http://dx.doi.org/10.5012/bkcs.2013.34.12.3539

Organocatalytic Enantioselective Friedel-Crafts Reaction of Naphthol with β,γ-Unsaturated α-Keto Esters

Hyun A Lee and Dae Young Kim*

*Department of Chemistry, Soonchunhyang University, Asan, Chungnam 336-745, Korea. *E-mail: dyoung@sch.ac.kr*
Received August 16, 2013, Accepted September 3, 2013

Key Words : Asymmetric catalysis, β,γ-Unsaturated α-keto esters, Friedel-Crafts reaction, Organocatalysis, Chromanes

The chromane and benzopyrane structures are present as a characteristic structural motif in a large number of natural products that possess a broad array of biological activities such as antimicrobial, antiviral, antitumor, and central nerve system activity.[1] Although many synthetic methods for these compounds have been reported,[2] the enantioselective construction of this chiral scaffold has been rarely explored.[3] The Friedel-Crafts (FC) alkylation is important reaction for the formation of C-C bonds.[4] The asymmetric FC reaction can afford enantiomerically enriched alkylated arene products. A large number of effort has been devoted to the development for catalytic enantioselective FC reaction of arenes to α,β-unsaturated carbonyl compounds using chiral metal complexes[5] as well as organocatalysts.[6] Recently, Yang and Wang groups independently reported the enantioselective FC reaction of naphthols with β,γ-unsaturated α-keto esters catalyzed by thiourea-type organocatalysts.[7] However, there are still some drawbacks in the previously reported procedures, such as high catalyst loading and enantioselectivity. Accordingly, the development of alternative catalysts for the enantioselective FC reactions between naphthols and β,γ-unsaturated α-keto esters is desirable.

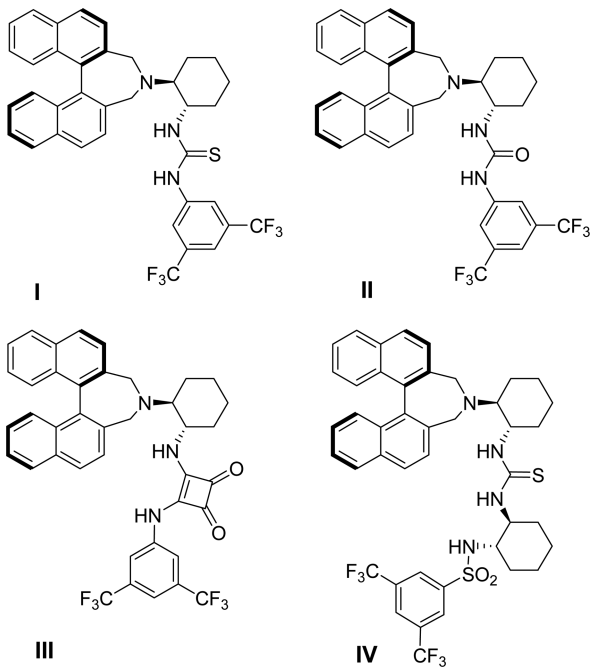
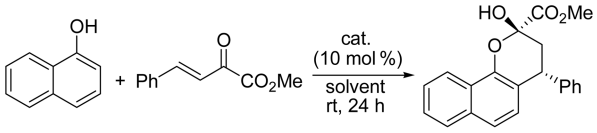


Figure 1. Structure of chiral bifunctional organocatalysts.

In the framework of our research program for the development of synthetic methods for the enantioselective construction of stereogenic carbon centers,[8] we recently reported asymmetric Michael-type reactions with β,γ-unsaturated α-keto esters and phosphonates using chiral catalysts.[9] Herein, we wish to describe the enantioselective FC alkylation of 1-naphthol with β,γ-unsaturated α-keto esters catalyzed by binaphthyl-modified organocatalysts.

We initially investigated a reaction system with 1-naphthol (**1**) and (*E*)-methyl 2-oxo-4-phenylbut-3-enoate (**2a**) in the presence of 10 mol % bifunctional organocatalysts (Fig. 1) at room temperature. As shown in Table 1, change to the (thio)urea-moiety to squaramide organocatalyst improved enantioselectivities (entries 1-4), and the highest enantiselec-

Table 1. Optimization of the reaction conditions[a]

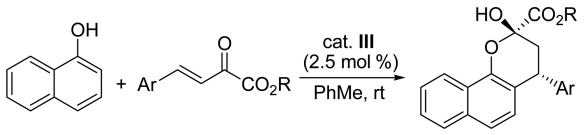


1 **2a** **3a**

Entry	Cat.	Solvent	Yield (%)[b]	dr[c]	ee (%)[d]
1	**I**	CH_2Cl_2	65	9:1	72
2	**II**	CH_2Cl_2	65	8:1	81
3	**III**	CH_2Cl_2	86	10:1	94
4	**IV**	CH_2Cl_2	52	8:1	82
5	**III**	Et_2O	67	7:3	74
6	**III**	PhMe	95	8:1	97
7	**III**	*p*-xylene	84	8:1	96
8	**III**	*m*-xylene	89	8:1	96
9	**III**	*o*-xylene	81	8:1	95
10	**III**	mesitylene	86	8:1	95
11	**III**	EtOH	n.r.	-	-
12[e]	**III**	PhMe	88	10:1	97
13[f]	**III**	PhMe	86	10:1	97
14[g]	**III**	PhMe	36	9:1	93

[a]Reaction conditions: 1-naphthol **1** (0.30 mmol), β,γ-unsaturated α-keto ester (**2a**, 0.30 mmol), catalyst (0.03 mmol) at room temperature. [b]Isolated yield. [c]Diastereomeric ratio was determined by ^{1}H NMR spectroscopic analysis of the crude reaction mixture. [d]Enantiopurity was determined by HPLC analysis using a Chiralpak AD-H column. [e]5 mol % catalyst loading. [f]2.5 mol % catalyst loading. [g]1.0 mol % catalyst loading.

Table 2. The asymmetric synthesis of modified chromanes **2**[a]



1 2 3

Entry	Ar	R	Time (h)	Yield (%)[b]	ee (%)[c]
1	Ph	Me	24	**3a**, 86	97
2	4-Me-C_6H_4	Me	19	**3b**, 78	93
3	4-MeO-C_6H_4	Me	23	**3c**, 62	86
4	4-Cl-C_6H_4	Me	6	**3d**, 95	91
5	4-Br-C_6H_4	Me	6	**3e**, 79	89
6	4-F-C_6H_4	Me	4	**3f**, 75	96
7	2-F, 5-Br-C_6H_3	Me	7	**3g**, 75	91
8	2-F-C_6H_4	Me	5	**3h**, 78	97
9	2-thienyl	Me	6	**3i**, 79	96
10	2-furyl	Me	5	**3j**, 62	89
11	2-naphthyl	Me	5	**3k**, 81	97
12	4-Cl-C_6H_4	Et	48	**3l**, 74	96

[a]Reaction conditions: 1-naphthol **1** (0.30 mmol), β,γ-unsaturated α-keto ester (**2**, 0.30 mmol), catalyst **III** (7.5 mmol) in toluene (1.2 mL) at room temperature and products were observed with > 10:1 dr. [b]Isolated yield. [c]Enantiopurity was determined by HPLC analysis using Chiralpak AD-H (for **3a**, **3b**, **3d**-**3f**, **3h**, **3k**, and **3l**) and IC (for **3c**, **3g**, and **3j**), and OD-H (for **3i**) columns.

tivities obtained with the binaphthyl-modified squaramide catalyst **III**. In order to further improve the selectivity, different solvents were then tested in the presence of 10 mol % of catalyst **III**. Among the solvents probed, the best results were achieved when the reaction was conducted in toluene (entry 7). The present catalytic system tolerates catalyst loading down to 5 or 2.5 mol %, and both the yield and enantioselectivity were retained (entries 6 and 12-14).

With the optimal reaction conditions in hand, we then carried on evaluating the generality of this protocol. The results of a representative selection of β,γ-unsaturated α-keto esters for the FC reaction are summarized in Table 2. As demonstrated, squaramide organocatalyst **III** catalyzed the FC reaction of 1-naphthol (**1**) to β,γ-unsaturated α-keto esters **2** proved to be a general approach for the synthesis of chromane derivatives **3** with high to excellent enantiomeric excess (up to 97% ee). Absolute configuration of products **3** was determined comparison of the optical rotation and chiral HPLC data with the literature values.[7]

In conclusion, we have developed organocatalytic enantioselective FC reaction of 1-naphthol (**1**) to β,γ-unsaturated α-keto esters **2** to afford biologically valuable chromane derivatives **3**. The binaphthyl-modified squaramide organocatalyst **III** showed excellent catalytic activity for this reaction to afford **3** in high yields with excellent enantioselectivities (up to 97% ee) under mild reaction conditions.

Acknowledgments. This work was supported by the Soonchunhyang University Research Fund.

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