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

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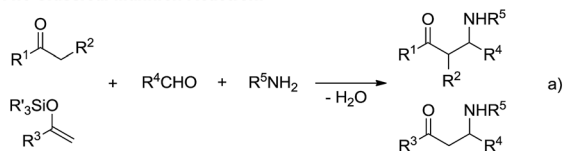
A highly efficient asymmetric Mannich-type reaction between α -tetralone-derived β -keto esters/amides and 1,3,5-triaryl-1,3,5-triazinanes was realized in the presence of chiral *N,N'*-dioxide–Ni(II) or Mg(II) complex. A variety of optically active β -amino compounds with all-carbon quaternary stereocenters 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,¹ the Mannich reaction has received a lot of attention since its discovery in the early 20th century (Scheme 1a).² It has become one of the most efficient methods to construct C–C bonds.³ Despite its important synthetic value, the development of the classical intermolecular

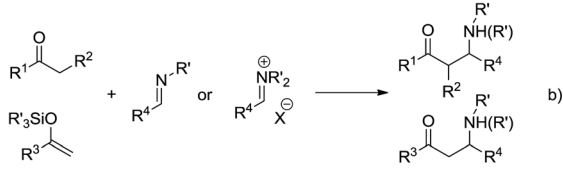
Mannich reaction has been plagued by a number of serious disadvantages such as the undesired side products formed in many cases, and the ability to control the regio- and stereo-selectivity is generally unsatisfactory.⁴ The first catalytic enantioselective approach was reported by Kobayashi using a novel chiral zirconium catalyst in 1997.⁵ To overcome the drawbacks of the classical Mannich reaction, preformed Mannich reagents such as imines and iminium salts have been developed (Scheme 1b).⁶ Subsequently, the catalytic asymmetric Mannich reaction has received a certain amount of development.⁷ 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,⁸ 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.⁹ 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.¹⁰ 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.¹¹ 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 β -amino compounds, each with an all-carbon quaternary stereocenter, were obtained.

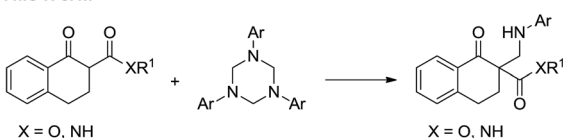
The Classical Mannich Reaction:



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 α -tetralone-derived β -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 CH_2Cl_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,¹¹ 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-PrPr₂** 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-PiPr₂** (Table 1, entry 8) was superior to *L*-proline derived **L-PrPr₂** and *L*-ramipril-derived **L-RaPr₂** (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 α -tetralone-derived β -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 α -tetralone-derived β -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 β -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 = C₆H₅, n = 1
L-PrPr₂: R = 2,6-*i*Pr₂C₆H₃, n = 1
L-PiPr₂: R = 2,6-*i*Pr₂C₆H₃, n = 2

Entry ^a	Substrate	Metal salt	Ligand	Yield ^b (%)	ee ^c (%)
1	1a	Sc(OTf) ₃	L-PrPh	83	0
2	1a	Yb(OTf) ₃	L-PrPh	84	0
3	1a	La(OTf) ₃	L-PrPh	90	13
4	1a	Mg(OTf) ₂	L-PrPh	85	18
5	1a	Ni(ClO ₄) ₂ · 6H ₂ O	L-PrPh	97	44
6	1a	Ni(ClO ₄) ₂ · 6H ₂ O	L-PrPr₂	67	53
7	1a	Ni(ClO ₄) ₂ · 6H ₂ O	L-RaPr₂	87	87
8	1a	Ni(ClO ₄) ₂ · 6H ₂ O	L-PiPr₂	94	96
9 ^d	1a	Ni(ClO ₄) ₂ · 6H ₂ O	L-PiPr₂	87	99
10 ^{d,e}	1a	Ni(ClO ₄) ₂ · 6H ₂ O	L-PiPr₂	97	99
11 ^{d,e}	2a	Ni(ClO ₄) ₂ · 6H ₂ O	L-PiPr₂	95	61
12 ^{d,f}	2a	Mg(OTf) ₂	L-PiPr₂	98	97

^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 CH_2Cl_2 at 30 °C for 8 h. ^b Isolated yield of the product. ^c Determined by HPLC analysis on a chiral stationary phase. ^d The reaction was performed at 0 °C for 12 h. ^e 5 mol% **L-PiPr₂** (0.005 mmol) and 5 mol% $\text{Ni}(\text{ClO}_4)_2 \cdot 6\text{H}_2\text{O}$ (0.005 mmol) were used. ^f The reaction was performed with **L-PiPr₂** (0.005 mmol) and $\text{Mg}(\text{OTf})_2$ (0.005 mmol).

Table 2 Substrate scope for β -keto esters^d

1, **3** → **4**

4a 97% yield^[b], 99% ee^[c] **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

^a The reactions were performed with **1** (0.10 mmol), **3** (0.034 mmol), **L-PiPr₂** (0.005 mmol), and $\text{Ni}(\text{ClO}_4)_2 \cdot 6\text{H}_2\text{O}$ (0.005 mmol) in 1.0 mL CH_2Cl_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 **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 crystallography¹² 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-methoxyphenyl)-1,3,5-triazinane, which gave the corresponding product in 84% ee. Besides this, five- and seven-membered

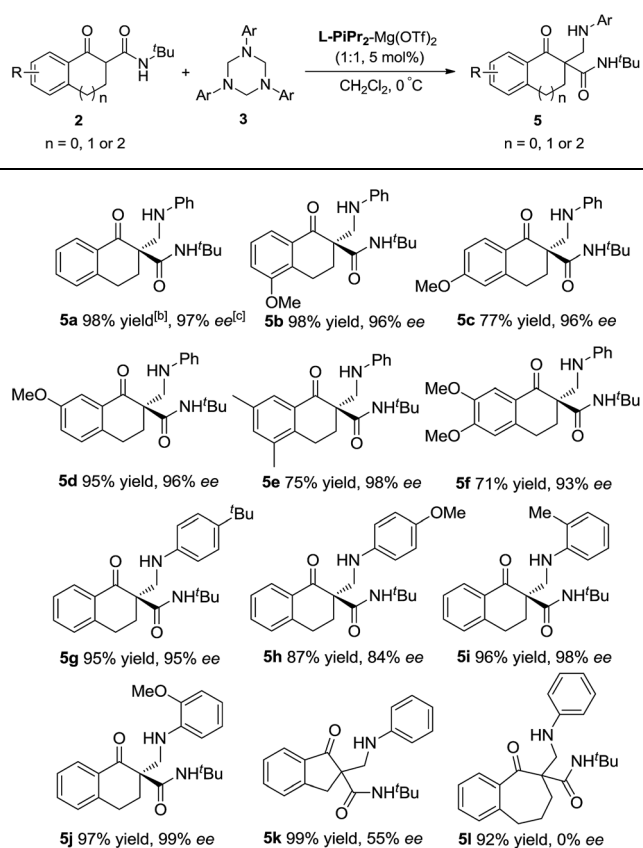
β -keto amide substrates were also examined. Unfortunately, the five-membered β -keto amide gave the corresponding product **5k** with only 55% ee, while the seven-membered β -keto amide gave a racemic product **5l** though the yields were excellent under the standard conditions. A cyclohexanone-derived 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 analysis¹² 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-PiPr₂-Ni(ClO₄)₂·6H₂O** 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).

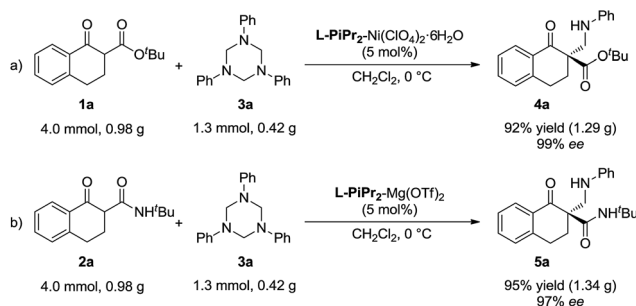
On the other hand, the product **4a** could be efficiently converted into useful β -hydroxyl ester **6** through reduction using NaBH₄ as a reducing agent (Scheme 3). The diastereomer of the product **6** was determined to be *trans*- using NOESY spectra (see the ESI† for details). The product **4h** 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 Boc₂O (see the ESI† for details).

To gain insight into the mechanism, the relationship between the ee value of the ligand **L-PiPr₂** and that of **4a** was investigated under the optimal reaction conditions.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 work¹¹ 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 after 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-PiPr₂**. In contrast, the *Re*-face is

Table 3 Substrate scope for β -keto amides^a

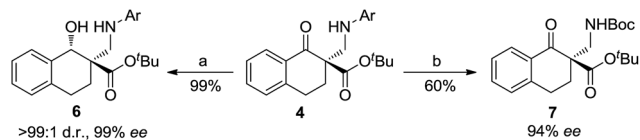


^a The reactions were performed with **2** (0.10 mmol), **3** (0.034 mmol), **L-PiPr₂** (0.005 mmol), and $\text{Mg}(\text{OTf})_2$ (0.005 mmol) in 1.0 mL CH_2Cl_2 at 0°C for 12 h. ^b Isolated yield of the product. ^c Determined by HPLC analysis on a chiral stationary phase.



Scheme 2 Gram-scale version of the reaction.





Scheme 3 Transformations of the product **4** into other derivatives; reaction conditions: (a) NaBH₄ and MeOH/CH₂Cl₂ (1 : 1), 0 °C (**4a**: Ar = Ph, 99% ee); (b) CAN, CH₃CN/H₂O; then Et₃N and Boc₂O (**4h**: Ar = 4-MeOC₆H₄, 94% ee). Boc = *tert*-butyloxycarbonyl.

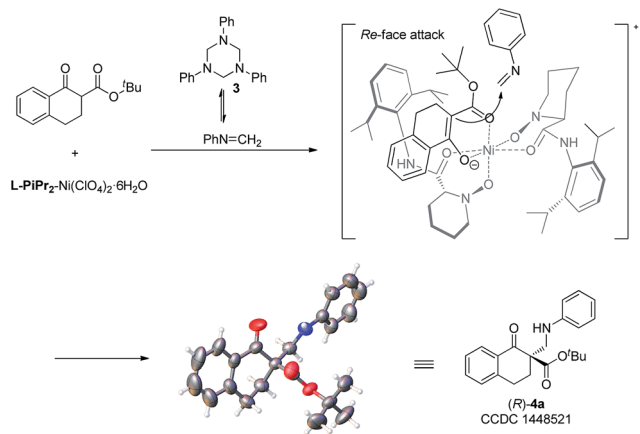


Fig. 1 Proposed transition state and the absolute configuration of **4a**.

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 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.

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