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

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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-aminooxazoles 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.

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## Introduction

Optically active heterocyclic compounds containing an oxazole motif appear extensively in natural products, pharmaceuticals, and synthetic intermediates. 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. 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 and  $\alpha$ -addition of isocyanides with carbonyls or imines, have been reported. In relation to the latter,  $\alpha$ -addition is a simple but very efficient route to obtain 5-aminooxazoles.

 $\alpha$ -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>4 $\alpha$ -c</sup> and Shibasaki<sup>4d</sup> as well as Zhong<sup>4c</sup> have made significant contributions to the catalytic enantioselective  $\alpha$ -addition of isocyanides to aldehydes, thus affording the desired 2-(1-hydroxyalkyl)-5-aminooxazoles. Recently, Wang

and Zhu described an enantioselective  $\alpha$ -addition of isocyanides to imines, providing a series of 2-(1-aminoalkyl)-5-aminooxazoles 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-aminooxazoles
- ♦ High ee values and broad substrate scope
- ♦ Useful oxazole skeleton and facile derivatization

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

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ring-chain isomerization of the  $\alpha$ -isocyanoacetamides inevitably provided byproducts, C-2 unsubstituted 5-aminooxazoles, in the presence of a Lewis acid (Scheme 1b). 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 $^{II}$  complex, $^{3,16}$  delivering 2-alkyl-5-aminooxazoles in good yields with high enantioselectivities.

## Results and discussion

Our investigation began with the addition of a DL-phenylalanine derived α-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 α-isocyanoacetamide

Table 1 Optimization of the reaction conditions

Entry <sup>a</sup>	Ligand	R	<i>T</i> (°C)	t (h)	$Yield^{b}$ (%)	ee <sup>c</sup> (%)
1	L-PrPr <sub>2</sub>	Bn (2a)	30	24	72	76
1	2	( )	30	24	12	70
2	L-PiPr <sub>2</sub>	Bn ( <b>2a</b> )	30	24	93	70
3	L-RaPr <sub>2</sub>	Bn (2a)	30	24	99	82
4	L-RaPr <sub>2</sub>	Bn (2a)	0	48	63	86
5	L-RaPr <sub>2</sub>	Ph (2b)	0	48	86	87
6	L-RaPr <sub>2</sub>	Me (2c)	0	72	61	86
7	L-RaPr <sub>2</sub>	iPr ( <b>2d</b> )	0	72	91	89
8	L-RaPr <sub>2</sub>	<i>t</i> Bu (2e)	0	72	75	92
$9^d$	$L$ -RaP $r_2$	<i>t</i> Bu (2e)	0	72	91	92

<sup>&</sup>lt;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%).

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-aminooxazole 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 2 Substrate scope for the alkylidene malonates 1

$$R^{1} \xrightarrow{CO_{2}R^{2}} + CN \xrightarrow{f_{BU}} O \xrightarrow{Mg(OTf)_{2}/L-RaPr_{2}} (1.2:1, 10 \text{ mol}\%) \\ CH_{2}Cl_{2}, 0 \text{ °C}, 3 \text{ d} \\ R^{1} \xrightarrow{f_{BU}} N \xrightarrow{f_{BU}} O$$
1 2e 3 or 4

Entry <sup>a</sup>	R <sup>1</sup>	$\mathbb{R}^2$	3 or 4	Yield <sup>b</sup> (%)	ee <sup>c</sup> (%)
1	$C_6H_5$	Me	3ae	91	92 (R) <sup>e</sup>
2	$C_6H_5$	Et	3be	71	91
3	$C_6H_5$	iPr	3ce	41	82
$4^d$	$2\text{-FC}_6\text{H}_4$	Me	3de	66	80
5	$3\text{-FC}_6\text{H}_4$	Me	3ee	92	91
6	$3-ClC_6H_4$	Me	3fe	77	91
7	$3$ -BrC $_6$ H $_4$	Me	3ge	96	91
8	$3\text{-MeC}_6H_4$	Me	3he	66	94
$9^d$	$3\text{-MeOC}_6H_4$	Me	3ie	81	90
10	$3-PhOC_6H_4$	Me	3je	84	88
11	$4\text{-FC}_6\text{H}_4$	Me	3ke	86	93
12	$4$ -ClC $_6$ H $_4$	Me	3le	96	94
13	$4$ -BrC $_6$ H $_4$	Me	3me	93	94
14	$4-F_3CC_6H_4$	Me	3ne	86	92
15	$4\text{-NCC}_6H_4$	Me	3oe	98	94
16	$4\text{-O}_2\text{NC}_6\text{H}_4$	Me	3pe	91	94
17	$4\text{-MeC}_6H_4$	Me	3qe	83	94
18	4-PhC <sub>6</sub> H <sub>4</sub>	Me	3re	98	91
$19^d$	$4 ext{-MeOC}_6H_4$	Me	3se	87	96
20	$4$ -PhOC $_6$ H $_4$	Me	3te	64	92
21	$4$ -BnOC $_6$ H $_4$	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	Ме	Me	4ae	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  $\alpha$ -isocyanoacetamide 2i was applied. The absolute configuration of compound 3ae was established unambiguously to be R using single-crystal X-ray structure analysis,  $^{17}$  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  $\alpha$ -isocyanoacetamide 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 $_4$  (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 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  $\alpha$ -isocyanoacetamides 2

<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.19 An initial decarboxylation of 7 gave the succinate derivative 8 in 47% yield as a racemic mixture, caused by subjecting the racemization-prone αsubstituted 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,20 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 deuteriated 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

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

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 Mg(OTf)<sub>2</sub>/L-RaPr<sub>2</sub> 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 [Mg2+ + L-RaPr2 +  $1a + OTf^{-}$  (cal. 1093.5034). Based on the above results and our previous work, 16b,g 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-RaPr2 coordinate to Mg<sup>2+</sup> 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 isonitrile 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/Mg<sup>II</sup> 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.

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Scheme 3 Control experiments.

## Notes and references

**Chemical Science** 

- 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., 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.
- 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 (a) M. Passerini, Gazz. Chim. Ital., 1921, 51, 126; (b)
   M. Passerini, Gazz. Chim. Ital., 1921, 51, 762.
- 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 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. Bonger, T. Wennekes, D. V. Filippov, G. Lodder, G. A. van de Marel and H. S. Overkleeft, Eur. J. Org. Chem., 2008, 3678.
- 11 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.
- 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 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.
- 13 For examples of α-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.
- 14 For examples of isocyano 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.
- 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. 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.
- 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.