High pressure *vs.* thermal activation in the conjugate addition of amines: a new access to spirocyclamines

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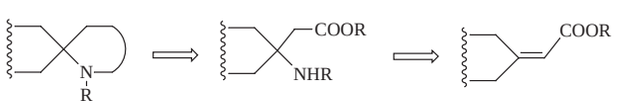
The reactions of methyl or ethyl 4-*tert*-butylcyclohexylidene bromoacetates 3-Me or 3-Et with amines afford various products depending on the experimental conditions and the nature of the amine. When the starting ester 3 is treated with benzylamine in refluxing methanol, the ester 5 and the corresponding amide 6 are isolated as the main reaction products. By contrast, the same reaction at room temperature and under high pressure leads to a spiro aziridine derivative 4 in good yield and high stereoselectivity. On the other hand, when ester 3 reacts with secondary amines in refluxing alcohol, the corresponding α-amino β,γ-unsaturated ester 7 is isolated as the sole product of the reaction in good yield. In toluene, the same reaction produces, in addition to the deconjugation–substitution compound 7, the isomeric γ-amino α,β-unsaturated ester 8. Finally, the hetero-Michael type addition of alcohol is the main reaction when substrate 3 is treated with methanol in the presence of a secondary or tertiary amine under high pressure, leading to β-substituted ester 9.

Introduction

Like their α-isomers, β-amino acids and esters have been the object of long-lasting interest[1] because of their direct involvement in the chemistry of various bioactive compounds. They provide for instance ready access to the β-lactam ring, a structure at the heart of the most widely used antibiotics, and have recently been the focus of renewed attention because of their implication in taxoid side-chain chemistry. One very direct route to β-amino esters relies on the hetero-Michael addition of a primary amine[2] or of a lithium amide derived from a secondary amine[3] onto an α,β-unsaturated ester. Such an approach has been shown to be very efficient in the highly diastereoselective construction of 3-aminobutyrates[2b] or of the 3-phenylisoserine unit[3d] for instance. However, most of these developments have been described for 1,2-disubstituted olefinic substrates, while the same strategy applied to β-disubstituted activated olefins could tackle the important problem of the construction of quaternary carbons bearing an amino group. We have recently considered the particular case of cycloalkylidene esters,[4] which, within the same framework, could be regarded as the key step of a very convergent access to spirocyclamines (Scheme 1). The results we present constitute the first application of this strategy.



Scheme 1

We considered that starting from cyclohexylidene α-halo acetates could render the ring-closing process featured above very simple. An intramolecular nucleophilic subtitution of the halogen by the newly secondary amine can indeed be expected following the hetero-Michael step, leading directly to the spiroaziridine skeleton (Scheme 2). The efficiency of this sequence towards α,β-unsaturated α-halo esters to prepare 'regular' aziridines has long been known,[5] while the strained spiroaziridines remain the subject of few reports.[6]

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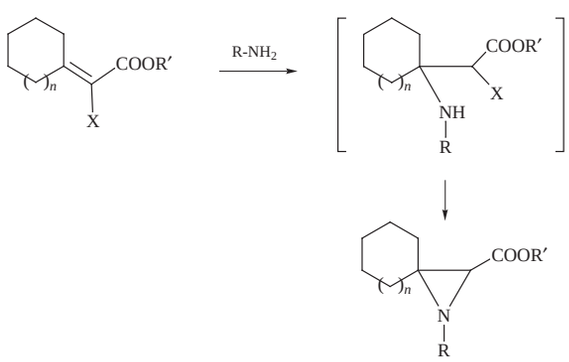


Scheme 2

Steric constraints were likely to jeopardize this overall scheme since the Michael reaction is known to depend strongly on the substitution level of both partners and to become almost impossible on β-disubstituted esters.[7] High pressure (HP) activation has been shown to alleviate this limitation, even making the creation of two adjacent quaternary centers possible.[8] The situation is very similar in the particular case of amine addition onto unsaturated esters: neither the thermal addition of secondary amines on β-monosubstituted esters nor that of primary amines on β-disubstituted ones works efficiently. Here too the addition yields are, in the latter case, dramatically increased, even at room temperature, under HP.[2b] The origin of this spectacular pressure-improved reactivity has recently been demonstrated by Jenner who has measured a large negative activation volume for this reaction (-40 to -50 cm^3 mol^{-1}).[9]

Our previous studies in α-halogenocarbonyl derivatives,[10] which have proved to be of particular interest because of their multi-functionality, prompted us to investigate the retrosynthetic pathway of Scheme 1 starting from primary and secondary amines under both thermal and high pressure activations.

Results and discussion

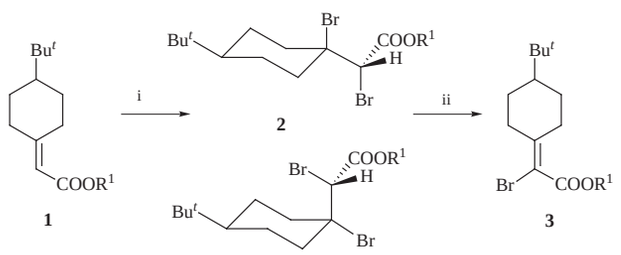
Synthesis of 4-*tert*-butylcyclohexylidene bromoacetates

To minimize the cyclohexyl conformational flexibility, we decided to concentrate on 4-*tert*-butylcyclohexylidene bromoacetates as test substrates. Ester **3** has been prepared by bromin-

Table 1 Reaction of esters **3** with amines

Entry	Reagents		Reaction conditions			Yields (%)[a]			
	Ester **3**	Amine	Solvent		*t*/d	**4**	**5**	**7**	**8**
1	Me	$BnNH_2$	MeOH	reflux, *P* atm	11		34[b]		
2	Me	$BnNH_2$	MeOH	RT, *P* atm	60	85[c]			
3	Me	$BnNH_2$	MeOH	RT, 11 kbar	4	83[d]			
4	Me	$BnNH_2$	CH_2Cl_2	RT, 11 kbar	4		No reaction		
5	Me	Et_2NH	MeOH	reflux, *P* atm	3			80	
6	Et	Et_2NH	EtOH	reflux, *P* atm	3			77	
7	Et	Bn_2NH	EtOH	reflux, *P* atm	25			79	
8	Et	Piperidine	EtOH	reflux, *P* atm	3			81	
9	Et	Piperidine	Toluene	RT, *P* atm	180[e]			42	10
10	Et	Piperidine	Toluene	reflux, *P* atm	6			55	32
11	Et	Morpholine	EtOH	RT, *P* atm	180[f]			25	
12	Et	Morpholine	EtOH	reflux, *P* atm	9			91	
13	Et	Morpholine	Toluene	reflux, *P* atm	12			30	32
14	Me	Et_2NH	MeOH	RT, 11 kbar	3			10[g]	

[a] Yields after purification by flash chromatography. [b] The yield of amide **6** is 18%. [c] Diastereomeric ratio **4a**:**4b** = 1.7:1. [d] Diastereomeric ratio **4a**:**4b** = 10:1. [e] Conversion of the starting ester **3-Et** is 70%. [f] Conversion of the starting ester **3-Et** is 35%. [g] Accompanied by 61% of compound **9**.



Scheme 3 *Reagents and conditions*: i, Br_2, CCl_4, 0 °C then RT; ii, K_2CO_3, acetone, reflux

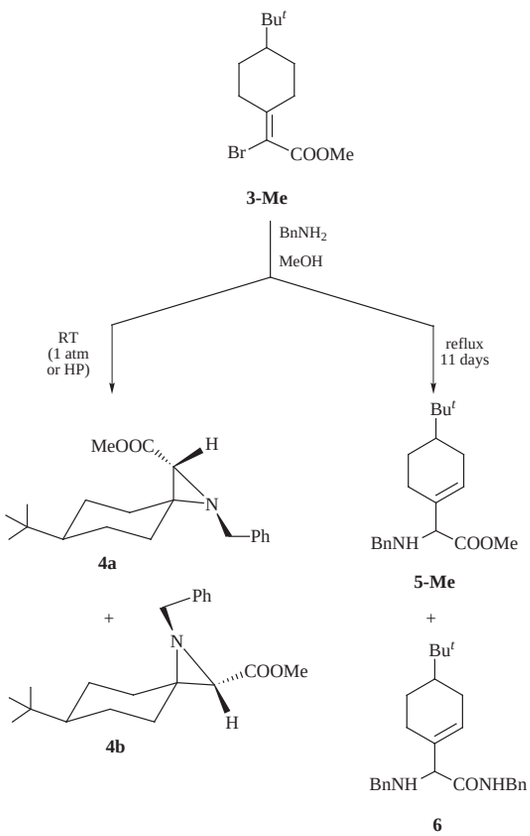
ation of methyl 4-*tert*-butylcyclohexylideneacetate **1** followed by HBr elimination on the intermediate dibromo ester **2** (Scheme 3).

Reaction with primary amines under thermal activation

Refluxing ester **3-Me** in methanol with 2 equiv. of benzylamine did not yield the expected aziridine **4** but a mixture of the α-amino β,γ-unsaturated ester **5** and its corresponding amide **6** (Scheme 4 and entry 1 of Table 1). Ester **5** is probably the initial product which is converted into amide **6** on prolonged warming with excess of amine. This has been checked by converting quantitatively pure ester **5** into **6** by treating it with benzylamine in refluxing methanol. Decreasing the temperature yields the aziridines **4**, which are obtained in 85% yield after 60 days at room temp. (Scheme 4 and entry 2 of Table 1). However, such a delay constitutes a major drawback to this method and definitely reduces its synthetic utility.

Reaction with primary amines under hyperbaric activation

As mentioned above, hyperbaric activation is particularly suited to this reaction, even in sterically hindered situations.[2b,11a] In practice benzylamine reacted with **3** to give **4** at 11 kbar under the conditions described above (methanol, room temp.) with a dramatic increase in both reaction rate and stereoselectivity (Scheme 4 and entry 3 of Table 1). The addition took less than four days and the diastereomeric ratio rose from a low 1.7:1 at atmospheric pressure to 10:1 at 11 kbar. Two arguments can be cited to rationalise such an increase in de; first, the relative crowding of the transition states resulting from the two possible approaches of the reagents, as reported in one related example.[11a] Second, the amine addition might become irreversible under pressure, placing the reaction under kinetic control under these conditions, while a thermodynamic mixture would be reached upon warming.‡ The relative configurations of



Scheme 4

diastereomers **4a** and **4b** have been established through a set of NOE experiments[4] and are as shown in Scheme 4 (only one enantiomer is presented).

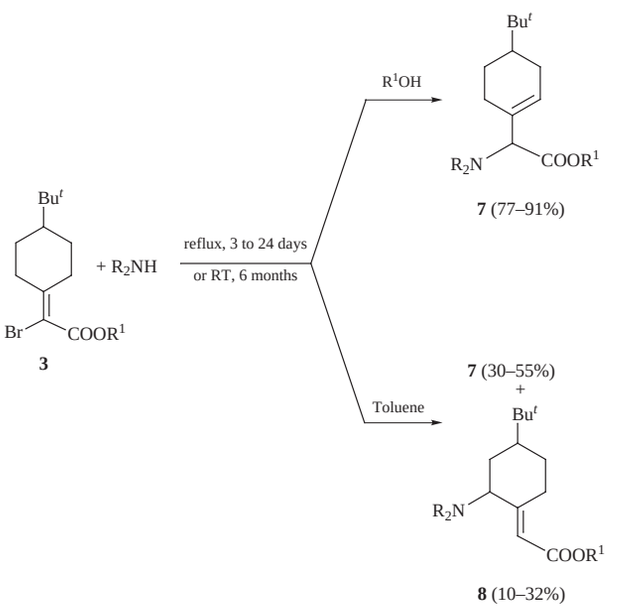
From a mechanistic point of view, the formation of unsaturated ester **5** and amide **6** could stem from the rearrangement of aziridine **4**. However, heating pure **4** in refluxing methanol with or without benzylamine did not lead to **5** and/or **6**, suggesting that the thermal pathway does not rely on the formation of **4** followed by a deprotonation and ring-opening sequence. The key steps in refluxing methanol thus seem to be: (i) deconjugation of the double bond leading to an intermediate α-bromo allylic ester;[12] (ii) substitution of the newly allylic bromine atom by benzylamine. On the other hand, experiments at room temperature under both atmospheric and high pressure clearly favor the hetero-Michael addition, which is immediately followed by the intramolecular bromine–secondary amine nucleo-

‡ We thank one of the referees for suggesting this point.

philic substitution. It is worth emphasizing that, as previously observed,[11a] this heteroaddition requires a protic solvent such as methanol: in methylene chloride, only starting material **3** was recovered after four days at 11 kbar at room temperature (entry 4 of Table 1).

Reaction with secondary amines under thermal activation

When treated with acyclic (diethyl- or dibenzyl-amine) or heterocyclic (piperidine, morpholine) secondary amines, esters **3** yield one or two products, depending on the solvent (Scheme 5 and entries 5–13 of Table 1). In alcohols (methanol, ethanol), only the deconjugation–substitution products **7** are recovered in good yields, at room temp. as well as at reflux. These same products are obtained in toluene, albeit at a slower rate, together with their γ-amino α,β-unsaturated isomers **8**. The chemical yields are good, except at room temp. where the reaction duration becomes, in both solvents, unacceptably long (entries 9 and 11 of Table 1). A sterically hindered secondary amine such as 2,2,6,6-tetramethylpiperidine does not react at all.

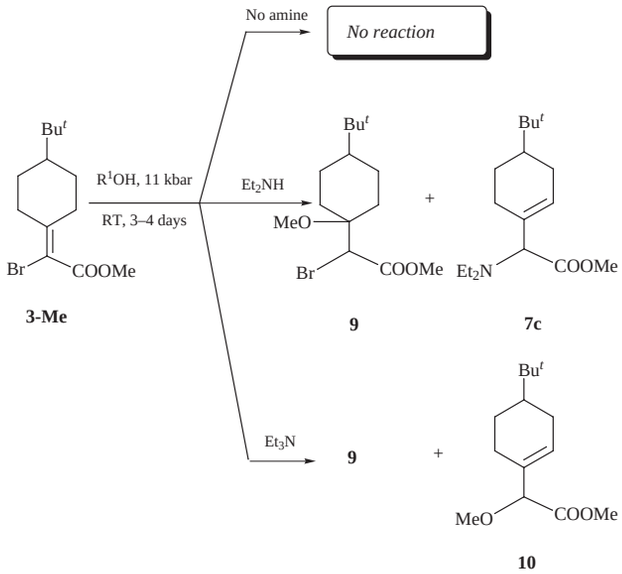


Scheme 5 R^1 = Et; R_2N = $(CH_2)_5N$ (**7a**), $O(CH_2CH_2)_2N$ (**7b**), Et_2N (**7c**), Bn_2N (**7d**) R^1 = Me; R_2N = Et_2N (**7e**)

Reaction with secondary amines under hyperbaric activation

It is known that secondary amines add in mediocre yields onto activated olefins,[2a] even under high pressure.[2b,11a] Indeed, pressurizing **3** in the presence of diethylamine did not afford the corresponding amino esters but resulted in a selective 1,4-addition of methanol (providing **9**, entry 14 of Table 1)§ this time, together with small amounts of deconjugation–substitution products **7c** with diethylamine, or **10** with triethylamine (Scheme 6). A similar competition between nitrogen and oxygen nucleophiles has recently been reported for a related reaction.[11a] Albeit apparently not directly involved, the amine is needed for the addition reaction to take place since pressurizing **3** in pure methanol does not give any addition at all. This could be due to some heightening of the methanol nucleophilicity by the amine. Interestingly, the ratio between diastereoisomers of **9** produced in both cases was 9:1, *viz*. almost identical to that measured for aziridine **4** in the experiments discussed above. This suggests that, in all cases, the transition state corresponding to an equatorial addition of nucleophiles on cyclohexylidene ester **3** is more compact, and thus favored under high pressure, than that corresponding to the axial approach.

§ From a mechanistic point of view, it is worth noting that **9** could formally constitute a common intermediate in the formation of **4**–**7**.



Scheme 6

Conclusion

The results presented herein indicate that the course of the reaction between amines and cyclohexylidene α-halo acetates is strongly dependent on the experimental conditions. While under thermal activation conditions, ester **3** reacts with primary amines to provide α-amino β,γ-unsaturated ester **5** and amide **6**—an attractive class[13] of organic compounds—spiroaziridine **4** is formed in high yields and with good diastereoselectivity under high pressure (11 kbar) in methanol. Replacing primary amines by secondary ones leads by contrast to the selective conjugate addition of methanol. Nevertheless, the latter reaction cannot occur in the absence of any amine. Further applications of high pressure induced heteroadditions (including the particular case of heteronucleophilic reagents previously studied by de Meijere and Wessjohann[14]) to the approach of various spiroheterocyclic compounds are under way.

Experimental

^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$ on Bruker AM-200 and 400-FT spectrometers. Coupling constants *J* are given in Hz. Gas chromatography analyses were performed on a Hewlett Packard 5890 apparatus equipped with a J&W high resolution DB-1 type column (30 m, 0.25 mm ID, 0.25 μm coating). GC–MS analyses (EI, 70 eV) were performed on a ATI-Unicam Automass apparatus equipped with the same column. Low and high resolution mass spectra (HRMS) were recorded with a JEOL JMS AX-500 spectrometer. IR spectra were taken on a Perkin-Elmer 16 PC FT-IR. Elemental analyses were performed by the Laboratoire de Chimie Analytique de l'INSA de Rouen, Mont St Aignan. High pressure reactions were performed in a Unipress piston-cylinder apparatus for pressure up to 14 kbar. The silica gel used for flash chromatography was from the SDS company (230–400 Mesh). Diethyl ether and THF were distilled from sodium–benzophenone. Toluene was pre-dried over $CaCl_2$ and distilled. Methylene chloride, methanol and ethanol were dried over 3 Å molecular sieves and then distilled.

The ethyl 4-*tert*-butylcyclohexylideneacetate **1-Et** was prepared from cyclohexanone by a Wittig–Horner reaction as previously reported.[15] Methyl 4-*tert*-butylcyclohexylideneacetate **1-Me** was prepared by saponification of **1-Et** followed by esterification of the corresponding acid utilizing standard literature procedures.

Preparation of esters 3

(i) Bromination of ester 1-Me. To a solution of ester **1-Me** (2.10 g, 10 mmol) in CCl_4 (10 ml) at 0 °C was added a solution of Br_2 (1.60 g, 10 mmol) in CCl_4 (25 ml) over a period of 2.5 h. When the addition was complete, the solution was allowed to warm slowly to room temperature, and stirred overnight. After evaporation of the solvent, ester **2-Me** was obtained (3.7 g, quant.) as an oil which was used without further purification. The same procedure was applied to **1-Et** to produce **2-Et** in quantitative yield.

Methyl (1-*bromo*-4-tert-*butylcyclohexyl*)*bromoacetate* **2-Me**.—δ_H major isomer (65%) 0.84 (s, 9H), 1.00–2.40 (m, 7H), 2.55 (m, 2H), 3.81 (s, 3H), 4.81 (s, 1H); minor isomer (35%) 0.86 (s, 9H), 1.00–2.40 (m, 7H), 2.81 (m, 2H), 3.78 (s, 3H), 4.65 (s, 1H); δ_C major isomer 23.7, 25.1, 27.5, 32.4, 40.4, 42.1, 46.3, 52.4, 52.8, 66.4, 167.1; minor isomer 23.4, 24.6, 27.4, 32.3, 35.7, 38.9, 46.7, 53.1, 54.7, 72.7, 167.9; ν_{max}/cm^{-1} 1726, 1752; *m*/*z* 369 ($M^+ - 1$), 289.

Ethyl (1-*bromo*-4-tert-*butylcyclohexyl*)*bromoacetate* **2-Et**.—δ_H major isomer (60%) 0.84 (s, 9H), 1.00–2.40 (m, 7H), 1.31 (t, 3H), 2.74 (m, 2H), 4.27 (q, 2H), 4.78 (s, 1H); minor isomer (40%) 0.87 (s, 9H), 1.00–2.40 (m, 7H), 1.30 (t, 3H), 2.81 (m, 2H), 4.23 (q, 2H), 4.63 (s, 1H); ν_{max}/cm^{-1} 1722, 1748; *m*/*z* 383 ($M^+ - 1$).

(ii) Dehydrobromination of bromoesters 2-Me. A solution of esters **2-Me** (3.7 g, 10 mmol) in acetone (55 ml) in the presence of K_2CO_3 (2.1 g) was refluxed for 48 h. After filtration and evaporation of the solvent, the product **3-Me** was isolated by flash chromatography (light petroleum–Et_2O, 75:1) in 86% yield. The ester **3-Et** was prepared from **2-Et** in a similar fashion in 76% yield.

Methyl 4-tert-*butylcyclohexylidenebromoacetate* **3-Me**.—δ_H 0.83 (s, 9H), 1.00–1.30 (m, 3H), 1.75–2.05 (m, 4H), 3.00–3.25 (m, 2H), 3.65 (s, 3H); δ_C 27.4, 27.7, 28.3, 32.3, 32.6, 35.5, 47.4, 52.6, 104.4, 153.0, 164.8; ν_{max}/cm^{-1} 1716, 1605; *m*/*z* 290, 288 (M^+), 207, 153, 93, 91 (Calc. for $C_{13}H_{21}BrO_2$: C, 53.99; H, 7.32. Found: C, 54.26; H, 7.39%).

Ethyl 4-tert-*butylcyclohexylidenebromoacetate* **3-Et**.—δ_H 0.83 (s, 9H), 1.00–2.10 (m, 7H), 1.31 (t, *J* 7, 3H), 3.00–3.20 (m, 2H), 4.23 (q, *J* 7, 2H); δ_C 13.9, 27.4, 27.7, 28.2, 32.3, 32.5, 35.3, 47.4, 61.6, 104.8, 151.9, 164.4; ν_{max}/cm^{-1} 1716, 1606; *m*/*z* 304, 302 (M^+), 167, 93, 91 (Calc. for $C_{14}H_{23}BrO_2$: C, 55.45; H, 7.64. Found: C, 55.28; H, 7.83%).

Reactions with primary amines

Reaction of ester 3-Me with benzylamine under reflux. A solution of ester **3-Me** (297 mg, 1.03 mmol) and benzylamine (303 mg, 2.83 mmol) in MeOH (4.0 ml) was stirred under reflux for 11 days. After evaporation of the solvent, the residue was chromatographed (light petroleum–Et_2O 50:50) to yield ester **5-Me** (112 mg, 34%) and amide **6** (67 mg, 18%).

Methyl (4-tert-*butylcyclohex*-1-*enyl*)*benzylaminoacetate* **5-Me**.—δ_H 0.91 (s, 9H), 1.0–2.3 (m, 8H), 3.74 (2 × s, 2H), 3.76 (s, 3H), 3.81, 3.83 (2 × s, 1H), 5.76 (m, 1H), 7.25–7.45 (m, 5H); δ_C 23.9, 25.8, 26.5, 26.8, 27.1, 32.1, 43.7, 51.1, 51.2, 51.9, 66.0, 66.2, 126.6, 126.9, 127.2, 128.2, 133.9, 134.1, 139.7; 173.4 (C=O); ν_{max}/cm^{-1} 1675, 1738, 3347; *m*/*z* 315 (M^+), 300, 257 (Calc. for $C_{20}H_{29}NO_2$: C, 76.15; H, 9.27; N, 4.44. Found: C, 76.06; H, 9.87; N, 4.56%).

N-*Benzyl* [N′-*benzyl*-2-(4-tert-*butylcyclohex*-1-*enyl*)-2-*benzylamino*]*acetamide* **6**.—δ_H 0.85 (s, 9H), 1.0–2.3 (m, 8H), 3.60–3.75 (m, 3H), 4.44, 4.47 (2 × s, 2H), 5.75 (m, 1H), 7.15–7.40 (m, 10H); δ_C 23.7, 25.9, 26.5, 26.7, 27.0, 30.1, 29.5, 31.9, 43.7, 52.0, 52.1, 68.1, 68.3, 125.3, 126.5, 127.0, 127.1, 127.2, 128.0, 128.2, 128.4, 138.3, 139.4, 127.4, 135.0, 135.3, 171.7, 171.9; ν_{max}/cm^{-1} 1604, 1654, 3313; *m*/*z* 390 (M^+), 375, 257 (Calc. for $C_{26}H_{34}N_2O$: C, 79.96; H, 8.77; N, 7.17. Found: C, 79.65; H, 9.43; N, 7.35%).

Reaction of ester 3-Me with benzylamine under high pressure. A solution of ester **3-Me** (228 mg, 0.79 mmol) and benzylamine (165 mg, 1.54 mmol) in MeOH (4.5 ml) was pressurized under 11 kbar at room temperature for 4 days. After return to atmospheric pressure, the solvent was removed and the residue was chromatographed (light petroleum–Et_2O 70:30) to give two pure diastereomers **4a** (179 mg, white solid, mp 90 °C) and **4b** (21 mg). Overall yield: 83%.

4-tert-*Butylcyclohexanespiro*-2′-(1-*benzyl*-3-*methoxycarbonyl*)*aziridines* **4a** *and* **4b**.—δ_H isomer **4a** 0.83 (s, 9H), 0.90–2.00 (m, 9H), 2.15 (s, 1H), 3.72 (s, 3H), 3.81 (q, 2H), 7.15–7.50 (m, 5H); isomer **4b** 0.75 (s, 9H), 0.85–2.00 (m, 9H), 2.11 (s, 1H), 3.70 (s, 3H), 3.63–3.99 (q, 2H), 7.20–7.55 (m, 5H); δ_C isomer **4a** 25.8, 26.8, 27.5, 29.0, 31.6, 32.2, 47.5, 48.3, 51.0, 51.7, 54.9, 126.6, 127.2, 128.2, 138.9, 170.6; isomer **4b**: 25.5, 25.8, 27.4, 28.0, 32.1, 32.3, 47.4, 48.7, 50.0, 51.8, 55.6, 126.8, 127.7, 128.3, 139.0, 170.6; ν_{max}/cm^{-1} 1738; *m*/*z* 315 (M^+), 300, 257 (Calc. for $C_{20}H_{29}NO_2$: C, 76.15; H, 9.27; N, 4.44. Found: C, 76.13; H, 9.41; N, 4.37%). NOEs: isomer **4a**: irradiation of CH_2 of benzyl group resulted in enhancements of H^2_{ax} and H^2_{eq} signals. Isomer **4b**: irradiation of CH of aziridine ring resulted in enhancements of H^2_{eq} signals while irradiations of CH_2 of benzyl group gives a small NOE on H^3_{ax} proton.

Reactions with secondary amines

General procedure for the reactions of esters 3 with secondary amines. A solution of the ester **3** (1 mmol) and amine (2–3 mmol) in corresponding alcohol or toluene (4 g) was stirred under reflux or was kept at room temperature. The solvent was evaporated; column chromatography (light petroleum–Et_2O) of the residue afforded compound **7** (or **7** and **8**).

Ethyl 2-(4-tert-*butylcyclohex*-1-*enyl*)-2-*piperidinoacetate* **7a**.—δ_H 0.83 (s, 9H), 1.0–2.5 (m, 7H), 1.23 (t, *J* 7, 3H), 1.56 (m, 6H), 3.26, 3.33 (2s, 1H), 3.68 (m, 4H), 4.00–4.20 (m, 2H), 5.72 (m, 1H); δ_C 14.2, 24.0, 24.4, 25.7, 25.8, 26.3, 26.4, 26.9, 27.1, 32.1, 43.8, 44.0, 52.0, 52.1, 60.1, 60.2, 76.4, 77.2, 128.0, 128.4, 133.3, 133.5, 171.6; ν_{max}/cm^{-1} 1670, 1736; *m*/*z* 307 (M^+), 292, 235 (Calc. for $C_{19}H_{33}NO_2$: C, 74.22; H, 10.82; N, 4.56. Found: C, 74.28; H, 10.63; N, 4.75%).

Ethyl 2-(4-tert-*butylcyclohex*-1-*enyl*)-2-*morpholinoacetate* **7b**.—δ_H 0.83 (s, 9H), 1.0–2.5 (m, 7H), 1.23 (t, *J* 7, 3H), 2.30–2.45 (m, 4H), 3.29, 3.34 (2s, 1H), 3.60–3.75 (m, 4H), 4.15 (q, *J* 7, 2H), 5.77 (m, 1H); δ_C 14.2, 23.9, 26.3, 26.5, 27.0, 27.1, 32.1, 43.8, 44.0, 51.2, 51.3, 60.4, 66.8, 76.0, 76.5, 129.1, 129.6, 132.3, 132.5, 170.9; ν_{max}/cm^{-1} 1652, 1740; *m*/*z* 309 (M^+), 294, 237 (Calc. for $C_{18}H_{31}NO_2$: C, 69.87; H, 10.10; N, 4.53. Found: C, 70.23; H, 10.42; N, 4.78%).

Ethyl 2-(4-tert-*butylcyclohex*-1-*enyl*)-2-*diethylaminoacetate* **7c**.—δ_H 0.84 (s, 9H), 0.96 (t, *J* 7, 6H), 1.0–2.8 (m, 7H), 1.24 (t, *J* 7, 3H), 2.5–2.7 (m, 4H), 3.78, 3.81 (2 × s, total 1H), 4.14 (m, 2H), 5.65 (m, 1H); δ_C 11.8, 12.6, 14.3, 27.0, 27.1, 27.3, 27.4, 32.1, 43.1, 43.7, 43.9, 44.1, 60.0, 60.1, 70.3, 71.6, 126.7, 127.4, 134.2, 172.4, 172.5; ν_{max}/cm^{-1} 1652, 1736; *m*/*z* 295 (M^+), 280, 222 (Calc. for $C_{18}H_{33}NO_2$: C, 73.17; H, 11.26; N, 4.74. Found: C, 72.83; H, 11.50; N, 5.14%).

Ethyl 2-(4-tert-*butylcyclohex*-1-*enyl*)-2-*dibenzylaminoacetate* **7d**.—δ_H 0.82 (s, 9H), 1.00–2.60 (m, 7H), 1.29 (t, *J* 7, 3H), 3.50–4.05 (m, 5H), 4.05–4.35 (m, 2H), 5.57 (m, 1H), 7.10–7.40 (m, 10H); δ_C 14.3, 23.9, 24.2, 27.1, 28.3, 29.4, 32.1, 43.7, 43.9, 54.2, 54.5, 59.8, 66.7, 68.3, 126.4, 126.8, 128.2, 128.6, 140.0, 133.7, 140.1, 172.2; ν_{max}/cm^{-1} 1654, 1732; *m*/*z* 419 (M^+), 404, 347 (Calc. for $C_{28}H_{37}NO_2$: C, 80.15; H, 8.89; N, 3.34. Found: C, 80.21; H, 9.06; N, 3.44%).

Methyl 2-(4-tert-*butylcyclohex*-1-*enyl*)-2-*diethylaminoacetate* **7e**.—δ_H 0.83 (s, 9H), 0.95 (t, *J* 7, 6H), 1.0–2.5 (m, 7H), 2.4–2.7 (m, 4H), 3.66, 3.67 (2 × s, 3H), 3.79, 3.83 (2 × s, 1H), 5.63 (m, 1H); δ_C 11.7, 12.7, 24.0, 26.9, 27.1, 27.4, 32.1, 43.1, 43.6, 43.9, 44.0, 51.1, 51.2, 70.1, 71.5, 126.8, 127.5, 134.1, 172.8, 172.9; ν_{max}/cm^{-1} 1654, 1742; *m*/*z* 281 (M^+), 266, 222 (Calc. for $C_{17}H_{31}NO_2$: C, 72.55; H, 11.10; N, 4.98. Found: C, 72.52; H, 11.10; N, 5.05%).

Reaction with amines under high pressure

Reaction of ester 3-Me with diethylamine under high pressure. A solution of ester **3-Me** (212 mg, 0.73 mmol) and diethylamine (171 mg, 2.34 mmol) in MeOH (4.5 ml) was allowed to stand under 11 kbar at room temperature for 3 days. Removal of the solvent and chromatography (light petroleum–Et_2O 83:17) gave **9** (**9a**: 126 mg **9b**: 17 mg, overall yield 61%) and **10** (58 mg).

Methyl (1-*methoxy*-4-tert-*butylcyclohexyl*)*bromoacetates* **9a** *and* **9b**.—δ_H **9a** 0.84 (s, 9H), 1.0–2.30 (m, 9H), 3.34 (s, 3H), 3.77 (s, 1H), 4.65 (s, 1H); **9b** 0.82 (s, 9H), 1.0–2.10 (m, 9H), 3.21 (s, 3H), 3.75 (s, 1H), 4.42 (s, 1H); δ_C **9a** 23.6, 24.4, 27.7, 32.8, 32.4, 33.0, 47.2, 50.5, 52.6, 53.1, 76.2, 168.5; **9b** 22.0, 22.2, 27.4, 30.3, 30.9, 32.3, 47.1, 48.8, 51.6, 52.8, 75.9, 168.8; ν_{max}/cm^{-1} 1724, 1760; *m*/*z* 321, 323 (M^+), 289, 291 (Calc. for $C_{14}H_{25}BrO_3$: C, 52.34; H, 7.84. Found: C, 52.54; H, 7.84%).

Reaction of ester 3-Me with triethylamine under high pressure. A solution of ester **3-Me** (194 mg, 0.67 mmol) and triethylamine (65 mg, 0.65 mmol) in MeOH (4.5 ml) was allowed to stand under 11 kbar at room temperature for 3 days. After returning to atmospheric pressure, removal of the solvent and chromatography (light petroleum–Et_2O 83:17), **9a** (133 mg) and **9b** (10 mg, overall yield 67%) were obtained together with compound **10** (15 mg, 9%).

Methyl 2-(4-tert-*butylcyclohex*-1-*enyl*)-2-*methoxyacetate* **10**.—δ_H 0.83 (s, 9H), 1.0–2.3 (m, 7H), 3.28, 3.31 (2 × s, 3H), 3.73 (s, 3H), 4.12 (s, 1H), 5.83 (m, 1H); δ_C 23.6, 24.7, 25.9, 26.8, 26.9, 27.1, 30.2, 32.1, 43.6, 43.7, 52.0, 56.7, 84.4, 84.7, 129.0, 129.6, 132.6, 132.8, 171.1, 171.3; ν_{max}/cm^{-1} 1674, 1748; *m*/*z* 240 (M^+), 208, 181.

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