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Enantioselective Synthesis of 3-Substituted 1,2-Oxazinanes Via Organocatalytic Intramolecular Aza-Michael Addition

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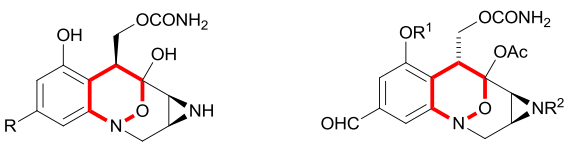
A highly enantioselective intramolecular *6-exo-trig* aza-Michael addition was developed to afford chiral 3-substituted 1,2-oxazinanes in high yields (up to 99% yield) and good enantioselectivities (up to 98/2 er). These reactions were enabled by a quinine-derived primary-tertiary diamine as a catalyst and pentafluoropropionic acid (PFP) as a co-catalyst.

Chiral 1,2-oxazinanes are valuable chiral building blocks frequently seen in various biologically active compounds[1] (Figure 1). For example, the natural products FR900482 (**1**) and FR66979 (**2**) exhibit anticancer activity. Both FK973 (**3**)[2] and FK317 (**4**),[3] the semisynthetic derivatives of FR900482 (**1**), have shown highly promising antitumor activity in human clinical trials in Japan.[2] Chiral 1,2-oxazinanes also possess remarkable synthetic utilities and are often manipulated via a reductive N−O bond cleavage to form functionalized chiral 1,4-amino alcohols found in a number of bioactive natural products.



1. FR900482 R = CHO
2. FR66979 R = CH_2OH
3. FK973, $R^1 = R^2$ = Ac
4. FK317, R^1 = Me, R^2 = Ac

Figure 1 Structures of FR900482 (**1**) and congeners (**2**-**4**).

Due to the importance of the 1,2-oxazinane, several strategies have been developed to achieve this motif.[4-7] For example, Yamamoto and co-workers reported a general route for 1,2-oxazinanes using the sequential nitroso aldol/Michael addition of cyclic enones (Scheme 1A).[5a,b] Sibi group synthesized 1,2-oxazinanes via the addition of nitrones to activated cyclopropanes (Scheme 1B).[5c] Zhong *et al* developed organocatalytic asymmetric domino α-aminoxylation/aza-Michael reactions for the synthesis of functionalized 1,2-oxazinanes.[6] Very recently, Sun and Lin reported a asymmetric α-aminoxylation/aza-Michael/Mannich cascade reaction for the construction of fully substituted chiral 1,2-oxazinane derivatives.[7]

As a powerful tool to prepare enantioenriched nitrogen hetereocycles,[8] the organocatalytic intramolecular aza-Michael addition has achieved significant progresses recently.[9] As a part of our ongoing projects on intramolecular aza-Michael additions and

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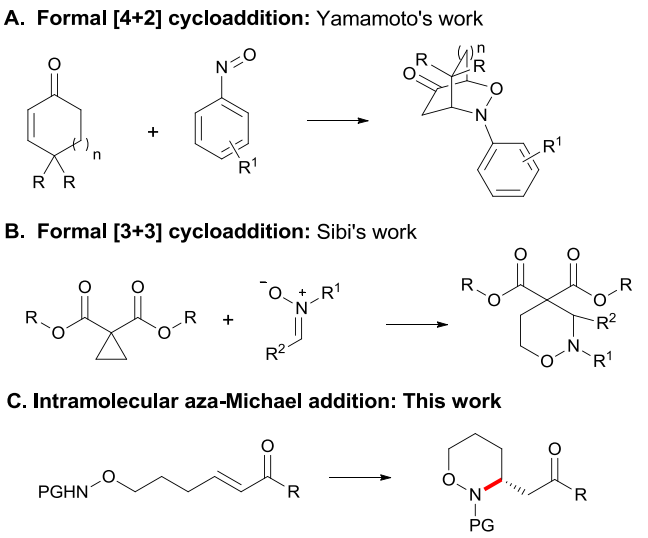
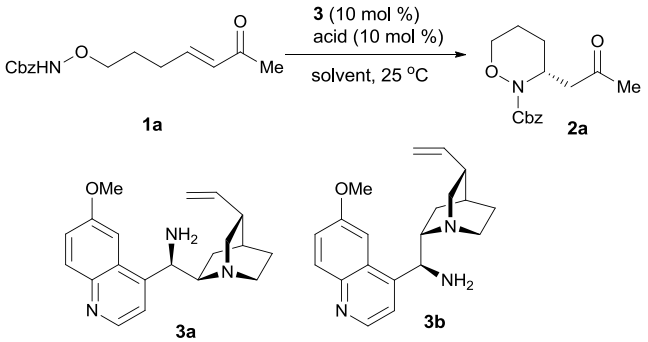
their application in the total synthesis of alkaloids,[10] we envisaged that chiral 1,2-oxazinane derivatives could also been synthesized by 6-*exo* aza-Michael addition of hydroxylamine-derived enones (Scheme 1C). Herein we would like to report a highly enantioselective synthesis of 3-substituted 1,2-oxazinanes using organocatalytic *6-exo* aza-Michael addition.



Scheme 1 Strategies for synthesis of 1,2-oxazinane derivatives.

A chiral catalyst salt formed *in situ* from quinidine-derived primary-tertiary diamine **3a** and trifluoroacetic acid (TFA) was firstly employed to promote the aza-Michael addition of hydroxylamine-derived enone **1a** in THF. To our delight, the catalytic system was highly efficient at room temperature and the desired aza-Michael adduct **2b** was isolated in 94% yield and 8/92 er value (Table 1, entry 1). The acids played an important role in the conversation and stereocontrol of this aza-Michael addition reaction. When other acids, such as TfOH, TsOH•H_2O, $PhCO_2H$, D-CSA, Cl_3CCO_2H and $MeSO_3H$, were used as co-catalysts, poorer yields and lower stereoselectivities were obtained (Table 1, entries 2-7). Notably, the aza-Michael addition was operated in 89% yield and 5/95 er value using $CF_3CF_2CO_2H$ (PFP) (Table 1, entry 8). When **3a** was replaced with quinine-derived primary-tertiary diamine **3b**, nearly quantitative yield and better enantioselectivity (96/4 er value) were achieved (Table 1, entry 9). Then the solvent was evaluated using **3b** as the catalyst and PFP as the co-catalyst (Table 1, entries 10-13). Among the solvents tested, 1,4-dioxane was found to be most suitable solvent with 99% chemical yield and 98/2 er value (Table 1, entry 11).

Table 1 Conditions screening.[a]



Entry	3	Acid	Solvent	Yield/%[b]	Er[c]
1	**3a**	TFA	THF	94	8/92
2	**3a**	TfOH	THF	31	51/49
3	**3a**	TsOH•H_2O	THF	47	25/75
4	**3a**	$PhCO_2H$	THF	<5	ND
5	**3a**	D-CSA	THF	40	15/85
6	**3a**	Cl_3CCO_2H	THF	26	15/85
7	**3a**	$MeSO_3H$	THF	21	14/86
8	**3a**	PFP	THF	89	5/95
9	**3b**	PFP	THF	99	96/4
10	**3b**	PFP	$CHCl_3$	99	95/5
11	**3b**	**PFP**	**1,4-dioxane**	**99**	**98/2**
12	**3b**	PFP	CH_3CN	56	81/19
13	**3b**	PFP	Toluene	99	95/5

[a]Reaction conditions: A solution of **1a** (0.1 mmol), **3** (0.01 mmol) and acid (0.01 mmol) in the indicated solvent (1 mL) was stirred at 25 °C for 2 d. [b]Isolated yield. [c]The er values were determined by HPLC on chiral stationary phase. ND = not determined.

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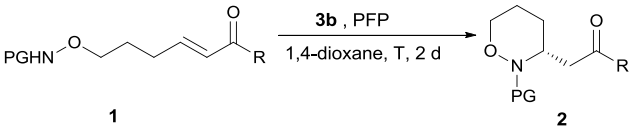
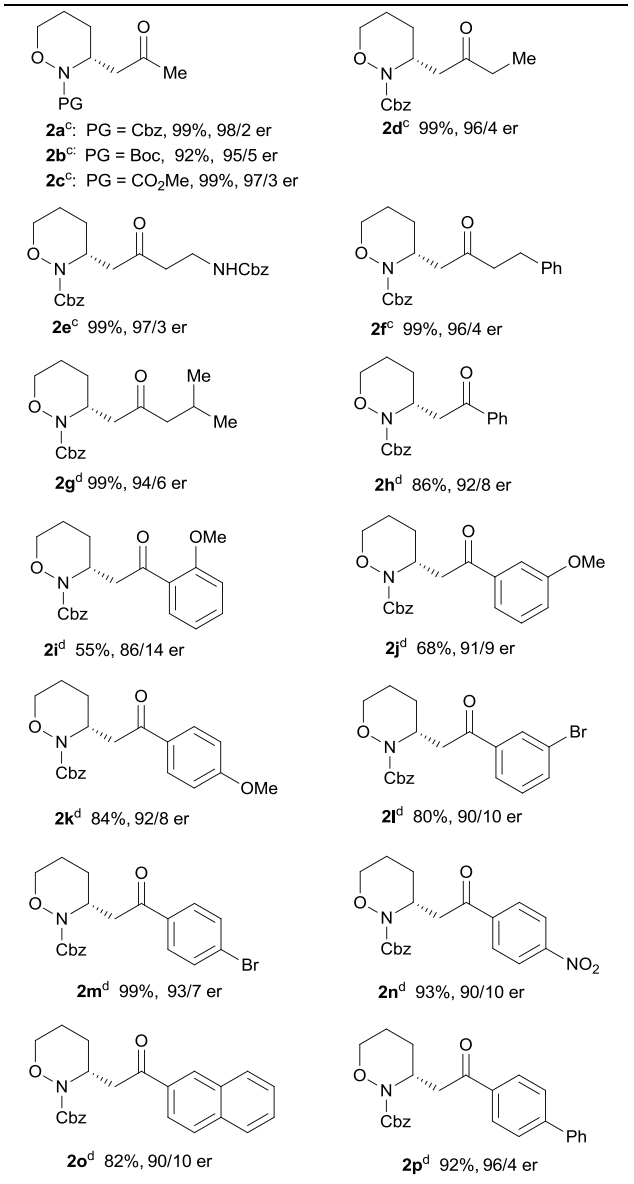
Table 2 Substrates scope.[a,b]

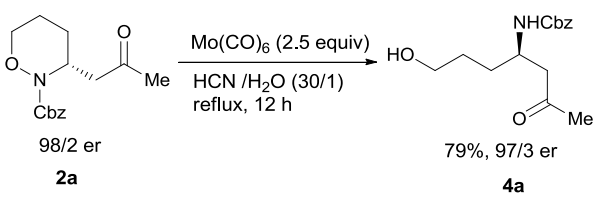




[a]Isolated yield. [b]The er values were determined by HPLC on chiral stationary phase. [c]Reaction conditions: a solution of **1** (0.1 mmol), **3b** (10 mol %) and PFP (10 mol %) in 1 mL of 1,4-dioxane was stirred at 25 °C for 2 d. [d]Reaction conditions: a solution of **1** (0.1 mmol), **3b** (20 mol %) and PFP (20 mol %) in 1 mL of 1,4-dioxane was stirred at 60 °C for 2 d.

With the optimized reaction conditions in hand, we next explored the scope of this transformation (Table 2). All of the substrates could afford the corresponding products in good to excellent yields and good enantioselectivities under the optimized reaction conditions. The protecting group on the nitrogen had significant influence on the outcome of this reaction. Methoxycarbonyl group was as good as Cbz group and Boc group gave lower yield and er value (**2a-c**). Less hindered aliphatic enones were active substrates and could undergo this reaction with perfect yields and pretty good enantioselectivities (**2d-f**). The reaction with bulky aliphatic enone, such as *i*-butyl, was sluggish. However satisfactory result (99% yield and 94/6 er value for **2g**) could be gotten with more catalyst and co-catalyst (20 mol %) at 60 °C. Aromatic enones were less effective substrates than their aliphatic counterparts. The aza-Michael could take place and the desired 1,2-oxazinanes (**2h-p**) could be generated with slightly lower yields (55-92% yields) and acceptable er values (90/10-96/4 er). Electronic property of substituents on the aromatic rings did not affect this reaction significantly (see **2k, m, n** and **p**). Steric effect had dramatic impact on the results of this reaction. More hindered substrates gave poorer yields and er values (see **2i-k**).

The chiral 1,2-oxazinanes are good precursors for enantio-enriched 1,4-amino alcohol via N-O bond cleavage. For example, the chiral 1,2-oxazinane **2a** could be reduced by $Mo(CO)_6$ to the corresponding chiral 1,4-amino alcohol **4a** in 79% yield without affecting the stereochemistry and optical purity (Scheme 2).[11] Our method presented here provides a powerful route to chiral 1,4-amino alcohols, which are potential chiral building blocks for the synthesis of biologically active molecules. [12]



Scheme 2 N-O bond cleavage of the chiral 3-substituted 1,2-oxazinane **2a**.

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In order to account for the stereochemical outcome of this reaction, a mechanistic rationale was proposed (Figure 2). First, the primary amine moiety of catalyst would react with the enone to form an iminium ion. Simultaneously the tertiary amine would interact with amide hydrogen of hydroxylamine through a hydrogen bond. The transition state A is disfavoured due to the additional interaction between the hydroxylamine moiety with quinoline ring of the catalyst. Hydrogen bond of the favoured transition state B directs the nucleophilic attack from *Re* face, which leads to the (*R*)-1,2-oxazinane. The absolute configuration of **2n** was established unambiguously by a single crystal X-ray diffraction analysis.[13]

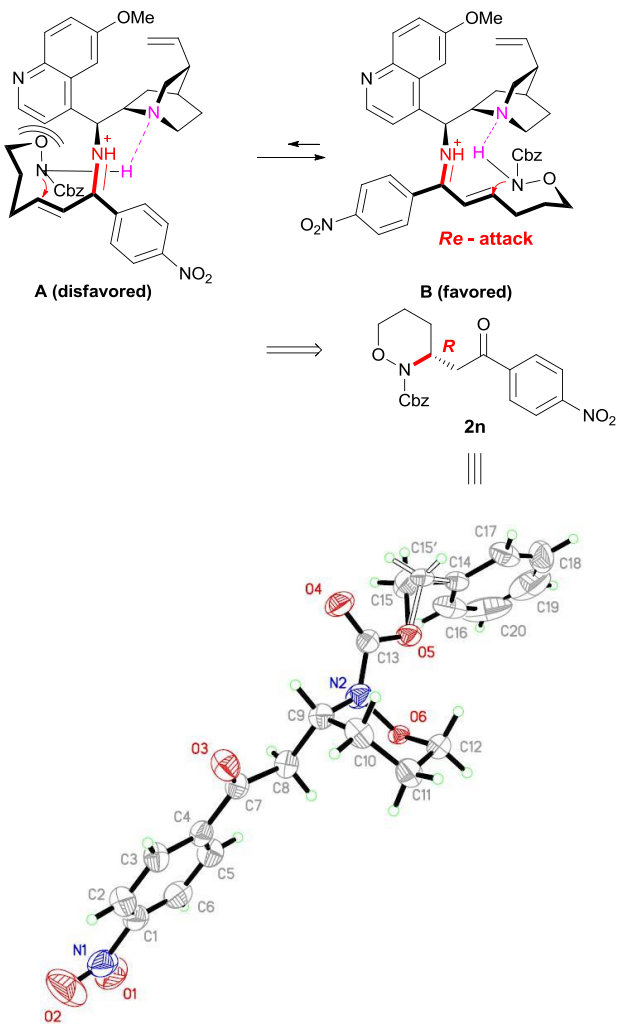

Figure 2 Proposed mechanistic model.

In summary, an asymmetric synthesis of chiral 3-substituted 1,2-oxazinanes with hydroxylamine-derived enones *via* intramolecular *6-exo-trig* aza-Michael addition was developed. This method provides an access to chiral 3-substituted 1,2-oxazinane derivatives in good to excellent yields (up to 99%) and er values (up to 98/2) under mild conditions. The method features operational convenience, high efficiency and well tolerance with various substrates. The 1,2-oxazinanes can be transformed into the chiral amino alcohol derivatives, which are useful chiral building blocks for the synthesis of biologically active natural and unnatural compounds.

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Notes and references

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Electronic Supplementary Information (ESI) available: Full experimental procedures; ^{1}H and ^{13}C NMR spectra of new compounds. For ESI and crystallographic data in CIF or other electronic format See DOI: 10.1039/c000000x/.

1 For selected examples, see: (*a*) P. G. Tsoungas, *Heterocycles*, 2002, **57**, 915; (*b*) R. Pulz, A. Al-Harrasi and H.-U. Reißig, *Org. Lett.*, 2002, **4**, 2353; (*c*) A. A. Tishkov, H.-U. Reißig and S. L. Loffe, *Synlett*, 2002, 863; (*d*) M. Buchholz and H.-U. Reißig, *Eur. J. Org. Chem.*, 2003, 3524; (*e*) A. Al-Harrasi and H.-U. Reißig, *Angew. Chem., Int. Ed.*, 2005, **44**, 6227; For the total synthesis of (+)-phyllantidine from a cyclopropane, see: (*f*) C. A. Carson and M. A. Kerr, *Angew. Chem., Int. Ed.*, 2006, **45**, 6560; (*g*) Q.-S. Yu, X. Zhu, H. W. Holloway, N . F. Whittaker, A. Brossi and N. H. Greig, *J. Med. Chem.*, 2002, **45**, 3684; (*h*) T. C. Judd and R. M. Williams, *Angew. Chem., Int. Ed.*, 2002, **41**, 4683; (*i*) M. Suzuki, J. Kambe, H.

Organic & Biomolecular Chemistry Accepted Manuscript

This journal is © The Royal Society of Chemistry 2012

Tokuyama and T. Fukuyama, *Angew. Chem., Int. Ed.*, 2002, **41**, 4686; (*j*) T. Katoh, E. Itoh, T. Yoshino and S. Terashima, *Tetrahedron* 1997, **53**, 10229; (*k*) I. Uchida, S. Takase, H. Kayakiri, S. Kiyoto, M. Hashimoto, T. Tada, S. Koda and Y. Morimoto, *J. Am. Chem. Soc*., 1987, **109**, 4108; (*l*) P. D. Bass, D. A. Gubler, T. C. Judd and R. M. Williams, *Chem. Rev*., 2013, **113**, 6816; For a selected review, see: (*m*) A. Y. Sukhorukov and S. L. Ioffe, *Chem. Rev.*, 2011, **111**, 5004.

2 (*a*) K. Shimomura, T. Manda, S. Mukumoto, K. Masuda, T. Nakamura, T. Mizota, S. Matsumoto, F. Nishigaki, T. Oku, J. Mori and F. Shibayama, *Cancer Res*., 1988, **48**, 1166; (*b*)T . Nakamura, K. Masuda, S. Matsumoto, T. Oku, T. Manda, J. Mori and K. Shimomura, *Jpn. J. Pharmacol*., 1989, **49**, 317; (*c*) K. Masuda, T. Nakamura, T. Mizota, J. Mori and K. Shimomura, *Cancer Res*., 1988, **48**, 5172; (*d*) K. Masuda, T. Nakamura and K. Shimomura, *J. Antibiot*., 1988, **41**, 1497.

3 (*a*) Y. Naoe, M. Inami, S. Matsumoto, F. Nishigaki, S. Tsujimoto, I. Kawamura, K. Miyayasu, T. Manda and K. Shimomura, *Cancer Chemother. Pharmacol*., 1998, **42**, 31; (*b*) Y. Naoe, M. Inami, I. Kawamura, F. Nishigaki, S. Tsujimoto, S. Matsumoto, T. Manda, K. Shimomura, *Jpn. J. Cancer Res*., 1998, **89**, 666; (*c*) Y. Naoe, M. Inami, S. Takagaki, S. Matsumoto, I. Kawamura, F. Nishigaki, S. Tsujimoto, T. Manda and K. Shimomura, *Jpn. J. Cancer Res*., 1998, **89**, 1047; (*d*) Y. Naoe, M. Inami, S. Matsumoto, S. Takagaki, T. Fujiwara, S. Yamazaki, I. Kawamura, F. Nishigaki, S. Tsujimoto, T. Manda and K. Shimomura, *Jpn. J. Cancer Res*., 1998, **89**, 1306; (*e*) Y. Naoe, I. Kawamura, M. Inami, S. Matsumoto, F. Nishigaki, S. Tsujimoto, T. Manda and K. Shimomura, *Jpn. J. Cancer Res*., 1998, **89**, 1318; (*f*) M. Inami, I. Kawamura, S. Tsujimoto, F. Nishigaki, S. Matsumoto, Y. Naoe, Y. Sasakawa, M. Matsuo, T. Manda and T. Goto, *Cancer Lett*., 2002, **181**, 39.

4 (*a*) P. F. Vogt and M. J. Miller, *Tetrahedron*, 1998, **54**, 1317; (*b*) S. E. Denmark and A. Thorarensen, *Chem. Rev*., 1996, **96**, 137; (*c*) X. Ding, Y. Ukaji, S. Fujinami and K. Inomata, *Chem. Lett*., 2003, **32**, 582; (*d*) K. Koide, J. M. Finkelstein, Z. Ball and G. L. Verdine, *J. Am. Chem. Soc*., 2001, **123**, 398; (*e*) I. S. Young and M. A. Kerr, *Angew. Chem. Int. Ed*., 2003, **42**, 3023; (*f*) I. S. Young and M. A. Kerr, *Org. Lett*., 2004, **6**, 139; (*g*) M. D. Ganton and M. A. Kerr, *J. Org. Chem*., 2004, **69**, 8554; (*h*) S. Kumarn, D. M. Shaw, D. A. Longbottom and S. V. Ley, *Org. Lett.*, 2005, **7**, 4189; (*i*) S. Kumarn, D. M. Shaw and S. V. Ley, *Chem. Commun*., 2006, 3211; (*j*) N. Vemula; A. C. Stevens; T. B. Schon and B. L. Pagenkopf, *Chem. Commun*., 2014, **50**, 1668.

5 (*a*) Y. Yamamoto, N. Momiyama and H. Yamamoto, *J. Am. Chem. Soc*., 2004, **126**, 5962;(*b*) N. Momiyama, Y. Yamamoto and H. Yamamoto, *J. Am. Chem. Soc*., 2007, **129**, 1190; (*c*) M. P. Sibi, Z. H. Ma and C. P. Jasperse, *J. Am. Chem. Soc*., 2005, **127**, 5764.

6 (*a*) M. Lu, D. Zhu, Y. Lu, Y. Hou, B. Tan and G. Zhong, *Angew. Chem., Int. Ed*., 2008, **47**, 10187; (*b*) D. Zhu, M. Lu, P. J. Chua, B. Tan, F. Wang, X. Yang and G. Zhong, *Org. Lett*., 2008, **10**, 4585.

7 H. Lin, X. Sun and G. Lin, *Org. Lett*., 2014, **16**, 752.

8 For recent reviews on asymmetric aza-Michael additions, see: (*a*) M. Liu and M. P. Sibi, *Tetrahedron*, 2002, **58**, 7991; (*b*) L.-W. Xu and C.-G. Xia, *Eur. J. Org. Chem.*, 2005, 633; (*c*) J. L. Vicario, D. Bada, L. Carrillo, J. Etxebarria, E. Reyes and N. Ruiz, *Org. Prep. Proced. Int.*, 2005, **37**, 513; (*d*) J. L. Vicario, D. Bada and L. Carrillo, *Synthesis*, 2007, 2065; (*e*) P. R. Krishna, A. Sreeshailam and R. Srinivas, *Tetrahedron*, 2009, **65**, 9657; (*f*) D. Enders, C. Wang and J. X. Liebich, *Chem. Eur. J*., 2009, **15**, 11058; (*g*) S. Fustero, M. Snchez-Rosell and C. del Pozo, *Pure Appl. Chem*., 2010, **82**, 669; (*h*) A. Y. Rulev, *Russ. Chem. Rev*., 2011, **80**, 197; (*i*) J. Wang, P. F. Li, P. Y. Choy, A. S. C. Chan and F. Y. Kwong, *ChemCatChem*, 2012, **4**, 917; (*j*) Z. Amara, J. Caron and D. Joseph, *Nat. Prod. Rep*., 2013, **30**, 1211.

9 For organocatalytic *exo*-type aza-Michael additions, see: (*a*) K. Takasu, S. Maiti and M. Ihara, *Heterocycles*, 2003, **59**, 51; (*b*) S. Fustero, D. Jiménez, J. MoscardÓ, S. Catalán and C. del Pozo, *Org. Lett*., 2007, **9**, 5283; (*c*) E. C. Carlson, L. K. Rathbone, H. Yang, N. D. Collett and R. G. Carter, *J. Org. Chem*., 2008, **73**, 5155; (*d*) S. Fustero, J. MoscardÓ, D. Jiménez, M. D. PérezCarriÓn, M. SánchezRosellÓ and C. del Pozo, *Chem. Eur. J*., 2008, **14**, 9868; (*e*) Q. Cai, C. Zheng and S.-L. You, *Angew. Chem. Int. Ed*., 2010, **49**, 8666; (*f*) Q. Gu and S.-L. You, *Chem. Sci*., 2011, **2**, 1519; (*g*) J.-D. Liu, Y.-C. Chen, G.-B. Zhang, Z.-Q. Li, P. Chen, J.-Y. Du, Y.-Q. Tu and C.-A. Fan, *Adv. Synth. Catal*., 2011, **353**, 2721; (*h*) S. Fustero, C. del Pozo, C. Mulet, R. Lazaro and M. Sánchez-Rosellá, *Chem. Eur. J*., 2011, **17**, 14267; (*i*) R. Miyaji, K. Asano and S. Matsubara, *Org. Lett*., 2013, **15**, 3658.

10 (*a*) C. Zeng, H. Liu, M. Zhang, J. Guo, S. Jiang and S. Yu, *Synlett*, 2012, **23**, 2251; (*b*) H. Liu, C. Zeng, J. Guo, M. Zhang and S. Yu, *RSC Adv*.,

Organic & Biomolecular Chemistry Accepted Manuscript

2013, **3**, 1666; (*c*) S. Cheng, L. Zhao and S. Yu, *Adv. Synth. Catal*., 2014, **356**, 982; (*d*) J. Guo, X. Sun and S. Yu, *Org. Biomol. Chem.*, 2014, **12,** 265.

11 R. Yamasaki, K. Kato, D. Hanitani, Y. Mutoh and S. Saito, *Tetrahedron Lett*., 2013, **54**, 3507.

12 (*a*) I. S. Young, J. L. Williams and M. A. Kerr, *Org. Lett.*, 2005, **7**, 953; (*b*) I. S. Young and M. A. Kerr, *J. Am. Chem. Soc*., 2007, **129**, 1465; (*c*) A. Y. Sukhorukov and S. L. Ioffe, *Chem. Rev*., 2011, **111**, 5004.

13 CCDC 1013940 (**2n**) contains the supplementary crystallographicdata for this paper.

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