

# Synthesis and selective transformation of nitrogen-containing compounds via radical pathways

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This paper is dedicated to the memory of the late Professor Jean-Marie Surzur.

**Abstract** – This account presents the recent contribution of our group to the development of radical methodologies, and their application to the synthesis and the reactivity of nitrogen-containing compounds. The scope of several cascade processes involving sulphur-centred radicals is discussed first, then the synthetic potential of radical additions to C=N bonds mediated by triethylborane and diethylzinc is examined. Special attention is given to 1,3-stereoselection in the perspective of enantioselective synthesis. *To cite this article: M. Bertrand et al., C. R. Chimie 5 (2002) 623–638* © 2002 Académie des sciences / Éditions scientifiques et médicales Elsevier SAS

radical cyclisations / sulfonyl radicals / thiyle radicals / radical additions / glyoxylate imines / triethylborane / diethylzinc / 1,3-stereoselection

**Résumé** – Cette revue présente notre récente contribution au développement de méthodologies radicalaires et à leur application à la synthèse et à la réactivité des composés azotés. Une première partie est consacrée à des processus en cascade, impliquant les radicaux centrés sur le soufre. La deuxième partie illustre le potentiel synthétique des réactions d'addition sur doubles liaisons C=N utilisant le triéthylborane et le diéthylzinc comme médiateurs. Une attention particulière est portée à la stéréoselection-1,3 dans ces réactions, dans la perspective de synthèses énantiosélectives. *Pour citer cet article : M. Bertrand et al., C. R. Chimie 5 (2002) 623–638* © 2002 Académie des sciences / Éditions scientifiques et médicales Elsevier SAS

cyclisations radicalaires / radicaux sulfonyle / radicaux thiyle / additions radicalaires / imines de glyoxylates / triéthylborane / diéthylzinc / stéréoselection-1,3

## 1. Introduction

Radical chemistry has known exponential development over the last twenty years, due to the 'domestication' of the highly reactive radical species and to the ongoing demand for mild and stereoselective transformations [1–3]. Our group has long been interested in exploring the synthetic potential and the diastereoselectivity of free radical reactions. This article

gives a survey of our contribution in the field of nitrogen-containing compounds. These results include: the sulfonyl radical-mediated preparation of pyrrolidines (or pyrrolidinones) through a radical addition/5-exo-ring closure/atom transfer sequence, and other related complex cascade processes; the cleavage of allylic amines using thiols as stoichiometric reagents; and new methodologies making use of triethylborane and diethylzinc to promote radical additions to imines, oxime ethers and hydrazones.

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## 2. Sulfonyl radical-mediated preparation of functionalised pyrrolidines and pyrrolidinones

Sulfonyl radicals are versatile intermediates that add readily to unsaturated systems. As shown in equation (1), their addition to C=C bonds is a reversible process [4]. This is a characteristic feature common to all sulphur-centred radicals, which makes them good radical leaving groups [5–6]. In other words, the reaction can be driven in the forward or the backward direction, depending on the experimental conditions (Fig. 1).

The cascade combination of radical addition, 5-exo-trig closure, and atom transfer is an efficient route for the construction of cyclic skeletons [7–12]. The basic principle of the methodology, applied to the preparation of pyrrolidines is summarised in Fig. 2.

Such a procedure presents an obvious advantage as compared to the tin methodology, which is still the most universally used method to carry out radical cyclisations [1–3]. Contrary to the reactions performed with tin hydrides, which end with a hydrogen atom transfer, no reductive step occurs at the final stage. In a unique step, one can build the cyclic framework and introduce two new functionalities that can be used for further transformations. Furthermore, a variety of precursors (sulfonyl halides, phenylselenosulfonates, sulfonyl cyanides...) are available for this purpose [4–6]. Good yields in cyclic adducts can be obtained, provided that the concentrations of the reactants are

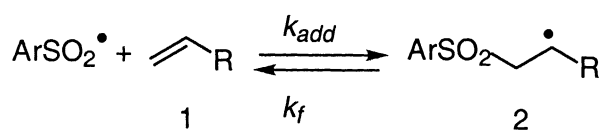


Fig. 1. Addition of sulfonyl radicals to alkenes.

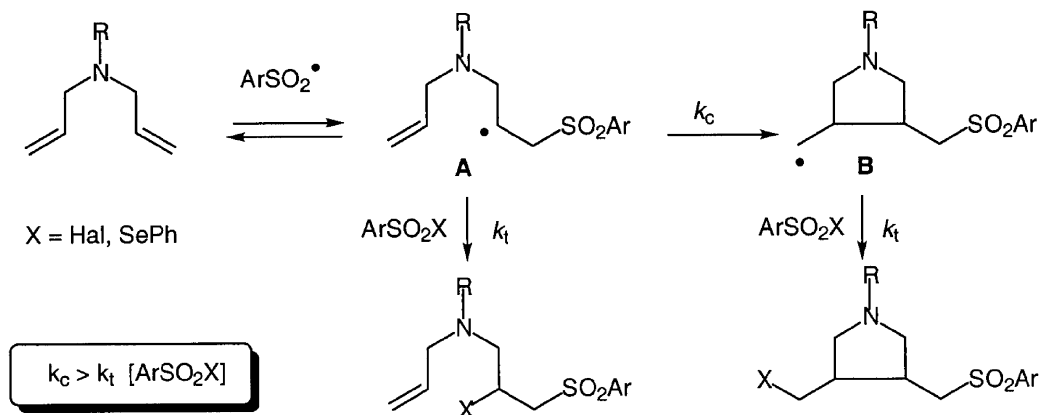


Fig. 2. Sulfonyl radical-mediated cyclisation of 3-aza-1,6-dienes.

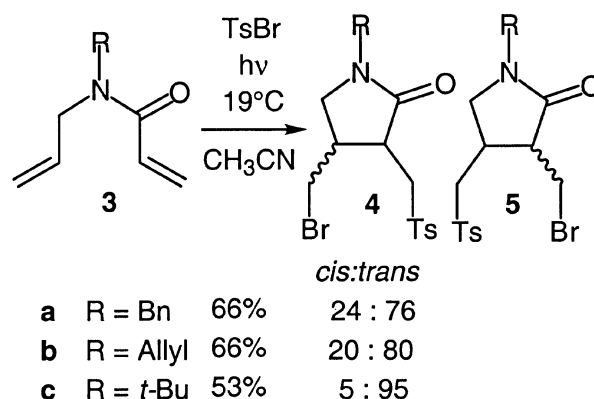


Fig. 3. Addition of tosyl bromide to *N*-allyl acrylamides.

adjusted in such a way that the bimolecular transfer of atom (or group of atoms) X to radical A is slow as compared to the unimolecular rearrangement leading to B.

### 2.1. Synthesis of $\gamma$ -lactams

As exemplified in Fig. 3, the addition of tosylbromide to *N*-allyl acrylamides (3) leads to functionalised  $\gamma$ -lactams (4) [13–14]. These substrates illustrate the great chemoselectivity of the reaction, when applied to non-symmetrical dienes.

The products resulted exclusively from the initial addition of tosyl radical to the acrylic double bond. It must be noted that a very high diastereomeric ratio was reached when a bulky substituent was attached to the nitrogen. No trace amount of compound 5 was detected. In the case of amide 3b, the acylated pyrrolidine that would result from the initial addition of tosyl radical to one *N*-allyl terminal double bond, followed by a fast intramolecular trapping by the second *N*-allyl unsaturation, was not detected either. These data clearly demonstrate that chemoselectivity is not determined by the polar properties of the attacking

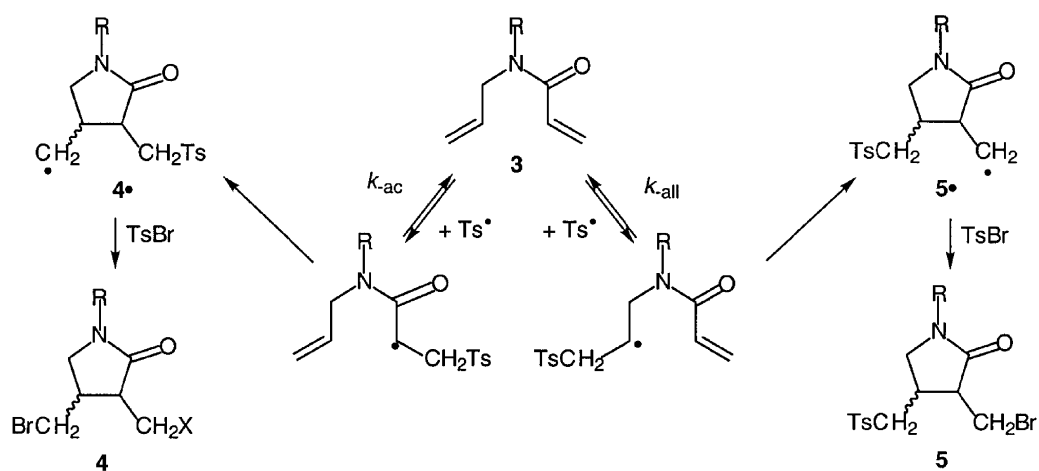


Fig. 4. Mechanism of the cyclisations of *N*-allyl acrylamides.

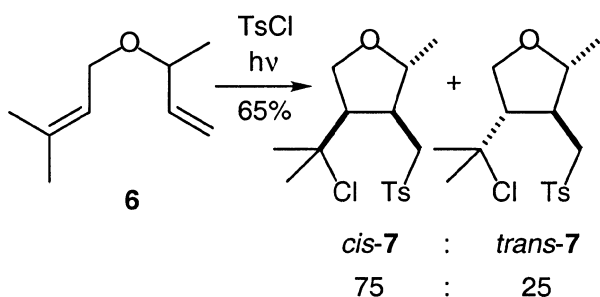


Fig. 5. Addition of tosyl chloride to methallyl prenyl ether.

tosyl radical, whose electrophilic character is reliable only with respect to its addition to a series of analogous olefins. We believe that the rates of fragmentation of the two  $\beta$ -sulfonylated radicals potentially involved in this process might have as much influence on the course of these reactions as the rates of addition of tosyl radical to the two different double bonds (Fig. 4). The kinetic problem is complex, further mechanistic studies are ongoing in our group.

## 2.2. Application to the synthesis of ( $\pm$ )-kainic acid

A strategy based on the general mechanism displayed in Fig. 1 was investigated as a potential route toward kainic acids [15]. A previous study in the field of the cyclofunctionalisation of 3-oxa-1,6-dienes had demonstrated that trisubstituted tetrahydrofurans could be prepared with a high stereoselectivity [16]. As summarised in Fig. 5, only two stereoisomers were isolated among the four possible ones, after addition of TsCl to methallyl prenyl ether. The reaction resulted in a total 2,3-*trans* stereochemistry, the major isomer being the 3,4-*cis* isomer. This is in good agreement with the predictive rules stated by Beckwith and Houk [17–19]. They are based on the assumption (verified in most cases) that the lowest

energy transition state adopts a ‘chair-like’ conformation with the substituents in equatorial position. Theoretical calculations have shown that the minor isomer resulted in fact in this case from a ‘boat-like’ transition state [16].

The  $\alpha$ -kainic acid is a rigid analogue of glutamic acid, which presents three adjacent stereocentres. This structural analogy is likely to be responsible for its neurological activity. A plausible retrosynthetic analysis is shown in Fig. 6. By analogy, with the results described in Fig. 2, one would expect selenide **9** to be the major stereomer resulting from the addition of TsSePh to diene **8**. The sulfonyl group could formally be used to introduce the second carboxylic function via acylation of the  $\alpha$ -carbanion, and the isopropenyl chain would then be available through oxidative elimination of selenide **9**.

Reactions performed on simple models were rather disappointing, the diastereoselectivity was very low (Fig. 7). No improvement of the diastereomeric ratio could be obtained through photochemical initiation at room temperature, since the adducts, which are ter-

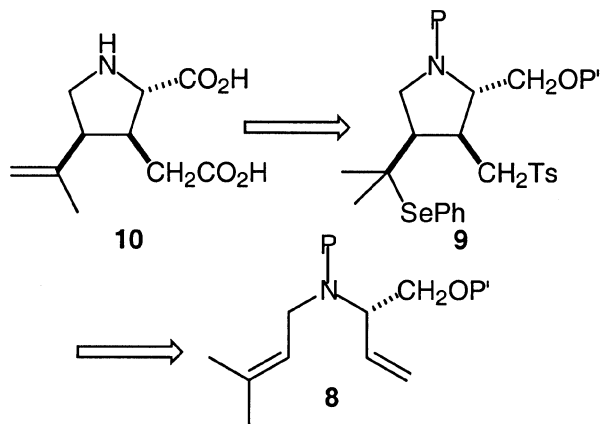
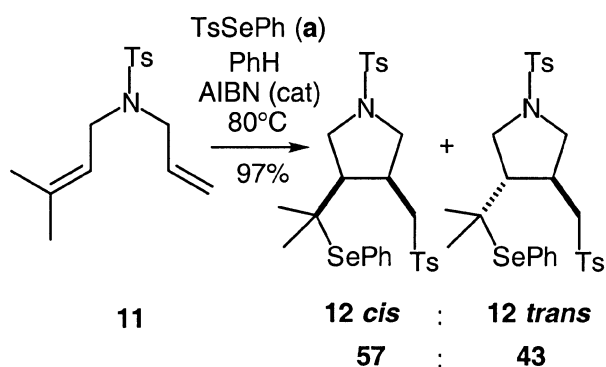


Fig. 6. Retrosynthetic analysis of kainic acids.

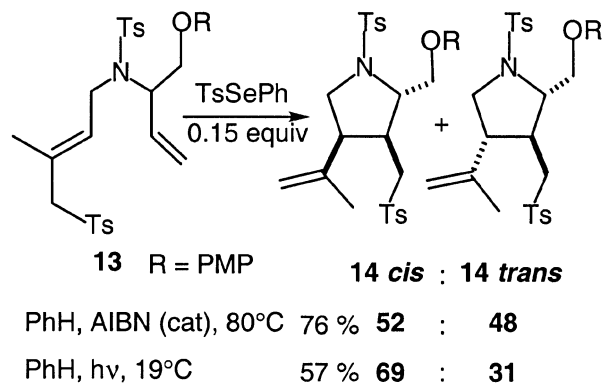
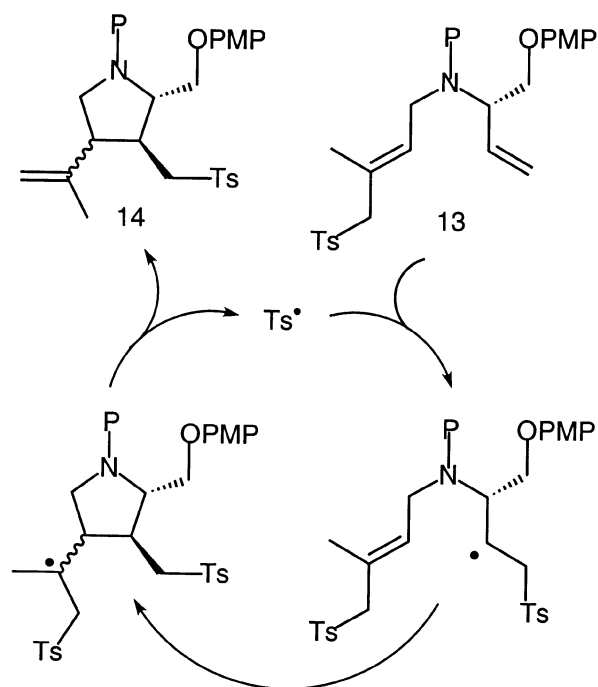
Fig. 7. Addition of TsSePh to **11**.

tiary phenyl selenides, were unstable under these experimental conditions.

Furthermore, when treated with  $\text{H}_2\text{O}_2$  at  $0^\circ\text{C}$ , only the trans isomer gave a regioselective oxidative elimination allowing the introduction of the isopropenyl group. The cis isomer led predominantly to the tetra-substituted double bond. It was necessary to revise completely our strategy, and to find a procedure in which the elimination step would be avoided. As shown in Fig. 8, the solution resides in carrying out the radical rearrangement of sulfone **13**.

The reaction led to a mixture of diastereomers with, as expected, a total control of the stereochemistry regarding the carbons 2 and 3 of the pyrrolidine ring. No stereoselectivity was observed as concerned with the substituents at positions 3 and 4. A 69:31 ratio, in favour of the cis isomer, could be reached by performing the reaction at lower temperature, under photochemical initiation. The mechanism of this transformation is summarised in Fig. 9.

The procedure takes advantage of the reversibility of the addition of tosyl radical to double bonds. Tosyl radical, which is the chain carrier, adds selectively to the terminal double bond. This leads to a carbon-centred radical, which undergoes 5-exo ring closure.

Fig. 8. Addition of TsSePh to **13**.Fig. 9. Mechanism of the rearrangement of sulfone **13**.

This step determines the diastereoselectivity. It generates a  $\beta$ -sulfonylated radical, which undergoes  $\beta$ -fragmentation. Thus, the last step of the cascade process generates the expected product and regenerates tosyl radical. The transformation of **14-cis** into  $\alpha$ -kainic acid was later achieved in six steps by Japanese workers [20, 21] who demonstrated the viability of the strategy.

### 2.3. Influence of nitrogen quaternisation or complexation with Lewis acids

According to the models developed by Beckwith and Houk [17–19], each stereomer can originate from two transition states: one chair conformer, and one boat conformer. A rapid examination of the transition structures leads to the prediction that, in the case of cyclisations leading to 3,4-disubstituted pyrrolidines, the presence of an additional substituent (an alkyl group in quaternary ammonium salts, or alternatively a Lewis acid in an acid-base complex) should enhance the diastereomeric ratio in favour of the cis isomer. As shown in Fig. 10, this should decrease the contribution of boat transition structures, and favour the one chair transition state that bears the substituent on the radical centre in a pseudo-equatorial position, i.e. C1 [22, 23].

The addition of TsSePh to amine **15** led to a mixture of cis and trans adducts in a 78:22 ratio when the reaction was photoinitiated at  $19^\circ\text{C}$  (cf. Fig. 11, conditions **a**). The quaternisation induces an approximate

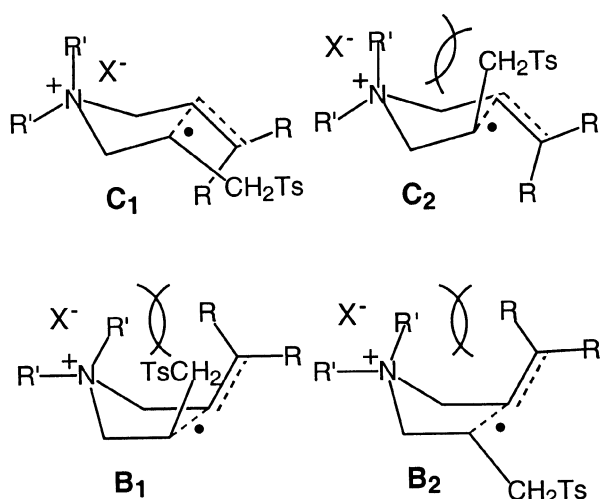
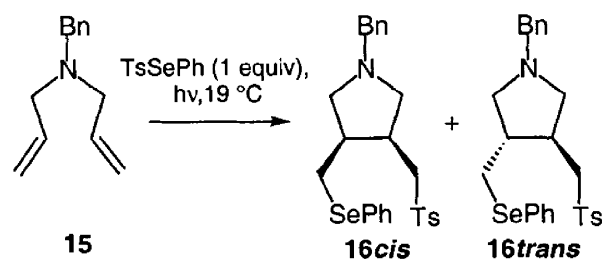


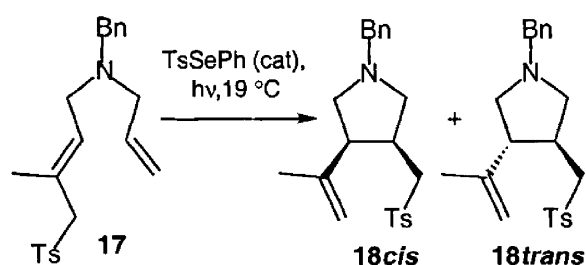
Fig. 10. Transition structures for cyclisations leading to 3,4-disubstituted pyrrolidines.

20% increase of the diastereomeric excess (cf. Fig. 11, conditions **b**). In the case of the rearrangement of amine **17**, the diastereomeric ratio was far lower. It was 41:59 (thus in favour of the *trans* isomer) at 19 °C under standard conditions (conditions **a**). When the reaction was performed on the corresponding quaternary ammonium salt, the selectivity was reversed, the *cis* isomer becoming the major adduct (conditions **b**). The major drawback of the procedure is that it necessitates two additional ionic steps, i.e. the quaternisation with benzyl tosylate, and the dequaternisation via reduction by NaBH<sub>4</sub> subsequent to the radical reaction.



Conditions	Yield %	<i>cis</i> : <i>trans</i>
<b>a</b>	55	78 : 22
<b>b</b>	27 (3 steps)	87 : 13
<b>c</b>	66	80 : 20
<b>d</b>	53	88 : 12

**a** : in benzene. **b** : (i) Bn-OTs (67%); (ii) TsSePh in CH<sub>3</sub>CN, hv, 19 °C; (iii) NaBH<sub>4</sub>, *i*-PrOH, reflux (40% for the 2 steps).  
**c** : in CH<sub>2</sub>Cl<sub>2</sub> + BF<sub>3</sub>•Et<sub>2</sub>O (1 equiv.).  
**d** : (i) BH<sub>3</sub>•SMe<sub>2</sub> (1 equiv.) then TsSePh in CH<sub>2</sub>Cl<sub>2</sub>, hv, 19 °C; (ii) HCl 6N, MeOH, reflux.



Conditions	Yield %	<i>cis</i> : <i>trans</i>
<b>a</b>	41	41 : 59
<b>b</b>	40 (3 steps)	64 : 36
<b>c</b>	55	73 : 27
<b>d</b>	60	62 : 38

**a** : in benzene. **b** : (i) Bn-OTs (81%); (ii) TsSePh (cat) in CH<sub>3</sub>CN, hv, 19 °C; (iii) NaBH<sub>4</sub>, *i*-PrOH, reflux (50% for the 2 steps).  
**c** : in CH<sub>2</sub>Cl<sub>2</sub> + BF<sub>3</sub>•Et<sub>2</sub>O (1 equiv.).  
**d** : (i) BH<sub>3</sub>•SMe<sub>2</sub> (1 equiv.) then TsSePh (cat) in CH<sub>2</sub>Cl<sub>2</sub>, hv, 19 °C; (ii) HCl 6N, MeOH, reflux.

The same effects could be obtained in one step through complexation of the amine with a Lewis acid [23]. The results are reported in Fig. 11 (conditions **c** or **d**). They strongly suggest that the Lewis acid occupies a pseudo-axial position in the transition structures; otherwise, its effects would be similar to quaternisation in all cases. It must be noted that complexation with BF<sub>3</sub> gave results more or less similar to quaternisation in the case of **17**, where the double bond, which plays the role of the radical acceptor in the cyclisation step, is trisubstituted. In the case of **15**, where the double bond is terminal, it was necessary to use a Lewis acid more strongly associated to nitrogen atom i.e., BH<sub>3</sub> with N–B bond length comparable to the N–C bond in quaternary ammonium salts (1.66 Å in amine–borane complex, versus 1.50 Å in ammonium salts) to observe an increase of the diastereomeric ratio.

### 3. A new method of cleavage of allylic amines mediated with thiyl radicals

The above-mentioned studies concerning the synthesis of nitrogen-containing heterocycles led us to study the radical addition of PhSH to bis-allylic amines, and to discover an unexpected reaction, namely the selective cleavage of allylic C–N bonds [24]. Mechanistic investigations point to the following mechanism, exemplified in Fig. 12 on the glycine derivative **19**: the thiyl radical promotes the isomerisation of allylic amines into enamines via two consecutive hydrogen-

Fig. 11. Compared effects of quaternisation and complexation with a Lewis acid upon the diastereoselectivity.

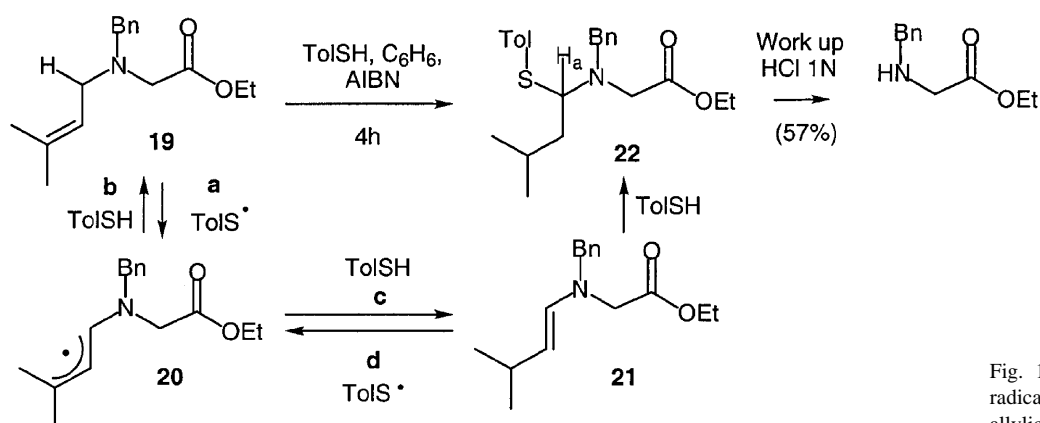


Fig. 12. Mechanism of the thiyl radical mediated cleavage of allylic amines.

atom abstraction steps. Thiyl radical abstracts the allylic hydrogen atom, which leads to radical **20**. The delocalised radical transfers back a hydrogen atom from thiocresol to give the enamine **21**. Both reactions **a** and **c** are formally reversible. The equilibrium is displaced due to the ready addition of the thiol to the enamine. In agreement with this proposal, the more acidic the thiol, the faster the reaction. Thus, the subsequent polar addition of the corresponding thiol to the enamine results in the cleavage of the C–N bond via the hydrolysis of the thioaminal intermediate.

It is to be noted that the hydrogen atom transfer between the electron rich C–H bond in **19** and the electrophilic thiyl radical is favoured on the ground of polar effects. The same assumption applies to step **c**, where the hydrogen atom is transferred from the thiol (acting as a ‘protic’ hydrogen atom donor [25–26]) to the nucleophilic carbon-centred radical.

This reaction provides a mild, metal-free methodology for the deprotection of N-allylated primary and secondary amines. It can be generalised to different types of allylic amines, with the exception of anilines

(Fig. 13). With regards to other limits, it must be noted that the cleavage does not take place when the nitrogen atom bears an electron-withdrawing group like Ts or Boc.

It is worth noting that a RCH<sub>2</sub>–N bond can be cleaved selectively in the presence of a RR’CH–N bond, as demonstrated by the reaction conducted on amines **23a,b** (Fig. 14).

The only products isolated, in 70 and 65% respectively, were amines **24a** and **24b**, resulting from the cleavage of the primary allylic C–N bond. No trace of any cyclisation product was detected. It is noteworthy that the amine **25** that would result from the cleavage of the second allylic C–N bond was not formed either.

The chemoselectivity can be ascribed to stereoelectronic. The preferred conformations are shown in Fig. 15. The C<sub>tert</sub>–H bond lies in the plane of the double bond. A 90° rotation around the C–N bond is necessary to reach a conformation favourable to hydrogen abstraction. On the contrary, there is always a C–H bond suitably oriented for the hydrogen atom to be abstracted from the prenyl chain. However, the

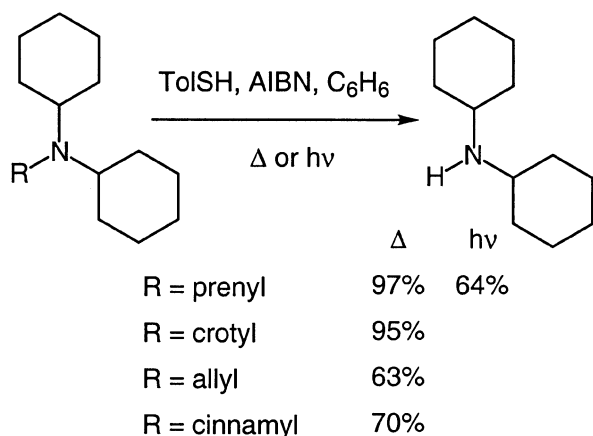


Fig. 13. Generalisation to different types of allylic amines.

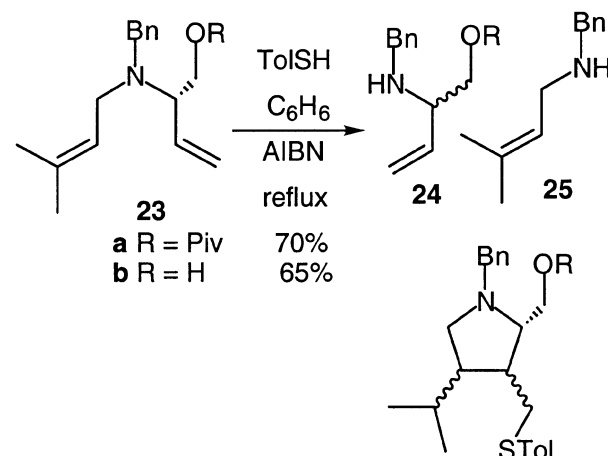


Fig. 14. Thiocresol-mediated cleavage of **23**.

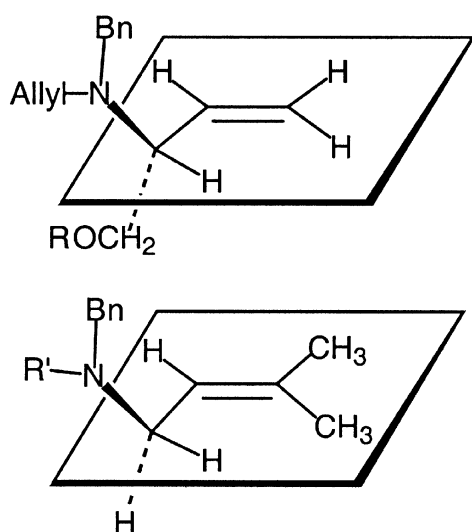


Fig. 15. Preferred conformations around the C=N bonds.

C–H bond dissociation energy is lower in the case of the tertiary allylic radical.

#### 4. Triethylborane and diethylzinc mediated radical addition to C=N bond

There is still a considerable demand for more efficient chiral amines and amino acids, and mild methodologies for preparing them. The additions of organometallics and enolates to imines are among the most widely explored strategies [27–30]. However, these reactions often suffer from limitations inherent to the low reactivity of the C=N bond, compared to the carbonyl group, and to the tendency of enolisable imines to undergo deprotonation rather than addition. Intermolecular radical additions to C=N bonds, conducted under neutral conditions, offer a mild alternative to the carbanionic reactions. However, at the very beginning of our study, very few examples had been reported in the literature [31–32].

##### 4.1. Additions to $\alpha$ -imino esters derived from 1-phenylethylamine

We started investigating triethylborane/oxygen-mediated additions to glyoxylate imines bearing a stereogenic N-substituent in order to evaluate the potential of the radical methodology regarding 1,3-stereoselection. In addition to the preparative interest of such a reaction, the choice of  $\alpha$ -imino esters as substrates was based on the assumption that the electronic effect of the carboxylic function should dramatically enhance the reactivity of the C=N bond with respect to nucleophilic alkyl radicals. The reaction was then extended to glyoxylic oxime ethers and hydrazones.

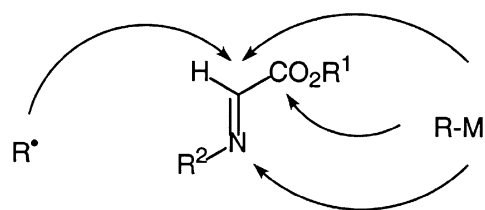


Fig. 16. Regioselectivity of radical and nucleophilic additions to glyoxylate imines.

The reaction of organometallics with glyoxylic imines suffer from the problem of chemo- and regioselectivity, since there are three possible electrophilic centres (Fig. 16). Preferential attack at nitrogen occurs with organometallic species like Grignards [33], and organozinc (under strictly anaerobic conditions) [34–36], whereas allylmetal derivatives (the most successful ones) give rise to the formation of a C–C bond [27–30, 34–36]. Radical addition results exclusively in C–C bond formation, within a few intramolecular exceptions, which are rather classified as *nitrogen-philic cyclisations* [32].

We very soon recognised that these reactions did not require the use of toxic tin reagents to form the alkyl radicals [37, 38]. As shown in Fig. 17, triethylborane plays a triple role in the procedure. By reacting with oxygen, it initiates the formation of an ethyl radical, which undergoes iodine atom transfer from an alkyl iodide to form the desired alkyl radical. The basic nitrogen of imines is an acceptor for Lewis acids; its complexation to triethylborane enhances the electrophilicity of the C=N bond with respect to the addition of the nucleophilic alkyl radical. Heteroatomic radicals are known to give  $S_H2$  reactions at boron [39, 40]. So does the ensuing nitrogen-centred radical during the addition step; therefore, triethylborane also acts as the chain transfer agent.  $Et^{\bullet}$  is regenerated during the last step. Since the addition of ethyl radical to the imine competes with the addition of  $R^{\bullet}$ , it is necessary to use an excess of alkyl iodide to

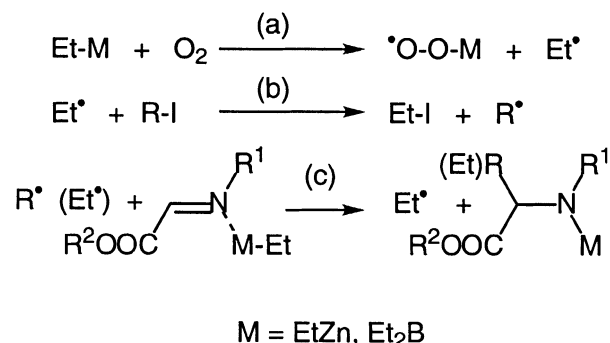


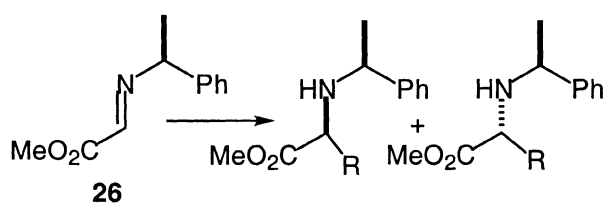
Fig. 17. General mechanism of  $\text{Et}_3\text{B}$ - and  $\text{Et}_2\text{Zn}$ -mediated radical addition to the C=N bond.

avoid this undesired reaction. This is a limit to the generalisation of the procedure to primary alkyl radicals, for which the thermoneutral step (b) is slow.

Owing to its fast reaction with oxygen, diethylzinc was recently recognised as an efficient radical initiator [41]. We have shown that it could advantageously replace triethylborane in the above reactions.

We started our study with imine **26** derived from 1-phenylethylamine. The auxiliary is commercially available in both enantiomeric forms, and can be easily removed by hydrogenolysis. Selected results are given in Fig. 18.

It can be noticed that the selectivity registered with triethyl borane is rather low (conditions (ii)). Not surprisingly, it increases with the bulk of the attacking radical. Furthermore, it is very close to that observed when tin methodology was used (conditions (i)). This points to the proposal that complexation with triethylborane does not change the nature of the reactive conformer of the imine. It is also worth noting that the diethylzinc-mediated reactions follow the opposite sense of asymmetric induction (conditions (iii)). Similar observations, leading to the conclusion that the same auxiliary may lead to opposite stereoselectivities depending on the nature of the nucleophilic reagent, have been reported for the addition of organometallics to imines [30].



RI		Yield (%)	<i>l</i> - <b>27</b>	<i>u</i> - <b>27</b>
EtI	(i)	67	58	42
none	(ii)	56	60	40
<i>c</i> -C <sub>6</sub> H <sub>11</sub> I	(ii)(-78 °C)	63	61	39
<i>t</i> -Bul	(ii)	48	70	30
none	(iii) (20 °C)	49	50	50
<i>t</i> -Bul	(iii)	66	40	60

(ii) RI (6 eq.); HSnBu<sub>3</sub> (2 eq.); AIBN (0.2 eq.); 80 °C  
**1** (0.2 M solution in PhH).

(ii) RI (none, or 6 eq.); Et<sub>3</sub>B (3 eq.); -40 °C  
**1** (0.2 M solution in CH<sub>2</sub>Cl<sub>2</sub>), air.

(iii) RI (none, or 6 eq.); Et<sub>2</sub>Zn (2 eq.); -40 °C  
**1** (0.2 M solution in CH<sub>2</sub>Cl<sub>2</sub>), air.

Fig. 18. 1,3-Stereinduction with 1-phenylethylamine as the auxiliary.

By analogy with polar reactions, and assuming a substrate-controlled stereinduction, several models can be considered for a tentative rationalization of these results. They are shown in Figs. 19 and 20, using the (*S*) configuration of the auxiliary.

The Felkin-type model (**A**) does not account for the preferential formation of the *like* isomer: it can easily be discarded. The Yamamoto proposals, in the absence (**B**) or in the presence of a Lewis acid (**C**), is in agreement with the experimental results. However, one would expect a much higher degree of differentiation between the less hindered *si* face and the *re* face. We propose that conformer **D**, which is the lowest energy conformer of the imine, due to the minimisation of 2-aza-A<sup>1,3</sup>-strain, is likely to account more satisfactorily for the selectivity observed in the cases of tin-mediated reactions, and therefore Et<sub>3</sub>B-mediated reactions would be accounted for by a LA/H-eclipsed model (**E**). Of course, this can only be valid if the phenyl group is oriented in such a manner that its steric bulk is less than that of the methyl group. This is not unprecedented in the literature.

According to Savoia [30], an alternative, and completely opposite, explanation can be considered. Depending on its nature, the Lewis acid would lead either to a H-eclipsed conformer (**E**) (with preferential attack of the nucleophile on the same side as the methyl group) or, to a conformation of type **F**, where the 'metal' eclipses the hydrogen atom (with still preferential attack on the same side as the methyl group). The latter would also account for the preferential formation of the *like* isomer, and one would predict a rather low diastereomeric excess.

The interpretation of Et<sub>2</sub>Zn-mediated additions follows from the observed opposite stereinduction. In this case, the Lewis acid is bidentate, the chelation must necessarily change the conformation around the C–N bond of the auxiliary (Fig. 20). Thus, if the conformation **E**, with preferential *si* face attack, were responsible for the selectivity of Et<sub>3</sub>B-mediated reactions, then a metal-eclipsed chelate **G** (Fig. 19), with preferential *re* face attack, should be preferred in the zinc-mediated ones. Of course, conversely, if the Savoia model were to be valid, then the H-eclipsed chelate **H**, with preferential attack at the *re* face, would account for the experimental selectivity in this case.

Clearly, unless reliable calculations of the complexes are carried out, it will be difficult to conclude. Our preference for models **D**, **E**, and **G** for the tin-, boron-, and zinc-mediated reactions respectively, is based essentially on the similarity of experimental results under conditions (i) and (ii), and on the lower selectivity noted under conditions (iii) as compared to conditions (ii) (cf. Fig. 18).



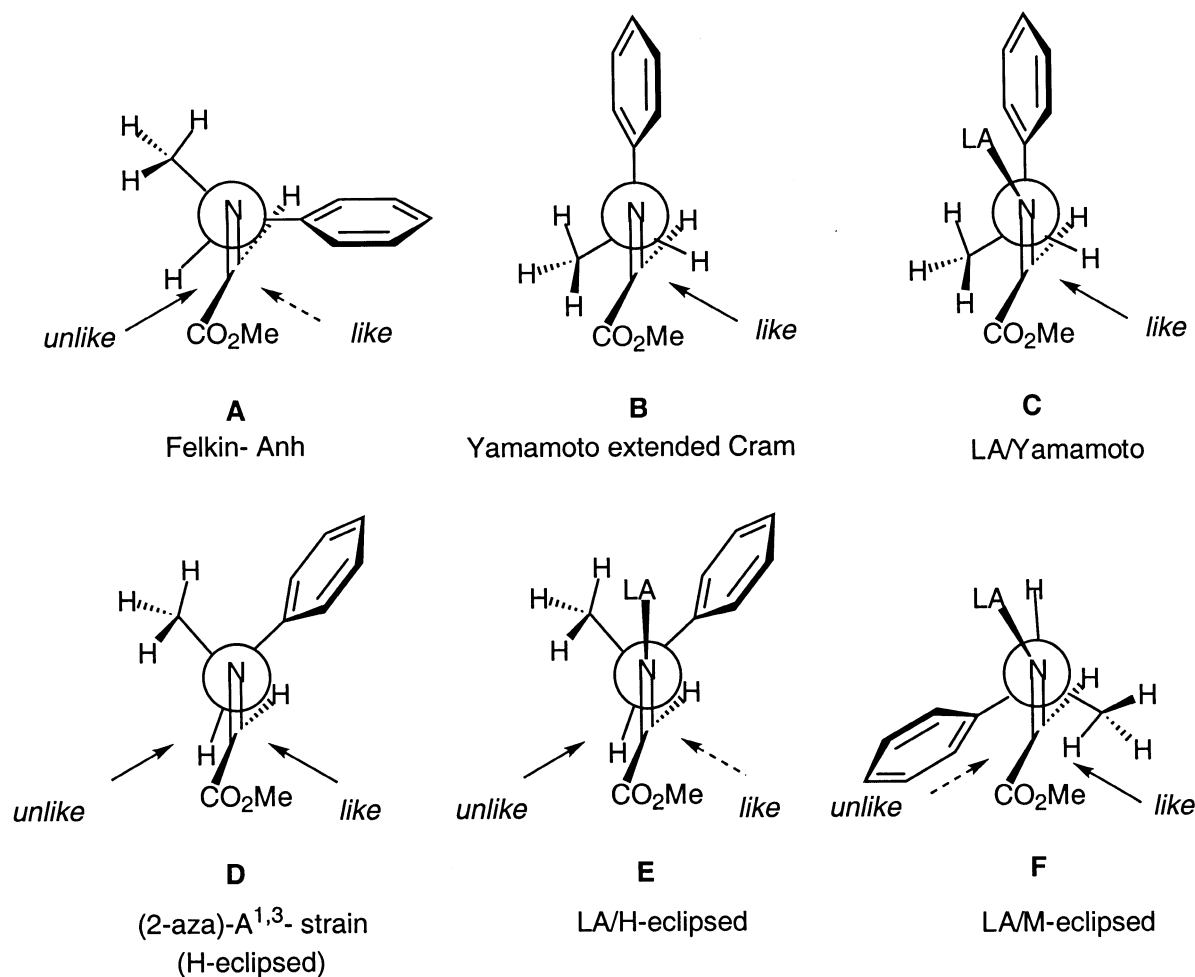


Fig. 19. Models for 1,3-stereoselection.

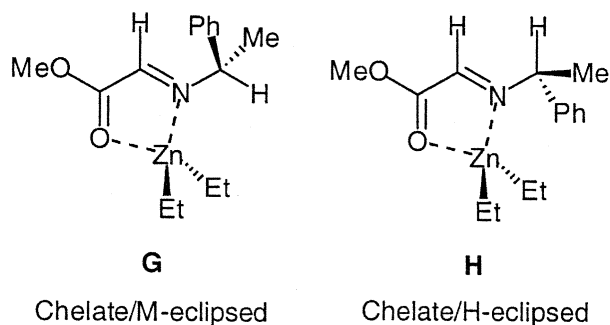


Fig. 20. Models for 1,3-stereoselection with Et<sub>2</sub>Zn.

#### 4.2. Additions to $\alpha$ -imino esters derived from *O*-substituted $\beta$ -aminoalcohols

*O*-Protected derivatives of  $\beta$ -amino alcohols, prepared from natural  $\alpha$ -amino acids like valinol and phenyl glycinol, and norephedrine, have frequently been used as chiral auxiliaries in the addition of organometallics to imines [27–30]. Our studies were naturally extended to the corresponding glyoxylic imines [37, 38, 42].

##### 4.2.1. Cyclic derivatives

Our first attempts to increase the diastereomeric excess of radical additions to the imino group of glyoxylic derivatives led us to perform the reactions on more rigid substrates [37]. For this purpose, we prepared dihydro-1,4-oxazin-2-ones (**29a,b**) via the oxidative rearrangement of oxazolines (**28a,b**), according to the literature (Fig. 21).

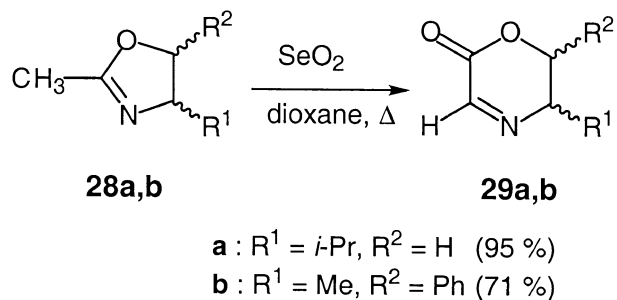


Fig. 21. Synthesis of cyclic glyoxylate imines.

Entry	Substrate	R	Yield (%)	d.r.	R	Yield (%)	d.r.
a	29a	Bu	(i) 59	58:42	-	-	-
b		c-C <sub>6</sub> H <sub>11</sub>	(i) 62	60:40	-	-	-
c		t-Bu	(i) 51	55:45	-	-	-
d	29b	Bu	(i) 45	75:25	-	-	-
e		c-C <sub>6</sub> H <sub>11</sub>	(i) 47	85:15	-	-	-
f		c-C <sub>6</sub> H <sub>11</sub>	(ii) 27	90:10	Et	(ii) 25	75:25
g		t-Bu	(i) 41	87:13	-	-	-
h	t-Bu	(ii) 25	> 99:1	Et	(ii) 25	75:25	

(i) RI (0.95 eq.); Bu<sub>3</sub>SnH (1.05 eq.); AIBN (0.2 eq.); 80 °C; 4 (0.2 M solution in benzene). (ii) RI (6 eq.); Et<sub>3</sub>B (3 eq.); -40 °C; 4 (0.2 M solution in CH<sub>2</sub>Cl<sub>2</sub>).

Fig. 22. Additions to dihydro-1,4-oxazin-2-ones.

Little was known about the reactivity of cyclic glyoxylate imines towards nucleophiles [43], nothing was known about their reactivity with respect to radicals. The results of radical additions carried out under various experimental conditions are given in Fig. 22.

With compound **29a**, 1,3-stereoselection did not reach a high level under tin-mediated conditions (entries a–c); it was more or less the same as in the acyclic series. When the disubstituted oxazinone **29b** was submitted to the same experimental conditions, the diastereomeric excess was strongly increased (entries d, e, g). Higher diastereomeric ratios were observed when triethylborane was used as the mediator. However, due to the greater reactivity of the substrate, compared to the preceding open-chain imine, in all cases the product resulting from the addition of ethyl radical was formed in equal amount with respect to the addition of R• (entries f, h). Thus, the methodology presented little preparative interest, unless large

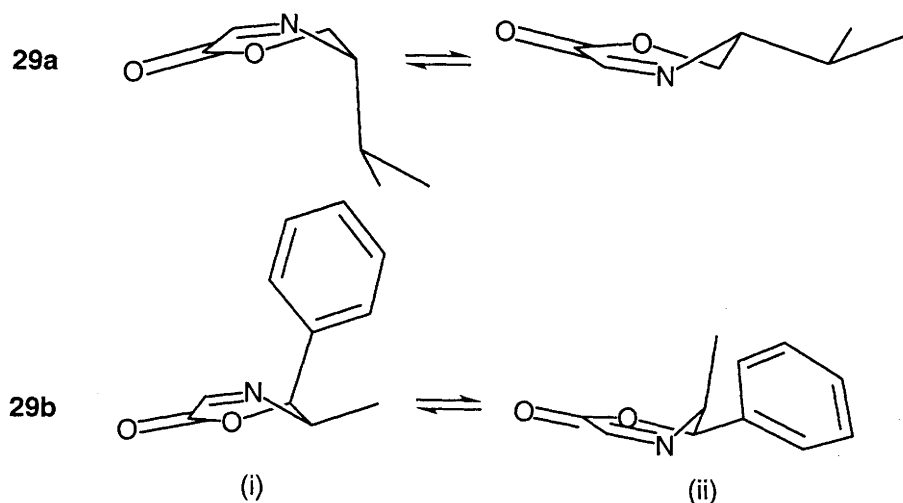
excesses of alkyl iodide were introduced in the reaction medium.

According to calculations conducted with the *GenMol* program, the energy difference between the two conformers of **29a** would be as low as 0.1 kcal mol<sup>-1</sup>. This explains the lack of facial selectivity in this case.

The preferred conformation of **29b** is (ii), where the methyl group is pseudo-axial and the phenyl group is equatorial (the calculated energy difference between the two conformers is 0.9 kcal mol<sup>-1</sup>). If one assumes a substrate-controlled diastereoselection, then, whatever the conformer of **29b** being attacked by the radical, either the methyl (ii) or the phenyl group (i) should hinder approach from the upper face (Fig. 23).

#### 4.2.2. Open-chain derivatives

Zinc-mediated additions to compounds **29** gave even poorer results. We moved to analogous acyclic substrates bearing an auxiliary likely to form a chelate

Fig. 23. Conformational equilibrium of imines **29a** and **29b**.

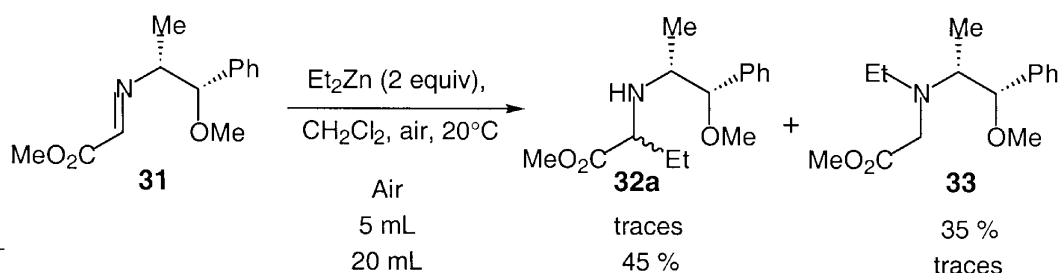


Fig. 24. Diethylzinc addition to **31**.

with the bidentate zinc reagent [38, 42]. The case of imine **31**, derived from the O-methylated norephedrine, will be discussed in detail. The results obtained using diethylzinc alone are reported in Fig. 24.

The regioselectivity clearly depends on the amount of air injected in the reaction medium, owing to the competition between the radical and the nucleophilic pathways. Under our standard experimental conditions, in the presence of air, **31** led to the iminoester **33** as the major product. The iminoester **32a** resulting from the formation of a C–C bond was formed in trace amount. When the reaction was conducted in the presence of a larger amount of oxygen, the ratio of the two regioisomers was completely reversed.

This can be rationalised according to Fig. 25. Imine **31** can form two different chelates with diethylzinc. Owing to steric repulsions between the phenyl and the methyl groups in **A**, the equilibrium is shifted towards **B**, for which the rate of the nucleophilic attack on nitrogen leading to the zinc enolate **33** is greatly increased. A higher stationary concentration of ethyl radical is necessary for the radical pathway leading to

**32a** to be predominant. Both conformers lead to preferential attack of  $\text{Et}^\bullet$  at the *re* face.

This is no longer the case in the presence of an alkyl iodide. In all likelihood, the rate of the radical pathway is accelerated by enhancing the nucleophilic character of the radical going from a primary, to a secondary, or a tertiary radical. The diastereomeric excess increases with the bulk of the radical. It is very high for the addition of *t*-Bu $^\bullet$ . As shown in Fig. 26, the iminoester **32b** was formed in 71% yield, as a 95:5 mixture of diastereomers, when the reaction was conducted at  $-78^\circ\text{C}$  in the presence of 5 ml of air.

It must be noted that the  $\text{Et}_3\text{B}$ -mediated reactions carried out on **31** led, as mentioned above, to the opposite stereoinduction, although the diastereomeric ratios were lower (d.r. = 58:42 instead of 66:34, for the addition of  $\text{Et}^\bullet$  at  $20^\circ\text{C}$ ). This is in agreement with the models proposed in Fig. 27.

Experiments were also conducted with the imines derived from *O*-methyl phenylglycinol (**34**) and

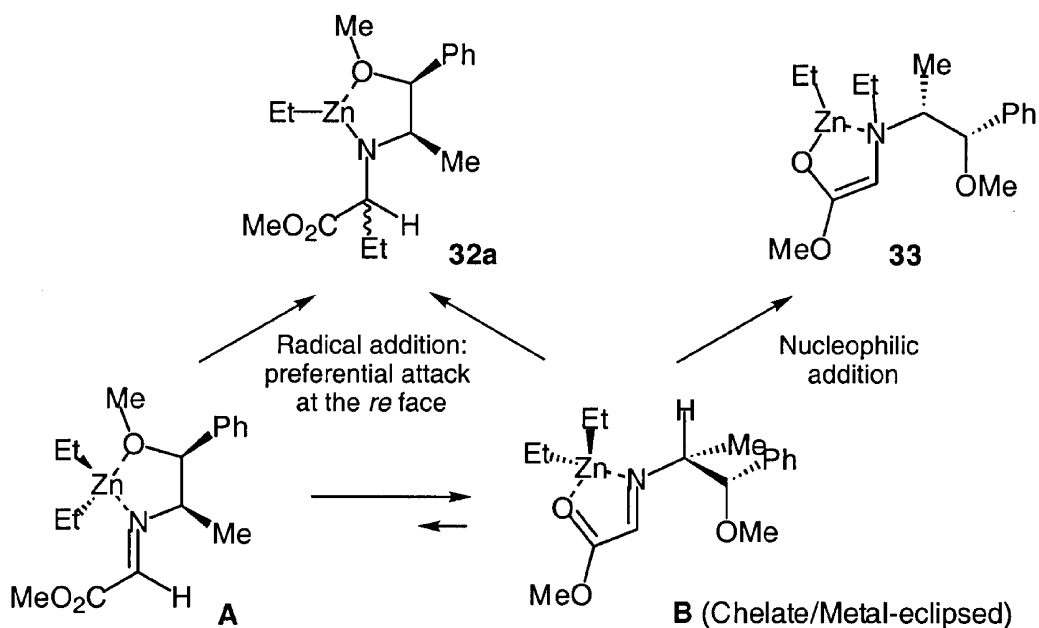
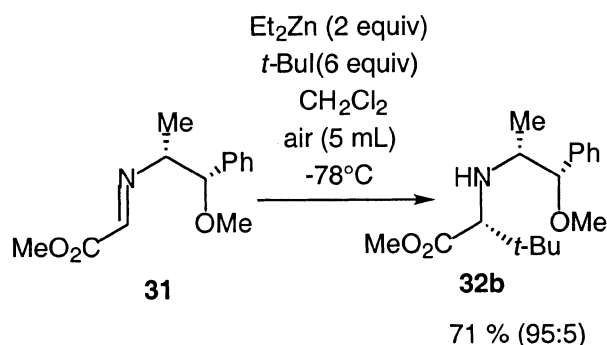
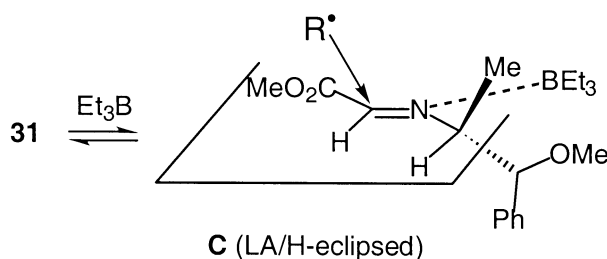


Fig. 25. Stereochemical models for zinc-mediated addition to imine **31**.

Fig. 26. Zinc-mediated addition of *t*-Butyl radical to **31**.Fig. 27. Stereochemical model for boron-mediated radical additions to **31**.

*O*-methyl valinol (**36**), which led to adducts **35** and **37**, respectively. Selected data are reported in Fig. 28.

Several observations must be underlined. First, the diethylzinc-mediated reactions gave generally far better yields, provided that the reactions are conducted at low temperature. At the same time, they led to much higher selectivities. It can also be underlined that the two reagents led once again to opposite stereoinductions in the case of **34**, whereas 1,3-stereoinduction followed the same sense for both reagents in the case of **36**. These results can be rationalised on the basis of the models proposed in Figs. 29 and 30.

Imine **34** can lead to three types of complexes depending on the nature of the mediator (Fig. 29). Let us consider first the case of zinc-mediated addition. The equilibrium between the two possible chelates is shifted in this case towards chelate **B**, owing to the enhanced basicity of the ether as compared to the carbonyl. Preferential attack of the radical occurs at the *re* face. If one admits conformation **A** as the preferred conformation in the case of  $\text{Et}_3\text{B}$ -mediated addition, and a little less sterically hindered *si* face (shielded by the phenyl group), then as with imine **36**, one could account for a slight preference of the formation of the *unlike* isomer (Fig. 28, conditions (i)).

As shown in Fig. 30, both the LA/H-eclipsed complex **A** and the chelate **C** account for preferential attack of the radical at the *si* face. This explains why stereoinduction follows the same sense whatever the

experimental conditions in the case of imine **36**. The LA/Metal eclipsed complex **B** has probably a very low contribution.

In conclusion, 1,3-stereoinduction in radical additions to glyoxylic imines bearing the same chiral *N*-substituent, and carried out in the presence of Lewis acids cannot be predicted by a single stereochemical model. The conformation around the C–N bond strongly depends on whether the substrate is chelated or not.

#### 4.3. Double stereoinduction

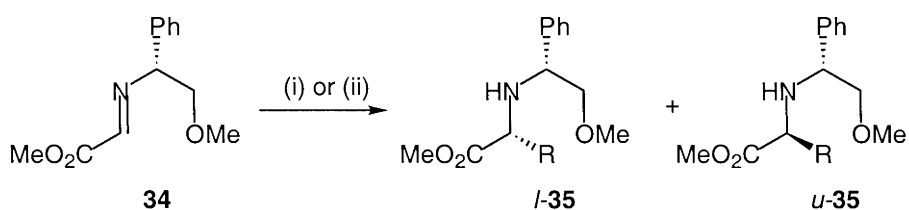
Continuing on the road of drawing a parallel with nucleophilic additions, we have also investigated the influence of a double stereoinduction on the diastereoselectivity of the reaction [44]. Since (–)-menthylglyoxylate is commercially available, we selected the imines derived from (*R*)- and (*S*)-1-phenylethylamine as the substrates for these studies. The results for the addition of *t*-Bu $^\bullet$  are given in Fig. 31.

Although the diastereomeric ratio is slightly higher in the case of **38**, it can be noted that stereoinduction follows the same sense for both diastereomeric imines. The new stereogenic centre has predominantly a (*S*) configuration.

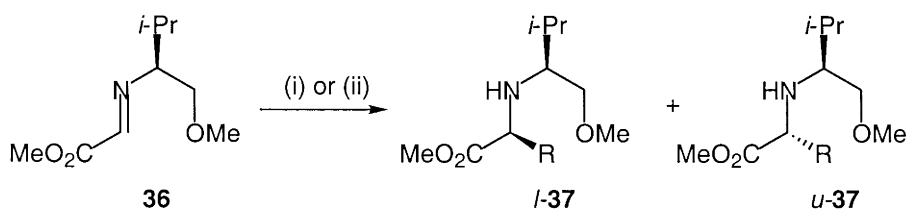
This can only be interpreted if one considers that the influence of menthol incorporated to the ester function outweighs the effect of the *N*-substituent, with a better match between the two auxiliaries in the case of **38**. This is again in agreement with the preference for metal-eclipsed chelate conformer. The results can thus be rationalised according to the conformations in Fig. 32, where, whatever the conformation around the C–N bond, the *re* face is more shielded by the menthyl group than the *si* face. These results are similar to the results of the addition of organometallics to the same substrates [45].

#### 4.4. Extension to oxime ethers and hydrazones

The zinc- and boron-mediated procedures can be extended to oxime ethers and hydrazones, as exemplified in Fig. 33 [46]. The yields are in all cases higher than those reported for imines. The major drawback of the enhanced reactivity is that the competition between the addition of a secondary or a tertiary radical, and the addition of ethyl radical is more severe than in the case of the imines. Thus, a larger excess of alkyl iodide is needed for the reaction to become chemoselective. For the sake of comparison, the experiments have been conducted under experimental conditions strictly similar to the previous ones.



Substrate	RI	Conditions	Yield (%)	<i>l</i> -35	:	<i>u</i> -35
<b>34</b>	none	(i)	72	41	:	59
<b>34</b>	<i>t</i> -Bul	(i)	48	42	:	58
<b>34</b>	none	(ii)	40	62	:	38
<b>34</b>	none	(ii)(- 40 °C)	62	69	:	31
<b>34</b>	<i>t</i> -Bul	(ii)	43	70	:	30
<b>34</b>	<i>t</i> -Bul	(ii)(- 40 °C)	66	77	:	23



Substrate	RI	Conditions	Yield (%)	<i>l</i> -37	:	<i>u</i> -37
<b>36</b>	none	(i)	39	56	:	44
<b>36</b>	<i>t</i> -Bul	(i)	42	55	:	45
<b>36</b>	none	(ii)(- 40 °C)	70	85	:	15
<b>36</b>	<i>t</i> -Bul	(ii) (- 40 °C)	67	92	:	8

(i) RI (none, or 6 eq.); Et<sub>3</sub>B (3 eq.); 20 °C; **1** (0.2 M solution in CH<sub>2</sub>Cl<sub>2</sub>), air.  
 (ii) RI (none, or 6 eq.); Et<sub>2</sub>Zn (2 eq.); 20, or - 40 °C; **1** (0.2 M solution in CH<sub>2</sub>Cl<sub>2</sub>), air.

Fig. 28. Compared stereoinductions for Et<sub>3</sub>B- and Et<sub>2</sub>Zn-mediated additions to imines **34** and **36**.

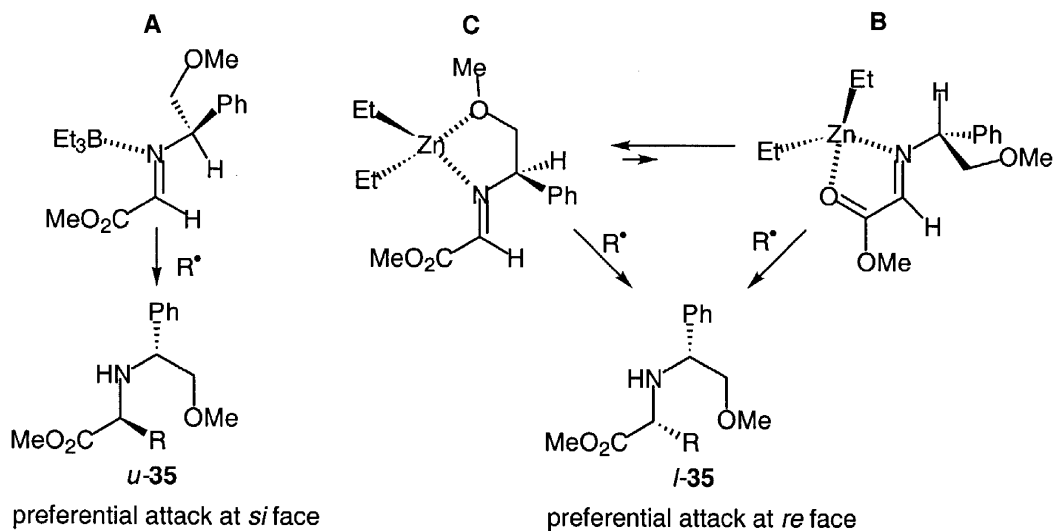


Fig. 29. Models accounting for stereoinduction in the case of imine **34**.

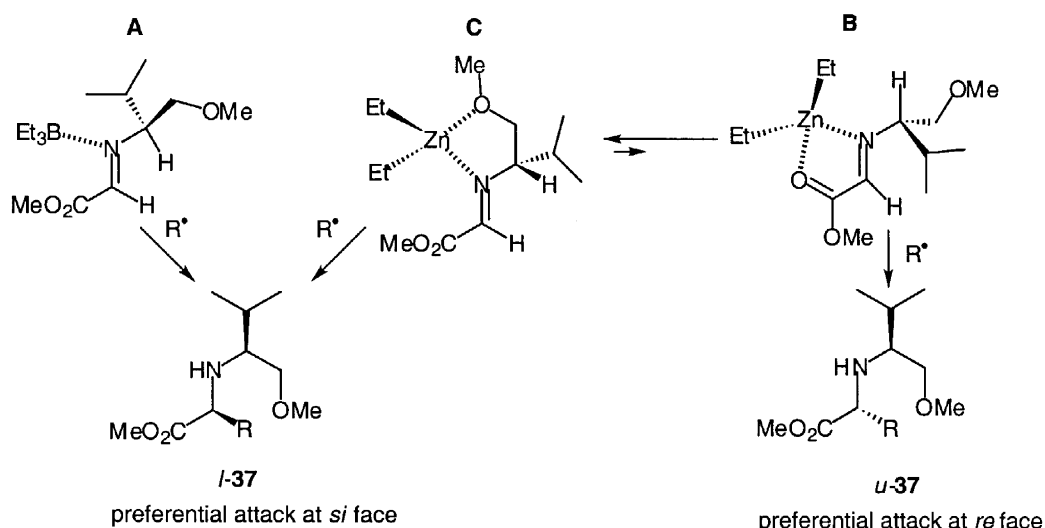


Fig. 30. Models accounting for stereoselection in the case of imine **36**.

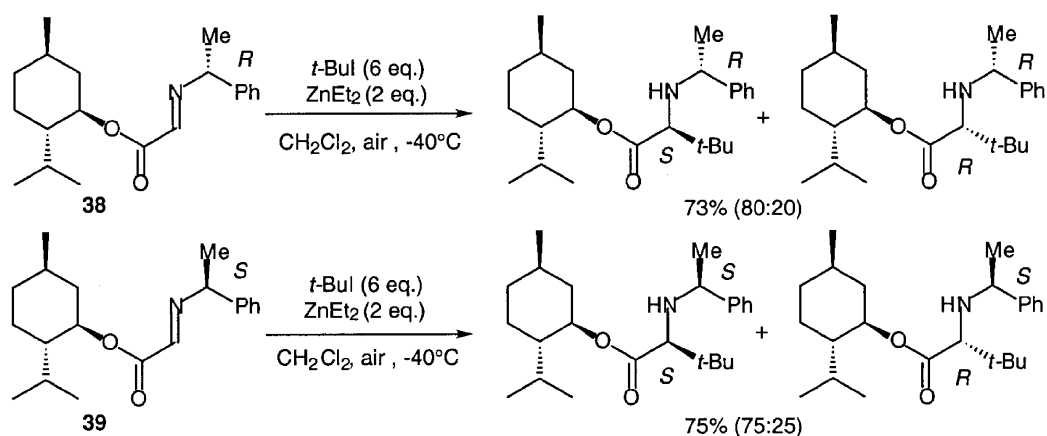


Fig. 31. Diethylzinc-mediated additions of  $t\text{-Bu}^\bullet$  to (–)-menthylglyoxylic imines **38** and **39**.

## 5. Diethylzinc-mediated conjugated radical additions

Since the pioneering work of Brown, boranes are well known to give rise to radical conjugated additions to enones [47–49]. It was tempting to investigate the behaviour of diethylzinc regarding these substrates. The results obtained with cyclohexenone are reported in Fig. 34 [46].

The mechanism can be rationalised as shown in Fig. 35. The proposal is very similar to the mechanism reported by Brown for the addition of boranes. Two events may be considered, the addition of the alkyl radical can take place either at the complexed enone or at the uncomplexed substrate. In both cases, the enoxyl radical undergoes homolytic substitution at zinc.

It must be noted that the reaction cannot be extrapolated to other types of Michael acceptors such as acrylates, which do not react under these condi-

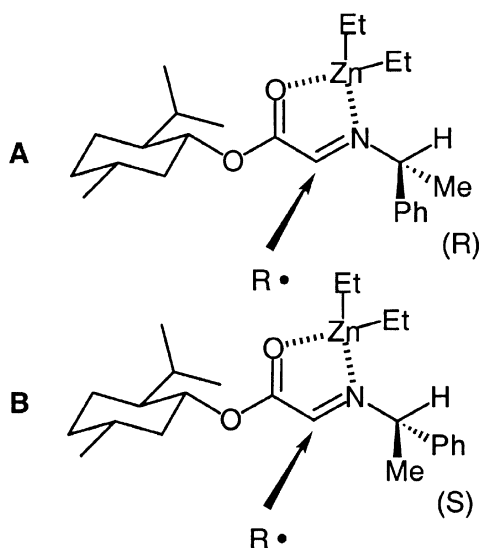


Fig. 32. Rationale for stereoselection in the addition to imines derived from (–)-menthylglyoxylate.

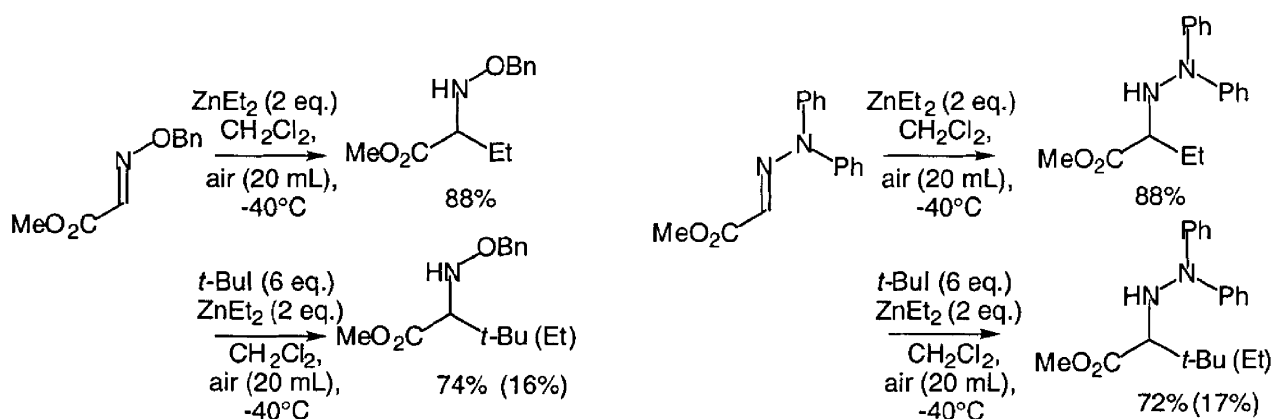


Fig. 33. Radical additions to glyoxylic oxime ethers and hydrazones.

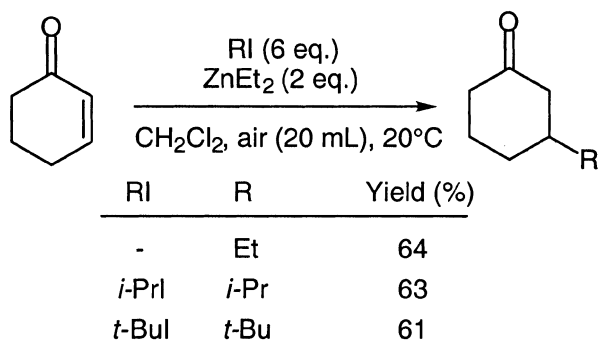


Fig. 34. Diethylzinc-mediated conjugated additions to cyclohexenone.

tions. Some attempts made with nitro olefins failed. On the other hand, azodicarboxylates like DEAD are too good electrophiles, and therefore the nucleophilic addition of the ethyl group is the only observed pathway. The reactivity of enoyloxazolidinones is currently under investigation.

## 6. Conclusion

Our interest in the investigation of new radical methodologies led us to explore cascade processes initiated via the addition of sulfonyl radicals to 3-aza-1,6-dienes. We have thus been able to propose new stereoselective routes to prepare functionalised pyrrolidines and pyrrolidinones. The same strategy has also been applied to the synthesis of polysubstituted car-

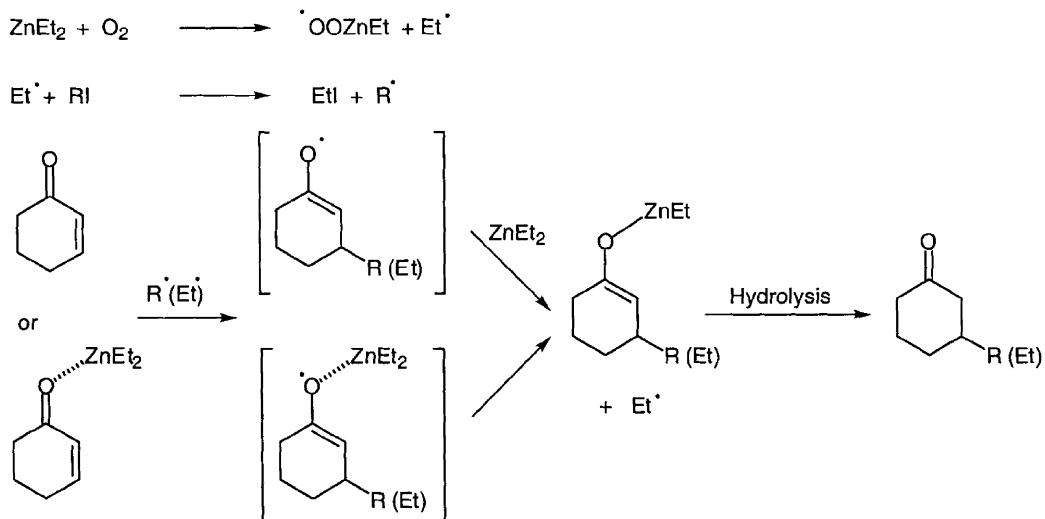


Fig. 35. Mechanism for the zinc-mediated conjugated additions.

bocycles and heterocycles [7–9], branched sugars [10–12], and to the synthesis of  $\gamma$ -lactones [50]. The development of triethylborane-, and diethylzinc-based radical additions to C=N bonds allowed a stimulating

comparative study of stereinduction in radical and polar reactions. The evaluation of the synthetic potential of new multi-components zinc-mediated reactions is currently under investigation.

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