



Cite this: *Org. Biomol. Chem.*, 2014, **12**, 7482

Received 2nd July 2014,
Accepted 6th August 2014

DOI: 10.1039/c4ob01384k

www.rsc.org/obc

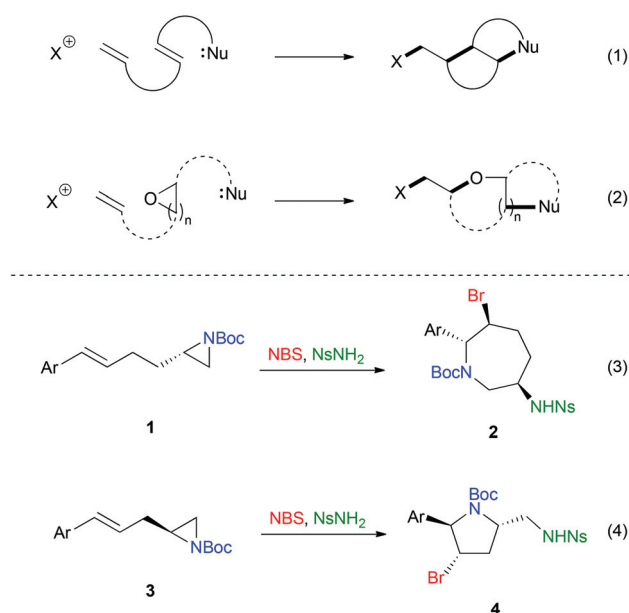
Diastereoselective synthesis of functionalized pyrrolidines through *N*-bromosuccinimide-induced aziridine ring expansion cascade of cinnamylaziridine†

Jing Zhou and Ying-Yeung Yeung*

An efficient aziridine ring expansion cascade of cinnamylaziridine has been developed. *N*-Bromosuccinimide was used as the promoter. The resulting functionalized pyrrolidines are the fundamental units of many useful molecules.

Inefficient chemical synthesis does cause problems in pharmaceutical industry and obstructs the development of life-saving drugs.¹ The negative impact of inefficient synthetic processes on the environment has also become an important concern in recent years.² Electrophilic halogen-induced cascade reactions, which are considered as efficient and environmentally benign processes since multiple bonds can be formed (sometimes multiple stereocentres can also be obtained) in a single chemical operation,^{3,4} have been developed in recent years.⁵ For instance, transformations such as polyene cyclization (Scheme 1, eqn (1))⁶ and domino cyclization/cyclic ether ring expansion (Scheme 1, eqn (2)) have been documented.⁷ These reactions have proven to be highly valuable as a number of applications have been demonstrated. In contrast, the utilization of aziridine in such kind of cascade is less studied.⁸ Recently, we have reported a novel bromonium ion-initiated asymmetric aminocyclization–aziridine ring expansion cascade to afford substituted azepanes **2**, which could be further transformed to other functional molecules (Scheme 1, eqn (3)).⁹ We reasoned that the same reaction protocol can be applied to the homolog cinnamylaziridine **3**. Herein, we are pleased to report the diastereoselective synthesis of pyrrolidine **4**,¹⁰ which contains three stereocenters through the electrophilic aminocyclization–ring expansion cascade using *N*-bromosuccinimide (NBS) as the halogen source (Scheme 1, eqn (4)).

It is noteworthy that functionalized pyrrolidines have been widely applied in various areas such as medicinal chemistry,¹¹



Scheme 1 NBS-induced aminocyclization–aziridine ring expansion cascade.

organocatalysts,¹² and chiral metal complexations.¹³ Some examples are shown in Fig. 1.

3 was readily achievable by metathesis of L-aspartic acid-derived ethenylaziridine **6** and substituted styrene using Grubbs 2nd generation catalyst (Scheme 2).¹⁴

Initially, **3a** was subjected to the investigation using *p*-nosyl amide as the nucleophilic partner. In this kind of cyclization cascade, two possible products, pyrrolidine and piperidine, can be obtained through path a and path b, respectively (*vide infra*, Scheme 3). Ethyl acetate, which was found to be a superior solvent medium for the cascade reaction of **1** in our previous study,^{9a} gave poor selectivity of **4a**:**5a** (1.1:1.0) despite the high overall reaction yield (Table 1, entry 1). The selectivity was slightly improved when reducing the reaction temperature to −20 °C (entry 3). After screening some common organic solvents, it was found that relatively

Department of Chemistry, National University of Singapore, 3 Science Drive 3, Singapore 117543, Singapore. E-mail: chmyyy@nus.edu.sg; Fax: (+)65 6779 1691; Tel: (+)65 6516 7760

†Electronic supplementary information (ESI) available. CCDC 970435. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c4ob01384k



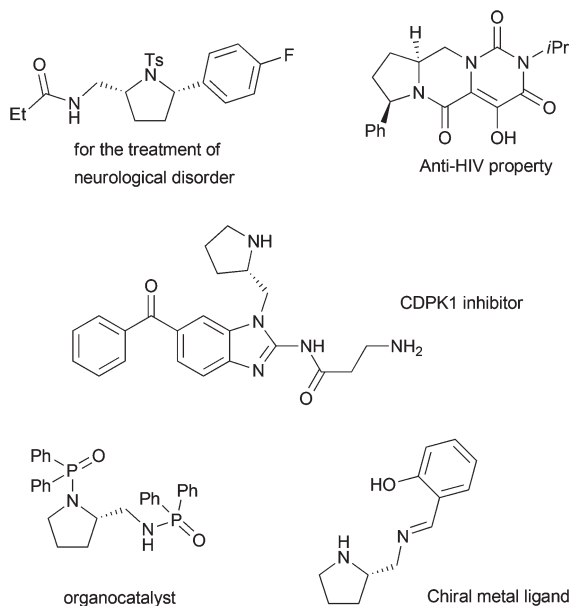
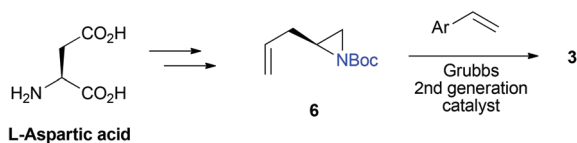
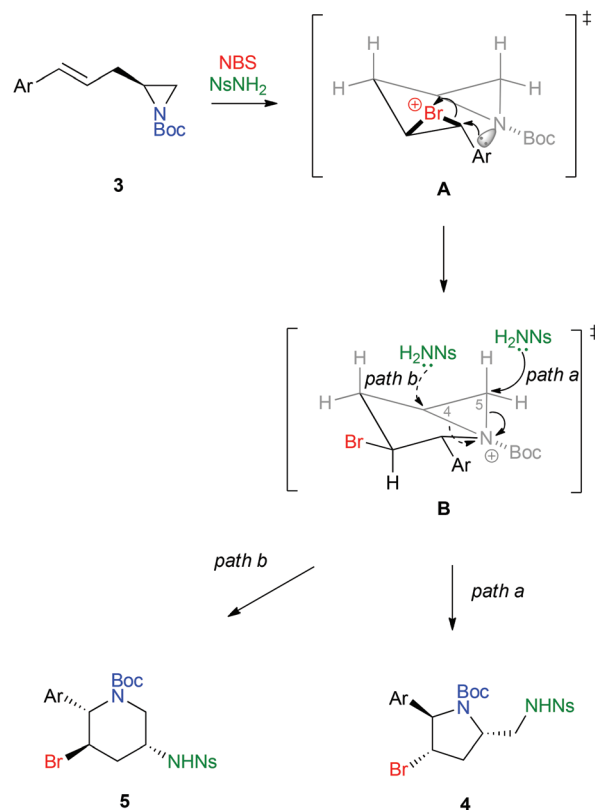


Fig. 1 Examples of pyrrolidine-containing functional molecules.

Scheme 2 The synthesis of **3**.

non-polar solvents such as diethyl ether and toluene gave a sluggish reaction while polar solvents generally gave much better conversion (entries 4–12). Finally, the optimal solvent and temperature were found to be acetonitrile and $-20\text{ }^{\circ}\text{C}$, respectively, which gave the selectivity of **4a**:**5a** up to 3.2 : 1.0 (entry 7). Other halogenation sources, including *N*-chlorosuccinimide (NCS) and *N*-iodosuccinimide (NIS), were also examined under the optimal conditions and the reactions were found to be sluggish (entries 13 and 14). The structure of pyrrolidine **4a** was determined by 2D-NMR analysis while piperidine **5a** was confirmed by an X-ray crystallographic study on its tosylated derivative (CCDC 970435).¹⁵

Having identified the optimal conditions, we then explored the scope of the reaction and the results are listed in Table 2. In all cases, good yields of aziridine ring expansion products were obtained. No aromatic bromination was observed even for the electron-rich substituted systems (Table 2, entries 1–4). Compared with other substrates, *ortho*-CH₃ phenyl system gave slightly lower reaction yield (72%), presumably due to the steric repulsion. Similar to our previous discovery,^{9a} it appears that the electronic effect has no significant effect on the yield of the reaction. Generally, substrates with electron-rich substituents gave better regioselectivity, while substrates with relatively electron-poor substituents returned lower selectivity. The best selectivity (**4e**:**5e** = 4 : 1) was obtained with the *tert*-butyl



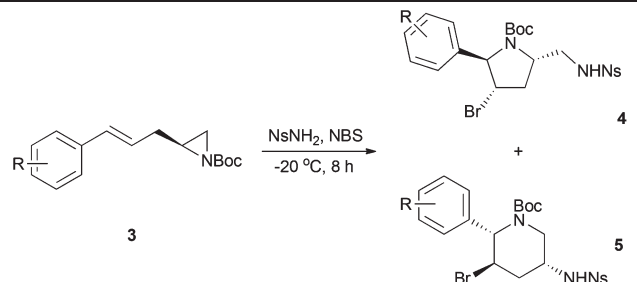
Scheme 3 Proposed mechanism.

Table 1 Reaction optimization

Entry ^a	Solvent	Temp (°C)	Time (h)	Yield ^b (%)	4a : 5a ^c
1	EtOAc	25	1	82	1.1 : 1.0
2	EtOAc	0	2	81	1.3 : 1.0
3	EtOAc	-20	8	82	1.7 : 1.0
4	THF	-20	8	79	1.3 : 1.0
5	Acetone	-20	8	80	2.0 : 1.0
6	MeNO ₃	-20	8	73	3.1 : 1.0
7	MeCN	-20	8	82	3.2 : 1.0
8	MeCN	-40	16	81	3.2 : 1.0
9	CH ₂ Cl ₂	-20	16	76	2.0 : 1.0
10	CHCl ₃	-20	16	70	1.5 : 1.0
11	Et ₂ O	25	24	Trace	—
12	Toluene	25	24	Trace	—
13 ^d	MeCN	-20	24	Trace	—
14 ^e	MeCN	-20	24	Trace	—

^a Reactions were conducted using aziridine **3a** (0.1 mmol), NBS (0.15 mmol), and NsNH₂ (0.15 mmol) in solvent (1 mL). ^b Isolated yield of the mixture **4a** and **5a**. ^c The ratios were determined by ¹H NMR analysis of the product mixture. ^d NCS was used. ^e NIS was used.



Table 2 NBS-induced aminocyclization–aziridine ring expansion cascade of **3**


Entry ^a	Substrate	R	Yield ^b (%)	4 : 5 ^c
1	3b	4-OCH ₃	80	2.1 : 1.0
2	3c	4-CH ₃	82	3.0 : 1.0
3	3d	2-CH ₃	72	3.8 : 1.0
4	3e	4- <i>t</i> -Bu	80	4.0 : 1.0
5	3f	4-F	85	3.5 : 1.0
6	3g	3-F	82	2.7 : 1.0
7	3h	3-Cl	84	2.6 : 1.0
8	3i	4-Br	83	3.0 : 1.0
9	3j	4-COOCH ₃	74	2.3 : 1.0
10 ^d	3k	3-NO ₂	67	1.1 : 1.0

^a Reactions were conducted using aziridine **3** (0.1 mmol), NBS (0.15 mmol), and NsNH₂ (0.15 mmol) in MeCN (1 mL) at –20 °C for 8 h. ^b Isolated yield of the mixture **4** and **5**. ^c Ratios were determined by ¹H NMR analysis of the product mixture. ^d The reaction time was 16 h.

phenyl substrate **3e** (entry 4). It is noteworthy that only one diastereomer for both **4** and **5** was observed.

For the mechanism of this type of cascade, we believe that the cyclization might involve intermediate **A** through the bromination of **3** by the NBS/NsNH₂ protocol (Scheme 3).⁹ Subsequently, the aziridine in **A** could react with the bromonium ion to give the aziridinium ion intermediate **B**.¹⁶ At this stage, NsNH₂ could attack at either C-5 (path a) or C-4 (path b) position to give pyrrolidine **4** or piperidine **5**, respectively. The preference on the formation of pyrrolidine **4** could be attributed to the substitution taken place at the less hindered C-5 position. The excellent diastereoselectivity in the formation of the cyclic amine products also suggests that the nucleophilic attacks in **A** and **B** occur in a S_N2 manner.

Conclusions

In conclusion, we have developed an efficient bromonium ion-induced aziridine ring expansion cascade to afford functionalized pyrrolidines containing three stereocenters. These compounds are potential building blocks in various areas, and their possible synthetic applications are currently being studied.

Acknowledgements

We acknowledge the financial supports from the ASTAR-Public Sector Funding (grant no. 143-000-536-305), the NEA-ETRP

(grant no. 143-000-547-490) and the GSK-EDB (grant no. 143-000-564-592). We acknowledge the receipt of a NUS Research Scholarship (to J.Z.).

Notes and references

- In a US Food and Drug Administration (FDA) report in 2004, it clearly stated that the problem of inefficient chemical synthesis has on the production of life-saving pharmaceuticals. For reference, see: U.S. Food and Drug Administration, *Innovation and Stagnation: Challenge and Opportunity on the Critical Path to New Medical Products*, 2004.
- (a) D. J. C. Constable, P. J. Dunn, J. D. Hayler, G. R. Humphrey, J. L. Leazer, R. J. Linderman Jr., K. Lorenz, J. Manley, B. A. Pearlman, A. Wells, A. Zaks and T. Y. Zhang, *Green Chem.*, 2007, **9**, 411; (b) D. J. C. Constable, A. D. Curzons, L. M. F. dos Santos, G. R. Geen, R. E. Hannah, J. D. Hayler, J. Kitteringham, M. A. McGuire, J. E. Richardson, P. Smith, R. L. Webb and M. Yu, *Green Chem.*, 2001, **3**, 7; (c) A. D. Curzons, D. J. C. Constable, D. N. Mortimer and V. L. Cunningham, *Green Chem.*, 2001, **3**, 1; (d) D. J. C. Constable, A. D. Curzons and V. L. Cunningham, *Green Chem.*, 2002, **4**, 521.
- For selected reviews, see: (a) I. Ugi, A. Dömling and W. Hörl, *Endeavour*, 1994, **18**, 115; (b) A. Dömling and I. Ugi, *Angew. Chem., Int. Ed.*, 2000, **39**, 3168; (c) J. Zhu and H. Bienaymé, *Multicomponent Reactions*, Wiley-VCH, Weinheim, 2005; (d) A. Dömling, *Chem. Rev.*, 2006, **106**, 17; (e) B. B. Touré and D. G. Hall, *Chem. Rev.*, 2009, **109**, 4439; (f) J. D. Sunderhaus and S. F. Martin, *Chem. – Eur. J.*, 2009, **15**, 1300; (g) B. Ganem, *Acc. Chem. Res.*, 2009, **42**, 463; (h) D. J. Ramón and M. Yus, *Angew. Chem., Int. Ed.*, 2005, **44**, 1602.
- (a) Y. A. Serguchev, M. V. Ponomarenko, L. F. Lourie and A. N. Chernega, *J. Fluorine Chem.*, 2003, **123**, 207; (b) V. Nair, R. S. Menon, P. B. Beneesh, V. Sreekumar and S. Bindu, *Org. Lett.*, 2004, **6**, 767; (c) V. Nair, P. B. Beneesh, V. Sreekumar, S. Bindu, R. S. Menon and A. Deepthi, *Tetrahedron Lett.*, 2005, **46**, 201; (d) Y.-Y. Yeung, X. Gao and E. J. Corey, *J. Am. Chem. Soc.*, 2006, **128**, 9644; (e) T. L. Church, C. M. Byrne, E. B. Lobkovsky and G. W. Coates, *J. Am. Chem. Soc.*, 2007, **129**, 8156; (f) S. Hajra, S. Bar, D. Sinha and B. Maji, *J. Org. Chem.*, 2008, **73**, 4320; (g) T. Abe, H. Takeda, Y. Miwa, K. Yamada, R. Yanada and M. Ishikura, *Helv. Chim. Acta*, 2010, **93**, 233; (h) D. C. Braddock, *Org. Lett.*, 2006, **8**, 6055; (i) D. C. Braddock, D. S. Millan, Y. Pérez-Fuertes, R. H. Pouwer, R. N. Sheppard, S. Solanki and A. J. P. White, *J. Org. Chem.*, 2009, **74**, 1835; (j) K. J. Bonney, D. C. Braddock, A. J. P. White and M. Yaqoob, *J. Org. Chem.*, 2011, **76**, 97; (k) K. J. Bonney and D. C. Braddock, *J. Org. Chem.*, 2012, **77**, 9574; (l) S. A. Snyder, D. S. Treitler, A. P. Brucks and W. Sattler, *J. Am. Chem. Soc.*, 2011, **133**, 15898; (m) S. A. Snyder, A. P. Brucks, D. S. Treitler and I. Moga, *J. Am. Chem. Soc.*,



- 2012, **134**, 17714; (n) J. Tanuwidjaja, S.-S. Ng and T. F. Jamison, *J. Am. Chem. Soc.*, 2009, **131**, 12084; (o) H. Fujioka, Y. Ohba, H. Hirose, K. Murai and Y. Kita, *Angew. Chem., Int. Ed.*, 2005, **44**, 734; (p) C. Recsei, B. Chan and C. S. P. McErlean, *J. Org. Chem.*, 2014, **79**, 880.
- 5 (a) T. E. Müller and M. Beller, *Chem. Rev.*, 1998, **98**, 675; (b) R. Severin and S. Doye, *Chem. Soc. Rev.*, 2007, **36**, 1407; (c) O. Delacroix and A. C. Gaumont, *Curr. Org. Chem.*, 2005, **9**, 1851.
- 6 (a) J. Barluenga, J. M. González, P. J. Campos and G. Asensio, *Angew. Chem., Int. Ed. Engl.*, 1988, **27**, 1546; (b) J. Barluenga, M. Trincado, E. Rubio and J. M. González, *J. Am. Chem. Soc.*, 2004, **126**, 3416; (c) G. Stork and A. W. Burgstahler, *J. Am. Chem. Soc.*, 1955, **77**, 5068; (d) A. Eschenmoser and D. Arigoni, *Helv. Chim. Acta*, 2005, **88**, 3011; (e) J. N. Carter-Franklin, J. D. Parrish, R. A. Tschirret-Guth, R. D. Little and A. Butler, *J. Am. Chem. Soc.*, 2003, **125**, 3688; (f) A. Sakakura, A. Ukai and K. Ishihara, *Nature*, 2007, **445**, 900; (g) Y. Sawamura, H. Nakatsuji, A. Sakakura and K. Ishihara, *Chem. Sci.*, 2013, **4**, 4181.
- 7 (a) G. Haufe, *J. Fluorine Chem.*, 1990, **46**, 83; (b) H. Fujioka, H. Kitagawa, Y. Nagatomi and Y. Kita, *J. Org. Chem.*, 1996, **61**, 7309; (c) H. Fujioka, K. Nakahara, H. Hirose, K. Hirano, T. Oki and Y. Kita, *J. Org. Chem.*, 2011, **47**, 1060; (d) N. Khan, H. Xiao, B. Zhang, X. Cheng and D. R. Mootoo, *Tetrahedron*, 1999, **55**, 8303; (e) F. Bravo, F. E. McDonald, W. A. Neiwert and K. I. Hardcastle, *Org. Lett.*, 2004, **6**, 4487; (f) D. C. Braddock, D. S. Millan, Y. Pérez-Fuertes, R. H. Pouwer, R. N. Sheppard, S. Solanki and A. J. P. White, *J. Org. Chem.*, 2009, **74**, 1835; (g) S. A. Snyder and D. S. Treitler, *Angew. Chem., Int. Ed.*, 2009, **48**, 7899; (h) S. A. Snyder, D. S. Treitler and A. P. Brucks, *J. Am. Chem. Soc.*, 2010, **132**, 14303; (i) S. A. Snyder, D. S. Treitler and A. Schall, *Tetrahedron*, 2010, **66**, 4796; (j) D. C. Braddock, S. A. Hermitage, L. Kwok, R. Pouwer, J. M. Redmond and A. J. P. White, *Chem. Commun.*, 2009, 1082; (k) D. C. Braddock, J. S. Marklew and A. J. F. Thomas, *Chem. Commun.*, 2011, 47, 9051; (l) D. C. Braddock, J. S. Marklew, K. M. Foote and A. J. P. White, *Chirality*, 2013, **25**, 692.
- 8 (a) M. D'hooghe, T. Vanlangendonck, K. W. Törnroos and N. De Kimpe, *J. Org. Chem.*, 2006, **71**, 4678; (b) M. Sasaki and A. K. Yudin, *J. Am. Chem. Soc.*, 2003, **125**, 14242.
- 9 (a) J. Zhou and Y.-Y. Yeung, *Org. Lett.*, 2014, **16**, 2134. For other related efforts from our research group, see: (b) J. Zhou and Y.-Y. Yeung, *J. Org. Chem.*, 2014, **79**, 4644; (c) D. W. Tay, I. T. Tsoi, J. C. Er, G. Y. C. Leung and Y.-Y. Yeung, *Org. Lett.*, 2013, **15**, 1310; (d) J. Zhou, L. Zhou and Y.-Y. Yeung, *Org. Lett.*, 2012, **14**, 5250; (e) J. Chen, S. Chng, L. Zhou and Y.-Y. Yeung, *Org. Lett.*, 2011, **13**, 6456; (f) L. Zhou, J. Chen, J. Zhou and Y.-Y. Yeung, *Org. Lett.*, 2011, **13**, 5804; (g) L. Zhou, J. Zhou, C. K. Tan, J. Chen and Y.-Y. Yeung, *Org. Lett.*, 2011, **13**, 2448; (h) L. Zhou, C. K. Tan, J. Zhou and Y.-Y. Yeung, *J. Am. Chem. Soc.*, 2010, **132**, 10245.
- 10 (a) N. De Kimpe and M. Boelens, *J. Chem. Soc., Chem. Commun.*, 1993, 916; (b) J. Cossy, C. Dumas and D. G. Pardo, *Eur. J. Org. Chem.*, 1999, 1693; (c) N. De Kimpe, M. Boelens, J. Piqueur and J. Baele, *Tetrahedron Lett.*, 1994, **35**, 1925; (d) H. A. Dondas and N. De Kimpe, *Tetrahedron Lett.*, 2005, **46**, 4179; (e) E. R. Alonso, K. A. Tehrani, M. Boelens and N. De Kimpe, *Synlett*, 2005, 1726.
- 11 (a) Z. Zhang, K. K. Ojo, S. M. Johnson, E. T. Larson, P. He, J. A. Geiger, A. Castellanos-Gonzalez, A. C. White Jr., M. Parsons, E. A. Merritt, D. J. Maly, C. L. M. J. Verlinde, W. C. Van Voorhis and E. Fan, *Bioorg. Med. Chem. Lett.*, 2012, **22**, 5264; (b) V. Mutel and J. Wichmann, *PCT Int. Appl.*, WO 2002002554, 2002; (c) P. D. Williams, J. S. Wai, M. W. Embrey, D. D. Staas, L. Zhuang and H. M. Langford, *PCT Int. Appl.*, WO 2005092099, 2005.
- 12 (a) M. Bonsignore, M. Benaglia, F. Cozzi, A. Genoni, S. Rossi and L. Raimondi, *Tetrahedron*, 2012, **68**, 8251; (b) S. Guizzetti and M. Benaglia, *Eur. J. Org. Chem.*, 2010, 5529; (c) M. Bonsignore, M. Benaglia, R. Annunziata and G. Celentano, *Synlett*, 2011, 1085.
- 13 Y. N. Belokon, V. I. Maleev, M. North, V. A. Larionov, T. F. Savel'yeva, A. Nijland and Y. V. Nelyubina, *ACS Catal.*, 2013, **3**, 1951.
- 14 (a) M. Suhartono, A. E. Schneider, G. Durner and M. W. Gobel, *Synthesis*, 2010, 293; (b) M. Venkataiah, G. Reddipalli, L. S. Jasti and N. W. Fadnavis, *Tetrahedron: Asymmetry*, 2011, **22**, 1855; (c) P. Wessig and J. Schwarz, *Synlett*, 1997, 893; (d) A. K. Chatterjee, T.-L. Choi, D. P. Sanders and R. H. Grubbs, *J. Am. Chem. Soc.*, 2003, **125**, 11360.
- 15 The details appear in ESI.†
- 16 Different strategies for the synthesis of pyrrolidine from aziridine, see M. D'hooghe, W. Aelterman and N. De Kimpe, *Org. Biomol. Chem.*, 2009, **7**, 135.

