DOI: 10.1002/asia.201000040

Asymmetric Catalytic Aziridination of Cyclic Enones

Francesco De Vincentiis,[c] Giorgio Bencivenni,[c] Fabio Pesciaioli,[c] Andrea Mazzanti,[c] Giuseppe Bartoli,[c] Patrizia Galzerano,[c] and Paolo Melchiorre*[a, b]

Abstract: The first catalytic method for the asymmetric aziridination of cyclic enones is described. The presented organocatalytic strategy is based on the use of an easily available organocatalyst that is able to convert a wide range of cyclic enones into the desired aziridines with very high enantiomeric purity and good chemical yield. Such a method may very well open up new opportunities to stereoselectively prepare complex chiral molecules that possess an indane moiety, a framework that is found in a large number of bioactive and pharmaceutically important molecules

Keywords: asymmetric · catalysis · aziridines · domino reactions · enones · organocatalysis

Introduction

Enantiomerically pure aziridines exhibit numerous important features, including serving as essential motifs of biologically interesting compounds and as valuable chiral synthons that can be stereoselectively converted into useful amine derivatives.[1] As a consequence, the development of reliable methods for their asymmetric synthesis from nonchiral precursors represents a continuing synthetic target.[2] Among the existing strategies, the catalytic asymmetric aziridinations of olefins provide direct and useful access to such a privileged scaffold, and great efforts and progress have been made in this field.[3] Although there are powerful solutions for several different classes of olefins,[4] a highly enantioselective aziridination of cyclic enones has, to our knowledge, not been described. Herein, we report an efficient solution to this synthetic problem based on the use of an easily available organocatalyst that is able to convert a wide range of cyclic enones into the desired aziridines with very high enantiomeric purity and good chemical yield.

In their pioneering works, Pellacani, Tardella, and coworkers highlighted the potential of a conjugate addition–cyclization strategy to directly access aziridines from electron-deficient olefins.[5] This sequential approach is based on the use of a suitable compound that should first act as an N-centered nucleophile, and then should become electrophilic to facilitate an intramolecular cyclization step. In principle, this strategy can be viewed as a powerful platform for developing asymmetric catalytic aziridinations: a chiral catalyst able to promote the first aza-Michael step while enforcing a high level of stereocontrol would lead to the one-step preparation of highly enantioenriched chiral aziridines (Scheme 1). However, previously described asymmetric variants—based on phase-transfer catalysis[5d,6a] or chiral tertiary amines[6b,c]—often lack scope, reactivity, and selectivity.[6]

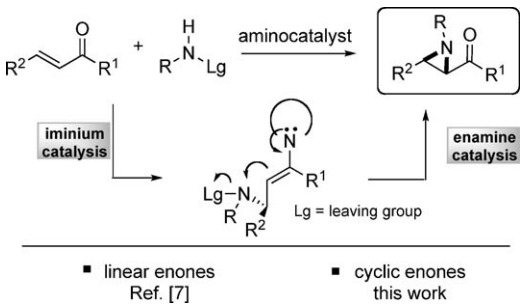
Very recently, we successfully exploited this sequential approach by discovering a highly enantioselective aziridination

[a] Prof. Dr. P. Melchiorre
ICIQ—Institute of Chemical Research of Catalonia
Av. Països Catalans 16, 43007 Tarragona (Spain)
Fax: (+34) 977-920-823
E-mail: pmelchiorre@iciq.es

[b] Prof. Dr. P. Melchiorre
ICREA—Institució Catalana de Recerca i Estudis Avançats
Pg. Lluís Companys 23, 08010 Barcelona (Spain)

[c] F. De Vincentiis, Dr. G. Bencivenni, F. Pesciaioli, Dr. A. Mazzanti, Prof. G. Bartoli, Dr. P. Galzerano
Dipartimento di Chimica Organica "A. Mangini"
Università di Bologna, Viale Risorgimento 4, 40136 Bologna (Italy)

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/asia.201000040.



Scheme 1. The aziridination strategy applied in the present study.

of linear α,β-unsaturated ketones[7] catalyzed by 9-amino(9-deoxy)*epi*-hydroquinine (**9-*epi*-NH$_2$-HQ**), a chiral primary amine that we and others, independently,[8] have established as a highly stereoselective catalyst for ketone functionalization (Figure 1). The success of the aziridination method was dependent on the ability of **9-*epi*-NH$_2$-HQ** to promote a well-defined iminium–enamine tandem sequence[9] delivering enantiopure *N*-Cbz- (Cbz = benzyloxycarbonyl) and *N*-Boc-protected (Boc = *tert*-butyloxycarbonyl) *trans*-aziridines (Scheme 1).

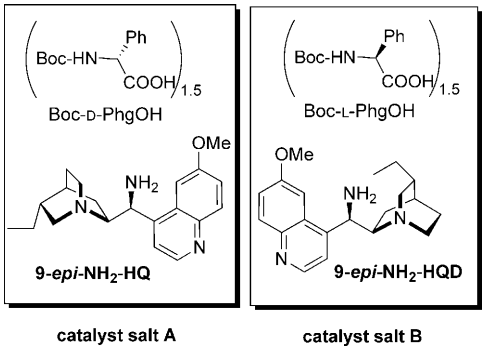


Figure 1. The primary amine–acid combinations used in this study.

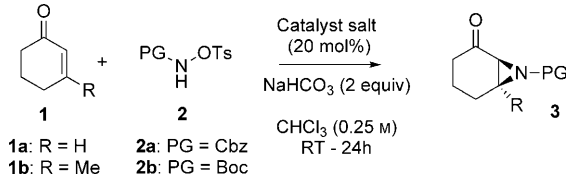
Triggered by the lack of any asymmetric strategy for the aziridination of cyclic enones and in an effort to expand the scope of our method, we turned our attention to cyclic α,β-unsaturated ketones. Herein, we report the results of our investigations, which provide easy and fast access to both of the antipodes of synthetically valuable aziridines with very high enantiomeric purity.

Results and Discussion

Initially, we focused on the aziridination of cyclohexanone **1a** by using the catalyst primary amine salt **A** (Figure 1)—made by combining the easily available **9-*epi*-NH$_2$-HQ** with D-*N*-Boc phenylglycine (1:1.5 ratio of amine to acid)—which exhibited high reactivity and selectivity in the aziridination of linear enones.[7] After extensive screening of the standard reaction parameters,[10] we found that treating 1.2 equiv of **1a** with tosylated hydroxycarbamate **2a**,**b** in the presence of 2 equiv of $NaHCO_3$[11] and catalyst salt **A** (20 mol%) in chloroform for 24 h directly resulted in the formation of *N*-Cbz or *N*-Boc bicyclic adducts **3a** and **3b**, respectively, in high yield and almost perfect stereoselectivity [diastereomeric ratio (d.r.) and enantiomeric ratio (e.r.) ≥99:1, entries 1 and 2, Table 1].

Interestingly, the method is also effective with β-methyl cyclohexenone **1b**, a challenging compound leading to a heterocyclic adduct with a quaternary stereocenter. The reaction with **2a** furnishes the corresponding *N*-Cbz aziridine **3c** with moderate enantioselectivity (entry 3).[10] Fortunately, by using the *N*-Boc-protected nucleophile **2b** we found that the aziridination proceeds with greatly improved selectivity, thereby delivering compound **3d** in 92% *ee* (entry 4).

Table 1. Catalyst investigations for the aziridination of cyclic enones.[a]



Entry	1	2	Catalyst salt amine	Catalyst salt acid	3	Yield [%][b]	e.r.[c]
1	**a**	**a**	catalyst salt **A**		**a**	86	99:1
2	**a**	**b**	catalyst salt **A**		**b**	73	99.5:0.5
3	**b**	**a**	catalyst salt **A**		**c**	84	86:14
4	**b**	**b**	catalyst salt **A**		**d**	75	96:4
5	**a**	**a**	catalyst salt **B**		**a**	98	0.5:99.5
6	**a**	**b**	catalyst salt **B**		**b**	76	0.5:99.5
7	**b**	**b**	catalyst salt **B**		**d**	88	7:93
8	**b**	**b**	**9-*epi*-NH$_2$-HQD**	D-PhgOH	**d**	56	9:91
9	**b**	**b**	**9-*epi*-NH$_2$-HQ**	L-PhgOH	**d**	54	94:6

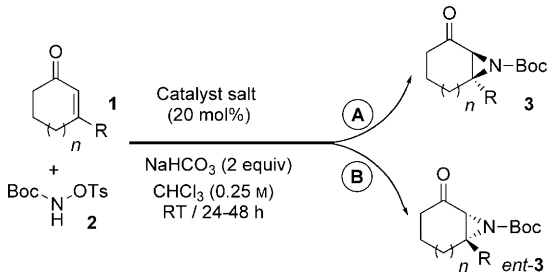
[a] Abbreviations: Ts = tosyl; PhgOH: *N*-Boc phenylglycine. A single diastereoisomer has always been detected by ^{1}H NMR spectroscopic analysis of the crude mixture. Reactions carried out on a 0.2 mmol scale at room temperature for 24 h using 1.2 equiv of enone **1** and 20 mol% of the catalyst salt (1:1.5 amine to acid ratio). [b] Yield of isolated product after chromatography. [c] Enantiomeric ratio determined by HPLC analysis on chiral stationary phases.

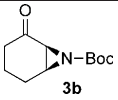
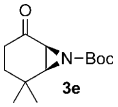
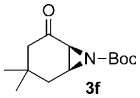
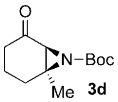
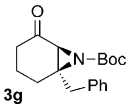
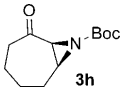
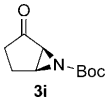
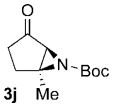
The efficiency of an asymmetric method is not only measured by its selectivity and reliability, but also by the possibility of accessing both of the antipodes of the products by simply selecting the appropriate catalyst enantiomer. The present case is complicated by the fact that catalyst salt **A** is composed of two distinct chiral entities, one of which is derived from the *Cinchona* alkaloid. Notably, the combination of the pseudoenantiomer **9-*epi*-NH$_2$-HQD**, derived from hydroquinidine, with L-*N*-Boc phenylglycine in a 1:1.5 ratio (catalyst salt **B**) and its use in the aziridination of both **1a** and **1b** affords the corresponding aziridines **3** with opposite absolute configuration while maintaining a very high level of selectivity (entries 5–7).

Conceptually, the foundations for rationalizing the influence of chiral counteranions on both the reactivity and stereoselectivity of iminium catalysis have already been established.[12] To gain more insight into the role played by the two chiral entities of catalyst salts **A** and **B** within the present chemistry, we used the missmatched combinations to promote the reaction of **1b** with **2b** (entries 8 and 9). The observed lower reactivity and slightly decreased stereoselectivity (88% *ee* vs. 92% *ee*) and the sense of asymmetric induction clearly indicate that although the chiral primary amine is mainly responsible for directing the process toward a stereoselective path, the chiral cocatalyst is important to improve the general efficiency of the aziridination.[13]

The scope and limitations of the asymmetric aziridination of cyclic enones were investigated next, by using **2b** as the nucleophile and both catalyst salts **A** and **B** to access the two enantiomeric aziridines **3** (Table 2). In addition to cyclo-

Table 2. Scope of the aziridination of cyclic enones.[a]



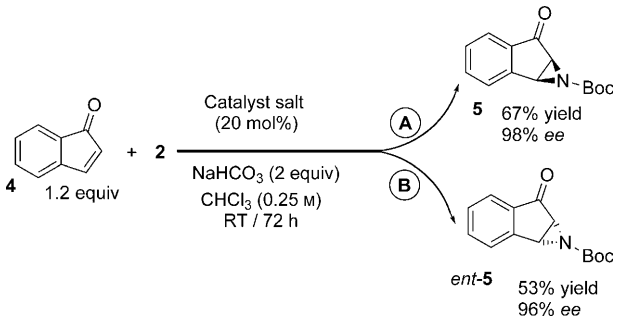
Entry	Aziridine	Catalyst salt	Yield [%][b]	*ee* [%][c]
1	 3b	**A**	73 (51)[d]	99 (99)[d]
		B	76	99
2	 3e	**A**	84	98
		B	84	98
3	 3f	**A**	33	98
		B	53	98
4	 3d	**A**	75	92
		B	88	86
5[e]	 3g	**A**	93	95
		B	85	93
6	 3h	**A**	90	98
		B	98	94
7	 3i	**A**	39	93
		B	44	97
8[f]	 3j	**A**	52	85
		B	68	61

[a] A single diastereoisomer has always been detected by ^{1}H NMR spectroscopic analysis of the crude mixture. Reactions carried out at room temperature for 24 h using 1.2 equiv of enone **1** on a 0.2 mmol scale. [b] Yield of isolated product. [c] *ee* of **3** was determined by HPLC analysis. [d] Number in parenthesis refers to reaction carried out using 10 mol% of catalyst salt **A**. [e] 48 h reaction time. [f] Using 2 equiv of enone, 72 h reaction time.

hexanone itself, various substituted cyclic enones could be converted into *N*-Boc-protected aziridines with excellent results (entries 2 and 3). The process allows the creation of quaternary stereogenic centers with high fidelity when employing β-substituted cyclohexanones (entries 4 and 5). Both 2-cycloheptanones and 2-cyclopentanone turned out to be excellent substrates, although the latter shows a reduced reactivity (entries 6 and 7). Also, β-methyl 2-cyclopentanone reacts under the reported conditions, but the corresponding aziridine **3j** is formed with moderate enantioselectivity (entry 8), whereas α-substituted cyclic enones proved to be unreactive.

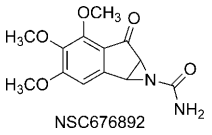
The relative and absolute configurations of aziridines **3d**, **3e**, and **3h** were assigned by NMR NOE spectroscopic analyses and by means of time-dependent (TD) DFT calculations of the electronic circular dichroism (ECD) spectra, as described in the Supporting Information.

Finally, we explored the possibility of extending the aziridination method to indenone derivative **4**, a challenging compound that has never served before as a suitable substrate for iminium catalysis due to the severe steric hindrance, which hampers the condensation with the catalyst. Notably, both the antipodes of the corresponding tricyclic aziridine derivative **5** can be prepared with good chemical yield and very high enantioselectivity (Scheme 2).



Scheme 2. Aziridination of 1*H*-inden-1-one.

Extension to such a compound class opens up new opportunities to stereoselectively prepare complex chiral molecules that possess an indane moiety, a framework that is found in a large number of bioactive and pharmaceutically important molecules.[14] NSC676892[14b] is only one example of the potentially bioactive tricyclic, aziridine-containing heterocycle that may be synthesized by using the present method. Efforts toward this aim are underway in our laboratories.



NSC676892

Conclusion

In summary, we have disclosed the first catalytic and highly enantioselective aziridination of cyclic α,β-unsaturated ketones, further illustrating the increasing utility gained by chiral primary amine catalysis in the realm of asymmetric synthesis. The method uses easily available reagents and catalysts and provides reliable and highly stereoselective access to a wide variety of *N*-Boc-protected aziridines. Our current efforts aim to further extend the utility of the method to the synthesis of biologically interesting compounds as well as to determine a more detailed mechanistic understanding.

Experimental Section

General Methods

The ^1H and ^{13}C NMR spectra were recorded at 600 and 150 MHz, respectively. The chemical shifts (δ) for ^1H and ^{13}C are given in ppm relative to residual signals of the solvents ($CHCl_3$). Coupling constants are given in Hz. Carbon types were determined from distortionless enhancement by polarization transfer (DEPT) ^{13}C NMR spectroscopy experiments. The following abbreviations are used to indicate the multiplicity: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br s, broad signal. Purification of the reaction products was carried out by flash chromatography (FC) on silica gel (230–400 mesh). For thin-layer chromatography (TLC) analysis throughout this work, Merck precoated TLC plates (silica gel 60 GF_{254}, 0.25 mm) were used. Optical rotations are reported as follows: $[\alpha]_D^{RT}$ (c in g per 100 mL, solvent). The diastereomeric ratio (d.r.) was determined by ^1H NMR spectroscopic analysis of the crude reaction mixture, and confirmed by HPLC analysis on chiral stationary phases columns. High-performance liquid chromatography (HPLC) was performed an Agilent 1100 series instrumentation. A Daicel Chiralpak AD-H column with *i*PrOH/hexane as the eluent proved to be effective for all the aziridines synthesized. HPLC traces were compared with racemic samples obtained by carefully mixing the two product antipodes obtained by performing the individual reactions with 9-amino(9-deoxy)*epi*-hydroquinine (catalyst salt **A**) and its pseudoenantiomer 9-amino(9-deoxy)*epi*-hydroquinidine (catalyst salt **B**) separately.

Syntheses

General procedure for the organocatalytic asymmetric aziridination of cyclic enones (Table 2): All the reactions were carried out with no precautions to exclude air or moisture and using the appropriate catalytic salt combination **A** or **B**. In an ordinary vial equipped with a Teflon-coated stirrer bar, the chiral primary amine (0.04 mmol, 13 mg, 20 mol%) was dissolved in $CHCl_3$ (0.8 mL). After addition of *N*-Boc phenylglycine (0.06 mmol, 15 mg, 30 mol%), the solution was stirred for 10 min at room temperature. Cyclic enone **1** (0.24 mmol, 1.2 equiv) was added, and stirring continued for an additional 10 min. Then nucleophile **2** (0.2 mmol) was added followed by the addition of $NaHCO_3$ (0.4 mmol, 32 mg, 2 equiv) in one portion. Stirring was continued for 1 d, then the crude reaction mixture was diluted with CH_2Cl_2 (1 mL) and flushed through a short plug of silica, using CH_2Cl_2/Et_2O 1:1 as the eluent. The solvent was removed in vacuo, and the residue was purified by flash chromatography (FC) to yield the desired aziridine **3**.

3b: Prepared by following the general procedure using catalyst salt **A** to furnish the crude product as a single diastereomer. The title compound was isolated as a colorless oil by column chromatography (hexane/acetone 8:2) in 73% yield and 99% *ee*. The *ee* was determined by HPLC analysis on a Chiralcel AD-H column: 90:10 hexane/*i*PrOH, flow rate 0.75 mL min^{-1}, λ=214, 254 nm: τ_{major}=7.6 min, τ_{minor}=8.2 min. $[\alpha]_D^{RT}$=−95.5 (c=0.74, $CHCl_3$, 99% *ee*); ^1H NMR: δ=1.45 (s, 9H), 1.63–1.68 (m, 1H) 1.74–1.82 (m, 1H), 1.92–1.08 (m, 2H), 2.20–2.27 (m, 1H), 2.47–2.52 (m, 1H), 2.88 (d, J=5.89 Hz, 1H), 3.05–3.09 ppm (m, 1H); ^{13}C NMR: δ=17.5 (CH_2), 22.8 (CH_2), 28.0 (CH_3), 37.1 (CH_2), 40.6 (CH), 43.4 (CH), 82.5 (C), 160.8 (C), 204.5 ppm (C); ESIMS: m/z: 234 $[M+Na]^+$, 212 $[M+1]^+$.

3d: Prepared by following the general procedure using catalyst salt **A** to furnish the crude product as a single diastereomer. The title compound was isolated as a white solid by column chromatography (hexane/Et_2O/$CHCl_3$ 5:3:2) in 75% yield and 92% *ee*. The *ee* was determined by HPLC analysis on a Chiralcel AD-H column: 95:5 hexane/*i*PrOH, flow rate 0.75 mL min^{-1}, λ=214, 254 nm: τ_{minor}=8.20 min τ_{major}=10.38 min. ^1H NMR: δ=1.44 (s, 3H), 1.51 (s, 9H), 1.64–1.75 (m, 2H), 2.01–2.10 (m, 2H), 2.14–2.22 (m, 1H), 2.44–2.52 (m, 1H), 2.83 ppm (s, 1H); ^{13}C NMR: δ=17.4 (CH), 20.2 (CH_3), 27.9 (CH_3), 29.1 (CH), 36.0 (CH), 47.4 (C), 49.5 (CH), 81.9 (C), 158.9 (C), 205.4 ppm (C); ESIMS: m/z: 248 $[M+Na]^+$, 226 $[M+1]^+$.

3e: Prepared by following the general procedure using catalyst salt **A** to furnish the crude product as a single diastereomer. The title compound was isolated as a white solid by column chromatography (hexane/acetone 8:2) in 84% yield and 98% *ee*. HPLC analysis on a Chiralcel AD-H column: 90:10 hexane/*i*PrOH, flow rate 0.75 mL min^{-1}, λ=214, 254 nm: τ_{minor}=5.98 min, τ_{major}=6.86 min. $[\alpha]_D^{RT}$=−106.7 (c=0.98, $CHCl_3$, 98% *ee*); ^1H NMR: δ=1.03 (s, 3H), 1.21 (s, 3H), 1.26–1.38 (m, 1H), 1.44 (s, 9H), 1.88–1.95 (m, 1H), 2.12–2.20 (m, 1H), 2.35 (ddd, J=19.23, 8.93, 19.11 Hz, 1H), 2.64–2.67 (dd, J=5.89, 1.47 Hz, 1H), 2.92 ppm (d, J=5.91 Hz, 1H); ^{13}C NMR: δ=23.4 (CH_3), 27.8 (CH_3), 28.0 (CH_3), 30.42 (CH_2), 33.82 (CH_2), 44.25 (CH), 50.2 (CH), 82.3 (C), 160.5 (C), 204.8 ppm (C); ESIMS: m/z: 262 $[M+Na]^+$, 240 $[M+1]^+$.

3f: Prepared by following the general procedure using catalyst salt **A** to furnish the crude product as a single diastereomer. The title compound was isolated as a colorless oil by column chromatography (hexane/ethyl acetate 8:2) in 33% yield and 98% *ee*. The *ee* was determined by HPLC analysis on a Chiralcel AD-H column: 99:1 hexane/*i*PrOH, flow rate 0.650 mL min^{-1}, λ=214, 254 nm: τ_{minor}=18.44 min, τ_{major}=20.47 min. $[\alpha]_D^{RT}$=+43.4 (c=0.65, $CHCl_3$, 98% *ee*); ^1H NMR: δ=0.88 (s, 3H), 1.00 (s, 3H), 1.44 (s, 9H), 1.78–1.83 (m, 2H), 1.94 (d, J=14.60 Hz, 1H), 2.58 (d, J=14.00 Hz, 1H), 2.87 (d, J=6.46 Hz, 1H), 2.97 ppm (t, J=6.18 Hz, 1H); ^{13}C NMR: δ=27.4 (CH_3), 27.8 (CH_3), 30.8 (CH_3), 36.8 (CH_2), 37.7 (C), 41.0 (CH), 42.8 (CH), 48.8 (CH_2), 82.3 (C), 160.3 (C), 206.0 ppm (C); ESIMS: m/z: 262 $[M+Na]^+$, 240 $[M+1]^+$.

3g: Prepared by following the general procedure over the course of 48 h using catalyst salt **A** to furnish the crude product as a single diastereomer. The title compound was isolated as a colorless oil by column chromatography (hexane/Et_2O 7:3) in 93% yield and 95% *ee*. The *ee* was determined by HPLC analysis on a Chiralcel AD-H column: 95:5 hexane/*i*PrOH, flow rate 0.75 mL min^{-1}, λ=214, 254 nm: τ_{minor}=12.52 min, τ_{major}=15.15 min. $[\alpha]_D^{RT}$=−59.7 (c=0.73, $CHCl_3$, 95% *ee*); ^1H NMR: δ=1.48 (s, 9H), 1.51–1.59 (m, 2H), 1.86–1.98 (m, 2H), 2.01–2.07 (m, 1H), 2.35–2.41 (m, 1H), 2.46 (d, J=14.45 Hz, 1H), 3.05 (s, 1H), 3.23 (d, J=14.53 Hz, 1H), 7.20 (d, J=7.79 Hz, 2H), 7.23–7.27 (m, 1H), 7.28–7.32 ppm (m, 2H); ^{13}C NMR: δ=1.2 (CH_3), 17.6 (CH_2), 26.3 (CH_2), 28.2 (CH), 36.3 (CH_2), 41.5 (CH_2), 48.9 (CH), 51.3 (C), 82.4 (C), 127.4 (CH), 128.9 (CH), 129.6 (CH), 136.5 (C), 205.2 ppm (C); ESIMS: m/z: 324 $[M+Na]^+$.

3h: Prepared by following the general procedure using catalyst salt **A** to furnish the crude product as a single diastereomer. The title compound was isolated as a colorless oil by column chromatography (hexane/Et_2O 7:3) in 90% yield and 98% *ee*. The *ee* was determined by HPLC analysis on a Chiralcel AD-H column: 95:5 hexane/*i*PrOH, flow rate 0.75 mL min^{-1}, λ=214, 254 nm: τ_{major}=8.07 min, τ_{minor}=8.88 min. $[\alpha]_D^{RT}$=−103.2 (c=0.8, $CHCl_3$, 98% *ee*); ^1H NMR: δ=0.92–1.01 (m, 1H), 1.44 (s, 9H), 1.60–1.67 (m, 1H), 1.67–1.68 (m, 2H), 1.79–1.85 (m, 1H), 2.23–2.30 (m, 1H), 2.39–2.46 (m, 1H), 2.72–2.78 (m, 1H), 2.84–2.88 (m, 1H), 3.00–3.02 ppm (dd, J=1.61, 7.22 Hz, 1H); ^{13}C NMR: δ=23.67 (CH_2), 23.85 (CH_2), 28 (CH_2), 28.08 (CH_3), 40.57 (CH_2), 40.99 (CH), 47.57 (CH), 82.20 (C), 161.11 (C), 209.50 ppm (C); ESIMS: m/z: 248 $[M+Na]^+$, 226 $[M+1]^+$.

3i: Prepared by following the general procedure using catalyst salt **A** to furnish the crude product as a single diastereomer. The title compound was isolated as a pale yellow oil by column chromatography (hexane/ethyl acetate 8:2) in 39% yield and 93% *ee*. The *ee* was determined by HPLC analysis on a Chiralcel AD-H column: 90:10 hexane/*i*PrOH, flow rate 0.750 mL min^{-1}, λ=214, 254 nm: τ_{minor}=10.66 min, τ_{major}=11.42 min. $[\alpha]_D^{RT}$=+43.4 (c=0.72, $CHCl_3$, 93% *ee*); ^1H NMR: δ=1.46 (s, 9H), 1.93–2.03 (m, 1H), 2.07–2.22 (m, 2H), 2.47–2.51 (m, 1H), 3.01 (d, J=3.09 Hz, 1H), 3.38 ppm (t, J=3.11 Hz, 1H); ^{13}C NMR: δ=21.5 (CH_2), 28.1 (CH_3), 31.7 (CH2), 44.1 (CH), 44.3 (CH), 129.9 ppm (C) ; ESIMS: m/z: 220 $[M+Na]^+$, 198 $[M+1]^+$.

3j: Prepared by following the general procedure over the course of 72 h to furnish the crude product as a single diastereomer. The title compound was isolated as a colorless oil by column chromatography (hexane/acetone 8:2) in 52% yield and 85% *ee*. The *ee* was determined by HPLC analysis on a Chiralcel AD-H column: 90:10 hexane/*i*PrOH, flow rate 0.750 mL min^{-1}, λ=214, 254 nm: τ_{minor}=6.83 min, τ_{major}=12.54 min. $[\alpha]_D^{RT}$=+39.9 (c=0.90, $CHCl_3$, 85% *ee*); ^1H NMR: δ=1.45 (s, 9H), 1.51 (s, 3H), 1.94–2.04 (m, 2H), 2.19–2.28 (m, 1H), 2.46–2.54 (m, 1H), 2.83 ppm (s, 1H); ^{13}C NMR: δ=19.5 (CH_3), 26.3 (CH_2), 28.1 (CH_3), 33.6

(CH_2), 50.3 (CH), 52.6 (C), 82.4 (C), 158.1 (C), 207.9 ppm (C); ESIMS: m/z: 234 $[M+Na]^+$, 212 $[M+1]^+$.

5 (Scheme 2): Prepared by following the general procedure over the course of 72 h using catalyst salt **A** to furnish the crude product as a single diastereomer. The title compound was isolated as a red solid by column chromatography (hexane/acetone 85:15) in 67% yield and 98% *ee*. The *ee* was determined by HPLC analysis on a Chiralcel AD-H column: 95:50 hexane/*i*PrOH, flow rate 0.75 mL min^{-1}, $\lambda = 214$, 254 nm: $\tau_{major} = 15.71$ min, $\tau_{minor} = 16.39$ min. $[\alpha]_D^{RT} = +24.5$ ($c = 0.86$, $CHCl_3$, 98% *ee*); ^{1}H NMR: $\delta = 1.12$ (s, 9H), 3.53 (d, $J = 2.87$ Hz, 1H), 4.09 (d, $J = 2.77$ Hz, 1H), 7.41 (td, $J = 1.16$, 7.46 Hz, 1H), 7.58 (dt, $J = 1.26$, 7.40 Hz, 1H), 7.62 (dt, $J = 1.09$, 7.60 Hz, 1H), 7.70 ppm (dt, $J = 0.59$, 7.59 Hz, 1H); ^{13}C NMR: $\delta = 27.6$ (CH_3), 42.4 (CH), 43.1 (CH), 82.6 (C), 125.4 (CH), 127.1 (CH), 129.6 (CH), 133.1 (C), 134.5 (CH), 146.6 (C), 157.8 (C), 195.3 ppm (C); ESIMS: m/z: 268 $[M+Na]^+$.

Acknowledgements

This work was supported by Bologna University and the Institute of Chemical Research of Catalonia (ICIQ) Foundation.

[1] For overviews focusing on aziridine transformations, see: a) W. McCoull, F. A. Davies, *Synthesis* **2000**, 1347; b) B. Zwanenburg, P. ten Holte, *Top. Curr. Chem.* **2001**, *216*, 93; c) A. Cardillo, L. Gentilucci, A. Tolomelli, *Aldrichimica Acta* **2003**, *36*, 39; d) X. E. Xu, *Tetrahedron* **2004**, *60*, 2701; e) I. D. G. Watson, L. Yu, A. K. Yudin, *Acc. Chem. Res.* **2006**, *39*, 194.

[2] For reviews on aziridination reactions, see: a) D. Tanner, *Angew. Chem.* **1994**, *106*, 625; *Angew. Chem. Int. Ed. Engl.* **1994**, *33*, 599; b) J. B. Sweeney, *Chem. Soc. Rev.* **2002**, *31*, 247; c) P. Müller, *Chem. Rev.* **2003**, *103*, 2905; d) P. Dauban, R. H. Dodd, *Synlett* **2003**, 1571; e) C. Moessner, C. Bolm in *Transition Metals for Organic Chemistry: Building Blocks and Fine Chemicals*, *Vol. 2* (Eds.: M. Beller, C. Bolm), 2nd ed., Wiley-VCH, Weinheim, **2004**, p. 389; f) *Aziridines and Epoxides in Organic Synthesis* (Ed.: A. K. Yudin), Wiley-VCH, Weinheim, **2006**.

[3] For a review of catalytic asymmetric aziridinations up to the year 2003, see: P. Müller, C. Fruit, *Chem. Rev.* **2003**, *103*, 2905.

[4] For selected examples of metal-catalyzed asymmetric aziridinations of alkenes, see: a) Z. Li, K. R. Conser, E. N. Jacobsen, *J. Am. Chem. Soc.* **1993**, *115*, 5326; b) D. A. Evans, M. M. Faul, M. T. Bilodeau, B. A. Anderson, D. M. Barnes, *J. Am. Chem. Soc.* **1993**, *115*, 5328; c) C. J. Sanders, K. M. Gillespie, D. Bell, P. Scott, *J. Am. Chem. Soc.* **2000**, *122*, 7132; d) J. X. Xu, L. G. Ma, P. Jiao, *Chem. Commun.* **2004**, 1616; e) X. Wang, K. Ding, *Chem. Eur. J.* **2006**, *12*, 4568.

[5] a) S. Fioravanti, L. Pellacani, S. Stabile, P. A. Tardella, R. Ballini, *Tetrahedron* **1998**, *54*, 6169; b) S. Fioravanti, L. Pellacani, S. Tabanella, P. A. Tardella, *Tetrahedron* **1998**, *54*, 14105; c) S. Fioravanti, A. Morreale, L. Pellacani, P. A. Tardella, *J. Org. Chem.* **2002**, *67*, 4972; d) S. Fioravanti, M. G. Mascia, L. Pellacani, P. A. Tardella, *Tetrahedron* **2004**, *60*, 8073; e) D. Colantoni, S. Fioravanti, L. Pellacani, P. A. Tardella, *J. Org. Chem.* **2006**, *71*, 6295.

[6] a) S. Minakata, Y. Murakami, R. Tsuruoka, S. Kitanaka, M. Komatsu, *Chem. Commun.* **2008**, 6363 and references therein; b) Y.-M. Shen, M.-X. Zhao, J. Xu, Y. Shi, *Angew. Chem.* **2006**, *118*, 8173; *Angew. Chem. Int. Ed.* **2006**, *45*, 8005; c) A. Armstrong, C. A. Baxter, S. G. Lamont, A. R. Pape, R. Wincewicz, *Org. Lett.* **2007**, *9*, 351. For a highly enantioselective aziridination of α,β-unsaturated aldehydes catalyzed by chiral secondary amines, see: d) J. Vesely, I. Ibrahem, G.-L. Zhao, R. Rios, A. Córdova, *Angew. Chem.* **2007**, *119*, 792; *Angew. Chem. Int. Ed.* **2007**, *46*, 778; e) H. Arai, N. Sugaya, N. Sasaki, K. Makino, S. Lectard, Y. Hamada, *Tetrahedron Lett.* **2009**, *50*, 3329.

[7] F. Pesciaioli, F. De Vincentiis, P. Galzerano, G. Bencivenni, G. Bartoli, A. Mazzanti, P. Melchiorre, *Angew. Chem.* **2008**, *120*, 8831; *Angew. Chem. Int. Ed.* **2008**, *47*, 8703.

[8] For recent reviews, see: a) G. Bartoli, P. Melchiorre, *Synlett* **2008**, 1759; b) Y.-C. Chen, *Synlett* **2008**, 1919. For meaningful examples, see: c) J.-W. Xie, W. Chen, R. Li, M. Zeng, W. Du, L. Yue, Y.-C. Chen, Y. Wu, J. Zhu, J.-G. Deng, *Angew. Chem.* **2007**, *119*, 393; *Angew. Chem. Int. Ed.* **2007**, *46*, 389; d) G. Bartoli, M. Bosco, A. Carlone, F. Pesciaioli, L. Sambri, P. Melchiorre, *Org. Lett.* **2007**, *9*, 1403.

[9] For our recent contributions demonstrating the ability of **9-*epi*-NH_2-HQ** to combine orthogonal catalysis modes (iminium and enamine activations) into one mechanism, thus promoting tandem reactions, see: with α,β-unsaturated ketones: a) L.-Y. Wu, G. Bencivenni, M. Mancinelli, A. Mazzanti, G. Bartoli, P. Melchiorre, *Angew. Chem.* **2009**, *121*, 7332; *Angew. Chem. Int. Ed.* **2009**, *48*, 7196; b) G. Bencivenni, L.-Y. Wu, A. Mazzanti, B. Giannichi, F. Pesciaioli, M.-P. Song, G. Bartoli, P. Melchiorre, *Angew. Chem.* **2009**, *121*, 7336; *Angew. Chem. Int. Ed.* **2009**, *48*, 7200; with α-substituted α,β-unsaturated aldehydes: c) P. Galzerano, F. Pesciaioli, A. Mazzanti, G. Bartoli, P. Melchiorre, *Angew. Chem.* **2009**, *121*, 8032; *Angew. Chem. Int. Ed.* **2009**, *48*, 7892. Recently, a similar strategy and catalytic system have been applied to the highly enantioselective epoxidation of cyclic enones: d) X. Wang, C. M. Reisinger, B. List, *J. Am. Chem. Soc.* **2008**, *130*, 6070.

[10] The choice of the solvent, the stoichiometry of the reaction, and the nature of the acidic cocatalyst turned out to be crucial parameters for the method optimization. Selected results for reactions between **1b** and **2a**, leading to **3c**, to be compared with entry 3, Table 1: solvent screening: $CHCl_3$, 90% conversion, 72% *ee*; toluene, 60% conversion, 67% *ee*; dioxane, 23% conversion, 79% *ee*. Acidic cocatalyst (using **9-*epi*-NH_2-HQ** in $CHCl_3$ as the solvent): D-*N*-Boc phenylglycine, 90% conversion, 72% *ee*; *N*-Boc glycine, 93% conversion, 65% *ee*; 2-F benzoic acid, 22% conversion, 71% *ee*; no acidic cocatalyst, less than 5% conversion.

[11] The presence of an inorganic base has a beneficial effect on both the reaction rate and the selectivity of the aziridination. The role of $NaHCO_3$ is likely to neutralize the *p*-toluenesulfonic acid generated during the enamine-induced intramolecular ring closing step, which otherwise might affect the activity of the catalyst. Other inorganic bases tested (e.g., K_2CO_3, KF) afforded much worse results.

[12] List and co-workers have recently introduced asymmetric counter-ion-directed catalysis (ACDC) as an efficient strategy for enantioselective transformations that proceed via cationic species, including iminium-ion intermediates, see: a) S. Mayer, B. List, *Angew. Chem.* **2006**, *118*, 4299; *Angew. Chem. Int. Ed.* **2006**, *45*, 4193; b) N. J. A. Martin, B. List, *J. Am. Chem. Soc.* **2006**, *128*, 13368.

[13] This type of matched/mismatched catalyst–ion pair combination is consistent with previous observations: using the opposite enantiomeric counteranion (L-*N*-Boc phenylglycine) with **9-*epi*-NH_2-HQ** afforded the same enantiomeric product with lower reactivity and selectivity, see: a) P. Ricci, A. Carlone, G. Bartoli, M. Bosco, L. Sambri, P. Melchiorre, *Adv. Synth. Catal.* **2008**, *350*, 49; b) A. Carlone, G. Bartoli, M. Bosco, F. Pescaioli, P. Ricci, L. Sambri, P. Melchiorre, *Eur. J. Org. Chem.* **2007**, 5492.

[14] a) A. Minatti, X. Zheng, S. Buchwald, *J. Org. Chem.* **2007**, *72*, 9253 and references therein. The tricyclic aziridine NSC676892 has been identified as a promising HIV-1 integrase inhibitor: b) H. Hong, N. Neamati, H. E. Winslow, J. L. Christensen, A. Orr, Y. Pommier, G. W. A. Milne, *Antiviral Chem. Chemother.* **1998**, *9*, 461.

Received: January 15, 2010
Published online: May 28, 2010

