Chemical Science

N,N'-Dioxide/Mg(OTf)2 Complex Catalyzed Enantioselective α-Addition of Isocyanides to Alkylidene Malonates

Journal:	*Chemical Science*
Manuscript ID	SC-EDG-02-2016-000689.R1
Article Type:	Edge Article
Date Submitted by the Author:	02-Apr-2016
Complete List of Authors:	Luo, Weiwei; Key Laboratory of Green Chemistry + Technology, Ministry of Education, College o Chengdu, China Chengdu, China Chengdu, China Chengdu, China Chengdu, China Chengdu, China Chengdu, China Chengdu, China, Yuan, Xiao; Key Laboratory of Green Chemistry + Technology, Ministry of Education, College o Chengdu, China Chengdu, China Chengdu, China Chengdu, China, Lin, Lili; Key Laboratory of Green Chemistry & Technology, Ministry of Education, College of Chemistry, Sichuan University, Zhou, Pengfei; a. Key Laboratory of Green Chemistry & Technology, Ministry of Education, College of Chemistry Liu, Xiaohua; Key Laboratory of Green Chemistry & Technology, Ministry of Education, College of Chemistry, Sichuan University, Feng, Xiaoming; Key Laboratory of Green Chemistry + Technology, Ministry of Education, College o,

Journal Name

ARTICLE

N,N'-Dioxide/Mg(OTf)$_2$ Complex Catalyzed Enantioselective α-Addition of Isocyanides to Alkylidene Malonates

Received 00th January 20xx,
Accepted 00th January 20xx

DOI: 10.1039/x0xx00000x

www.rsc.org/

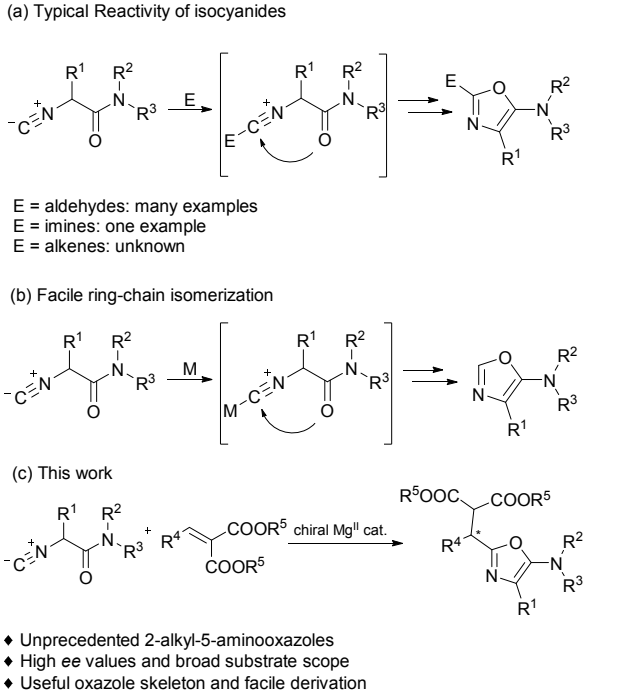
Weiwei Luo,[a] Xiao Yuan,[a] Lili Lin,[a] Pengfei Zhou,[a] Xiaohua Liu,*[a] Xiaoming Feng*[a,b]

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

Introduction

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

α-Additions of isocyanides with both electrophiles and nucleophiles,[6] have been found wide application in organic syntheisis since the early studies on Passerini[7] and Ugi reactions.[8] Although various diastereoselective methods using chiral substrates and/or chiral auxiliaries have been developed in the past decades,[9-11] the development of the enantioselective α-addition of isocyanides still remains a challenging.[4, 5, 12] The groups of Wang and Zhu,[4a-c] Shibasaki[4d] as well as Zhong[4e] have made significant contributions to the catalytic enantioselective α-addition of isocyanides to aldehydes, thus affording the desired 2-(1-hydroxyalkyl)-5-aminooxazoles. Recently, Wang and Zhu described an enantioselective α-addition of isocyanides to imines, providing a series of 2-(1-aminoalkyl)-5-aminooxazoles in moderate to good enantioselectivities (Scheme 1a).[5] To the best of our knowledge, the reaction of isocyanides with unactivated alkenes remains elusive, which might be caused by the the low reactivity of alkenes or complicated regiochemistry of isocyanides.[13, 14] Furthermore, ring-chain isomerization of α-isocyanoacetamides inevitably provided the byproduct C-2 unsubstituted 5-aminooxazoles in the presence of Lewis acid (Scheme 1b).[15] To further expand the scope of reaction partners and complement established methods for synthesizing enantioenriched oxazole derivatives, we describe



Scheme 1 Construction of oxazole ring by using α-isocyanoacetamide

[a] *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.*
[b] *Collaborative Innovation Center of Chemical Science and Engineering, Tianjin (China).*

Electronic Supplementary Information (ESI) available: [details of any supplementary information available should be included here]. See DOI: 10.1039/x0xx00000x

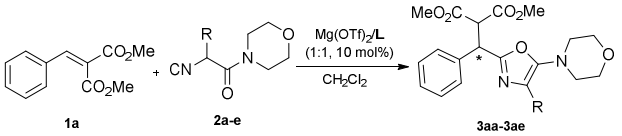
herein an efficient asymmetric α-addition of isocyanides to activated alkenes catalyzed by a chiral *N,N'*-dioxide/Mg^{II} complex[3, 16], delivering 2-alkyl-5-aminooxazoles in good yields with high enantioselectivities.

Results and discussion

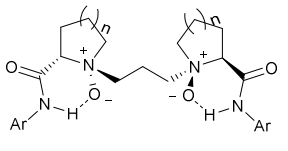
Our investigation began with the addition of DL-phenylalanine derived α-isocyanoacetamide (**2a**) to methyl 2-benzylidenemalonate (**1a**) as the model reaction to optimize the reaction conditions. Initially, various chiral *N,N'*-dioxide ligands complexing with $Mg(OTf)_2$ were evaluated (Table 1, entries 1–3). The observations suggested that L-ramipril derived **L-RaPr$_2$** exhibited superior reactivity compared with L-proline derived **L-PrPr$_2$** and L-pipecolic acid derived **L-PiPr$_2$**, 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 enantioselectivity (63% yield and 86% *ee*; entry 4). In order to improve the reactivity, the structure of α-isocyanoacetamide was then examined (entries 5–8). With an increase of the steric hindrance of α-substituent on the isocyanoacetamide, a positive effect was observed. Efficient product formation was also observed by applying sterically demanding DL-tert-Leucine derived α-isocyanoacetamide (**2e**; entry 8), furnishing the corresponding 5-aminooxazole **3ae** in 75% yield with 92% *ee*. Importantly, the yield improved noticeably to 91% with the enantioselectivity remained when the reaction was carried out in 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 entailed as $Mg(OTf)_2$/**L-RaPr$_2$** as catalyst in CH_2Cl_2 at 0 °C for 72 h.

Having established the optimized conditions, we next investigated the scope of alkylidene malonates. As shown in Table 2, by reacting with α-isocyanoacetamide **2e**, a wide range of alkylidene malonates were transformed to the corresponding 2-alkyl-5-aminooxazoles smoothly. Generally, the reactivities and enantioselectivities gradually decreased with the increased steric hindrance of ester group (Table 2, entries 1-3). An *o*-fluoro group on the phenyl ring in **1d** decreased the reactivity and required 7 days to achieve 66% yield and 80% *ee*, which might be caused by both electronic

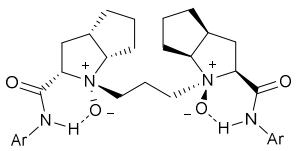
Table 1 Optimization of the reaction conditions



1a 2a-e 3aa-3ae



L-PrPr$_2$: Ar = 2,6-*i*Pr$_2$C$_6$H$_3$, n = 1
L-PiPr$_2$: Ar = 2,6-*i*Pr$_2$C$_6$H$_3$, n = 2

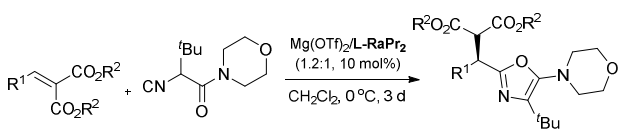


L-RaPr$_2$: Ar = 2,6-*i*Pr$_2$C$_6$H$_3$

Entry[a]	Ligand	R	T (°C)	*t* (h)	Yield (%)[b]	*ee* (%)[c]
1	**L-PrPr$_2$**	Bn (**2a**)	30	24	72	76
2	**L-PiPr$_2$**	Bn (**2a**)	30	24	93	70
3	**L-RaPr$_2$**	Bn (**2a**)	30	24	99	82
4	**L-RaPr$_2$**	Bn (**2a**)	0	48	63	86
5	**L-RaPr$_2$**	Ph (**2b**)	0	48	86	87
6	**L-RaPr$_2$**	Me (**2c**)	0	72	61	86
7	**L-RaPr$_2$**	*i*Pr (**2d**)	0	72	91	89
8	**L-RaPr$_2$**	*t*Bu (**2e**)	0	72	75	92
9[d]	**L-RaPr$_2$**	*t*Bu (**2e**)	0	72	91	92

[a] Unless specified otherwise, reactions were performed with $Mg(OTf)_2$/**L** (1:1, 10 mol%), **1a** (0.1 mmol), **2** (0.15 mmol) in 1.0 mL CH_2Cl_2. [b] Isolated yield. [c] Determined by HPLC analysis on a chiral stationary phase. [d] Reaction was carried out with $Mg(OTf)_2$/**L -RaPr$_2$** (1.2:1, 10 mol%).

Table 2 Substrate scope of the alkylidene malonates **1**

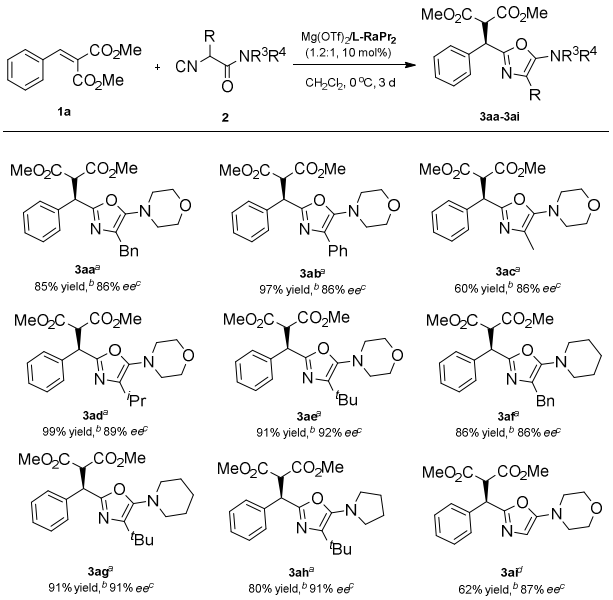


1 2e 3 or 4

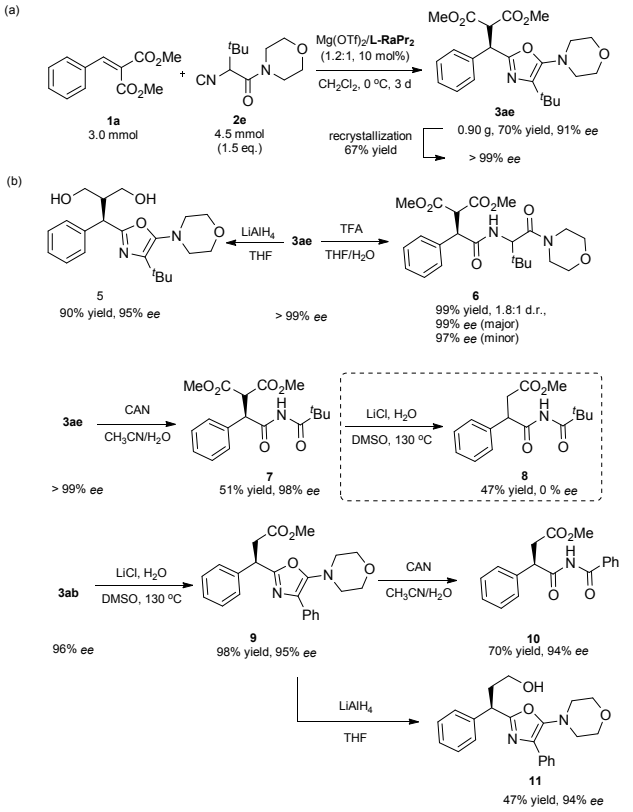
Entry	R^1	R^2	**3** or **4**	Yield (%)	*ee* (%)
1	C_6H_5	Me	**3ae**	91	92 (*R*)[e]
2	C_6H_5	Et	**3be**	71	91
3	C_6H_5	*i*Pr	**3ce**	41	82
4[d]	2-FC_6H_4	Me	**3de**	66	80
5	3-FC_6H_4	Me	**3ee**	92	91
6	3-ClC_6H_4	Me	**3fe**	77	91
7	3-BrC_6H_4	Me	**3ge**	96	91
8	3-MeC_6H_4	Me	**3he**	66	94
9[d]	3-$MeOC_6H_4$	Me	**3ie**	81	90
10	3-$PhOC_6H_4$	Me	**3je**	84	88
11	4-FC_6H_4	Me	**3ke**	86	93
12	4-ClC_6H_4	Me	**3le**	96	94
13	4-BrC_6H_4	Me	**3me**	93	94
14	4-$F_3CC_6H_4$	Me	**3ne**	86	92
15	4-NCC_6H_4	Me	**3oe**	98	94
16	4-$O_2NC_6H_4$	Me	**3pe**	91	94
17	4-MeC_6H_4	Me	**3qe**	83	94
18	4-PhC_6H_4	Me	**3re**	98	91
19[d]	4-$MeOC_6H_4$	Me	**3se**	87	96
20	4-$PhOC_6H_4$	Me	**3te**	64	92
21	4-$BnOC_6H_4$	Me	**3ue**	64	92
22	3,4-$Cl_2C_6H_3$	Me	**3ve**	90	92
23	2-naphthyl	Me	**3we**	81	90
24[d]	2-thienyl	Me	**3xe**	28	85
25[d]	3-furyl	Me	**3yw**	76	89
26	c-hexyl	Me	**3ze**	81	86
27	Me	Me	**4ae**	90	72

[a] Unless specified otherwise, reactions were performed with $Mg(OTf)_2$/**L-RaPr$_2$** (1.2:1, 10 mol%), **1a** (0.1 mmol), **2** (0.15 mmol) in 1.0 mL CH_2Cl_2 at 0 °C for 3 days. [b] Isolated yield. [c] Determined by HPLC analysis using a chiral stationary phase. [d] The reaction was carried out for 7 days. [e] The absolute configuration of **3ae** was determined by X-Ray analysis.

Table 3 Substrate scope of α-isocyanoacetamides **2**



[a] Unless specified otherwise, reactions were performed with $Mg(OTf)_2$/**L-RaPr$_2$** (1.2:1, 10 mol%), **1a** (0.1 mmol), **2** (0.15 mmol) in 1.0 mL CH_2Cl_2 at 0 °C for 3 days. [b] Isolated yield. [c] Determined by HPLC analysis using a chiral stationary phase. [d] The reaction was carried out for 7 days.

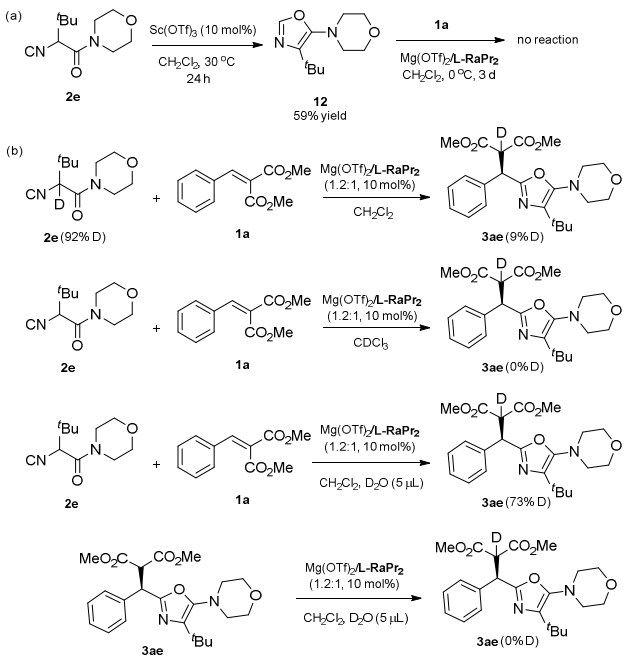


Scheme 2 (a) Gram-scale version of the reaction. (b) Synthetic utility.

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 reactivities or enantioselectivities (entries 5-7). Meanwhile, electron-donating *meta* substituents are also well tolerated (entries 8-10). Substitutions 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 the *m*-methoxy and *p*-methoxy group in **1** decreased the reactivities and also required a longer reaction time to achieve high conversion (entries 9 and 19), results we attribute to the decreased electrophilicity of the alkylidene malonates with an electronic-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). *ortho*-Substituted heteroaromatic substrate proved detrimental to both reactivity and selectivity, while *meta* substitution one led to a satisfactory result (entries 24 and 25). The aliphatic substrates can also be employed but gave moderate enantioselectivities (entries 26 and 27).

Then, various α-substituted isocyanides were examined. Gratefully, isocyanides **2a**-**2e** with different alkyl or phenyl substituents were applicable, giving the corresponding products **3aa**-**3ae** in 60-99% yields 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 Glycine derived α-isocyanoacetamide **2i** was applied. The absolute configuration of compound **3ae** was established unambiguously to be *R* by a single-crystal X-ray structure analysis,[17] and those of 5-aminooxazoles exhibited a similar (+) Cotton effect in their CD (circular dichroism) spectra (for details, see the Supporting Information).

To show the prospect of the methodology in the synthesis, a gram scale synthesis of **3ae** was performed. Under the optimal conditions, 4.5 mmol of α-isocyanoacetamide **2e** reacted with 3.0 mmol of methyl 2-benzylidenemalonate well, providing 0.90 g (70% yield) of the corresponding 5-aminooxazoles **3ae** with an *ee* of 91% (Scheme 2a). The enantiopure product could be obtained by a simple recrystallization with a yield of 67%. Next, simple derivations of the product were conducted (Scheme 2b). The product **3ae** could be efficiently converted into the useful 1,3-diol **5** through reduction with $LiAlH_4$ (90% yield, 95% *ee*). In addition, 5-aminooxazole **3ae** was readily hydrolyzed in the presence of trifluoroacetic acid,[18] and dipeptide **6** could be obtained in 99% yield with the maintained enantioselectivity (1.8:1 d.r., 99% *ee*). Those of which are important structural motifs towards many biologically active compounds. Next, in the presence of ceric ammonium nitrate, the oxazole ring was opened up, giving the imide product **7** in 51% yield with 98% *ee*.[19] Initial decarboxylation of **7** gave the succinate derivative **8** in 47% yield with a racemic mixture, caused by racemization-prone α-substituted carbonyl compound **7** in high temperature. Considering that optically active 2-substituted succinic acid derivatives are useful motifs in numerous biologically active



Scheme 3 Control experiments.

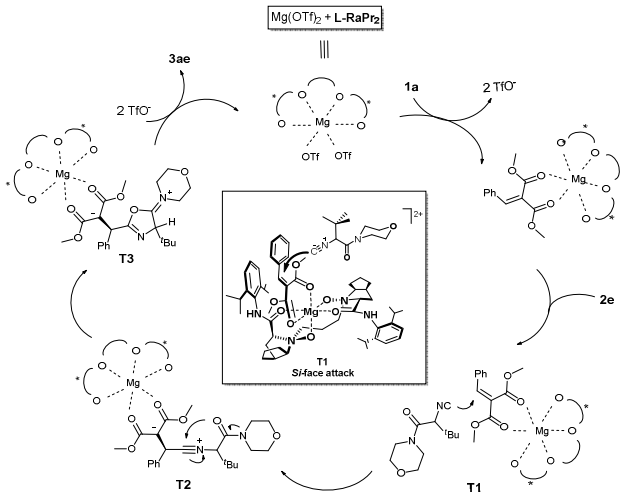


Figure 1 Proposed catalytic cycle.

compounds and natural products,[20] we turned our attention to accessing these compounds. To our delight, the monoester product **9** is obtained in excellent yield with the maintained enantioselectivity (98% yield, 94% *ee*). Subsequently, opening of the oxazole ring gave the target chiral succinate derivative **10** in 70% yield with 94% *ee*. In the mean time, monoester oxazole **9** underwent facile reduction with $LiAlH_4$ to provide **11** in 47% yield.

During the course of this study, an authentic 5-aminooxazole (**12**; see Scheme 3a) as by-product was formed in some cases.[15] In order to understand the reaction profile, **12** was applied to react with alkylidene malonate **1a** under the standard reaction conditions. However, no desired product **3ae** was obtained after three days, suggesting that the Friedel-Crafts pathway wasn't involved in the formation of the final product. Moreover, deuterium labeling studies were carried out (Scheme 3b). While the use of D-isocyanide led to low deuterium labeling on the product, the use of a small amount of D_2O resulted in significant deuterium labeling on the product. This interesting observation suggests that proton transfer is facilitated by a trace amount of water (T3 to product in Figure 1).

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

Conclusions

In summary, we developed a chiral *N,N'*-dioxide/Mg^{II} catalyst system to realize the asymmetric α-addition of isocyanides with alkylidene malonates. A range of 2-alkyl-5-aminooxazoles were obtained in moderate to excellent yields (up to 99%) with excellent *ee* values (up to 96%). This represented the first example of enantioselective α-addition of isocyanides to activated alkenes and may lay the foundation for the development of long-awaited enantioselective α-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

1 (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.* **Vol. 60** (Ed.: D. C. Palmer), Wiley, Hoboken, NJ, 2003, pp. 138–149; (c) Z. Jin, *Nat. Prod. Rep.,* 2013, **30**, 869.
2 (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.
3 (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.
4 (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.
5 (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.
6 (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.
7 L. Banfi and R. Riva in *Organic Reactions*, **Vol. 65** (Ed.: A. B. Charette), Wiley, New York, 2005, pp. 1–140.
8 (a) A. Dömling and I. Ugi, *Angew. Chem. Int. Ed.,* 2000, **39**, 3168; (b) S. Marcaccini and T. Torroba, *Nat. Protoc.,* 2007, **2**, 632.
9 (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-Montaño and J. Zhu, *Tetrahedron,* 2004, **60**, 4879; (d) P. R. Krishna, G. Dayaker and P. V. N. Reddy, *Tetrahedron Lett.,* 2006, **47**, 5977.
10 (a) H. Kunz, W. Pfrengle, *J. Am. Chem. Soc.,* 1988, **110**, 651; (b) R. J. Linderman, S. Binet, S. R. Petrich, *J. Org. Chem.,* 1999, **64**, 336; (c) G. F. Ross, E. Herdtweck, I. Ugi, *Tetrahedron,* 2002, **58**, 6127; (d) A. Basso, L. Banfi, R. Riva, G. Guanti, *J. Org. Chem.,* 2005, **70**, 575; (e) L. Banfi, A. Basso, G. Guanti, S. Merlo, C. Repetto, R. Riva, *Tetrahedron,* 2008, **64**, 1114; (f) K. M. Bonger, T. Wennekes, D. V. Filippov, G. Lodder, G. A. van de Marel, H. S. Overkleeft, *Eur. J. Org. Chem.,* **2008**, 3678.
11 "Asymmetric Isocyanide-based MCRs": L. Banfi, A. Basso, G. Guanti and L. Banfi in *Multicomponent reactions* (Eds.: J. Zhu and H. Bienaymé), Wiley-VCH, Weinheim, 2005, pp. 1–32.
12 (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 Yu 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.
13 For examples of α-carbanion attacking, 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.
14 For examples of isocyano group attacking, 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.
15 Y. Odabachian, Q. Wang and J. Zhu, *Chem.-Eur. J.,* 2013, **19**, 12229.
16 (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. Sinica,* 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. Sinica,* 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.
17 CCDC 1416058 (**3ae**).
18 (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.
19 D. A. Evans, P. Nagorny and R. Xu, *Org. Lett.,* 2006, **8**, 5669.
20 Y.-C. Chung, D. Janmanchi and H.-L. Wu, *Org. Lett.,* 2012, **14**, 2766.