Organocatalytic asymmetric ring-opening of aziridines†

Márcio W. Paixão, Martin Nielsen, Christian Borch Jacobsen and Karl Anker Jørgensen*

Received 18th July 2008, Accepted 6th August 2008
First published as an Advance Article on the web 20th August 2008
DOI: 10.1039/b812369a

The organocatalytic ring-opening of *N*-tosyl protected aziridines by β-ketoesters under chiral PTC-conditions, leading to the formation of optically active aminoethyl functionalised compounds with up to 99% ee, has been developed.

Ring-opening transformations of small aza-heterocycles provide excellent routes for the construction of important synthetic targets containing the aminoethyl fragment.[1] This fragment is found in a wide variety of natural products and nitrogen-containing pharmaceuticals (Fig. 1),[2] and both the biological activity and structural complexity of these compounds have made them prominent synthetic targets.

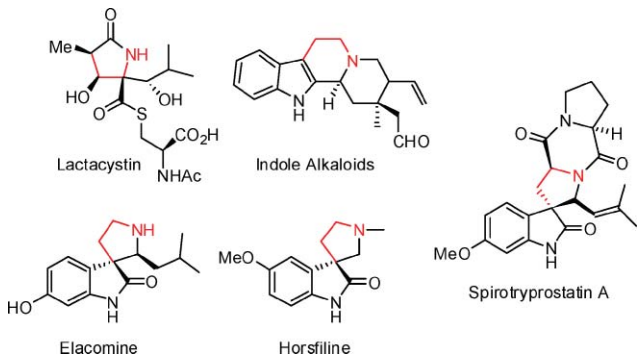
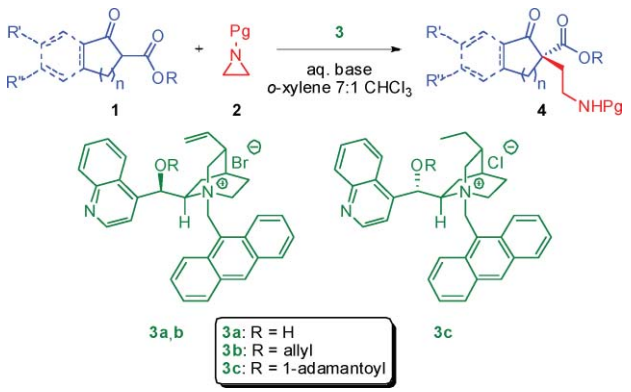


Fig. 1 Nitrogen heterocycles containing the aminoethyl fragment.

In recent years, the asymmetric ring-opening of aziridines catalysed by chiral metal complexes has emerged as an important synthetic strategy for the preparation of these versatile chiral building blocks.[3] The recent well-designed work by Shibasaki *et al.*[4] on the lanthanide-catalysed enantioselective ring-opening of meso-aziridines with trimethylsilyl-protected nucleophiles (TMSCN and $TMSN_3$) and the application of this methodology towards a practical synthesis of Tamiflu[5] highlights the importance of such processes.

However, the organocatalytic version of the asymmetric ring-opening of aziridines is a more difficult task. Although there has been some success using phase-transfer catalysis (PTC)[6] and Brønsted acid catalysis,[7] employing the highly reactive PhSH[8] or trimethylsilyl protected cyanide (TMSCN)[9] as nucleophilic species, the utilization of less reactive carbon-based pronucleophiles, such as β-ketoesters, is yet to be explored. A recent paper by Dixon *et al.* prompted us to present our contribution to enantioselective ring-opening reactions of aziridines.[10]

Recently, our group has shown that the *N*-9-anthracenylmethyl *O*-adamantoyl derivatised cinchonine **3c** is a privileged catalyst in the sense of conducting the electrophilic functionalisation of a range of β-ketoesters in a generally highly stereoselective manner.[6g,11,12] Therefore, we envisioned that employing PTC conditions, using **3** as the catalyst, for the reaction of β-ketoester **1** with *N*-protected aziridine **2** might lead to the enantioselective formation of **4** (Scheme 1).[10] Indeed, reacting **1a** with **2a** in the presence of an aqueous base and catalytic amounts of **3c** led to the formation of enantioenriched alkylated product **4a**.



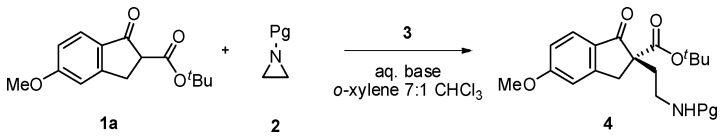
Scheme 1 General scheme of the asymmetric organocatalytic ring-opening of *N*-protected aziridines.

For the optimization screening, compound **1a** was used as a representative nucleophile. Various conditions, including base-strength, temperature and choice of catalyst, were modified in order to achieve satisfactory levels of enantioselectivity and yield. Table 1 shows some representative results leading to the finding of optimal conditions. Starting with the screening of catalysts, it was quickly recognized that the 9-*OR* substituent was crucial for the enantioselectivity.[12] Having 1-adamantoyl at the 9-*O* position of **3** (**3c**, R = 1-adamantoyl) was vital for obtaining a high stereoselectivity. Thus, exchanging a proton (**3a**)[13] with the far more bulky 1-adamantoyl (**3c**) resulted in a tremendous increase in stereoselectivity—from a racemate to an almost enantiopure product (Table 1, entries 1 *vs.* 3). As expected, the less bulky allyl group (**3b**) also led to lower enantioselectivity (entry 2). High yields were obtained for all three catalysts. Entries 3 to 5 show the effect of the reaction temperature on the enantioselectivity. Increasing the temperature from 2 °C to ambient temperature had a decremental effect on the enantioselectivity (84% *versus* 97% ee, entries 4, 3). Likewise, decreasing the temperature to −20 °C had an incremental effect (99% *vs.* 97% ee, entries 5, 3). Unfortunately, the yield was reduced to an unacceptable level of 20%. Next, the

Danish National Research Foundation: Center for Catalysis, Department of Chemistry, Aarhus University, DK-8000, Aarhus C, Denmark. E-mail: kaj@chem.au.dk; Fax: +45 8619 6199; Tel: +45 8942 3910

† Electronic supplementary information (ESI) available: Experimental details and spectra. CCDC reference number 695828. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/b812369a

Table 1 Optimization screening for the addition of **1a** to **2** under PTC conditions[a]



Entry	Pg	Cat (6 mol%)	Aq. base (wt%)	Temp/°C	Yield (%)[b]	Ee (%)[c]
1	Ts (**2a**)	**3a**	K_2CO_3 (33%)	2	83	0
2	Ts (**2a**)	**3b**	K_2CO_3 (33%)	2	78	26
3	Ts (**2a**)	**3c**	K_2CO_3 (33%)	2	87	97
4	Ts (**2a**)	**3c**	K_2CO_3 (33%)	rt	80	84
5	Ts (**2a**)	**3c**	K_2CO_3 (33%)	−20	20	99
6[d]	Ts (**2a**)	**3c**	K_2CO_3 (33%)	2	80	80
7[e]	Ts (**2a**)	**3c**	K_2CO_3 (33%)	2	56	70
8	Ts (**2a**)	**3c**	K_2HPO_4 (50%)	2	68	53
9	Ts (**2a**)	**3c**	Cs_2CO_3 (66%)	2	78	74
10	Boc (**2b**)	**3c**	K_2CO_3 (33%)	2	traces	nd
11	Cbz (**2c**)	**3c**	K_2CO_3 (33%)	2	traces	nd

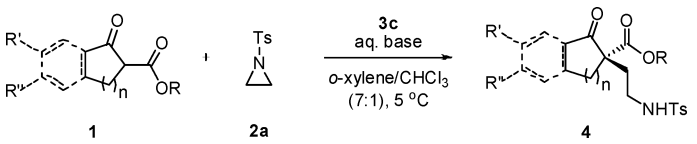
[a] All the reactions were performed using 0.2 mmol of **1a**, 0.1 mmol of **2**, 6 mol% of the catalyst **3** (except for entries 6 and 7), 1.5 mL *o*-xylene–$CHCl_3$ (7 : 1) and 0.4 mL of aqueous phase. [b] Isolated yield. [c] Ee was determined by CSP-HPLC. [d] 3 mol% of the catalyst **3c** was used. [e] 1.5 mol% of the catalyst **3c** was used.

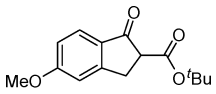
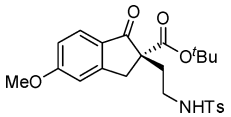
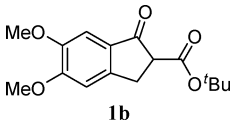
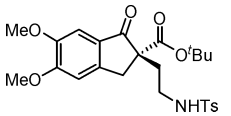
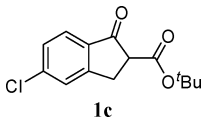
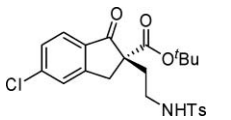
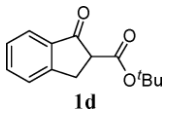
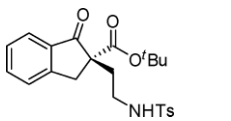
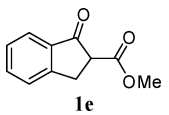
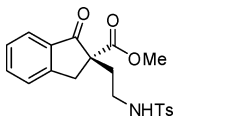
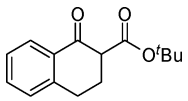
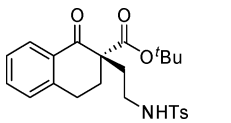
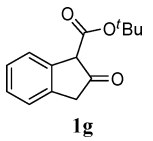
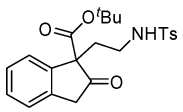
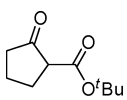
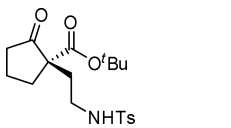
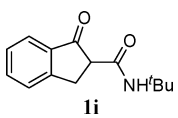
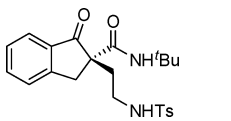
amount of catalyst **3c** was modified in order to observe a possible effect on the yield and enantioselectivity. Using 6 mol% of the catalyst led to an excellent enantioselectivity of 97% ee (entry 3), whereas employing 3 mol% resulted in 80% ee, though still with good yield (entry 6). Lowering the catalytic loading further to 1.5 mol% led to an even further decrease in enantioselectivity and a moderate yield (entry 7). Investigating the effect of the aziridine protecting group, we found that replacing the tosyl group with the less activating Cbz or Boc protecting groups only led to the isolation of traces of the product (entries 10, 11). It was thus concluded that a more electron-withdrawing protecting group, like the tosyl, was necessary in order for the reaction to proceed under these mild conditions. Finally, it was recognized that for aziridine **2a**, 33% aq. K_2CO_3 was the optimal base for obtaining high yield and enantioselectivity (entries 3 *vs.* 8 and 9).

Having in our hands a general and efficient protocol for the asymmetric ring-opening of aziridine **2a**, we focused on the scope and limitations of the procedure. A range of pro-nucleophiles were examined, modified with respect to steric and electronic effects. As shown in Table 2, different cyclic β-ketoesters were found to be appropriate for this catalytic transformation, providing the opened adduct generally in good to excellent yields and enantioselectivities. As expected, the catalytic system had to be fine-tuned for some nucleophile species, primarily through variation of the aqueous base. Adjoining a second methoxy group on the aromatic moiety (**1b**, Table 2, entry 2), still using 33% aq. K_2CO_3 as base, led to **4b** in 86% yield and with a slight decrease in enantioselectivity—90% ee—compared to **4a** (entry 2 *vs.* 1). While the dimethoxy-indanone derivative **1b** worked optimally with the initially established conditions, the β-ketoester **1c**, bearing an electron-withdrawing group attached at the aromatic group, gave 87% ee with 33% aq. K_2CO_3, whereas changing to the milder base 50% aq. K_2HPO_4 gave the desired product with an increased enantioselectivity of 93% ee (entry 3). For the non-substituted indanone derivative **1d**, both 33% aq. K_2CO_3 and 50% aq. K_2HPO_4 gave the desired product **4d** with 87% ee. In addition, the yields were a comparable 84% and 87%, respectively (entry 4). In order to establish the steric effect of the ester moiety, the *tert*-butyl ester group was replaced by a methyl ester. Previous studies have shown a decremental effect when lowering the bulk of the ester moiety.[12] Entries 4 and 5 clearly show the effect for this system. The more bulky *tert*-butyl ester version **1d** led to a much more enantioenriched adduct (87% ee) than the corresponding methyl ester version (70% ee). We also attempted to enhance the scope by increasing the size of the non-aromatic ring from a cyclopentyl to a cyclohexyl moiety (entry 6), but unfortunately no conversion was observed, even with the strong bases 50% aq. K_3PO_4 or 10% aq. NaOH. Realising that only five-membered ring systems would be reactive enough for the ring-opening of the *N*-tosyl protected aziridines, we then examined the effect of regioisomerism. Thus, reacting **1g** at 2 °C using 50% aq. K_2HPO_4 as base led to a disappointing 60% ee (entry 7). Then we re-investigated the effect of the temperature and, surprisingly, an increase in enantioselectivity was observed when conducting the reaction at ambient temperature. Further increasing the temperature to 40 °C caused a lower enantioselectivity of 53%. Interestingly, there appears to be a temperature between 2 °C and 40 °C in which optimal conditions are met for achieving the highest stereoselectivity with **1g**. Finally, we tested the non-phenyl-fused cyclopentanone derivative **1h** (entry 8). As expected, this substrate proved to be much less reactive than its phenyl-fused counterparts. Thus, the strongly basic 50% aq. K_3PO_4 and an increase in concentration were necessary in order to achieve acceptable amounts of product **4h** within a reasonable period of time. The enantiomeric excess of this compound was 77% ee.

Having completed the scope of the ring-opening of *N*-tosyl protected aziridines with cyclic β-ketoesters we studied the β-ketoamide **1i**. This secondary amide gave a disappointing enantioselectivity of 23% ee (entry 9). A small screening of catalysts **3a–c** and the aqueous bases did not improve the stereoselectivity. A protection of the nitrogen atom, in order to avoid any possible pivotal hydrogen-bonding between the amide functionality and the catalyst, was not attempted.

Table 2 Scope of the ring-opening of *N*-tosyl protected aziridines by various β-ketoesters[a]



Entry	β-Ketoester	Aq. base (wt%)	Temp/°C	Product	Yield (%)[b]	Ee (%)[c]
1	 **1a**	K_2CO_3 (33%)	2		**4a**—87	97
2	 **1b**	K_2CO_3 (33%)	2		**4b**—86	90
3	 **1c**	K_2CO_3 (33%) K_2HPO_4 (50%)	2		**4c**—79 83	87 93
4	 **1d**	K_2HPO_4 (50%) K_2CO_3 (33%)	2		**4d**—84 87	87 87
5	 **1e**	K_2HPO_4 (50%)	2		**4e**—89	70
6	 **1f**	K_3PO_4 (50%) 10% NaOH	2		**4f**—0 0	nd nd
7	 **1g**	K_2HPO_4 (50%)	2 rt 40		**4g**—nd 74 nd	60 76 53
8[d]	 **1h**	K_3PO_4 (50%)	2		**4h**—53	77
9	 **1i**	K_3PO_4 (50%)	2		**4i**—82	23

[a] All reactions were performed with 0.2 mmol **1**, 0.1 mmol **2a** and 6 mol% of the catalyst **3c**, 1.5 mL *o*-xylene–$CHCl_3$ (7 : 1) (except for entry 8) and 0.4 mL of aqueous phase were used. [b] Isolated yield. [c] Ee was determined by CSP-HPLC. [d] 0.5 mL of *o*-xylene–$CHCl_3$ (7 : 1) was used.

To prove the synthetic applicability of the developed protocol, a gram-scale reaction was set up. Following the general procedure, reacting **1a** with 2.5 mmol of **2a** for 24 h, yielded the product in 82% yield with 84% ee, which crystallises to be an enantiopure compound.

The absolute configuration of the product **4a** was established by X-ray crystallography to be *S* (Fig. 2).[14] As such, it is in agreement with previous findings[11] when catalyst **3c** was used for electrophilic functionalisations of β-keteoesters.

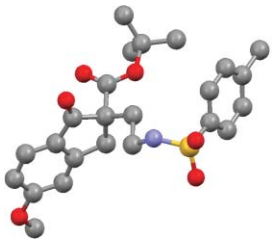


Fig. 2 X-Ray structure of **4a**. For clarity, the structure has been simplified by removal of selected atoms. (C = grey, O = red, N = blue, S = yellow)

In conclusion, we have presented an organocatalytic asymmetric ring-opening of *N*-tosyl protected aziridines catalysed by the phase-transfer *N*-9-anthracenylmethyl *O*-adamantoyl derivatised cinchonine catalyst, recently developed by our own group. The absolute configuration of the products was determined to be *S* by X-ray crystallography. Finally, it was shown that a gram-scale process is feasible, proving the synthetic value of the procedure.

Acknowledgements

This work was made possible by a grant from the Danish National Research Foundation and OChemSchool. We would like to thank Dr Jacob Overgaard for X-ray crystallographic analysis.

Notes and references

1 (*a*) X. E. Hu, *Tetrahedron*, 2004, **60**, 2701; (*b*) G. S. Singh, M. D'hoogle and N. De Kimpe, *Chem. Rev.*, 2007, **107**, 2080.
2 (*a*) C. Kibayashi, *Chem. Pharm. Bull.*, 2005, **53**, 1375; (*b*) O. V. Miroshnikova, T. H. Hudson, L. Gerena and D. E. Kyle, *J. Med. Chem.*, 2007, **50**, 889.
3 (*a*) Z. Li, M. Fernández and E. N. Jacobsen, *Org. Lett.*, 1999, **1**, 1611; (*b*) T. Mita, I. Fujimori, R. Wada, J. Wen, M. Kanai and M. Shibasaki, *J. Am. Chem. Soc.*, 2005, **127**, 11252; (*c*) K. Arai, S. Lucarini, M. M. Salter, K. Ohta, Y. Yamashita and S. Kobayashi, *J. Am. Chem. Soc.*, 2007, **129**, 8103; (*d*) P. Muller and P. Nury, *Org. Lett.*, 1999, **1**, 439.
4 Y. Fukuta, T. Mita, N. Fukuda, M. Kanai and M. Shibasaki, *J. Am. Chem. Soc.*, 2006, **128**, 6312.
5 For a review on current synthesis to Tamiflu see: (*a*) S. Abrecht, P. Harrington, H. Iding, M. Karpf, R. Trussardi, B. Wirz and U. Zutter, *Chimia*, 2004, **58**, 621; (*b*) For a highlight, see V. Farina and J. D. Brown, *Angew. Chem., Int. Ed.*, 2006, **45**, 7330.
6 (*a*) For reviews, see: M. J. O'Donnel in *Catalytic Asymmetric Synthesis*, ed. I. Ojima, Wiley-VHC, Weinheim, Germany, 2nd edn, 2000, p. 727; (*b*) T. Ooi and K. Maruoka, *Angew. Chem., Int. Ed.*, 2007, **46**, 4222; (*c*) T. Hashimoto and K. Maruoka, *Chem. Rev.*, 2007, **107**, 5656; (*d*) For recent examples, see: F. Fini, V. Sgarzani, D. Pettersen, R. P. Herrera, L. Bernadi and A. Ricci, *Angew. Chem., Int. Ed.*, 2005, **44**, 7975; (*e*) A. Okada, T. Shibuguchi, T. Ohshima, H. Masu, K. Yamaguchi and M. Shibasaki, *Angew. Chem., Int. Ed.*, 2005, **44**, 4564; (*f*) C. Palomo, M. Oiarbide, A. Laso and R. López, *J. Am. Chem. Soc.*, 2005, **127**, 17622; (*g*) P. Elsner, L. Bernardi, G. Dela Salla, J. Overgaard and K. A. Jørgensen, *J. Am. Chem. Soc.*, 2008, **130**, 4897.
7 For reviews, see: (*a*) A. G. Doyle and E. N. Jacobsen, *Chem. Rev.*, 2007, **107**, 5713; (*b*) T. Akiyama, *Chem. Rev.*, 2007, **107**, 5744; (*c*) For recent examples, see: C. H. Cheon and H. Yamamoto, *J. Am. Chem. Soc.*, 2008, **130**, 9246; (*d*) J. Itoh, K. Fuchibe and T. Akiyama, *Angew. Chem., Int. Ed.*, 2008, **47**, 4016; (*e*) D. Kampen, A. Ladépêche, G. Classen and B. List, *Adv. Synth. Catal.*, 2008, **350**, 962.
8 Z.-B. Luo, X.-L. Hou and L.-X. Dai, *Tetrahedron: Asymmetry*, 2007, **18**, 443.
9 E. B. Rowland, G. B. Rowland, E. Rivera-Otero and J. C. Antilla, *J. Am. Chem. Soc.*, 2007, **129**, 12084.
10 Dixon *et al.* have reported similar work on organocatalytic enantioselective and diastereoselective ring-opening of *N*-protected aziridines with β-ketoesters: T. A. Moss, D. R. Fenwick and D. J. Dixon, *J. Am. Chem. Soc.*, 2008, **130**, 10076.
11 (*a*) T. B. Poulsen, L. Bernardi, J. Alemán, J. Overgaard and K. A. Jørgensen, *J. Am. Chem. Soc.*, 2007, **129**, 441; (*b*) L. Bernardi, J. López-Cantarero, B. Niess and K. A. Jørgensen, *J. Am. Chem. Soc.*, 2007, **129**, 5772; (*c*) J. Alemán, E. Reyes, B. Richter, J. Overgaard and K. A. Jørgensen, *Chem. Commun.*, 2007, 3921.
12 For investigations concerning steric effects of the ester moiety of the β-ketoester and of the 9-*OR* group of the catalyst, see: T. B. Poulsen, L. Bernardi, M. Bell and K. A. Jørgensen, *Angew. Chem., Int. Ed.*, 2006, **45**, 6551.
13 Catalysts **3a** and **3b** are the commercially available pseudoenantiomers of **3c**.
14 Crystal data for **4a**: $C_{24}H_{29}NO_6S$, $M = 459.5552$, orthorhombic, space group $P\ 21\ 21\ 21$ (no. 115), $a = 5.7683(2)$ Å, $b = 9.0468(3)$ Å, $c = 43.5087(17)$ Å, $V = 2270.49(14)$ Å^3, $T = 100$ K, $Z = 4$, $D_c = 1.344$ g cm^{-3}, μ(Mo Kα, $\lambda = 0.71073$ Å) $= 0.183$ mm^{-1}, 4819 reflections collected, 4819 unique [$R_{int} = 0.0443$], which were used in all calculations. Refinement on F^2, final $R(F) = 0.0604$, $R_w(F2) = 0.1296$. CCDC 695828.

