



# Asymmetric aza-Michael additions of 4-nitrophthalimide to nitroalkenes and preliminary study of the products for herbicidal activities



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## ABSTRACT

The first application of 4-nitrophthalimide as nitrogen nucleophile for enantioselective aza-Michael addition to nitroalkenes has been developed. The process is promoted by chiral thiourea catalyst derived from cinchonine to give corresponding Michael adducts with up to 87% ee. Activity test showed that some products of the reaction have moderate or good herbicidal activity against cole and barnyard grass at 100 µg/ml.

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## 1. Introduction

Stereogenic centers containing C–N bonds are found in many compounds, which have broad application in synthetic, materials as well as biological chemistry.<sup>1</sup> Therefore, development of efficient stereoselective catalytic C–N bonding forming reactions to synthesize these compounds is of significant interest. The conjugate addition reactions of nitrogen nucleophiles to Michael acceptors represent an especially interesting field. Since organocatalysis has become one of the most competitive fields in asymmetric catalysis during the last decade, the organocatalytic aza-Michael reaction has attracted considerable attention in recent years.<sup>2</sup> Stimulated by the seminal work of Miller,<sup>3</sup> many efficient nitrogen nucleophiles have been developed for the reaction, elegant examples include Macmillan's carbamates,<sup>4</sup> Wang's benzotriazole,<sup>5</sup> Ding's 3-methyl-2-pyrazolin-5-ones,<sup>6</sup> Jørgensen's hydrazones,<sup>7</sup> Sibi's *O*-benzylhydroxylamines<sup>8</sup> and so on. However, due to the difficulties of designing new nitrogen nucleophiles with high activity, the nitrogen nucleophiles reported for asymmetric organocatalytic aza-Michael addition are very limited.<sup>9</sup>

Phthalimide is an important organic intermediate and widely used in various fields of chemical, pharmaceutical, and pesticide.<sup>10</sup> Córdova<sup>11</sup> and co-workers reported the first application of

phthalimide as nitrogen nucleophile in 2007, utilizing enals as the Michael acceptor, diphenylprolinol TMS ether as catalyst. In this process, enals are activated by the catalyst through the formation of an iminium ion, facilitating the attack of phthalimide on the  $\beta$ -carbon atom, providing the corresponding adducts in good yields with low enantioselectivities. However, the nucleophile does not apply to other Michael acceptors, such as nitroalkenes, which are attractive acceptors due to their strongly electron withdrawing nitro group<sup>12</sup> can be transformed into many other functionalities.<sup>13</sup> In order to search for new and high efficiency nitrogen nucleophiles, we envisaged that nitrophthalimide should be suitable nucleophiles for the asymmetric organocatalytic aza-Michael addition to nitroalkenes, because they might have an enhanced nucleophilicity due to the electronic effect of the nitro group. Herein we investigated two different nitrophthalimides and reported the first example of an organocatalytic aza-Michael reaction of 4-nitrophthalimide to nitroalkenes catalyzed by chiral thiourea catalysts. Furthermore, a preliminary study of some products for their herbicidal activities has been made and a good result obtained.

## 2. Results and discussion

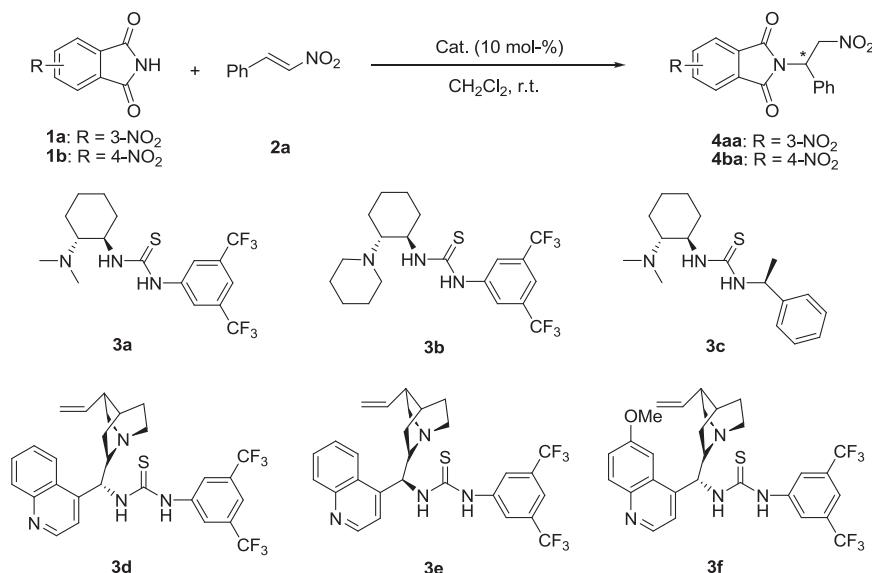
For the screening we considered two nitrophthalimides, 3-nitrophthalimide **1a** and 4-nitrophthalimide **1b**, and their reactions with *trans*- $\beta$ -nitroalkene **2a** as model reactions, the

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results of this investigation are shown in Table 1. Compared with **1a**, we were pleased to find that **1b** was efficient nitrogen nucleophile, and the reaction gave high yield (87%) at a satisfactory rate (**1d**) (entry 2). In the next stage, six tertiary amine thioureas organocatalysts **3a–f** were screened for their ability to promote asymmetric organocatalytic aza-Michael reaction of **1b** and **2a** in  $\text{CH}_2\text{Cl}_2$  at room temperature (entries 3–8). The results revealed that the catalysts differed significantly with regard to catalytic activity and stereocontrol of the progress. The typical Takemoto's catalyst **3a** gave better result (43% yield, 73% ee, entry 3) than other catalysts **3b** and **3c** derived from (1*R*,2*R*)-1,2-diaminocyclohexane (entries 4 and 5). Further screening tertiary amine thioureas catalysts derived from cinchona alkaloid **3d–f** showed that higher yields of the product could be obtained (entries 6–8). To our delight, catalyst **3d** gave the highest enantioselectivity (76% ee) while **3e** afforded 74% ee of the opposite enantiomer of **4ba**, and **3d** was selected for the further investigation.

To present the scope of this aza-Michael addition, the conjugation addition reactions of 4-nitrophthalimide **1b** with a variety of nitroalkenes **2** under optimized conditions were investigated (Table 3). The results showed that in general the reactions took place efficiently with moderate to good enantioselectivity (60–87% ee). Aromatic nitroalkenes, bearing both electron-donating (entries 2, 3 and 7) and electron-withdrawing (entries 4–6 and 8–11) substituents on the phenyl ring, participated in this reaction. But the substitution pattern on the phenyl ring has a significant effect on yield and enantioselectivity. Reactions of nitroalkenes with electron-withdrawing substituents in the *para* position (entries 4–6) gave higher yields (59–73%) and enantioselectivities (79–85% ee) than nitroalkenes with electron-donating substituents in the *para* position (entries 2–3). However, lower enantioselectivities (60–71% ee) accompanied reactions of substrates with substituents in the other position of the phenyl ring (entries 7–11). An interesting finding was that the products **4bg**

**Table 1**  
Screening of nucleophiles and catalysts<sup>a</sup>



Entry	Nitrophthalimide	Cat	T [d]	Yield <sup>b</sup> [%]	ee [%] <sup>c</sup>
1	<b>1a</b>	TEA	3	—	—
2	<b>1b</b>	TEA	1	87	<i>rac</i>
3	<b>1b</b>	<b>3a</b>	2	43	73
4	<b>1b</b>	<b>3b</b>	2	31	48
5	<b>1b</b>	<b>3c</b>	2	35	39
6	<b>1b</b>	<b>3d</b>	2	60	76
7	<b>1b</b>	<b>3e</b>	2	56	–74
8	<b>1b</b>	<b>3f</b>	2	46	57

<sup>a</sup> Unless otherwise noted, reactions performed on a 0.1 mmol scale of **1** and **2a** using 10 mol % of catalyst in  $\text{CH}_2\text{Cl}_2$  (1 ml).

<sup>b</sup> Isolated yield.

<sup>c</sup> Determined by HPLC analysis.

Having found the optimal nucleophile and catalyst, we initiated optimizing the conditions of this reaction (Table 2). First, we screened various solvents (entries 1–10). We found that toluene gave the product **4ba** with high enantioselectivity in low yield (25% yield, 79% ee, entry 7). In order to improve the yield without any significant lowering of enantioselectivity,  $\text{CH}_2\text{Cl}_2$  was added with different proportion and it was found that the ratio of 1:1 gave higher enantioselectivity (78% ee) in moderate yield (51%) (entry 9). By reducing the catalyst loading to 5 mol %, higher yield and increased enantioselectivity of **4ba** were observed in 4 days (entry 11). Next we examined the effects of different additives. To our great delight, the reaction gave the best result in the presence of 4 Å MS (57% yield, 84% ee, entry 14).

and **4bh** gave negative ee values respectively (–71% and –64%, entries 7 and 8). To our delight, the process was also applicable to 1-naphthyl, 2-thiophene and 2-furyl-substituted nitroalkenes (entries 12–14) with moderate yields (62–66%) and excellent enantioselectivities (85–87% ee). Aliphatic nitroalkene **2o** (entry 15) were also evaluated for the process and it was found that the reaction took place in the highest yield (75%), but only moderate enantioselectivity (65% ee) obtained.

As we all know, this is the first example of the addition of 4-nitrophthalimide as nitrogen nucleophile onto nitroalkenes, and the products have not been reported yet. On the other hand, phthalimide derivatives have good biological activities<sup>14</sup> and often used for the production of various herbicides,<sup>10</sup> so we took

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