

CrossMark  
click for updatesCite this: *Chem. Sci.*, 2016, 7, 4736

# A *N,N'*-dioxide/Mg(OTf)<sub>2</sub> complex catalyzed enantioselective $\alpha$ -addition of isocyanides to alkylidene malonates†

Weiwei Luo,<sup>a</sup> Xiao Yuan,<sup>a</sup> Lili Lin,<sup>a</sup> Pengfei Zhou,<sup>a</sup> Xiaohua Liu<sup>\*a</sup> and Xiaoming Feng<sup>\*ab</sup>

A highly efficient catalytic asymmetric  $\alpha$ -addition of isocyanides to alkylidene malonates was accomplished. The process was based on the utilization of a chiral *N,N'*-dioxide/Mg<sup>II</sup> catalyst, delivering a variety of 2-alkyl-5-aminoxazoles in up to 99% yield and 96% ee under mild reaction conditions. Besides, a chiral imide and dipeptide could be easily obtained by ring-opening of the oxazole product, both of which are important structural motifs for many biologically active compounds. Based on the experimental investigations and previous work, a possible transition state model was proposed.

Received 15th February 2016

Accepted 12th April 2016

DOI: 10.1039/c6sc00689b

www.rsc.org/chemicalscience

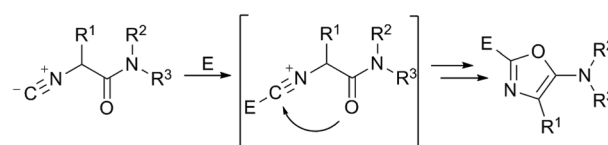
## Introduction

Optically active heterocyclic compounds containing an oxazole motif appear extensively in natural products, pharmaceuticals, and synthetic intermediates.<sup>1</sup> Because of the importance of these compounds, versatile approaches have been reported towards nonracemic oxazole derivatives. Early successful examples, such as cyclodehydration reactions and metal-catalyzed cross-coupling reactions were limited to the use of stoichiometric quantities of chiral precursors.<sup>2</sup> In contrast, direct catalytic asymmetric synthesis of these compounds is less developed. Until now, only two methods, an asymmetric heteroene reaction of 5-methyleneoxazolines with carbonyls<sup>3</sup> and  $\alpha$ -addition of isocyanides with carbonyls or imines,<sup>4,5</sup> have been reported. In relation to the latter,  $\alpha$ -addition is a simple but very efficient route to obtain 5-aminoxazoles.

$\alpha$ -Additions of isocyanides with both electrophiles and nucleophiles<sup>6</sup> have found wide application in organic synthesis since early studies on the Passerini<sup>7</sup> and Ugi reactions.<sup>8</sup> Although various diastereoselective methods using chiral substrates and/or chiral auxiliaries have been developed in recent decades,<sup>9–11</sup> the development of the enantioselective  $\alpha$ -addition of isocyanides still remains challenging.<sup>4,5,12</sup> The groups of Wang and Zhu,<sup>4a–c</sup> and Shibasaki<sup>4d</sup> as well as Zhong<sup>4e</sup> have made significant contributions to the catalytic enantioselective  $\alpha$ -addition of isocyanides to aldehydes, thus affording the desired 2-(1-hydroxyalkyl)-5-aminoxazoles. Recently, Wang

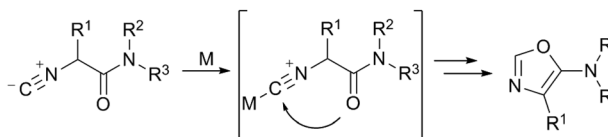
and Zhu described an enantioselective  $\alpha$ -addition of isocyanides to imines, providing a series of 2-(1-aminoalkyl)-5-aminoxazoles in moderate to good enantioselectivities (Scheme 1a).<sup>5</sup> To the best of our knowledge, the reaction of isocyanides with unactivated alkenes remains elusive, which might be due to the low reactivity of the alkenes or the complicated regiochemistry of isocyanides.<sup>13,14</sup> Furthermore,

(a) Typical Reactivity of isocyanides

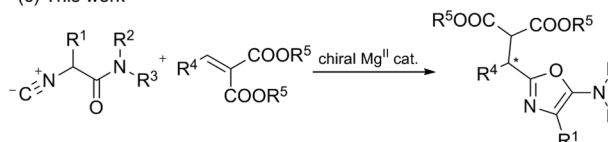


E = aldehydes: many examples  
E = imines: one example  
E = alkenes: unknown

(b) Facile ring-chain isomerization



(c) This work



- ♦ Unprecedented 2-alkyl-5-aminoxazoles
- ♦ High ee values and broad substrate scope
- ♦ Useful oxazole skeleton and facile derivatization

**Scheme 1** Construction of an oxazole ring using  $\alpha$ -isocyanoacetamide.

<sup>a</sup>Key Laboratory of Green Chemistry & Technology, Ministry of Education, College of Chemistry, Sichuan University, Chengdu 610064, China. E-mail: liuxh@scu.edu.cn; xmfeng@scu.edu.cn; Fax: +86 28 85418249; Tel: +86 28 85418249

<sup>b</sup>Collaborative Innovation Center of Chemical Science and Engineering, Tianjin, China

† Electronic supplementary information (ESI) available. CCDC 1416058. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c6sc00689b

ring-chain isomerization of the  $\alpha$ -isocyanoacetamides inevitably provided byproducts, C-2 unsubstituted 5-aminoxazoles, in the presence of a Lewis acid (Scheme 1b).<sup>15</sup> To further expand the scope in terms of the reaction partners and to complement the established methods for synthesizing enantioenriched oxazole derivatives, we describe herein an efficient asymmetric  $\alpha$ -addition of isocyanides to activated alkenes catalyzed by a chiral  $N,N'$ -dioxide/Mg<sup>II</sup> complex,<sup>3,16</sup> delivering 2-alkyl-5-aminoxazoles in good yields with high enantioselectivities.

## Results and discussion

Our investigation began with the addition of a DL-phenylalanine derived  $\alpha$ -isocyanoacetamide (**2a**) to methyl 2-benzylidenemalonate (**1a**), as a model reaction used to optimize the reaction conditions. Initially, various chiral  $N,N'$ -dioxide ligands complexing with Mg(OTf)<sub>2</sub> were evaluated (Table 1, entries 1–3). The results suggest that L-ramipril derived L-RaPr<sub>2</sub> exhibited superior reactivity compared with L-proline derived L-PrPr<sub>2</sub> and L-pipecolic acid derived L-PiPr<sub>2</sub>, and the desired product **3aa** was obtained in 99% yield with 82% ee (entry 3 vs. entries 1 and 2). Decreasing the reaction temperature to 0 °C resulted in a dramatic loss of reactivity but a slight improvement of the enantioselectivity (63% yield and 86% ee; entry 4). In order to improve the reactivity, the structure of the  $\alpha$ -isocyanoacetamide

was then examined (entries 5–8). With an increase of the steric hindrance of the  $\alpha$ -substituent on the isocyanoacetamide, a positive effect was observed (entry 5). Efficient product formation was also observed by applying a sterically demanding DL-tert-leucine derived  $\alpha$ -isocyanoacetamide (**2e**; entry 8), furnishing the corresponding 5-aminoxazole **3ae** in 75% yield with 92% ee. Importantly, the yield improved noticeably to 91% with retention of the enantioselectivity when the reaction was carried out with a slight excess amount of the metal salt (entry 9). We also found that the catalytic system was insensitive to both atmospheric oxygen and moisture, making the catalytic system practical. Therefore, the optimized conditions were determined as Mg(OTf)<sub>2</sub>/L-RaPr<sub>2</sub> as the catalyst in CH<sub>2</sub>Cl<sub>2</sub> at 0 °C for 72 h.

Having established the optimized conditions, we next investigated the scope of the alkylidene malonates. As shown in Table 2, by reaction with  $\alpha$ -isocyanoacetamide **2e**, a wide range

Table 1 Optimization of the reaction conditions

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

Entry <sup>a</sup>	Ligand	R	T (°C)	t (h)	Yield <sup>b</sup> (%)	ee <sup>c</sup> (%)
1	L-PrPr <sub>2</sub>	Bn ( <b>2a</b> )	30	24	72	76
2	L-PiPr <sub>2</sub>	Bn ( <b>2a</b> )	30	24	93	70
3	L-RaPr <sub>2</sub>	Bn ( <b>2a</b> )	30	24	99	82
4	L-RaPr <sub>2</sub>	Bn ( <b>2a</b> )	0	48	63	86
5	L-RaPr <sub>2</sub>	Ph ( <b>2b</b> )	0	48	86	87
6	L-RaPr <sub>2</sub>	Me ( <b>2c</b> )	0	72	61	86
7	L-RaPr <sub>2</sub>	<i>i</i> Pr ( <b>2d</b> )	0	72	91	89
8	L-RaPr <sub>2</sub>	<i>t</i> Bu ( <b>2e</b> )	0	72	75	92
9 <sup>d</sup>	L-RaPr <sub>2</sub>	<i>t</i> Bu ( <b>2e</b> )	0	72	91	92

<sup>a</sup> Unless specified otherwise, reactions were performed with Mg(OTf)<sub>2</sub>/L (1 : 1, 10 mol%), **1a** (0.1 mmol) and **2** (0.15 mmol) in 1.0 mL CH<sub>2</sub>Cl<sub>2</sub>.

<sup>b</sup> Isolated yield. <sup>c</sup> Determined using HPLC analysis with a chiral stationary phase. <sup>d</sup> Reaction was carried out with Mg(OTf)<sub>2</sub>/L-RaPr<sub>2</sub> (1.2 : 1, 10 mol%).

Table 2 Substrate scope for the alkylidene malonates 1

Entry <sup>a</sup>	R <sup>1</sup>	R <sup>2</sup>	3 or 4	Yield <sup>b</sup> (%)	ee <sup>c</sup> (%)
1	C <sub>6</sub> H <sub>5</sub>	Me	<b>3ae</b>	91	92 ( <i>R</i> ) <sup>e</sup>
2	C <sub>6</sub> H <sub>5</sub>	Et	<b>3be</b>	71	91
3	C <sub>6</sub> H <sub>5</sub>	<i>i</i> Pr	<b>3ce</b>	41	82
4 <sup>d</sup>	2-FC <sub>6</sub> H <sub>4</sub>	Me	<b>3de</b>	66	80
5	3-FC <sub>6</sub> H <sub>4</sub>	Me	<b>3ee</b>	92	91
6	3-ClC <sub>6</sub> H <sub>4</sub>	Me	<b>3fe</b>	77	91
7	3-BrC <sub>6</sub> H <sub>4</sub>	Me	<b>3ge</b>	96	91
8	3-MeC <sub>6</sub> H <sub>4</sub>	Me	<b>3he</b>	66	94
9 <sup>d</sup>	3-MeOC <sub>6</sub> H <sub>4</sub>	Me	<b>3ie</b>	81	90
10	3-PhOC <sub>6</sub> H <sub>4</sub>	Me	<b>3je</b>	84	88
11	4-FC <sub>6</sub> H <sub>4</sub>	Me	<b>3ke</b>	86	93
12	4-ClC <sub>6</sub> H <sub>4</sub>	Me	<b>3le</b>	96	94
13	4-BrC <sub>6</sub> H <sub>4</sub>	Me	<b>3me</b>	93	94
14	4-F <sub>3</sub> CC <sub>6</sub> H <sub>4</sub>	Me	<b>3ne</b>	86	92
15	4-NCC <sub>6</sub> H <sub>4</sub>	Me	<b>3oe</b>	98	94
16	4-O <sub>2</sub> NC <sub>6</sub> H <sub>4</sub>	Me	<b>3pe</b>	91	94
17	4-MeC <sub>6</sub> H <sub>4</sub>	Me	<b>3qe</b>	83	94
18	4-PhC <sub>6</sub> H <sub>4</sub>	Me	<b>3re</b>	98	91
19 <sup>d</sup>	4-MeOC <sub>6</sub> H <sub>4</sub>	Me	<b>3se</b>	87	96
20	4-PhOC <sub>6</sub> H <sub>4</sub>	Me	<b>3te</b>	64	92
21	4-BnOC <sub>6</sub> H <sub>4</sub>	Me	<b>3ue</b>	64	92
22	3,4-Cl <sub>2</sub> C <sub>6</sub> H <sub>3</sub>	Me	<b>3ve</b>	90	92
23	2-Naphthyl	Me	<b>3we</b>	81	90
24 <sup>d</sup>	2-Thienyl	Me	<b>3xe</b>	28	85
25 <sup>d</sup>	3-Furyl	Me	<b>3yw</b>	76	89
26	<i>c</i> -Hexyl	Me	<b>3ze</b>	81	86
27	Me	Me	<b>4ae</b>	90	72

<sup>a</sup> Unless specified otherwise, reactions were performed with Mg(OTf)<sub>2</sub>/L-RaPr<sub>2</sub> (1.2 : 1, 10 mol%), **1** (0.1 mmol) and **2e** (0.15 mmol) in 1.0 mL CH<sub>2</sub>Cl<sub>2</sub> at 0 °C for 3 days. <sup>b</sup> Isolated yield. <sup>c</sup> Determined using HPLC analysis with a chiral stationary phase. <sup>d</sup> The reaction was carried out over 7 days. <sup>e</sup> The absolute configuration of **3ae** was determined using X-ray analysis.

of alkylidene malonates were transformed into the corresponding 2-alkyl-5-aminooxazoles smoothly. Generally, the reactivities and enantioselectivities gradually decreased with increased steric hindrance of the ester group (Table 2, entries 1–3). An *o*-fluoro group on the phenyl ring in **1d** decreased the reactivity and caused a reaction time of 7 days to be required to achieve 66% yield and 80% ee, which might be due to both the electronic nature and steric encumbrance at the reaction site (entry 4). Notably, electron-withdrawing *meta* substituents on the phenyl ring such as fluorine, chlorine or bromine have no significant influence on the reactivity or enantioselectivity (entries 5–7). Meanwhile, electron-donating *meta* substituents are also well tolerated (entries 8–10). Substituents at the *para* position are equally well tolerated and both electron-donating and electron-withdrawing groups provided the corresponding products in high yields and enantioselectivities (entries 11–21). It is noteworthy that having a *m*-methoxy or *p*-methoxy group in **1** decreased the reactivity and also caused a longer reaction time to be required to achieve high conversion (entries 9 and 19), results we attribute to the decreased electrophilicity of alkylidene malonates with an electron-donating group on the phenyl ring. Multisubstituted and fused-ring-substituted alkylidene malonates also proceeded well, providing the corresponding products in up to 90% yield and 92% ee (entries 22 and 23). An *ortho*-substituted heteroaromatic substrate proved detrimental to both the reactivity and selectivity, while a *meta* substituted one led to a satisfactory result (entries 24 and 25). Aliphatic substrates can also be employed but these gave moderate enantioselectivities (entries 26 and 27).

Then, various  $\alpha$ -substituted isocyanides were examined (Table 3). Thankfully, isocyanides **2a–2e** with different alkyl or phenyl substituents were applicable, giving the corresponding products **3aa–3ae** in 60–99% yield and 86–92% ee. The 2-alkyl-5-aminooxazoles generated from piperidine **2f**, **2g**, and pyrrolidine **2h** were also formed in high yield and stereoselectivity. Additionally, a moderate yield (62%) and good enantioselectivity (87% ee) were observed when a glycine derived  $\alpha$ -isocyanacetamide **2i** was applied. The absolute configuration of compound **3ae** was established unambiguously to be *R* using single-crystal X-ray structure analysis,<sup>17</sup> and the 5-aminooxazoles exhibited a similar (+) Cotton effect in their CD (circular dichroism) spectra (for details, see the ESI†).

To show the prospect of using this methodology in synthesis, a gram scale synthesis of **3ae** was performed. Under the optimal conditions, 4.5 mmol of  $\alpha$ -isocyanacetamide **2e** reacted well with 3.0 mmol of methyl 2-benzylidenemalonate, providing 0.90 g (70% yield) of the corresponding 5-aminooxazole **3ae** with an ee of 91% (Scheme 2a). The enantiopure product could be obtained using a simple recrystallization, with a yield of 67%. Next, simple derivatizations of the product were conducted (Scheme 2b). The product **3ae** could be efficiently converted into a useful 1,3-diol **5** through reduction with LiAlH<sub>4</sub> (90% yield, 95% ee). In addition, 5-aminooxazole **3ae** was readily hydrolyzed in the presence of trifluoroacetic acid,<sup>18</sup> and dipeptide **6** could be obtained in 99% yield with the enantioselectivity maintained (1.8 : 1 d.r., 99% ee). These derivatives are important structural motifs for the synthesis of many biologically

Table 3 Substrate scope for the  $\alpha$ -isocyanacetamides **2**

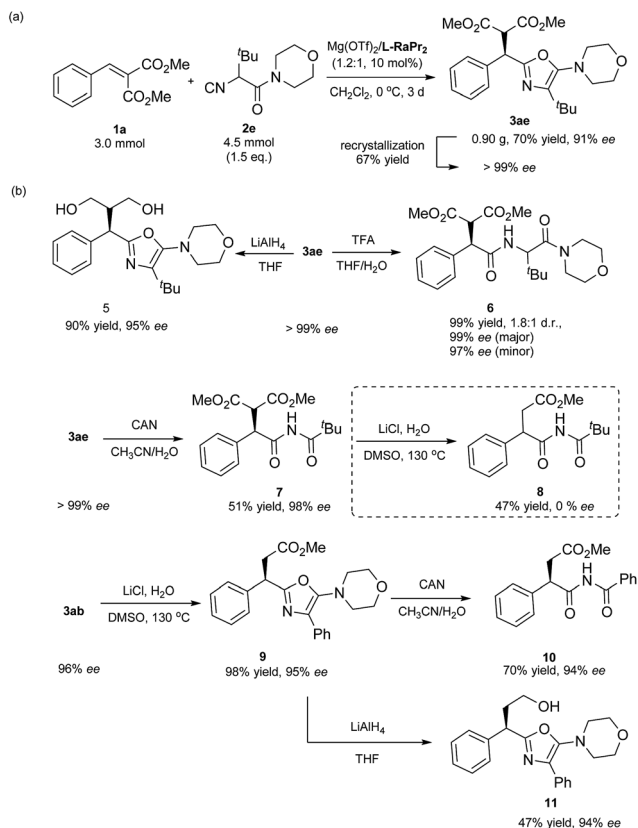
<b>3aa<sup>a</sup></b>	<b>3ab<sup>a</sup></b>	<b>3ac<sup>a</sup></b>
85% yield, <sup>b</sup> 86% ee <sup>c</sup>	97% yield, <sup>b</sup> 86% ee <sup>c</sup>	60% yield, <sup>b</sup> 86% ee <sup>c</sup>
<b>3ad<sup>a</sup></b>	<b>3ae<sup>a</sup></b>	<b>3af<sup>a</sup></b>
99% yield, <sup>b</sup> 89% ee <sup>c</sup>	91% yield, <sup>b</sup> 92% ee <sup>c</sup>	86% yield, <sup>b</sup> 86% ee <sup>c</sup>
<b>3ag<sup>a</sup></b>	<b>3ah<sup>a</sup></b>	<b>3ai<sup>d</sup></b>
91% yield, <sup>b</sup> 91% ee <sup>c</sup>	80% yield, <sup>b</sup> 91% ee <sup>c</sup>	62% yield, <sup>b</sup> 87% ee <sup>c</sup>

<sup>a</sup> Unless specified otherwise, reactions were performed with Mg(OTf)<sub>2</sub>/L-RaPr<sub>2</sub> (1.2 : 1, 10 mol%), **1a** (0.1 mmol) and **2** (0.15 mmol) in 1.0 mL CH<sub>2</sub>Cl<sub>2</sub> at 0 °C for 3 days. <sup>b</sup> Isolated yield. <sup>c</sup> Determined using HPLC analysis with a chiral stationary phase. <sup>d</sup> The reaction was carried out over 7 days.

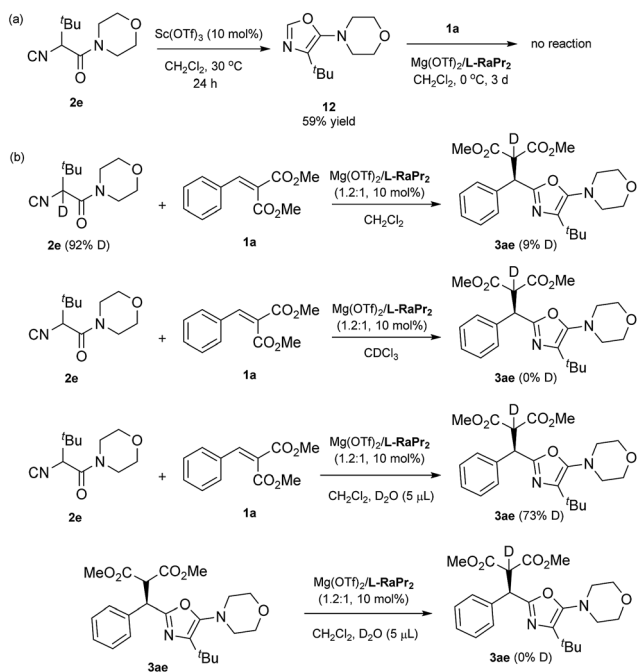
active compounds. Next, in the presence of ceric ammonium nitrate, the oxazole ring was opened up, providing an imide product **7** in 51% yield with 98% ee.<sup>19</sup> An initial decarboxylation of **7** gave the succinate derivative **8** in 47% yield as a racemic mixture, caused by subjecting the racemization-prone  $\alpha$ -substituted carbonyl compound **7** to high temperature. Considering that optically active 2-substituted succinic acid derivatives are useful motifs in numerous biologically active compounds and natural products,<sup>20</sup> we turned our attention to accessing these compounds. To our delight, monoester product **9** was obtained in excellent yield with the enantioselectivity maintained (98% yield, 94% ee). Subsequent opening of the oxazole ring gave the target chiral succinate derivative **10** in 70% yield with 94% ee. In the meantime, monoester oxazole **9** underwent a facile reduction with LiAlH<sub>4</sub> to provide **11** in 47% yield.

During the course of this study, a 5-aminooxazole by-product was formed in some cases, and to verify the identity of this by-product an authentic sample was obtained (**12**; see Scheme 3a).<sup>15</sup> In order to understand the reaction profile, **12** was applied in a reaction with alkylidene malonate **1a** under the standard reaction conditions. However, no desired product **3ae** was obtained after three days, suggesting that a Friedel–Crafts pathway isn't involved in the formation of the final product. Moreover, deuterium labeling studies were carried out (Scheme 3b). While the use of deuterated isocyanide led to low deuterium labeling of the product, the use of a small amount of D<sub>2</sub>O resulted in significant deuterium labeling of





Scheme 2 (a) Gram-scale version of the reaction. (b) Synthetic utility.



Scheme 3 Control experiments.

the product. This interesting observation suggests that the proton transfer is facilitated by a trace amount of water (T3 to product in Fig. 1).

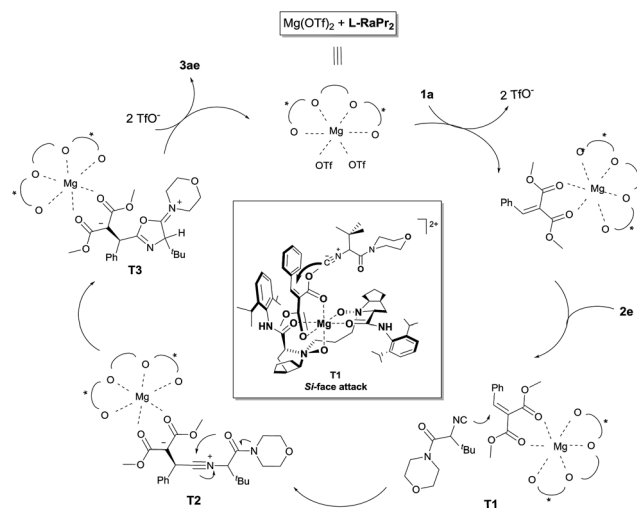


Fig. 1 Proposed catalytic cycle.

The HRMS spectrum of a mixture of  $\text{Mg}(\text{OTf})_2/\text{L-RaPr}_2$  and methyl 2-benzylidenemalonate **1a** (1 : 1 : 1) confirmed coordination of the substrate to the catalyst. A peak at  $m/z$  1093.5035 was detected and corresponds to the complex  $[\text{Mg}^{2+} + \text{L-RaPr}_2 + \text{1a} + \text{OTf}^-]^+$  (cal. 1093.5034). Based on the above results and our previous work,<sup>16b,g</sup> a possible reaction mechanism and a transition-state model were proposed and are shown in Fig. 1. At first, the *N*-oxide and amide oxygen atoms of **L-RaPr**<sub>2</sub> coordinate to  $\text{Mg}^{2+}$  in a tetradentate manner to form two six-membered chelate rings. Methyl 2-benzylidenemalonate **1a** could be activated by coordination to the magnesium atom in a bidentate fashion, and the *Re* face of the substrate would be shielded by the neighboring 2,6-diisopropylphenyl group of the ligand. So, nucleophilic addition of the divalent carbon atom of isocyanide **2e** onto the *Si* face of the substrate would afford the nitrilium intermediate **T2**, which could undergo cyclization to afford **T3**. Finally, deprotonation involving the proton on C4 of **T3** would provide the *R*-configured product, which is in accord with the X-ray crystal structure of **3ae**.

## Conclusions

In summary, we have developed a chiral *N,N'*-dioxide/ $\text{Mg}^{\text{II}}$  catalyst system to realize the asymmetric  $\alpha$ -addition of isocyanides to alkylidene malonates. A range of 2-alkyl-5-amino-oxazoles were obtained in moderate to excellent yields (up to 99%) with excellent ee values (up to 96%). This represents the first example of an enantioselective  $\alpha$ -addition of isocyanides to activated alkenes and may lay the foundation for the development of the long-awaited enantioselective  $\alpha$ -addition to simple alkenes. Further studies on applying this catalyst system to other related reactions are underway.

## Acknowledgements

The study was funded by the National Natural Science Foundation of China (Nos. 21372162, 21432006, and 21321061).



## Notes and references

- (a) P. Wipf, *Chem. Rev.*, 1995, **95**, 2115; (b) D. C. Palmer and S. Venkatraman, in *The Chemistry of Heterocyclic compounds, Oxazoles: Synthesis Reactions, and Spectroscopy: Part A*, ed. D. C. Palmer, Wiley, Hoboken, NJ, 2003, vol. 60, pp. 138–149; (c) Z. Jin, *Nat. Prod. Rep.*, 2013, **30**, 869.
- (a) P. Y. Coqueron, C. Didier and M. A. Ciufolini, *Angew. Chem., Int. Ed.*, 2003, **42**, 1411; (b) C.-K. Mai, M. F. Sammons and T. Sammakia, *Angew. Chem., Int. Ed.*, 2010, **49**, 2397; (c) Z. E. Wilson, S. Fenner and S. V. Ley, *Angew. Chem., Int. Ed.*, 2015, **54**, 1284; (d) H. Ding, P. L. DeRoy, C. Perreault, A. Larivée, A. Siddiqui, C. G. Caldwell, S. Harran and P. G. Harran, *Angew. Chem., Int. Ed.*, 2015, **54**, 4818.
- (a) W. W. Luo, J. N. Zhao, C. K. Yin, X. H. Liu, L. L. Lin and X. M. Feng, *Chem. Commun.*, 2014, **50**, 7524; (b) W. W. Luo, J. N. Zhao, J. Ji, L. L. Lin, X. H. Liu, H. J. Mei and X. M. Feng, *Chem. Commun.*, 2015, **51**, 10042.
- (a) S.-X. Wang, M.-X. Wang, D.-X. Wang and J. Zhu, *Eur. J. Org. Chem.*, 2007, 4076; (b) S.-X. Wang, M.-X. Wang, D.-X. Wang and J. Zhu, *Org. Lett.*, 2007, **9**, 3615; (c) T. Yue, M.-X. Wang, D.-X. Wang, G. Masson and J. Zhu, *J. Org. Chem.*, 2009, **74**, 8396; (d) H. Mihara, Y. Xu, N. E. Shepherd, S. Matsunaga and M. Shibasaki, *J. Am. Chem. Soc.*, 2009, **131**, 8384; (e) X. Zeng, K. Ye, M. Lu, P. J. Chua, B. Tan and G. Zhong, *Org. Lett.*, 2010, **12**, 2414.
- (a) T. Yue, M.-X. Wang, D.-X. Wang, G. Masson and J. Zhu, *Angew. Chem., Int. Ed.*, 2009, **48**, 6717; (b) Y. Su, M. J. Bouma, L. Alcaraz, M. Stocks, M. Furber, G. Masson and J. Zhu, *Chem.-Eur. J.*, 2012, **18**, 12624.
- (a) A. Dömling, *Chem. Rev.*, 2006, **106**, 17; (b) A. V. Gulevich, A. G. Zhdanko, R. V. A. Orru and V. G. Nenajdenko, *Chem. Rev.*, 2010, **110**, 5235.
- (a) M. Passerini, *Gazz. Chim. Ital.*, 1921, **51**, 126; (b) M. Passerini, *Gazz. Chim. Ital.*, 1921, **51**, 762.
- (a) A. Dömling and I. Ugi, *Angew. Chem., Int. Ed.*, 2000, **39**, 3168; (b) S. Marcaccini and T. Torroba, *Nat. Protoc.*, 2007, **2**, 632.
- (a) S. Marcaccini, D. Miguel, T. Torroba and M. García-Valverde, *J. Org. Chem.*, 2003, **68**, 3315; (b) R. Frey, S. G. Galbraith, S. Guelfi, C. Lamberth and M. Zeller, *Synlett*, 2003, 1536; (c) G. Cuny, R. Gámez-Montaña and J. Zhu, *Tetrahedron*, 2004, **60**, 4879; (d) P. R. Krishna, G. Dayaker and P. V. N. Reddy, *Tetrahedron Lett.*, 2006, **47**, 5977.
- (a) H. Kunz and W. Pfrengle, *J. Am. Chem. Soc.*, 1988, **110**, 651; (b) R. J. Linderman, S. Binet and S. R. Petrich, *J. Org. Chem.*, 1999, **64**, 336; (c) G. F. Ross, E. Herdtweck and I. Ugi, *Tetrahedron*, 2002, **58**, 6127; (d) A. Basso, L. Banfi, R. Riva and G. Guanti, *J. Org. Chem.*, 2005, **70**, 575; (e) L. Banfi, A. Basso, G. Guanti, S. Merlo, C. Repetto and R. Riva, *Tetrahedron*, 2008, **64**, 1114; (f) K. M. Bongers, T. Wennekes, D. V. Filippov, G. Lodder, G. A. van de Marel and H. S. Overkleeft, *Eur. J. Org. Chem.*, 2008, 3678.
- L. Banfi, A. Basso, G. Guanti and L. Banfi, Asymmetric Isocyanide-based MCRs, in *Multicomponent reactions*, ed. J. Zhu and H. Bienaymé, Wiley-VCH, Weinheim, 2005, pp. 1–32.
- (a) S. E. Denmark and Y. Fan, *J. Am. Chem. Soc.*, 2003, **125**, 7825; (b) U. Kusebauch, B. Beck, K. Messer, E. Herdtweck and A. Dömling, *Org. Lett.*, 2003, **5**, 4021; (c) P. R. Andreana, C. C. Liu and S. L. Schreiber, *Org. Lett.*, 2004, **6**, 4231; (d) S. E. Denmark and Y. Fan, *J. Org. Chem.*, 2005, **70**, 9667; (e) S.-X. Wang, M.-X. Wang, D.-X. Wang and J. Zhu, *Angew. Chem., Int. Ed.*, 2008, **47**, 388; (f) T. Yue, M.-X. Wang, D.-X. Wang and J. Zhu, *Angew. Chem., Int. Ed.*, 2008, **47**, 9454; (g) T. Hashimoto, H. Kimura, Y. Kawamata and K. Maruoka, *Angew. Chem., Int. Ed.*, 2012, **51**, 7279; (h) J. Zhang, S.-X. Lin, D.-J. Cheng, X.-Y. Liu and B. Tan, *J. Am. Chem. Soc.*, 2015, **137**, 14039.
- For examples of  $\alpha$ -carbanion attack, see: (a) H. Li, J. Song, X. Liu and L. Deng, *J. Am. Chem. Soc.*, 2005, **127**, 8948; (b) C. Guo, M.-X. Xue, M.-K. Zhu and L.-Z. Gong, *Angew. Chem., Int. Ed.*, 2008, **47**, 3414; (c) J. Song, C. Guo, P.-H. Chen, J. Yu, S.-W. Luo and L.-Z. Gong, *Chem.-Eur. J.*, 2011, **17**, 7786; (d) L.-L. Wang, J.-F. Bai, L. Peng, L.-W. Qi, L.-N. Jia, Y.-L. Guo, X.-Y. Luo, X.-Y. Xu and L.-X. Wang, *Chem. Commun.*, 2012, **48**, 5175; (e) J.-F. Bai, L.-L. Wang, L. Peng, Y.-L. Guo, L.-N. Jia, F. Tian, G.-Y. He, X.-Y. Xu and L.-X. Wang, *J. Org. Chem.*, 2012, **77**, 2947; (f) T. Buyck, Q. Wang and J. Zhu, *Angew. Chem., Int. Ed.*, 2013, **52**, 12714.
- For examples of isocyanide group attack, see: (a) T. Saegusa, Y. Ito, S. Tomita, H. Kinoshita and N. Taka-Ishi, *Tetrahedron*, 1971, **27**, 27; (b) M. A. Mironov, M. N. Ivantsova and V. S. Mokrushin, *Synlett*, 2006, 615; (c) I. Dias-Jurberg, F. Gagosz and S. Z. Zard, *Org. Lett.*, 2010, **12**, 416; (d) J. Li, Y. Liu, C. Li and X. Jia, *Adv. Synth. Catal.*, 2011, **353**, 913; (e) A. G. Neo, J. Díaz, S. Marcaccini and C. F. Marcos, *Org. Biomol. Chem.*, 2012, **10**, 3406.
- Y. Odabachian, Q. Wang and J. Zhu, *Chem.-Eur. J.*, 2013, **19**, 12229.
- (a) X. H. Liu, L. L. Lin and X. M. Feng, *Acc. Chem. Res.*, 2011, **44**, 574; (b) K. Zheng, C. K. Yin, X. H. Liu, L. L. Lin and X. M. Feng, *Angew. Chem., Int. Ed.*, 2011, **50**, 2573; (c) S.-H. Huang and K. Ding, *Angew. Chem., Int. Ed.*, 2011, **50**, 7734; (d) K. Zheng, L. L. Lin and X. M. Feng, *Acta Chim. Sin.*, 2012, **70**, 1785; (e) X. H. Liu, L. L. Lin and X. M. Feng, *Org. Chem. Front.*, 2014, **1**, 298; (f) M. S. Xie, X. X. Wu, G. Wang, L. L. Lin and X. M. Feng, *Acta Chim. Sin.*, 2014, **72**, 856; (g) X. H. Zhao, X. H. Liu, H. J. Mei, J. Guo, L. L. Lin and X. M. Feng, *Angew. Chem., Int. Ed.*, 2015, **54**, 4032.
- CCDC 1416058† (3ae).
- (a) B. H. Lipshutz, B. E. Huff, K. E. McCarthy, T. A. Miller, S. M. J. Mukarram, T. J. Siahaan, W. D. Vaccaro, H. Webb and A. M. Falick, *J. Am. Chem. Soc.*, 1990, **112**, 7032; (b) G. Zhao, X. Sun, H. Bienaymé and J. Zhu, *J. Am. Chem. Soc.*, 2001, **123**, 6700; (c) C. Bughin, G. Zhao, H. Bienaymé and J. Zhu, *Chem.-Eur. J.*, 2006, **12**, 1174.
- D. A. Evans, P. Nagorny and R. Xu, *Org. Lett.*, 2006, **8**, 5669.
- Y.-C. Chung, D. Janmanchi and H.-L. Wu, *Org. Lett.*, 2012, **14**, 2766.

