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ARTICLE

Diastereodivergent Asymmetric Michael-Alkylation Reaction by Chiral *N,N'*-Dioxide/Metal Complexes

Yulong Kuang,^{ac} Bin Shen,^{ac} Li Dai,^a Qian Yao,^a Xiaohua Liu,^{*a} Lili Lin,^a and Xiaoming Feng^{*ab}

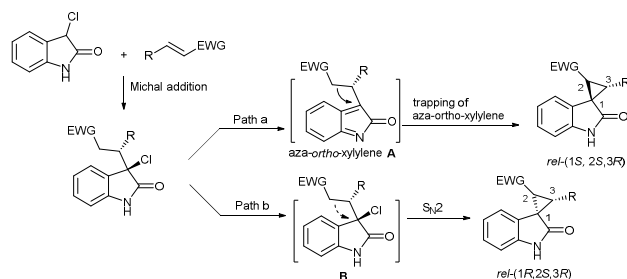
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A diastereodivergent asymmetric Michael-alkylation reaction between 3-chloro-oxindoles and β,γ -unsaturated- α -ketoesters has been achieved by using **L-RaPr₂/Sc(OTf)₃** and **L-PrPr₂/Mg(OTf)₂** metal complexes as catalysts. Both *rel*-(1*R*,2*S*,3*R*) and *rel*-(1*S*,2*S*,3*R*)¹ chiral spiro cyclopropane oxindoles were constructed in good yields, diastereoselectivities and ee values. The diastereodivergent control may originate from different alkylation pathways after the Michael addition, either intramolecular trapping of the *aza-ortho*-xylylene intermediate or direct S_N2 substitution.

Tuning diastereoselectivity in catalytic asymmetric synthesis is challenging due to the inherent preference for forming one of diastereomer in most reactions.² However, relative configurations are as important as absolute configurations in pharmacology and drug discovery because both can influence the physiological activity of a molecule.³ In general, diastereodivergence⁴ can be realized by changing the catalyst⁵, additive and solvent,⁶ substrate,⁷ and other methods. Nevertheless, diastereodivergent synthesis is still in its infancy. It's desirable to develop new strategies and discover more diastereodivergent reactions.



Scheme 1. Proposed processes for the diastereodivergent Michael-alkylation.

Oxindoles with a unique spirocyclopropane moiety exhibit diverse biological activities, such as non-nucleoside reverse transcriptase inhibitor and antitumor activity.⁸ Among the synthetic methodologies to prepare these molecules⁹, the cascade Michael-alkylation reactions¹⁰ of 3-chlorooxindole

with α,β -unsaturated olefins provides an operationally simple, stepwise pathway for diastereodivergence. Currently, only organic proline-based silyl ethers¹¹ and cinchona alkaloid-derived thioureas¹² and squaramides¹³ catalysts have been developed. These reactions proceed via the intramolecular trapping of the chiral *aza-ortho*-xylylene intermediates **A** after the Michael addition to afford the thermodynamically favored *rel*-(1*S*,2*S*,3*R*) products (Scheme 1, path a). On the other hand, if the Michael addition products undergo the direct S_N2 substitution pathway (intermediate **B**), the *rel*-(1*R*,2*S*,3*R*) products will be formed (Scheme 1, Path b). To the best of our knowledge, there is no precedent for synthesizing the *rel*-(1*R*,2*S*,3*R*) products as the major diastereomer, much less synthesizing both *rel*-(1*S*,2*S*,3*R*) and *rel*-(1*R*,2*S*,3*R*) products in high efficiency without drastically changing the reaction conditions. Herein, we reported a diastereodivergent asymmetric Michael-alkylation reaction between 3-chlorooxindoles and β,γ -unsaturated- α -ketoesters by chiral *N,N'*-dioxide/metal complexes,¹⁴ synthesizing *rel*-(1*S*,2*S*,3*R*) and *rel*-(1*R*,2*S*,3*R*) spirocyclopropane oxindoles in high yields, diastereoselectivities and enantioselectives.

Initially, the cascade reaction of 3-Cl oxindole **1a** with β,γ -unsaturated- α -ketoester **2a** was chosen as the model reaction to optimize the reaction conditions. First, a series of metal salts were investigated by complexing with chiral *N,N'*-dioxide **L-PrPr₂** in the presence of Na₂CO₃ as the base at 30°C. It was found that both Sc(OTf)₃ and Mg(OTf)₂ complexes could catalyze the reaction with a preference for forming different diastereomer. The enantioselectivity was moderate for each major diastereomer, which could be isolated by column chromatography. Next, other conditions were screened.¹⁵ The **L-RaPr₂/Sc(OTf)₃** complex elevated the isolated yield of the product *rel*-(1*R*,2*S*,3*R*)-**3aa** to 92% with 78% ee (entry 3). After lowering the reaction temperature to 0°C, increasing the stoichiometry of the base to 1.3 equivalents, and prolonging the reaction time to 72 h, the *rel*-(1*R*,2*S*,3*R*)-**3aa** could be obtained in 97% yield and 92% ee (entry 4).

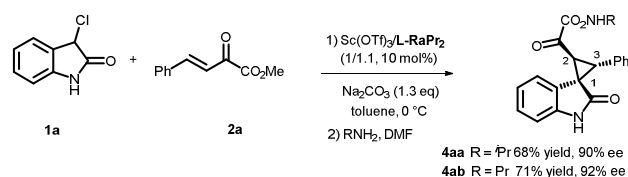
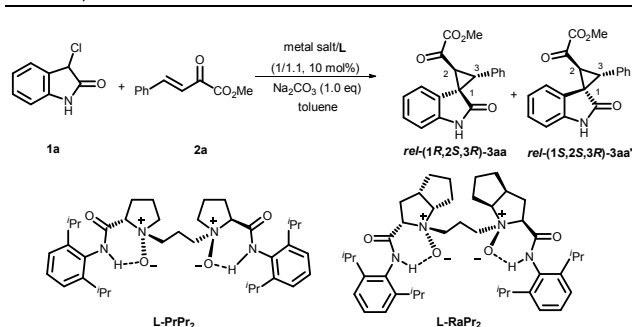
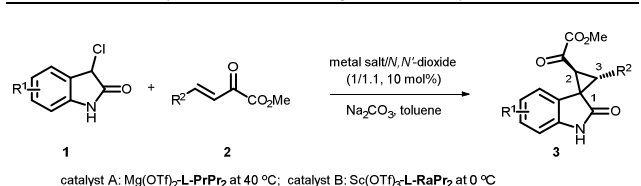
^a Key Laboratory of Green Chemistry & Technology, Ministry of Education, College of Chemistry, Sichuan University, Chengdu 610064, China. E-mail: liuxh@scu.edu.cn; xmfeng@scu.edu.cn; Fax: +86 28 85418249; Tel: +86 28 85418249.

^b Collaborative Innovation Center of Chemical Science and Engineering (Tianjin), P. R. China

^c These authors contributed equally to this work.

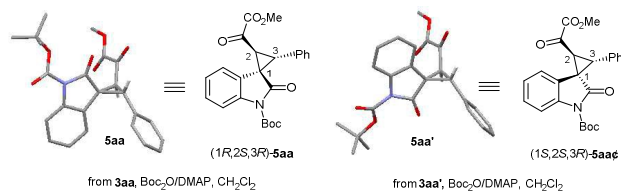
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Table 1. Optimization of the reaction conditions^a**Scheme 2.** The stabilization of spiro-cyclopropane oxindole by amination.**Table 2.** Substrate scope of the diastereodivergent Michael-alkylation reaction^a

Entry	Metal salt	L*	Yield (3aa/3aa') (%) ^b	ee (3aa/3aa') ^c
1	Sc(OTf) ₃	L-PrPr ₂	92/7	76/0
2	Mg(OTf) ₂	L-PrPr ₂	14/28	0/88
3	Sc(OTf) ₃	L-RaPr ₂	92/--	78/--
4 ^d	Sc(OTf) ₃	L-RaPr ₂	97/--	92/--
5 ^e	Mg(OTf) ₂	L-PrPr ₂	--/77	--/95

^a Unless otherwise noted, the reaction proceeded with **1a** (0.1 mmol), **2a** (0.1 mmol), metal salt/ligand (1:1.1, 10 mol%), and Na₂CO₃ (1.0 equiv.) in toluene (1.0 mL) at 30 °C for 24 h. ^b Isolated yield. ^c Determined by chiral HPLC on chiral stationary phase (Chiralcel IA and IE). ^d The reaction proceeded at 0 °C for 72 h and with 1.3 eq of Na₂CO₃. ^e At 40 °C for 72 h.

**Figure 1.** The wire-stick representation of *N*-Boc derivatives **5aa**^(b) of the product **3aa**^(b).

On the other hand, by using chiral L-PrPr₂/Mg(OTf)₂ as the catalyst and increasing the reaction temperature to 40 °C, the corresponding *rel*-(1*S*,2*S*,3*R*)-**3aa'** could be afforded in 77% yield and 95% ee after 72 hours (entry 5). It is worth mentioning that the metal cations dictate the diastereoselectivity and variation of chiral ligand structure and the reaction temperature did not change the major diastereoisomer once Sc(OTf)₃ or Mg(OTf)₂ were identified as suitable catalysts. The absolute configurations of the major enantiomers were determined separately by X-ray crystallographic analysis of the corresponding *N*-Boc protected derivatives **5**¹⁶ (Figure 1). Through this method, the *rel*-(1*S*,2*S*,3*R*)-**5aa'** obtained from the L-PrPr₂/Mg(OTf)₂ catalytic

Entry	3: R ¹ , R ²	<i>rel</i> -(1 <i>S</i> ,2 <i>S</i> ,3 <i>R</i>)- 3' (Cat A)		<i>rel</i> -(1 <i>R</i> ,2 <i>S</i> ,3 <i>R</i>)- 3 (Cat B)	
		Yield (%) ^b	ee (%) ^c	Yield (%) ^b	ee (%) ^d
1	3aa ^(b) : H; C ₆ H ₅	77	95	97	92
2	3ba ^(b) : 4-Me; C ₆ H ₅	-	-	67	86
3	3ca ^(b) : 4-F; C ₆ H ₅	84	96	76	86
4	3da ^(b) : 5-Me; C ₆ H ₅	72	96	96	89
5	3ea ^(b) : 5-F; C ₆ H ₅	67	92	96	81
6	3fa ^(b) : 5-Cl; C ₆ H ₅	61	88	-	-
7	3ga ^(b) : 6-F; C ₆ H ₅	70	89	91	90
8	3ha ^(b) : 6-Cl; C ₆ H ₅	63	84	98	88
9	3ia ^(b) : 6-Br; C ₆ H ₅	-	-	83	84
10	3ah ^(b) : H; 2-MeOC ₆ H ₄	69 ^e	95 ^e	71	91
11	3al ^(b) : H; 3-MeOC ₆ H ₄	70	96	98	95
12	3aj ^(b) : H; 4-MeOC ₆ H ₄	59	94	96	72
13	3ak ^(b) : H; 2-MeC ₆ H ₄	50	91	76	96
14	3al ^(b) : H; 4-MeC ₆ H ₄	77	93	93	87
15	3av ^(b) : H; 4-FC ₆ H ₄	-	-	96	90
16	3am ^(b) : H; 3-ClC ₆ H ₄	77	92	76	87
17	3an ^(b) : H; 4-ClC ₆ H ₄	63	91	79	93
18	3ao ^(b) : H; 2-BrC ₆ H ₄	62	94	-	-
19	3ap ^(b) : H; 4-BrC ₆ H ₄	81	94	83	94
20	3aq ^(b) : H; 4-PhC ₆ H ₄	74	98	96	92
21	3ar ^(b) : H;	71	93	91	93
22	3as ^(b) : H;	52	95	-	-
23	3at ^(b) : H; ^t Bu	71	93	95	99
24	3au ^(b) : H; cyclohexyl	-	-	99	99

^a Unless otherwise noted, reactions were performed with **1** (0.1 mmol), **2** (0.1 mmol), chiral catalyst (10 mol%), Na₂CO₃ in toluene (1.0 mL) for 72 h. For *rel*-(1*S*,2*S*,3*R*)-**3'**, L-PrPr₂/Mg(OTf)₂ (1.1/1) and 1.0 eq of Na₂CO₃ were used at 40 °C. For *rel*-(1*R*,2*S*,3*R*)-**3**, L-RaPr₂/Sc(OTf)₃ (1.1/1, 10 mol%) and 1.3 eq of Na₂CO₃ were used at 0 °C. ^b Isolated yield. ^c Determined by HPLC on a chiral stationary phase. ^d Determined by HPLC on a chiral stationary phase after transformation into **4**. ^e The diastereoselectivity of **3ah** was determined to be 94:6 by HPLC.

system was determined to be (1*S*, 2*S*, 3*R*), and the *rel*-(1*R*,2*S*,3*R*)-**5aa** generated from L-RaPr₂/Sc(OTf)₃ was found to be (1*R*, 2*S*, 3*R*).

Next, the enantioselective and diastereodivergent synthesis of a series of spirocyclopropane oxindoles was carried out



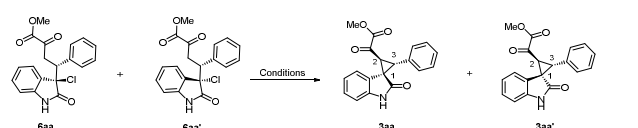
using these two chiral catalyst systems (Table 2). Under optimized conditions, all substrates gave one major diastereomer (higher than 94:6 diastereoselectivity) with moderate to excellent yields and enantioselectivities. It is noteworthy that most of the *rel*-(1*R*,2*S*,3*R*) products **3** were unstable under HPLC analysis conditions. Fortunately, the enantiomeric excess could be determined after conversion of the *rel*-(1*R*,2*S*,3*R*)-**3** into the corresponding derivatives *rel*-(1*R*,2*S*,3*R*)-**4** (Scheme 2). Generally, the *rel*-(1*S*,2*S*,3*R*)-diastereoisomers prepared from **L-PrPr₂/Mg(OTf)₂** catalyst were delivered in higher enantioselectivities than the *rel*-(1*R*,2*S*,3*R*) isomers from the **L-RaPr₂/Sc(OTf)₃** catalyst. For the synthesis of *rel*-(1*S*,2*S*,3*R*) cyclopropanes, 3-chlorooxindoles **1** with halo-substituents at the C4 and C5-positions gave higher enantioselectivities than C6-substituted ones (entries 3–8). Electron-donating or withdrawing substituents on the aromatic β,γ-unsaturated-α-ketoester **2** had a slight influence on the enantioselectivity (entries 10 – 22). 2-Naphthyl- and 2-thiophenyl substituted β,γ-unsaturated-α-ketoesters were also tolerated well (entries 21 and 22). Moreover, when the aliphatic substrates **2t** and **2u** were subjected to the reaction conditions, the corresponding *rel*-(1*R*,2*S*,3*R*)-products could be obtained in excellent yields with excellent enantioselectivities (up to 99% yield and 99% ee; entries 23 and 24).

Preliminary mechanistic studies were conducted to confirm our proposed diastereodivergent control mode. The relationship between the ee values of the ligand and product showed a linear correlation.¹⁵ Additionally, X-ray crystallographic analysis of the catalysts also showed a 1:1 ratio of ligand to metal.¹⁷ Both of these findings implied that the monomeric catalysts might be the main catalytically active species. What's more, crystal structures of both catalysts displayed similar geometries and showed no significant differences in the accessibility of the substrate's coordination site. To check whether the **L-PrPr₂/Mg(OTf)₂** and **L-RaPr₂/Sc(OTf)₃** coordinated with different substrates, *in situ* HRMS analysis was performed.¹⁵ Based on the HRMS spectra, both of them coordinate with the same substrate, 3-Cl oxindole, to initiate the reaction. All of these experiments excluded the possibility that the observed diastereodivergence resulted from different coordinative styles of the two catalysts.

The intermediates of Michael addition products were then synthesized and subjected to the optimized reaction conditions. The relative configuration of **6aa** was also confirmed by X-ray crystallographic analysis.¹⁸ As summarized in Table 3, the two diastereomers of **6** only transformed to the same **3aa'** with 76% yield and 31% yield respectively under the **L-PrPr₂/Mg(OTf)₂** system (Table 3, entries 2 and 4), which may be due to the chiral match or mismatch effect. On the contrary, the **3aa** or **3aa'** could be afforded from either **6aa** or **6aa'** in the **L-RaPr₂/Sc(OTf)₃** system with 18% yield and 74% yield, respectively (Table 3, entries 1 and 3). By comparing different results between **L-RaPr₂/Sc(OTf)₃** and **L-PrPr₂/Mg(OTf)₂** catalyzed reactions, **L-PrPr₂/Mg(OTf)₂** should promote this reaction by *aza-ortho*-xylylene intermediates, as has been reported previously, which induced thermodynamically favored *rel*-(1*S*,2*S*,3*R*) **3aa'** from different diastereomers **6**. However, in the **L-RaPr₂/Sc(OTf)₃** catalytic system, the chirality

inversion at the quaternary carbon from **6aa** to *rel*-(1*R*,2*S*,3*R*) **3aa** and from **6aa'** to *rel*-(1*S*,2*S*,3*R*) **3aa'** illustrated that alkylation proceeded through a direct S_N2 substitution pathway. Moreover, the chiral **6aa** (-73% ee) could produce another enantiomer of **3aa'** in 75% yield and 76% ee under the **L-PrPr₂/Mg(OTf)₂** conditions (Table 3, entry 5). Undoubtedly, the same enantioselectivity revealed that the first Michael addition step should be the chirality-determining step. For the result of entry 1, the product **3aa** was formed with 85% ee and the starting material was recovered in 80% yield with 84:16 diastereoselectivity (**6aa**:**6aa'**) from racemic **6aa** under the **L-RaPr₂/Sc(OTf)₃** catalytic system (Table 3, entry 1). We proposed this result came from the chemical equilibrium between the retro-Michael reaction and Michael addition, which could also account for the lack of formation of *rel*-(1*S*,2*S*,3*R*) **3aa'**. The low yield also implied that the rate of S_N2 substitution from the enolate ion is high and the Na₂CO₃ is not a strong enough base to deprotonate the Michael intermediate. To evaluate the role of *N*-H group, *N*-methylated 3-Cl oxindole was also subjected into the reaction, which showed poor result.¹⁵

Table 3. The comparative experiments for diastereodivergent control



Entry	6	Condition ^a	3aa ^b [yield, ee]	3aa' ^b [yield, ee]
1 ^c	(±) 6aa	L-RaPr₂/Sc(OTf)₃	18%, 85%	—
2	(±) 6aa	L-PrPr₂/Mg(OTf)₂	—	76%, -7%
3	(±) 6aa'	L-RaPr₂/Sc(OTf)₃	—	74%, 3%
4	(±) 6aa'	L-PrPr₂/Mg(OTf)₂	—	31%, race
5 ^d	(+) 6aa	L-PrPr₂/Mg(OTf)₂	—	75%, -76%

^a Unless otherwise noted, reactions were performed with corresponding **6** and catalyst (M/L = 1/1.1–10 mol%), and Na₂CO₃ (1.0 eq) in toluene (1.0 mL) at 0°C for 72 h. ^b Isolated yield. ee was determined by HPLC on a chiral stationary. ^c The recovered **6aa** was 80% yield, 84:16 dr, -17% ee/19% ee, the diastereoselectivity of corresponding of **3aa** was 84:16. ^d The ee of **6aa** was -73% ee.

Conclusions

A diastereodivergent asymmetric Michael-alkylation reaction between 3-Cl oxindoles and β,γ-unsaturated-α-ketoesters was accomplished by tuning metal catalysts and adjusting ligand and temperature. Under the optimized conditions, both *rel*-(1*R*,2*S*,3*R*) and *rel*-(1*S*,2*S*,3*R*) spiro cyclopropane oxindoles were synthesized with high yields, diastereoselectivities and enantioselectivities. Mechanistic studies also revealed that the diastereodivergent control should come from either trapping the *aza-ortho*-xylylene intermediates or direct S_N2 substitution in the alkylation step, which may be caused by the different characteristics of the metal catalysts. Developing other diastereodivergent asymmetric methodology by this strategy is ongoing.

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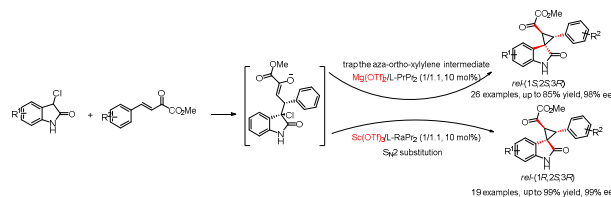
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Notes and references

- 1 Fletcher, Nomenclature of Organic Compounds, Advances in Chemistry; American Chemical Society: Washington, DC, 1974.
- 2 E. M. Carreira, L. Kvaerno, Classics in Stereoselective Synthesis, Wiley, Weinheim, 2009.
- 3 (a) C. Wolf, Dynamic stereochemistry of chiral compounds: principles and applications, Royal Society of Chemistry, 2008; (b) C. G. Wermuth, The Practice of Medicinal Chemistry, Elsevier, Amsterdam, 3rd ed., 2008; (c) W. O. Foye, Foye's Principles of Medicinal Chemistry, Lippincott Williams & Wilkins, 7th ed. 2013.
- 4 Reviews in asymmetric diastereodivergent synthesis: (a) L. Lin and X. M. Feng, *Chem. Eur. J.* 2017, **23**, 6464; (b) M. Bihani and J. C. G. Zhao, *Adv. Synth. Catal.* 2017, **359**, 534; (c) G. Zhan, W. Du and Y. C. Chen, *Chem. Soc. Rev.* 2017, **46**, 1675.
- 5 For selected examples of diastereodivergent asymmetric synthesis by changing catalysis and dual catalyst strategies, see: (a) E. E. Maroto, S. Filippone, M. Suárez, R. Martínez-Álvarez, A. de Cozar, F. P. Cossío and N. Martín, *J. Am. Chem. Soc.* 2014, **136**, 705; (b) S. Krautwald, D. Sarlah, M. A. Schafroth and E. M. Carreira, *Science* 2013, **340**, 1065; (c) M. T. Oliveira, M. Luparia, D. Audisio and N. Maulide, *Angew. Chem. Int. Ed.* 2013, **52**, 13149; (d) E. Conde, D. Bello, A. de Cózar and M. Sánchez, M. A. Vázquez, F. P. Cossío, *Chem. Sci.* 2012, **3**, 1486; (e) B. Simmons, A. M. Walji and D. W. C. MacMillan, *Angew. Chem. Int. Ed.* 2009, **48**, 4349; (f) S. Filippone, E. E. Maroto, A. Martín-Domenech and M. Suarez, *Nat. Chem.* 2009, **1**, 578; (g) X. X. Yan, Q. Peng, Y. Zhang, K. Zhang, W. Hong, X. L. Hou and Y. D. Wu, *Angew. Chem. Int. Ed.* 2006, **45**, 1979; (h) Y. Huang, A. M. Walji, C. H. Larsen and D. W. C. MacMillan, *J. Am. Chem. Soc.* 2005, **127**, 15051.
- 6 Selected examples: (a) X. Wu, Z. Chen, Y.-B. Bai and Vy M. D. J. *Am. Chem. Soc.* 2016, **138**, 12103; (b) X. Li, M. Lu, Y. Dong, W. Wu, Q. Qian, J. Ye and D. J. Dixon, *Nat. Commun.* 2014, **5**, 4479; (c) X. Tian, C. Cassani, Y. Liu, A. Moran, A. Urakawa, P. Galzerano, E. Arceo and P. Melchiorre, *J. Am. Chem. Soc.* 2011, **133**, 17934.
- 7 J. Zhu, Y. Liang, L. Wang, Z. B. Zheng, K. N. Houk and Y. Tang, *J. Am. Chem. Soc.* 2014, **136**, 6900.
- 8 (a) Y. He, T. Jiang, K. L. Kuhlen, Y. H. Ellis, B. Wu, T. Y. H. Wu and B. Bursulaya, Oxindoles with Anti-HIV Activity. U.S. Patent WO 2004/037247A1, 2004; (b) T. Jiang, K. L. Kuhlen, K. Wolff, H. Yin, K. Bieza, J. Caldwell, B. Bursulaya, T. Y. H. Wu and Y. He, *Bioorg. Med. Chem. Lett.* 2006, **16**, 2105; (c) P. B. Sampson, Y. Liu, S. W. Li, B. T. Forrest, H. W. Pauls, L. G. Edwards, M. Feher, N. K. B. Patel, R. Laufer and G. Pan, Kinase Inhibitors and Method of Treating Cancer with Same. U.S. Patent WO 2010/115279A1, 2010; (d) L. Chen, L. Feng, Y. He, M. Huang and H. Yun, Spiro Indole Cyclopropane Indolinones Useful as Ampk Modulators. U.S. Patent WO2011/70039A1, 2011; (e) H. W. Pauls, S. W. Li, P. B. Sampson and B. T. Forrest, Plk-4 Inhibitors and Methods of Treating Cancer with Same. U.S. Patent WO 2012/048411A1, 2012. (f) P. B. Sampson, Y. Liu, N. K. Patel, et al., *J. Med. Chem.*, 2015, **58**, 130; (g) P. B. Sampson, et al., *J. Med. Chem.*, 2015, **58**, 147.
- 9 Selected examples: (a) Z. Y. Cao, F. Zhou, Y. H. Yu, and J. Zhou, *Org. Lett.* 2013, **15**, 42; (b) Z. Y. Cao, X. M. Wang, C. Tan, X. L. Zhao, J. Zhou, and K. Ding, *J. Am. Chem. Soc.* 2013, **135**, 8197; (c) A. Noole, A. Malkov and T. Kanger, *Synthesis*, 2013, **45**, 2520; (d) A. Awata and T. Arai, Synlett, 2013, **24**, 29; (e) J. Guo, Y. B. Liu, X. Q. Li, X. H. Liu, L. L. Lin and X. M. Feng, *Chem. Sci.* 2016, **7**, 2717.
- 10 Examples of asymmetric Michael-alkylation reaction in three member ring formation: (a) G. J. Sun, J. Gong and Q. Kang, *J. Org. Chem.* 2017, **82**, 796; (b) B. L. Zhao and D. M. Du, *Eur. J. Org. Chem.* 2015, 5350; (c) C. Kim and S. G. Kim, *Tetrahedron-Asymmetry* 2014, **25**, 1376; (d) J. I. Martinez, E. Reyes, U. Uria, L. Carrillo and J. L. Vicario, *Chemcatchem* 2013, **5**, 2240; (e) L. Q. Lu, J. R. Chen and W. J. Xiao, *Acc. Chem. Res.* 2012, **45**, 1278; (f) X. W. Dou and Y. X. Lu, *Chem. Eur. J.* 2012, **18**, 8315; (g) F. Pesciaoli, P. Righi, A. Mazzanti, G. Bartoli and G. Bencivenni, *Chem. Eur. J.* 2011, **17**, 2842; (h) H. Xie, L. Zu, H. Li, J. Wang and W. Wang, *J. Am. Chem. Soc.* 2007, **129**, 10886.
- 11 (a) A. Noole, M. Ošeka, T. Pehk, M. Öeren, I. Järving, M. R. J. Elsegood, A. V. Malkov, M. Lopp and T. Kanger, *Adv. Synth. Catal.* 2013, **355**, 829. (b) R. C. da Silva, I. Chatterjee, E. Escudero-Adán, M. W. Paixão and P. Melchiorre, *Asian J. Org. Chem.*, 2014, **3**, 466.
- 12 (a) M. Ošeka, A. Noole, S. Žari, M. Öeren, I. Järving, M. Lopp and T. Kanger, *Eur. J. Org. Chem.* 2014, 3599; (b) X. W. Dou, W. J. Yao, B. Zhou and Y. X. Lu, *Chem. Commun.* 2013, **49**, 9224.
- 13 (a) J. H. Li; T. F. Feng and D. M. Du, *J. Org. Chem.*, 2015, **80**, 11369; (b) A. Noole, I. Järving, F. Werner, M. Lopp, A. Malkov and T. Kanger, *Org. Lett.* 2012, **14**, 4922.
- 14 Selected examples of *N,N'*-Dioxide in catalytic asymmetric reaction, see: (a) X. H. Liu, L. L. Lin and X. M. Feng, *Acc. Chem. Res.* 2011, **44**, 574; (b) X. H. Liu, L. L. Lin and X. M. Feng, *Org. Chem. Front.* 2014, **1**, 298; (c) X. H. Liu, H. F. Zheng, Y. Xia, L. L. Lin and X. M. Feng, *Acc. Chem. Res.* 2017, **50**, 2621 (d) K. Zheng, L. L. Lin and X. M. Feng, *Acta Chim. Sin.* 2012, **70**, 1785; (e) 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; (f) X. Hao, L. Lin, F. Tan, C. Yin, X. Liu and X. Feng, *ACS Catal.* 2015, **5**, 6052; (g) J. H. Feng, L. L. Lin, K. R. Yu, X. H. Liu and X. M. Feng, *Adv. Syn. Catal.* 2015, **357**, 1305; (h) J. H. Feng, X. Yuan, W. W. Luo, L. L. Lin, X. H. Liu and X. M. Feng, *Chem. Eur. J.* 2016, **22**, 15650. (i) J. F. Zheng, L. L. Lin, L. Dai, Q. Tang, X. H. Liu and X. M. Feng, *Angew. Chem. Int. Ed.* 2017, **56**, 13107.
- 15 For more details, see the Supporting Information.
- 16 CCDC 1411858 (5aa) and CCDC 1412691 (5aa') contain the supplementary crystallographic data for this paper. These data can be obtained free from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.
- 17 The ORTEP diagram of catalyst had been reported in our former research, the CCDC 804337 [Mg(OTf)₂/L-RaPr₂], CCDC 704000 [Sc(OTf)₃/L-PrPr₂] and CCDC 882608 [Sc(OTf)₃/L-RaPr₂]. These data can be obtained free from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.
- 18 CCDC 1545249 (6aa) contains the supplementary crystallographic data for this paper. These data can be obtained free from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.





A diastereodivergent asymmetric cascade Michael-Alkylation by switching the alkylation step of intramolecular trapping the aza-ortho-xylylene intermediate or direct S_N2 substitution has been developed.

