



Preliminary communication / Communication

Carbocyclisation of zinc enolates onto unactivated double bonds: a mechanistic point of view

Éric Sliwinski, Fabrice Prian, Fabrice Denes,
Fabrice Chemla *, Jean-François Normant

Laboratoire de chimie organique, université Pierre-et-Marie-Curie, tour 44–45, 2^e étage, boîte 183,
4, place Jussieu, 75252 Paris cedex 05, France

Received 21 October 2002; accepted 15 January 2003

Abstract

The recent results concerning the carbocyclisation reaction of zinc enolates onto an unactivated double bond are summarized, particularly on the stereochemical point of view. The implications of the observed stereochemistries on the mechanism of the reaction (O-centred zinc enolate vs C-centred zinc enolate) are discussed. Some new results leading stereoselectively to 1-amino-1-carbomethoxy-2-methyl cyclopentanes are reported, as well as the consequences of the observed stereochemistry as a strong evidence for a C-centred zinc enolate intermediate. *To cite this article: É. Sliwinski et al., C. R. Chimie 6 (2003) 67–78.*

© 2003 Académie des sciences. Published by Éditions scientifiques et médicales Elsevier SAS. All rights reserved.

Résumé

Les résultats récents concernant la réaction de carbocyclisation d'énolates de zinc sur des doubles liaisons non activées sont résumés, en mettant tout particulièrement l'accent sur les stéréochimies des produits. Les implications de ces stéréochimies sur le mécanisme de la réaction (énolate de zinc O-métallé ou C-métallé) sont discutées. De nouveaux résultats permettant de préparer stéréosélectivement des 1-amino-1-méthoxycarbonyl-2-méthyl cyclopentanes sont présentés, ainsi que les implications des stéréochimies observées sur le mécanisme. *Pour citer cet article : É. Sliwinski et al., C. R. Chimie 6 (2003) 67–78.*

© 2003 Académie des sciences. Published by Éditions scientifiques et médicales Elsevier SAS. All rights reserved.

Keywords: carbocyclisation; carbometalation; cyclopentanes; enolates; piperidines; pyrrolidines; Reformatsky reagents

Mots clés : carbocyclisations ; carbométallations ; cyclopentanes ; énolates ; pipéridines ; pyrrolidines ; réactifs de Réformatsky

1. Introduction

The intramolecular addition of a zinc ester enolate onto an unactivated double bond has recently been

reported simultaneously in our [1–5] and other laboratories [6–9]. This unusual reaction concerns the reaction of a Reformatsky-type reagent **1** on a terminal double bond leading to an alkylzinc reagent **2**, which then can be further functionalised to **3** through reaction with electrophiles (Fig. 1). This reaction is interesting

* Corresponding author.

E-mail address: fchemla@ccr.jussieu.fr (F. Chemla).

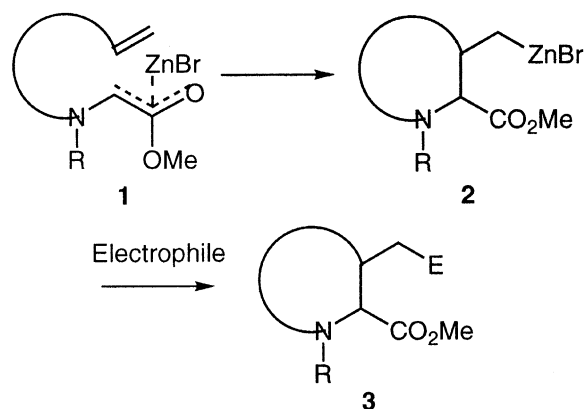


Fig. 1. Carbocyclisation reactions of zinc enolates.

both on the mechanistic and synthetic points of view. On the one hand, this reaction apparently seems contra-thermodynamic, since leading to an alkylmetal reagent from a starting material (enolate) with a lower basicity. On the other hand, this reaction allows the preparation of piperidines and pyrrolidines with an excellent diastereomeric and enantiomeric control, and then a straightforward route to substituted α - and β -prolines and pipercolic acids.

Although inter- and intramolecular carbometalation reactions (addition of organometallic species onto unactivated multiple bonds) have been widely developed [10,11], much little is known concerning the carbometalation of unactivated alkenes by *stabilized* enolate-type organometallics. Addition of ketones and malonates on styrenes under *t*-BuOK catalysis [12] is reported, as well as the intramolecular cyclisation of lithium enolates on $(\eta^2\text{-alkene})\text{Fe}$ complexes [13–16], $(\eta^4\text{-diene})\text{Fe}$ complexes [17–19], and of sodium malonates on $(\eta^4\text{-diene})\text{Mo}$ complexes [20–22]. Relatively few examples are involving totally unactivated alkenes: addition of enolates or malonates on alkenes in the presence of Pd(II) salts or under Pd(0) catalysis [23,24] have been described; in most cases, the organometallic species resulting from the carbometalation reaction undergoes dehydropalladation or reductive elimination. On the other hand, inter- or intramolecular carbometalations of unactivated olefins have been reported with tin malonates [25,26] and zincated hydrazones [27–30]. In these cases, the organometallic reagent resulting from the carbocyclisation process can be further functionalised by an external electrophile added at the end of the reaction.

We first present an overview of our previous results concerning the reaction of α -(*N*-homoallyl)-aminoesters leading to 2-carbomethoxy-pyrrolidines, of α -(*N*-4-pentenyl)-aminoesters leading to 2-carbomethoxy-piperidines and of β -(*N*-allyl)-aminoesters leading to 3-carbomethoxy-pyrrolidines, and then our latest results concerning the discrepancies of the steric outcome of these cyclisations.

2. Carbocyclisation reactions

2.1. Carbocyclisation reactions of α -(*N*-homoallyl)-aminoesters [1,3]

The deprotonation of α -(*N*-benzyl-*N*-homoallyl)-amino methyl ester **4** with LDA in ether followed by the addition of zinc bromide results in a smooth diastereoselective carbocyclisation leading to the *cis*-3-methyl-*N*-benzyl-2-carbomethoxy pyrrolidine **5** after hydrolysis (Fig. 2). The intermediacy of the 3-pyrrolidinylmethylzinc compound **6** in this reaction was shown by its reaction with various electrophiles. The diastereoselectivity of this carbocyclisation was attributed to a zinc-enolate-ene-type reactive intermediate **7**, where the double bond of the O-centred enolate is eclipsing the terminal reacting double bond, giving thus the observed *cis* stereoselectivity.

The *Z*-configuration of the enolate is dictated by the Zn–N coordination, which has been observed [31] both in solution and in the solid state for analogous Reformer-

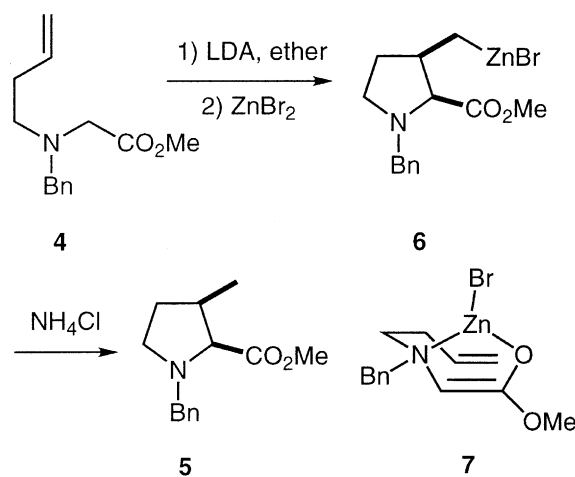


Fig. 2. Diastereoselectivity in the carbocyclisation reaction.

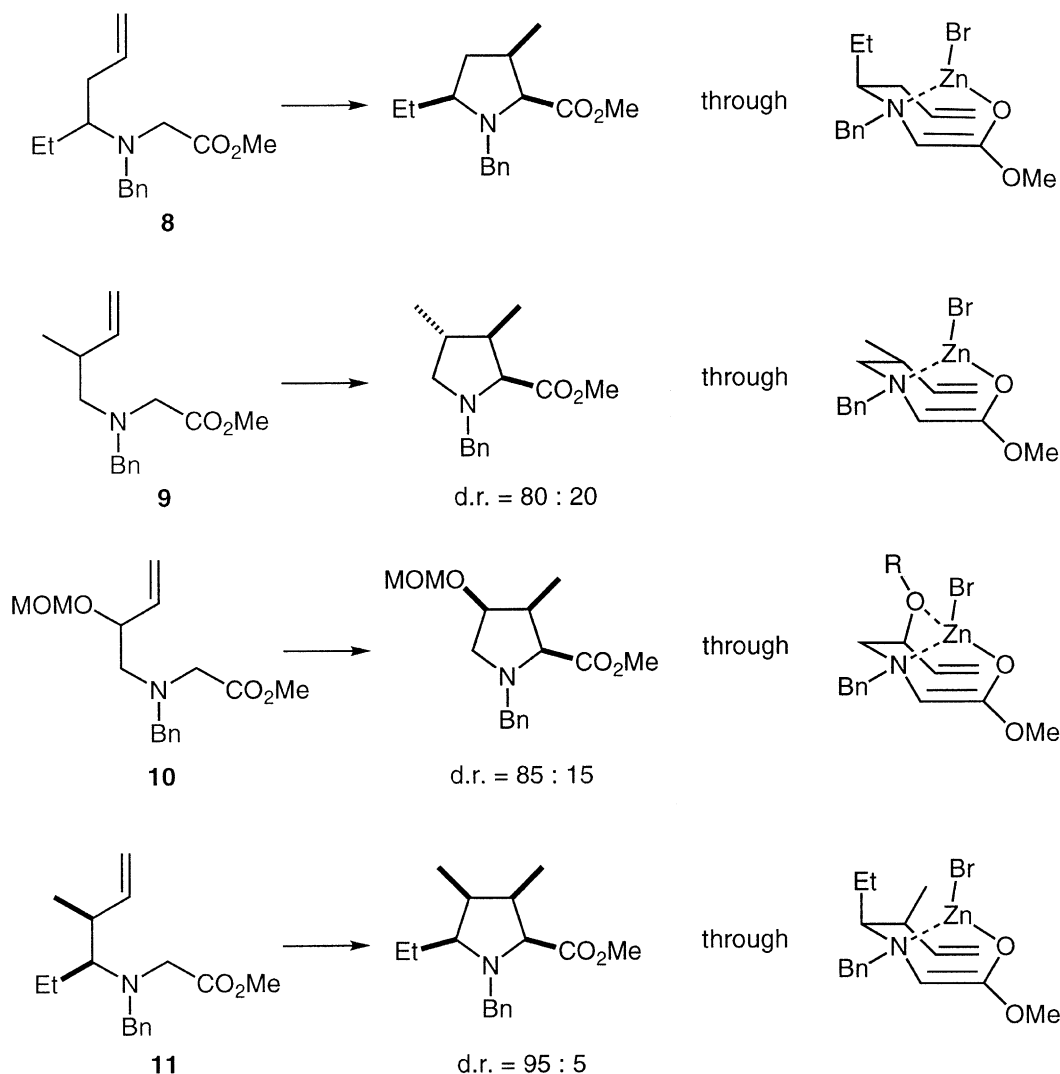


Fig. 3. Diastereoselectivity in the 2-carbomethoxy-pyrrolidine formation.

matsky reagents derived from *N,N*-silyl disubstituted α -aminoesters.

The presence of a substituent on the homoallyl chain is directing the diastereoselectivity of the reaction, the reactive intermediate in which this substituent is occupying the pseudo equatorial position (for an alkyl group) or the pseudoaxial position (for an acetal group) leading to the major observed diastereomer (Fig. 3, reaction of aminoesters **8**, **9** and **10**). When two substituents are present, as for the aminoester **11**, the homoallylic substituent was found to direct totally the diastereoselectivity.

In all cases, the resulting pyrrolidine is presenting a cis relationship between the carbomethoxy group and the methyl group coming from the methylzinc bromide moiety. This stereochemical feature was again attributed to the O-centred zinc-enolate-ene-type reactive intermediate.

2.2. Carbocyclisation reactions of α -(*N*-4-pentenyl)-aminoesters [2]

The carbocyclisation reaction of zinc enolates derived from α -(*N*-4-pentenyl)-aminoesters as **12** is much slower than in the case of α -(*N*-homoallyl)-

aminoesters, but the diastereoselectivity is excellent and the corresponding *cis*-2-carbomethoxy-3-methylpiperidine **13** is obtained as a single diastereomer. Here again, the organozinc reagent coming from the carbocyclisation reaction can be easily functionalised with various electrophiles. An oxygen-centred zinc-enolate-ene-type reactive intermediate as **14** (Fig. 4) was proposed, in order to explain the very high *cis* selectivity. The presence of a substituent in the homoallylic position (Fig. 4, aminoester **15**) results in the stereoselective construction of a trisubstituted piperidine through the reactive intermediate presenting the substituent in an equatorial position. However, when a substituent is present in both allylic and homoallylic positions (Fig. 4, aminoesters **16** and **17**), only the homoallylic one is directing the diastereoselectivity of the reaction. It is also directing the diastereoselectivity when a substituent is present in both homoallylic position and α to the nitrogen atom (Fig. 4, aminoester **18**). Finally, when three substituents are present in the allylic, homoallylic and α to nitrogen positions, the relative stereochemistries of the two latter being chosen to counterbalance the one of the former (Fig. 4, aminoester **19**), the resulting pentasubstituted piperidine was obtained with a low diastereoselectivity.

2.3. Carbocyclisation reactions of β -(*N*-allyl)-aminoesters [4]

The carbocyclisation reaction of zinc enolates derived from β -(*N*-allyl)-aminoesters is more difficult than the reaction on α -(*N*-homoallyl)-aminoesters due to the competing β -elimination reaction. However, for β -(*N*-allyl)-aminoesters **21** bearing a substituent α to the ester group, we have recently shown that this side-reaction is limited and carbocyclisation occurs smoothly to give the corresponding 3-carbomethoxy-4-methylzinc pyrrolidine reagent **22** (Fig. 5), and (in good yield) the pyrrolidine **23** upon hydrolysis. Here again, the intermediacy of the 4-pyrrolidinyl-methylzinc compounds **22** in this reaction was shown by their reactions with various electrophiles.

Surprisingly, the observed high diastereoselectivity was found in favour of the *trans* pyrrolidine. This diastereoselectivity *cannot* be explained by an O-centred zinc-enolate-ene-type reactive intermediate, as in the case of α -(*N*-homoallyl)-aminoesters, as the latter leads to *cis* pyrrolidines. We have proposed a

C-centred zinc-enolate-carbometallation-type reactive intermediate **24** (Fig. 5) to explain the observed diastereoselectivity. The main feature of this reactive intermediate is the pseudoaxial position of the carbomethoxy group due to (i) simple steric considerations, (ii) possible chelation of an extra zinc salt by nitrogen and the sp^2 oxygen of the carbomethoxy moiety.

The reaction of the parent unsubstituted β -(*N*-allyl)-aminoester **25** leads only to a β -elimination product. However, we have found that this unwanted reaction is limited by the use of zinc iodide for the Reformatsky preparation as well as by a 'reverse-addition' procedure of lithium enolate on zinc iodide. The diastereoselectivity is not as high as for **21**, but is still good as the corresponding pyrrolidine **26** is obtained in an 87:13 ratio in favour of the *trans* diastereomer (Fig. 6). For the substituted case **27**, a disappointing mixture of three diastereomers was obtained. By contrast, in the disubstituted case **28**, a very good diastereoselectivity was observed. However, lower diastereoselectivities were obtained in the disubstituted cases **29** and **30**. Finally, a mixture of three diastereomers in an 83:12:5 ratio was obtained starting from **31**, but the relative stereochemistries of the chiral centres in the major diastereomer could not be ascertained.

2.4. Pyrrolidine formation by domino Michael addition/carbocyclisation reaction [5]

In the course of our studies toward the carbocyclisation reaction of β -(*N*-allyl)-aminoesters, we have shown that the above-described formation of 3,4-disubstituted-3-carbomethoxy pyrrolidines can be also obtained by the three-component one-pot domino reaction depicted in Fig. 7. 1,4-Addition of lithium zincate or higher-order cyanocuprate reagents on the common starting material **32** leads to the enolate **33**. Further carbocyclisation reaction of **33** is observed upon the addition of zinc(II) salts to yield the metalated pyrrolidines **34**, which lead upon hydrolysis to the diversely 3,4-disubstituted 3-carbomethoxypyrrolidines **35**. This interesting domino reaction can also be performed in one step by using copper–zinc reagents. The resulting metalated pyrrolidine intermediate could be functionalised with various electrophiles to pyrrolidines **36**.

In all cases, pyrrolidines are obtained with a good control of the diastereoselectivity, again in favour of

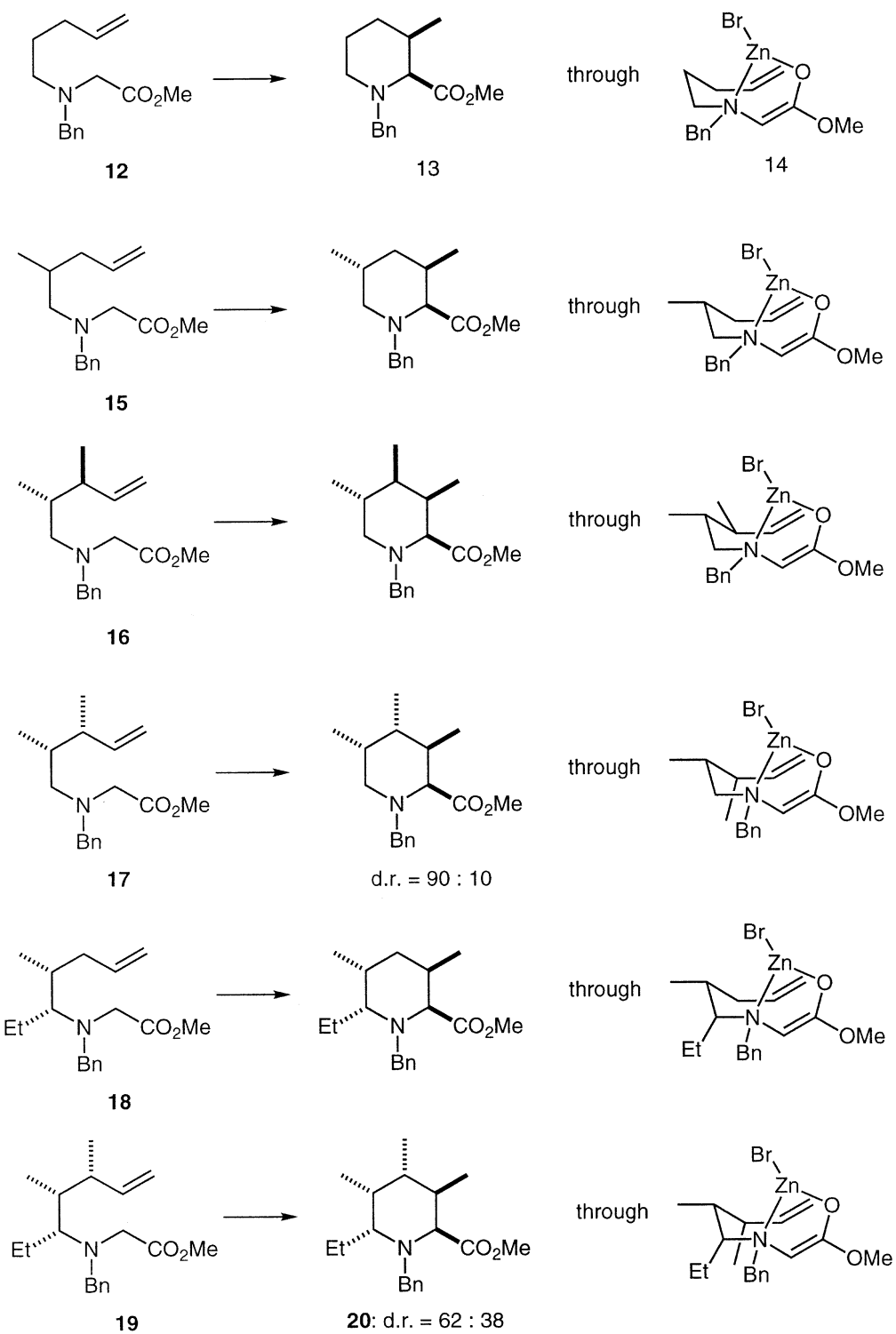


Fig. 4. Diastereoselectivity in the 2-carbomethoxypiperidine formation.

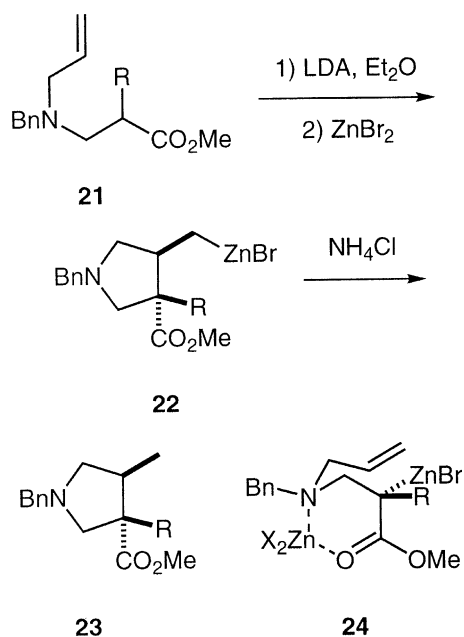


Fig. 5. Carbocyclisation reaction of substituted β -(*N*-allyl)-aminoesters.

the trans disubstituted diastereomer, as depicted in Fig. 8 for pyrrolidines **35** and **36**. The diastereoselectivity can be again explained by a C-centred zinc or copper–zinc–enolate–carbometallation-type reactive intermediate, as for the pyrrolidines obtained through deprotonation of the substituted β -(*N*-allyl)-aminoesters.

3. Considerations upon C-metalated versus O-metalated enolate-ene reactive intermediates

The puzzling dichotomy observed in the stereochemical behaviour of α -(*N*-homoallyl)-aminoesters and β -(*N*-allyl)-aminoesters is explained on the basis of O-metalated or C-metalated enolate-ene transition states. Zinc enolates derived from α -aminoesters have been found to be O-metalated [31] but, on the other hand, Reformatsky reagents have been shown to be C-metalated by NMR and X-ray crystallographic studies [32–35]. Moreover, the stereochemical outcome from α -(*N*-homoallyl)-aminoesters can be explained as well as by the original O-metalated transition state

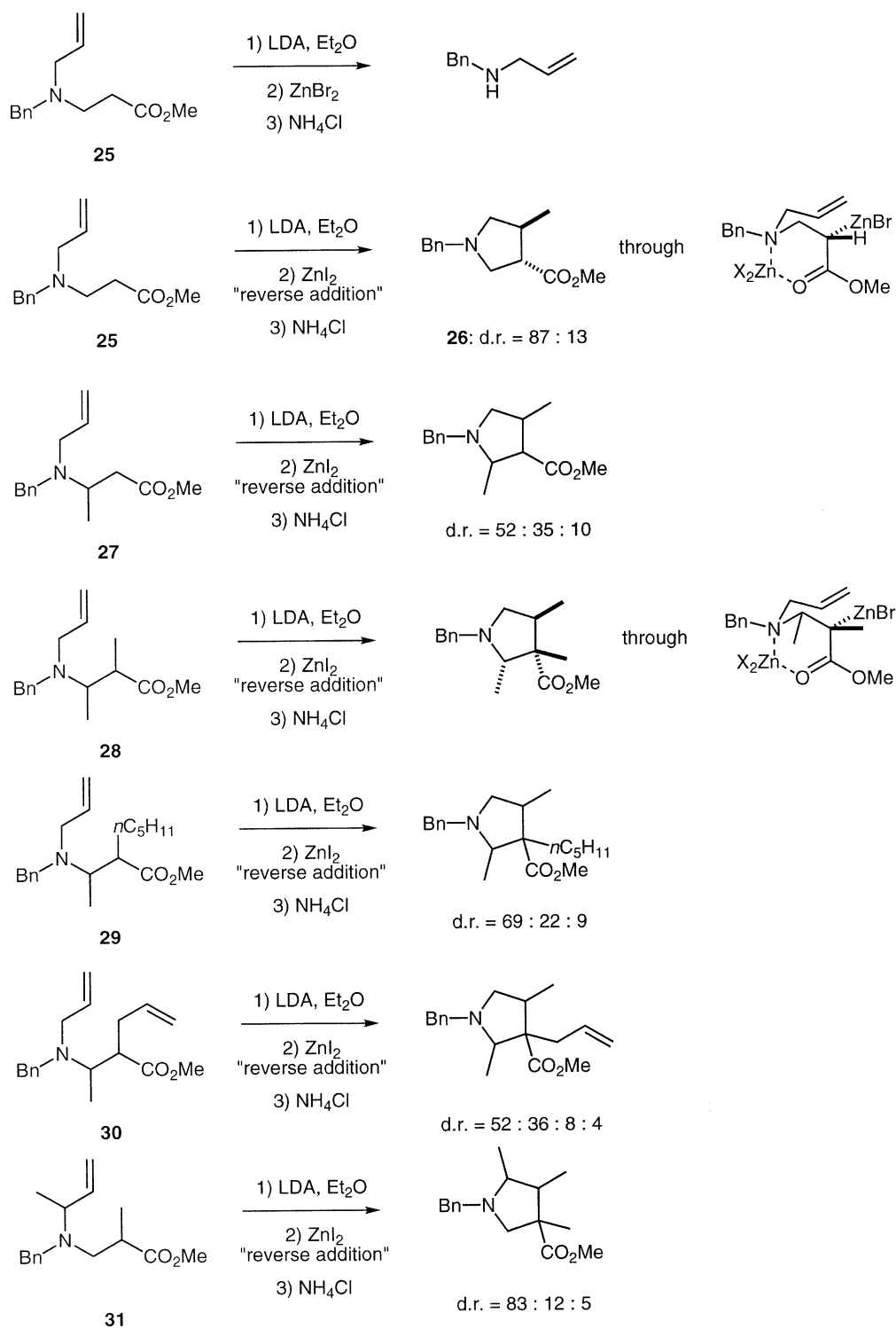
TS1 (Fig. 9), as on the basis of the C-metalated enolate-ene reactive intermediate TS2 analogous to the reactive intermediate TS3 proposed in the carbocyclisation of β -(*N*-allyl)-aminoesters.

The choice between O- and C-metalated reactive intermediates leads to a concept far beyond this simple difference. The intrinsic mechanism of the carbometallation reaction is concerned, since the O-metalated reactive intermediate mainly looks like an enolate-ene six-membered reactive intermediate, whereas in the case of a C-metalated reactive intermediate, a four-membered reactive intermediate is presumably involved.

In order to know whether carbocyclisation reactions from α -(*N*-homoallyl)-aminoesters are involving C- or O-metalated reactive intermediate, we have examined the feasibility and the stereochemical course of carbocyclisation from aminoesters **38** (Fig. 10) [36]. If an O-metalated enolate is necessary for a carbocyclisation, TS4 should be favoured over TS6 on the basis of steric hindrance between the R residue on the nitrogen atom and the vinylic moiety. The trans metalated pyrrolidine **39** should then be obtained. By contrast, if a C-metalated enolate is involved, TS7 should be favoured over TS5 (because of the interaction between this R residue and the alkyl chain) to yield the cis-metalated pyrrolidine **40**.

Compounds **38a**, **b** and **c** were prepared through alkylation of the lithium enolate derived from the corresponding *N,N*-disubstituted amino methyl acetates **41a**, **b**, **c** with 4-iodopentene in 75, 61 and 89% yield respectively (Fig. 11). Standard deprotonation of **38a**, **b**, **c** with LDA followed by zinc bromide addition gave cyclised products **42a**, **b**, **c** in 80, 36 and 19% unoptimized yields after hydrolysis and as a mixture of two diastereomers (based on ^1H and ^{13}C NMR analysis) in the 80:20 ratio. Reaction of the formed metalated cyclopentane derivative from **42a** with allylbromide in the presence of copper cyanide gave the cyclopentanyl aminoester **43** in 58% yield and as a single isolated diastereomer.

The relative stereochemistries of the compound **43** and of the major diastereomers of **42a**, **b**, **c** could not be determined by any NMR experiment. However, reaction of the major diastereomer of **42a** with an excess of *p*-tolyl Grignard reagent afforded the tertiary carbinol **44**, which could be analysed through X-ray crystallographic studies. The relative stereochemistry

Fig. 6. Carbocyclisation reactions of various β -(*N*-allyl)-aminoester.

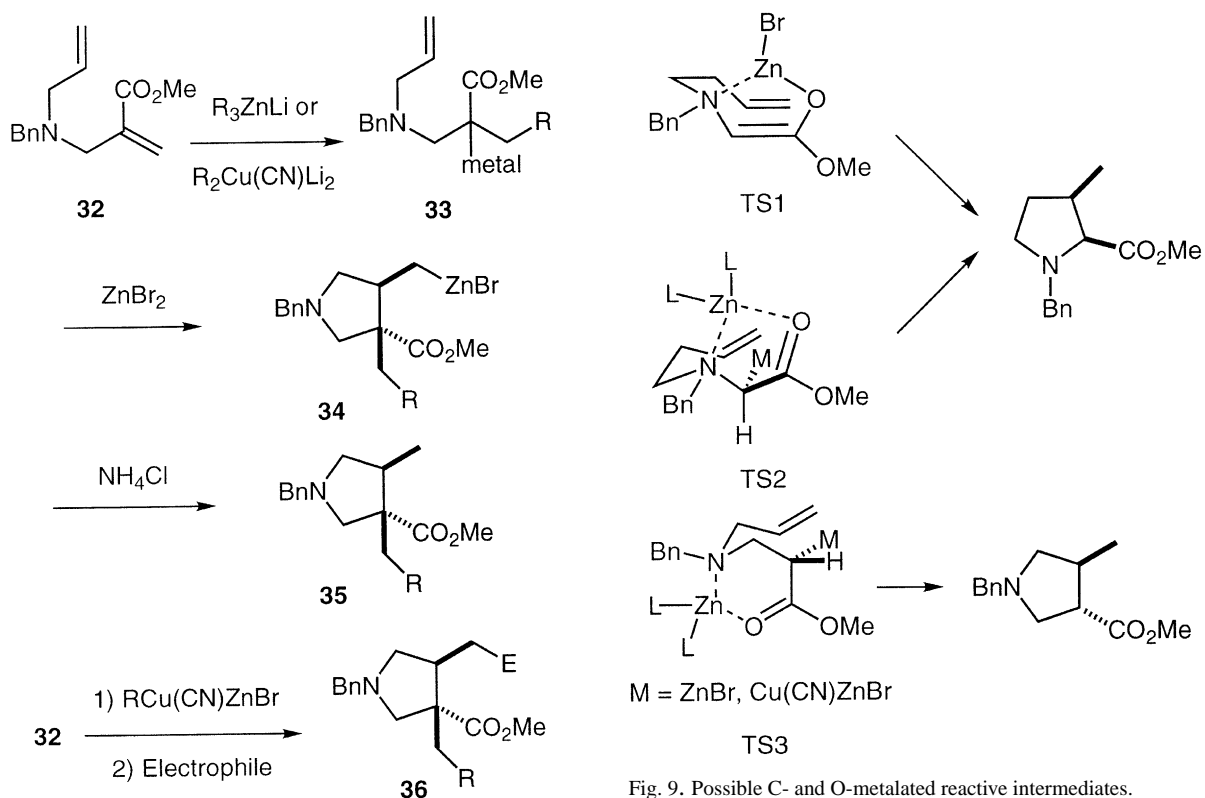


Fig. 9. Possible C- and O-metalated reactive intermediates.

Fig. 7. Domino Michael addition/carbocyclisation reaction.

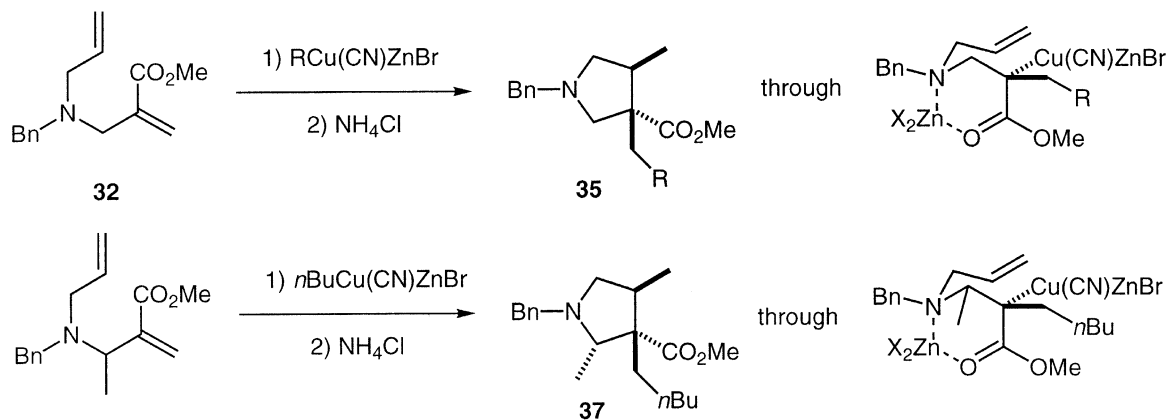


Fig. 8. Reactive intermediates for domino reactions.

was found to be *cis* (Fig. 12). We conclude that although being an α -amino ester, compound **38a** has cyclised through a C-metalated enolate-ene reactive intermediate (see **40** from TS7 in Fig. 10), as in the case of β -(*N*-allyl)-amino esters and, presumably, other α -(*N*-homoallyl)-amino esters. It should be noted that this

methodology affords a straightforward stereoselective route to 1-amino-1-carbomethoxy-2-methyl cyclopentanes difficult to prepare by other methods. We are currently working in our laboratory to enhance the yields and further explore the scope and limitations of this new promising methodology.

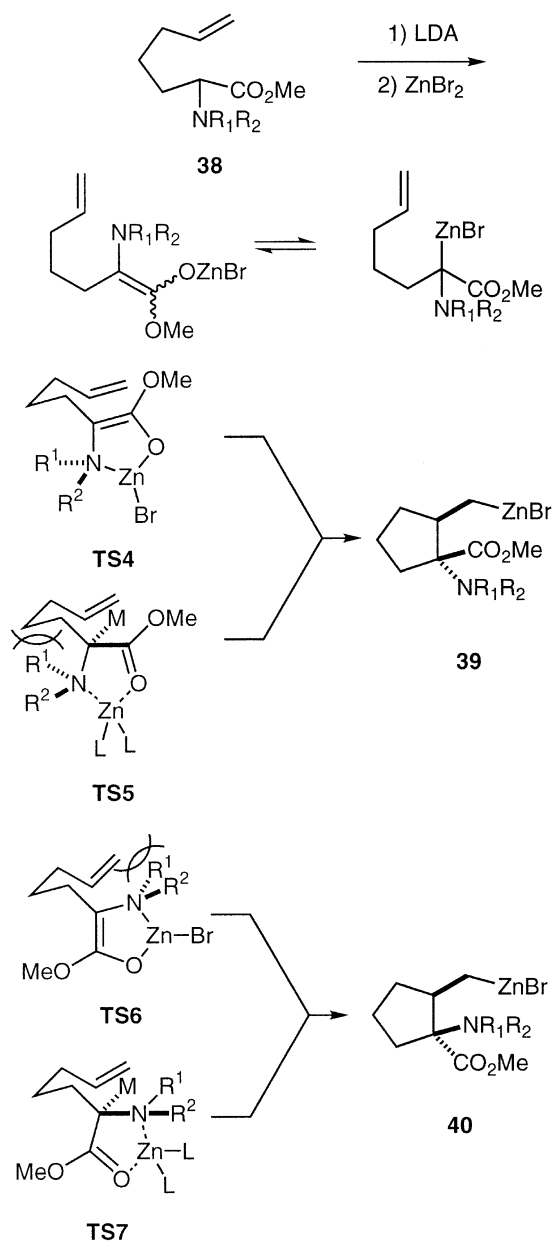


Fig. 10. Carbocyclisation from aminoesters 38.

4. Experimental Part

4.1. General remarks

Experiments involving organometallics were carried out in dried glassware under a positive pressure of

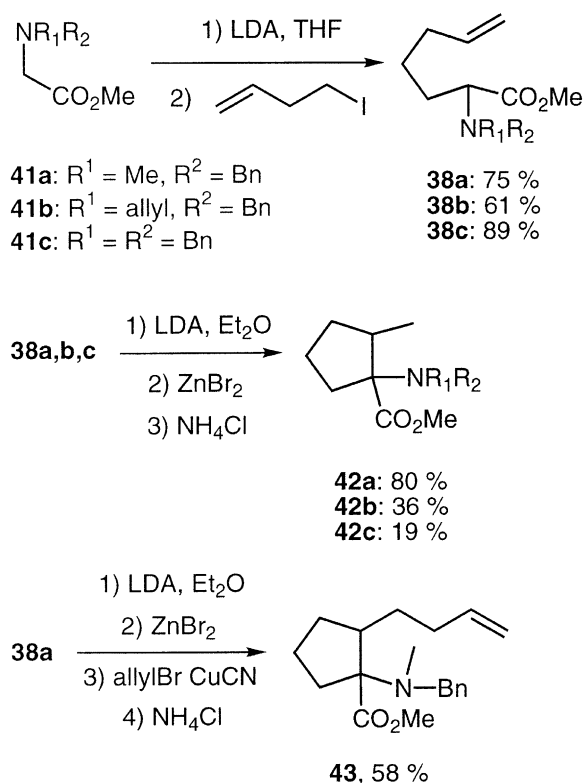


Fig. 11. Stereoselective access to 1-amino-1-carbomethoxy-2-methyl cyclopentanes.

dry nitrogen. Liquid nitrogen was used as a cryoscopic fluid. A round bottom flask equipped with an internal thermometer, a septum cap, a nitrogen inlet and a mechanic or magnetic stirring were used; THF was freshly distilled from sodium–benzophenone ketyl prior to use; zinc bromide (98%) was purchased from Aldrich. It was melted under dry nitrogen and, immediately after cooling down at room temperature, was dissolved in anhydrous THF; flash column chromatographic separations were carried out over Merck silica gel 60 (0.015–0.040 mm); ¹H NMR and ¹³C NMR spectra were recorded on a Bruker AC 200 (respectively 200 and 50.3 MHz). Chemical shifts are reported in δ relative to an internal standard of residual chloroform (δ = 7.27 for ¹H NMR and δ = 77.1 for ¹³C NMR); IR spectra were recorded with a Perkin-Elmer 1420 spectrophotometer; elemental analyses were performed by the ‘Service de microanalyses’ of the University Pierre-et-Marie-Curie (Paris-6).

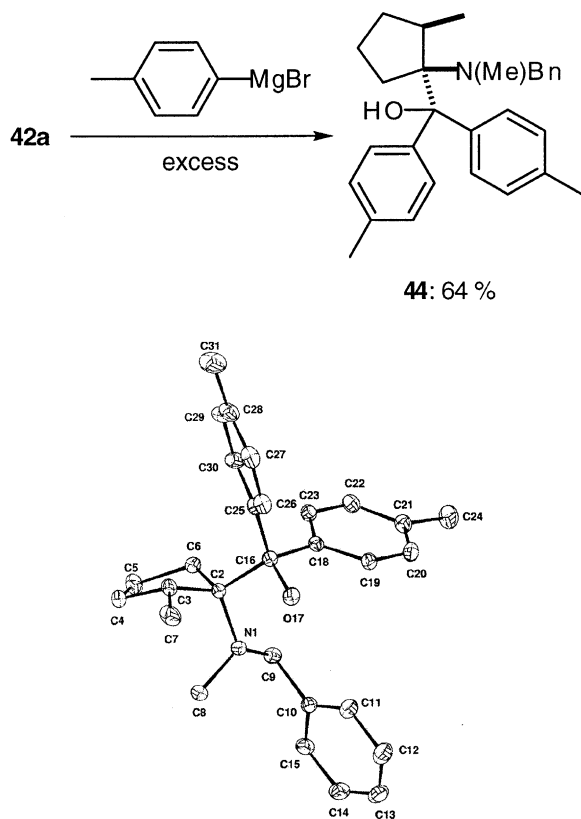


Fig. 12. Stereochemical determination of cyclopentane 42a and 44.

4.2. General preparation of compounds 38

In a 250-ml round bottom four necked flask is cooled to -78°C commercial LDA (36 mmol, 18 ml of a 2-M solution in *n*-heptane/THF) in THF (12 ml) and the methyl *N*-benzyl-*N*-alkylaminoacetate **41** (30 mmol) in THF (50 ml) is dropwise added. After stirring for 3 h at -78°C , 5-iodopent-1-ene (7.05 g, 36 mmol) in THF (50 ml) is added and the resulting yellow solution allowed to warm to room temperature. After stirring for 15 h, the reaction is hydrolysed with an aqueous solution of $\text{NH}_4\text{Cl}/\text{NH}_3$ (2:1) (100 ml). The resulting two layers are decanted, the aqueous one being extracted with ether (3×40 ml), the combined organic layers are washed with brine, dried over magnesium sulphate and the solvents evaporated under reduced pressure to give, after flash chromatography on silica gel, the title compounds **38**.

4.2.1. Methyl 2-(*N*-benzyl-*N*-methyl)-amino-hept-6-enoate **38a**

From aminoester **41a** (5.86 g, 75%). IR (film, KBr): cm^{-1} 3020, 2790, 1730, 1635; ^1H NMR (CDCl_3 , 200 M Hz): δ 7.32–7.23 (m, 5H), 5.85–5.75 (m, 1H), 5.03–4.94 (m, 2H), 3.78 and 3.68 (AB system, 2H, $J = 13.6$ Hz), 3.73 (s, 3H), 3.31 (t, 1H), 2.26 (s, 3H), 2.09–2.03 (m, 2H), 1.78–1.71 (m, 2H), 1.57–1.53 (m, 1H), 1.45–1.41 (m, 1H); ^{13}C NMR (CDCl_3 , 50 M Hz): δ 173.6, 140.0, 138.9, 129.1, 128.6, 127.3, 115.1, 65.8, 58.9, 51.3, 38.1, 33.8, 29.4, 25.9. Elemental analysis calcd (%) for $\text{C}_{16}\text{H}_{23}\text{NO}_2$: C 73.53, H 8.87, N 5.36; found C 73.50, H 8.92, N 5.23.

4.2.2. Methyl 2-(*N*-allyl-*N*-benzyl)-amino-hept-6-enoate **38b**

From aminoester **41b** (5.25 g, 61%). ^1H NMR (CDCl_3 , 200 M Hz): δ 7.31–7.18 (m, 5H), 5.89–5.64 (m, 2H), 5.24–4.90 (m, 4H), 3.94 and 3.49 (AB system, 2H, $J = 14$ Hz), 3.69 (s, 3H), 3.42–3.29 (m, 2H), 3.05 (ABX system, 1H, $J = 7.86$ Hz, $J' = 14.26$ Hz), 2.03–1.92 (m, 2H), 1.75–1.60 (m, 2H), 1.56–1.25 (m, 2H). ^{13}C NMR (CDCl_3 , 50 M Hz): δ 173.96, 140.17, 138.70, 136.90, 128.88, 128.41, 127.07, 117.38, 114.92, 61.32, 54.55, 53.69, 51.17, 33.54, 29.76, 25.62. Elemental analysis calcd (%) for $\text{C}_{18}\text{H}_{25}\text{NO}_2$: C 75.22, H 8.77, N 4.87; found C 75.20, H 8.85, N 4.82.

4.2.3. Methyl 2-*N,N*-dibenzylamino-hept-6-enoate **38c**

From aminoester **41c** (9.00 g, 89%). IR (film, KBr): cm^{-1} 3060, 3030, 2950, 2840, 1730, 1640, 1600, 1490, 1450, 1430, 1360, 1200, 1140, 1075, 1630, 990, 915, 820, 780, 745, 700; ^1H NMR (CDCl_3 , 200 M Hz): δ 7.40–7.20 (m, 10H), 5.80–5.70 (m, 1H), 4.98–4.92 (m, 2H), 3.95 et 3.53 (AB system, 4H, $J = 14$ Hz), 3.78 (s, 3H), 3.35 (dd, 1H, $J = 10$ Hz, $J' = 6.6$ Hz), 1.93 (q, 2H, $J = 7$ Hz), 1.84–1.67 (m, 2H), 1.63–1.52 (m, 1H), 1.40–1.30 (m, 1H); ^{13}C NMR (CDCl_3 , 50 M Hz): δ 173.68, 139.84, 138.60, 129.00, 128.39, 127.13, 114.87, 60.62, 54.65, 51.15, 33.38, 29.09, 25.44. Elemental analysis calcd (%) for $\text{C}_{22}\text{H}_{27}\text{NO}_2$: C 78.30, H 8.06, N 4.15; found C 78.14, H 8.13, N 4.08.

4.3. General procedure for the carbocyclisation to the compounds 42

In a 100-ml round bottom four-necked flask is cooled down to -40°C a solution of substituted aminoester **38** (2 mmol) in anhydrous THF (35 ml). Com-

mercial LDA (10 mmol, 5 ml of a 2-M solution in *n*-heptane/THF) is dropwise added and the mixture is allowed to warm to 10 °C for 10 min. After cooling down to –40 °C, ZnBr₂ (8 mmol, 8 ml of a 1-M solution in THF) is added and the reaction mixture is allowed to warm to room temperature and stirred 20 min for **38a** and 3 h for **38b**. After hydrolysis with an aqueous solution of NH₄Cl/NH₃ (2:1) (50 ml), the aqueous layer is extracted with ether (3 × 20 ml). The combined organic layers are washed with brine, dried over magnesium sulphate and the solvents evaporated under reduced pressure to give, after chromatography on silica gel, the title compounds **42**. Only the major diastereomer for **42a** and **42b** is described below. The compound **42c** could not be separated from the starting material.

4.3.1. Methyl 1-(*N*-benzyl-*N*-methylamino)-2-methyl-cyclopentanecarboxylate **42a**

From compound **38a** (80%, 0.42 g). IR (film, KBr): cm⁻¹ 2960, 2800, 1720, 1495, 1450, 1375, 1235, 1190, 1065, 910, 735, 700; ¹H NMR (CDCl₃, 200 M Hz): δ 7.36–7.30 (m, 5H), 3.76 (s, 3H), 3.60 (s, 2H), 2.69–2.64 (m, 1H), 2.42–2.37 (m, 1H), 2.09 (s, 3H), 1.82–1.76 (m, 3H), 1.62–1.58 (m, 1H), 1.51–1.45 (m, 1H), 1.03 (d, 3H, *J* = 7.08 Hz); ¹³C NMR (CDCl₃, 50 MHz): δ 174.0, 140.6, 128.30, 128.1, 127.7, 76.8, 58.0, 51.1, 37.8, 37.7, 31.7, 31.05, 20.2, 15.8; Elemental analysis calcd (%) for C₁₆H₂₃NO₂: C 73.53, H 8.87, N 5.36; found C 74.23, H 9.02, N 5.02.

4.3.2. Methyl 1-(*N*-allyl-*N*-benzylamino)-2-methyl-cyclopentanecarboxylate **42b**

From compound **38b** (36%, 0.21 g). IR (film, KBr): cm⁻¹ 2960, 1720, 1640, 1600, 1490, 1450, 1375, 1330, 1280, 1235, 1190, 1100, 1075, 1040, 1030, 1000, 975, 920, 795, 735, 700; ¹H NMR (CDCl₃, 200 M Hz): δ 7.37–7.13 (m, 5H), 5.81–5.60 (m, 1H), 4.99–4.83 (m, 2H), 3.90 and 3.73 (AB system, 2H, *J* = 16 Hz), 3.71 (s, 3H), 3.30 (ABX system, 1H, *J* = 4.92 Hz, *J*' = 15.51 Hz), 3.05 (ABX system, 1H, *J* = 7.86 Hz, *J*' = 14.76 Hz), 2.74–2.60 (m, 1H), 2.26–2.18 (m, 1H), 1.78–1.25 (m, 5H), 1.01 (d, 3H, *J* = 7.12 Hz); ¹³C NMR (CDCl₃, 50 M Hz): δ 175.35, 141.89, 136.59, 128.04, 128.01, 126.41, 116.40, 77.2, 55.20, 54.92, 51.24, 38.41, 31.96, 30.76, 20.34, 16.35; Elemental analysis calcd (%) for C₁₈H₂₅NO₂: C 75.22, H 8.77, N 4.87; found C 75.51, H 8.15, N 4.57.

4.4. Methyl 1-(*N*-benzyl-*N*-methylamino)-2-[but-3-enyl]-cyclopentanecarboxylate **43**

In a 100-ml round bottom three-necked flask is cooled down to –78 °C a solution of LDA (5 mmol, 2.5 ml of a 2-M solution in *n*-heptane/THF) in THF (5 ml). The substituted aminoester **38a** in THF (5 ml) is dropwise added, the mixture stirred for 30 min at –78 °C and allowed to warm to room temperature for 2 h. ZnBr₂ (5 mmol, 5 ml of a 1-M solution in THF) is added and the resulting mixture stirred for 4 h. The mixture is cooled down to –40 °C and CuCN (0.445 g, 5 mmol) is added in one portion. The mixture is warmed to room temperature, cooled down to –40 °C and allyl bromide 0.5 ml, 5 mmol: in THF (2 ml) is added. The reaction mixture is allowed to warm to room temperature and stirred overnight. The reaction is hydrolysed with an aqueous solution of NH₄Cl/NH₃ (2:1) (30 ml), the aqueous layer is extracted with ether (3 × 10 ml), the combined organic layers washed with brine, dried over magnesium sulphate and the solvents evaporated under reduced pressure to give, after flash chromatography on silica gel, the title compound (0.291 g, 58%). IR (film, KBr): cm⁻¹ 3060, 3020, 2960, 2800, 1720, 1635, 1600, 1495, 1450, 1360, 1280, 1195, 1170, 1120, 1070, 1030, 995, 910, 790, 735, 700; ¹H NMR (CDCl₃, 200 M Hz): δ 7.35–7.19 (m, 5H), 5.92–5.72 (m, 1H), 5.08–4.91 (m, 2H), 3.75 (s, 3H), 3.62 and 3.49 (AB system, 2H, *J* = 14 Hz), 2.47–2.37 (m, 2H), 2.25–2.15 (m, 1H), 2.05 (s, 3H), 1.99–1.04 (m, 8H); ¹³C NMR (CDCl₃, 50 M Hz): δ 173.07, 140.49, 139.07, 129.32, 129.23, 126.78, 114.75, 76.56, 57.94, 51.15, 42.73, 37.64, 32.9, 32.22, 27.43, 27.15, 20.17; Elemental analysis calcd (%) for C₁₉H₂₇NO₂: C 75.71, H 9.03, N 4.65; found C 76.02, H 9.32, N 4.48.

4.5. [1-(*N*-benzyl-*N*-methylamino)-2-methyl-cyclopentyl]di-*p*-tolyl-methanol **44**

A solution of 4-methyl phenyl bromide (1.44 g, 8.44 mmol) in anhydrous ether (20 ml) is cooled down to –80 °C and *t*BuLi (16.38 mmol, 9.6 ml of a 1.7-M solution in pentane) is dropwise added. The resulting mixture is stirred at 0 °C for 1 h. The compound **42a** (0.55 g, 2.11 mmol) in anhydrous ether (3 ml) is dropwise added at –5 °C and the reaction mixture allowed to warm to room temperature and stirred overnight. After hydrolysis with an aqueous solution of

NH₄Cl/NH₃ (2:1) (20 ml), the aqueous layer is extracted with ether (3 × 10 ml), the combined organic layers washed with brine, dried over magnesium sulphate and the solvents evaporated under reduced pressure to give, after flash chromatography, the title compound **44** (0.556 g, 64%) as a white solid. mp: 110–113 °C; IR (film, KBr): cm⁻¹ 3050, 2950, 1500, 1450, 1265, 1040, 1015, 945, 895, 810, 740, 705; ¹H NMR (CDCl₃, 200 MHz): δ 7.79–7.66 (m, 4H, H); 7.29–7.13 (m, 5H, H); 7.05–6.97 (m, 4H), 6.45 (s, 1H), 3.87 and 3.59 (AB system, 2H, *J* = 13.54 Hz), 2.62–2.43 (m, 2H), 2.39–1.26 (m, 5H), 2.27 (s, 3H), 2.23 (s, 3H), 2.04 (s, 3H), 1.26 (d, 3H); ¹³C NMR (CDCl₃, 50 MHz): δ 147.37, 144.32, 140.97, 135.62, 128.79, 128.66, 128.42, 127.08, 126.79, 126.63, 81.13, 79.95, 58.52, 42.02, 38.97, 33.12, 32.80, 29.99, 23.12, 21.09, 15.84; Elemental analysis calcd (%) for C₂₉H₃₅NO: C 84.22, H 8.53, N 3.39; found C 83.80, H 8.65, N 3.12.

Supplementary material

The supplementary material has been sent to the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK, as supplementary material No. 196065 (6 pages) and can be obtained by contacting the CCDV/FIZ.

Acknowledgements

Thanks are due to Carine Guyard-Duhayon, from the 'Laboratoire de chimie inorganique et moléculaires', University Pierre-et-Marie-Curie (Paris-6) for X-ray crystallographic studies.

References

- [1] E. Lorthiois, I. Marek, J.-F. Normant, *Tetrahedron Lett.* 38 (89) (1997).
- [2] E. Lorthiois, I. Marek, J.-F. Normant, *J. Org. Chem.* 63 (1998) 566.
- [3] E. Lorthiois, I. Marek, J.-F. Normant, *J. Org. Chem.* 63 (1998) 2442.
- [4] F. Denes, F. Chemla, J.-F. Normant, *Synlett* 919 (2002).
- [5] F. Denes, F. Chemla, J.-F. Normant, *Eur. J. Org. Chem.* (2002) 3536.
- [6] P. Karoyan, G. Chassaing, *Tetrahedron Lett.* 38 (85) (1997).
- [7] P. Karoyan, A. Triolo, R. Nannicini, D. Giannotti, M. Altamura, G. Chassaing, E. Perotta, *Tetrahedron Lett.* 40 (71) (1999).
- [8] G. Chassaing, P. Karoyan, *Tetrahedron: Asymm.* 8 (1997) 2025.
- [9] P. Karoyan, G. Chassaing, *Tetrahedron Lett.* 43 (2002) 253.
- [10] P. Knochel, in: B. Trost, I. Fleming (Eds.), *Comprehensive Organic Synthesis*, vol. 4, Pergamon Press, New York, 1991, pp. 865.
- [11] I. Marek, J.-F. Normant, in: D. Diederich, P. Stang (Eds.), *Cross Coupling Reactions*, VCH, 1997, pp. 271.
- [12] A.L. Rodriguez, T. Bunlakananusorn, P. Knochel, *Org. Lett.* 2 (2000) 3285.
- [13] M. Rosenblum, A. Rosan, J. Tancrede, *J. Am. Chem. Soc.* 95 (1973) 3062.
- [14] P. Lennon, A.M. Rosan, M. Rosenblum, *J. Am. Chem. Soc.* 99 (1977) 8426.
- [15] M. Rosenblum, *Acc. Chem. Res.* 122 (1974).
- [16] B. Roberts, J. Wong, *J. Chem. Soc., Chem. Commun.* 20 (1977).
- [17] L.W. Chuang, H.W. Fu, B.A. Sheu, S.I. Tau, M.C. Yeh, *J. Am. Chem. Soc.* 115 (1993) 5941.
- [18] M.L. Lai, S.C. Chang, C.C. Hwu, M.C. Yeh, *Tetrahedron Lett.* 37 (1996) 6149.
- [19] M.C.P. Yeh, L.W. Chuang, C.H. Ueng, *J. Org. Chem.* 61 (1996) 3874.
- [20] Md.N.I. Khan, A.J. Pearson, *J. Am. Chem. Soc.* 106 (1984) 1872.
- [21] J.C. Clardy, H. Cun-heng, Md.N.I. Khan, A.J. Pearson, *J. Am. Chem. Soc.* 107 (1985) 2748.
- [22] Md.N.I. Khan, A.J. Pearson, *Tetrahedron Lett.* 26 (1985) 1407.
- [23] G. Poli, G. Giambastiani, A. Heumann, *Tetrahedron* 56 (2000) 5959 and references therein.
- [24] G. Balme, D. Bouyssi, N. Monteiro, in: E.I. Negishi (Ed.), *Handbook of Organopalladium Chemistry for Organic Synthesis*, Wiley Interscience, 2002, pp. 2245.
- [25] O. Kitagawa, T. Suzuki, H. Fujiwara, T. Taguchi, *Tetrahedron Lett.* 40 (1999) 2549.
- [26] O. Kitagawa, H. Fujiwara, T. Suzuki, T. Taguchi, M. Shiro, *J. Org. Chem.* 65 (2000) 6819.
- [27] E. Nakamura, K. Kubota, *Tetrahedron Lett.* 38 (1997) 7099.
- [28] K. Kubota, E. Nakamura, *Angew. Chem. Int. Ed. Engl.* 36 (1997) 2491.
- [29] K. Kubota, E. Nakamura, *J. Org. Chem.* 62 (1997) 792.
- [30] E. Nakamura, G. Sakata, K. Kubota, *Tetrahedron Lett.* 391 (1998) 2157.
- [31] F.H. Van der Steen, H. Kleijn, G.J.P. Britovsek, J.T.B.H. Jastrzebski, G. Van Koten, *J. Org. Chem.* 57 (1992) 3906.
- [32] F. Orsini, F. Pelizzoni, G. Ricca, *Tetrahedron Lett.* 25 (1982) 3945.
- [33] J. Boersma, J. Dekker, G.J.M. Van der Kerk, *J. Chem. Soc., Chem. Commun.* 553 (1983).
- [34] J. Boersma, P.H.M. Budzelaar, J. Dekker, G.J.M. Van der Kerk, *Organometallics* 3 (1984) 1403.
- [35] F. Orsini, F. Pelizzoni, G. Ricca, *Tetrahedron* 40 (1984) 2781.
- [36] (a) E. Lorthiois, PhD thesis, University Pierre-et-Marie-Curie (Paris-6), France, 1998; (b) F. Prian, Mém. DEA, University Pierre-et-Marie-Curie (Paris-6), France.