DOI: 10.1002/ejoc.201000271

# Organocatalytic Enantioselective Friedel–Crafts Alkylation of Sesamol with Nitro Olefins

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**Keywords:** Alkenes / Organocatalysis / Alkylation / Enantioselectivity

A bifunctional chiral thiourea–tertiary amine organocatalyst derived from cinchonine was employed to promote the enantioselective Friedel–Crafts alkylation of sesamol and 2-substituted sesamols with various aromatic nitro olefins. The reactions proceeded smoothly to provide the corresponding products in good yields (up to 97%) and good enantioselectivities (up to 90% *ee*).

## Introduction

The Friedel–Crafts (F–C) reaction of electron-rich aromatic compounds represents an important C–C bond-forming process for the synthesis of valuable building blocks of biologically active compounds. Recently, organocatalytic enantioselective Friedel–Crafts alkylation reactions have attracted much attention due to the significance of this transformation for the synthesis of optically active aromatic compounds.[1] In 2004, Terada and co-workers first employed chiral phosphoric acid to promote the F–C alkylation of 2-methoxyfuran with *N*-Boc aldimines and furan-2-ylamines were obtained in excellent chemical yields and enantioselectivities.[2] Since then, many efforts have been devoted to enantioselective organocatalytic F–C alkylations of electron-rich arenes such as indole derivatives,[3] pyrrole derivatives,[4] and phenol derivatives[5] with various electrophiles. For example, Chen and co-workers reported the first highly enantioselective F–C alkylation of 1- and 2-naphthols with nitro olefins catalyzed by bifunctional chiral thiourea–tertiary amine organocatalysts.[5c] However, up to now, phenols other than naphthols were rarely utilized in enantioselective organocatalytic F–C alkylations[5a] so that the synthetic potential of this methodology was limited to some extent. Therefore, expansion of the scope of phenols in the above-mentioned reactions is of interest.

Sesamol is one of the representative structural motifs often observed in natural alkaloids and biologically active compounds.[6] Being electron-rich phenols, sesamol and its derivatives are good nucleophiles that can be employed in F–C reactions to construct complex natural products.[7] However, to the best of our knowledge, systematic research on asymmetric F–C alkylations of sesamol has not been reported.

Herein we describe the first enantioselective F–C alkylations of sesamol or 2-substituted sesamols with a wide variety of nitro olefins promoted by bifunctional chiral thiourea–tertiary amine organocatalysts. The reactions proceeded smoothly in the presence of only 5 mol-% of the optimal organocatalyst to provide the desired products in good yields (up to 97%) and good enantioselectivities (up to 90% *ee*).

## Results and Discussion

First, 5 mol-% of bifunctional chiral thiourea–tertiary amine organocatalyst **1a**[8a] (Figure 1) was employed in the F–C alkylation of sesamol (**2a**) with nitrostyrene (**3a**) in toluene at –15 °C. The reaction proceeded for 48 h to give almost quantitative yield of product **4a** in 60% *ee* (Table 1,

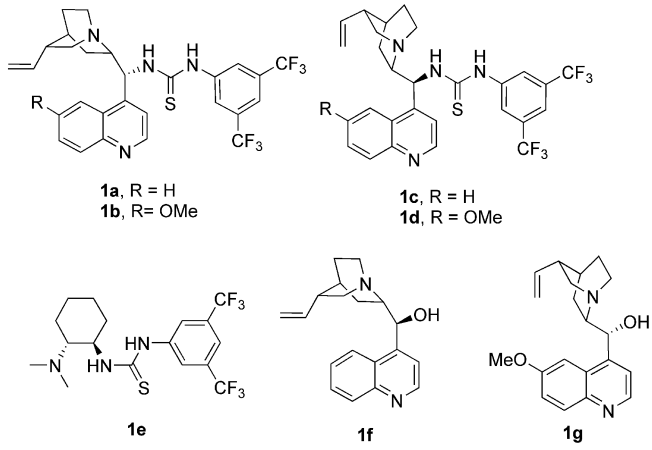


Figure 1. Organocatalysts evaluated in this study.

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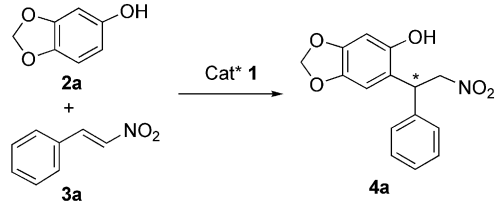
Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/ejoc.201000271.

Entry 1). Encouraged by this result, several bifunctional organocatalysts were screened in the titled reaction. All of these catalysts promoted the reaction efficiently to afford the products in almost quantitative yields. Catalysts **1a**–**d**[8a,8b] derived from cinchona alkaloids[9] resulted in close *ee* values (Table 1, Entries 1–4), in which **1a** delivered the best *ee*. However, catalyst **1e**[8c] derived from (1*R*, 2*R*)-cyclohexane-1,2-diamine resulted in much lower enantioselectivity (Table 1, Entry 5). Cinchonine (**1f**) and quinine (**1g**) gave very poor *ee* values as well (Table 1, Entries 6 and 7).

Table 1. Enantioselective F–C alkylation of sesamol (**2a**) with nitro olefin **3a**.



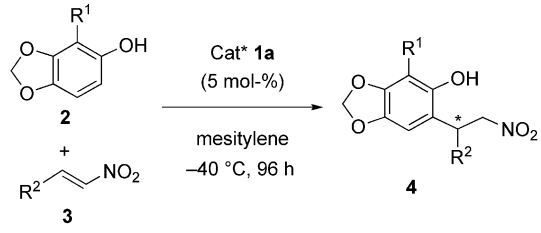

| Entry[a] | Catalyst (mol-%) | Solvent | *T* [°C] | Yield [%][b] | *ee* [%][c] |
|---|---|---|---|---|---|
| 1 | **1a** (5) | toluene | –15 | 98 | 60 |
| 2 | **1b** (5) | toluene | –15 | 97 | 53 |
| 3 | **1c** (5) | toluene | –15 | 98 | –56 |
| 4 | **1d** (5) | toluene | –15 | 98 | –57 |
| 5 | **1e** (5) | toluene | –15 | 93 | –29 |
| 6 | **1f** (5) | toluene | –15 | 98 | –19 |
| 7 | **1g** (5) | toluene | –15 | 99 | 24 |
| 8 | **1a** (5) | toluene | –40 | 98 | 75 |
| 9[d] | **1a** (5) | toluene | –40 | 97 | 69 |
| 10[e] | **1a** (5) | toluene | –40 | 87 | 67 |
| 11[f] | **1a** (5) | toluene | –40 | 98 | 68 |
| 12 | **1a** (5) | xylene | –40 | 86 | 76 |
| 13 | **1a** (5) | mesitylene | –40 | 91 | 81 |
| 14 | **1a** (5) | $CH_2Cl_2$ | –40 | 89 | 73 |
| 15 | **1a** (5) | $ClCH_2CH_2Cl$ | –40 | 84 | 67 |
| 16 | **1a** (5) | $CHCl_3$ | –40 | 87 | 78 |
| 17 | **1a** (5) | $Et_2O$ | –40 | 11 | 62 |
| 18 | **1a** (5) | THF | –40 | NR | – |
| 19 | **1a** (5) | EtOH | –40 | NR | – |
| 20 | **1a** (2.5) | mesitylene | –40 | 91 | 80 |
| 21 | **1a** (10) | mesitylene | –40 | 97 | 80 |
| 22[g] | **1a** (5) | mesitylene | –40 | 81 | 78 |
| 23[h] | **1a** (5) | mesitylene | –40 | 92 | 81 |
| 24[i] | **1a** (5) | mesitylene | –40 | 93 | 83 |
| 25[j] | **1a** (5) | mesitylene | –40 | 92 | 84 |

[a] Unless specified otherwise, reactions were carried out with **2a** (0.2 mmol), **3a** (0.3 mmol), and the catalyst in the solvent (0.5 mL) at –15 °C for 48 h or at –40 °C for 96 h. [b] Isolated yield based on **2a**. [c] The *ee* values were determined by using chiral HPLC. [d] With 3 Å MS as additive. [e] With 4 Å MS as additive. [f] With 5 Å MS as additive. [g] In 0.25 mL of mesitylene. [h] In 1 mL of mesitylene. [i] In 2 mL of mesitylene. [j] In 4 mL of mesitylene.

Therefore, **1a** was determined as the optimal catalyst and was employed in further investigations. Various reaction conditions involving temperature, additives, solvents, and concentrations were tested in search of the optimal conditions. Lowering the temperature to –40 °C gave rise to an obvious increase in the *ee* value (Table 1, Entry 8). However, attempts to further improve the *ee* values by adding 3, 4, or 5 Å molecular sieves to the reaction system proved to be in vain (Table 1, Entries 9–11) The survey of solvents revealed that nonpolar solvents were appropriate to the reaction in terms of yield and enantioselectivity. Chlorinated solvents led to good yields but inferior *ee* values (Table 1, Entries 14–16). Meanwhile, trace amounts of products or no reaction at all was observed in polar solvents (Table 1, Entries 17–19), perhaps due to the competitive coordination of the solvents with the catalyst. Among the non-polar solvents, mesitylene proved to be the most favorable one (Table 1, Entry 13). Reducing the catalyst loading from 5 to 2.5 mol-% gave rise to almost the same yield and *ee* value (Table 1, Entry 20), whereas enhancing the catalyst loading to 10 mol-% did not benefit the enantioselectivity at all (Table 1, Entry 21). Finally, we found that the concentration had an obvious influence on the reaction. High concentrations were deleterious to both yields and *ee* values (Table 1, Entry 22). To our delight, low concentrations were advantageous to the reaction (Table 1, Entries 23–25). When the reaction was conducted in 4 mL of mesitylene, the enantioselectivity increased to 84% (Table 1, Entry 25).

Having established the optimal conditions, the enantioselective F–C alkylation was expanded to a wide variety of nitro olefins and two 2-substituted sesamols. The results are summarized in Table 2. Generally, the F–C alkylation of

Table 2. Enantioselective F–C alkylation of sesamol or 2-substituted sesamols **2a**–**c** with nitro olefins **3a**–**q**.




| Entry[a] | $R^1$ (**2**) | $R^2$ (**3**) | **4** | Yield [%][b] | *ee* [%][c] | Config. |
|---|---|---|---|---|---|---|
| 1 | H (**2a**) | Ph | **4a** | 92 | 84 | *S* (–)[d] |
| 2 | H (**2a**) | 4-$MeOC_6H_4$ | **4b** | 97 | 85 | (+) |
| 3 | H (**2a**) | 2-$MeOC_6H_4$ | **4c** | 81 | 76 | (+) |
| 4 | H (**2a**) | 4-$BnOC_6H_4$ | **4d** | 92 | 82 | (+) |
| 5 | H (**2a**) | 4-$MeC_6H_4$ | **4e** | 91 | 83 | (–) |
| 6 | H (**2a**) | 3-$MeC_6H_4$ | **4f** | 92 | 83 | (–) |
| 7 | H (**2a**) | 4-$FC_6H_4$ | **4g** | 86 | 83 | (–) |
| 8 | H (**2a**) | 3-$FC_6H_4$ | **4h** | 75 | 85 | (+) |
| 9 | H (**2a**) | 4-$ClC_6H_4$ | **4i** | 96 | 88 | (–) |
| 10 | H (**2a**) | 2-$ClC_6H_4$ | **4j** | 89 | 59 | (–) |
| 11 | H (**2a**) | 2,4-$Cl_2C_6H_3$ | **4k** | 93 | 75 | (–) |
| 12 | H (**2a**) | 4-$BrC_6H_4$ | **4l** | 96 | 86 | (–) |
| 13 | H (**2a**) | 3-$BrC_6H_4$ | **4m** | 87 | 86 | (–) |
| 14 | H (**2a**) | 2-$BrC_6H_4$ | **4n** | 85 | 65 | (+) |
| 15 | H (**2a**) | 3-$CF_3C_6H_4$ | **4o** | 85 | 83 | (+) |
| 16 | H (**2a**) | 2-naphthyl | **4p** | 80 | 77 | (–) |
| 17 | H (**2a**) | 2-furanyl | **4q** | 96 | 82 | (–) |
| 18 | Me (**2b**) | Ph | **4r** | 88 | 83 | (–) |
| 19 | I (**2c**) | Ph | **4s** | 88 | 90 | (–) |

[a] Unless specified otherwise, reactions were carried out with **2** (0.2 mmol), **3** (0.3 mmol), and catalyst **1a** (5 mol-%) in mesitylene (4 mL) at –40 °C for 96 h. [b] Isolated yield based on **2**. [c] The *ee* values were determined by using chiral HPLC. [d] The absolute configuration of **4a** was determined by X-ray analysis of the ester derived from **4a** and (–)-camphanic acid.

aromatic nitro olefins bearing substituents in the *para* or *meta* position of the phenyl groups with sesamol proceeded smoothly to provide the corresponding products in good enantioselectivities (>80%*ee*), no matter whether the substituents were electron donating or electron withdrawing. However, aromatic nitro olefins bearing substituents in the *ortho* position of the phenyl groups reacted with sesamol in inferior enantioselectivities (Table 2, Entries 3, 10, 11, and 14). Perhaps the *ortho* substitution on the phenyl group made the nitro olefins sterically more hindered so that they displayed lower enantioselectivities. Inferior enantioselectivity was observed with (*E*)-2-(2-nitrovinyl)naphthalene (**3p**) as well (Table 2, Entry 16). Heteroaryl-substituted nitro olefin **3q** exhibited excellent reactivity and gave almost quantitative product with good enantioselectivity (Table 2, Entry 17). Furthermore, 2-methylsesamol (**2b**) and 2-iodosesamol (**2c**) were also subjected to the enantioselective F–C alkylation with nitro olefin **3a**. Compound **2b** underwent the reaction with good yield and *ee* value (Table 2, Entry 18). Gratifyingly, reaction of **2c** and **3a** provided the highest enantioselectivity (90%*ee*; Table 2, Entry 19).

Afterwards, product **4a** was acylated with (1*S*)-(–)-camphanic acid to give ester **5**. The absolute configuration of **4a** was assigned as (*S*) by X-ray crystallographic analysis of **5** (Figure 2).[10]

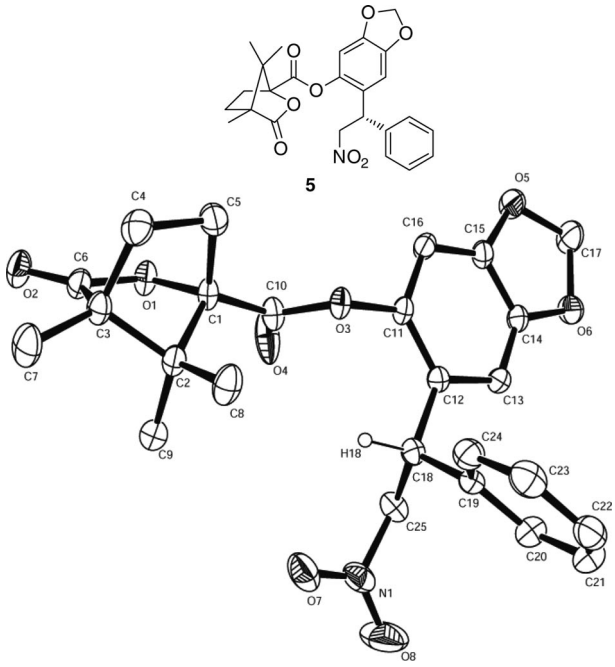



Figure 2. X-ray structure of ester **5**.

## Conclusions

In summary, we have developed an organocatalytic enantioselective F–C alkylation of sesamol and its 2-substituted derivatives with various aromatic nitro olefins by employing chiral thiourea–tertiary amine **1a** as catalyst. Through this methodology, a wide variety of chiral sesamol derivatives were synthesized in good yields (up to 97%) and good enantioselectivities (up to 90%*ee*). The absolute configuration of product **4a** was determined as (*S*) by X-ray crystallographic analysis of ester **5** derived from **4a** and (–)-camphanic acid. Further work is in progress to utilize this reaction in the construction of complex natural or unnatural products.

## Experimental Section

**General Procedure of the Enantioselective F–C Alkylation of Sesamol with Nitro Olefin:** Catalyst **1a** (5.6 mg, 0.01 mmol, 5 mol-%), sesamol (**2**; 0.2 mmol), and nitro olefin **3** (0.3 mmol) were added to a 10-mL tube and cooled to –40 °C under an atmosphere of argon. Then, dry mesitylene (4.0 mL) was added. After the reaction was conducted for 96 h, the mixture was subjected to flash chromatography on silica gel to give pure product **4**.

**Supporting Information** (see footnote on the first page of this article): Representative procedures for the enantioselective F–C alkylation of sesamol and 2-substituted sesamols with nitro olefins; spectroscopic data of products **4a**–**s**; HPLC chromatograms of **4a**–**s**.

## Acknowledgments

We are grateful for the financial support of the National Sciences Foundation of China (20772122) and National Basic Research Program of China (973 Program, 2010CB833301).

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[10] Crystals of **5** suitable for X-ray analysis were obtained from a mixture of *n*-hexane and ethyl acetate. CCDC-769758 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

Received: February 27, 2010
Published Online: May 6, 2010

  