Carbometalation of unactivated alkenes by zinc enolate derivatives

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The carbometalation reaction of zinc enolates and related stabilised organometallics on unactivated double bonds has emerged over the past decade as a mechanistically interesting and synthetically useful reaction. This *Perspective* is devoted to these challenging and apparently contra-thermodynamic transformations, with a special focus on recent mechanistic considerations involving radical–polar crossover reaction pathways.

1. Introduction

Inter- and intramolecular carbometalation reactions (addition of organometallic species onto unactivated multiple bonds) have been widely developed as powerful synthetic tools for C–C bond formation.[1–3] Yet, much less is known about the highly challenging carbometalation of unactivated alkenes by stabilised enolate-type organometallics, an apparently contra-thermodynamic reaction where the resulting alkyl metal is an organometallic species having a higher basicity than the starting enolate. Addition of ketones and malonates to styrenes under *t*BuOK catalysis has been reported,[4] as well as the intramolecular cyclisation of lithium enolates on (η^2-alkene)-Fe complexes[5–8] and (η^4-alkene)Fe complexes,[9–11] and of sodium malonates on (η^4-diene)Mo complexes.[12–14] Inter- and intramolecular addition of enolates, malonates and nitrile-stabilised carbanions across double bonds of (η^6-arene)$Cr(CO)_3$ and (η^6-arene)$Mn(CO)_3^+$ complexes are also known (dearomatisation reactions).[15]

Examples involving totally unactivated alkenes are quite uncommon. Several additions of enolates or malonates on alkenes in the presence of Pd(II) salts or under Pd(0) catalysis have been described,[16,17] along with carbostannylation with tin malonates.[18,19] Beyond these, zincated stabilised nucleophiles have emerged as reagents of choice to perform carbometalations of unactivated olefins.[20,21] In addition, unlike in most of the palladium chemistry where it undergoes dehydropalladation or reductive elimination, the resulting organometallic species can be used for various subsequent synthetic transformations.

The first examples of addition of a zinc enolate onto an unfunctionalised or non-strained double bond were disclosed only a decade ago.[22–24] From then on, a steady input has enriched this young and promising new field. On the one hand, Nakamura and co-workers have disclosed inter- and intramolecular carbozincations of zinc aza-enolates derived mainly from hydrazones or imines that lead, after hydrolysis, to α-alkylated ketones in an overall process that can be regarded as an "olefinic aldol reaction" (Scheme 1). On the other hand, in our group we have developed the intramolecular carbometalation (carbocyclisation) of zinc ester enolates on unactivated double bonds, paying special attention to the case of α- and β-amino esters (Scheme 2). On top of the mechanistic interest commented above, this transformation is also synthetically remarkable since, *via* the creation in one single operation of one C–C bond, one C–M bond and two new stereogenic centers (generally diastereoselectively), it offers a rapid access to substituted α- and β-prolines and pipecolic acids.

Hereafter we give an overview of the main findings on the carbometalation reaction of zinc enolate derivatives onto unactivated double bonds, emphasising recent developments and our current research.

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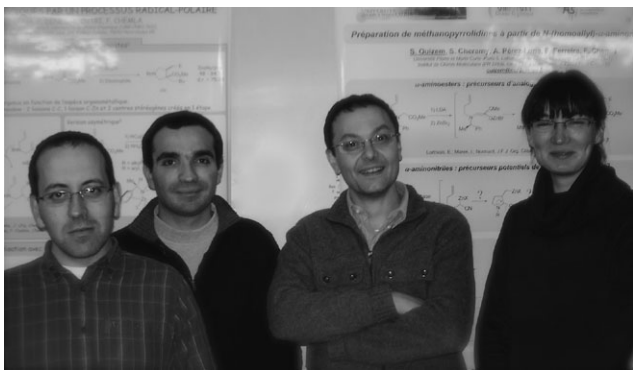
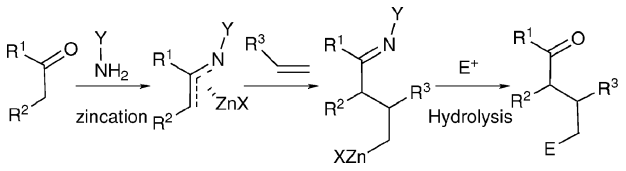
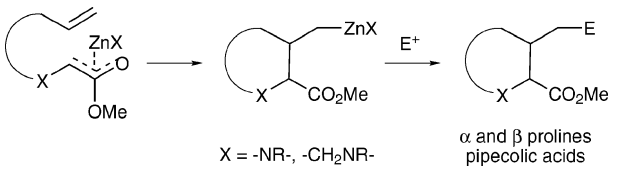


Franck Ferreira, Alejandro Pérez-Luna, Fabrice Chemla and Candice Botuha (left to right)

Fabrice Chemla was appointed as professor in the Pierre et Marie Curie University in 2001. His research interests are focused on the design and development of new functionalised carbenoids, as well as on carbometalation reactions. Alejandro Pérez-Luna became Chargé de Recherche in Prof. Chemla's group in 2004. His scientific interests include the fields of metal-mediated synthesis, organozinc chemistry and asymmetric synthesis. Candice Botuha is currently an assistant professor in Prof. Chemla's group, working on the synthesis of propargylic and allenic systems and applications in asymmetric synthesis. Franck Ferreira joined Prof. Chemla's group in 2001. His main research interests are focused on the use of 3-heterosubstituted propargylzincs in the asymmetric synthesis of acetylenic aziridines, of 1,2-amino alcohols, and of biologically interesting compounds.



Scheme 1 The "olefinic aldol reaction".



Scheme 2 Carbocyclisation reactions of amino zinc enolates.

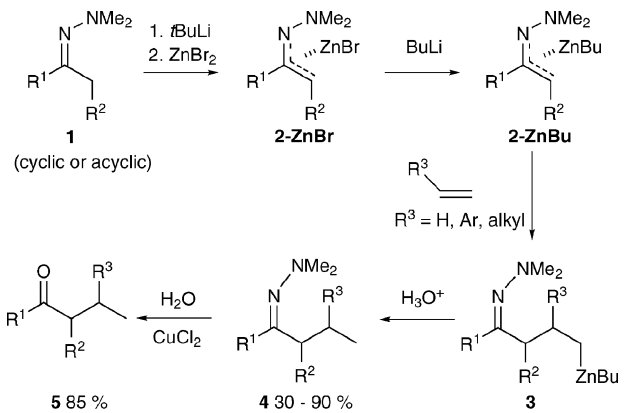
2. Carbometalation with aza-enolates

2.1 Carbometalation with zincated hydrazones

As a first approach to the "olefinic aldol reaction", Nakamura and co-workers have extensively studied the carbozincation of zincated hydrazones onto both simple alkenes and vinylmetals.

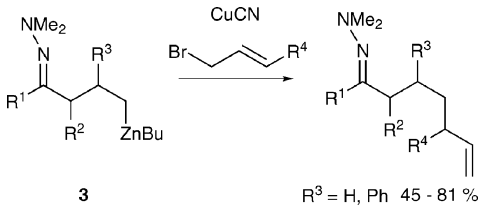
2.1.1 Addition onto simple alkenes.[22] Cyclic or acyclic *N*,*N*-dimethylhydrazones **1** can be metalated (in the case of non-symmetric substrates at the less hindered side) with *t*BuLi in diethyl ether (Scheme 3). Transmetalation with $ZnBr_2$, followed by ligand exchange with BuLi, leads to organozinc compounds **2-ZnBu** that afford carbometalation adducts **3** after stirring at 20–35 °C for several days in the presence of olefins. The use of butylated species **2-ZnBu** is essential for an efficient addition since other species such as **2-ZnBr**, **2-ZnMe**, or **2-Zn*t*Bu** are far less reactive.

Zinc hydrazones **3** are stable in the reaction media (do not isomerise to a more stable regioisomeric α-zincated hydrazone or add to the C=N bond of **3** or to another olefin) and give, after hydrolysis, hydrazones **4** (that can be further converted into the corresponding ketones **5** with $CuCl_2$ catalysis). Good yields are obtained in the case of addition to ethylene (R^3 = H; 83–90%). On the other hand, the reaction with monosubstituted alkenes, though regioselective since mainly the "branched" adducts are obtained (branched : linear >88 : 12), is much more sluggish and gives only moderate yields (R^3 = Ar, alkyl; 33–69%). Moreover, a complete lack of



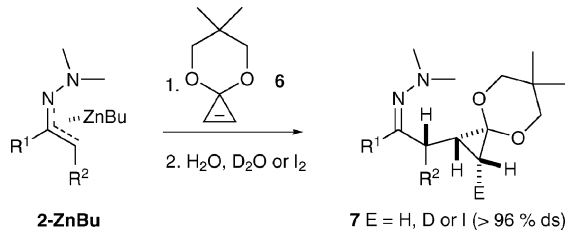
Scheme 3 Carbometalation of simple alkenes by zincated hydrazones.

diastereoselectivity is observed. Zinc hydrazones **3** can also be reacted with carbon electrophiles after transmetalation with copper salts, thus providing a one-pot three component coupling reaction (Scheme 4).



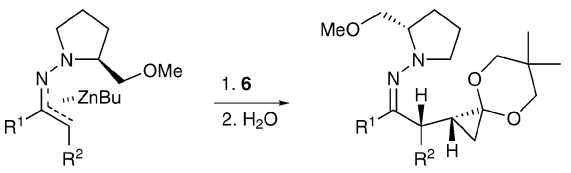
Scheme 4 Functionalisation of carbozincation adducts **3**.

As evidenced in the addition to the constrained cyclopropenone-acetal **6**, carbometalation with zinc aza-enolates **2** takes place in a *cis* manner (Scheme 5).[25] Remarkably, in this case a generally high level of 1,2-diastereoselectivity (>96%) for the newly formed C–C bond is obtained.



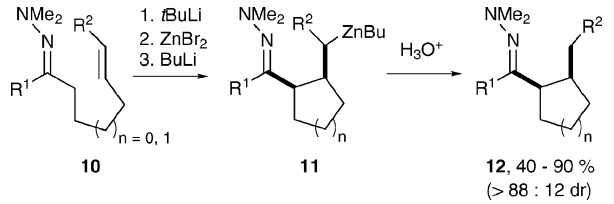
Scheme 5 Addition of zinc hydrazones to cyclopropenone-acetal **6**.

The reaction starting from SAMP ((*S*)-(−)-1-amino-2-methoxymethylpyrrolidine) hydrazones has been considered in an initial approach to an asymmetric version of the "olefinic aldol reaction" but it has proven to be limited in scope. Whereas addition to cyclopropenone-acetal **6** affords the β-cyclopropylcarbonyl in very good yield (79–87%) and synthetically useful selectivities (Scheme 6),[25] addition to ethylene results in lower diastereoselectivity (82 : 18) and moderate yield (42%).[22]



Scheme 6 Addition of zinc SAMP hydrazones to **6**.

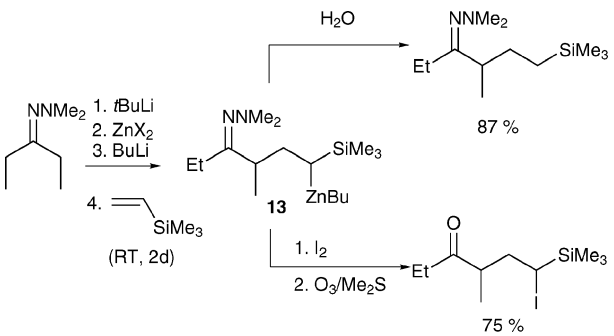
Zincated hydrazones also add to unactivated double bonds intramolecularly (Scheme 7).[26] 5-*Exo* and 6-*exo* cyclisations on terminal alkenes were observed following zincation of compounds **10** (R^2 = H). After hydrolysis, the corresponding carbocycles were obtained in good yields with substrates bearing an isopropyl group (R^1 = *i*Pr, R^2 = H, 83–90%). On the other hand, carbocyclisation was far more sluggish onto a disubstituted double bond (R^1 = *t*Bu, R^2 = Ph) or with substrates bearing the bulkier *tert*-butyl group (R^1 = *t*Bu, R^2 = H). Good diastereoselectivities (dr >88 : 12) in favor of the *cis* isomers were observed in all cases.



Scheme 7 Intramolecular addition of zincated hydrazones.

2.1.2 Addition onto vinylmetals. Besides simple unactivated alkenes, vinylmetals have proved to be excellent electrophiles towards aza-enolates, leading to original bimetallic intermediates.

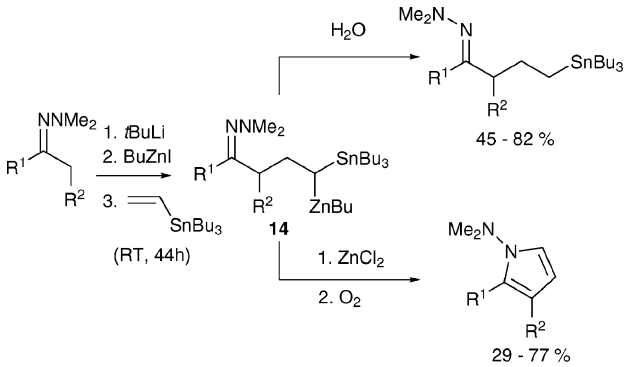
Unsubstituted vinylsilanes react with zincated hydrazones completely regioselectively to give silicon derivatives of type **13** (Scheme 8).[27] The factors that govern the overall reactivity of the addition reaction are rather subtle and not fully understood. As for previous examples, the use of $ZnBu^+$ countercation is crucial. However, in this case the solvent also plays an essential role, the reaction being considerably faster in ether than in DME or THF, albeit to the expense of an increase of competitive C-silylation. Significant effects of the substituents on the silicon atom are also observed, trialkylvinylsilanes and triphenylvinylsilanes being much less reactive than alkoxyvinylsilanes. The ability of the carbometalation adducts to retain their regiochemical integrity was shown to be dependent on hydrazone structure. Compound **13** was stable under the reaction conditions and could thus be reacted with strong electrophiles such as D_2O or I_2 (trapping with carbon electrophiles was unsuccessful). No selectivity regarding the newly created chiral centers was observed.



Scheme 8 Addition of zinc hydrazones to vinylsilanes.

Tributylvinylstannane reacts with zincated hydrazones (with a higher rate than vinylsilanes) to afford only *gem*-Zn–Sn adducts **14** (Scheme 9).[28] These bimetallic species were found to be regiochemically stable under nitrogen for several days at room temperature. Upon hydrolysis they lead to γ-stannylhydrazones in good yields (45–82%). Alternatively, they can be oxidised under an oxygen atmosphere to afford synthetically useful 1-(dimethylamino)-1*H*-pyrroles (29–77%).

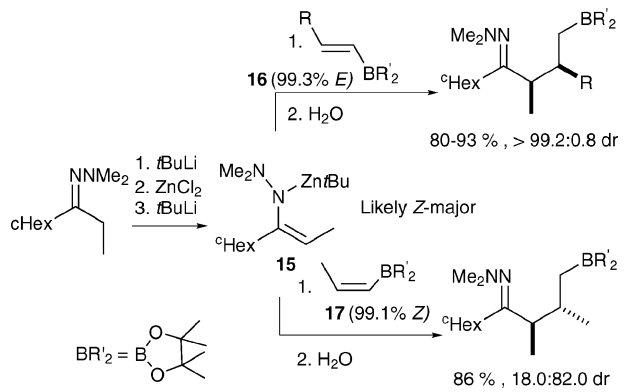
E- (And *Z*-) alkenylboronates undergo diastereoselective addition with zincated hydrazones in what constitutes to date the most efficient example of carbozincation of a 1,2-disubstituted alkene with a stabilised nucleophile.[29] Zinc aza-enolate **15** (likely in its *Z*-diastereomeric form) reacts with *E*-alkenylboronate **16** (resp. *Z*-alkenylboronate **17**) to afford after hydrolysis *syn*- (resp. *anti*-) γ-borylhydrazones with



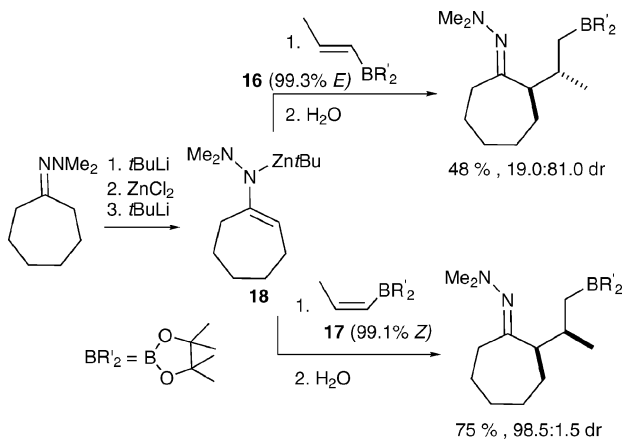
Scheme 9 Addition of zinc hydrazones to vinylstannanes.

syn : *anti* selectivities up to 99.6 : 0.4 (resp. 18.0 : 82.0) (Scheme 10). On the other hand, aza-enolate **18**, derived from a cyclic hydrazone (thus necessarily in its *E*-diastereomeric form), leads to *anti*- (resp. *syn*-) γ-borylhydrazones after addition onto *E*-alkenylboronate **16** (resp. *Z*-alkenylboronate **17**) and hydrolysis (Scheme 11). These stereochemical outcomes can be accounted for by a six-centered boat-like transition state involving a *syn*-carbometalation.

Regarding C–Zn stereochemistry, *gem*-Zn–B bimetallic intermediates **19** epimerise to their thermodynamically more stable configuration that involves intramolecular complexation between zinc and nitrogen. Electrophilic trapping with carbon electrophiles in the presence of CuCl occurs with

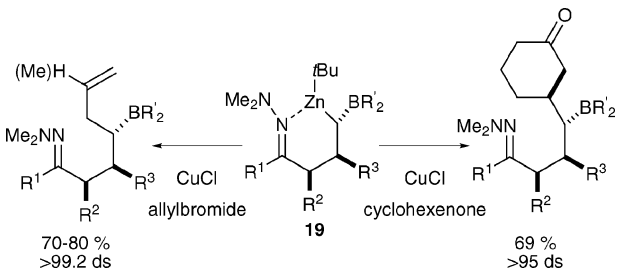


Scheme 10 Addition of (*Z*) zinc hydrazones to alkenylboronates.



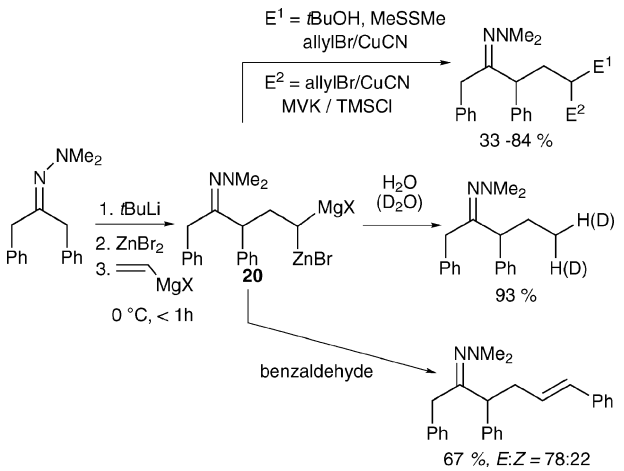
Scheme 11 Addition of (*E*) zinc hydrazones to alkenylboronates.

overall retention of configuration, thus offering the opportunity to create one or two additional stereogenic centers with excellent overall diastereoselectivities (Scheme 12).



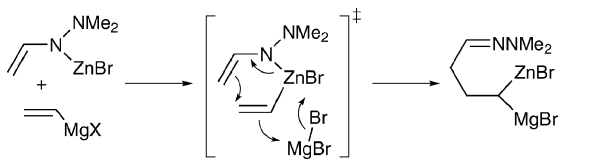
Scheme 12 Electrophilic trapping of γ-*gem*-Zn–B hydrazones.

As for delocalised organozinc nucleophiles such as allyl- and propargylzinc reagents, vinylmagnesium halides are excellent electrophiles[30,31] towards zincated hydrazones and undergo rapid addition to afford *gem*-Zn–Mg dimetalated hydrazones (Scheme 13).[32] As exemplified in the case of hydrazone **20**, the nucleophilic behavior of these adducts is rich. Electrophilic trapping can occur for both C–M bonds either with the same electrophile or sequentially with two different electrophiles. Interestingly, reaction with benzaldehyde gives benzylidenated products after addition of the C–Mg bond and subsequent β-elimination of BrMgOZnBr.



Scheme 13 Reaction of zinc hydrazones with vinylmagnesium halides.

Though synthetically related to the examples described above, the mechanism for reaction with vinyl Grignard reagents is completely different since it involves most likely a metalla-aza-Claisen rearrangement rather than a direct carbozincation (Scheme 14).

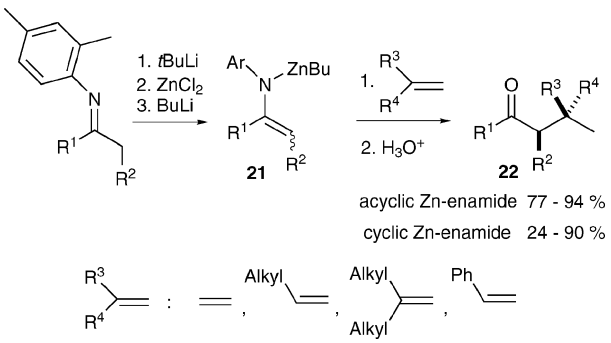


Scheme 14 Metalla-aza-Claisen mechanism for zinc hydrazone addition to vinylmagnesium halides.

2.2 Carbometalation with zinc enamides

While addition of zincated hydrazones proceeds conveniently onto ethylene or vinylmetals, addition onto substituted alkenes is generally too slow to be synthetically useful. Seeking a higher degree of generality as for the olefinic partner of the "olefin aldol reaction", and in particular to be able to carry out carbozincations of simple industrially abundant substrates, Nakamura and co-workers envisaged the use of zinc enamides.[33]

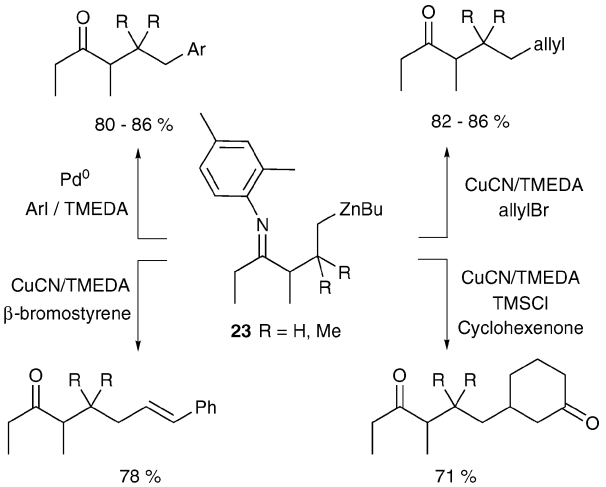
The latter zinc aza-enolates were prepared from the corresponding imines by deprotonation with *tert*-butyllithium or LDA (at the less hindered side for non-symmetric ones) followed by transmetalation with a suitable zinc salt. As for zincated hydrazones, subsequent ligand exchange with butyllithium was necessary to accelerate the addition reaction. The effect of the substituent on the enamide nitrogen atom was studied in detail. The best reactivities were obtained with *N*-aryl zinc enamides, while *N*-cyclohexyl and *N*-2-methoxyethyl enamides showed poorer reactivity than zincated *N*,*N*-dimethyl hydrazones. As a general trend, both *para*-substitution by electron-donating substituents and *ortho*-substitution (to increase steric bulk) of the aromatic moiety increased the reaction rate. Optimum reactivity was obtained with *N*-(2,4-dimethylphenyl) substituted enamides (Scheme 15).



Scheme 15 Alkene carbometalation by zinc enamides.

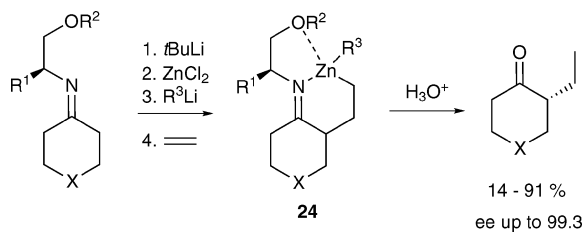
Carbozincation affording, following hydrolysis, ketones **22** in good yields (24–94%) could be achieved with a range of enamides **21** in synthetically exploitable conditions, not only on ethylene (1 atm, 50–65 °C, 12–24 h), but also on simple monosubstituted alkenes (propylene (1–8 atm), octene (1.2 eq.), 65 °C, 12–60 h), styrene (1.2–2 eq., 30–50 °C, 12 h) and 1,1-disubstituted alkenes (isoprene (4 atm), methylenecyclohexane (3 eq.), 65 °C, 60–72 h). Zinc enamides derived from acyclic ketones showed a higher reactivity than cyclic ones. In general, total regioselectivity in favor of the branched regioisomer (>99 : 1) was observed. Nevertheless, the case of styrene was somewhat specific since variable mixtures of branched/linear adducts were obtained depending on the starting enamine. In particular, unlike zincated hydrazones, cyclic enamines led exclusively to linear products. When two stereogenic centers were created, diastereoselectivity was low.

As exemplified with organozinc compounds **23**, the carbometalation adducts are stable in the reaction media and can thus undergo subsequent functionalisation by electrophilic trapping with or without Pd catalysis or copper salt addition (Scheme 16).



Scheme 16 Functionalisation of carbozincation adducts **23**.

Zinc enamides prepared from imines derived from (*S*)-valinol or (*S*)-*tert*-leucinol add to ethylene diastereoselectively (Scheme 17).[34] In the optimised conditions (R^1 = *t*Bu, R^2 = TMS, R^3 = Me) very high levels of stereoinduction can be obtained for a range of cyclic enamides. Upon hydrolysis, organometallic intermediates **24** afford the corresponding α-alkylated ketones with enantiomeric excesses higher than 90% in what can be regarded as an enantioselective version of the "olefin aldol reaction". The enantiomeric purity of the final ketones does not reflect the selectivity of the carbometalation reaction since racemisation of the chiral center resulting from epimerisation of an imine intermediate during hydrolysis was evidenced. In fact, enantiomeric excesses as high as 99.3% could be obtained after only several minutes of hydrolysis, albeit at the expense of a dramatic drop in the overall yield. The sense of stereoinduction was rationalised by a six-centered transition state **25** involving a Zn–O interaction that results in shielding of one of the faces of the imine by the bulky *t*Bu group (Fig. 1).



Scheme 17 Carbometalation of ethylene by (*S*)-valinol- and (*S*)-*tert*-leucinol-derived zinc enamides.

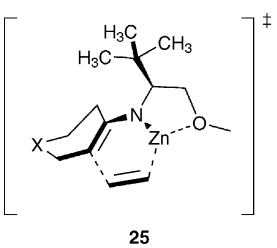
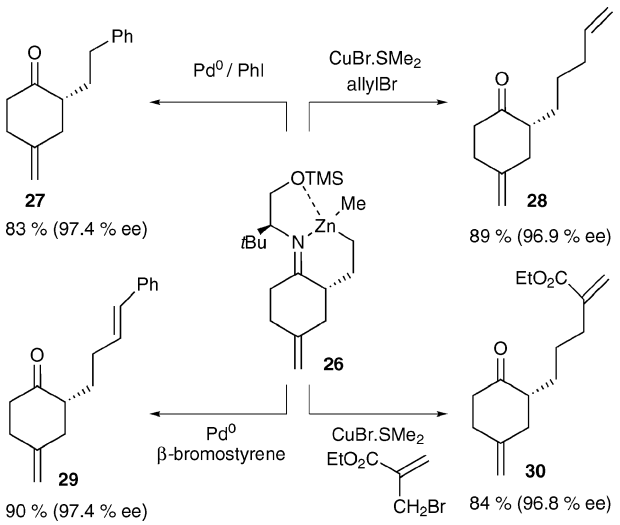


Fig. 1 Transition state for the carbometalation of ethylene by the (*S*)-*tert*-leucinol zinc enamide derived from cyclohexanone.

γ-Zincioimine intermediates such as **26** could also be trapped by an electrophile without significant erosion of enantioselectivity under Pd- or Cu-catalysis. For example, ketones **27**–**30**, resulting from the three-component sequence, were obtained in high yields and enantioselectivities (Scheme 18).



Scheme 18 Functionalisation of zincioimine **26**.

Generalisation of this method to alkenes other than ethylene resulted in lower yields and/or diastereoselectivities and was thus found to be non-practical.

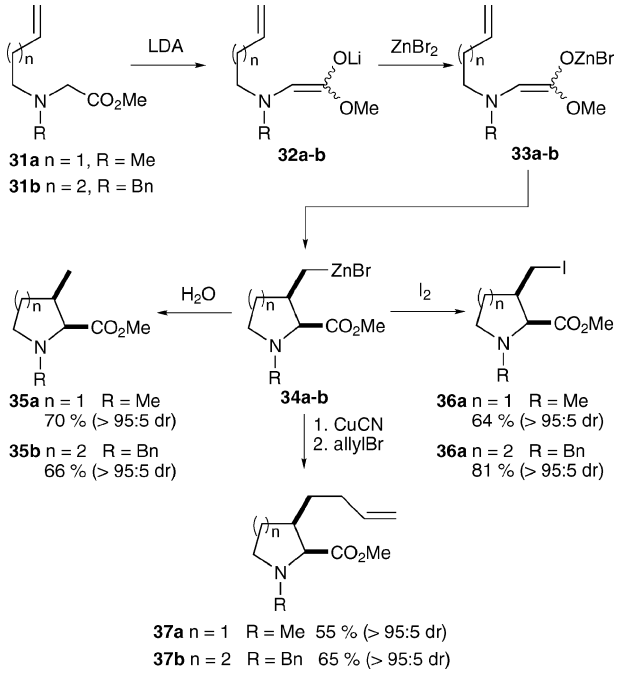
3. Carbocyclisation of zincated α- and β-aminoesters

Along with the studies on aza-enolates, the second major field of development of carbometalation reactions of unactivated alkenes with zinc enolate derivatives has involved the use of zincated aminoesters. Both the ready availability of the precursors and the high synthetic potential of the resulting compounds has oriented research towards intramolecular carbozincations (carbocyclisations).

3.1 Carbocyclisation of zinc enolates derived from α-(*N*-homoallyl)- and α-(*N*-4-pentenyl)aminoesters

Building on their work concerning the zinca-ene-allene reaction, Normant's group reported,[23,35] simultaneously with others,[24] the carbometalation reaction of α-(*N*-homoallyl)-aminoesters (Scheme 19). Initially it was shown that Reformatsky-type reagent **33a**, obtained by deprotonation of α-aminoester **31a** followed by transmetalation with $ZnBr_2$, underwent (unlike its parent lithium enolate **32a**) an intramolecular addition leading to **34a**. The resulting alkyl zinc species was reacted further with different electrophiles to afford diversely substituted pyrrolidines **35a**–**37a**. Remarkably, a similar behavior was observed with α-(*N*-pentenyl)aminoesters leading this time to polysubstituted piperidines **35b**–**37b**.[36]

In both cases the carbocyclisation was completely diastereoselective, affording exclusively the *cis* diastereoisomer. Zinc-enolate-ene-type intermediates **38**–**39**, where the O-centered enolate eclipses the terminal reacting double bond, were



Scheme 19 Carbocyclisation of α-aminoester zinc enolates and subsequent functionalisation.

proposed to explain this selectivity (Fig. 2). Further studies concerning the stereochemical outcome of the reaction with substituted homoallylic chains (or pentenylic chains for 6-*exo*-trig cyclisations) gave results in agreement with such intermediates.

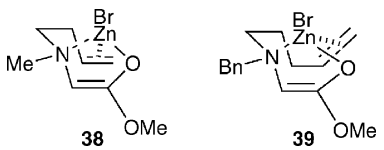
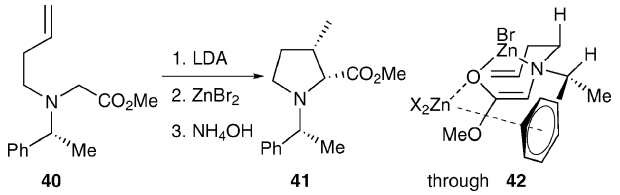


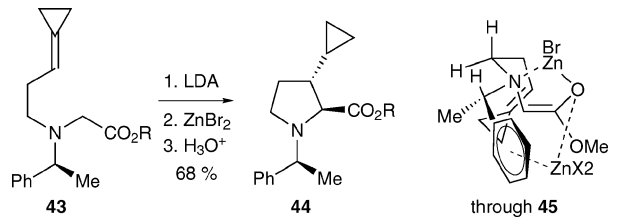
Fig. 2 O-Metalated reactive intermediates in the carbocyclisation of α-aminoester zinc enolates.

An enantioselective version of the carbocyclisation of α-(*N*-homoallyl)aminoester zinc enolates was also developed. Whereas attempts to induce stereoselectivity by means of a chiral ester (menthyl or phenylmenthyl) or chiral amide (camphorsultam) were reported to be unsuccessful (lack of reactivity or limited diastereoselectivity),[24] very high levels of stereoinduction were achieved using the inexpensive, readily available (in both enantiomeric forms) 1-phenylethylamino group as stereoinductor (Scheme 20). Thus, carbocyclisation of the enolate derived from **40**, led to pyrrolidine **41** as a single diastereoisomer. The key role played by the aromatic ring regarding the chiral induction was evidenced by the complete loss of selectivity when the phenyl group was replaced by a cyclohexyl moiety. This result, combined with the fact that two equivalents of zinc salt were found to be necessary to achieve high selectivities, led to the proposal of a chair like zinc-enolate-ene-type transition state **42** where the excess of zinc salt is chelated by the aromatic ring (zinc(II)–Ar interaction) and the amino zinc enolate.



Scheme 20 Carbocyclisation of α-(*N*-homoallyl)aminoester zinc enolates bearing the α-methylbenzylamino stereodirecting group.

Interestingly, this asymmetric version was also reported with substrate **43** bearing a cyclopropylethylene moiety (Scheme 21).[37] Intramolecular carbozincation leading to **44** was once again totally diastereoselective. However, while the same relative configuration was observed between the chiral inductor and C-2, a *trans* relationship was obtained between the newly created centers. It was suggested that in this case the bulkier cyclopropyl group disfavors the chair-like zinc-enolate-ene-type transition state similar to **42** and the carbometalation rather takes place through a boat-like transition state **45**.

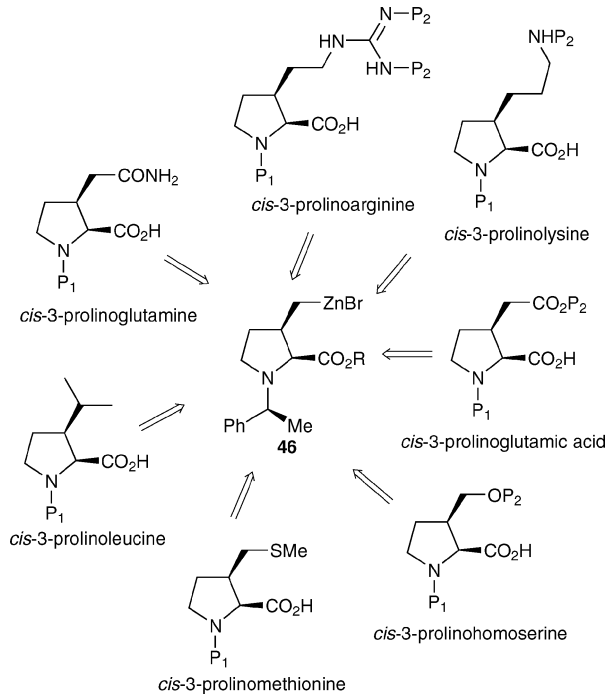


Scheme 21 Carbocyclisation of α-aminoester zinc enolates onto a cyclopropylethylene moiety.

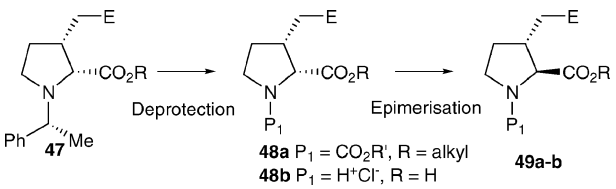
The synthetic usefulness of the α-amino zinc enolate carbocyclisation reaction has been very nicely exploited by Karoyan and co-workers to prepare proline chimeras of proteinogenic amino acids, valuable for structure–activity relationship studies of biologically active peptides.[24,37–40] By functionalisation, with a variety of electrophiles, of the enantiopure *cis*-3-zincioprolines **46** resulting from carbometalation of α-(*N*-homoallyl)aminoesters bearing the (*S*)-α-methylbenzyl stereodirecting group, *cis*-3-prolinomethionines, -glutamic acids, -arginines, -homoserines, -lysines, -glutamines and -leucines suitable for peptide synthesis have been prepared (Scheme 22). Furthermore, intramolecular carbozincation of α-amino enolates has been carried out on solid-phase, thus allowing the preparation of libraries of 3-substituted prolines.[41]

It is worthy of note that the analogous enantiopure *trans*-3-substituted prolines **49a**–**49b** can also be synthesised *via* the carbocyclisation method (Scheme 23). Precursors bearing the (*R*)-α-methylbenzyl group lead to *cis*-substituted prolines (C-2(*R*)) **47**. Epimerisation of the C-2 stereogenic center to afford the more stable *trans* isomers (C-2(*S*)) **49a**–**49b** has been performed, either by deprotonating (LDA)–reprotonating the carbamate protected proline esters[38] **48a** or by heating the free amino acids **48b** at 200 °C.[39,42]

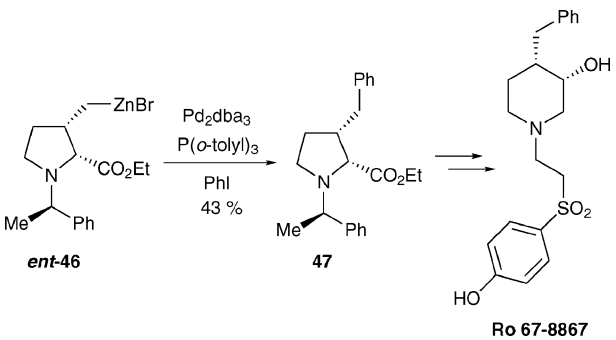
More recently, a one-pot sequence involving carbocyclisation and subsequent trapping of the organozinc adduct with aryl iodide under palladium catalysis has been developed[42] and applied[43] to the asymmetric synthesis of Ro 67-8867, an NMDA 2B receptor antagonist (Scheme 24).



Scheme 22 Preparation of proteinogenic amino acid *cis*-3-substituted proline chimeras by functionalisation of *cis*-3-zincioproline **46**.



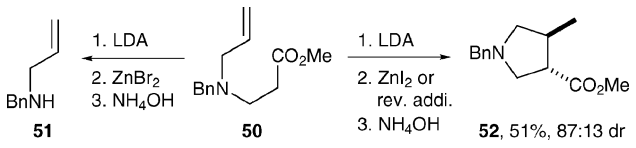
Scheme 23 Preparation of *trans*-3-substituted proline chimeras from their *cis*-3-substituted proline counterparts.



Scheme 24 One-pot carbocyclisation–Pd-coupling sequence for the synthesis of Ro 67-8867.

3.2 Carbocyclisation of zinc enolates derived from β-(*N*-allyl)aminoesters

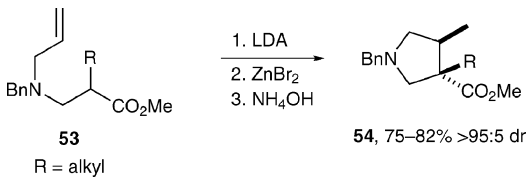
Following the work on α-amino zinc enolates, we turned our attention to the carbocyclisation of zinc enolates derived from β-aminoesters as a possible route to β-proline analogues. We first studied the behavior of zinc enolates obtained from β-(*N*-allyl)aminoesters by deprotonation with LDA followed by transmetalation with a zinc salt (Scheme 25).[44] As expected, competitive β-elimination made the carbocyclisation trouble-



Scheme 25 Carbocyclisation of unsubstituted β-(*N*-allyl)aminoester zinc enolates.

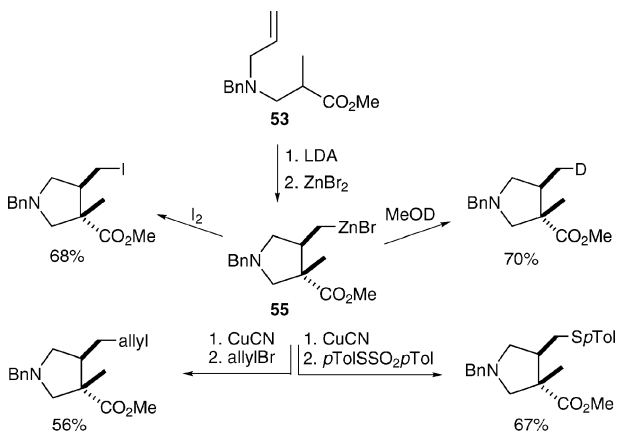
some. With unsubstituted substrate **50**, addition, as previously, of $ZnBr_2$ onto the lithium enolate led exclusively to amine **51** after work-up. Reverse addition (addition of the enolate to an ethereal zinc bromide solution) or replacement of $ZnBr_2$ by ZnI_2 limited considerably the elimination side reaction and the carbocyclisation product **52** was obtained smoothly.

On the other hand, β-elimination was not a problem with the more reactive substituted β-(*N*-allyl)aminoesters **53**, which afforded pyrrolidines **54** in good yields without any detectable amounts of the free amine even when transmetalation was carried out with $ZnBr_2$ (Scheme 26).



Scheme 26 Carbocyclisation of substituted β-(*N*-allyl)aminoester zinc enolates.

Here again, as evidenced with substrate **53** (R = Me), the metalated pyrrolidine **55**, resulting from the intramolecular carbozincation, could be further functionalised with several electrophiles in good yields under standard conditions (Scheme 27).[45]



Scheme 27 Functionalisation of the pyrrolidinylzinc intermediate in the carbocyclisation of β-(*N*-allyl)aminoester zinc enolates.

Diastereoselectivity was excellent in the case of substituted aminoesters **53** (>95 : 5) and good (87 : 13) with the unsubstituted **50**. Unlike with α-aminoesters, and much to our surprise, the *trans*-pyrrolidine was obtained as unique (or major) compound. To account for this stereochemical outcome, which cannot be explained by an O-centered zinc-

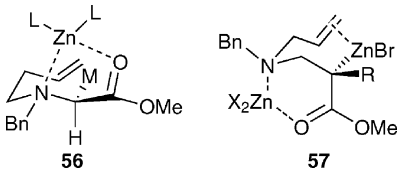
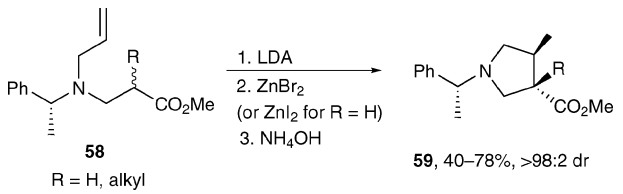


Fig. 3 C-Metalated reactive intermediates for the carbocyclisation of α- and β-aminoester zinc enolates.

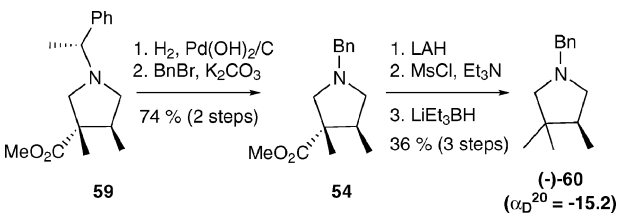
enolate-ene-type reactive intermediate, we proposed a C-centered zinc-enolate-carbometalation-type reactive intermediate **57** (Fig. 3). Its main features are the *pseudo*-axial position of the carbomethoxy group due to both simple steric interactions and the chelation of an extra zinc salt by nitrogen and the sp^2 oxygen of the carbomethoxy moiety. The stereochemical outcome observed with β-(*N*-allyl)aminoesters bearing additional substituents α to the nitrogen was also in agreement with this model.[46]

The high stereoselectivities obtained in the carbocyclisation of β-(*N*-allyl)aminoesters **53** prompted us to develop an enantioselective version.[47] Here again, we were glad to see that the 1-phenylethylamino group proved to be a stereodirecting group of choice (Scheme 28).



Scheme 28 Carbocyclisation of β-(*N*-allyl)aminoester zinc enolates bearing the α-methylbenzylamino stereodirecting group.

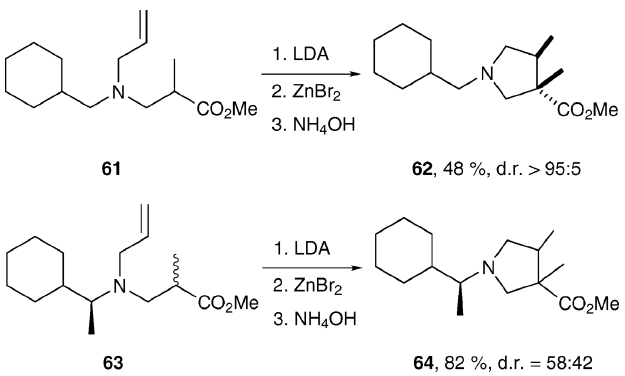
Thus, deprotonation of aminoesters **58** followed by transmetalation with $ZnBr_2$ (ZnI_2 in the case where R = H to prevent competitive β-elimination) resulted in a highly stereoselective carbocyclisation, leading, after aqueous work-up, to the corresponding *trans*-pyrrolidines **59** in diastereo- and enantiomerically pure form (even in the case of the unsubstituted aminoester, *i.e.* when R = H). The sense of stereoinduction was determined through chemical correlation in the case of **59** (R = CH_3) (Scheme 29). Cleavage of the chiral auxiliary by hydrogenolysis followed by benzylation led to the *trans*-pyrrolidine **54** (R = CH_3) that we had previously obtained in racemic form. Reduction of the ester moiety to the alcohol followed by mesylation and further reduction to the methyl group finally led us to (−)-**60**, the enantiomer of which had been reported previously.



Scheme 29 Sense of stereoinduction determination by chemical correlation.

Intrigued by the very high levels of induction brought about by the stereodirecting group, if one considers the fact that the stereogenic center of the α-methylbenzylamino group lies very far away from the reaction center, we studied in further detail the enantioselectivity transfer process. In view of our postulated reaction intermediate **57** for the achiral reaction, initially we thought that the nitrogen atom could operate as a chiral relay *via* a diastereoselective complexation by the zinc salt. This possibility was however ruled out by NMR monitoring of the reaction between the starting tertiary amines and ZnI_2, which showed that a complex is indeed formed, albeit with no diastereoselectivity.

In fact, the phenyl group of the 1-phenylethylamino moiety was found to play a crucial role in the transfer of chirality. Indeed, running the reaction with the cyclohexyl analogue **61** leads to pyrrolidine **62** with an excellent diastereoselectivity (>95 : 5), showing that the aromaticity of the nitrogen substituent has no influence on the intrinsic diastereoselectivity of the carbocyclisation step (*i.e.* the *trans* relationship between C-3 and C-4) (Scheme 30). On the other hand, starting from the (*S*)-α-methylcyclohexyl analogue **63**, pyrrolidine **64** was obtained as a mixture of two diastereoisomers and with very poor stereoselectivity (dr = 58 : 42).



Scheme 30 Carbocyclisations starting from aminoesters **61** and **63**.

Thus, to account for the observed diastereoselectivity we propose reactive intermediate **65**, which involves a zinc chelation between the carbomethoxy group and the nitrogen as in **57** (the relative configuration of the two newly created centers remains the same as for the achiral substrates), and where the chirality transfer results from an interaction between the chelated zinc salt and the aryl moiety (Fig. 4).

As for before, the organometallic species resulting from carbozincation could be reacted further with electrophiles to afford diversely substituted β-prolines such as **67** (Scheme 31).

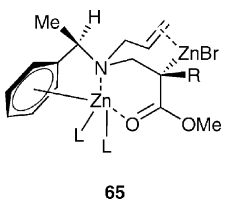
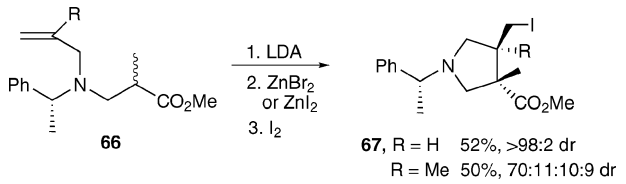


Fig. 4 Reactive intermediate of the carbocyclisation of β-aminoester zinc enolates bearing the α-methylbenzylamino group.



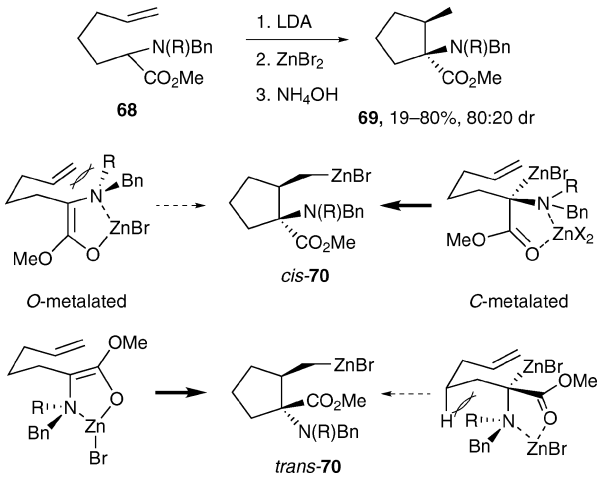
Scheme 31 Carbocyclisation of β-(*N*-allyl)aminoester zinc enolates bearing the α-methylbenzylamino group and functionalisation.

Interestingly, intramolecular addition also took place on a methallyl moiety, offering the opportunity to generate stereoselectively two contiguous quaternary carbon centers. As a proof of principle, carbocyclisation starting with **66**, with R = Me, and subsequent iodine quench led to the corresponding pyrrolidine **67**, though the levels of selectivity were somewhat disappointing.

3.3 Mechanistic considerations concerning C-metalated *versus* O-metalated enolate-ene reactive intermediates

A puzzling dichotomy is thus observed between β-(*N*-allyl)-aminoesters and α-(*N*-homoallyl)aminoesters that lead respectively to *trans*- and *cis*-pyrrolidines in very high selectivities. It was initially explained on the basis of C-metalated or O-metalated enolate-ene transition states. Indeed, while Reformatsky esters[48–51] have been shown to be C-metalated by NMR and X-ray crystallographic studies, zinc enolates derived from α-aminoesters have been found to be O-metalated.[52] However, reconsideration of the carbocyclisation of α-(*N*-homoallyl)amino enolates through a C-metalated transition state **56** showed that it could also account for the observed diastereoselectivity (Fig. 3). The choice between C- and O-metalated reactive intermediates leads to a concept far beyond this simple difference. The intrinsic mechanism of the carbozincation is concerned, since the O-metalated intermediate mainly looks like an enolate-ene six-membered reactive intermediate, whereas the C-metalated one involves presumably a four-membered transition state.

To shed some light on this issue we studied the carbocyclisation of amino enolates derived from **68** (Scheme 32).[46] We reasoned that if carbozincation involved an O-metalated species, metalated cyclopentane *trans*-**70** would be favored over *cis*-**70**, and on the other hand if a C-metalated intermediate was involved, cyclopentane *cis*-**70** should be predominant. Deprotonation of **68** followed by transmetalation with $ZnBr_2$ resulted in a smooth carbocyclisation leading to *cis*-1-amino-1-carbomethoxy-2-methyl cyclopentanes **69** as major compounds.[53] In consequence, although being α-aminoesters, compounds **68** cyclised through a C-metalated intermediate as in the case of β-(*N*-allyl)aminoesters and thus most likely of α-(*N*-homoallyl)aminoesters.

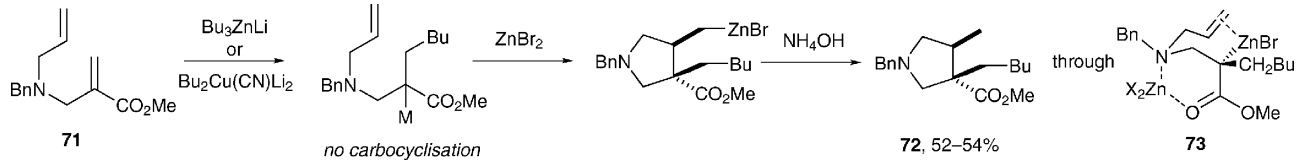


Scheme 32 Carbocyclisation from amino enolates derived from **68**.

3.4 Domino 1,4-addition–carbocyclisation of (*N*-allyl) methyl enoates

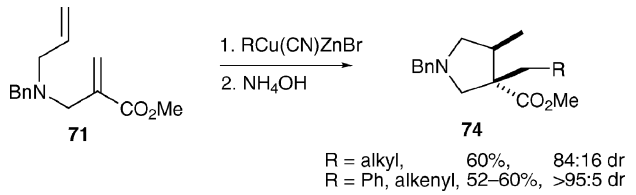
3.4.1 Stepwise polar domino 1,4-addition–carbozincation reaction. Our next interest focused on the possibility of generating β-amino zinc enolates by 1,4-addition of organometallic reagents onto an appropriate Michael acceptor, with the idea of developing a three-component one-pot reaction with the concomitant formation of two C–C bonds, one C–M bond and two stereogenic centers. Starting from enoate **71**, we surveyed a number of organometallic species known to react with α,β-unsaturated esters.[54] Alkyl copper (*n*BuCu–LiI) and cyanocuprate (*n*BuCu(CN)Li) reagents underwent 1,4-addition but led only to products resulting from β-elimination. This side reaction was more limited in the case of triorganozincates and higher order cyanocuprates and thus, following Michael addition, transmetalation with $ZnBr_2$ was carried out, leading to a zinc enolate that underwent carbocyclisation (Scheme 33). It should be noted that without zinc salt addition no carbometalation took place, stressing again the distinctive reactivity of zinc enolates. The cyclisation was totally diastereoselective and afforded, *via* intermediate **73**, the same *trans*-isomer **72** obtained previously from β-(*N*-allyl)-aminoesters, which tends to prove that the intermediate zinc enolate shows a similar behavior regardless of its preparation method (deprotonation–transmetalation or 1,4-addition–transmetalation).

3.4.2 Radical/polar crossover domino 1,4-addition–carbocyclisation reaction. Much more unexpectedly, species previously described to undergo 1,4-addition processes only under Lewis acid activation or in the presence of TMSCl,[45] also afforded a clean 1,4-addition–carbocyclisation domino reaction without any additives. Alkyl-, vinyl- and arylcopper–zinc reagents



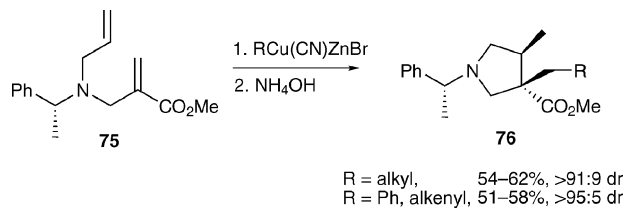
Scheme 33 Stepwise domino 1,4-addition–carbozincation of (*N*-allyl) methyl enoates.

RCu(CN)ZnBr reacted with enoate **71** to afford the desired *trans*-2,3-disubstituted pyrrolidines **74** in good yields and good to excellent selectivities (in the optimised reaction conditions) (Scheme 34).[54]



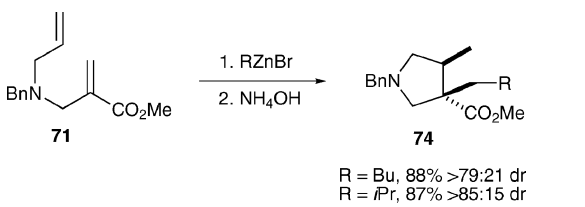
Scheme 34 Domino reaction of (*N*-allyl) methyl enoates with copper–zinc mixed reagents.

Very gratifyingly, reaction of the same nucleophiles on enoate **75**, bearing the enantiopure α-methylbenzylamino group, resulted in a smooth domino process leading, with an excellent chirality transfer, to the corresponding β-prolines **76** in basically enantio- and diastereomerically pure form (Scheme 35).[47]



Scheme 35 Domino reaction of (*N*-allyl) methyl enoates bearing the α-methylbenzylamino stereodirecting group with copper–zinc reagents.

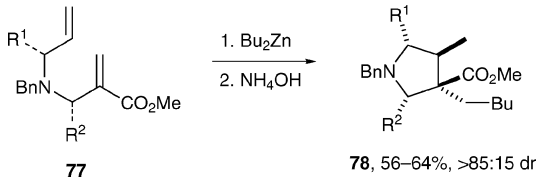
Even less reactive dialkylzinc derivatives and organozinc halides also undergo the domino process. Reaction of *n*BuZnBr and *i*PrZnBr with **71** gave the corresponding cyclised derivatives **74** with good yields but slightly lower diastereoselectivities than that observed with copper–zinc reagents (Scheme 36).[55]



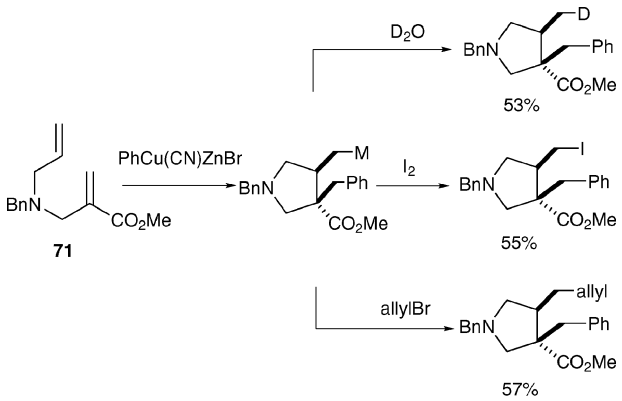
Scheme 36 Domino reaction of (*N*-allyl) methyl enoates with organozinc reagents.

Di-*n*-butylzinc was reacted with different enoates **77** and afforded the corresponding pyrrolidines with good diastereoselectivities, but this time in favor of the *cis*-isomers **78** (Scheme 37).[56] Disappointingly, reaction with enantiopure enoate **75** showed no chirality transfer, as a mixture of all possible diastereoisomers was obtained.[47]

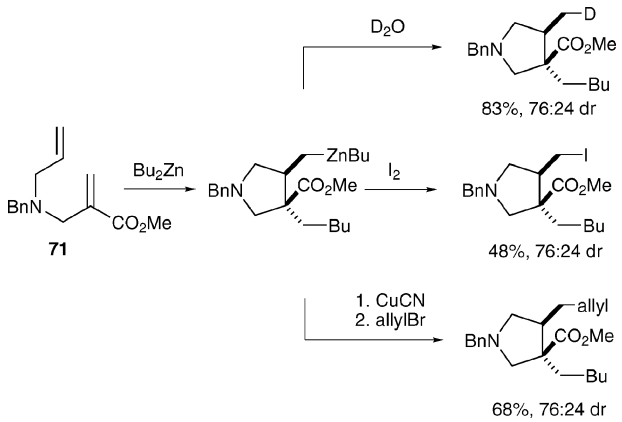
As illustrated with the particular cases of PhCu(CN)ZnBr[54] (Scheme 38) and Bu_2Zn (Scheme 39),[56] the intermediacy of metalloprolines, in both the domino processes with copper–zinc reagents and dialkylzinc reagents, was evidenced by their further functionalisation with several electrophiles.



Scheme 37 Domino reaction of (*N*-allyl) methyl enoates with dialkylzinc reagents.



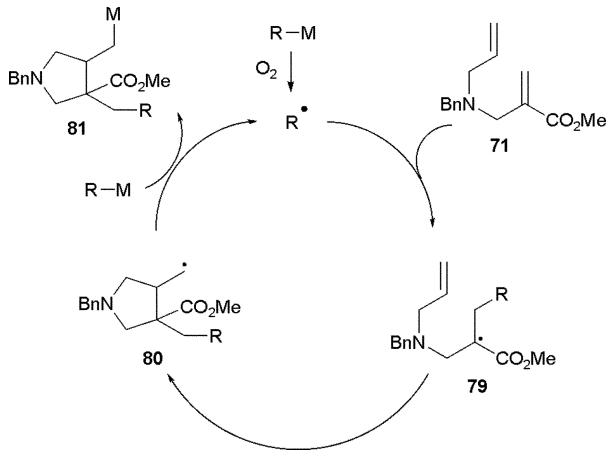
Scheme 38 Functionalisation of the pyrrolidinylzinc intermediate in the reaction of (*N*-allyl) methyl enoates with copper–zinc reagents.



Scheme 39 Functionalisation of the pyrrolidinylzinc intermediate in the reaction of (*N*-allyl) methyl enoates with dialkylzinc reagents.

At this stage, the domino sequence with copper–zinc, dialkylzinc and organozinc reagents appeared to be completely analogous to the polar sequence described above, that involves stepwise 1,4-addition followed by transmetalation and carbozincation. However, several rather awkward experimental details such as the fact that we never isolated either the addition intermediates prior to cyclisation or any β-elimination side products, and the difference in kinetics in the presence or absence of oxygen,[56] prompted us to carry out a full mechanistic investigation of the process.[55] Extensive experimentation led us to the conclusion that with copper–zinc, dialkylzinc and organozinc reagents the domino 1,4-addition–cyclisation reaction on enoates is not fully polar

in nature but instead involves an original radical–polar crossover mechanism (Scheme 40).[57–60]



Scheme 40 Mechanism of the radical–polar crossover domino reaction.

The overall process can be depicted as follows. Oxygen initiation produces a radical from the organometallic species.[61–70] This nucleophilic radical adds to enoate **71** to give the electrophilic enol radical **79** that undergoes a 5-*exo*-trig cyclisation to form radical **80**. Reduction by the organometallic species gives the pyrrolidinylmethylzinc compound **81** and a radical which propagates the radical chain. This remarkable reduction seems to be unfavorable (thermoneutral for alkylmetals or contra-thermodynamic for aryl- and vinylmetals), but the driving force of the reaction could be the chelation of the resulting organozinc species by the methoxycarbonyl moiety.

According to the proposed radical–polar crossover mechanism, and since we have also shown that *cis*- and *trans*-metallopyrrolidines **81** do not equilibrate,[55] the diastereoselectivity of the domino process results from the diastereoselectivity of the 5-*exo* radical cyclisation (Fig. 5).

Following the Beckwith–Houk model,[71,72] for $A^{1,3}$-strain[73] and intramolecular dipole–dipole effect[74] minimisation, the carbomethoxy moiety should adopt a *pseudo*-equatorial position, thus affording the *cis*-pyrrolidine. This is indeed the case when Bu_2Zn is used and cyclisation occurs *via* **79**. However, in the presence of stronger Lewis acids, chelation between the nitrogen atom, the oxygen atom of the carboxyl group and a metal salt [Zn(II) or Cu(I)] counterbalances $A^{1,3}$-strain minimisation. As a result, when organozinc and copper–zinc reagents are used, cyclisation takes place *via* **82** leading to *trans*-pyrrolidines. Finally, the high diastereoselectivities observed for reactions of copper–zinc mixed reagents with enoate **75** having the stereodirecting α-methylbenzyl group can be again explained on the basis of an Ar–metal interaction. Radical intermediate **83**, similar to organometallic intermediate **65**, accounts for the observed selectivity. Remarkably, the bases of stereoselectivity are the same in both polar and radical–polar mechanisms, although they proceed through a different intermediate (organometallic or radical species).

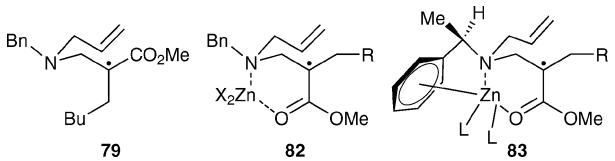


Fig. 5 Origin of diastereoselectivity in the radical–polar crossover domino process.

4. Conclusions and perspectives

Though still very young, the addition reactions of zinc enolate derivatives to unactivated alkenes have already shown a great synthetic potential for the preparation of functionalised organometallic compounds. Once optimised, the experimental protocols are generally simple and involve rather inexpensive reagents, allowing us to foresee a continuation of its development.

In our case, the study of the carbocyclisation of β-aminoesters, initiated as a rather "straightforward" extension of the carbozincation of α-(*N*-homoallyl)amino zinc enolates has taken us through unforeseen paths, through which we have learnt a great deal.

Regarding the mechanism of the carbozincation of unactivated alkenes by zinc enolates it has been shown that, unlike previously believed, it proceeds through a C-metalated four-membered transition state. Demonstrated only for the particular case of amino enolates, this trend might be in fact much more general. Indeed, zinc enolates derived from amides have been reported to undergo carbocyclisation[26] and recently it has been shown that they are C-metalated.[75] On the other hand, zinc enolates derived from ketones, known to be O-metalated, have been reported recently not to undergo 6-*exo*-trig carbocyclisation onto unactivated alkenes.[76]

From a synthetic point of view, bearing in mind the considerable interest raised by β-amino acids,[77] we believe that, as for their α-amino counterpart, the recent disclosure of a highly selective non-racemic route to β-prolines should foster further synthetic applications.

The rather unusual radical–polar domino 1,4-addition–carbocyclisation on (*N*-allyl) methyl enoates has brought about a two-fold interest. On the one hand, the radical nature of the 1,4-addition and the cyclisation should enable further development, first with enoates bearing moieties prone to anionic β-elimination excluded from the "anionic path", and second in an intermolecular version. On the other hand, it has proved to be a great probe to evidence the unprecedented[78] ability of organozinc halides and copper–zinc mixed species to promote radical 1,4-addition in a manner similar to dialkylzinc reagents.[79–85] This trend should be linked on a more general level to the latest developments in enantioselective 1,4-additions of organozinc compounds catalysed by Cu^I complexes.[76,86–89]

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