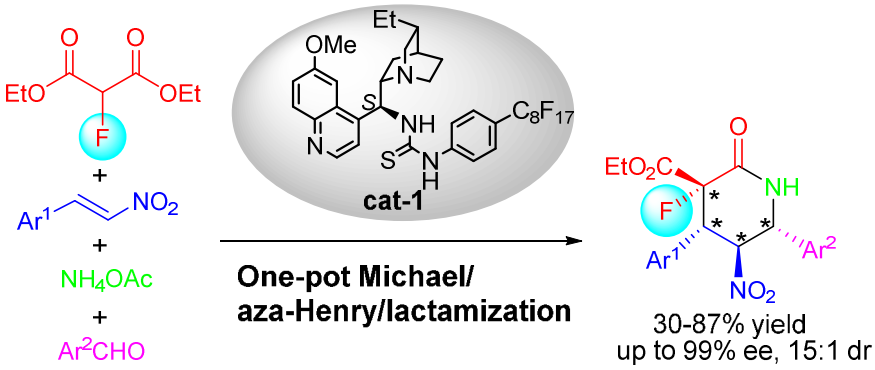
RSC Advances

ROYAL SOCIETY OF CHEMISTRY

www.rsc.org/advances

Graphical abstract



Journal Name

COMMUNICATION

Recyclable Organocatalyst-promoted One-pot Michael/aza-Henry/lactamization Reactions for Fluorinated 2-Piperidinones Bearing Four Stereogenic Centres

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

DOI: 10.1039/x0xx00000x

www.rsc.org/

Xin Huang,[a] Kenny Pham,[a] Xiaofeng Zhang,[a] Wen-Bin Yi,[b] Jeremy H. Hyatt,[a] Anthony P. Tran,[a] Jerry P. Jasinski,[c] and Wei Zhang*[a]

A one-pot Michael/aza-Henry/lactamization reaction promoted by recyclable fluorous bifunctional cinchona alkaloid/thiourea organocatalyst has been developed for asymmetric synthesis of fluorine-containing 2-piperidinones bearing four stereogenic centers. The asymmetric Michael adducts induce the formation of other three stereogenic centers to afford products with up to 99% ee and 15:1 dr.

The 2-piperidinone (δ-lactam) moiety[1] can be found in a number of natural products and biologically active compounds such as awajanomycin **A**,[2] tedanalactam **B**,[3] meloscine **C**,[4] MDM2 inhibitor AM-8553 **D**,[5] as well as fluorine-containing H3 receptor antagonist **E**[6] and androgen receptor **F** (Fig. 1).[7] Introduction of fluorine atom could have significant impact on molecule's biological activity. It is an active topic in medicinal and agricultural chemistry.[8] Chiral 2-piperidinones are a key building block for compounds with medical utility.[9] Optical enriched β-lactams can be prepared by arrange of methods[10] including enolate-imine condensations,[11] Kinugasa reactions,[12] intramolecular C–H insertion reactions,[13] and Staudinger reactions.[14] Synthesis of chiral δ-lactam, however, is less explored. Reported methods include lactamization of chiral precursors[15] and asymmetric cycloaddition of electron-deficient olefins.[16,17] Introduced in this paper is a new method for fluorinated 2-piperidinones by integration of asymmetric Michael addition, aza-Henry, and lactamization into a one-pot reaction process.

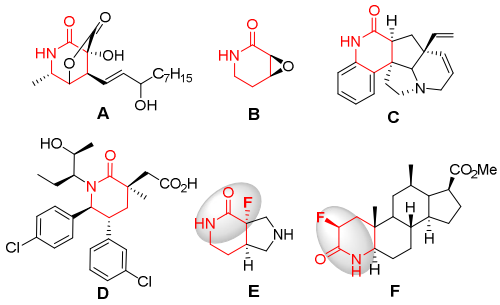
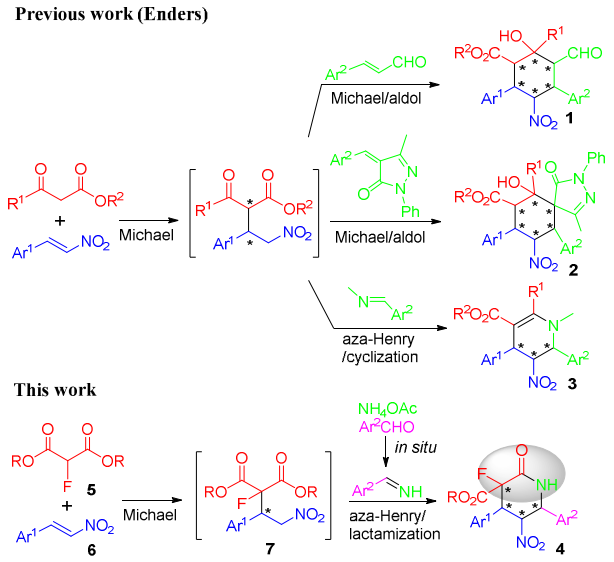


Fig. 1 Biologically active 2-piperidinones

There are several recent publications on organocatalytic asymmetric synthesis of 6-membered carbon- and nitrogen-containing ring systems[18] such as dihydropyridinones,[19] piperidinones,[20] and dihydroquinolinones[21] through the sequences involving Michael, Mannich, Henry, and aldol reactions.[22,23] The Enders group reported 1,3-dicarbonyl compound-based Michael/Michael/aldol sequence for hexasubstituted cyclohexanols **1**[24] and spirocyclohexanepyrazolones **2** (Scheme 1).[25] They also reported a Michael/aza-Henry/cyclization sequence for *N*-methyl tetrahydropyridines **3**.[26] However, only alkylated imines were used for the aza-Henry reaction. We like to introduce here



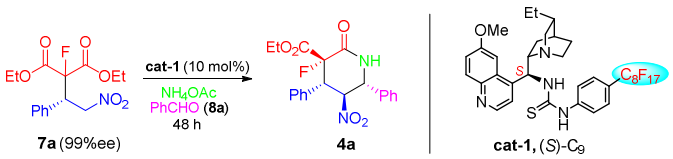
Scheme 1 1,3-Dicarbonyl-based sequential reactions

[a] Department of Chemistry, University of Massachusetts Boston, 100 Morrissey Boulevard, Boston, MA 02125, USA. E-mail: wei2.zhang@umb.edu
[b] School of Chemical Engineering, Nanjing University of Science and Technology, Nanjing 210094, China
[c] Department of Chemistry, Keene State College, Keene, NH 03435-2001, USA
Electronic Supplementary Information (ESI) available: [details of any supplementary information available should be included here]. See DOI: 10.1039/x0xx00000x

Journal Name

COMMUNICATION

Table 1 Optimization of aza-Henry and lactamization reactions[a]



7a (99%ee) **4a**

Entry	Base (equiv)	Solvent	T (°C)	**4a** Yield (%)[b]	dr[c]	ee (%)[d]
1	K_2CO_3 (0.5)	EtOH	25	trace	nd	nd
2	Cs_2CO_3 (0.5)	EtOH	25	trace	nd	nd
3	NaOH (0.5)	EtOH	25	23	5:5:1	nd
4	piperidine (0.5)	EtOH	25	42	6:1	98
5	piperidine (0.5)	EtOH	40	72	6:1	98
6	piperidine (0.25)	EtOH	40	36	6:1	98
7	piperidine (0.75)	EtOH	40	68	6:1	98
8	piperidine (0.5)	EtOH	0	75	1.25:1	93(89)[e]
9	piperidine (0.5)	EtOH	60	75	1.25:1	nd
10	piperidine (0.5)	PhMe	40	27	5:1	98
11	piperidine (0.5)	CH_2Cl_2	40	12	nd	nd
12	piperidine (0.5)	MeCN	40	10	nd	nd
13[f]	piperidine (0.5)	EtOH	40	68	5:3:1	25

[a] Reaction of 0.2 mmol **7a** in 1.0 mL of solvent, 1:1:1.2 of **7a**:**8a**:NH_4OAc. [b] Yield of isolated product. [c] Determined by ^1H NMR. [d] Determined by HPLC on Venusil chiral OD-H column with 90:10 hexane/*i*-PrOH as a mobile phase. [e] ee of the minor diastereomer. [f] Without catalyst.

a Michael/aza-Henry/lactamization sequence for fluorinated 2-piperidinones **4** using *in-situ* generated imines as aza-Henry donors. The recyclable fluorous organocatalyst-promoted reaction efficiently produces tetrasubstituted 2-piperidinones bearing four stereogenic centres.

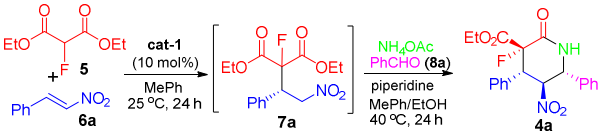
Step-economic one-pot reactions, toxic transition metal-free organocatalysis, and catalyst recovery are favourable green synthetic techniques. As part of our continuous efforts to develop recyclable fluorous organocatalysts[27] for asymmetric synthesis of organofluorine compounds,[28] we have recently reported a one-pot fluorination and Michael addition reaction for α-fluorinated and alkylated 1,3-dicarbonyl compounds **7**.[29] The reaction was promoted with fluorous bifunctional cinchona alkaloid/thiourea organocatalyst **cat-1**. It could be easily recovered by fluorous solid-phase extraction (F-SPE).[30] Since the fluorinated carbon of the 1,3-dicarbonyl compounds **5** is more acidic and nucleophilic, they are favourable Michael donors for **6**. We envisioned that compounds **7** could be suitable for the Michael/aza-Henry/lactamization sequence to form fluorinated 2-piperidinones **4**.

We first explored the aza-Henry and sequential lactamization reactions of enantiomerically pure Michael adduct **7a** (99% ee),[28a,b] benzaldehyde **8a**, and NH_4OAc by using **cat-1** as a catalyst (Table 1).[29] After screening bases (K_2CO_3, Cs_2CO_3, NaOH, piperidine) and solvents (EtOH, MePh, CH_2Cl_2, MeCN) at temperatures between 0 to 60 °C, we found the optimized condition of using 0.5 equiv. of piperidine as a base and EtOH as a solvent at 40 °C for 48 h. It gave fluorinated 2-piperidinone **4a** in 72% yield with 6:1 diastereoselectivity and 98% ee (Table 1, entry 5). The reaction with NaOH afforded the product with three diastereomers in a ratio of 5:5:1 (Table 1, entry 3). Reactions at higher temperatures (50 to 60 oC) were able to increase product yields to 75% but decreased the diastereomeric ratio to 1.25:1 (entries 8 and 9). A reaction using toluene as a solvent gave the product in high dr and ee, but with a low yield (entry 10). A control reaction without using a catalyst gave three diastereomeric products (5:3:1) in low ee (25%) (entry 13).

The success of the asymmetric aza-Henry/lactamization reactions encouraged us to develop the Michael/aza-Henry/lactamization sequence (Table 2). Commercially available 2-fluoro-1,3-diester **5** was used as a starting material. Toluene was found a good solvent for the Michael reaction,[29] and EtOH was the choice for the aza-Henry reaction. After the Michael reaction was over, EtOH was added to the reaction mixture for the sequential aza-Henry reaction. The best solvent

ratio was 1:2 PhMe:EtOH (Table 2, entry 8). The best ratio of the reactants was 1.5:1:1:1.2 **5**:**6a**:PhCHO:NH_4OAc. The time for the aza-Henry and lactamization reactions could be reduced from 48 to 24 h.

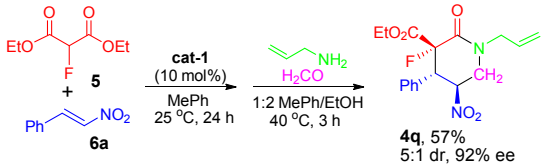
Table 2 Optimization of Michael/aza-Henry/lactamization reactions[a]



Entry	**5**:**6a**	MePh/EtOH[b]	Yield (%)[c]	dr[d]	ee (%)[e]
1	1:1	1:0	22	5:1	98
2	1:1	1:0.5	39	5:1	98
3	1:1	1:1	47	6:1	99
4	1:1	1:1.5	65	6:1	99
5	1:1	1:2	67	6:1	99
6	1:1	1:2.5	65	6:1	99
7	1.25:1	1:2	72	6:1	99
8	1.5:1	1:2	78	6:1	99
9	2:1	1:2	69	6:1	99

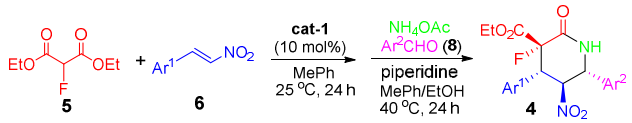
[a] Reaction of 0.1 mmol of **6a** in 0.5 mL of MePh. [b] Ratio of solvents for the 2nd reaction. [c] Yield of isolated product **4a**. [d] Determined by ^{1}H NMR. [e] Determined by HPLC on Venusil Chiral OD-H column

Reactions with different nitroalkenes **6** and benzaldehydes **8** were carried out to explore the scope of the one-pot reactions (Table 3). Benzaldehydes **8** with electron-withdrawing groups (F, Br, NO_2, CF_3) at the para-position gave products **4b-e** in 83-87% yields with >8:1 dr and >96% ee (Table 3, entries 2-5). Benzaldehydes **8** with an electron-donating group such as *t*-Bu and OMe or disubstituted groups gave products **4f-i** in 30-62% yields and 2:1 to 4:1 dr due to unfavorable stereoelectronic effect (Table 3, entries 6-9). Reactions of nitroalkenes bearing different Ar^1 groups gave products **4j-m** in 55-69% yields and 3:1 to 3.5:1 dr (entries 10-13). A reaction of nitroalkene bearing a furyl ring gave product **4n** in good yield and enantioselectivity (entry 14). Similar results were obtained from the reactions with 4-bromobenzaldehyde and other substituted nitroalkenes (entries 15-16). A reaction using formaldehyde and allylamine was also attempted. Highly reactive formaldehyde reduced the time of the aza-Henry reaction to 3 h and gave *N*-allylated 2-piperidinone **4q** in 57% yield with a good dr and ee (Scheme 2). The configuration of four stereogenic centers of 2-piperidinones **4** was assigned by the investigation of related Michael addition products reported in literature[23-25,31] and also by obtaining X-ray single crystal structure of **4c** (Fig. 2).



Scheme 2 Synthesis of N-alkylated 2-piperidinone **4q**

Table 3 Scope of the one-pot Michael/aza-Henry/lactamization reactions[a,b]



Entry	Product	Ar^1	Ar^2	Yield (%)[c]	dr[d]	ee (%)[e]
1	**4a**	C_6H_5	C_6H_5	78	6:1	99
2	**4b**	C_6H_5	4-FC_6H_4	85	8:1	98
3	**4c**	C_6H_5	4-BrC_6H_4	87	10:1	96
4	**4d**	C_6H_5	4-$NO_2C_6H_4$	83	10:1	96
5	**4e**	C_6H_5	4-$CF_3C_6H_4$	85	15:1	97
6	**4f**	C_6H_5	4-^{t}butylC_6H_4	35	4:1	97
7	**4g**	C_6H_5	4-$OMeC_6H_4$	30	4:1	95
8	**4h**	C_6H_5	2,3-ClC_6H_3	55	3.5:1	97
9	**4i**	C_6H_5	4-F,3-$OMeC_6H_3$	62	2:1	93(90)[f]
10	**4j**	3-ClC_6H_4	C_6H_5	65	3:1	90
11	**4k**	4-BrC_6H_4	C_6H_5	68	3.5:1	93
12	**4l**	4-MeC_6H_4	C_6H_5	55	5:1	95
13	**4m**	4-$OMeC_6H_4$	C_6H_5	69	3:1	91(90)[f]
14	**4n**	2-Furyl	C_6H_5	62	3.5:1	96(99)[f]
15	**4o**	4-BrC_6H_4	4-BrC_6H_4	67	4:1	99
16	**4p**	4-$OMeC_6H_4$	4-BrC_6H_4	65	3:1	98(99)[f]

[a] Reaction of 0.1 mmol of **6** in 0.5 mL of MePh. [b] Add 1.0 mL of EtOH for the aza-Henry reaction, 1.5:1:1:1.2 of **5**:**6**:**8**:NH_4OAc. [c] Yield of isolated product. [d] Determined by ^{1}H NMR. [e] Determined by HPLC on chiral column with hexane/*i*-PrOH as the eluent. [f] ee of the minor diastereomer.

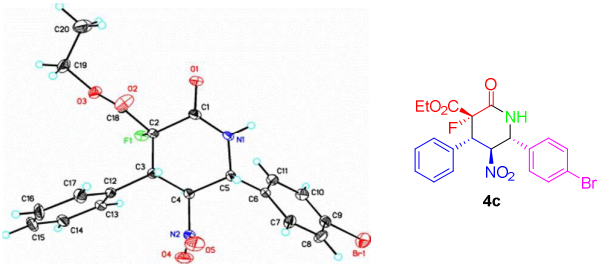
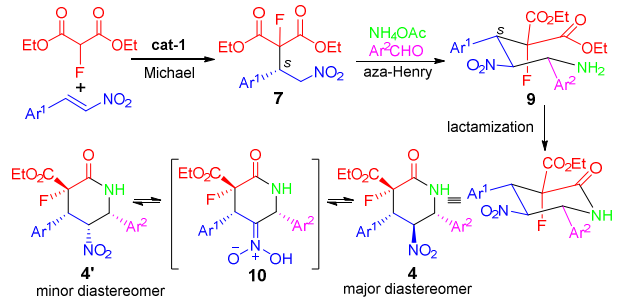


Fig. 2 X-ray crystal structure of **4c**

In the one-pot Michael/aza-Henry/lactamization reactions, fluorous **cat-1** with an (*S*)-C9 stereogenic centre induces the Michael addition to form **7** (Scheme 3). This compound undergoes the aza-Henry reaction with a benzaldehyde and NH_4OAc to form compound **9** which is then cyclized to form 2-piperidinone **4** bearing four stereogenic centres. Since only two diastereomers were detected in most cases, the minor diastereomer **4'** could be a tautomer of major diastereomer **4** through the formation of *N*-oxide oxime 10.[32]



Scheme 3 Stereochemistry of the one-pot reactions

Synthesis of **4a** was carried out using 0.5 mmol of **6a** and 30 mg of **cat-1** to evaluate catalyst recovery. After completion of the one-pot reactions, the concentrated reaction mixture was loaded onto a fluorous SPE cartridge. The cartridge was eluted with 80:20 MeOH/H_2O for product and other none-fluorous components, and then with MeOH for **cat-1**. Product **4a** was obtained in 79% yield with 6:1 dr and 99% ee. The catalyst was recovered in 94% yield (28.3 mg) and 98% purity.

In summary, we have developed a recyclable fluorous organocatalyst-promoted one-pot Michael/aza-Henry/lactamization sequence for asymmetric synthesis of fluorinated 2-piperidinones. This one-pot reaction of fluorinated 1,3-diester, *β*-nitroolefins, aldehydes and amines gave products bearing four stereogenic centres in good yields and excellent stereoselectivity. The organocatalyst could be recovered by simple F-SPE. This simple reaction process provides a highly efficient way for making novel polysubstituted chiral 2-piperidinones.

Notes and references

1 Selected examples: (*a*) A. R. MacKenzie, A. P. Marchington, D. S. Middleton, S. D. Newman and B. C. Jones, *J. Med. Chem.,* 2002, **45**, 5365; (*b*) S. Nara, R. Tanaka, J. Eishima, M. Hara, Y. Takahashi, S. Otaki, R. J. Foglesong, P. F. Hughes, S. Turkington and Y. Kanda, *J. Med. Chem.*, 2003, **46**, 2467; (*c*) D. S. Middleton, A. R. MacKenzie, S. D. Newman, M. Corless, A. Warren, A. P. Marchington and B. C. Jones, *Bioorg. Med. Chem. Lett.*, 2005, **15**, 3957; (*d*) A. Kaiser, D. Ulmer, T. Goebel, U. Holzgrabe, M. Saeftel and A. Hoerauf, *Mini-Rev. Med. Chem.*, 2006, **6**, 1231; (*e*) Z. Pei, X. Li, W. T. Von Geldern, K. Longenecker, D. Pireh, D. K. Stewart, J. B. Backes, C. Lai, H. T. Lubben, J. S. Ballaron, W. A. D. Beno, J. A. Kempf-Grote, L. H. Sham and M. J. Trevillyan, *J. Med. Chem.*, 2007, **50**, 1983; (*f*) B. S. Lucas, B. Fisher, L. R. McGee, S. H. Olson, J. C. Medina and E. J. Cheung, *J. Am. Chem. Soc.*, 2012, **134**, 12855; (*g*) Y. Rew, D. Sun, F. Gonzalez-Lopez De Turiso, M. D. Bartberger, H. P. Beck, J. Canon, A. Chen, D. Chow, J. Deignan, B. M. Fox, D. Gustin, X. Huang, M. Jiang, X. Jiao, L. Jin, F. Kayser, D. J. Kopecky, Y. Li, M. C. Lo, A. M. Long, K. Michelsen, J. D. Oliner, T. Osgood, M. Ragains, A. Y. Saiki, S. Schneider, M. Toteva, P. Yakowec, X. Yan, Q. Ye, D. Yu, X. Zhao, J. Zhou, J. C. Medina and S. H. Olson, *J. Med. Chem.* 2012, **55**, 4936.

2 J. H. Jang, K. Kanoh, K. Adachi and Y. Shizuri, *J. Nat. Prod.*, 2006, **69**, 1358.

3 M. S. Majik, P. S. Parameswaran and S. G. Tilve, *J. Org. Chem.*, 2009, **74**, 6378.

4 (*a*) K. Bernauer, G. Englert, W. Vetter and E. Weiss, *Helv. Chim. Acta*, 1969, **52**, 1886; (*b*) W. E. Oberhaensli, *Helv. Chim. Acta*, 1969, 52, 1905; (*c*) M. Daudon, H. Mehri, M. M. Plat, E. W. Hagaman, F. M. Schell and E. Wenkert, *J. Org. Chem.,* 1975, **40**, 2838.

5 D. Bernard and Y. S. Zhao, *J. Med. Chem.*, 2012, **55**, 4934.

6 L. Tan, B. T. Dorner, W. Li, N. Yasuda and F. W. Hartner, WO/2006/121655, 2006.

7 W. Shi, Z. Bai, X. Chen, X. Zhang, Y. Xiao, H. He and S. Chen, CN102952139, 2013.

8 Selected book and reviews: (*a*) I. Ojima Ed., Fluorine in Medicinal Chemistry and Chemical Biology, Wiley-Blackwell, Chichester, 2009; (*b*) K. Mikami, Y. Itoh and M. Yamanaka, *Chem. Rev.*, 2004, **104**, 1; (*c*) H. Ibrahim and A. Togni, *Chem. Commun.,* 2004, 1147; (*d*) R. Smits, C. D. Cadicamo and K. Burger, B. Koksch, *Chem. Soc. Rev.,* 2008, **37**, 1727; (*e*) J. Ma and D. Cahard, *Chem. Rev.*, 2004, **104**, 6119; (*f*) G. Valero, X. Companyo and R. Rios, *Chem. Eur. J.*, 2011, **17**, 2018; (*g*) N. Shibata, T. Ishimaru, S. Nakamura and T. Toru, *J. Fluorine Chem.*, 2007, **128**, 469; (*h*) J. H. Lin and J. C. Xiao, *Tetrahedron Lett.* 2014, **55**, 6147.

9 (*a*) J. B. Koepfly and J. F. Mead, J. A. Brockman, *J. Am. Chem. Soc.*, 1947, **69**, 1837; (*b*) G. Ratle, X. Monseur, B. C. Das, J. Yassi, Q. Khuong-Huu and R. Goutarel, *Bull. Soc. Chim. Fr.,* 1966, **9**, 2945; (*c*) M. C. Desai, S. L. Lefkowitz, P. F. Thadeio, K. P. Longo and R. M. Snider, *J. Med. Chem.*, 1992, **35**, 4911.

10 (*a*) C. R. Pitts and T. Lectka, *Chem. Rev*., 2014, **114**, 7930; (*b*) S. France, A. Weatherwax, A. E. Taggi and T. Lectka, *Acc. Chem. Res.,* 2004, **37**, 592; (*c*) P. A. Magriotis, *Eur. J. Org. Chem.*, 2014, 2647.

11 (*a*) K. Tomioka, H. Fujieda, S. Hayashi, M. A. Hussein, T. Kambara, Y. Nomura, M. Kanai and K. Koga, *Chem. Commun.*, 1999, 715; (*b*) S. Hata, T. Iwasawa, M. Iguchi, K. Yamada and K. Tomioka, *Synthesis* 2004, 1471; (*c*) L. Hao, S. Chen, J. Xu, B. Tiwari, Z. Fu, T. Li, J. Lim and Y. R. Chi, *Org. Lett.*, 2013, **15**, 4956; (*d*) S. R. Smith, J. Douglas, H. Prevet, P. Shapland, A. M. Z. Slawin and A. D. Smith, *J. Org. Chem.*, 2014, **79**, 1626.

12 (*a*) M. M. C. Lo and G. C. Fu, *J. Am. Chem. Soc.*, 2002, **124**, 4572; (*b*) R. Shintani and G. C. Fu, *Angew. Chem., Int. Ed.*, 2003, **42**, 4082; (*c*) M. C. Ye, J. Zhou and Y. Tang, *J. Org. Chem.*, 2006, **71**, 3576; (*d*) T. F. Knopfel and E. M. Carreira, *J. Am. Chem. Soc.*, 2003, **125**, 6054; (*e*) J. H. Chen, S. H. Liao, X. L. Sun, Q. Shen and Y. Tang, *Tetrahedron,* 2012, **68**, 5042; (*f*) B. Baeza, L. Casarrubios and M. A.

Sierra, *Chem. Eur. J.,* 2013, **19**, 11536; (*g*) S. Stecko, B. Furman and M. Chmielewski, *Tetrahedron,* 2014, **70**, 7817.

13 M. Anada, N. Watanabe and S. Hashimoto, *Chem. Commun.,* 1998, 1517.

14 (*a*) E. C. Lee, B. L. Hodous, E. Bergin, C. Shih and G. C. Fu, *J. Am. Chem. Soc.,* 2005, **127**, 11586; (*b*) H.-M. Zhang, Z.-H. Gao and S. Ye, *Org. Lett.*, 2014, **16**, 3079.

15 (*a*) N. A. White, D. A. DiRocco and T. Rovis, *J. Am. Chem. Soc.,* 2013, **135**, 8504; (*b*) D. Guijarro, Ó. Pablo and M. Yus, *J. Org. Chem.*, 2013, **78**, 3647; (*c*) A. Albrecht, F. Morana, A. Fraile and K. A. Jørgensen, *Chem. Eur. J.*, 2012, **18**, 10348.

16 (*a*) Y. He, T.-R. Kang, Z.-Q. Liu, L.-M. Chen, Y.-L. Tu, Y.-J. Liu, T.-B. Chen, Z.-Q. Wang, J. Liu, Y.-M. Xie, J.-L. Yang and L. He, *Org. Lett.*, 2013, **15**, 4054; (*b*) H. Suga, Y. Hashimoto, S. Yasumura, R. Takezawa, K. Itoh and A. Kakehi, *J. Org. Chem.*, 2013, **78**, 10840; (*c*) D. Xie, L. Yang, Y. Lin, Z. Zhang, D. Chen, X. Zeng and G. Zhong, *Org. Lett.,* 2015, **17**, 2318; (*d*) J. Cheng, Z. Huang and Y. B. Chi, *Angew. Chem. Int. Ed.,* 2013, 52, 8592.

17 (*a*) Z. Chen, L. Lin, D. Chen, J. Li, X. Liu and X. Feng, *Tetrahedron Lett.*, 2010, **51**, 3088; (*b*) J. Itoh, K. Fuchibe and T. Akiyama, *Angew. Chem. Int. Ed.,* 2006, **45**, 4796; (*c*) N. T. Kipassa, H. Okamura, K. Kina, T. Hamada and T. Iwagawa, *Org. Lett.*, 2008, **10**, 815; (*d*) X. Zhao, K. E. Ruhl and T. Rovis, *Angew. Chem. Int. Ed.,* 2012, **51**, 12330.

18 Selected papers: (*a*) K. C. Nicolaou, D. J. Edmonds and P. G. Bulger, *Angew. Chem. Int. Ed.,* 2006, **45**, 7134; (*b*) D. Enders, C. Grondal and M. R. M. Hüttl, *Angew. Chem. Int. Ed.*, 2007, **46**, 1570; (*c*) A. M. Walji and D. W. C. MacMillan, *Synlett,* 2007, 1477; (*d*) J. Vesely and R. Rios, *Curr. Org. Chem.*, 2011, **15**, 4046; (*e*) X. Yang, J. Wang and P. Li, *Org. Biomol. Chem.*, 2014, **12**, 2499; (*f*) X. Yu and W. Wang, *Org. Biomol. Chem.*, 2008, **6**, 2037; (*g*) C. Grondal, M. Jeanty and D. Enders, *Nat. Chem.*, 2010, **2**, 167; (*h*) A. Moyano and R. Rios, *Chem. Rev.,* 2011, **111**, 4703; (*i*) Ł. Albrecht, H. Jiang and K. A. Jørgensen, *Angew. Chem. Int. Ed.*, 2011, **50**, 8492; (*j*) A. Grossmann and D. Enders, *Angew. Chem. Int. Ed.*, 2012, **51**, 314; (*k*) H. Pellissier, *Adv. Synth. Catal.*, 2012, **354**, 237; (*l*) L. Q. Lu, J. R. Chen and W. J. Xiao, *Acc. Chem. Res.*, 2012, **45**, 1278; (*m*) S. Goudedranche, W. Raimondi, X. Bugaut, T. Constantieux, D. Bonne and J. Rodriguez, *Synthesis*, 2013, **45**, 1909; (*n*) P. Chauhan and D. Enders, *Angew. Chem. Int. Ed.*, 2014, **53**, 1485; (*o*) P. Chauhan, S. Mahajan, U. Kaya, D. Hack and D. Enders, *Adv. Synth. Catal.*, 2015, **357**, 253.

19 (*a*) B. Wanner, J. Mahatthananchai and J. W. Bode, *Org. Lett.*, 2011, **13**, 5378; (*b*) L. Hao, S. Chen, J. Xu, B. Tiwari, Z. Fu, T. Li, J. Lim and Y. R. Chi, *Org. Lett.* 2013, **15**, 4956; (*c*) J. Xu, Z. Jin and Y. R. Chi, *Org. Lett.*, 2013, **15**, 5028.

20 (*a*) Z. Pei, X. Li, T. W. von Geldern, K. Longenecker, D. Pireh, K. D. Stewart, B. J. Backes, C. Lai, T. H. Lubben, S. J. Ballaron, D. W. A. Beno, A. J. Kempf-Grote, H. L. Sham and J. M. Trevillyan, *J. Med. Chem.,* 2007, **50**, 1983; (*b*) P. S. Hynes, P. A. Stupple and D. J. Dixon, *Org. Lett.*, 2008, **10**, 1389; (*c*) P. Jakubec, M. Helliwell and D. J. Dixon, *Org. Lett.*, 2008, **10**, 4267; (*d*) P. Jakubec, D. M. Cockfield, M. Helliwell, J. Raftery and D. J. Dixon, *Beilstein J. Org. Chem.,* 2012, **8**, 567.

21 (*a*) Y. J. Yang, H. R. Zhang, S. Y. Zhu, P. Zhu and X. P. Hui, *Org. Lett.*, 2014, **16**, 5048; (*b*) O. D. Engl, S. P. Fritz, A. Kaslin and H. Wennemers, *Org. Lett.,* 2014, **16**, 5454.

22 Selected papers: (*a*) Ł. Albrecht, H. Jiang and K. A. Jørgensen, *Angew. Chem. Int. Ed.*, 2011, **50**, 8492; (*b*) S. Goudedranche, W. Raimondi, X. Bugaut, T. Constantieux, D. Bonne and J. Rodriguez, *Synthesis*, 2013, **45**, 1909; (*c*) C. M. R. Volla, I. Atodiresei and M. Rueping, *Chem. Rev.,* 2014, **114**, 2390; (*d*) P. Chauhan, G. Urbanietz, G. Raabe and D. Enders, *Chem. Commun.*, 2014, **50**, 6853; (*e*) P. Chauhan, S. Mahajan, G. Raabe and D. Enders, *Chem. Commun.*, 2015, **51**, 2270; (*f*) B. Han, W. Huang, W. Ren, G. He, J. Wang and C. Peng, *Adv. Synth. Catal.*, 2015, **357**, 561.

23 Selected reviews: (*a*) C. Simon, T. Constantieux and J. Rodriguez, *Eur. J. Org. Chem.*, 2004, 4957; (*b*) D. Bonne, Y. Coquerel, T. Constantieux and J. Rodriguez, *Tetrahedron: Asymmetry*, 2010, **21**, 1085.

24 D. Enders, G. Urbanietz, E. Cassens-Sasse, S. Keeß and G. Raabe, *Adv. Synth. Catal.*, 2012, **354**, 1481.

25 P. Chauhan, S. Mahajan, C. C. J. Loh, G. Raabe and D. Enders, *Org. Lett.,* 2014, **16**, 2954.

26 M. Blümel, P. Chauhan, R. Hahn, G. Raabe and D. Enders, *Org. Lett.,* 2014, **16**, 6012.

27 (*a*) W. Zhang, *Top. Curr. Chem.*, 2012, 308, 175; (*b*) Q. Chu, W. Zhang and D. P. Curran, *Tetrahedron Lett.*, 2006, **47**, 9287; (*c*) L. Wang, C. Cai, D. P. Curran and W. Zhang, *Synlett*, 2010, **3**, 433.

28 (*a*) W. B. Yi, X. Huang, Z. Zhang, D. Zhu, C. Cai and W. Zhang, *Beilstein J. Org. Chem.*, 2012, **8**, 1233; (*b*) X. Huang, W. B. Yi, D. Ahad and W. Zhang, *Tetrahedron Lett.*, 2013, **54**, 6064.

29 W. B. Yi, Z. Zhang, X. Huang, A.; Tanner, C. Cai and W. Zhang, *RSC Adv.*, 2013, **3**, 18267.

30 W. Zhang and D. P. Curran, *Tetrahedron*, 2006, **62**, 11837.

31 (*a*) A. M. Flock, A. Krebs, C. Bolm, *Synlett*, 2010, 1219; (*b*) D. Enders, G. Urbanietz and G. Raabe, *Synthesis*, 2011, 1905.

32 H. Liu, Z. Zhou, Q. Sun, Y. Li, Y. Li, J. Liu, P. Yan, D. Wang and C. Wang, *ACS Comb. Sci.*, 2012, **14**, 366.