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# Highly diastereoselective and enantioselective direct Michael addition of phthalide derivatives to nitroolefins†

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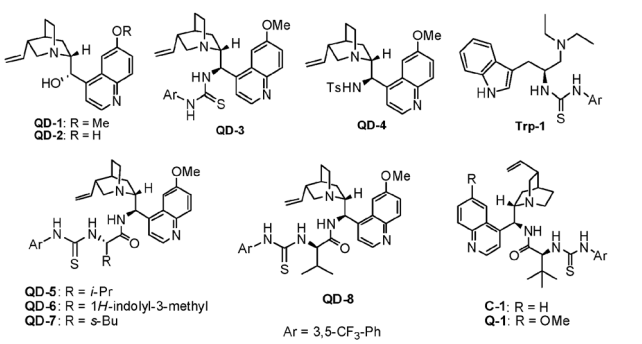
**The first asymmetric Michael addition of 3-substituted phthalides to nitroolefins promoted by amino acid-incorporating multifunctional catalysts has been developed. The reported method led to the synthesis of 3,3-disubstituted phthalide derivatives in high yields, and in a highly diastereoselective and enantioselective manner. Facile synthesis of a chiral bicyclic lactam has also been demonstrated.**

Functionalized phthalides are structural motifs widely present in many natural products and therapeutically useful agents.[1] Given their biological importance, a range of catalytic methods have been devised for the facile construction of chiral 3-substituted phthalides. The first catalytic asymmetric example was reported by Noyori *et al.*, in which an enantioselective transfer hydrogenation reaction was utilized.[2] Later, Butsugan *et al.* disclosed an approach utilizing a chiral amine alcohol mediated addition of zinc reagent to aldehydes.[3] A Ni(II)–(*S*)-BINAP complex catalyzed tandem addition–cyclization reaction was reported by Lin *et al.*, for the synthesis of halogen-substituted phthalides.[4] Yamamoto *et al.* then described a Rh(I)-catalyzed one-pot four-component coupling method.[5] Recently, Trost and Weiss reported a ProPhenol-promoted enantioselective alkynylation as the key step in the preparation of enantioenriched phthalides.[6] Cheng *et al.* devised a cobalt-catalyzed cocyclization reaction of 2-iodobenzoates with aldehydes to afford substituted phthalide derivatives in one pot.[7] Very recently, Wang *et al.* developed an organocatalytic approach for the synthesis of 3-substituted phthalides, involving an enantioselective sequential aldol-lactonization reaction.[8] The above methods, however, focus on the asymmetric synthesis of 3-monosubstituted phthalides. The 3,3-disubstituted phthalides bearing a quaternary stereogenic center are molecules of biological significance,[9] and approaches to these challenging synthetic targets are much less common. In 2007, Tanaka *et al.* described a rhodium-catalyzed one-pot transesterification and [2+2+2] cycloaddition for the synthesis of enantioenriched 3,3-disubstituted phthalides.[10] As part of our ongoing research efforts towards the construction of quaternary stereogenic centers,[11] we are interested in effective asymmetric methods for creating 3,3-disubstituted chiral phthalide derivatives. Our previous studies demonstrated that phthalides containing an activating group at the 3-position are suitable substrates for the direct Mannich reaction,[12] as well as for the asymmetric allylic alkylations with MBH carbonates.[13] Herein, we describe a highly diastereoselective and enantioselective Michael addition of 3-substituted phthalides to nitroolefins.

The organocatalysts containing a tertiary amine and a Brønsted acid moiety seem to be suitable for promoting the projected Michael addition. The bifunctional organic catalysts employed in this study are summarized in Scheme 1. We have recently developed a series of novel Cinchona and amino acid derived tertiary amine catalysts. Quinidine-derived sulfonamide (**QD-4**) was found to be a good catalyst for the Michael addition of α-ketoesters to nitroolefins.[11j] L-Tryptophan-derived




**Scheme 1** Bifunctional and multifunctional catalysts screened in the study.

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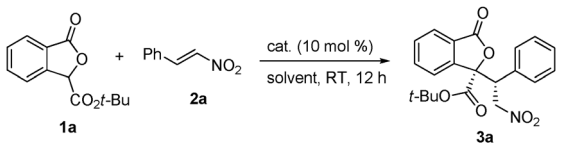
(**Trp-1**) and L-threonine-based thioureas were shown to be effective in promoting the Mannich reaction of fluorinated methines,[11k] cascade reactions[14] and vinylogous aldol reaction of furanones.[15] We also incorporated amino acids into the Cinchona alkaloid structural scaffolds to create a series of novel multifunctional catalysts (**QD-5-8**, **C-1**, **Q-1**), and these catalysts have been applied successfully in conjugate addition to vinyl sulfone,[11f] and cyclopropanation of oxindoles.[16]

For our preliminary investigation, we chose Michael addition of phthalide derivative **1a** to nitroolefins[17] **2a** as a model reaction, and the results are summarized in Table 1. Commercially available quinidine and 6′-demethylated quinidine only led to poor enantioselectivities (entries 1 and 2). Quinidine-derived thiourea **QD-3**, a powerful catalyst amply demonstrated in the literature, also turned out to be disappointing (entry 3). Quinidine-derived sulfonamide **QD-4** and L-tryptophan-based **Trp-1** were also found to be ineffective (entries 4 and 5). We next turned our attention to our recently developed amino acid-incorporating multifunctional catalysts. To our delight, when different amino acid residues were incorporated into the quinidine core, the enantioselectivity of the reaction was substantially improved (entries 6–9). The subsequent solvent screening revealed that dichloroethane (DCE) was the solvent of choice (entries 10–14). Further improvement on the enantioselectivity of the reaction was achieved by employing multifunctional catalysts containing a *tert*-leucine moiety (entries 15–17). Under optimized reaction conditions, the desired Michael adduct could be obtained in 91% yield, and with >19 : 1 dr and 94% ee.

With the best reaction conditions in hand, we next studied the scope of the reaction by employing different phthalides and nitroolefins (Table 2). Consistently high enantioselectivities and excellent diastereoselectivities were observed for a wide range of aryl nitroolefins (entries 1–14). Alkyl nitroolefins could be tolerated, and the Michael adducts were obtained virtually as one diastereomer and with good enantioselectivities (entries 15 and 16). The aryl moiety of the phthalide could also be varied, and excellent diastereoselectivity and enantioselectivity were maintained (entry 17). The X-ray crystal structure of **3f** (Fig. 1) was obtained, and its absolute configuration was assigned accordingly. A proposed transition state is illustrated in Scheme 2.

The asymmetric Michael reaction described here represents a novel method for the preparation of chiral 3,3-disubstituted phthalides which are of biological significance. In addition, the Michael products are rich in functionality, and thus serve as valuable synthetic intermediates. As an illustration, **3a** was treated with TFA, followed by methylation to give intermediate **4**. The nitro group was then reduced, and the subsequent

**Table 1** Catalyst screening for asymmetric Michael addition of phthalide **1a** to nitroolefin **2a**[a]

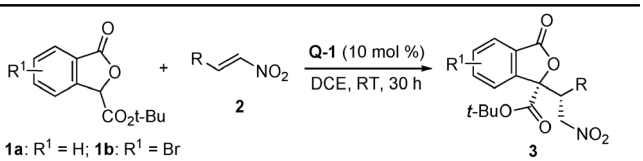



**1a** **2a** **3a**

| Entry | Solvent | Cat. | Yield[b] (%) | dr[c] | ee[d] (%) |
|---|---|---|---|---|---|
| 1 | $CH_2Cl_2$ | **QD-1** | 89 | >19 : 1 | 30 |
| 2 | $CH_2Cl_2$ | **QD-2** | 91 | >19 : 1 | 25 |
| 3 | $CH_2Cl_2$ | **QD-3** | 90 | >19 : 1 | 33 |
| 4 | $CH_2Cl_2$ | **QD-4** | <50 | — | — |
| 5 | $CH_2Cl_2$ | **Trp-1** | 93 | >19 : 1 | 11 |
| 6 | $CH_2Cl_2$ | **QD-5** | 92 | >19 : 1 | 73 |
| 7 | $CH_2Cl_2$ | **QD-6** | 90 | >19 : 1 | 70 |
| 8 | $CH_2Cl_2$ | **QD-7** | 88 | >19 : 1 | 73 |
| 9 | $CH_2Cl_2$ | **QD-8** | 85 | >19 : 1 | −72 |
| 10 | Toluene | **QD-5** | 92 | >19 : 1 | 63 |
| 11 | $CHCl_3$ | **QD-5** | 91 | >19 : 1 | 66 |
| 12 | THF | **QD-5** | 82 | >19 : 1 | 39 |
| 13 | $Et_2O$ | **QD-5** | 88 | >19 : 1 | 56 |
| 14 | DCE | **QD-5** | 95 | >19 : 1 | 81 |
| 15 | DCE | **C-1** | 92 | >19 : 1 | 84 |
| 16 | DCE | **Q-1** | 92 | >19 : 1 | 88 |
| 17[e] | DCE | **Q-1** | 91 | >19 : 1 | 94 |

[a] Reactions were carried out using **1a** (0.05 mmol), **2a** (0.06 mmol), the catalyst (0.005 mmol) in the solvent specified (0.5 mL) at room temperature. [b] Yield of the isolated product. [c] Determined by $^1$H NMR analysis of the crude products. [d] Determined by chiral HPLC analysis on a chiral stationary phase. [e] The reaction was performed in 2.5 ml solvent.

**Table 2** Substrate scope[a]




**1a**: $R^1$ = H; **1b**: $R^1$ = Br **2** **3**

| Entry | 1 | R | 3 | Yield[b] (%) | dr[c] | ee[d] (%) |
|---|---|---|---|---|---|---|
| 1 | **1a** | 4-Me-Ph | **3b** | 89 | >19 : 1 | 93 |
| 2 | **1a** | 2-Naphthyl | **3c** | 86 | >19 : 1 | 87 |
| 3 | **1a** | 1-Naphthyl | **3d** | 91 | >19 : 1 | 85 |
| 4 | **1a** | 3,4-OMe-Ph | **3e** | 85 | >19 : 1 | 88 |
| 5 | **1a** | 4-Br-Ph | **3f** | 93 | >19 : 1 | 91 |
| 6 | **1a** | 3-Br-Ph | **3g** | 82 | >19 : 1 | 91 |
| 7 | **1a** | 2-Br-Ph | **3h** | 83 | >19 : 1 | 86 |
| 8 | **1a** | 4-Cl-Ph | **3i** | 87 | >19 : 1 | 93 |
| 9 | **1a** | 2-Cl-Ph | **3j** | 86 | >19 : 1 | 98 |
| 10 | **1a** | 4-F-Ph | **3k** | 93 | >19 : 1 | 92 |
| 11 | **1a** | 2-F-Ph | **3l** | 91 | >19 : 1 | 92 |
| 12 | **1a** | 4-CN-Ph | **3m** | 85 | >19 : 1 | 97 |
| 13 | **1a** | 3-CN-Ph | **3n** | 87 | >19 : 1 | 92 |
| 14 | **1a** | 2-Furan | **3o** | 90 | >19 : 1 | 92 |
| 15[e] | **1a** | *n*-Propanyl | **3p** | 81 | >19 : 1 | 80 |
| 16[e] | **1a** | i-Butyl | **3q** | 65 | >19 : 1 | 81 |
| 17 | **1b** | Ph | **3r** | 90 | >19 : 1 | 98 |

[a] Reactions were carried out using **1** (0.05 mmol), **2** (0.06 mmol), **Q-1** (0.005 mmol) in DEC (2.5 mL) at room temperature. [b] Isolated yield. [c] Determined by $^1$H NMR analysis of the crude products. [d] Determined by chiral HPLC analysis on a chiral stationary phase. [e] The reaction time was 60 h.

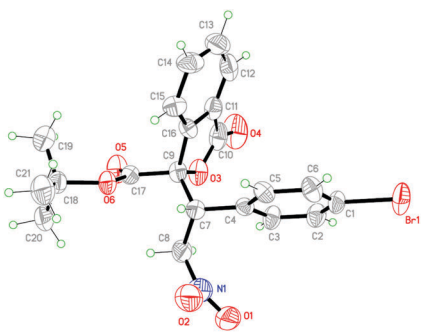
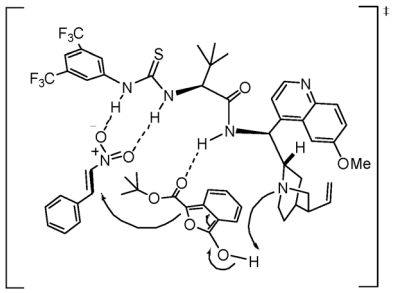
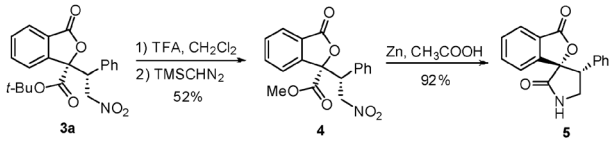



**Fig. 1** ORTEP structure of **3f**.



**Scheme 2** Proposed transition state.




**Scheme 3** Preparation of a bicyclic lactam.

spontaneous cyclization afforded a chiral bicyclic lactam **5** in excellent yield (Scheme 3).

In conclusion, we have developed the first asymmetric Michael addition of 3-substituted phthalide derivatives to nitroolefins, catalyzed by an amino acid-incorporating multifunctional catalyst. The Michael products were obtained in high yields, and with very high diastereoselectivities and enantioselectivities. The synthetic method reported represents an effective approach to access the biologically important 3,3-disubstituted phthalides. We are currently evaluating the biological activities of our novel synthetic chiral phthalides.

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