

CHIRAL LIGAND-CONTROLLED CATALYTIC ASYMMETRIC  
EPOXIDATION OF ENONE WITH HYDROPEROXIDE<sup>†</sup>

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**Abstract** – Conjugate addition-type asymmetric epoxidation of an enone with lithium cumene hydroperoxide was mediated by a chiral ligand. The catalytic process was realized under conditions of a slow addition of cumene hydroperoxide.

We have been involved in the development of an asymmetric catalysis based on the fundamental concept that involves both activation of the reaction species and control of the stereochemistry by using an external chiral ligand.<sup>1</sup> We have already developed some chiral ligands for asymmetric reactions of a variety of nucleophiles such as organolithiums, organocuprates, lithium ester enolates, and lithium thiolates.<sup>2</sup> As an extension of this methodology, we designed a conjugate addition-type asymmetric epoxidation reaction of lithium alkyl hydroperoxide with an electron-deficient olefin.<sup>3,4</sup> The methodology is complementary to the other approach directed toward a catalytic asymmetric epoxidation of an isolated olefin with oxone–chiral ketone reagent.<sup>5,6</sup> Thus chiral amino diether ligand (**1**) is

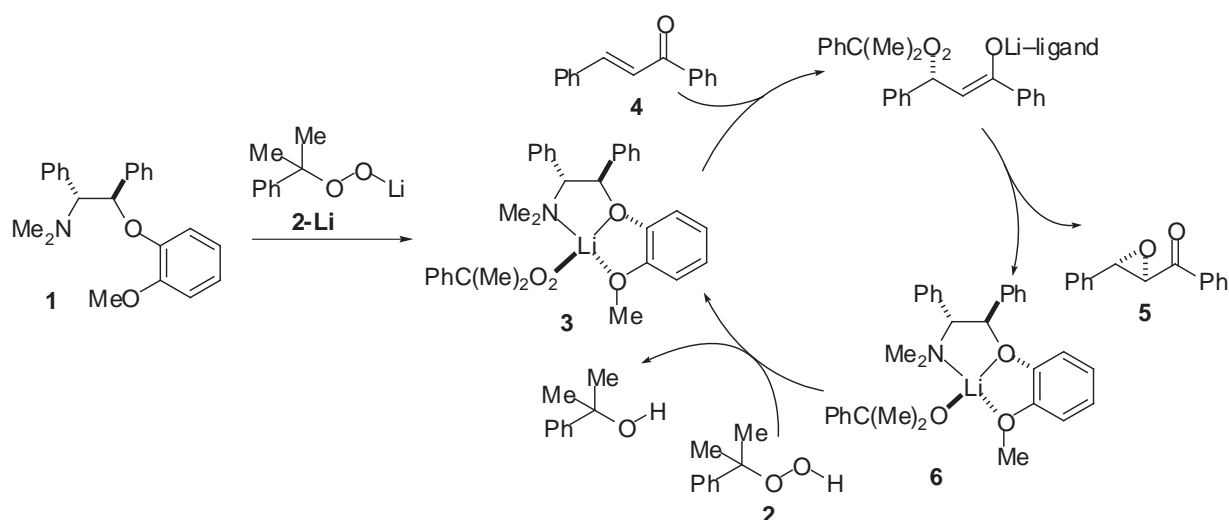
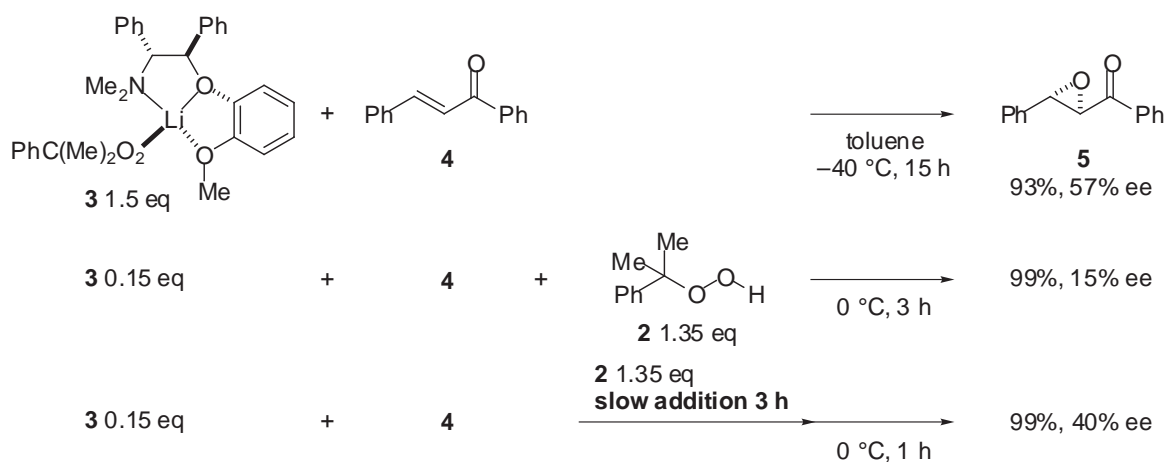


Figure 1. Design of catalytic asymmetric epoxidation of chalcone

<sup>†</sup> We dedicate this paper to Professor A. I. Meyers on the occasion of celebration of his 70th birthday.

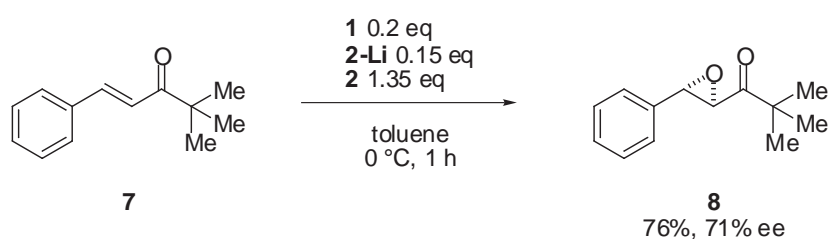
expected to form a bicyclo[3.3.0] complex (**3**) by forming a chelate with lithium cumene hydroperoxide (**2-Li**) as an oxygen nucleophile (Figure 1). The addition of **3** to chalcone (**4**) proceeds enantioselectively<sup>7</sup> to form a lithium enolate, from which a chiral ligand–lithium alkoxide (**6**) eliminates to give epoxide (**5**). Ligand exchange of **6** with hydroperoxide (**2**) regenerates **3**, completing a catalytic cycle as shown.

At first, we examined a reaction of 1.5 equiv of **3**, generated from cumene hydroperoxide, butyllithium and **1**, with chalcone (**4**) in toluene at 0 °C. The reaction proceeded within 0.5 h to give a desired epoxide (**5**)<sup>8</sup> in 75% yield and 47 % ee. The enantioselectivity was improved to 57% by carrying out the reaction at the lower temperature of –40 °C for 15 h giving **5** in 93% yield (Figure 2).



**Figure 2.** Catalytic asymmetric epoxidation of chalcone by slow addition method

Encouraged by the results above, we extended the stoichiometric reaction to a catalytic asymmetric epoxidation of **4** with a catalytic amount of a chiral ligand (**1**) (Figure 2). Thus, the reaction of **4** was examined by using 0.15 equiv of **3** and 1.35 equiv of cumene hydroperoxide (**2**). However, the reaction in toluene at 0 °C for 3 h gave **5** in 99% yield but only in 15% ee. The disappointingly poorer enantioselectivity was ascribable to the presence of an excess of hydroperoxide (**2**). Coordination of the excess of **2** to a lithium cation and subsequent kicking out of a chiral ligand (**1**) would generate an achiral reactive lithiated hydroperoxide species, which is responsible for the production of racemic **5**. The solution to this problem came from a slow addition of cumene hydroperoxide to the reaction mixture, which excludes the negative influence of an excess of hydroperoxide. Thus, upon a continuous addition



**Figure 3.** Catalytic asymmetric epoxidation of *tert*-butyl ketone

of 1.35 equiv of **2** over 3 h the reaction of **4** was catalyzed by 0.15 equiv of **3** in toluene at 0 °C for additional 1 h to afford **5** in 99% yield and 40 % ee.

The reaction was influenced by the terminal group of the ketone. The *tert*-butyl ketone instead of phenyl ketone provided a better enantioselectivity as has been shown by the reaction of **7** giving **8**<sup>9</sup> in 71% ee and 76% yield (Figure 3).

In conclusion, we have developed a conjugate addition-type asymmetric epoxidation reaction of an enone with cumene hydroperoxide, which is catalyzed by lithiated hydroperoxide and a chiral ligand. For the catalytic asymmetric reaction, slow addition of cumene hydroperoxide is a key for the success.

## ACKNOWLEDGMENT

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