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# A new approach to the asymmetric Mannich reaction catalyzed by chiral *N,N'*-dioxide–metal complexes†

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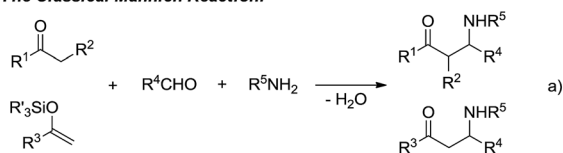
A highly efficient asymmetric Mannich-type reaction between  $\alpha$ -tetralone-derived  $\beta$ -keto esters/amides and 1,3,5-triaryl-1,3,5-triazinanes was realized in the presence of chiral *N,N'*-dioxide–Ni(II) or Mg(II) complex. A variety of optically active  $\beta$ -amino compounds with all-carbon quaternary stereocenters were obtained in good yields with excellent enantioselectivities. A possible transition state was proposed based on these experiments and previous reports.

Because the resulting nitrogen-containing compounds are widely distributed in nature and include many biologically important molecules,<sup>1</sup> the Mannich reaction has received a lot of attention since its discovery in the early 20th century (Scheme 1a).<sup>2</sup> It has become one of the most efficient methods to construct C–C bonds.<sup>3</sup> Despite its important synthetic value, the development of the classical intermolecular

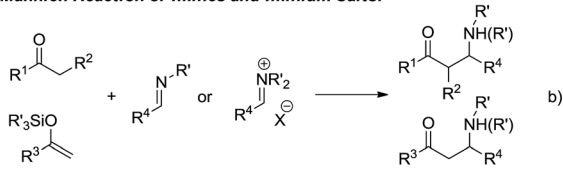
Mannich reaction has been plagued by a number of serious disadvantages such as the undesired side products formed in many cases, and the ability to control the regio- and stereo-selectivity is generally unsatisfactory.<sup>4</sup> The first catalytic enantioselective approach was reported by Kobayashi using a novel chiral zirconium catalyst in 1997.<sup>5</sup> To overcome the drawbacks of the classical Mannich reaction, preformed Mannich reagents such as imines and iminium salts have been developed (Scheme 1b).<sup>6</sup> Subsequently, the catalytic asymmetric Mannich reaction has received a certain amount of development.<sup>7</sup> However, such preformed Mannich reagents also have some defects such as low activity, sensitivity to moisture and instability, and therefore the development of new Mannich reagents is desirable.

1,3,5-Triaryl-1,3,5-triazinanes, which are conveniently prepared through the condensation of paraformaldehyde and aromatic amines,<sup>8</sup> can generate the corresponding imines in solvent, which can be used as Mannich reagents. Very recently, Krische reported investigations on the hydroaminomethylation of allenes and 1,3-dienes with 1,3,5-triaryl-1,3,5-triazinanes catalyzed by ruthenium.<sup>9</sup> Inspired by Krische's work, we think that the *in situ* generated imines from 1,3,5-triaryl-1,3,5-triazinanes might be used as Mannich reagents. On the other hand, all-carbon quaternary stereocenters are widely present in natural products and to build such structures is still a challenge, especially in a catalytic enantioselective manner.<sup>10</sup> In recent years, our group has been committed to utilizing *N,N'*-dioxide–metal complexes as catalysts and has achieved a series of catalytic asymmetric reactions, including the construction of compounds with chiral all-carbon quaternary stereocenters.<sup>11</sup> Herein, we report the first asymmetric Mannich reaction employing 1,3,5-triaryl-1,3,5-triazinanes as new Mannich reagents catalyzed by *N,N'*-dioxide–metal complexes, and a variety of optically active  $\beta$ -amino compounds, each with an all-carbon quaternary stereocenter, were obtained.

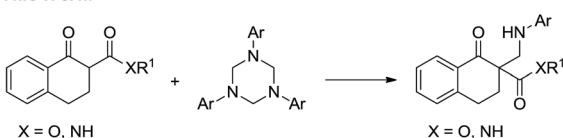
### The Classical Mannich Reaction:



### Mannich Reaction of Imines and Iminium Salts:



### This Work:



Scheme 1 Classical Mannich-type reaction and the new approach.

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In our preliminary screening, the  $\alpha$ -tetralone-derived  $\beta$ -keto ester **1a** and 1,3,5-triphenyl-1,3,5-triazinane **3a** were chosen as the model substrates to optimize the reaction conditions (Table 1). Initially, the performance of various metal salts was evaluated when combined with the chiral  $N,N'$ -dioxide ligand **L-PrPh**, which is derived from *L*-proline, and the reactions were performed in  $\text{CH}_2\text{Cl}_2$  at 30 °C (Table 1, entries 1–5). Lanthanides, the  $N,N'$ -dioxide complexes of which have proved to be efficient catalysts for many reactions,<sup>11</sup> can only provide the desired product **4a** with low ee values or as a racemate, although the yields were good (Table 1, entries 1–3). The complex of  $\text{Mg}(\text{OTf})_2$  could give the desired product in 85% yield but with only 18% ee (Table 1, entry 4). To our delight, the complex of  $\text{Ni}(\text{ClO}_4)_2 \cdot 6\text{H}_2\text{O}$  provided **4a** with a better ee value (44% ee, Table 1, entry 5 *versus* entries 1–4). Increasing the steric hindrance of the amide substituents on the chiral  $N,N'$ -dioxide ligand further improved the enantioselectivity. Chiral  $N,N'$ -dioxide **L-PrPr<sub>2</sub>** with a more sterically hindered *i*-Pr at the *ortho*-positions of aniline improved the enantioselectivity to 53% ee (Table 1, entry 6 *versus* entry 5). Then we investigated the effect of the chiral

backbone moiety, the (*S*)-pipercolic acid derived  $N,N'$ -dioxide **L-PiPr<sub>2</sub>** (Table 1, entry 8) was superior to *L*-proline derived **L-PrPr<sub>2</sub>** and *L*-ramipril-derived **L-RaPr<sub>2</sub>** (Table 1, entries 6 and 7), giving the product in 94% yield with 96% ee. In addition, lowering the temperature to 0 °C improved the enantioselectivity to 99% ee albeit with a lower yield (Table 1, entry 9). Remarkably, upon reducing the catalyst loading to 5 mol% the yield improved to 97% with the enantioselectivity maintained (Table 1, entry 10). When the  $\alpha$ -tetralone-derived  $\beta$ -keto amide **2a** was employed in this reaction instead of **1a**, the desired product **5a** was obtained in good yield but with unsatisfactory enantioselectivity (Table 1, entry 11). Then we replaced the metal salt with  $\text{Mg}(\text{OTf})_2$  and got comparable results (Table 1, entry 12).

With the optimized reaction conditions in hand, we firstly investigated the scope of the reactions between  $\alpha$ -tetralone-derived  $\beta$ -keto esters and 1,3,5-triaryl-1,3,5-triazinanes (Table 2). Delightfully, the electronic nature and the positions of the substituents on the  $\beta$ -keto esters had little influence on both the yields and enantioselectivities (83–98% yield, 81–99% ee; **4a–4f**). Next, the 1,3,5-triaryl-1,3,5-triazinanes were varied. As it shown in Table 2 (**4g–4k**), the positions of the substituents have a certain influence on the yields, but the enantioselectivities were good in all cases. Generally, the 2-substituted 1,3,5-triaryl-

Table 1 Optimization of the reaction conditions

**1a**: X = O  
**2a**: X = NH  
**3a**  
**4a**: X = O  
**5a**: X = NH

**L-PrPh**: R = C<sub>6</sub>H<sub>5</sub>, n = 1  
**L-PrPr<sub>2</sub>**: R = 2,6-*i*Pr<sub>2</sub>C<sub>6</sub>H<sub>3</sub>, n = 1  
**L-PiPr<sub>2</sub>**: R = 2,6-*i*Pr<sub>2</sub>C<sub>6</sub>H<sub>3</sub>, n = 2

| Entry <sup>a</sup> | Substrate | Metal salt   | Ligand                    | Yield <sup>b</sup> (%) | ee <sup>c</sup> (%) |
|--------------------|-----------|--|---------------------------|------------------------|---------------------|
| 1                  | <b>1a</b> | Sc(OTf) <sub>3</sub>                                   | <b>L-PrPh</b>             | 83                     | 0                   |
| 2                  | <b>1a</b> | Yb(OTf) <sub>3</sub>                                   | <b>L-PrPh</b>             | 84                     | 0                   |
| 3                  | <b>1a</b> | La(OTf) <sub>3</sub>                                   | <b>L-PrPh</b>             | 90                     | 13                  |
| 4                  | <b>1a</b> | Mg(OTf) <sub>2</sub>                                   | <b>L-PrPh</b>             | 85                     | 18                  |
| 5                  | <b>1a</b> | Ni(ClO <sub>4</sub> ) <sub>2</sub> · 6H <sub>2</sub> O | <b>L-PrPh</b>             | 97                     | 44                  |
| 6                  | <b>1a</b> | Ni(ClO <sub>4</sub> ) <sub>2</sub> · 6H <sub>2</sub> O | <b>L-PrPr<sub>2</sub></b> | 67                     | 53                  |
| 7                  | <b>1a</b> | Ni(ClO <sub>4</sub> ) <sub>2</sub> · 6H <sub>2</sub> O | <b>L-RaPr<sub>2</sub></b> | 87                     | 87                  |
| 8                  | <b>1a</b> | Ni(ClO <sub>4</sub> ) <sub>2</sub> · 6H <sub>2</sub> O | <b>L-PiPr<sub>2</sub></b> | 94                     | 96                  |
| 9 <sup>d</sup>     | <b>1a</b> | Ni(ClO <sub>4</sub> ) <sub>2</sub> · 6H <sub>2</sub> O | <b>L-PiPr<sub>2</sub></b> | 87                     | 99                  |
| 10 <sup>d,e</sup>  | <b>1a</b> | Ni(ClO <sub>4</sub> ) <sub>2</sub> · 6H <sub>2</sub> O | <b>L-PiPr<sub>2</sub></b> | 97                     | 99                  |
| 11 <sup>d,e</sup>  | <b>2a</b> | Ni(ClO <sub>4</sub> ) <sub>2</sub> · 6H <sub>2</sub> O | <b>L-PiPr<sub>2</sub></b> | 95                     | 61                  |
| 12 <sup>d,f</sup>  | <b>2a</b> | Mg(OTf) <sub>2</sub>                                   | <b>L-PiPr<sub>2</sub></b> | 98                     | 97                  |

<sup>a</sup> Unless otherwise noted, the reactions were performed with **1a** or **2a** (0.10 mmol), **3a** (0.034 mmol), ligand (0.01 mmol), and metal salt (0.01 mmol) in 1.0 mL  $\text{CH}_2\text{Cl}_2$  at 30 °C for 8 h. <sup>b</sup> Isolated yield of the product. <sup>c</sup> Determined by HPLC analysis on a chiral stationary phase. <sup>d</sup> The reaction was performed at 0 °C for 12 h. <sup>e</sup> 5 mol% **L-PiPr<sub>2</sub>** (0.005 mmol) and 5 mol%  $\text{Ni}(\text{ClO}_4)_2 \cdot 6\text{H}_2\text{O}$  (0.005 mmol) were used. <sup>f</sup> The reaction was performed with **L-PiPr<sub>2</sub>** (0.005 mmol) and  $\text{Mg}(\text{OTf})_2$  (0.005 mmol).

Table 2 Substrate scope for  $\beta$ -keto esters<sup>d</sup>

**1**, **3** → **4**

**4a** 97% yield<sup>[b]</sup>, 99% ee<sup>[c]</sup>    **4b** 83% yield, 98% ee    **4c** 90% yield, 91% ee  
**4d** 90% yield, 92% ee    **4e** 84% yield, 96% ee    **4f** 98% yield, 81% ee  
**4g** 96% yield, 95% ee    **4h** 91% yield, 94% ee    **4i** 95% yield, 98% ee  
**4j** 82% yield, 99% ee    **4k** 50% yield, 91% ee    **4l** 99% yield, 93% ee

<sup>a</sup> The reactions were performed with **1** (0.10 mmol), **3** (0.034 mmol), **L-PiPr<sub>2</sub>** (0.005 mmol), and  $\text{Ni}(\text{ClO}_4)_2 \cdot 6\text{H}_2\text{O}$  (0.005 mmol) in 1.0 mL  $\text{CH}_2\text{Cl}_2$  at 0 °C for 12 h. <sup>b</sup> Isolated yield of the product. <sup>c</sup> Determined by HPLC analysis on a chiral stationary phase.



1,3,5-triazinanes showed a slight decrease in yield compared with the 4-substituted ones. What's more, 1-adamantanol substituted  $\beta$ -keto ester **1l** was also a suitable substrate for this reaction and the corresponding product **4l** was obtained in 99% yield with 93% ee (Table 2, **4l**). Additionally, the absolute configuration of **4a** was determined to be *R* by X-ray crystallography<sup>12</sup> and the configurations of the others were determined to be *R* by circular dichroism (for details see the ESI†).

Subsequently, we turned our attention to investigate the substrate scope of the reactions between  $\alpha$ -tetralone-derived  $\beta$ -keto amides and 1,3,5-triaryl-1,3,5-triazinanes (Table 3). To our delight, a variety of  $\beta$ -keto amides with different substituents were tolerated and gave the corresponding products with excellent enantioselectivities (Table 3, 93–98% ee; **5a–5f**). Then the scope of 1,3,5-triaryl-1,3,5-triazinanes was examined. The results are different from the results for the reactions of the  $\beta$ -keto esters, and both 2- and 4-substituted 1,3,5-triazinanes afforded the corresponding products in excellent yields and enantioselectivities (95–99% yields, 95–99% ee, **5g, 5i** and **5j**) except the 4-MeO substituted 1,3,5-tris(4-methoxyphenyl)-1,3,5-triazinane, which gave the corresponding product in 84% ee. Besides this, five- and seven-membered

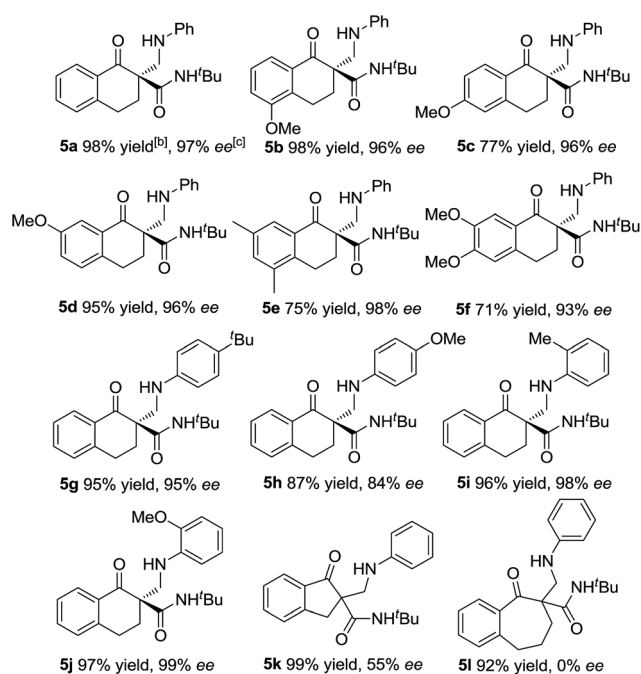
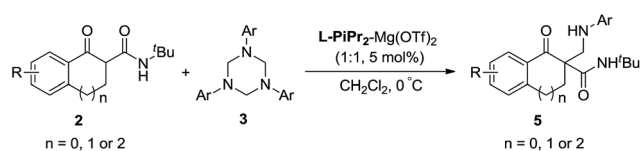
$\beta$ -keto amide substrates were also examined. Unfortunately, the five-membered  $\beta$ -keto amide gave the corresponding product **5k** with only 55% ee, while the seven-membered  $\beta$ -keto amide gave a racemic product **5l** though the yields were excellent under the standard conditions. A cyclohexanone-derived  $\beta$ -keto amide was also tested under the standard reaction conditions, but the reaction didn't occur. Meanwhile, the absolute configuration of **5a** was determined to be *R* by X-ray crystallography analysis<sup>12</sup> and configurations of the others were also determined to be *R* by circular dichroism (for details see the ESI†).

To evaluate the synthetic value of this catalytic system, gram-scale reactions were performed (Scheme 2). In the presence of the **L-PiPr<sub>2</sub>-Ni(ClO<sub>4</sub>)<sub>2</sub>·6H<sub>2</sub>O** complex (5 mol%), the starting material **1a** (4.0 mmol) reacted with **3a** (1.3 mmol, 1.0 equivalent) smoothly, and the corresponding product **4a** was obtained in 92% yield with 99% ee (Scheme 2a). In the system of  $\alpha$ -tetralone-derived  $\beta$ -keto amides and 1,3,5-triaryl-1,3,5-triazinanes, the reaction between 0.98 g **2a** and 0.42 g **3a** was performed under the optimized reaction conditions, affording 1.34 g (95% yield) of the corresponding product **5a** with 97% ee (Scheme 2b).

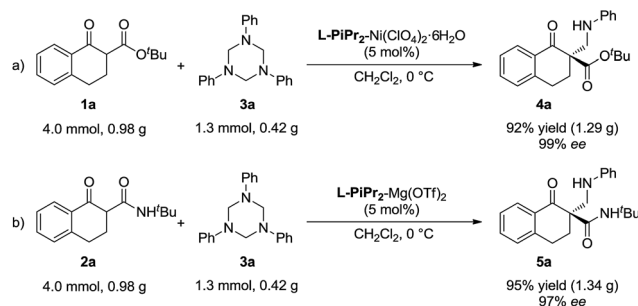
On the other hand, the product **4a** could be efficiently converted into useful  $\beta$ -hydroxyl ester **6** through reduction using NaBH<sub>4</sub> as a reducing agent (Scheme 3). The diastereomer of the product **6** was determined to be *trans*- using NOESY spectra (see the ESI† for details). The product **4h** could be converted into *N*-Boc- $\beta$ -amino ester **7** by deprotection with cerium ammonium nitrate (CAN) followed by Boc protection of the amino group with Boc<sub>2</sub>O (see the ESI† for details).

To gain insight into the mechanism, the relationship between the ee value of the ligand **L-PiPr<sub>2</sub>** and that of **4a** was investigated under the optimal reaction conditions.<sup>13</sup> A linear effect was observed (see the ESI† for details), which suggested that a monomeric catalyst may be the main catalytically active species in the reaction system. Based on the experiments and our previous work<sup>11</sup> as well as the absolute configuration of the products, a possible transition state model is proposed in Fig. 1 to elucidate the origin of the asymmetric induction. In the transition state, the oxygens of the *N,N'*-dioxides and the amide oxygens coordinate to Ni(II) in a tetradentate manner. The  $\beta$ -keto ester **1a** could be activated after coordinating to the nickel atom in a bidentate fashion. The *Si*-face of  $\beta$ -keto ester **1a** is effectively shielded by the amide moiety and the piperidine ring on the underside of the ligand **L-PiPr<sub>2</sub>**. In contrast, the *Re*-face is

Table 3 Substrate scope for  $\beta$ -keto amides<sup>a</sup>

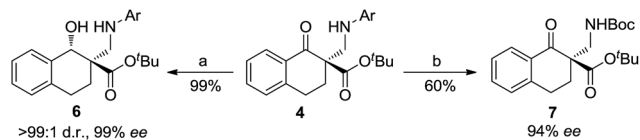


<sup>a</sup> The reactions were performed with **2** (0.10 mmol), **3** (0.034 mmol), **L-PiPr<sub>2</sub>** (0.005 mmol), and Mg(OTf)<sub>2</sub> (0.005 mmol) in 1.0 mL CH<sub>2</sub>Cl<sub>2</sub> at 0 °C for 12 h. <sup>b</sup> Isolated yield of the product. <sup>c</sup> Determined by HPLC analysis on a chiral stationary phase.

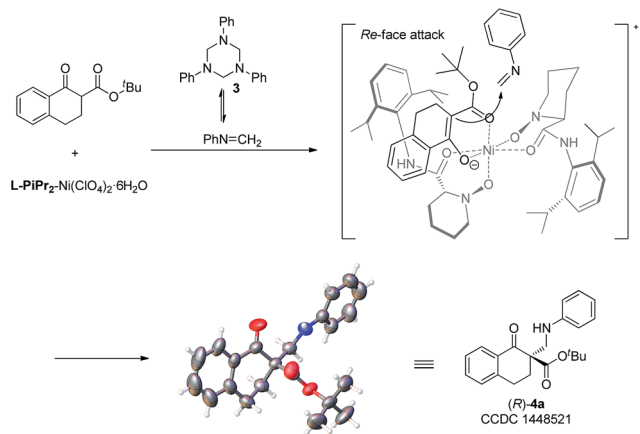


Scheme 2 Gram-scale version of the reaction.





**Scheme 3** Transformations of the product **4** into other derivatives; reaction conditions: (a) NaBH<sub>4</sub> and MeOH/CH<sub>2</sub>Cl<sub>2</sub> (1 : 1), 0 °C (**4a**: Ar = Ph, 99% ee); (b) CAN, CH<sub>3</sub>CN/H<sub>2</sub>O; then Et<sub>3</sub>N and Boc<sub>2</sub>O (**4h**: Ar = 4-MeOC<sub>6</sub>H<sub>4</sub>, 94% ee). Boc = *tert*-butyloxycarbonyl.



**Fig. 1** Proposed transition state and the absolute configuration of **4a**.

located in a relatively open space. The highly selective approach of the *in situ* generated *N*-methylethaniline toward the *Re*-face of the bidentate-coordinated  $\beta$ -keto ester leads to the desired product with an *R* configuration, which is consistent with the observed absolute configuration of the product.

## Conclusions

In summary, a highly enantioselective Mannich-type reaction between  $\alpha$ -tetralone-derived  $\beta$ -keto esters/amides and 1,3,5-triaryl-1,3,5-triazinanes was realized. In the presence of chiral *N,N'*-dioxide-Ni(II) or *N,N'*-dioxide-Mg(II) complex, a variety of corresponding  $\beta$ -amino compounds each with an all-carbon quaternary stereocenter were obtained in good to excellent enantioselectivities (up to 99% ee) and good to excellent yields (up to 99%). In particular, this is the first time that 1,3,5-triaryl-1,3,5-triazinanes were used as electrophilic reagents in the catalytic asymmetric Mannich reaction. Further studies focused on the reactions of 1,3,5-triaryl-1,3,5-triazinanes are under way.

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