Enantioselective Michael addition of 2-hydroxy-1,4-naphthoquinones to nitroalkenes catalyzed by binaphthyl-derived organocatalysts

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Abstract
The highly enantioselective Michael addition of 2-hydroxy-1,4-naphthoquinones to nitroalkenes, promoted by binaphthyl-modified chiral bifunctional organocatalysts is described. This reaction afforded the chiral functionalized naphthoquinones in high yields (81–95%) and excellent enantioselectivities (91–98% ee) under low catalyst loading (1 mol %).

Introduction
Quinone and naphthoquinone structures exist in a large number of natural products and biologically active molecules [1-4]. Many of these naturally occurring naphthoquinones and their synthetic analogues are important precursors for the synthesis of natural products and pharmaceuticals [5-9]. The stereoselective formation of C–C bonds is of great importance for the synthesis of enantiomerically pure, biologically active organic compounds [10,11]. It is widely recognized that the Michael addition is one of the most versatile and general methods for C–C bond formation in organic synthesis [12], and intensive research efforts have been directed toward the development of enantioselective catalytic protocols for this reaction [13-15]. The organocatalyst-mediated enantioselective conjugate addition reactions, which are both powerful and environmentally friendly, have been subjected to rigorous investigation in recent years [16-22]. The asymmetric Michael addition of various nucleophiles to nitroalkenes is of great interest, because the products obtained are versatile intermediates in organic synthesis [23-26]. Extensive studies have been devoted to the development of asymmetric conjugate additions of 1,3-dicarbonyl compounds to various Michael acceptors [27-33]. Recently, the groups of Du and Zhou reported a highly enantioselective Michael addition of 2-hydroxy-1,4-naphthoquinones to nitroalkenes catalyzed by chiral, bifunctional tertiary-amine thioureas, thiophosphorodiamides, and squaramide-based organocatalysts [34-36].
Findings

In the framework of our research program for the development of synthetic methods for the enantioselective construction of stereogenic carbon centers [37-42], we recently reported the enantioselective Michael addition of active methines to nitroalkenes [43,44]. Herein, we describe the direct enantioselective Michael addition of 2-hydroxy-1,4-naphthoquinone with nitroalkenes, catalyzed by bifunctional organocatalysts (Figure 1) that bear both central and axial chiral elements [45-47].

We initially investigated the reaction system with 2-hydroxy-1,4-naphthoquinone (1) and nitrostyrene 2a in the presence of 10 mol % of Takemoto’s catalyst I in acetonitrile at room temperature, to determine the optimum reaction conditions for the catalytic, enantioselective Michael addition. This reaction exhibited good yield and high enantioselectivity (89% ee, Table 1, entry 1). In order to enhance the enantioselectivity, other bifunctional organocatalysts II–VIII were evaluated in the model reaction (Table 1, entries 2–8). The quinine-derived thiourea catalyst II was less effective (Table 1, entries 1 and 2),
whereas the binaphthyl-modified, chiral, bifunctional organocatalysts III–VIII, bearing both central and axial chiral elements, effectively promoted the addition reaction in high yield, with high enantioselectivity (78–97% ee, Table 1, entries 3–8). Catalyst III gave the desired product 3a with high enantioselectivity (97%, Table 1, entry 3), whereas the diastereomeric catalyst VII afforded product 3a in lower enantioselectivity (78% ee, Table 1, entry 7). These results demonstrate that the central and axial chiral elements in the chiral amine-thiourea catalyst III are matched, thus enhancing the stereochemical control, whereas in the diastereomeric catalyst VII this is not the case.

Different solvents were then tested in the presence of 10 mol % of catalyst III together with 2-hydroxy-1,4-naphthoquinone (1) and nitrostyrene 2a in order to further improve the selectivity of the reaction. Aprotic solvents, such as acetonitrile, toluene, dichloromethane, THF, diethyl ether, were well tolerated in this conjugate addition without a significant decrease of enantiomeric selectivities (89–99% ee, Table 1, entries 3 and 9–12). Remarkably, water and brine also afforded products in good yields; however, the selectivity dropped significantly (Table 1, entries 13 and 14). Among the solvents probed, the best results (92% yield and 99% ee) were achieved when the reaction was conducted in THF (Table 1, entry 11). The present catalytic system tolerates catalyst loading down to 5, 2.5, and 1 mol % without compromising the yield or enantioselectivity (Table 1, entries 11 and 15–17).

With the optimized reaction conditions in hand, the scope of the methodology was investigated in reactions with 2-hydroxy-1,4-naphthoquinone (1) and various nitroalkenes 2a–l in the presence of 1 mol % of catalyst III in THF at room temperature (Table 2). A range of electron-donating and electron-withdrawing substitutions on the β-aryl ring of the nitroalkenes 2b–h provided reaction products in high yields and excellent enantioselectivities. Heteroaryl- and naphthyl-substituted nitroalkenes 2i and 2j provided products with high selectivity.

**Table 1: Optimization of the reaction conditions.**

| entry | cat. | solvent | time (h) | yield (%)<sup>a</sup> | ee (%)<sup>b</sup> |
|-------|------|---------|----------|----------------------|-----------------|
| 1     | I    | CH₃CN   | 2        | 84                   | 89              |
| 2     | II   | CH₃CN   | 2        | 87                   | 77              |
| 3     | III  | CH₃CN   | 2        | 96                   | 97              |
| 4     | IV   | CH₃CN   | 2        | 95                   | 87              |
| 5     | V    | CH₃CN   | 2        | 93                   | 81              |
| 6     | VI   | CH₃CN   | 2        | 90                   | 93              |
| 7     | VII  | CH₃CN   | 2        | 85                   | 78              |
| 8     | VIII | CH₃CN   | 2        | 88                   | 93              |
| 9     | III  | toluene  | 4        | 75                   | 95              |
| 10    | III  | DCM     | 4        | 93                   | 89              |
| 11    | III  | THF     | 2        | 92                   | 99              |
| 12    | III  | Et₂O    | 3        | 81                   | 91              |
| 13    | III  | H₂O     | 17       | 89                   | 19              |
| 14    | III  | brine    | 17       | 86                   | 37              |
| 15<sup>c</sup> | III | THF     | 2        | 90                   | 98              |
| 16<sup>d</sup> | III | THF     | 2        | 90                   | 99              |
| 17<sup>e</sup> | III | THF     | 2        | 89                   | 99              |

<sup>a</sup>Isolated yield.
<sup>b</sup>Enantiopurity was determined by HPLC analysis using chiralcel OJ-H column.
<sup>c</sup>Reaction was carried out in the presence of 5 mol % catalyst.
<sup>d</sup>Reaction was carried out in the presence of 2.5 mol % catalyst.
<sup>e</sup>Reaction was carried out in the presence of 1 mol % catalyst.
Table 2: Catalytic asymmetric Michael addition of 2-hydroxy-1,4-naphthoquinone 1 to nitroalkenes 2.

| entry | 2, R       | time (h) | yield (%)a | ee (%)b |
|-------|------------|----------|------------|---------|
| 1     | 2a, Ph     | 2        | 3a, 89     | 99      |
| 2     | 2b, p-MeC6H4 | 2       | 3b, 93     | 95      |
| 3     | 2c, p-MeOC6H4 | 4     | 3c, 81     | 99      |
| 4     | 2d, p-FC6H4 | 3       | 3d, 95     | 95      |
| 5     | 2e, p-ClC6H4 | 3       | 3e, 90     | 91      |
| 6     | 2f, p-BrC6H4 | 3       | 3f, 95     | 95      |
| 7     | 2g, o-FC6H4 | 4       | 3g, 95     | 95      |
| 8     | 2h, o-BrC6H4 | 4      | 3h, 95     | 95      |
| 9     | 2i, 2-thienyl | 5     | 3i, 93     | 93      |
| 10    | 2j, 2-naphthyl | 5     | 3j, 93     | 99      |
| 11    | 2k, isobutyl | 5      | 3k, 90     | 97      |

aIsolated yield.
bEnantiopurity was determined by HPLC analysis using chiralcel OJ-H (3a–j) and chiralpak AD-H (for 3k) columns.

(93–99% ee, Table 2, entries 9 and 10). The β-alkyl-substituted nitroalkene, 4-methyl-1-nitropent-1-ene (2k), was also an acceptable starting material and provided the corresponding Michael adducts in high yield and excellent enantioselectivity (97% ee, Table 2, entry 11).

In conclusion, we have developed a highly efficient catalytic, enantioselective Michael addition of 2-hydroxy-1,4-naphthoquinone to nitroalkenes using a binaphthyl-derived tertiary amine-thiourea organocatalyst. The various types of nitroalkylated naphthoquinone derivatives were obtained in good to high yields with excellent enantioselectivities (91–99% ee) for all the substrates examined in this work. We believe that this method should provide a practical entry for the preparation of chiral nitroalkylated naphthoquinone derivatives. Further details and application of this asymmetric Michael addition of 2-hydroxy-1,4-naphthoquinone nucleophiles will be presented in due course.

Experimental

General procedure for the Michael addition of 2-hydroxy-1,4-naphthoquinone (1) with nitroalkenes 2: A mixture of 2-hydroxy-1,4-naphthoquinones (1, 34.8 mg, 0.2 mmol) and catalyst III (1.3 mg, 0.002 mmol) in THF (0.4 mL) was stirred at room temperature for 5 min. A solution of nitroalkene 2 (0.2 mmol) was added. The reaction mixture was stirred for 2–5 h at room temperature. After completion of the reaction, the resulting solution was concentrated in vacuo and the obtained residue was purified by flash chromatography (EtOAc–hexane) to afford the corresponding Michael adducts 3. Products 3 are known compounds, and their data were identical to those reported in the literature [34-36].

Supporting Information

Supporting Information File 1
Characterization data of products 3. [http://www.beilstein-journals.org/bjoc/content/supplementary/1860-5397-8-78-S1.pdf]

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