RSC Advances

PAPER

View Article Online
View Journal | View Issue

Cite this: *RSC Adv.*, 2017, **7**, 38077

Direct stereoselective construction of cyclopropane α-amino acid with contiguous quaternary centers *via* [4 + 2] annulation reaction†

Jun-Hao Hu,[b] Yun-Chao Xu,[a] Dan-Dan Liu,[a] Bing Sun,[a] Ying Yi*[a] and Fang-Lin Zhang *[a]

Received 9th June 2017
Accepted 13th July 2017

DOI: 10.1039/c7ra06465a

rsc.li/rsc-advances

A direct diastereoselective synthetic approach to useful cyclopropane α-amino acid was established *via* base-promoted [4 + 2] annulations between *o*-aminobenzaldehydes and alkyl 2-aroyl-1-chlorocyclopropanecarboxylates. The annulation reaction proceeded quickly under mildly basic conditions, affording α-aminocyclopropanecarboxylic acid derivatives in moderate to excellent yields with high diastereoselectivities (up to 19 : 1).

Since α-aminocyclopropanecarboxylic acid (ACC) was first isolated from cowberries by Vähätalo and Virtanen in 1955, ACC motifs and their derivatives have attracted considerable attention.[1] ACC not only exists in many natural products, bioactive compounds and pharmaceuticals,[2] but also serves as valuable tool for the mechanistic study and characterization of enzymes.[3] Some representative bioactive examples bearing this skeleton are given in Fig. 1. Great interest has been shown in the efficient construction of ACC frameworks, especially those with tertiary–quaternary carbon centers.[4] In addition, recent medicinal research revealed that compound **I** and its derivatives as a combination of 1-aminocyclopropane-1-carboxylic acid and 1,2,3,4-tetrahydroquinoline-2-carboxylic acid moieties have strong affinities with the glycine binding site of the NMDA receptor,[5] and also play an important role in neuronal cell death during ischaemic or hypoxic conditions such as stroke or epilepsy.[6–8] Unfortunately, however, a multiple-step synthesis is essential to construct two contiguous quaternary centers.[9] Therefore, the development of more efficient and general methods for the synthesis of ACC derivatives containing contiguous quaternary centers is highly desirable.

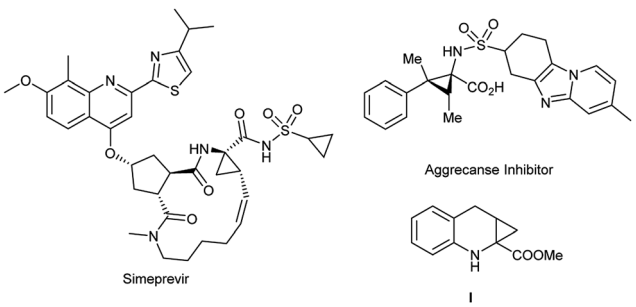


Fig. 1 Typical bioactive molecules containing ACC motifs.

The previously reported synthetic methods of ACC framework, such as insertion reaction of transition-metal-mediated α-nitroacetate carbene with disubstituted alkenes (Scheme 1A),[10] [3 + 2] cycloaddition (Scheme 1B)[11] and multi-step synthesis (Scheme 1C),[9] are outlined in Scheme 1. The main disadvantages for these routes include low functional group tolerance and the expensive precursors prepared through multiple steps. Thus, it still remains a challenge to develop a more practical method for this core structure.

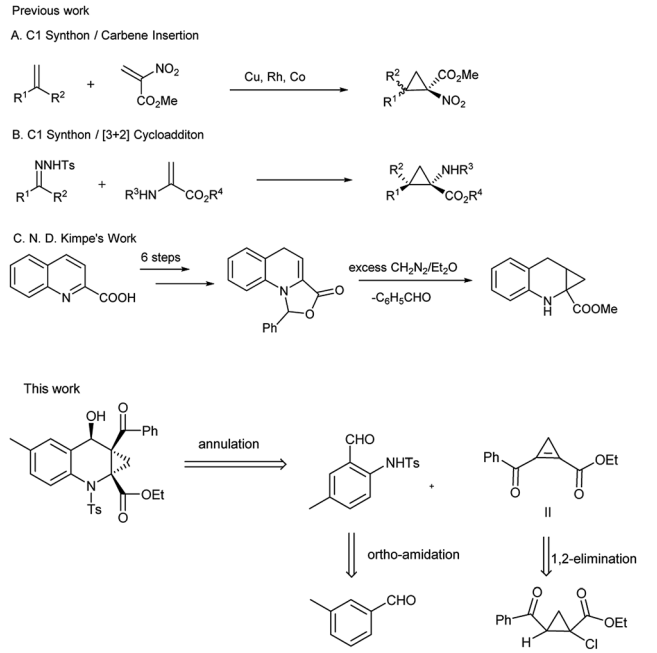
Over the last decade, the field of transition-metal-catalyzed aromatic C–H bond functionalization has gained significant development, and these strategies to form carbon–carbon and carbon–heteroatom bond have become increasingly commonplace.[12] Recently, Yu *et al.* reported the use of glycine as a transient directing group for functionalization of C(sp^3)–H bond of aldehyde.[13] Then, Yu and our group have collectively demonstrated an *ortho*-C(sp^2)–H functionalization of benzaldehyde using transient directing groups.[14] As part of our ongoing work, we found that the products **3** derived from *ortho*-amidation of aldehydes were donor–acceptor species substantially which can be further transformed into useful core architectures. In addition, Gong *et al.* developed a convenient way to prepare a new type of electron-deficient cyclopropene intermediate **II** (marked in Scheme 1) *in situ* by carrying out a simple 1,2-elimination of

[a]*School of Chemistry, Chemical Engineering and Life Sciences, Wuhan University of Technology, Wuhan 430070, People's Republic of China. E-mail: fanglinzhang@whut.edu.cn; yying630@163.com*

[b]*Department of Chemistry and Material Science, Key Laboratory of Functional Organometallic Materials of Hunan Provincial College, Hengyang Normal University, Hengyang, Hunan 421008, People's Republic of China*

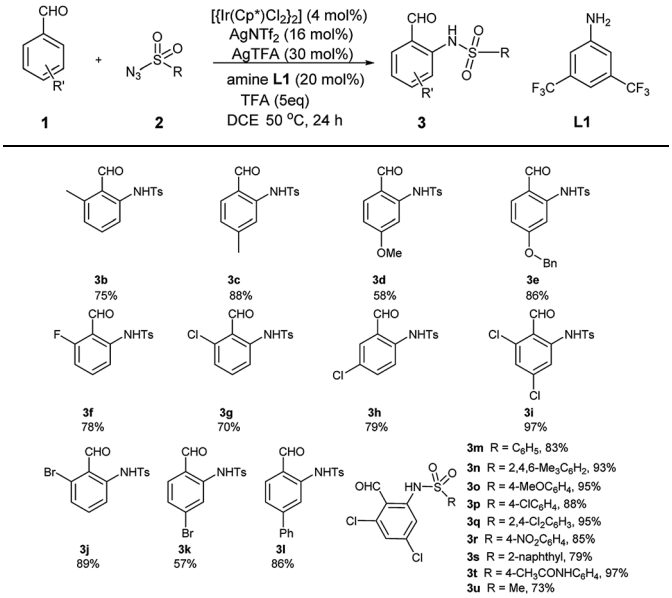
† Electronic supplementary information (ESI) available. CCDC 1525861. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c7ra06465a

‡ J. H. and Y. X. contributed equally to this work.



Scheme 1 Diastereoselective synthesis of contiguous quaternary centers containing ACC.

Table 1 Ir(III)-Catalyzed *ortho*-amidation of aldehydes[a,b]



[a] 0.2 mmol **1** and 0.3 mmol **2** in 2.0 mL DCE. [b] Isolated yields given.

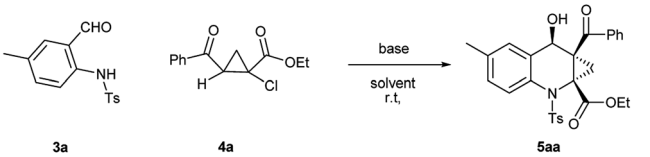
alkyl 2-aroyl-1-chlorocyclopropanecarboxylates under basic conditions.[15] This reagent has been successfully applied to construct strained ring-fused bioactive molecules through its base-promoted annulation reactions.[16] The above progress encouraged us to assess the possibility of constructing the important ACC subunit **I** directly through the designed [4 + 2] annulation reaction between donor–acceptor reagents **3** and alkyl 2-aroyl-1-chlorocyclopropanecarboxylates. To our delight, the expected products were obtained in moderate to high yields under mildly basic conditions. The details about the Ir-catalyzed amidation of benzaldehydes with sulfonyl azides and subsequent [4 + 2] annulation reaction with alkyl 2-aroyl-1-chlorocyclopropanecarboxylates are described herein.

Firstly, the preparation of donor–acceptor reagents **3** followed our previous work.[14] Under the same conditions, the yield of **3a** was obtained only in 50%. Therefore, we preliminarily screened the influence of various amines, and found that amine **L1** gave the desired product **3a** in 75% yield (Table S1†).

Under the optimal reaction conditions, we obtained various *ortho*-aminobenzaldehyde products **3**, which are summarized in Table 1, in good (57%) to excellent (97%) yields.

With *ortho*-aminobenzaldehyde products **3** in hand, we envisioned the construction of ACC subunit though annulation reaction of **3** with ethyl 2-aroyl-1-chlorocyclopropanecarboxylates **4**, the reaction of **3a** with **4a** was first carried out in the presence of Cs_2CO_3 as model. In THF, the reaction readily proceeded at room temperature, and **4a** was almost completely consumed after 12 h. The product, isolated through silica gel column chromatography in 15% yield with 9 : 1 dr value, was identified to be the fused ACC ester **5aa** by spectroscopic means (Table 2, entry 1). The diastereomeric ratio of **5aa** was determined by ^{1}H NMR spectroscopy. The stereochemistry for this process was confirmed by single crystal X-ray diffraction analysis.[17] To optimize the reaction conditions, various solvents were taken into account. As shown in Table 2, in aprotic polar solvents such as *N*,*N*-dimethylformamide (DMF) and dimethyl sulfoxide (DMSO), this reaction proceeded smoothly to produce **5aa** with high dr value (Table 2, entries 2 and 3), and a satisfactory yield (84%) was

Table 2 Optimization of the annulation reaction between **3a** and **4a**[a]



Entry	Solvent	Base	T (h)	Yield[b] (%)	dr[c]
1	THF	Cs_2CO_3	12	15	9 : 1
2	DMSO	Cs_2CO_3	2	84	13 : 1
3	DMF	Cs_2CO_3	2	86	14 : 1
4	CH_3CN	Cs_2CO_3	12	70	14 : 1
5	1,4-Dioxane	Cs_2CO_3	12	<5	—
6	DMF	NaOH	1	23	10 : 1
7	DMF	K_3PO_4	12	56	9 : 1
8	DMF	K_2CO_3	12	<5	—
9	DMF	TEA	12	—	—
10	DMF	DBU	12	—	—

[a] Reactions carried out using 0.10 mmol of **3a**, 0.11 mmol of **4a** and 0.20 mmol of Cs_2CO_3 in 1.0 mL of solvent at room temperature. [b] Isolated yields given. [c] Diastereomeric ratio (*cis* : *trans*) of the crude product determined by ^{1}H NMR.

observed in DMF. In acetonitrile, the reaction proceeded slowly, and the yield of **5aa** was relatively lower than the observed in DMF (Table 2, entry 4). In weakly polar solvent 1,4-dioxane, almost none of the desired product was detected (Table 2, entry 5).

In view of the yields observed above, we chose DMF as the most promising solvent to optimize the various bases. As shown in Table 2, the yield of **5aa** was remarkably dependent on the properties of the bases used. Strong inorganic base like NaOH could greatly promote this reaction, giving **5aa** only in 23% yield (Table 2, entry 6). In contrast, a satisfactory result was achieved when K_3PO_4 was employed (Table 2, entry 7). On the other hand, the common inorganic base K_2CO_3, the organic base Et_3N and strong organic base DBU (Table 2, entries 8, 9 and 10) were hardly able to promote this process.

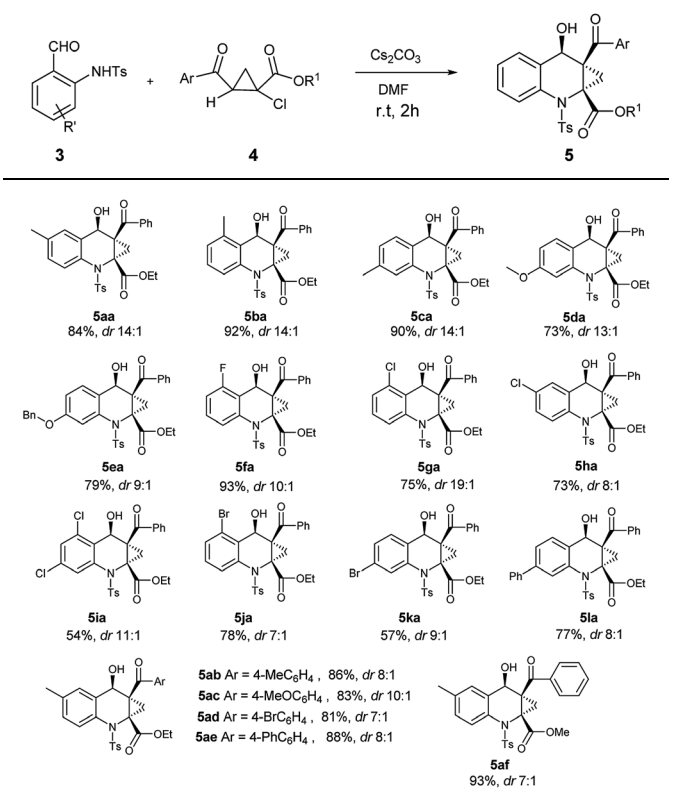
With the optimized conditions of annulation reaction in hand, we subsequently examined the substrate scope of this reaction. First, the range of substrates **3** was investigated and the observed results are summarized in Table 3. Under the optimal reaction conditions, substrates **3a–3e** with electron-donating groups at the benzene ring afforded the products **5aa–5ea** in good yields and good dr values, respectively. Among the substrates **3f–3k** with electron-withdrawing groups, the substrate **3f** with 2-fluoro group afforded the highest yield and high dr value of the annulation product **5fa**, whereas the substrate **3g** with 2-chloro group furnished a high yield of the product **5ga** with an excellent dr value (19 : 1) and the substrate **5i** with 2,4-dichloro group gave the lowest yield of **5ia**. Besides, substrate **3l** with phenyl group was well tolerated in this reaction, producing the product **5la** in a high yield with a good dr value.

Next, we further investigated the structure effect of 2-aroyl-1-chlorocyclopropanecarboxylates **4** on the reaction. As shown in Table 3, the electronic nature of the Ar group couldn't obviously influence the product yields and the diastereomeric ratios, affording the products **5ab–5ae** in high yields with good dr values, respectively. When the R^1 group was replaced with a small methyl group, the corresponding product **5af** could be obtained in the highest yield and good dr value.

As known to all, stereoselective construction of ACC subunits is a challenging but demanding target. Encouraged by above results, we chose substrates **4** containing chiral auxiliary to expand this protocol to the synthesis of chiral ACC subunits. To our delight, the substrates **4g–4i** underwent a smooth transformation to afford products **5ag–5ai** in high yields and good dr values, respectively (Table 4).

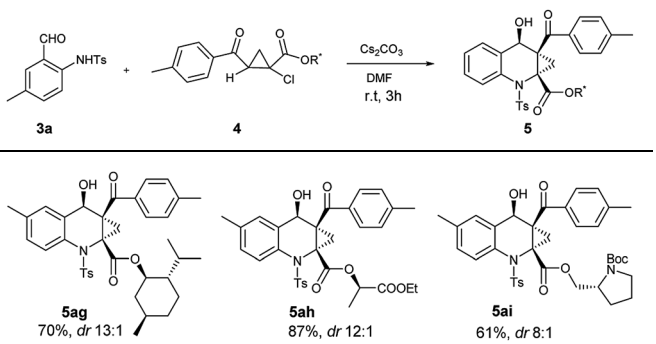
Based on the above observations, we proposed a possible reaction mechanism as shown in Scheme 2. The reaction could

Table 3 Scope of the annulation reaction between **3** and **4**[a,b,c]

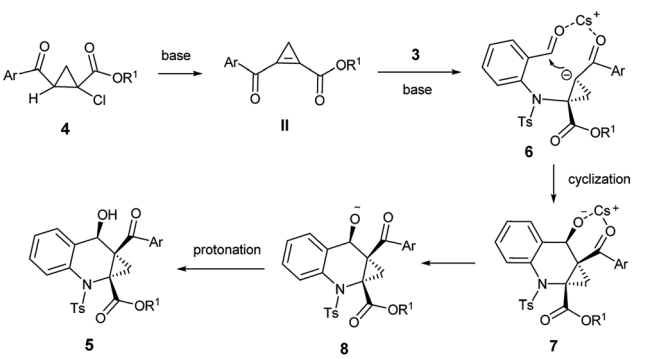


[a] Reactions carried out using 0.10 mmol of **3**, 0.11 mmol of **4** and 0.20 mmol of Cs_2CO_3 in 1.0 mL of DMF at room temperature. [b] Isolated yields given. [c] Diastereomeric ratio (*cis* : *trans*) of the crude product determined by ^{1}H NMR.

Table 4 Scope of the annulation reaction between **3a** and **4**[a,b,c]



[a] Reactions carried out using 0.10 mmol of **3**, 0.11 mmol of **4** and 0.20 mmol of Cs_2CO_3 in 1.0 mL of DMF at room temperature. [b] Isolated yields given. [c] Diastereomeric ratio (*cis* : *trans*) of the crude product determined by ^{1}H NMR.



Scheme 2 A possible mechanistic process for the [4 + 2] annulation.

proceed through a highly regioselective aza-Michael addition to the strained C=C bond of the highly reactive cyclopropene intermediate **II**, generated *in situ* in the presence of base. We realize that the diastereoselectivity of the reaction may be dominated by the coordination state of the intermediate **6**. Owing to the apparent steric hindrance, the coordination state **6** was converted into fused polycyclic intermediate **7** with high dr value. Then **7** was subsequently protonated into the final product **5**.

In summary, we have developed an efficient and practical [4 + 2] annulation reaction between alkyl 2-aroyl-1-chlorocyclopropanecarboxylates and donor–acceptor reagents derived from *ortho*-amidation of aldehydes in the presence of an inorganic base. This protocol is suitable for directly constructing the biologically and pharmaceutically useful cyclopropane α-amino acid bearing three continuous chiral carbon atoms and two quaternary stereogenic centers. This base-promoted cascade process does not require a transition metal catalyst, and avoids multiple steps. This reaction is tolerant to the steric hindrance and electronic properties of the reactants and can be easily performed under very mild conditions, giving ACC subunits in high yields and diastereoselectivities. Notably, ACC subunits can be stereoselectively constructed in high yields and diastereoselectivities through chiral auxiliary.

Notes and references

1 C. Cativiela and M. D. Díaz-de-Villegas, *Tetrahedron: Asymmetry*, 2000, **11**, 645; W. A. Donaldson, *Tetrahedron*, 2001, **57**, 8589; F. Brackmann and A. de Meijere, *Chem. Rev.*, 2007, **107**, 4493.

2 H. Kakeya, H.-P. Zhang, K. Kobinata, R. Onose, C. Onozawa, T. Kudo and H. Osada, *J. Antibiot.*, 1997, **50**, 370; M. Hara, S. Soga, M. Itoh, K. Shono, J. Eishima and T. Mizukami, *J. Antibiot.*, 2000, **53**, 720; M. Nishio, J. Kohno, M. Sakurai, S.-I. Suzuki, N. Okada, K. Kawano and S. Komatsubara, *J. Antibiot.*, 2000, **53**, 724.

3 K. R. Hill, S. R. Prakash, R. Wiesendanger, W. Angst, B. Martinoni, D. Arigoni, H. W. Liu and C. T. Walsh, *J. Am. Chem. Soc.*, 1984, **106**, 795; M. F. White, J. Vasquez, S. F. Yang and J. F. Kirsch, *Proc. Natl. Acad. Sci. U. S. A.*, 1994, **91**, 12428; J. Zhou, A. M. Rocklin, J. D. Lipscomb, L. Que and E. I. Solomon, *J. Am. Chem. Soc.*, 2002, **124**, 4602.

4 P. K. Mykhailiuk, S. Afonin, A. S. Ulrich and I. V. Komarov, *Synthesis*, 2008, **2008**, 1757; V. N. G. Lindsay, W. Lin and A. B. Charette, *J. Am. Chem. Soc.*, 2009, **131**, 16383; C.-L. Zhu, L.-J. Yang, S. Li, Y. Zheng and J.-A. Ma, *Org. Lett.*, 2015, **17**, 3442.

5 R. Nagata, N. Tanno, T. Kodo, N. Ae, H. Yamaguchi, T. Nishimura, F. Antoku, T. Tatsuno, T. Kato, Y. Tanaka and M. Nakamura, *J. Med. Chem.*, 1994, **37**, 3956; S. Katayama, N. Ae and R. Nagata, *Tetrahedron: Asymmetry*, 1998, **9**, 4295; G. Dannhardt, M. Gruchalla, K. B. Kohl and G. C. Parsons, *Arch. Pharm.*, 2000, **333**, 267.

6 B. Meldrum and J. Garthwaite, *Trends Pharmacol. Sci.*, 1990, **11**, 379; S. M. Rothman and J. W. Olney, *Trends Neurosci.*, 1995, **18**, 57.

7 A. J. Robl, S. D. Karanewsky and M. M. Assad, *Tetrahedron Lett.*, 1995, **36**, 1593; P. G. Zecchini and P. M. Paradisi, *J. Heterocycl. Chem.*, 1979, **16**, 1589.

8 N. Gruenfeld, *US Pat.* 4,401,818, 1983Chem. Abstr. 1984, 100, 34421.

9 M. Shiozaki, K. Maeda, T. Miura, M. Kotoku, T. Yamasaki, I. Matsuda, K. Aoki, K. Yasue, H. Imai, M. Ubukata, A. Suma, M. Yokota, T. Hotta, M. Tanaka, Y. Hase, J. Haas, A. M. Fryer, E. R. Laird, N. M. Littmann, S. W. Andrews, J. A. Josey, T. Mimura, Y. Shinozaki, H. Yoshiuchi and T. Inaba, *J. Med. Chem.*, 2011, **54**, 2839; Z. Szakonyi, F. Fülöp, D. Tourwé, N. De and Kimpe, *J. Org. Chem.*, 2002, **67**, 2192.

10 B. Moreau and A. B. Charette, *J. Am. Chem. Soc.*, 2005, **127**, 18014; S. Zhu, J. A. Perman and X. P. Zhang, *Angew. Chem., Int. Ed.*, 2008, **47**, 8460; A. Pons, H. Beucher, P. Ivashkin, G. Lemonnier, T. Poisson, A. B. Charette, P. Jubault and X. Pannecoucke, *Org. Lett.*, 2015, **17**, 1790.

11 C. Zhu, J. Li, P. Chen, W. Wu, Y. Ren and H. Jiang, *Org. Lett.*, 2016, **18**, 1470.

12 D. A. Colby, R. G. Bergman and J. A. Ellman, *Chem. Rev.*, 2010, **110**, 624; T. W. Lyons and M. S. Sanford, *Chem. Rev.*, 2010, **110**, 1147; G. Song, F. Wang and X. Li, *Chem. Soc. Rev.*, 2012, **41**, 3651; I. P. Beletskaya and A. V. Cheprakov, *Organometallics*, 2012, **31**, 7753; P. B. Arockiam, C. Bruneau and P. H. Dixneuf, *Chem. Rev.*, 2012, **112**, 5879; G. Rouquet and N. Chatani, *Angew. Chem*, 2013, **125**, 11942; *Angew. Chem. Int. Ed*, 2013, **52**, 11726.

13 F. L. Zhang, K. Hong, T. J. Li, H. Park and J. Q. Yu, *Science*, 2016, **351**, 252.

14 X. H. Liu, H. Park, J. H. Hu, Y. Hu, Q. L. Zhang, B. L. Wang, B. Sun, K. S. Yeung, F. L. Zhang and J. Q. Yu, *J. Am. Chem. Soc.*, 2017, **139**, 888.

15 M. Zhang, Y. F. Gong and W. Z. Wang, *Eur. J. Org. Chem.*, 2013, 7372.

16 M. Zhang, J. K. Guo and Y. F. Gong, *Eur. J. Org. Chem.*, 2014, 1942; M. Zhang, F. Luo and Y. F. Gong, *J. Org. Chem.*, 2014, **79**, 1335; J. H. Hu, M. Zhang and Y. F. Gong, *Eur. J. Org. Chem.*, 2015, 1970; Y. Q. Zhu, M. Zhang, H. L. Yuan and Y. F. Gong, *Org. Biomol. Chem.*, 2014, **12**, 8828; Y. Q. Zhu and Y. F. Gong, *J. Org. Chem.*, 2015, **80**, 1446; Z. M. Huang, J. H. Hu and Y. F. Gong, *Org. Biomol. Chem.*, 2015, **13**, 8561; J. H. Hu, Y. Liu and Y. F. Gong, *Adv. Synth. Catal.*, 2015, **357**, 2781.

17 CCDC 1525861 contains the supplementary crystallographic data for this paper.†

