Domino Reaction Mechanism

Domino 1,4-Addition/Carbocyclization Reaction through a Radical–Polar Crossover Reaction[**]

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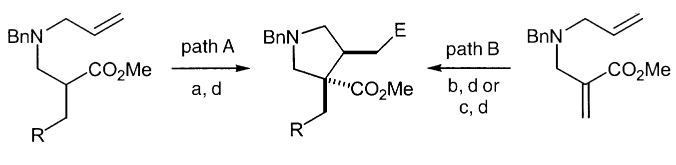
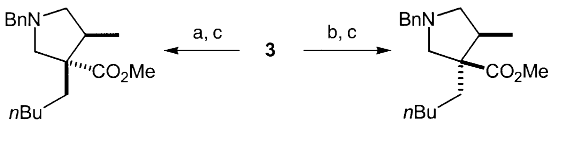
Dedicated to Professor Reinhardt W. Hoffmann
on the occasion of his 70th birthday

We have recently shown that 3,4-disubstituted 3-methoxycarbonylpyrrolidines **1** can be constructed diastereoselectively by carbocyclization[1] of the zinc enolates derived from β-*N*-allyl aminoesters **2** (Scheme 1, path A) or by the domino 1,4-addition/carbocyclization/functionalization[2] of zincates and copper–zinc mixed organometallic compounds with the Michael acceptor **3a** (Scheme 1, path B). In the course of our studies on the latter domino reaction (which involves the stereoselective formation of three carbon–carbon bonds in a two- or three-step, one-pot sequence), we have examined the reactivity of dialkylzinc reagents. We were very surprised to see that with di-*n*-butylzinc, a smooth domino reaction occurs leading predominantly to the pyrrolidine derivative *cis*-**4a**, diastereoisomeric to *trans*-**4a** which is produced by the domino reaction with the copper–zinc reagents (Scheme 2). Product **4a** is obtained as a mixture of *cis/trans* diastereomers in a 75:25 ratio and in good overall yield (88%).



2 **1** **3a**

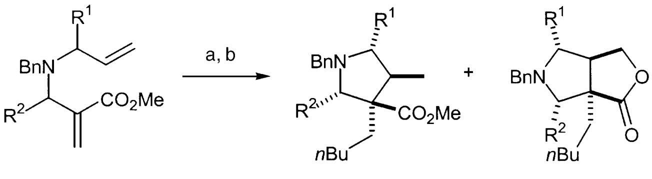
Scheme 1. Diastereoselective formation of pyrrolidines **1**. a) 1. LDA, Et_2O, 2. $ZnBr_2$; b) RCu(CN)ZnBr, LiBr, $ZnBr_2$; c) 1. R_3ZnLi, 2. $ZnBr_2$; d) Electrophile (E). LDA = lithium diisopropyl amide.



trans-**4a** **4a** (*cis*/*trans* = 75:25)

Scheme 2. Diastereodivergency in the domino reaction of **3** with zinc *n*-butylcyanocuprate and di-*n*-butylzinc. a) *n*BuCu(CN)ZnBr, LiBr, $ZnBr_2$; b) $(nBu)_2Zn$; c) NH_4OH.

The same smooth domino reaction occurs with di-*n*-butylzinc and the substituted Michael acceptors **3b–e**, leading after hydrolysis to the *cis* pyrrolidines **4b–e** in good yields (Scheme 3). It should be noted that the *cis* and *trans* diastereomers of compounds **4a–e** can be separated easily by chromatography on silica gel. The diasteroselectivity of the reaction is better with these substituted Michael acceptors than with **3a**, and small amounts of the lactones **5b–e** can also be isolated.



3b: R^1 = H, R^2 = Me	**4b**: 49 %, *cis* / *trans* = 87 : 13	**5b**: 9 %
3c: R^1 = Me, R^2 = H	**4c**: 64 %, *cis* / *trans* = 85 : 15	**5c**: 5 %
3d: R^1 = Ph, R^2 = H	**4d**: 64 %, *cis* / *trans* = 92 : 8	**5d**: 14 %
3e: R^1 = *i*Pr, R^2 = H	**4e**: 56 %, *cis* / *trans* = 96 : 4	**5e**: 7 %

Scheme 3. Domino reaction of **3b–e** with di-*n*-butylzinc. a) $(nBu)_2Zn$; b) NH_4OH.

The diastereoselectivity in the domino reaction with zincates and copper–zinc reagents was attributed to a chelation of a zinc species with the nitrogen and the sp^2 oxygen atoms of the ester moiety.[1,2] The reversal in the diastereoselectivity with di-*n*-butylzinc could be attributed to its weaker Lewis acidity. However, we examined the reaction of **3a** with di-*n*-butylzinc in various solvents (pentane, ether, THF, and DMF). Surprisingly, the polarity and the Lewis basicity of the solvent did not affect the diastereoselectivity, rate, or yield of the domino reaction.

This negligible influence of the solvent was intriguing, as 1,4-addition of organozinc reagents has been reported[3] to occur only in polar solvents (THF/*N*-methylpyrrolidone) in the presence of trimethylsilyl chloride or under the activation of a strong Lewis acid.[4] On the other hand, radical-mediated 1,4-addition of dialkylzinc reagents to unsaturated ketones,[5a,b] *N*-enoyloxazolidinones,[5c] and imines[6] has been reported. However, these radical 1,4-additions fail with unsaturated esters.[5a,c] These reactions are considered to be initiated by oxygen[5,7] or by light.[8] The small amounts of lactones **5b–e** obtained in the domino reaction could be an indication of mediation by molecular oxygen. Indeed, when our reaction was conducted in rigorously degassed solvents, the rate was very slow and the reaction reached 60% conversion only after 48 h. On the other hand, when the reaction was conducted in THF under dry air, total conversion was observed after two hours, thus providing good evidence for radical involvement in the overall process.

To determine which step of this domino reaction proceeds via radicals, we conducted the reaction of **3a** with di-*n*-butylzinc in the presence of isopropyl iodide (top reaction in Scheme 4). The major product was pyrrolidine **6** bearing the

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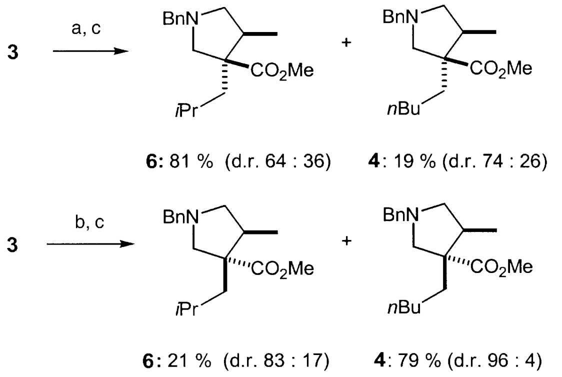
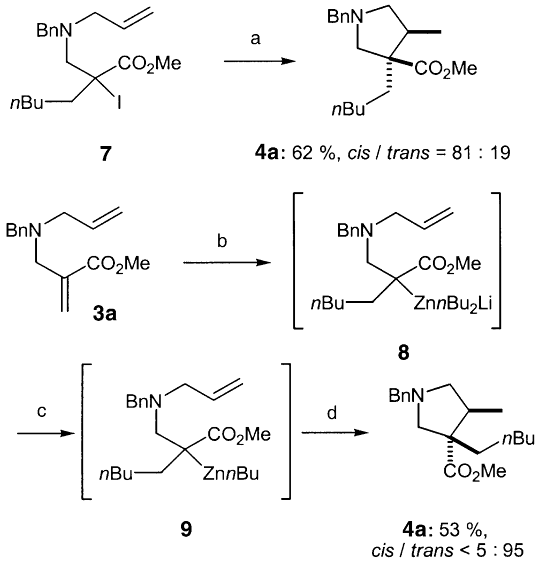


Scheme 4. Competition reactions in the domino reaction. a) $n\mathrm{Bu_2Zn}$, *i*PrI (10 equiv); b) *n*BuCu(CN)ZnBr, LiBr, $\mathrm{ZnBr_2}$, *i*PrI (10 equiv); c) $\mathrm{NH_4OH}$.

*i*Pr moiety, which was obtained as a mixture of two diastereomers. By contrast, the same competition reaction with *n*BuCu(CN)ZnBr (bottom reaction in Scheme 4) gave predominantly the pyrrolidine *trans*-**4a** accompanied by a small amount of **6**. It should be noted that in the second reaction compound **6** was obtained as a 83:17 mixture of diastereomers, with the diastereoselectivity opposite to that of the first reaction.

These cross experiments give strong evidence of the radical character of the 1,4-addition of di-*n*-butylzinc to the substrate **3**, as well as of the strong anionic character of the 1,4-addition of *n*BuCu(CN)ZnBr. In the first case, radical exchange occurs between the $n\mathrm{Bu_2Zn}$ and the *i*PrI, leading to the more stable isopropyl radical and its major reaction to give **6**. In the case of the copper–zinc reagent, this exchange takes place to a much lower extent, as the resulting isopropyl carbanion is less stable than the incipient *n*-butyl carbanion. The same type of cross experiments have been used to establish the radical nature of the 1,4-addition of dialkylzinc compounds to other Michael acceptors.[5]

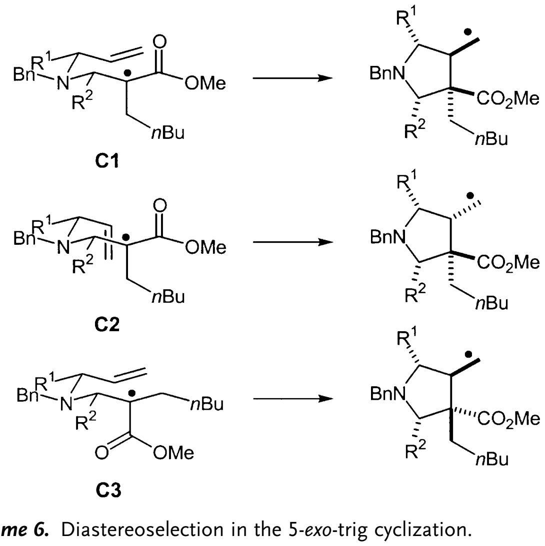
Having thus established the radical nature of the 1,4-addition, we examined the carbocyclization step in greater detail. It was reported very recently that in the radical 1,4-additions of dialkyzinc reagents to Michael acceptors, the resulting radical is further reduced by dialkylzinc to a zinc enolate.[5c] On the other hand, 5-*exo*-trig cyclization reactions of radicals have been widely reported. To determine whether the carbocyclization step occurs by a radical or an anionic mechanism, we have conducted a pure radical cyclization reaction starting from iodide **7** (Scheme 5). Pyrrolidine **4a** was obtained with a diastereoselectivity similar to that observed in the domino reaction with di-*n*-butylzinc. On the other hand, the 1,4-addition step was performed with **3a** and tri-*n*-butyl lithium zincate, as described previously.[2] The resulting zincate enolate **8** was allowed to react with *n*-butylzinc bromide. The diorganozinc enolate **9** (Scheme 5) formed through Schlenk equilibrium should be the same as that obtained if the reduction of the radical formed after the 1,4-addition would occur. However, the carbocyclization reaction gave, after hydrolysis, the *trans* pyrrolidine *trans*-**4a** as a single diastereomer, without any trace of the *cis* isomer obtained by the domino reaction.



Scheme 5. a) $\mathrm{Bu_3SnH}$ (1.5 equiv), $\mathrm{Et_3B}$ (0.15 equiv), THF, RT; b) $n\mathrm{Bu_3ZnLi}$ (2 equiv), ether; c) *n*BuZnBr (2 equiv), THF; d) $\mathrm{NH_4OH}$. RT = room temperature.

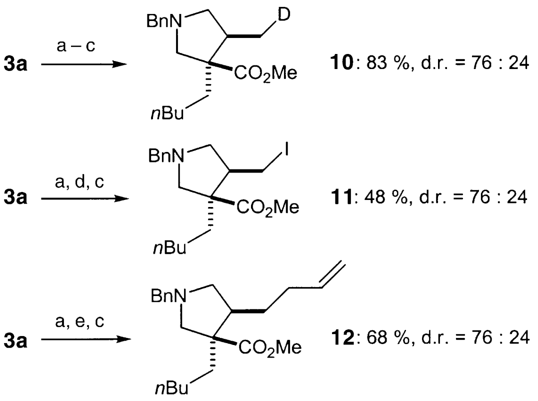
Finally, the domino reaction was conducted with **3d** and **3e** at −70 °C, and the yields and diastereoselectivities of **4d** and **4e** were the same as in Scheme 3, although the reaction was slower. This reactivity at low temperature is not compatible with an anionic cyclization, as this process is not observed below 0 °C.[2] All these results show unambiguously that the mechanism of the carbocyclization step is of a radical nature.

The diastereoselectivity of the 5-*exo*-trig cyclization can be interpreted in terms of conformational preferences of the enol radical in the cyclization. The major pyrrolidine is obtained from the cyclization of conformer **C1** (Scheme 6), which follows the Beckwith–Houk model[9] and minimizes the $A^{1,3}$ strain.[10] The minor diastereomer is obtained by the cyclization of conformer **C2**, as the other possible conformer **C3** is disfavored by the strong $A^{1,3}$ strain and dipolar interactions.[11]



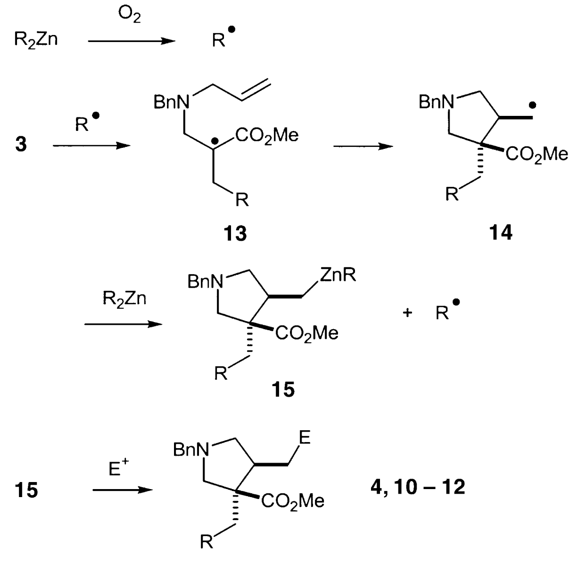
Scheme 6. Diastereoselection in the 5-*exo*-trig cyclization.

Since both the 1,4-addition and carbocyclization reactions follow a radical pathway, the question of the behavior of the final pyrrolidinylmethyl radical arises. This radical could be quenched through hydrogen abstraction from the solvent or reduced by di-*n*-butylzinc to promote the radical chain. The species resulting from the domino reaction was allowed to react with various electrophiles (Scheme 7). We were pleased to obtain the substituted pyrrolidines **10**–**12** in good yields. Thus the pyrrolidinyl radical formed from the cascade 1,4-addition/5-*exo*-trig cyclization is further reduced to a pyrrolidinylmethylzinc species, which can be quenched by electrophiles. This remarkable reduction seems to be thermoneutral and disfavored, but the driving force of the reaction could be the chelation of the resulting organozinc species by the methoxycarbonyl moiety.[12]



Scheme 7. Reactions of the pyrrolidinylzinc species with electrophiles. a) $n\mathrm{Bu_2Zn}$ (2 equiv); b) D_2O; c) NH_4OH; d) I_2; e) CuCN (0.25 equiv), then allylbromide.

The overall process can then be depicted as follows. Oxygen initiation produces an alkyl radical from dialkylzinc (Scheme 8). This radical adds to the enoate moiety of **3** to produce the enol radical **13**. This radical undergoes a 5-exo-trig cyclization to form stereoselectively the alkyl radical **14**, which is further reduced by dialkylzinc to produce the pyrrolidinylmethylzinc compound **15** and an alkyl radical which can promote the radical chain. This compound **15** can be further functionalized by electrophiles. This unusual mechanism has a number of very interesting features. First, radical addition of dialkylzincs on unsaturated esters can occur. Second, the reduction of **14** to give **15** occurs at a faster rate than the quenching of **14** by an alkyl iodide in the reaction mixture. Third, the reduction of **13** to give zinc enolate **8** is slower than the 5-*exo*-trig cyclization to give **14**.



Scheme 8. Mechanism of the radical domino reaction.

In conclusion, we have shown that the reaction of dialkylzinc reagents with Michael acceptors **3** occurs through a radical 1,4-addition/5-*exo*-trig cyclization/reduction reaction with electrophiles and results in the formation of 3,4-disubstituted 3-methoxycarbonylpyrrolidines with interesting diastereoselectivity. This procedure constitutes a novel example of a one-pot, two- or three-component, radical–polar crossover reaction and one of the few examples[5c,13–16] of a radical reaction that begins with an organometallic species and is ended by the reduction of another organometallic species. The viability of this process suggests application to intermolecular reactions as well as living polymerization processes. Further studies in this field will be reported in due course.

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