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# Radical-Polar Crossover Domino Reactions Involving Organozinc and Mixed Organocopper/Organozinc Reagents

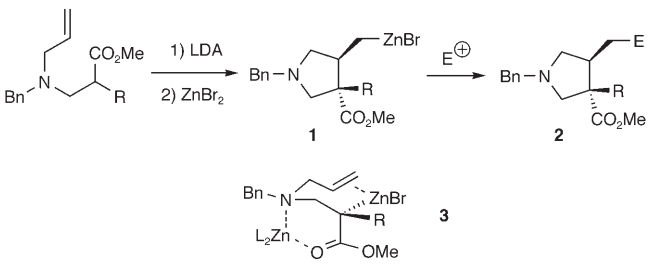
**Fabrice Denes, Sabrina Cutri, Alejandro Perez-Luna, and Fabrice Chemla*[a]**

**Abstract:** A domino process involving Michael addition and carbocyclization has been developed starting from β-*N*-allylamino enoates and various organometallic reagents (organozinc halides, diorganozinc reagents, and copper/zinc mixed species). In all cases the mechanism of this domino reaction has been evidenced to involve a radical-polar crossover mechanism.

**Keywords:** copper · domino reactions · Michael addition · radical reactions · zinc

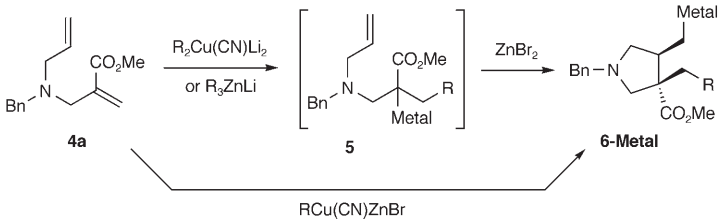
## Introduction

We have recently shown (Scheme 1) that zinc enolates derived from β-*N*-allyl amino esters undergo smooth and diastereoselective carbocyclization to *trans* 3-carboxymethyl-4-methylzinc compounds **1**, which can be further functionalized to substituted *trans*-pyrrolidines **2**.[1] The diastereoselectivity was explained[2] by a transition state involving C-centered[3] zinc enolate **3**.



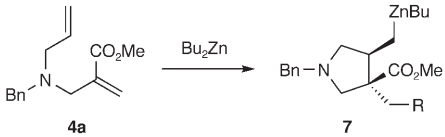

Scheme 1. Carbocyclization of β-*N*-allyl amino esters via zinc enolates.[1,2]

We later showed[4] that the same substituted pyrrolidines can be obtained from the starting *N*-allyl methyl enoate **4a** by a domino process (Scheme 2) involving a Michael addition followed by a carbocyclization reaction. A stepwise process was observed with higher order cyanocuprates or zincates. By contrast the reaction occurs by a direct pathway with mixed organocopper/organozinc reagents, without any detection of the enolate **5** formed by Michael addition. Diastereoselectivity is excellent in both processes, again in favour of the *trans*-disubstituted metallated pyrrolidine **6-Metal**, which can be further functionalized.




Scheme 2. Domino reaction with β-*N*-allyl amino enoates.[4]

Furthermore, in a preliminary communication[5] we also reported that the same domino process can be carried out with diorganozinc species. However, in this case the diastereoselectivity is reversed, since the *cis*-substituted metallated pyrrolidine **7-ZnBu** is formed as the major product [Eq. (1)]. This behaviour was attributed to a radical-polar crossover mechanism involving molecular oxygen as initiator.[6,7]



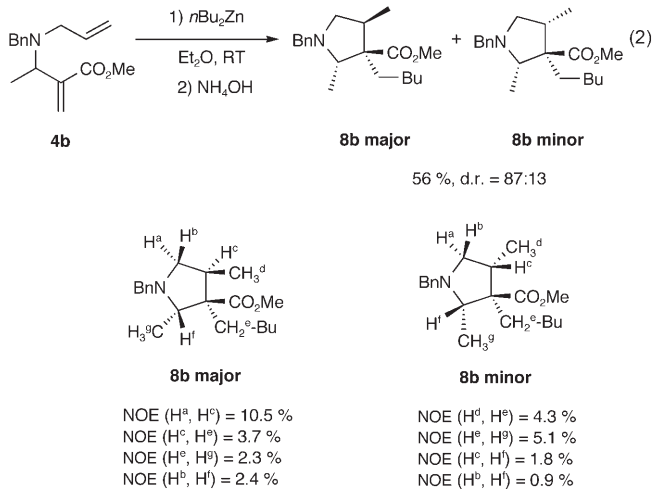

Hereafter we give a full account of our results concerning the mechanism (polar versus radical-polar crossover) of this domino reaction.

[a] Dr. F. Denes, Dr. S. Cutri, Dr. A. Perez-Luna, Prof. F. Chemla
Université Pierre et Marie Curie - Paris 6
Laboratoire de chimie organique (UMR CNRS 7611)
Institut de chimie moléculaire (FR 2769)
case 183, 4 place Jussieu, 75252 Paris cedex 05 (France)
Fax: (+33) 144-277-567
E-mail: fchemla@ccr.jussieu.fr

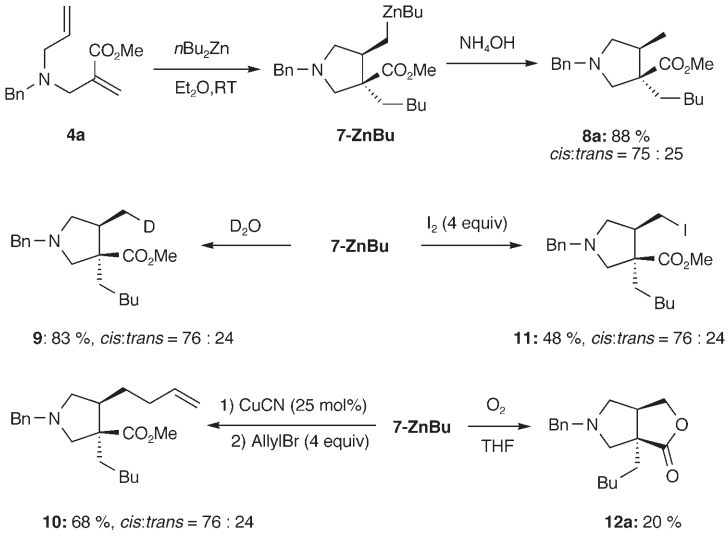
## Results and Discussion

**Reaction of enoates 4a–e with di-*n*-butylzinc**: Di-*n*-butylzinc reacted smoothly with Michael acceptor **4a** at room temperature. Pyrrolidine **8a** was isolated in 88% yield after hydrolysis of the resulting organometallic species **7-ZnBu**. Moreover, **7-ZnBu** was functionalized with various electrophiles to give substituted pyrrolidines **9**–**11** in good yields (Scheme 3). In situ oxidation by molecular oxygen during the domino reaction afforded the corresponding lactone **12a**. Solvent polarity seems to have no impact on the stereoselectivity of the reaction, as a similar *cis*:*trans* ratio was observed in pentane (*cis*:*trans* = 75:25), diethyl ether (76:24), THF (72:28), and DMF (77:23).

The domino reaction was also performed on Michael acceptors bearing a substituent α to the nitrogen atom. Di-*n*-butylzinc reacted at room temperature with Michael acceptor **4b** to afford after hydrolysis the corresponding pyrrolidine **8b** in moderate yield (Scheme 4). Of the four possible diastereomers, only two were observed. The structure of each diastereomer was determined by NOE experiments.




Scheme 4. Domino reaction with enoate **4b**.

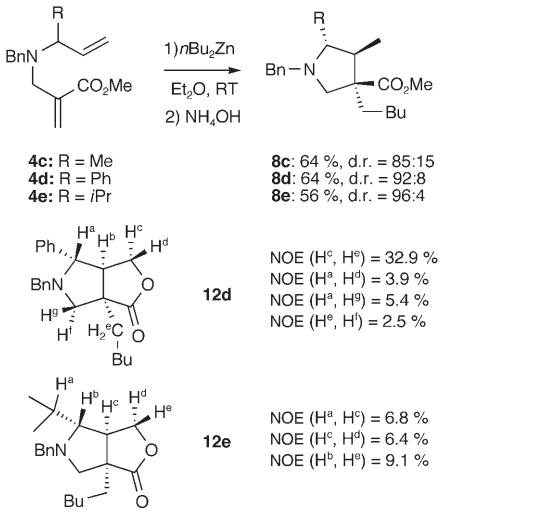



Scheme 3. Functionalization of **7-ZnBu**.

The diastereoselectivity of the domino process is also good with a substituent at the allylic position. When performed with starting enoates **4c–e** (Scheme 5), the reaction led to a major or unique diastereomer **8c–e** in good yields. The structure of the major (or unique) diastereomer was inferred from NOE experiments on the corresponding bicyclic lactone **12d** or **12e** obtained from the starting enoates **4d** or **4e** after domino reaction and oxidation with molecular oxygen.

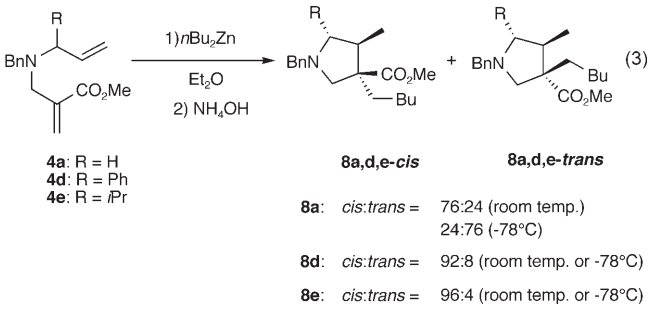
In the reaction with **4a** temperature has a strong influence on the diastereoselectivity, which is reversed by performing the reaction at low temperature [Eq. (2)]. Surprisingly, this temperature effect was not observed for **4d** and **4e**, as no difference in diastereoselectivity was found.

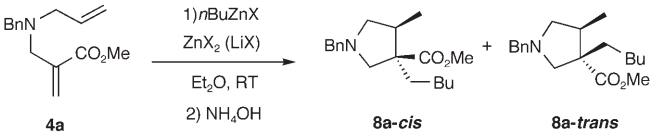
**Reaction of enoate 4a with alkylzinc halides**: Organozinc halides are known to perform 1,4-addition processes only under Lewis acid activation.[8] However, we found that *n*-butylzinc bromide undergoes a smooth domino process with enoate **4a** to afford pyrrolidine **8a** in good yield. The diastereoselectivity of this domino process was found to be reversed compared to the reaction with di-*n*-butylzinc and the same as with copper/zinc mixed reagents, that is the *trans* diastereomer was the major one [Eq. (3)].




Scheme 5. Domino reactions with enoates **4c–e**.




Interestingly, the diastereoselectivity is highly dependent on the presence and amount of Li or Zn salts, as shown in Table 1. For example, the diastereoselectivity is better with

Table 1. Domino reaction of *n*-butylzinc bromide with Michael acceptor **4a** [Eq. (3)].

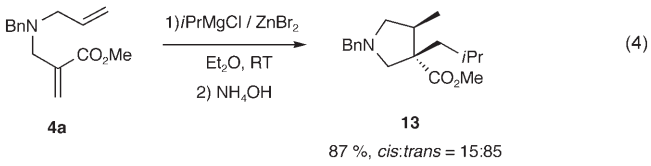
| Entry | X | BuZnX (equiv) | $ZnX_2$ (equiv) | Formed LiX [a] (equiv) | *cis*:*trans* ratio[b] |
|---|---|---|---|---|---|
| 1 | Br | 2 | 0 | **2** | 41:59[c] |
| 2 | Br | 2 | 1 | 2 | 17:83[d] |
| 3 | Br | 2 | 0 | 0[e] | 27:73[c] |
| 4 | Br | 1 | 2 | 1 | 15:85[d] |
| 5 | Cl | 1 | 2 | 1 | 33:67[c] |
| 6 | Br | 1.2 | 1[f] | 1.2 | 24:76[c] |
| 7 | Br | 3 | 1.5 | 3 | 21:79[c] |

[a] *n*BuZnBr was formed by mixing equimolar amounts of *n*BuLi and $ZnBr_2$ before reaction with **4a**. [b] *cis*:*trans* ratios were determined by GC. [c] 12 h were necessary to reach completion. [d] 24 h were necessary to reach completion. [e] *n*BuZnBr formed by mixing equimolar amounts of $nBu_2Zn$ and $ZnBr_2$ before reaction with **4a**. [f] Enoate **4a** was precomplexed with $ZnBr_2$ before addition of *n*BuZnBr.

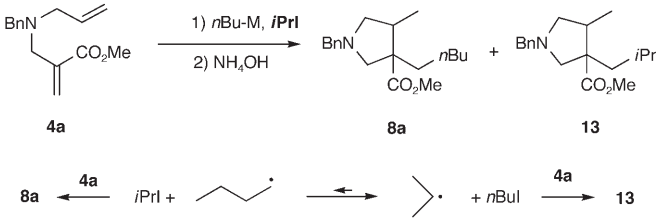
salt-free *n*BuZnBr (formed by mixing equimolar amounts of $nBu_2Zn$ and $ZnBr_2$, Table 1, entry 3) than with *n*BuZnBr containing lithium salts (formed by a transmetallation of *n*BuLi and $ZnX_2$, Table 1, entries 1 and 5). The best compromise (in terms of diastereoselectivity and reaction time) is obtained by using an excess of *n*BuZnBr (prepared from *n*BuLi and $ZnBr_2$) with an excess of $ZnBr_2$ (Table 1, entry 7). Under these conditions, the use of $ZnCl_2$ instead of $ZnBr_2$ is detrimental (compare Table 1, entries 4 and 5), and the precomplexation of the starting material with $Zn^{II}$ salt has no effect on the stereoselectivity (Table 1, entry 6).

The reaction is also efficient when the organozinc species is prepared from a Grignard reagent. Starting from *i*PrMgCl we obtained a good yield and a similar selectivity [Eq. (4)].

**Mechanism of the domino reaction with organozinc reagents and copper/zinc mixed reagents**: To establish the radical or




polar nature of the 1,4-addition process, we performed our domino reaction with enoate **4a** and various *n*-butyl metals in the presence of *i*PrI (Scheme 6).




Scheme 6. Scrambling experiments.

At first, we reasoned that if the 1,4-addition follows a radical mechanism, the initially formed *n*Bu radical should react rapidly with *i*PrI in an iodine-exchange reaction to afford the more stable *i*Pr radical, and the major product should be **13** after addition of the *i*Pr moiety. Our results are reported in Table 2.

Table 2. Scrambling experiments with various *n*BuM and *i*PrI (Scheme 6).

| Entry | *n*BuM | *i*PrI (equiv) | **8a**/**13**[a] ratio | d.r.[a] **8a** (*cis*:*trans*) | d.r.[a] **13** (*cis*:*trans*) |
|---|---|---|---|---|---|
| 1 | *n*BuZnBr | 1 | 60:40 | 20:80 | 13:87 |
| 2 | *n*BuZnBr | 5 | 26:74 | 14:86 | 11:89 |
| 3 | $nBu_2Zn$ | 5 | 19:81 | 74:26 | 64:36 |
| 4 | *n*BuCu(CN)ZnBr | 5 | 30:70 | 10:90 | 11:89 |

[a] Determined by $^1H$ NMR spectroscopy on the crude material.

In all cases *i*Pr incorporation is competitive with the *n*BuM reaction, or even the major pathway when *i*PrI is used in excess. These results seem to indicate a radical nature of the 1,4-addition step. However, we have no data concerning the relative reaction rates of *n*BuM versus *i*PrM in these 1,4-additions. These scrambling experiments make sense only if there is no (or negligible) equilibrium between *n*BuM and *i*PrM.[9] Equilibrium between dialkylzincs (or alkylzinc iodides) and alkyl iodides has been reported only under irradiation[10] or at high temperature in the presence of CuCN or CuI,[11] albeit in both cases with experimental conditions very different to ours. We thus examined possible exchange between various *n*BuM and dodecyl iodide under our conditions [Eq. (5), Table 3].

The results show that in our reaction media little exchange between alkylzinc bromide or dialkylzinc and alkyl iodide is expected, but this exchange is accelerated in the presence of $Cu^I$ salts. Thus, at least in the case of copper/zinc mixed reagents, the possibility of exchange prior to 1,4-

Table 3. Exchange between various *n*BuM and *n*-$C_{12}H_{25}I$ [Eq. (5)]

| Entry | *n*BuM | *n*-$C_{12}H_{25}I$/*n*-$C_{12}H_{25}M$ ratio[a] |
|---|---|---|
| 1 | *n*-BuZnBr[b] | 93:7 |
| 2 | $nBu_2Zn$ | 93:7 |
| 3 | *n*BuCu(CN)ZnBr[c] | 76:24 |
| 4 | *n*BuCu(CN)ZnBr[c,d] | 60:40 |

[a] Determined by measuring (GC with internal standard) the ratio *n*-$C_{12}H_{25}I$:*n*-$C_{12}H_{26}$ after hydrolysis. [b] Prepared from *n*BuLi and $ZnBr_2$ in diethyl ether [c] Prepared by adding *n*BuLi to a CuCN/$ZnBr_2$ mixture in diethyl ether. [d] After a reaction time of 24 h.

$$nBu-M + nC_{12}H_{25}-I \underset{\text{room temp.}}{\overset{Et_2O,\ 2\ h}{\rightleftharpoons}} nBu-I + nC_{12}H_{25}-M \qquad (5)$$

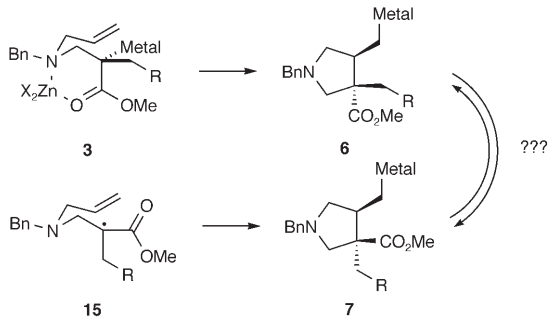
addition, and therefore a polar addition step, cannot be excluded. Besides, whatever the nature of the addition process is (radical or polar), the scrambling experiments give no information regarding the nature (radical or polar) of the carbocyclization step.

To try to solve the problem, we thus examined the reactivity of Michael acceptor **14** with various organometallic species. We observed that no 1,4-addition occurred between **14** and $nBu_2Zn$ or *n*BuZnBr. More surprisingly, no reaction was observed with either *n*BuCu(CN)ZnBr or PhCu(CN)ZnBr (Scheme 7). By contrast, rapid reaction of **14** occurs in the presence of $nBu_3ZnLi$, although we were unable to isolate any product (presumably due to β elimination and polymerization).

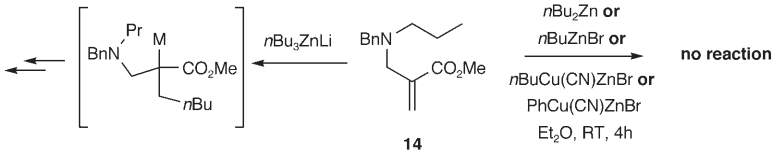
These results show unequivocally that the first step of our domino reaction, that is, the 1,4-addition process, follows a radical mechanism (Scheme 8). Moreover, the fact that no reaction is observed for **14** shows that the cyclization step also follows a radical mechanism, and that the radical formed by 1,4-addition is not reduced to metal enolate **5**. Indeed, in the case of **14**, the radical resulting from 1,4-addition is not trapped by an unsaturated group, and thus the radical chain is broken. By contrast, in the case of **4a**, radical **15** adds to the unsaturated group in an easy 5-*exo*-trig process to give new radical **16**, which is then reduced to organometallic species **6** or **7**, depending on the nature of the metal.

This radical domino pathway is followed in the case of alkylzinc bromide, dialkylzinc, and, more surprisingly, in the case of mixed organocopper/zinc reagents.

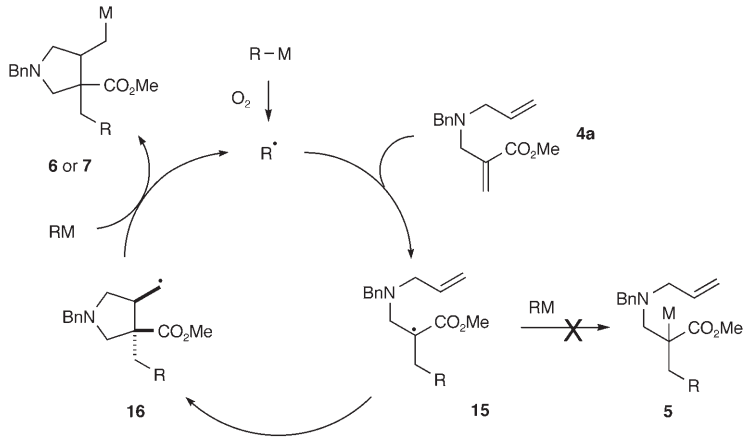
**Diastereoselectivity**: The diastereoselectivity of the carbocyclization step via zinc enolates has been explained by transition state **3** (Scheme 9) involving a C-centred zinc enolate.




Scheme 9. Possible equilibration between **6** and **7**.




Scheme 7. Reaction with enoate **14**.

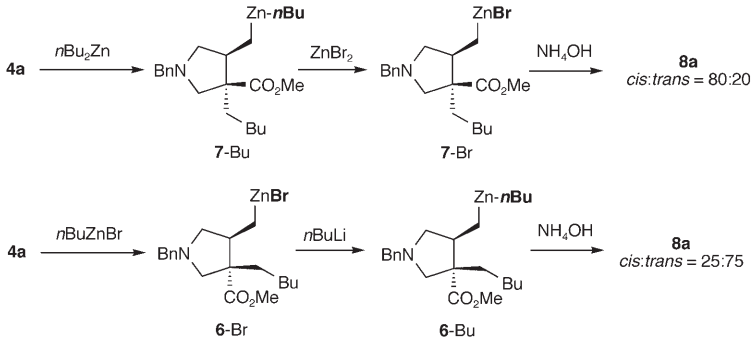



Scheme 8. Mechanism of the radical-polar crossover domino reaction.

The diastereoselectivity of the radical-polar crossover reaction involving $nBu_2Zn$ can be explained through cyclization of radical **15**.

Considering the diastereodivergency of our domino radical-polar crossover reaction, it was interesting to verify that the diastereoselectivity was not the result of thermodynamic control. Indeed an equilibrium between **6** and **7** (Scheme 9) could be envisioned, and a thermodynamic preference could favor one of these organometallic species depending on the nature of the metal ligand (–ZnBu versus –ZnBr). To check this, we prepared independently each organometallic species **7-Bu** and **6-Br** (Scheme 10) and transformed them into their **7-Br** and **6-Bu** counterparts through Schlenk

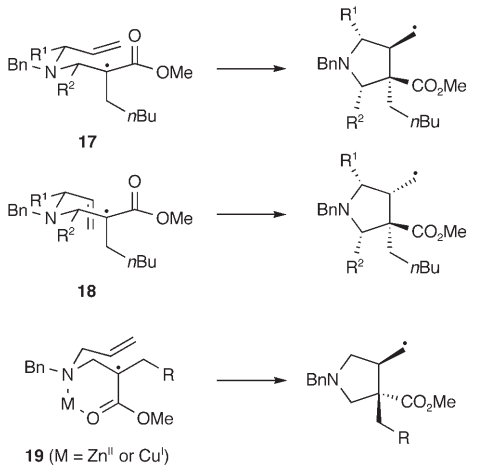
  




Scheme 10. Impact of the nature of the metal ligand of the cyclized organometallic species.

equilibrium displacement or addition of *n*BuLi. No change in stereoselectivity after hydrolysis was observed, that is, no equilibrium exists between **7-Bu** and **6-Bu**, or between **7-Br** and **6-Br**. Thus, the diastereoselectivity of the domino reaction results only from the radical cyclization step.

The diastereoselectivity of the $n$Bu$_2$Zn domino reaction can be explained (Scheme 11) by radical intermediate **17**




Scheme 11. Origin of diastereoselectivity in the radical-polar crossover domino process.

following the Beckwith–Houk model.[12] For $A^{1,3}$ strain[13] minimization, the carbomethoxyl moiety should adopt a pseudoequatorial position. The minor diasteromer could be formed through cyclization of conformer **18**. Again on the basis of $A^{1,3}$ strain minimization, this less favoured conformer should be further disfavoured when a sterically demanding group $R^1$ is present, and this explains the enhanced diastereoselectivity observed for **4b–e**.

By contrast, with organometallic species containing stronger Lewis acids such as organozinc and mixed copper/zinc species, the cyclization reaction should occur through radical intermediate **19** (similar to organometallic species **3** involved in the carbocyclization of zinc enolates), in which chelation between the nitrogen atom, the oxygen atom of the carboxyl group, and a metal salt ($Zn^{II}$ or $Cu^{I}$) would counterbalance $A^{1,3}$ strain minimization. This radical intermediate could also be involved in the case of $n$Bu$_2$Zn at low temperature, although it is still unclear why the reversal of stereoselectivity is observed only in the case where no substituent is present on the ring.

## Conclusion

We have shown that the domino Michael addition/carbocyclization reaction of organozinc halides, diorganozinc compounds and organocopper/zinc mixed species with enoates **4a–e** follows a pure radical-polar crossover mechanism.[14] The radical 1,4-addition[15] is followed by a 5-*exo*-trig radical cyclization and subsequent reduction of the radical to an organometallic species. By this process 3,4-disubstituted 3-carbomethoxyl pyrrolidines have been prepared in good yields and good to excellent diastereoselectivity. This diastereoselectivity is highly dependent on the nature of the starting organometallic species. To the best of our knowledge, the fact that organozinc halides and copper/zinc mixed species can behave as radical precursors is unprecedented[16] and these results could be linked to the latest developments in enantioselective 1,4-addition of organozinc compounds catalyzed bu $Cu^{I}$ complexes.[17]

## Experimental Section

**General remarks**: Experiments involving organometallics were carried out in dried glassware under a positive pressure of dry nitrogen. Liquid nitrogen was used as a cryoscopic fluid. A three-necked round-bottom flask equipped with an internal thermometer, a septum cap, a nitrogen or argon inlet and a magnetic stirrer was used. $Et_2O$ 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 to room temperature, was dissolved in anhydrous $Et_2O$. Commercial *n*BuLi was titrated with a 1 M solution of *s*BuOH in toluene in the presence of 2,2′-biquinoline. All other reagents and solvents were of commercial quality and were used without purification. Flash column chromatographic separations were carried out over Merck silica gel 60 (0.015–0.040 mm). $^1$H NMR and $^{13}$C NMR spectra were recorded on a Bruker AVANCE 400 spectrometer. Chemical shifts are reported in ppm relative to an internal standard of residual chloroform ($\delta = 7.27$ ppm for $^1$H NMR and $\delta = 77.1$ ppm for $^{13}$C NMR). IR spectra were recorded with a ATRD Bruker Tensor 27 spectrophotometer. MS and HRMS were performed at the Service de Spectrométrie de Masse de l′Ecole Normale Supérieure, 24 rue Lhomond, 75231 Paris Cedex 05. Elemental analyses were performed at the Service de Microanalyses de l′Université Pierre et Marie Curie, Bat F, case 55-4 place Jussieu, 75252 Paris Cedex 05.

**General procedure 1: preparation of enoates 4a–e:** Enoates **4a,b** were prepared as previously reported.[4] Substituted enoates **4c–e** were prepared from the corresponding substituted *N*-benzyl-*N*-allyl amines[18] by the following general procedure: $K_2CO_3$ (6.90 g, 50 mmol) and NaI (0.75 g, 5 mmol) were added to a stirred solution of amine (52 mmol) in DMF (50 mL). The mixture was cooled to −10 °C and a solution of bromomethyl acrylic acid methyl ester (50 mmol) in DMF (50 mL) was added dropwise. The reaction mixture was allowed to warm to room tem-

perature and stirred for 12–24 h. The reaction was quenched with brine (100 mL). $Et_2O$ (50 mL) was added, the layers were separated and the aqueous layer was extracted three times with $Et_2O$. The combined organic layers were washed six times with brine and dried over $MgSO_4$, and the solvents were evaporated under reduced pressure to yield crude enoates **4c–e**.

**Methyl 2-[{*N*-benzyl-*N*-(1-methylallyl)amino}methyl]acrylate (4c)**: Prepared according to general procedure 1 from *N*-benzyl-*N*-(1-methylallyl)-amine (8.05 g, 50 mmol). The residue was purified by chromatography with cyclohexane/AcOEt (90/10) as eluent to give the title compound (12.32 g, 95%) as a yellow oil. IR (neat): $\tilde{\nu}$ = 3063, 3027, 2970, 2950, 2931, 2831, 1721, 1635, 1494, 1437, 1371, 1263, 1195, 1133, 1073, 1028, 998, 955, 921, 739, 699 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$): $\delta$ = 1.14 (d, 3H, $J$ = 6.6 Hz), 3.22–3.38 (m, 3H), 3.56 (d, 1H, $J$ = 14.2 Hz), 3.63 (d, 1H, $J$ = 14.2 Hz), 3.72 (s, 3H), 5.06–5.16 (m, 2H), 5.84–5.93 (m, 1H), 5.96 (s, 1H), 6.23 (s, 1H), 7.20–7.34 ppm (m, 5H); $^{13}C$ NMR (100 MHz, $CDCl_3$): $\delta$ = 15.08, 49.96, 51.78, 54.17, 56.01, 115.76, 125.61, 126.84, 128.30 (2C), 128.50 (2C), 139.18, 139.70, 140.43, 167.75 ppm; elemental analysis (%) calcd for $C_{16}H_{21}NO_2$: C 74.10, H 8.16, N 5.40; found: C 74.29, H 8.24, N 5.24.

**Methyl 2-[{*N*-benzyl-*N*-(1-phenylallyl)amino}methyl]acrylate (4d)**: Prepared according to general procedure 1 from *N*-benzyl-*N*-(1-phenylallyl)-amine (2.23 g, 10 mmol). The residue was purified by chromatography with cyclohexane/AcOEt (95/5) as eluent to give the title compound (2.83 g, 88%) as a yellow oil. IR (neat): $\tilde{\nu}$ = 3083, 3062, 2949, 2931, 2836, 1721, 1634, 1601, 1494, 1449, 1437, 1384, 1370, 1303, 1263, 1195, 1154, 1116, 1072, 1029, 929, 747, 699 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$): $\delta$ = 3.34 (s, 2H), 3.57 (d, 1H $J$ = 14.0 Hz), 3.69 (d, 1H, $J$ = 14.0 Hz), 3.70 (s, 3H), 4.28 (d, 1H, $J$ = 8.6 Hz), 5.19 (d, 1H, $J$ = 17.0 Hz), 5.42 (dd, 1H, $J$ = 10.1, 1.8 Hz), 6.00–6.07 (m, 1H), 6.08 (s, 1H), 6.28 (s, 1H), 7.21–7.44 ppm (m, 10H); $^{13}C$ NMR (100 MHz, $CDCl_3$): $\delta$ = 50.14, 51.78, 54.45, 66.16, 119.58, 125.79, 126.98, 127.12, 128.08 (2C), 128.30 (2C), 128.40 (2C), 128.56 (2C), 135.54, 138.66, 139.72, 141.26, 167.57 ppm; elemental analysis (%) calcd for $C_{21}H_{23}NO_2$: C 78.47, H 7.21, N 4.36; found: C 78.42, H 7.22, N 4.26.

**Methyl 2-[{*N*-Benzyl-*N*-(1-isopropylallyl)amino}methyl]acrylate (4e)**: Prepared according to general procedure 1 from *N*-benzyl-*N*-(1-isopropylallyl)amine (1.89 g, 10 mmol). The residue was purified by chromatography with cyclohexane/AcOEt (90/10) as eluent to give the title compound (2.21 g, 77%) as a yellow oil. IR (neat): $\tilde{\nu}$ = 3066, 3027, 2953, 2871, 2834, 1722, 1634, 1494, 1437, 1383, 1369, 1304, 1264, 1195, 1155, 1137, 1092, 1071, 1028, 1000, 922, 742, 699 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$): $\delta$ = 0.75 (d, $J$ = 6.6 Hz, 3H), 0.99 (d, $J$ = 6.6 Hz, 3H), 1.78 (m, 1H), 2.47 (dd, $J$ = 10.2, 9.7 Hz, 1H), 3.07 (d, $J$ = 15.8 Hz, 1H), 3.30 (d, $J$ = 14.0 Hz, 1H), 3.49 (dd, $J$ = 15.8, 2.0 Hz, 1H), 3.73 (s, 3H), 3.82 (d, $J$ = 14.0 Hz, 1H), 4.93 (dd, $J$ = 17.3, 2.0 Hz, 1H), 5.30 (dd, $J$ = 10.2, 2.5 Hz, 1H), 5.63 (dt, $J$ = 17.3, 9.7 Hz, 1H), 5.97 (m, 1H), 6.23 (m, 1H), 7.21–7.35 ppm (m, 5H); $^{13}C$ NMR (100 MHz, $CDCl_3$): $\delta$ = 20.52, 20.88, 29.34, 50.19, 51.78, 54.47, 69.19, 119.18, 125.75, 126.84, 128.26 (2C), 128.91 (2C), 135.19, 139.04, 140.17, 167.89 ppm.

**General procedure 2: domino reactions with di-*n*-butylzinc**: $nBu_2Zn$ (2 mL, ca. 2N in heptane, 4 mmol) was added to a stirred solution of acrylic ester (2 mmol) in $Et_2O$ (10 mL) at room temperature. The reaction mixture was stirred at room temperature for 12 h. The reaction mixture was hydrolyzed with an aqueous solution of $NH_4Cl/NH_4OH$ (2/1). The layers were separated, and the aqueous layer was extracted three times with ethyl acetate. The combined organic layers were washed with brine, dried over $MgSO_4$ and the solvents evaporated under reduced pressure.

**Methyl (3*R**,4*S**)-1-benzyl-4-methyl-3-pentylpyrrolidine-3-carboxylate (*cis*-8a)**: Prepared according to general procedure 2 from enoate **4a** (490 mg, 2 mmol). The residue was purified by chromatography with cyclohexane/AcOEt (80/20) as eluent to give *cis*-**8a** (400 mg, 66%): IR (neat): $\tilde{\nu}$ = 3027, 2954, 2931, 2859, 2790, 1731, 1495, 1454, 1377, 1346, 1253, 1231, 1197, 1142, 1070, 1029, 985, 739, 699 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$): $\delta$ = 0.86 (t, $J$ = 7.1 Hz, 3H), 0.91 (d, $J$ = 6.6 Hz, 3H), 1.11–1.31 (m, 6H), 1.47–1.54 (m, 1H), 1.82–1.90 (m, 1H), 2.07–2.16 (m, 2H), 2.76 (d, $J$ = 9.8 Hz, 1H), 2.92–3.00 (m, 1H), 2.99 (d, $J$ = 9.8 Hz, 1H), 3.66 (s, 2H), 3.68 (s, 3H), 7.21–7.35 ppm (m, 5H); $^{13}C$ NMR (100 MHz, $CDCl_3$): $\delta$ = 14.09, 15.16, 22.54, 25.61, 32.39, 38.48, 43.69, 51.32, 56.75, 60.19, 60.31, 61.23, 126.90, 128.30 (2C), 128.68 (2C), 139.66, 175.74 ppm; elemental analysis (%) calcd for $C_{19}H_{29}NO_2$: C 75.21, H 9.63, N 4.62; found: C 75.04, H 9.64, N 4.62; further elution gave *trans*-**8a**[4] (132 mg, 22%).

**Methyl (2*S**,3*R**,4*S**)-1-benzyl-2,4-dimethyl-3-pentylpyrrolidine-3-carboxylate (8b)**: Prepared according to general procedure 2 from enoate **4b** (520 mg, 2 mmol) to yield the corresponding pyrrolidine as a mixture of two diastereoisomers in a ratio of 87/13 (determined by GC). The residue was purified by chromatography with cyclohexane/AcOEt (90/10) as eluent to give the title compound (major diastereomer, 311 mg, 49%) as a yellow oil. IR (neat): $\tilde{\nu}$ = 3027, 2933, 2872, 2795, 1728, 1495, 1454, 1379, 1329, 1230, 1197, 1140, 1096, 1028, 740, 699 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$): $\delta$ = 0.88 (t, $J$ = 6.9 Hz, 3H), 0.90 (d, $J$ = 7.1 Hz, 3H), 1.06 (d, $J$ = 6.6 Hz, 3H), 1.21–1.39 (m, 6H), 1.55–1.67 (m, 2H), 1.93 (t, $J$ = 9.4 Hz, 1H), 2.10 (dquint, $J$ = 10.2, 6.6 Hz, 1H), 2.95 (dd, $J$ = 8.7, 6.6 Hz, 1H), 3.17 (q, $J$ = 6.6 Hz, 1H), 3.32 (d, $J$ = 12.7 Hz, 1H), 3.69 (s, 3H), 3.99 (d, $J$ = 12.7 Hz, 1H), 7.21–7.34 ppm (m, 5H); $^{13}C$ NMR (100 MHz, $CDCl_3$): $\delta$ = 14.23, 15.18, 16.25, 22.68, 25.37, 33.00, 33.75, 40.78, 51.22, 58.56, 58.72, 60.40, 64.62, 126.82, 128.26 (2C), 128.95 (2C), 140.35, 176.06 ppm; elemental analysis (%) calcd for $C_{20}H_{31}NO_2$: C 75.67, H 9.84, N 4.41; found: C 75.70, H 9.94, N 4.42. Further elution gave methyl (2*S**,3*R**,4*R**)-1-benzyl-2,4-dimethyl-3-pentylpyrrolidine-3-carboxylate.

**Methyl (2*S**,3*R**,4*R**)-1-benzyl-2,4-dimethyl-3-pentylpyrrolidine-3-carboxylate**: (minor diastereomer, 45 mg, 7%): IR (neat): $\tilde{\nu}$ = 3063, 3027, 2955, 2931, 2871, 2794, 1731, 1605, 1454, 1378, 1232, 1196, 1127, 698 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$): $\delta$ = 0.84 (t, $J$ = 6.9 Hz, 3H), 0.98 (d, $J$ = 7.1 Hz, 3H), 1.05 (d, $J$ = 6.6 Hz, 3H), 1.17–1.28 (m, 6H), 1.49–1.63 (m, 2H), 2.44 (dd, $J$ = 9.2, 4.6 Hz, 1H), 2.52 (dd, $J$ = 9.2, 7.6 Hz, 1H), 2.58–2.66 (m, 1H), 3.09 (q, $J$ = 6.6 Hz, 1H), 3.30 (d, $J$ = 13.3 Hz, 1H), 3.63 (s, 3H), 3.87 (d, $J$ = 13.3 Hz, 1H), 7.16–7.27 ppm (m, 5H); $^{13}C$ NMR (100 MHz, $CDCl_3$): $\delta$ = 14.19, 14.51, 15.89, 22.62, 25.80, 29.50, 32.84, 37.30, 51.80, 57.77, 58.09, 59.00, 64.26, 126.76, 128.24 (2C), 128.58 (2C), 140.29, 177.70 ppm.

**Methyl (3*R**,4*S**,5*R**)-1-benzyl-4,5-dimethyl-3-pentylpyrrolidine-3-carboxylate (8c)**: Prepared according to general procedure 2 from enoate **4c** (519 mg, 2 mmol). The residue was purified by chromatography with cyclohexane/AcOEt (90/10) as eluent to give **8c** (406 mg, 64%) as a yellow oil. IR (neat): $\tilde{\nu}$ = 3027, 2932, 2861, 2795, 1729, 1495, 1454, 1375, 1323, 1227, 1194, 1143, 1029, 739, 699 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$): $\delta$ = 0.83 (t, $J$ = 6.9 Hz, 3H), 0.88 (d, $J$ = 7.1 Hz, 3H), 1.05–1.14 (m, 2H), 1.12 (d, $J$ = 5.6 Hz, 3H), 1.15–1.28 (m, 4H), 1.42–1.49 (m, 1H), 1.57–1.65 (m, 1H), 1.78–1.85 (m, 1H), 2.23 (dq, $J$ = 8.7, 5.6 Hz, 1H), 2.78 (d, $J$ = 10.2 Hz, 1H), 2.82 (d, $J$ = 10.2 Hz, 1H), 3.29 (d, $J$ = 13.2 Hz, 1H), 3.65 (s, 3H), 4.01 (d, $J$ = 13.2 Hz, 1H), 7.21–7.35 ppm (m, 5H); $^{13}C$ NMR (100 MHz, $CDCl_3$): $\delta$ = 13.79, 14.09, 18.20, 22.48, 25.52, 32.41, 38.25, 51.22, 51.26, 55.20, 57.90, 59.32, 66.10, 126.72, 128.24 (2C), 128.66 (2C), 140.27, 176.00 ppm; elemental analysis (%) calcd for $C_{20}H_{31}NO_2$: C 75.67, H 9.84, N 4.41; found: C 75.75, H 9.71, N 4.31.

**Methyl (3*R**,4*S**,5*R**)-1-benzyl-4-methyl-3-pentyl-5-phenylpyrrolidine-3-carboxylate (8d)**: Prepared according to general procedure 2 from enoate **4d** (683 mg, 2 mmol). The residue was purified by chromatography with cyclohexane/AcOEt (90/10) as eluent to give **8d** (486 mg, 64%) as a yellow oil. $^1H$ NMR (400 MHz, $CDCl_3$): $\delta$ = 0.73 (d, $J$ = 7.1 Hz, 3H), 0.76 (t, $J$ = 6.9 Hz, 3H), 1.04–1.25 (m, 6H), 1.48–1.56 (m, 1H), 1.73–1.84 (m, 2H), 2.81 (d, $J$ = 10.2 Hz, 1H), 2.92 (d, $J$ = 10.2 Hz, 1H), 3.10 (d, $J$ = 10.2 Hz, 1H), 3.11 (d, $J$ = 13.2 Hz, 1H), 3.61 (s, 3H), 3.69 (d, $J$ = 13.2 Hz, 1H), 7.10–7.38 ppm (m, 10H); $^{13}C$ NMR (100 MHz, $CDCl_3$): $\delta$ = 13.26, 14.13, 22.54, 25.56, 32.47, 38.32, 51.42, 53.04, 55.60, 57.75, 58.90, 76.41, 126.74, 127.53, 128.06 (2C), 128.24 (2C), 128.46 (2C), 128.56 (2C), 140.11, 142.33, 175.98 ppm; elemental analysis (%) calcd for $C_{25}H_{33}NO_2$: C 79.11, H 8.76, N 3.69; found: C 79.07, H 8.94, N 3.59. Further elution gave (2a*R**,5*S**,5a*S**)-4-benzyl-2a-pentyl-5-phenylhexahydropyrrolo[3,4-*c*]furan-2-one (**12d**).

**(2a*R**,5*S**,5a*S**)-4-Benzyl-2a-pentyl-5-phenylhexahydropyrrolo[3,4-*c*]furan-2-one (12d)**: Yield: 102 mg, 14%: $^1H$ NMR (400 MHz, $CDCl_3$): $\delta$ = 0.88 (t, $J$ = 6.9 Hz, 3H), 1.26–1.40 (m, 6H), 1.73–1.87 (m, 2H), 2.63

(d, $J=10.2$ Hz, 1H), 2.67 (m, 1H), 2.99 (d, $J=13.2$ Hz, 1H), 3.11 (d, $J=10.2$ Hz, 1H), 3.32 (d, $J=9.2$ Hz, 1H), 3.76 (d, $J=13.2$ Hz, 1H), 4.19–4.27 (m, 2H), 7.21–7.51 ppm (m, 10H); $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta=$ 14.05, 22.52, 24.77, 31.99, 36.60, 52.77, 54.45, 56.96, 61.97, 68.89, 76.11, 127.17, 127.75, 128.38 (4C), 128.58 (2C), 129.13 (2C), 138.43, 140.15, 181.78 ppm; HRMS calcd for $C_{24}H_{30}NO_2$ $[M-H]^+$: $m/z$ 364.2277; found: 364.2281.

**Methyl (3*R**,4*S**,5*R**)-1-benzyl-5-isopropyl-4-methyl-3-pentylpyrrolidine-3-carboxylate (8e)**: The product was prepared according to general procedure 2 from enoate **4e** (575 mg, 2 mmol). The residue was purified by chromatography with cyclohexane/AcOEt (90/10) as eluent to give the title compound (387 mg, 56%) as a yellow oil. IR (neat): $\tilde{\nu}=$3027, 2956, 2931, 2872, 2789, 1732, 1495, 1454, 1384, 1372, 1289, 1254, 1223, 1197, 1134, 1029, 1005, 738, 698 cm$^{-1}$; $^1$H NMR (400 MHz, $CDCl_3$): $\delta=$ 0.84 (t, $J=6.9$ Hz, 3H), 0.90 (d, $J=7.1$ Hz, 3H), 0.96 (d, $J=7.1$ Hz, 3H), 1.01 (d, $J=7.1$ Hz, 3H), 1.16–1.28 (m, 6H), 1.61–1.68 (m, 1H), 1.76–1.86 (m, 2H), 2.03–2.05 (m, 2H), 2.53 (d, $J=10.2$ Hz, 1H), 2.78 (d, $J=$ 10.2 Hz, 1H), 3.16 (d, $J=13.7$ Hz, 1H), 3.64 (s, 3H), 4.02 (d, $J=13.7$ Hz, 1H), 7.19–7.34 ppm (m, 5H); $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta=14.11$, 17.51, 18.46, 20.02, 22.48, 25.29, 28.81, 32.29, 37.59, 43.39, 51.20, 55.58, 57.06, 58.56, 76.70, 126.68, 128.28 (4C), 140.76, 175.72 ppm; elemental analysis (%) calcd for $C_{22}H_{35}NO_2$: C 76.47, H 10.21, N 4.05; found: C 76.56, H 10.29, N 3.96. Further elution gave (2a*R**,5*S**,5a*S**)-4-benzyl-2a-pentyl-5-isopropylhexahydropyrrolo[3,4-*c*]furan-2-one (**12e**).

**(2a*R**,5*S**,5a*S**)-4-Benzyl-2a-pentyl-5-isopropylhexahydropyrrolo[3,4-*c*]furan-2-one (12e)**: (20 mg, 3%). $^1$H NMR (400 MHz, $CDCl_3$): $\delta=0.87$ (t, $J=6.9$ Hz, 3H), 0.94 (d, $J=6.6$ Hz, 3H), 0.99 (d, $J=7.1$ Hz, 3H), 1.15–1.39 (m, 6H), 1.61–1.77 (m, 2H), 2.12–2.20 (m, 1H), 2.44–2.46 (m, 1H), 2.45 (d, $J=10.2$ Hz, 1H), 2.60 (dt, $J=7.6$, 3.1 Hz, 1H), 2.87 (d, $J=$ 10.2 Hz, 1H), 3.05 (d, $J=13.2$ Hz, 1H), 3.99 (d, $J=13.2$ Hz, 1H), 4.13 (dd, $J=9.7$, 3.6 Hz, 1H), 4.33 (dd, $J=9.7$, 8.7 Hz, 1H), 7.21–7.34 ppm (m, 5H); $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta=14.07$, 15.57, 20.22, 22.48, 24.73, 27.64, 32.03, 36.25, 43.39, 44.16, 52.49, 57.18, 62.99, 71.52, 127.19, 128.48 (2C), 128.58 (2C), 138.96, 181.38 ppm; HRMS calcd for $C_{21}H_{32}NO_2$ $[M-H]^+$: $m/z$ 330.2433; found: 330.2434.

**Methyl (3*R**,4*S**)-1-benzyl-4-but-3-enyl-3-pentylpyrrolidine-3-carboxylate (10)**: $n$Bu$_2$Zn (2 mL, ca. 2N in heptane, 4 mmol) was added to a stirred solution of acrylic ester **4a** (491 mg, 2 mmol) in $Et_2O$ (10 mL) at room temperature. The reaction mixture was stirred at room temperature for 12 h. CuCN (36 mg, 0.4 mmol) was added at room temperature in one portion. The reaction mixture was stirred for 30 min. Degassed THF (10 mL) was added, followed by allyl bromide (0.7 mL, 8 mmol). The reaction mixture was stirred at room temperature for 15 h. After workup, the residue was purified by chromatography with cyclohexane/AcOEt (80/20) as eluent to give **10** (466 mg, 68%) as a mixture of two diastereoisomers in a 76:24 ratio (determined by GC). Purification by chromatography afforded *cis*-**10** (260 mg, 38%) as a yellow oil. IR (neat): $\tilde{\nu}=$ 3027, 2931, 2859, 2790, 1729, 1641, 1495, 1454, 1378, 1345, 1228, 1198, 1140, 1072, 1028, 993, 911, 739, 699 cm$^{-1}$; $^1$H NMR (400 MHz, $CDCl_3$): $\delta=0.86$ (t, $J=6.9$ Hz, 3H), 1.10–1.32 (m, 7H), 1.46–1.61 (m, 2H), 1.84–1.96 (m, 2H), 1.97–2.07 (m, 2H), 2.16 (t, $J=8.9$ Hz, 1H), 2.80 (d, $J=$ 9.7 Hz, 1H), 2.95 (d, $J=9.7$ Hz, 1H), 3.04 (dd, $J=8.7$, 6.1 Hz, 1H), 3.65 (d, $J=13.2$ Hz, 1H), 3.68 (s, 3H), 3.71 (d, $J=13.2$ Hz, 1H), 4.92–4.99 (m, 2H), 5.75 (ddt, $J=17.3$, 10.2, 6.6 Hz, 1H), 7.22–7.35 ppm (m, 5H); $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta=14.11$, 22.54, 25.62, 29.42, 32.43, 32.77, 38.44, 48.79, 51.44, 56.45, 59.24, 60.36, 60.48, 114.91, 127.01, 128.36 (2C), 128.74 (2C), 138.41, 139.46, 175.76 ppm; HRMS calcd for $C_{22}H_{34}NO_2$ $[M-H]^+$: $m/z$ 344.2590; found: 344.2585.

**Methyl (3*R**,4*S**)-1-benzyl-4-iodomethyl-3-pentylpyrrolidine-3-carboxylate (11)**: $n$Bu$_2$Zn (2 mL, ca. 2N in heptane, 4 mmol) was added to a stirred solution of acrylic ester **4a** (491 mg, 2 mmol) in $Et_2O$ (10 mL) at room temperature. The reaction mixture was stirred at room temperature for 12 h. the reaction mixture was cooled to −40°C and a solution of $I_2$ (2.03 g, 8 mmol) in degassed THF (10 mL) was added dropwise. After 30 min at −40°C, the reaction mixture was hydrolyzed with an aqueous solution of $NH_4Cl/NH_4OH$ (2/1). The layers were separated, and the aqueous layer was extracted three times with $Et_2O$. The combined organic layers were washed with brine and $Na_2SO_3$, dried over $MgSO_4$ and the solvents were evaporated under reduced pressure. The residue was purified by chromatography with cyclohexane/AcOEt (80/20) as eluent to give **83** (412 mg, 48%) as an inseparable mixture of two diastereoisomers. Major diastereoisomer: $^1$H NMR (400 MHz, $CDCl_3$): $\delta=0.86$ (t, $J=$ 6.9 Hz, 3H), 1.04–1.30 (m, 6H), 1.57–1.65 (m, 1H), 1.84–1.91 (m, 1H), 2.38 (t, $J=8.7$ Hz, 1H), 2.44–2.52 (m, 1H), 2.75 (d, $J=9.7$ Hz, 1H), 3.01 (dd, $J=11.7$, 9.2 Hz, 1H), 3.07 (d, $J=9.7$ Hz, 1H), 6.19 (m, 1H), 3.37 (dd, $J=9.7$, 3.6 Hz, 1H), 3.63–3.73 (m, 2H), 3.70 (s, 3H), 7.23–7.35 ppm (m, 5H); $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta=6.39$, 14.05, 22.46, 25.19, 32.15, 38.94, 51.34, 51.85, 57.20, 59.81, 60.86, 61.08, 127.09, 128.40 (2C), 128.56 (2C), 139.02, 174.44 ppm; elemental analysis (%) calcd for $C_{19}H_{28}INO_2$: C 53.15, H 6.57, N 3.26; found: C 53.26, H 6.58, N 3.31.

**(2a*R**,5a*S**)-4-Benzyl-2a-pentylhexahydropyrrolo[3,4-*c*]furan-2-one (12a)**: $n$Bu$_2$Zn (2 mL, ca. 2N in heptane, 4 mmol) was added to a stirred solution of **4a** (491 mg, 2 mmol) in THF (10 mL) in a flask topped by a drying tube fitted with $CaCl_2$ at room temperature. The reaction mixture was stirred at room temperature for 12 h. Activated zinc (for reduction of potential peroxo intermediates, 120 mg) was added and the reaction mixture stirred at room temperature for 1 h. The reaction mixture was hydrolyzed with an aqueous solution of $NH_4Cl/NH_4OH$ (2/1). The layers were separated, and the aqueous layer was extracted three times with ethyl acetate. The combined organic layers were washed with brine, dried over $MgSO_4$ and the solvents evaporated under reduced pressure. The residue was purified by chromatography with cyclohexane/AcOEt (90/10) to give **12a** (115 mg, 20%) as a yellow oil. $^1$H NMR (400 MHz, $CDCl_3$): $\delta=0.87$ (t, $J=6.6$ Hz, 3H), 1.21–1.43 (m, 6H), 1.51–1.58 (m, 1H), 1.74–1.81 (dt, $J=12.7$, 4.1 Hz, 1H), 2.17 (d, $J=9.2$ Hz, 1H), 2.47 (dd, $J=9.2$, 6.6 Hz, 1H), 2.64–2.71 (m, 1H), 2.82 (d, $J=9.7$ Hz, 1H), 3.27 (d, $J=$ 9.2 Hz, 1H), 3.50 (d, $J=13.2$ Hz, 1H), 3.61 (d, $J=13.2$ Hz, 1H), 4.04 (dd, $J=9.2$, 3.6 Hz, 1H), 4.39 (t, $J=9.2$ Hz, 1H), 7.21–7.33 ppm (m, 5H); $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta=14.07$, 22.50, 25.17, 32.09, 34.63, 42.58, 55.00, 58.98, 61.19, 64.06, 72.93, 127.21, 128.42 (2C), 128.52 (2C), 138.43, 181.78 ppm; HRMS calcd for $C_{18}H_{26}NO_2$ $[M-H]^+$: $m/z$ 288.1964; found: 288.1961.

**Methyl 1-benzyl-3-isobutyl-4-methylpyrrolidine-3-carboxylate (13)**: $i$PrMgCl (2.2M in $Et_2O$, 1.35 mL, 3 mmol)was added to $ZnBr_2$ (1M in $Et_2O$, 4.5 mL, 4.5 mmol) at −78°C. The temperature was raised to 0°C and the mixture stirred for 25 min. A solution of enoate **4a** (245 mg, 1 mmol) was added via canula and the cooling bath was removed. The mixture was stirred at room temperature for 4 h and an aqueous solution of $NH_4Cl/NH_4OH$ (2:1) (8 mL) was added. The aqueous layer was extracted with EtOAc (3×20 mL). The combined organic layers were washed with brine (20 mL), dried over $MgSO_4$, filtered and concentrated. Purification by flash chromatography (cyclohexane/ethyl acetate 60/40) afforded the title compound (250 mg, 87%) as a mixture of two diastereoisomers (d.r.=87:13 by $^1$H NMR spectroscopy) as a colorless oil. IR ($CHCl_3$): $\tilde{\nu}=$3027, 2955, 2872, 2789, 1731, 1454, 1138, 739, 699; $^1$H NMR ($CDCl_3$, 400 MHz): $\delta=0.80$ (d, $J=6.6$ Hz, 3H), 0.90 (d, $J=6.6$ Hz, 3H), 1.04 (d, $J=7.1$ Hz, 3H), 1.42 (dd, $J=13.4$, 5.3 Hz, 1H), 1.52 (m, 1H), 1.71 (dd, $J=13.4$, 7.6 Hz, 1H), 2.03 (t, $J=8.8$ Hz, 1H), 2.19 (d, $J=9.9$ Hz, 1H), 2.47 (ddd, $J=15.8$, 14.3, 7.2 Hz, 1H), 2.98 (dd, $J=8.9$, 7.1 Hz, 1H), 3.56 (d, $J=2.8$ Hz, 1H), 3.59 (d, $J=6.6$ Hz, 1H), 3.68 (d, $J=6.6$ Hz, 1H), 3.70 (s, 3H), 7.22–7.40 ppm (m, 5H); $^{13}$C NMR ($CDCl_3$, 100 MHz): $\delta$ 13.7, 22.7, 24.5, 25.4, 41.0, 41.5, 51.7, 53.4, 60.2, 61.2 (2C), 126.8, 128.2 (2C), 128.5 (2C), 139.2, 177.8 ppm; MS (CI $NH_3$): 290 ($[M]^+$); elemental analysis (%) calcd for $C_{18}H_{27}NO_2$: C 74.70, H 9.40, N 4.84; found: C 74.34, H 9.21, N 4.45.

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