. Diastereoselective photodimerization of chromone-2-carboxamides to construct C_2 chiral scaffolds.

2. Results and discussion

Chromone-2-carboxamides possessing chiral substituents were easily obtained from the commercially available 2-chromonecarboxylic acids and corresponding chiral amines.

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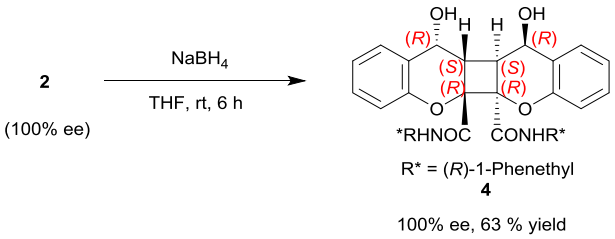
When the amide **1** was irradiated in MeCN at room temperature (20 °C), the diastereoselective formation of the *anti*-head-to-head type dimer occurred in 56% de. Decreasing the temperature of the reaction to −40 °C gave a better de value of 66%. Moreover, a higher diastereoselectivity of 84% de was obtained by irradiation at −80 °C using propionitrile as a solvent.[2]

The absolute configuration of both dimers was established by X-ray crystallographic analysis. The major isomer exhibited *R* configuration of all carbon atoms in the cyclobutane ring, and the minor isomer had an all *S* configuration in the four-membered ring. Major isomer **2** was easily optically resolved by crystallization on the basis of the big difference in crystallinity. When a 56% de mixture of photodimers was recrystallized from a mixed solvent of $CHCl_3$ and hexane, a pseudo-racemic crystal composed of a 1:1 mixture of **2** and **3** with higher crystallinity crystallized from the first crystallization. The minor isomer **3** was nearly removed by this first crystallization, and enantiopure **2** was easily obtained by a second crystallization from the mother liquor. In other words, enantiopure **2** could be isolated by crystallization twice from the photoreaction mixture. Further purification was not required to use **2** in subsequent asymmetric syntheses. On the other hand, optical resolution by preparative HPLC was required to obtain optically pure **3**.

For enantioselective alkylations using dialkylzinc, diols have commonly been used as effective chiral ligands.[5] The chromone dimer has a convertible functional carbonyl group, and reduction was examined to provide chiral alcohols. When optically pure **2** was reacted with $NaBH_4$ in THF and the reaction mixture was separated by column chromatography on silica gel, enantiopure **4** was obtained in 63% yield without any cumbersome experimental procedures. The stereochemistry of the newly formed chiral center was determined as (*R*) by X-ray structural analysis. The hydride attacked from the vacant side so as to avoid the bulk of the chromone structure (Scheme 2, Fig. 1).



Scheme 2. Synthesis of diol **4** by stereoselective reduction of **2**.

We herein report the behavior of these chiral chromone derivatives **2**–**4** as a new class of ligands in the enantioselective alkylation of aryl aldehydes as a representative model asymmetric reaction because many chiral ligands effectively catalyze the asymmetric alkylation of aldehydes with high ees.[6]

Before the asymmetric reaction using the chiral photodimers, we tried the reaction using the monomer **1**; however, **1** did not work as an effective ligand for the asymmetric ethylation (Scheme 3, Table 1, entry 1). Next, when chiral dimer **2** was used, 70% ee of (*R*)-1-phenyl-1-propanol was obtained in 75% yield (entry 2). Diastereomeric dimer **3**, with a different stereochemistry of the cyclobutane ring, also worked, and 65% ee of enantiomeric (*S*)-alcohol was obtained in a better chemical yield of 81%. The chiral phenethyl group did not affect the enantioselectivity, suggesting that the dimer structure controlled the enantioselectivity considerably.

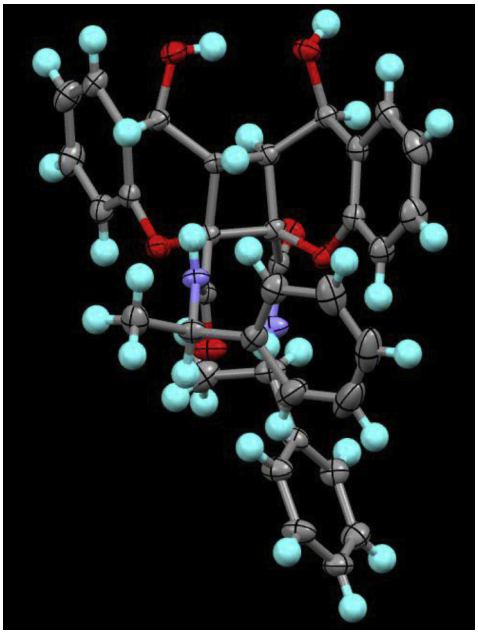
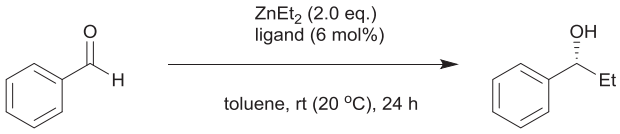


Fig. 1. Perspective view of reduced chromone dimer **4**.



Scheme 3. Asymmetric ethylation of benzaldehyde using chromone ligands.

Table 1
Asymmetric ethylation of benzaldehyde using chromone ligands

Entry	Ligand	Yield (%)[a]	ee (%)[b]	Config[c]
1	**1**	20	0	—
2	**2**	75	70	*R*
3	**3**	81	−65	*S*
4	**4**	77	71	*R*

[a] Isolated yield.
[b] Determined by HPLC analysis using a CHIRALCEL OD column.
[c] Determined by comparison with an authentic sample.

It is known that many diols serve as good ligands for catalytic asymmetric alkylation using diethylzinc, and it was expected that the dimeric diol **4** would be more effective for the asymmetric reaction.[5] The chiral diol **4** was slightly more stereoselective for the asymmetric reaction (entry 4), and gave the (*R*)-alcohol in 71% ee.

We then examined the effect of the reaction temperature by using the dimer ligands, **2** and **4** (Scheme 4). Decreasing the temperature to 0 °C from 20 °C resulted in decreased reactivity (Table 2, entries 3 and 4), but the ee value was almost the same (entries 2 and 4). On the other hand, increasing the temperature decreased the stereoselectivity, and the ee values were reduced (entries 5 and 6). These results showed that a temperature of 20 °C was the best condition for ethylation using photodimer ligands. Furthermore, there was little difference between the reactions using **2** and the diol **4** in the chemical yields, ees, and stereochemistry.

Next, enantioselective addition using a variety of arylaldehydes was examined with the photodimer ligands at 20 °C (Scheme 5, Table 3). In the case of the reaction of 2-chlorobenzaldehyde, both ligands worked and gave moderate chemical yields and ee values