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

Xiangjin Lian, Lili Lin, Kai Fu, Baiwei Ma, Xiaohua Liu and Xiaoming Feng*

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, the Mannich reaction has received a lot of attention since its discovery in the early 20th century (Scheme 1a). It has become one of the most efficient methods to construct C–C bonds. 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. The first catalytic enantioselective approach was reported by Kobayashi using a novel chiral zirconium catalyst in 1997. To overcome the drawbacks of the classical Mannich reaction, preformed Mannich reagents such as imines and iminium salts have been developed (Scheme 1b). Subsequently, the catalytic asymmetric Mannich reaction has received a certain amount of development. 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, 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. Inspired by Krische’s work, we think that the \textit{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. 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.

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.

Scheme 1 Classical Mannich-type reaction and the new approach.
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 \( \alpha \)-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,\(^1\) 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 Mg(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 Ni(ClO\(_4\))\(_2\)-6H\(_2\)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\(_2\) with a more sterically hindered \( i \)-Pr at the \( \text{o} \)-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)-pipelic acid derived \( N,N' \)-dioxide L-PiPr\(_2\) (Table 1, entry 8) was superior to \( \alpha \)-proline derived L-PrPh and \( \alpha \)-ramipril-derived L-RaPr\(_2\) (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 Mg(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

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>Metal salt</th>
<th>Ligand</th>
<th>Yield a (%)</th>
<th>ee ((%))</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1a</td>
<td>Sc(OTf)(_2)</td>
<td>L-PrPh</td>
<td>83</td>
<td>0</td>
</tr>
<tr>
<td>2</td>
<td>1a</td>
<td>Yb(OTf)(_3)</td>
<td>L-PrPh</td>
<td>84</td>
<td>0</td>
</tr>
<tr>
<td>3</td>
<td>1a</td>
<td>La(OTf)(_3)</td>
<td>L-PrPh</td>
<td>90</td>
<td>13</td>
</tr>
<tr>
<td>4</td>
<td>1a</td>
<td>Mg(OTf)(_2)</td>
<td>L-PrPh</td>
<td>85</td>
<td>18</td>
</tr>
<tr>
<td>5</td>
<td>1a</td>
<td>Ni(ClO(_4))(_2)-6H(_2)O</td>
<td>L-PrPh</td>
<td>97</td>
<td>44</td>
</tr>
<tr>
<td>6</td>
<td>1a</td>
<td>Ni(ClO(_4))(_2)-6H(_2)O</td>
<td>L-PrPr(_2)</td>
<td>67</td>
<td>53</td>
</tr>
<tr>
<td>7</td>
<td>1a</td>
<td>Ni(ClO(_4))(_2)-6H(_2)O</td>
<td>L-RaPr(_2)</td>
<td>87</td>
<td>87</td>
</tr>
<tr>
<td>8</td>
<td>1a</td>
<td>Ni(ClO(_4))(_2)-6H(_2)O</td>
<td>L-PiPr(_2)</td>
<td>94</td>
<td>96</td>
</tr>
<tr>
<td>9</td>
<td>1a</td>
<td>Ni(ClO(_4))(_2)-6H(_2)O</td>
<td>L-PiPr(_2)</td>
<td>87</td>
<td>99</td>
</tr>
<tr>
<td>10</td>
<td>1a</td>
<td>Ni(ClO(_4))(_2)-6H(_2)O</td>
<td>L-PiPr(_2)</td>
<td>97</td>
<td>99</td>
</tr>
<tr>
<td>11</td>
<td>1a</td>
<td>Ni(ClO(_4))(_2)-6H(_2)O</td>
<td>L-PiPr(_2)</td>
<td>95</td>
<td>61</td>
</tr>
<tr>
<td>12</td>
<td>2a</td>
<td>Mg(OTf)(_2)</td>
<td>L-PiPr(_2)</td>
<td>98</td>
<td>97</td>
</tr>
</tbody>
</table>

a 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. a Isolated yield of the product. b Determined by HPLC analysis on a chiral stationary phase. c The reaction was performed at 0 °C for 12 h. d 5 mol% L-PrPr\(_2\) (0.005 mmol) and 5 mol% Ni(ClO\(_4\))\(_2\)-6H\(_2\)O (0.005 mmol) were used. e The reaction was performed with L-PiPr\(_2\) (0.005 mmol) and Mg(OTf)\(_2\) (0.005 mmol).

### Table 2 Substrate scope for \( \beta \)-keto esters a

<table>
<thead>
<tr>
<th>Substrate</th>
<th>Yield a (%)</th>
<th>ee b (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>4a</td>
<td>97% yield</td>
<td>99% ee</td>
</tr>
<tr>
<td>4b</td>
<td>83% yield</td>
<td>98% ee</td>
</tr>
<tr>
<td>4c</td>
<td>90% yield</td>
<td>91% ee</td>
</tr>
<tr>
<td>4d</td>
<td>90% yield</td>
<td>92% ee</td>
</tr>
<tr>
<td>4e</td>
<td>94% yield</td>
<td>96% ee</td>
</tr>
<tr>
<td>4f</td>
<td>96% yield</td>
<td>81% ee</td>
</tr>
<tr>
<td>4g</td>
<td>96% yield</td>
<td>95% ee</td>
</tr>
<tr>
<td>4h</td>
<td>91% yield</td>
<td>94% ee</td>
</tr>
<tr>
<td>4i</td>
<td>95% yield</td>
<td>98% ee</td>
</tr>
<tr>
<td>4j</td>
<td>82% yield</td>
<td>99% ee</td>
</tr>
<tr>
<td>4k</td>
<td>50% yield</td>
<td>91% ee</td>
</tr>
<tr>
<td>4l</td>
<td>99% yield</td>
<td>93% ee</td>
</tr>
</tbody>
</table>

a The reactions were performed with 1 (0.10 mmol), 3 (0.034 mmol), L-PrPr\(_2\) (0.005 mmol), and Ni(ClO\(_4\))\(_2\)-6H\(_2\)O (0.005 mmol) in 1.0 mL \( \text{CH}_2\text{Cl}_2 \) at 0 °C for 12 h. b Isolated yield of the product. c 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 β-keto ester 1f was also a suitable substrate for this reaction and the corresponding product 4f was obtained in 99% yield with 93% ee (Table 2, 4f). Additionally, the absolute configuration of 4a was determined to be R by X-ray crystallography\textsuperscript{12} 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 α-tetralone-derived β-keto amides and 1,3,5-triaryl-1,3,5-triazinanes (Table 3). To our delight, a variety of β-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 β-keto esters, and both 2- and 4-substituted 1,3,5-triaryl-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-methoxypheryl)-1,3,5-triazinane, which gave the corresponding product in 84% ee. Besides this, five- and seven-membered β-keto amide substrates were also examined. Unfortunately, the five-membered β-keto amide gave the corresponding product 5k with only 55% ee, while the seven-membered β-keto amide gave a racemic product 5l though the yields were excellent under the standard conditions. A cyclohexanone-derived β-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\textsuperscript{12} 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\textsubscript{2}–Ni(ClO\textsubscript{4})\textsubscript{2}·6H\textsubscript{2}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 α-tetralone-derived β-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 β-hydroxyl ester 6 through reduction using NaBH\textsubscript{4} 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-β-amino ester 7 by deprotection with cerium ammonium nitrate (CAN) followed by Boc protection of the amino group with Boc\textsubscript{2}O (see the ESI† for details).

To gain insight into the mechanism, the relationship between the ee value of the ligand L-PiPr\textsubscript{2} and that of 4a was investigated under the optimal reaction conditions.\textsuperscript{13} 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\textsuperscript{13} 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 β-keto ester 1a could be activated a face coordinating to the nickel atom in a bidentate fashion. The Si-face of β-keto ester 1a is effectively shielded by the amide moiety and the piperidine ring on the underside of the ligand L-PiPr\textsubscript{2}. In contrast, the Re-face is

\begin{table}[h]
\centering
\caption{Substrate scope for β-keto amides\textsuperscript{a}}
\begin{tabular}{llll}
\hline
R & 2 & 3 & 5  \\
\hline
  & n = 0, 1 or 2 & n = 0, 1 or 2 & \\
\hline
OMe & 90% yield, 93% ee & 77% yield, 96% ee &  \\
MeO & 5b 95% yield, 96% ee &  \\
Me & 5e 75% yield, 98% ee & \\
Me & 5f 71% yield, 93% ee & \\
OMe & 5g 95% yield, 95% ee & \\
MeO & 5h 87% yield, 84% ee &  \\
Me & 5i 96% yield, 98% ee & \\
OMe & 5j 97% yield, 99% ee &  \\
MeO & 5k 99% yield, 55% ee &  \\
Me & 5l 92% yield, 0% ee &  \\
\hline
\end{tabular}
\textsuperscript{a} The reactions were performed with 2 (0.10 mmol), 3 (0.034 mmol), L-PiPr\textsubscript{2} (0.005 mmol), and Mg(OT\textsubscript{f})\textsubscript{2} (0.005 mmol) in 1.0 mL CH\textsubscript{2}Cl\textsubscript{2} at 0 °C for 12 h.\textsuperscript{b} Isolated yield of the product.\textsuperscript{c} Determined by HPLC analysis on a chiral stationary phase.
\end{table}

\begin{scheme}
\caption{Gram-scale version of the reaction.}
\begin{tikzpicture}
\end{tikzpicture}
\end{scheme}
Highly selective approach of the in situ generated N-methyleaniline toward the Re-face of the bidentate-coordinated β-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 α-tetralone-derived β-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 β-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.

Acknowledgements

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Notes and references


2 C. Mannich and W. Krosche, Arch. Pharm., 1912, 250, 647.


12 CCDC 1448521 (4a) and CCDC 1480808 (5a) contain the supplementary crystallographic data for this paper.