A Journal of the Gesellschaft Deutscher Chemiker

Angewandte International Edition GDCh Chemie

www.angewandte.org

Accepted Article

Title: Chiral ZnII Complex Catalyzed Enantioselective Tandem α-Alkenyl Addition/Proton Shift Reaction of Silyl Enol Ethers with Ketimines

Authors: Tengfei Kang, Weidi Cao, Liuzhen Hou, Qiong Tang, Sijia Zou, Xiaohua Liu, and Xiaoming Feng

To be cited as: *Angew. Chem. Int. Ed.* 10.1002/anie.201810961
Angew. Chem. 10.1002/ange.201810961

Link to VoR: http://dx.doi.org/10.1002/anie.201810961
http://dx.doi.org/10.1002/ange.201810961

WILEY-VCH

10.1002/anie.201810961

WILEY-VCH

Chiral Zn^{II} Complex Catalyzed Enantioselective Tandem α-Alkenyl Addition/Proton Shift Reaction of Silyl Enol Ethers with Ketimines

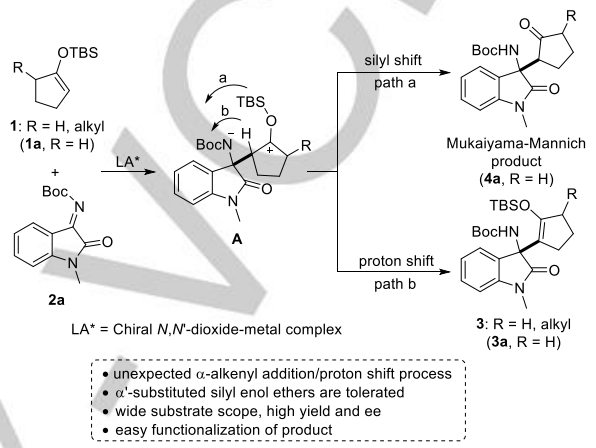
Tengfei Kang, Weidi Cao, Liuzhen Hou, Qiong Tang, Sijia Zou, Xiaohua Liu and Xiaoming Feng*

Dedication ((optional))

Abstract: A new catalytic asymmetric tandem α-alkenyl addition/proton shift reaction of silyl enol ethers with ketimines was serendipitously discovered in the presence of chiral *N*,*N*'-dioxide/Zn^{II} complexes. Proton shift preferentially occurred than silyl shift after α-alkenyl addition of silyl enol ether to ketimine. A wide range of *β*-amino silyl enol ethers were achieved in high yields with good to excellent *ee* values. Control experiments suggested that the Mukaiyama-Mannich reaction and tandem α-alkenyl addition/proton shift reaction were competitive reactions in the current catalytic system. Meanwhile, the obtained *β*-amino silyl enol ethers could be easily transformed into *β*-fluoroamines containing two vicinal tetrasubstituted carbon centers.

Silyl enol ethers are isolable and versatile intermediates serving as convenient carbonyl equivalent donors in organic synthesis due to their high reactivity and operability, which have enabled broad synthetic utilization.[1] In our previous studies on silyl enol ethers, several types of reactions were realized by using chiral Lewis acid catalysts, including [2+2] cycloaddition between alkynones and cyclic silyl enol ethers,[2] [4+2] cycloaddition of silyloxyvinylindoles with *β*,γ-unsaturated α-ketoesters[3] and so on.[4] To further expand the application of silyl enol ethers, we explored a reaction of silyl enol ethers with imines which anticipated Mukaiyama−Mannich reaction to afford the corresponding *β*-amino carbonyl compounds.[5-7] The reaction of cyclopentanone-derived silyl enol ether **1a** and isatin-derived ketimine **2a** underwent α-alkenyl addition of silyl enol ether to C=N double bonds of imine in the presence of the chiral *N,N'*-dioxide-metal complex, forming a zwitterionic intermediate **A**, subsequent silyl group shift[5b,8] from oxygen atom to nitrogen atom and rapid desilylation afforded the Mukaiyama−Mannich product **4a** (Scheme 1, path a). Actually, to our surprise, a mixture of *β*-amino ketone and *β*-amino silyl enol ether (**3a**) was serendipitously observed. We conceived that proton shift of the intermediate **A** took place to give the unexpected product **3a** (Scheme 1, path b).

The unexpected skeletal reorganization triggered our interest. To the best of our knowledge, the α-alkenyl addition of silyl enol ether to imine followed by proton shift has not been reported previously.[9] Herein, we wish to describe a chiral *N,N'*-dioxide/Zn^{II} complex[10] catalyzed enantioselective tandem α-alkenyl addition/proton shift process between silyl enol ethers and ketimines to give the desired enantiopure *β*-amino silyl enol ethers with high efficiency.



Scheme 1. Two pathways of the reaction of cyclopentanone-derived silyl enol ether **1** with isatin-derived ketimine **2a**.

After the preliminary investigation between silyl enol ether **1a** and ketimine **2a** (see Table S1−S3 in the SI for more details), we found that the reaction proceeded smoothly in CH_2Cl_2 at 35 °C with **L_2-RaPr$_2$**-Zn(OTf)$_2$ as the catalyst and **3a** was obtained in 86% yield and 92% *ee* (Table 1, entry 1). Decreasing the steric hindrance of the amide moiety improved the enantioselectivity, however, sharply decreased yield of **3a** and increased yield of byproduct **4a** were observed (entry 3 vs entries 1 and 2). Changing the reaction temperature to 40 °C in CH_2ClCH_2Cl, the substrate **2a** was completely transformed into **3a** within 3 hours, giving the same yield and *ee* value of **3a** (entry 4 vs entry 2). To our delight, the yield of **3a** could be increased to 85% without loss of the enantioselectivity (95% *ee*) by employing isopropanol as the additive (entry 5). Decreasing the steric hindrance of silyl group from TBS to TES and TMS, increased yields of Mukaiyama-Mannich byproduct **4a** were obtained (entries 5-7). It may because the large repulsion between TBS and Boc group of the amine make the proton shift favored to give the product **3a**.

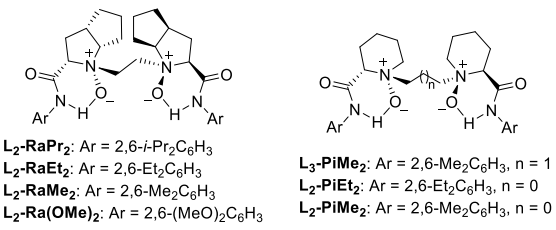


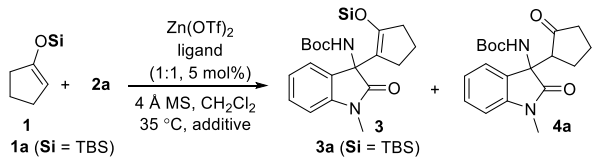
Figure 1. Ligands used in this study.

[a] T. F. Kang, Dr. W. D. Cao, L. Z. Hou, Q. Tang, S. J. Zou, Prof. Dr. X. H. Liu, Prof. Dr. X. M. Feng
Key Laboratory of Green Chemistry & Technology, Ministry of Education, College of Chemistry, Sichuan University, Chengdu 610064 (China)
E-mail: xmfeng@scu.edu.cn

Supporting information for this article is given via a link at the end of the document.((Please delete this text if not appropriate))

10.1002/anie.201810961

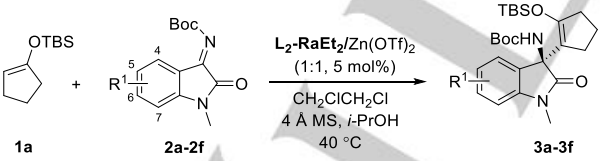
Table 1. Optimization of the reaction conditions.

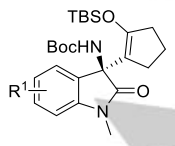


Entry[a]	ligand	Si	additive	t [h]	Yield [%][b] 3/4a	*Ee* [%][c] 3
1	**L$_2$-RaPr$_2$**	TBS	—	7	86/13	92
2	**L$_2$-RaEt$_2$**	TBS	—	7	68/27	95
3	**L$_2$-RaMe$_2$**	TBS	—	7	44/52	95
4[d]	**L$_2$-RaEt$_2$**	TBS	—	3	68/31	95
5[d][e]	**L$_2$-RaEt$_2$**	TBS	*i*-PrOH	3	85/14	95
6[d][e]	**L$_2$-RaEt$_2$**	TES	*i*-PrOH	9	76/22	95
7[d][e]	**L$_2$-RaEt$_2$**	TMS	*i*-PrOH	5	0/90	-

[a] Unless otherwise noted, the reactions were carried out with **2a** (0.10 mmol), **1a** (1.5 equiv), metal salt (5 mol%), ligand (5 mol%), solvent (0.1 M) and 4 Å MS (50 mg). MS = molecular sieve. [b] Isolated yields. [c] Determined by HPLC on a chiral stationary phase. [d] CH_2ClCH_2Cl (0.6 mL) was used at 40 °C instead of CH_2Cl_2. [e] *i*-PrOH (1.0 equiv) was added.

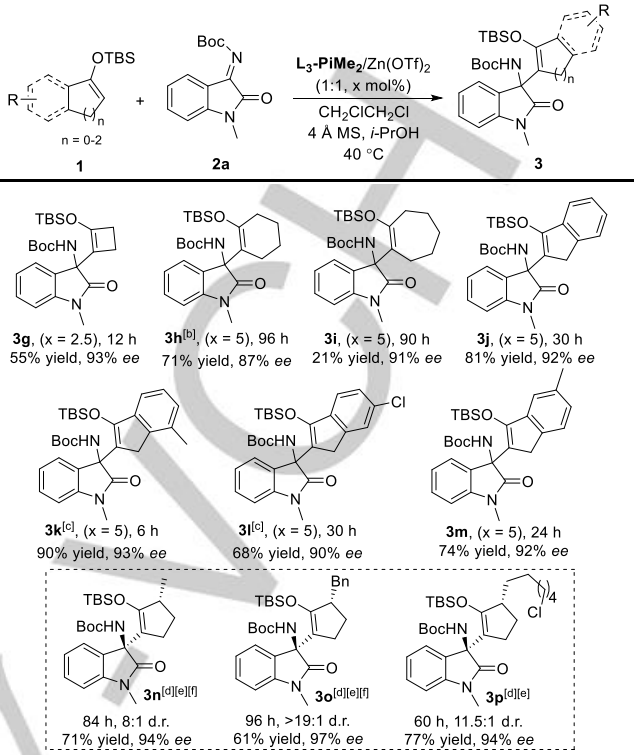
With the optimized conditions established (Table 1, entry 5), a series of isatin-derived ketimines **2** were probed to react with **1a**, giving the corresponding proton shift products **3a**–**3f** in high yields with excellent *ee* values (Scheme 2, 83–90% yields, 94–95% *ee*). Other isatin-derived ketimines with different protecting groups of the nitrogen atom, such as -Cbz and -CO_2Et, gave a little decreased yields and enantioselectivities which was likely attributed to the decreased steric hindrance compared with the Boc group. In addition, the low reactivities of aryl and -$SO_2{}^t$Bu protected ketimines could not give the target products (see Table S3 in the SI for details). The absolute configuration of product **3a** was determined to be *S* by X-ray crystallography analysis.[11] A gram-scale reaction between **1a** (6 mmol) and **2a** (4 mmol) provided **3a** in 86% yield with 95% *ee*.[12]





3a, R^1 = H, 3 h, 85% yield, 95% *ee*
3a[b], R^1 = H, 24 h, 86% yield, 95% *ee*
3b, R^1 = 5-I, 3 h, 88% yield, 94% *ee*
3c, R^1 = 5-Me, 12 h, 90% yield, 94% *ee*
3d, R^1 = 5-OMe, 4 h, 83% yield, 94% *ee*
3e, R^1 = 6-F, 3 h, 86% yield, 95% *ee*
3f, R^1 = 7-Br, 3 h, 87% yield, 94% *ee*

Scheme 2. Substrate scope of ketimines[a]. [a] Unless otherwise noted, all reactions were performed with **L$_2$-RaEt$_2$**/Zn(OTf)$_2$ (1:1, 5 mol%), **1a** (0.15 mmol), **2** (0.10 mmol), 4 Å MS (50 mg) and *i*-PrOH (1.0 equiv) in CH_2ClCH_2Cl (0.6 mL) at 40 °C. Yields are those of the isolated products. Chiral-phase HPLC analysis was used to determine *ee* values. [b] 4.0 mmol scale of **2a**.

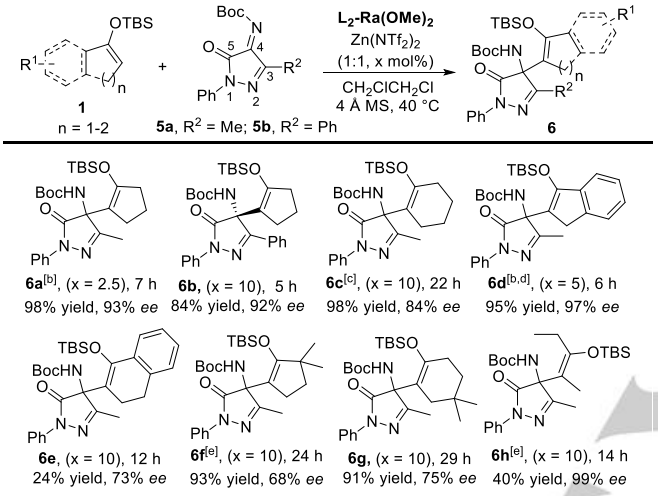


Scheme 3. Substrate scope of silyl enol ethers[a]. [a] Unless otherwise noted, all reactions were performed with **L$_3$-PiMe$_2$**/Zn(OTf)$_2$, **1a** (0.15 mmol), **2a** (0.10 mmol), 4 Å MS (50 mg) and *i*-PrOH (1.0 equiv) in CH_2ClCH_2Cl (0.6 mL) at 40 °C. [b] **L$_2$-PiEt$_2$** was used as ligand. [c] **L$_2$-PiMe$_2$** was used as ligand. [d] **1** (0.20 mmol). [e] D.r. was determined by HPLC or ^{1}H NMR analysis. [f] Isolated yield of major diastereoisomer.

Subsequently, we turned our attention to broadening the substrate scope of the silyl enol ethers (Scheme 3). Four-, six- and seven-membered cyclic silyl enol ethers were tolerated in this reaction and afforded the desired products **3g**-**3i** in 21−71% yields with 87−93% *ee*. 1-Indanone-derived substrates could be smoothly transformed into the corresponding products **3j**-**3m** in good yields (68–90%) with excellent *ee* values (90–93%). α′-Substituted cyclic silyl enol ethers were also tested in the current catalytic system. The silyl enol ethers bearing α′-methyl, benzyl, and chloro-alkyl underwent the reaction smoothly, delivering **3n**−**3p** in 61−77% yields, 8:1−>19:1 d.r. and 94−97% *ee*. Based on the experimental results (see Table S5 in the SI for more details), a kinetic resolution process of α′-substituted cyclic silyl enol ethers was proposed to explain the observed diastereoselectivities. The absolute configuration of the product **3n** was determined to be *S*,*R* by X-ray crystallography analysis.[11]

We next explored the tandem α-alkenyl addition/proton shift reaction between pyrazolinone-derived ketimines[13] and silyl enol ethers (Scheme 4). Under the optimized conditions (see Table S6 in the SI for detailed screening of the reaction conditions), 98% yield with 93% *ee* of **6a** could be obtained. Changing the substituent at C3-position of ketimine **5** from methyl to phenyl, the desired product **6b** was obtained in 84% yield with 92% *ee*. The absolute configuration of product **6b** was determined to be *R* by X-ray crystallography analysis.[11]

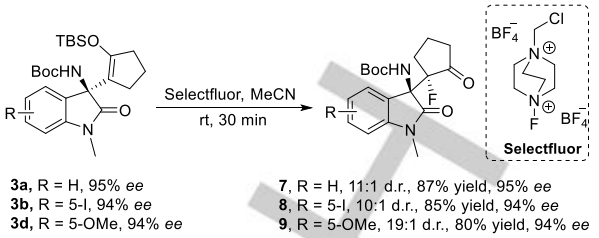
Cyclohexanone-derived cyclic silyl enol ether was also explored in the current catalytic system, providing the corresponding products **6c** in 98% yield with 84% *ee*. 1-Indanone-derived cyclic silyl enol ethers reacted with **5a** smoothly, delivering **6d** in excellent yield (95%) and *ee* value (97%). Only 24% yield and 73% *ee* of **6e** was obtained when 1-tetralone-derived silyl enol ether was utilized. Besides, α′,α′-dimethyl cyclopentanone- and γ,γ-dimethyl cyclohexanone-derived silyl enol ethers were also suitable nucleophiles to give the desired products **6f** and **6g** in 93% yield with 68% *ee* and 91% yield with 75% *ee*, respectively. It was worthy to note that acyclic silyl enol ether could also be transformed into the corresponding product **6h** in 40% yield with 99% *ee*.



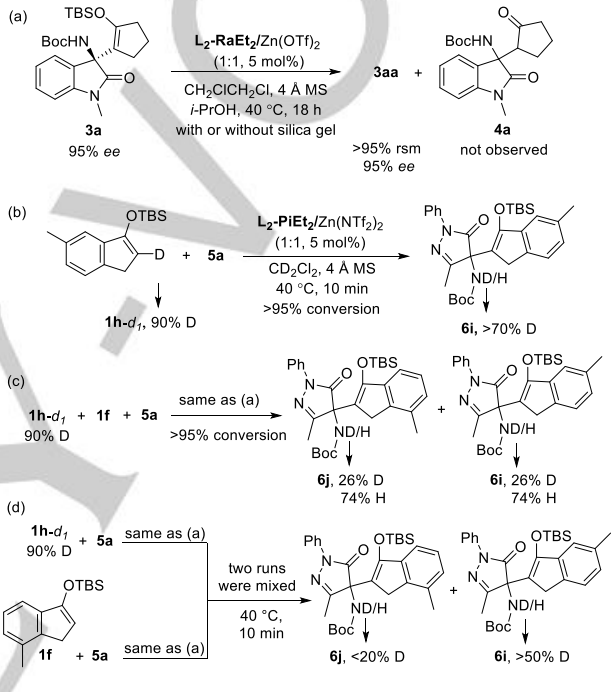
Scheme 4. Substrate scope for silyl enol ethers with pyrazolinone-derived ketimines[a]. [a] Unless otherwise noted, all reactions were performed with **L_2-Ra(OMe)$_2$**/Zn(NTf$_2$)$_2$, **1** (1.5 equiv), **5** (0.05 mmol) and 4 Å MS (25 mg) in CH_2ClCH_2Cl (0.6 mL) at 40 °C. [b] At −20 °C. [c] At 0 °C. [d] **L** = **L_2-PiEt$_2$**. [e] **L** = **L_2-RaMe$_2$**.

To show the synthetic utility of this methodology, the fluorination of α-alkenyl addition/proton shift products was carried out. β-Fluoroamine motif[14] is an important skeleton which is found in numerous of drug candidates.[15] Manipulating the β-amino silyl enol ethers **3a**, **3b** and **3d** with Selectfluor in acetonitrile at room temperature within 30 min afforded the chiral β-fluoroamines **7**−**9** in 80−87% yields, 10:1−>19:1 d.r. with maintained *ee* values, which contained two vicinal tetrasubstituted carbon centers (Scheme 5).[11]

To gain insight into the mechanism of tandem α-alkenyl addition/proton shift in the current catalytic system, control experiments were studied. No Mukaiyama-Mannich byproduct **4a** was observed when treating **3a** under the standard conditions with or without silica gel for 18 h (Scheme 6a). Additionally, when a tagged product of **3a**-d_2 was mixed with **1a** and **2a** under the optimized conditions, only trace amount of tagged **4a**-d_2 was detected (see Scheme S7 in the SI). These experimental results indicated that the Mukaiyama−Mannich reaction is a competitive reaction in this system, the possibility of Mukaiyama−Mannich product comes from **3a** is ruled out. To make clear the proton shift process, isotopic labeled **1h**-d_1 (90% D) reacted with **5a** in dichloromethane-d_2, affording the product



Scheme 5. The fluorination of the α-alkenyl addition/proton shift products.



Scheme 6. Control experiments and deuterium labeling studies.

6i with >70% D on the nitrogen atom of the formed amine which revealed that the H of NHBoc come from silyl enol ether indeed (Scheme 6b). In addition, the same H/D ratio (26% D) was observed in the products **6j** and **6i** when a cross-over experiment was conducted by treating the mixture of **1h**-d_1 and **1f** under the optimized conditions at 40 °C in CD_2Cl_2 (Scheme 6c). When **1h**-d_1 and **1f** severally reacted with **5a** in the presence of **L_2-PiEt$_2$**/Zn(NTf$_2$)$_2$ for 10 min and then they were mixed to stir for another 10 min, <20% D of **6j** and >50% D of **6i** were observed (Scheme 6d). These results proved that the proton shift in this reaction underwent an intermolecular process, and the inference was also in accordance with the experimental result that the addition of isopropanol could improve the yield of **3a** (Table 1, entry 5). Isopropanol may act as a medium of transmitting proton from carbon atom to nitrogen atom.

In summary, we have serendipitously discovered and developed the first catalytic asymmetric tandem α-alkenyl addition/proton shift reaction of silyl enol ethers with ketimines by utilizing chiral *N,N′*-dioxide/Zn^{II} complexes as the catalysts,

affording a wide range of β-amino silyl enol ethers in up to 98% yield and 99% *ee*. The desired products could be easily transformed into β-fluoroamines with high diastereo- and enantioselectivities under mild conditions. Deuterium labeling study suggested a key proton shift was involved in this reaction. Further studies on the mechanism of this reaction are ongoing.

Acknowledgements

We appreciate the National Natural Science Foundation of China (Nos. 21772127 and 21432006) and the Fundamental Research Funds for the Central Universities (No. 2012017yjsy101) for financial support.

Keywords: α-alkenyl addition • asymmetric catalysis • deuterium labeling • proton shift • tandem reaction

[1] (a) M. B. Boxer, B. J. Albert, H. Yamamoto, *Aldrichimica Acta* **2009**, *42*, 3-15; (b) L. M. Geary, P. G. Hultin, *Tetrahedron: Asymmetry* **2009**, *20*, 131-173; (c) T. Brodmann, M. Lorenz, R. Schäckel, S. Simsek, M. Kalesse, *Synlett* **2009**, 174-192; (d) J. Matsuo, M. Murakami, *Angew. Chem.* **2013**,*125*, 9280-9289; *Angew. Chem. Int. Ed.* **2013**, *52*, 9109-9118; (e) G. L. Beutner, S. E. Denmark, *Angew. Chem.* **2013**, *125*, 9256-9266; *Angew. Chem. Int. Ed*. **2013**, *52*, 2-13; (f) T. Kitanosono, S. Kobayashi, **2013**, *355*, 3095-3118; (g) S. B. J. Kan, K. K. H. Ng, I. Paterson, *Angew. Chem.* **2013**, *125*, 9267-9279; *Angew. Chem. Int. Ed.* **2013**, *52*, 9097-9108; (h) G. D. Roiban, A. Ilie, M. T. Reetz, *Chem. Lett.* **2014**, *43*, 2-10.

[2] T. F. Kang, S. L. Ge, L. L. Lin, Y. Lu, X. H. Liu, X. M. Feng, *Angew. Chem.* **2016***, 128*, 5631-5634; *Angew. Chem. Int. Ed.* **2016**, *55*, 5541-5544.

[3] X. H. Zhao, H. J. Mei, Q. Xiong, K. Fu, L. L. Lin, X. H. Liu, X. M. Feng, *Chem. Commun.* **2016**, *52*, 10692-10695.

[4] (a) S. K. Chen, Z. R. Hou, Y. Zhu, J. Wang, L. L. Lin, X. H. Liu, X. M. Feng, *Chem. Eur. J.* **2009**, *15*, 5884-5887; (b) K. Fu, J. F. Zheng, L. L. Lin, X. H. Liu, X. M. Feng, *Chem. Commun.* **2015**, *51*, 3106-3108; (c) K. Fu, J. C. Zhang, L. L. Lin, J. Li, X. H. Liu, X. M. Feng, *Org. Lett.* **2017**, *19*, 332-335.

[5] Selected examples of asymmetric Mukaiyama−Mannich reactions catalyzed by chiral Lewis acids: (a) S. Kobayashi, Y. Mori, J. S. Fossey, M. M. Salter, *Chem. Rev.* **2011**, *111*, 2626-2704; (b) H. Ishitani, M. Ueno, S. Kobayashi, *J. Am. Chem. Soc.* **1997**, *119*, 7153-7154; (c) S. Kobayashi, H. Ishitani, M. Ueno, *J. Am. Chem. Soc.* **1998**, *120*, 431-432; (d) E. Hagiwara, A. Fujii, M. Sodeoka, *J. Am. Chem. Soc.* **1998**. *120*, 2474-2475; (e) S. Xue, S. Yu, Y. Deng, W. D. Wulff, *Angew. Chem.* **2001**, *113*, 2331-2334; *Angew. Chem. Int. Ed.* **2001**, *40*, 2271-2274; (f) S. Kobayashi, M. Ueno, S. Saito, Y. Mizuki, H. Ishitani, Y. Yamashita, *Proc. Natl. Acad. Sci. USA* **2004**, *101*, 5476-5481; (g) S. Nakamura, H. Nakashima, H. Sugimoto, H. Sano, M. Hattori, N. Shibata, T. Toru, *Chem. Eur. J.* **2008**, *14*, 2145-2152.

[6] Selected examples of asymmetric Mukaiyama−Mannich reactions catalyzed by phosphoric acids: (a) T. Akiyama, Y. Saitoh, H. Morita, K. Fuchibe, *Adv. Synth. Catal.* **2005**, *347*, 1523-1526; (b) M. Yamanaka, J. Itoh, K. Fuchibe, T. Akiyama, *J. Am. Chem. Soc.* **2007**,*129*, 6756-6764; (c) J. Itoh, K. Fuchibe, T. Akiyama, *Synthesis* **2008**, 1319-1322; (d) T. Akiyama, T. Katoh, K. Mori, K. Kanno, *Synlett* **2009**, 1664-1666; (e) W. Kashikura, K. Mori, T. Akiyama, *Org. Lett.* **2011**, *13*, 1860-1863; (f) F. Zhou, H. Yamamoto, *Angew. Chem.* **2016**, *128*, 9116-9120; *Angew. Chem. Int. Ed.* **2016**, *55*, 8970-8974; (g) F. Zhou, H. Yamamoto, *Org. Lett.* **2016**, *18*, 4974-4977.

[7] Selected examples of other organocatalytic asymmetric Mukaiyama−Mannich reactions: (a) A. G. Wenzel, E. N. Jacobsen, *J. Am. Chem. Soc.* **2002**, *124*, 12964-12965; (b) A. Hasegawa, Y. Naganawa, M. Fushimi, K. Ishihara, H. Yamamoto, *Org. Lett.* **2006**, *8*, 3175-3178; (c) Q. Wang, M. Leutzsch, M. Gemmeren, B. List, *J. Am. Chem. Soc.* **2013**, *135*, 15334-15337; (d) C. D. Gheewala, B. E. Collins, T. H. Lambert, *Science* **2016**, *351*, 961-965; (e) J.-S. Yu, J. Zhou, *Org. Chem. Front.* **2016**, *3*, 298-303.

[8] For selected example on silyl group shift from oxygen atom to nitrogen atom: (a) H. Ishitani, T. Kitazawa, S. Kobayashi, *Tetrahedron Lett*. **1999**, *40*, 2161-2164; (b) H. Ishitani, M. Ueno, S. Kobayashi, *J. Am. Chem. Soc.* **2000**, *122*, 8180-8186; (c) H. Fujisawa, E. Takahashi, T. Mukaiyama, *Chem. Eur. J.* **2006**, *12*, 5082-5093.

[9] The α-alkenyl addition/proton shift process of silyl enol ether with fluoral was previously found. A. Ishii, J. Kojima, K. Mikami, *Org. Lett.* **1999**, *1*, 2013-2016.

[10] For reviews and selected examples: (a) X. H. Liu, L. L. Lin, X. M. Feng, *Acc. Chem. Res.* **2011**, *44*, 574-587; (b) X. H. Liu, L. L. Lin, X. M. Feng, *Org. Chem. Front.* **2014**. *1*, 298-302; (c) X. H. Liu, H. F. Zheng, Y. Xia, L. L. Lin, X. M. Feng, *Acc. Chem. Res.* **2017**, *50*, 2621-2631; (d) X. H. Liu, S. X. Dong, L. L. Lin, X. M. Feng, *Chin. J. Chem.* **2018**, *36*, 791-797; (e) Q. Yao, H. Zhang, H. Yu, Q. Xiong, X. H. Liu, X. M. Feng, *Org. Chem. Front.* **2017**, *4*, 2012-2015.

[11] Crystallographic data for **3a**, **3n**, **6b** and **7**: CCDC 1857353, 1857355, 1857361 and 1857362 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre.

[12] In the gram scale reaction, the byproduct **4a** was obtained in 13% yield, 6:1 d.r. and 80% *ee*/61% *ee.*

[13] For selected catalytic enantioselective examples on pyrazolinone-derived ketimines: (a) S. Mahajan, P. Chauhan, U. Kaya, K. Deckers, K. Rissanen, D. Enders, *Chem. Commun.* **2017**, *53*, 6633-6636; (b) P. Chauhan, S. Mahajan, U. Kaya, A. Peuronen, K. Rissanen, D. Enders, *J. Org. Chem.* **2017**, *82*, 7050-7058; (c) U. Kaya, P. Chauhan, S. Mahajan, K. Deckers, A. Valkonen, K. Rissanen, D. Enders, *Angew. Chem.* **2017**, *129*, 15560-15564; *Angew. Chem. Int. Ed.* **2017**, *56*, 15358-15362; (d) Z. Yang, W. Yang, L. Chen, H. Sun, W. Deng, *Adv. Synth. Catal.* **2018**, *360*, 2049-2054.

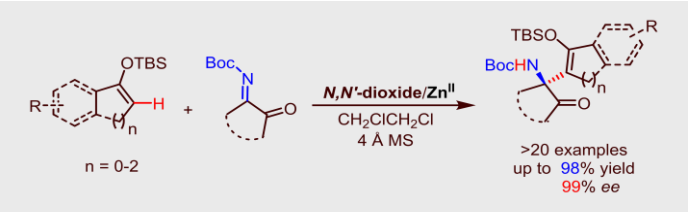
[14] Selected examples on catalytic asymmetric methods accessing to β-fluoroamine building blocks: (a) X. Yang, T. Wu, R. J. Phipps, F. D. Toste, *Chem. Rev.* **2015**, *115*, 826-870; (b) O. O. Fadeyi, C. W. Lindsley, *Org. Lett.* **2009**, *11*, 943-946; (c) C. Appayee, S. E. Brenner-Moyer, *Org. Lett.* **2010**, *12*, 3356-3359. (d) J. Wu, Y. Wang, A. Drljevic, V. Rauniyar, R. J. Phipps, F. D. Toste, *Proc. Natl. Acad. Sci. USA* **2013**, *110*, 13729-13733; (e) H. P. Shunatona, N. Früh, Y. Wang, V. Rauniyar, F. D. Toste, *Angew. Chem.* **2013**, *125*, 7878-7881; *Angew. Chem. Int. Ed.* **2013**, *52*, 7724-7727; (f) J. A. Kalow, A. G. Doyle, *Tetrahedron* **2013**, *69*, 5702-5709; (g) X. Liu, J. Zhang, L. Zhao, S. Ma, D. Yang, W. Yan, R Wang, *J. Org. Chem.* **2015**, *80*, 12651-12658; (h) B. M. Trost, T. Saget, A. Lerchen, C.-I. Hung, *Angew. Chem.* **2016***, 128, 791-794; Angew. Chem. Int. Ed.* **2016**, *55*, 781-784; (i) B. Li, D.-M. Du, *Adv. Synth. Catal.* **2018**, *360*, 3164-3170.

[15] (a) T. C. Nugent, *Chiral Amine Synthesis: Methods, Develepments and Applications*. Wiley-VCH: Weinheim, Germany (**2010**); (b) T. K. Murray, K. Whalley, C. S. Robinson, M. A. Ward, E. A. Hicks, D. Lodge, J. L. Vandergriff, P. Baumbarger, E. Siuda, M. Gates, A. M. Ogden, P. Skolnick, D. M. Zimmerman, E. S. Nisenbaum, D. Bleakman, M. J. O'neill, *J. Pharmacol. Exp. Ther.* **2003**, *306*, 752-762.

10.1002/anie.201810961

WILEY-VCH

COMMUNICATION



*Tengfei Kang, Weidi Cao, Liuzhen Hou, Qiong Tang, Sijia Zou, Xiaohua Liu, Xiaoming Feng**

Page No. – Page No.

Chiral Zn^{II} Complex Catalyzed Enantioselective Tandem α-Alkenyl Addition/Proton Shift Reaction of Silyl Enol Ethers with Ketimines

We have developed an efficient route to the synthesis of optically *β*-amino silyl enol ethers via α-alkenyl addition/proton shift process of silyl enol ethers to ketimines. Good to excellent enantioselectivities with a broad substrate scope were achieved catalyzed by chiral *N,N'*-dioxide/Zn^{II} complexes. Deuterium labeling study suggested a key proton shift process was involved in this reaction. This case provides an easy access to enantiopure *β*-fluoroamines with two vicinal tetrasubstituted carbon centers.