Allenylzinc reagents: new trends and synthetic applications

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The last developments in our research efforts involving allenylzinc reagents are summarized. These interesting organometallic compounds allow the stereoselective and enantioselective synthesis of acetylenic epoxides, aziridines and amino alcohols. Some synthetic applications of these highly functionalized substrates are also presented through the synthesis of homopropargylic alcohols and allenic ketones. Further applications in the total synthesis of heterocyclic natural products are also discussed.

1. Introduction

From its beginning in 1849 with the preparation of diethylzinc by Frankland, organozinc chemistry developed rapidly until 1880.[1] However, the limited reactivity of organozinc species led to a large decline in their use (except Reformatskii type and Simmons–Smith type reagents). However, this lack of reactivity has been turned into an advantage since the end of the 1950s by the development of functionalized organozinc reagents,[2,3] the mastering of the activation processes of such organometallic species, and the discovery of specific modes of reactivity. The Université Pierre et Marie Curie has been deeply involved in such progress through the work of M. Gaudemar[4–7] and J.-F. Normant.[8,9] Following these research contributions, our team has been largely involved in organozinc chemistry developments. We have particularly focused our research interest on the reactivity of propargyl/allenyl organozinc compounds and their use in stereo- and enantioselective synthesis. The following article presents an overview of our main results in this field.

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2. 3-Chloro- and 3-alkoxyallenylzincs as useful synthetic tools

In the last ten years, a large part of our research interest focused on the synthetic use of allenylzinc reagents. We were more particularly involved in the development of new ways to synthesize acetylenic epoxides (*via* halohydrins), aziridines and 1,2-amino alcohols in a stereo- and enantioselective manner. We envisaged developing highly diastereoselective approaches to such interesting compounds, using the reaction of racemic 3-hetero-substituted allenylzinc reagents (±)-Zn-**1** and (±)-Zn-**2** with carbonyl derivatives and imines (Scheme 1).

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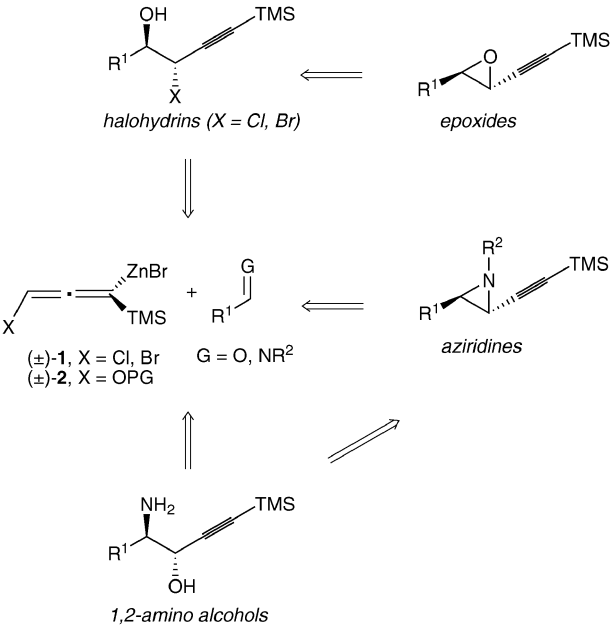
Professor Fabrice Chemla was born in Paris, France, in 1963. After his diploma degree from the Ecole Supérieure de Physique et Chimie Industrielles de Paris in 1987, he received his PhD degree in 1990 from the Ecole Normale Supérieure under the supervision of Professor M. Julia. After a one-year postdoctoral fellowship with Professor R. W. Hoffmann (Marburg, Germany), he joined Professor J. F. Normant's group (Paris) as an assistant professor in 1992. He was appointed as a full professor at the Université Pierre et Marie Curie in 2001. His research interests are focused on the design and the development of new functionalized carbenoids, as well as on carbometallation reactions.

2.1 Stereoselective synthesis of acetylenic halohydrins and epoxides

2.1.1 Preparation of propargylic zinciocarbenoids. Whereas classical synthesis of epoxides using oxidation of the corresponding enynes is somewhat tedious, mainly because of the preparation of starting material using transition metal catalysed coupling reactions,[10] we reasoned that reacting racemic propargylic zinc carbenoids (±)-Zn-**1** with aldehydes would lead to acetylenic chlorohydrins which could further be easily transformed into acetylenic epoxides by ring closure. In order to achieve our goal, we were first confronted with the preparation of such propargylic zinc carbenoids. Allenyl- and propargylmetal compounds have been widely used in organic synthesis.[11–14] Reactions of allenylmetals with aldehydes have been well studied and require a proper choice of the metal to obtain good regioselectivity and stereoselectivity. For example, the use of allenylzinc,[15–18] allenyltin[19] and allenylindium[15] has been reported to show total control of the regio- and stereoselectivity, whereas the use of allenylboron,[20–22] chromium,[23] magnesium[24,25] and titanium[26] reagents leads generally to lower regio- and stereoselectivity. However reactions using propargylic carbenoids are not well developed and a limited number of examples have been reported, such as α,α-difluoropropargylzinc,[27] and propargylindium carbenoids[28–32] as have α,α-dichloropropargyllithium,[33] α,α-dichoropropargylpotassium,[34] lithiated α,α-difluoropropargylphosphonate,[35] and heterocuprate carbenoids.[36,37]



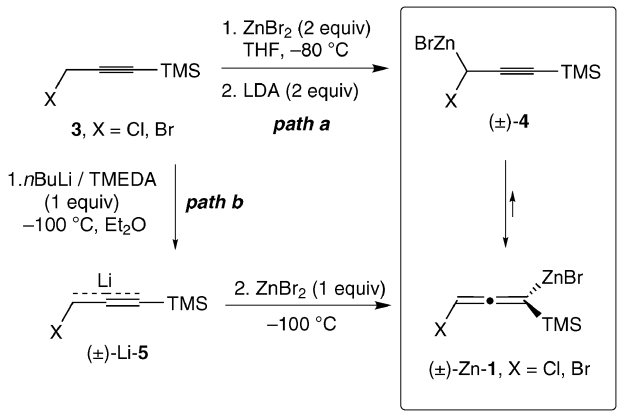
Scheme 1 Retrosynthetic scheme for the preparation of acetylenic halohydrins, epoxides, aziridines and 1,2-amino alcohols. PG = protecting group.

Among them propargylic lithiocarbenoids generated by the deprotonation of the corresponding propargyl halides were reported to display low stability and to undergo coupling to form enediynes.[38–43] These lithiocarbenoids are mostly obtained as a mixture of propargylic and allenic species in rapid equilibrium. Due to their self-coupling and their thermal instability[45] we then turned our research towards the use of zinciocarbenoids.[44,45] We were particularly interested in the preparation of racemic chloro- and bromoallenylzinc carbenoids (±)-Zn-**1** from the corresponding 3-chloro- and 3-bromo-1-trimethylsilylpropynes, respectively, **3**. These carbenoids can be prepared by two pathways *a* and *b* depicted in Scheme 2. Synthesis of the zinciocarbenoids (±)-Zn-**1** was

Dr Franck Ferreira received his PhD degree from the Université Pierre et Marie Curie in 1996 under Professor J.-P. Genêt's supervision. After a one-year postdoctoral stay with Professor J.-Y. Lallemand at the Ecole Polytechnique, he joined Professor J. F. Normant's group as an assistant professor. In 2001 he joined Professor F. Chemla's group. His main research interests are focused on the use of 3-hetero-substituted propargylzincs in the asymmetric synthesis of acetylenic aziridines, of 1,2-amino alcohols, and of biologically interesting compounds.

Dr Alejandro Pérez-Luna was born in London in 1977. He obtained an engineer diploma from the Ecole Nationale Supérieure de Chimie de Paris in 2000. After his PhD in the laboratory of Professor Husson (Université Paris V) under the guidance of Dr Micouin in 2003, he joined Peter Kündig's group in Geneva (Switzerland) for a postdoctoral stay. He took up a permanent position in CNRS in 2004 as Chargé de Recherche in Professor Fabrice Chemla's group (Université Pierre et Marie Curie, Paris VI). His scientific interests include the fields of metal-mediated synthesis, organozinc chemistry and asymmetric synthesis.

Dr Brindaban Roy received his BSc (1992) and MSc (1994) degrees from the University of Kalyani, India. Since 1996 he has been a member of faculty at the Department of Chemistry, University of Kalyani. In 2003, he completed his PhD degree under the supervision of Professor K. C. Majumdar of the same Department. He did his postdoctoral work (2005–2006) with Professor Fabrice Chemla at the Université Pierre et Marie Curie in Paris with a BOYSCAST fellowship (Govt. of India).



Scheme 2 Methods for the preparation of zinciocarbenoids (±)-Zn-**1**.

achieved by slow addition of two equivalents of LDA[46] to a mixture of $ZnBr_2$ and the corresponding 3-halogeno propargylic compound at −80 °C in THF (*path a*). These zinciocarbenoids (±)-Zn-**1** show a much higher stability than their lithio counterparts and decomposition occurs only above 0 °C.

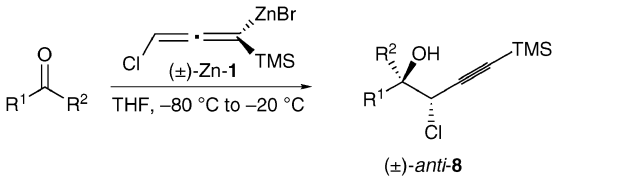
This methodology is highly efficient regarding the preparation of zinciocarbenoids but inappropriate for the preparation of other propargylic/allenic metallocarbenoids. It was then necessary to develop a general access through lithiocarbenoids (±)-Li-**5** by the direct deprotonation of the corresponding propargyl halides and transmetallation into the zinciocarbenoids by adding zinc bromide in a second step (*path b*, Scheme 2). Practically, we found that the direct deprotonation can be performed at −100 °C with *n*BuLi (1 equiv.) in the presence of TMEDA (1 equiv.) in Et_2O without any notable decomposition, usually reported in the literature for deprotonation of 3-chloro-1-trimethylsilylpropyne **3** and analogues at –78 °C.[43] Then in the second step, $ZnBr_2$ (1 equiv.) can be added to the reaction mixture at –100 °C to produce the desired zinciocarbenoids. The zinciocarbenoids obtained by both paths (*a* and *b*) can exist as the propargylzinc carbenoids **4**, but owing to their reactivity are better represented as the corresponding allenylzinc carbenoid metallotropic forms (±)-Zn-**1**.

2.1.2 Diastereoselective addition of allenylzinc carbenoids to aldehydes: access to acetylenic epoxides

2.1.2.1 Reactivity towards non-aromatic aldehydes. As expected, chloroallenylzinc (±)-Zn-**1** (X = Cl) exhibited excellent reactivity towards aliphatic aldehydes and high regioselectivity for the formation of the *anti*-chlorohydrin **8** since *anti* : *syn* ratios ranging from 80 : 20 to >98 : 2 were obtained (Scheme 3).

With bulky substituents R^1, the best result was obtained with R^1 = *t*Bu for which only the *anti*-isomer was detected (Scheme 3).

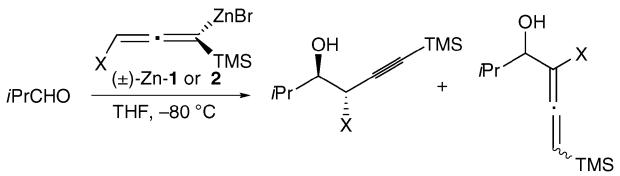
With less hindered aldehydes like crotonaldehyde (R^1 = CH_3–CH=CH–) and cinnamaldehyde (R^1 = Ph–CH=CH–), selectivities were as good as with *n*-butyraldehyde (R^1 = *n*Bu) with *anti* : *syn* ratios of 85 : 15 and 80 : 20. When performed with cyclohexanone the reaction affords the corresponding chlorohydrin **8** in good yield (Scheme 3).



R^1 bulkier than R^2, 78–82%, 83:17 to 98:2 dr
$R^2 = R^1 = -(CH_2)_5-$, 70%

Scheme 3 Preparation of acetylenic chlorohydrins *anti*-(±)-**8**.

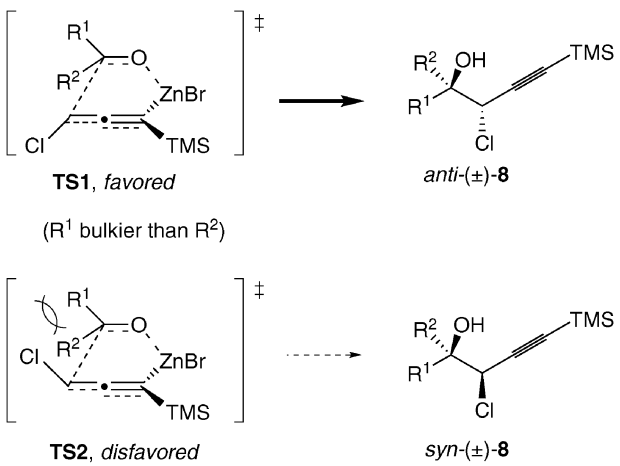
However lower regioselectivity was observed when we ran the condensation with bromoallenylzinc (±)-Zn-**1** (X = Br). Metallation under the same conditions gave, after treatment with *i*PrCHO, the corresponding bromohydrin **6** with a similar yield and a similar diastereoselectivity (*anti* : *syn* ratio of 93 : 7) but with the formation of a small amount of the bromoallenyl regioisomer **7**[44,45] (Scheme 4). Thus, further investigations were concentrated on the condensation of chloroallenylzinc (±)-Zn-**1** with various aldehydes and ketones.



X = Br **6**, 77%, 93:7 *anti:syn* **7**, 17%
X = Cl **8**, 75%, 95:5 *anti:syn* **9**, 0%

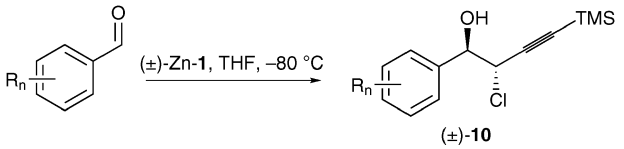
Scheme 4 Reactivity of (±)-Zn-**1** towards isobutyraldehyde.

The excellent diastereoselectivity of this reaction for the formation of the *anti*-acetylenic isomer can be rationalized by proceeding *via* chelate type transition state **TS1** in which the C=O bond and the allenyl moiety are eclipsed and in which the chlorine atom and the bulkiest group R^1 adopt an *anti*-position[11,47] (Scheme 5). The relationship between the *anti* : *syn* ratio and the size of the substituent R^1 could be explained by the disfavored chelate transition state **TS2** in which the chlorine atom and R^1 adopt a *syn*-position. Thus, due to the more important steric interactions, **TS2** is certainly disfavored relative to **TS1**.[48]



Scheme 5 Proposed transition state **TS1** for the formation of *anti*-(±)-**8**.

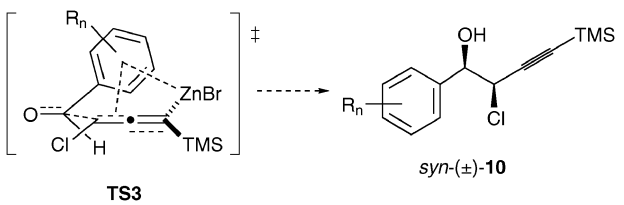
2.1.2.2 Reactivity towards aromatic aldehydes. While aliphatic aldehydes led to acetylenic chlorohydrins with high *anti* diastereoselectivities, dramatic loss of selectivity was observed with aromatic aldehydes in the reaction with (±)-Zn-**1**. For example, the condensation of (±)-Zn-**1** with benzaldehyde afforded the corresponding chlorohydrin (±)-**10** in good yield and with a diastereomeric ratio of 66 : 34 in favor of the *anti*-isomer (Scheme 6).



R_n = H	85%	66:34 *anti:syn*
R_n = EDG	66–85%	up to 71:29 *anti:syn*
R_n = EWG	69–74%	up to 35:65 *anti:syn*

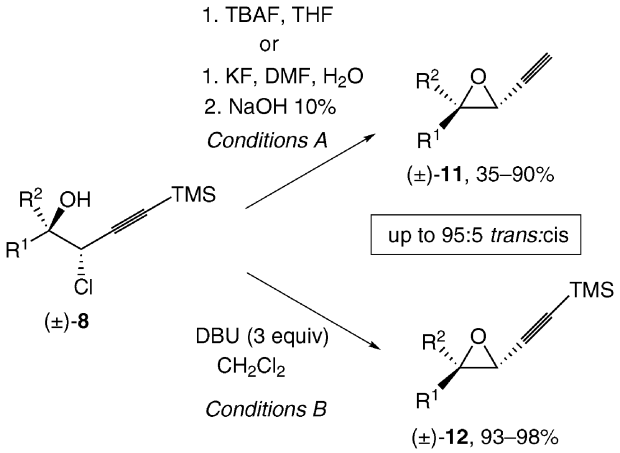
Scheme 6 Addition of (±)-Zn-**1** to aromatic aldehydes.

To explain the low selectivity of the reaction of (±)-Zn-**1** with aromatic aldehydes we first tried to consider the chelate transition state **TS1**. However, this transition state did not reflect the steady decrease of the *anti* : *syn* ratio with the electron-withdrawing ability of the substituent on the aromatic ring. In order to explain the substituent effects observed, we considered a competitive open transition state **TS3**. The presence of a strongly electron-withdrawing moiety on the aldehyde should decrease the Lewis basicity on the sp^2-oxygen atom and should then weaken the O–Zn interaction essential to the transition state **TS1**. An additional π-stacking-type interaction[49] between the electron-poor aromatic ring and the electron-rich allenyl moiety could favor the open transition state **TS3** (Scheme 7). Studies of these hypotheses are under way in our laboratory and will be reported in due course.



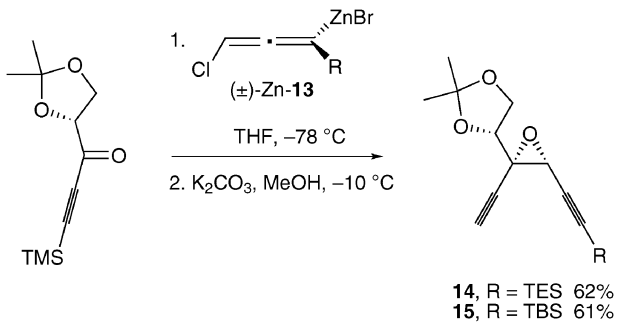
Scheme 7 Possible transition state **TS3** for the formation of *syn*-aromatic chlorohydrins (±)-**10**.

2.1.3 Conversion of propargylic chlorohydrins into epoxides. This highly stereoselective method for the preparation of the propargylic chlorohydrin (±)-**8** allowed us to convert it into the corresponding desilylated and silylated acetylenic epoxides **11** and **12** under basic conditions. Both epoxides **11** and **12** can be obtained as major *trans*-isomers in high yields depending upon the reaction conditions. Thus, when the cyclisation is run with KF and TBAF in a mixture of DMF and H_2O followed by 10% NaOH (*conditions A*), the desilylated acetylenic epoxides **11** are obtained as single products, while the use of DBU (3 equiv.) in CH_2Cl_2 (*conditions B*) allows the formation of the silylated epoxides **12**[50] (Scheme 8).



Scheme 8 Formation of epoxides (±)-*trans*-**11** and **12** from chlorohydrin (±)-*anti*-**8**.

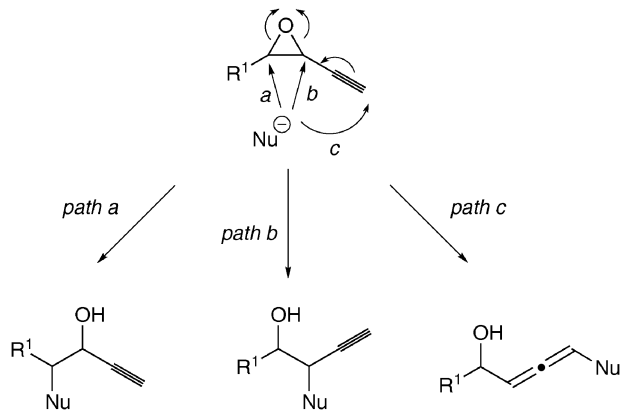
Using our reported methodology to prepare chloroallenylzinc compounds from the corresponding propargyl chlorides, Caddick *et al.* have recently reported[51] an efficient preparation of epoxydiynes which can be used as a key fragment in the synthesis of the neocarzinostatin chromophore. The stereochemical outcome of the addition of a different chloroallenylzinc (±)-Zn-**13** to a chiral propargyl ketone including a bulky substituent in the α-position was studied. While the diastereoselectivity of the addition was not determined on the crude product, the corresponding enantioenriched epoxydiynes **14** and **15** were isolated after purification as single isomers with good yields[51] (Scheme 9).



Scheme 9 Caddick's synthesis of silylated epoxydiynes.

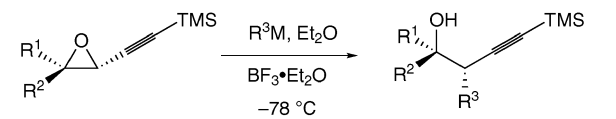
2.1.4 Stereoselective synthesis of homopropargylic alcohols by the regioselective ring-opening of acetylenic epoxides. 1,2-Disubstituted homopropargylic alcohols constitute a class of compounds which has been widely used as a key intermediate in the total synthesis of natural products such as erythronolide B,[52] neomethynolide,[53] oudemansin C,[54] N-BOC ADDA,[55–57] maytansinol[58,59] and some approaches to milbemycins[60] and avermectins.[61] Whereas methodologies relative to regioselective access to both *syn*- and *anti*-1,2-homopropargylic alcohols reported by Marshall *et al.* involving addition of allenylmetals to aldehydes are well known,[12,19,62–64] we envisaged a new approach to these compounds involving the regioselective ring opening of acetylenic epoxides by simple organometallics.

2.1.4.2 By regioselective epoxide ring-opening under Lewis acid activation. Three competitive ring-opening reactions can occur on acetylenic epoxides. Ring opening at the homopropargylic carbon (*path a* in Scheme 10) leads to the corresponding propargylic alcohol. By contrast, ring opening at the propargylic carbon through *path b* gives the corresponding homopropargylic alcohol. These two pathways would occur through inversion of the configuration at the attacked carbon center. A competitive process through *path c* involving ring opening with the participation of the triple bond in an S_N2'-like process finally gives the isomeric allenic alcohol (Scheme 10).



Scheme 10 Competitive pathways in the ring opening of acetylenic epoxides with nucleophiles.

We have demonstrated that the presence of a Lewis acid like $BF_3 \cdot Et_2O$ has a strong influence on the reactivity and regioselectivity in the ring opening of acetylenic epoxides.[44,65] The reaction of epoxides **12** with salt-free organolithium or Grignard reagents derived from alkyl chlorides in the presence of $BF_3 \cdot Et_2O$ gives regioselectively the corresponding homopropargylic alcohol **16** through ring opening at the propargylic position (*path b* in Scheme 10). The reaction occurs with complete stereoselectivity which means that starting from a *cis* (or *trans*)-epoxide leads to a *syn* (or *anti*)-homopropargylic alcohol (Scheme 11).



(±)-**12** (*cis* or *trans*)

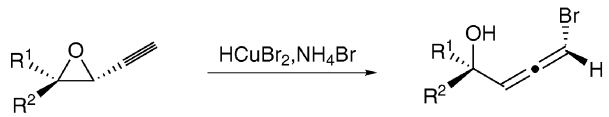
syn-(±)-**16**, 75–92% (from *cis*-(±)-**12**)
anti-(±)-**16**, 60–65% (from *trans*-(±)-**12**)

Scheme 11 Stereospecific ring opening reactions of acetylenic epoxides (±)-**12**.

However the difference in the reaction yield between *cis*- and *trans*-epoxides reflects a strong difference in reactivity. This has been demonstrated through the kinetic resolution of acetylenic epoxides through ring opening.[44]

Unsubstituted acetylenic epoxides ($R^1 = R^2 = H$) could also be regioselectively opened, for example with *i*PrMgCl in the presence of $BF_3 \cdot Et_2O$, with a yield of 75% for the homopropargylic alcohol without the formation of any propargylic alcohol regioisomer.[66]

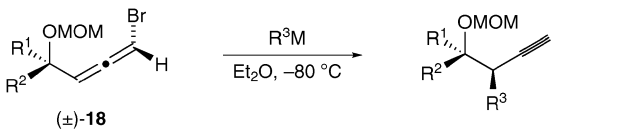
2.1.4.3 By nucleophilic substitution. Homopropargylic alcohols can also be prepared efficiently through bromoallenol formation by a stereospecific double S_N2' substitution starting from the desilylated acetylenic epoxides.[56,57,67] Bromoallenols **17** have been prepared with high stereospecificity from both *cis*- and *trans*-acetylenic epoxides **11** in good yields by a pure *anti*-S_N2' ring-opening using CuBr–HBr complex (Scheme 12).[44,68–70] It is worthy of note that HBr itself led only to the corresponding chlorohydrins though S_N2 ring opening.



(±)-**11** (*cis* or *trans*) (±)-**17**, 65–73%

Scheme 12 Formation of bromoallenols (±)-**17** from acetylenic epoxides (±)-**11**.

Finally the S_N2' substitution of bromoallenols **18**, with the alcohol protected as a MOM ether, with cyanocuprates[67,71] or with Grignard reagents with or without Cu(I) salts gives stereospecific displacement of the bromide ion. Displacement occurs in an *anti*-fashion (Scheme 13).



(±)-**18**

anti-(±)-**19**, 53–95%, dr up to 98:2
(R^1 bulkier than R^2)

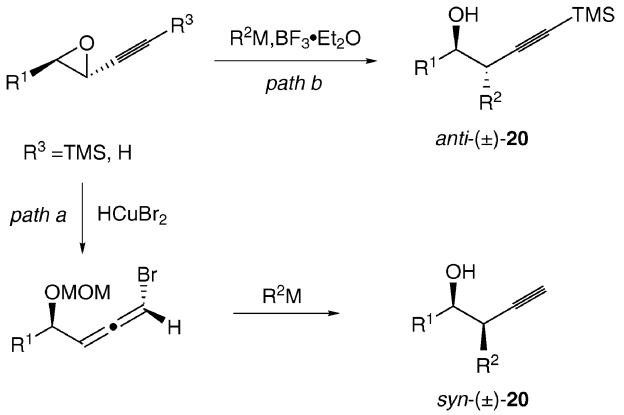
syn-(±)-**19**, 83–91%, dr > 98:2
(R^2 bulkier than R^1)

Scheme 13 Substitution of protected bromoallenols (±)-**18** with organometallic reagents.

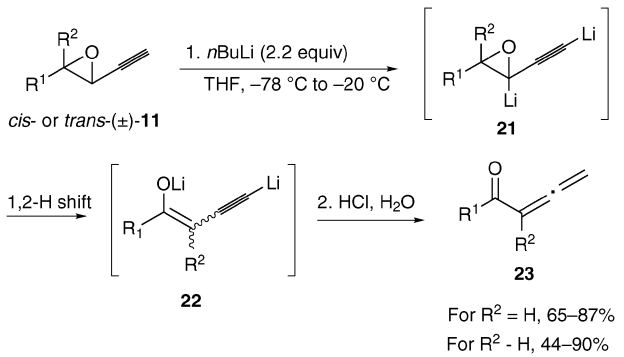
The overall process for the preparation of homopropargylic alcohols *anti*- or *syn*-(±)-**19** from acetylenic epoxides through the formation of bromoallenols is then the result of a formal S_N2 substitution with *retention of configuration*.

In summary, we found that both *syn*- and *anti*-homopropargylic alcohols (±)-**20** can be synthesized from the same *trans*-acetylenic epoxides **11** or **12** using a diastereo-divergent and totally controlled methodology involving either for the synthesis of the *syn*-isomer the formation of a bromoallenol intermediate by a S_N2' substitution (*path a*) or for the synthesis of the *trans*-isomer by a direct nucleophilic ring-opening (*path b*) (Scheme 14).[45]

2.1.5 Synthesis of allenic ketones by double deprotonation of acetylenic epoxides. Some other synthetic applications of acetylenic epoxides have also been developed in our group. We have recently discovered the formation of allenic ketones from acetylenic epoxides through the rearrangement of an oxiranyl anion intermediate.[72–74] Treatment of the *trans*-acetylenic epoxides **11** ($R^2 = H$, Scheme 15) with an excess of *n*-BuLi (2.2 equiv.) leads to an oxiranyl anion **21** which undergoes a



Scheme 14 Diastereo-divergent synthesis of both *syn*-and *anti*-homopropargylic alcohols (±)-**20**.



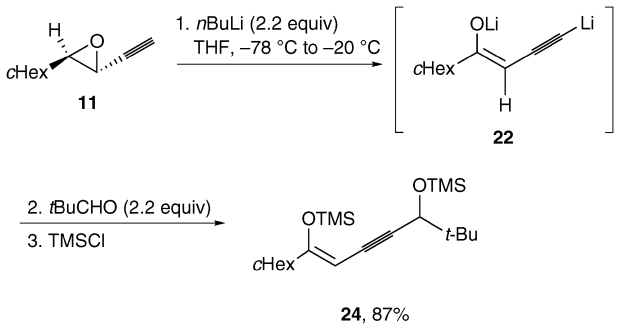
Scheme 15 Synthesis of allenic ketones **23** from acetylenic epoxides (±)-**11**.

1,2-H shift to generate a dilithio ynenolate **22**. A double protonation upon hydrolysis gives the corresponding allenone **23** in good isolated yields.[75] Interestingly, the same reactivity has been observed when running the double deprotonation on the *cis*-cyclohexyl acetylenic epoxide (R^1 = H, Scheme 15).

In the case of 2,2-disubstituted acetylenic epoxides such a reaction is also observed. However, although 1,2-Ph shift occurs in 90% yield from the 2,2-diphenyl acetylenic epoxide (R^1 = R^2 = Ph), 1,2-alkyl shift arises with a lower yield of 44% and side reactions from 2,2-dipentyl acetylenic epoxide (R^1 = R^2 = Pent).

The ynenolate intermediate **22** shows interesting reactivity and can also be quenched with various electrophiles. For example, reaction of ynenolate **22** derived from *trans*-epoxide **11** (R^1 = *c*Hex and R^2 = H) with an excess of pivalaldehyde followed by TMSCl gave the (*Z*)-TMS-enolate **24** as a single isomer (Scheme 16). The configuration of this isomer could not be determined, but this stereoselectivity seems to be related to the stereochemistry of ynenolate intermediate **22** which was shown to be mainly (*Z*)-configured upon quenching with TMSCl.

These encouraging first results led us to study further the interesting reactivity of ynenolate intermediates and to develop a general access to allenic ketones which have been shown to possess high reactivity,[76,77]as Michael acceptors,[78,79] as Diels–Alder dienophiles[77] and in furan formation.[80–82]



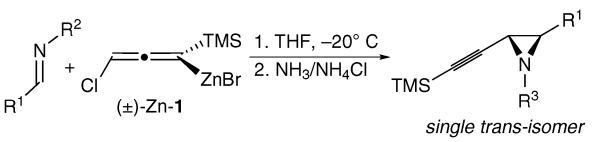
Scheme 16 Reaction of ynenolate **22** with aldehydes as electrophiles.

2.1.6 Perspectives. We have developed a highly stereospecific access to acetylenic epoxides and to homopropargylic alcohols by using propargyl/allenyl zinciocarbenoids. Because of the intrinsic chirality of the allenylzinc carbenoids, studies on the chemical behavior as well as the configurational stability of carbenoids **1** and their applications in asymmetric synthesis will represent a major part of our further research. We are also involved in the synthesis of optically pure acetylenic epoxides *via* the enantioselective direct addition of allenylzinc carbenoids to aldehydes by using chiral ligands,[83] a method which could constitute a powerful means to access chiral homopropargylic alcohols and natural products.

2.2 Stereoselective synthesis of acetylenic aziridines and 1,2-amino alcohols

2.2.1 Synthesis of acetylenic aziridines

2.2.1.1 Initial work. Five years ago, in the continuation of our pioneering work on the stereoselective synthesis of acetylenic epoxides, we reasoned that the condensation of racemic 3-chloro allenylzinc reagent (±)-Zn-**1** with imines could give access to acetylenic aziridines. When we started our study, only a few syntheses of acetylenic aziridines had been reported involving the reaction of a nitrene or a nitrene equivalent with an enyne,[84,85,] the condensation of a propargylic sulfonium ylide[86–88] or of a lithiated cinnamyl chloride with imines,[89] or from acetylenic epoxides in a two-step procedure.[90] As for us, we envisaged the formation of acetylenic aziridines through the reaction of (±)-Zn-**1** with imines followed by the ring closure of the α-chloro amine intermediates. *N*-Benzyl and *N*-trimethylsilylimines **25** and **26** were used in this reaction. Surprisingly, all these imines were found to be less reactive than the corresponding aldehydes since they have to be stirred overnight at room temperature to afford acetylenic aziridines **27** and **28** in variable yields (Scheme 17).[91]



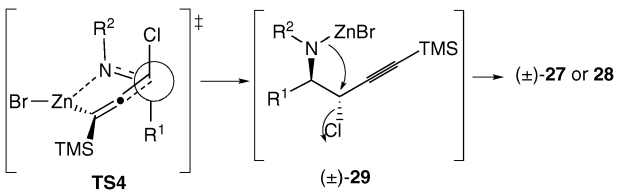
25, R^2 = Bn
26, R^2 = TMS

(±)-**27**, R^3 = Bn, 12–98%
(±)-**28**, R^3 = H, 40–79%

Scheme 17 Synthesis of *N*-benzyl- and *N*-H-aziridines *trans*-(±)-**27** and **28**.

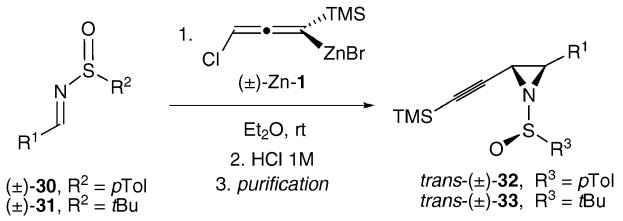
Unlike the aldehydes, the diastereoselectivity is not dependent upon the nature of the substituent of the imine since aziridines **27** and **28** were isolated as single *trans*-diastereomers, even in the case of aromatic *N*-benzylimines. Furthermore, most of the acetylenic *N*-benzylaziridines **27** were isolated as single invertomers, the benzyl moiety being assumed to lie on the less hindered side of the aziridine ring, *i.e.* on the same side as the trimethylsilylethynyl group. As a matter of fact, only the aziridine obtained from a symmetrical ketimine could be observed as an equimolar mixture of the two inseparable invertomers. On the other hand, it is noteworthy that *N*-H-aziridines **28** were formed as mixtures of inseparable invertomers resulting in broad ^{1}H NMR signals.

As for aldehydes and ketones, we have explained the excellent *trans*-stereoselectivity by a chelate transition state **TS4**, analogous to **TS1** in Scheme 5 wherein the zinc atom is coordinated by the nitrogen of the imine, and wherein the chlorine atom and the substituent R^1 of the imine adopt an *anti*-relationship (Scheme 18). It is noteworthy that in all cases no trace of the α-chloro amine intermediates **29** is observed. However, at this time we did not know whether the aziridine ring-closure occurred in the reaction mixture or upon basic hydrolysis.



Scheme 18 Postulated transition state **TS4** for the formation of *trans*- aziridines (±)-**27** and **28**.

2.2.1.2 Stereoselective synthesis of enantioenriched trans-acetylenic aziridines. Having in hand a good method for preparing diastereo-enriched *trans*-acetylenic aziridines, we wondered whether our methodology could be extended to the synthesis of such aziridines in enantioenriched form. When we started our study only a few enantioselective syntheses of acetylenic aziridines had been reported either through the asymmetric aziridination of *N*-tosylimines with D-(+)-camphor derived sulfonium ylides[86,87,92] or from α-amino acids.[93–96] We then examined the addition of (±)-Zn-**1** to imines bearing a chiral directing group on the nitrogen atom. We soon envisaged reaching our goal by the addition of reagent (±)-Zn-**1** to chiral sulfinimines following the pioneering work of both Davis'[97–102] and Ellman's[103–111] groups on the stereoselective addition of organometallics to enantiomerically pure *p*-toluenesulfinyl- (*p*TS-) and *t*-butanesulfinyl- (*t*BS-) imines, respectively. With such imines, in order to reach high conversions, (±)-Zn-**1** has to be prepared by the deprotonation of 3-chloro-1-trimethysilylprop-1-yne by *n*BuLi in the presence of TMEDA (1 equiv.) in Et_2O above −95 °C (see Scheme 2). Controlling the temperature appeared to be critical since the lithio carbenoidic intermediate (±)-Li-**5** decomposes at temperatures higher than −95 °C. Fortunately, transmetallation of (±)-Li-**5** with zinc bromide as mentioned above affords Zn-**1** which exhibits a much higher thermal stability

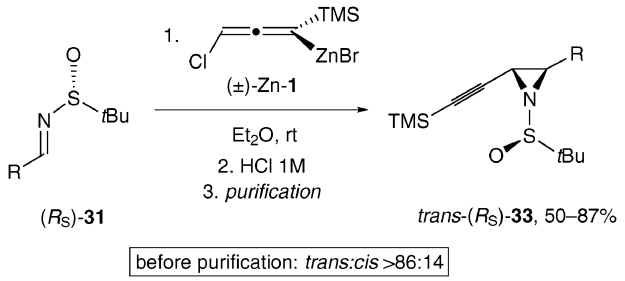


Scheme 19 Addition of (±)-Zn-**1** to racemic *p*TS- and *t*BS-imines (±)-**30** and **31**.

than the analogous lithio carbenoid Li-**1**. Thanks to its striking stability, reagent (±)-Zn-**1** can be used at room temperature. Various *racemic* sulfinimines (±)-**30** and (±)-**31** were then tested with (±)-Zn-**1** (Scheme 19).[112] *p*TS-imines (±)-**30** were shown to be highly reactive towards (±)-Zn-**1**. In all cases, the reaction is complete within 1 h at −80 °C and in most cases, after the usual acidic work-up, complex mixtures of diastereomers are obtained. In fact, only α,α-disubstituted *p*TS-imines (with R^1 = *i*Pr or *c*Hex) afford the corresponding *trans*-aziridines (±)-**32** as single isomers.

On the other hand, *t*BS-imines (±)-**31**[113] appeared to be much less reactive as the completion of the reaction is attained only after 4 h at room temperature. However, under these conditions, in order to circumvent its thermal carbenoidic decomposition, (±)-Zn-**1** has to be used in excess: depending on the bulkiness of the *t*BS-imines, 1.5 to 6.0 equivalents of (±)-Zn-**1** must be used. Under these conditions, in most cases *t*BS-imines give better stereoselectivities than the analogous *p*TS-imines as previously reported by others in the addition of various nucleophiles to such imines.[114–121] So far, such imines have been intensively used in asymmetric synthesis.[122–135] The *trans*-acetylenic aziridines (±)-**33** are then formed as major isomers (*trans* : *cis* > 91 : 9). Moreover, in all cases only one *trans*-aziridine (dr > 98 : 2) was formed suggesting that the *t*BS-group has fully played its role of a chiral directing group.

Encouraged by these results, we then undertook the extension of this method to the synthesis of enantioenriched *trans*-*t*BS-aziridines from enantiopure *t*BS-imines (>99% ee). Since the procedure for the preparation of (±)-Zn-**1** affords only a racemic mixture, we were confronted with the reaction between this racemic nucleophile (±)-Zn-**1** and enantiopure *t*BS-imines. When performed in Et_2O at room temperature with 1.5 equiv. of (±)-Zn-**1**, the enantiopure imine (R_S)-**31**, with R = Pr, gives a mixture of the corresponding *trans*- and *cis*-aziridines (R_S)-**33** with a selectivity of 79 : 21 in favor of the *trans*-isomer (Scheme 20).[139] The *trans* : *cis* selectivity significantly deviates from that obtained (*i.e.* 90 : 10) when racemic imine **31** is reacted with 1.5 equiv. of (±)-Zn-**1**. In this context, according to Hoffmann's work on the configurational stability of organometallic reagents,[136–138] (±)-Zn-**1** could be regarded as at least partially configurationally stable with respect to the time scale defined by the reaction rate. Under these conditions, as predicted by Hoffmann, using a large excess of (±)-Zn-**1** (6.0 equiv.) allowed the stereoselectivity to be improved up to a *trans* : *cis* ratio of 89 : 11, very close to the maximum 90 : 10

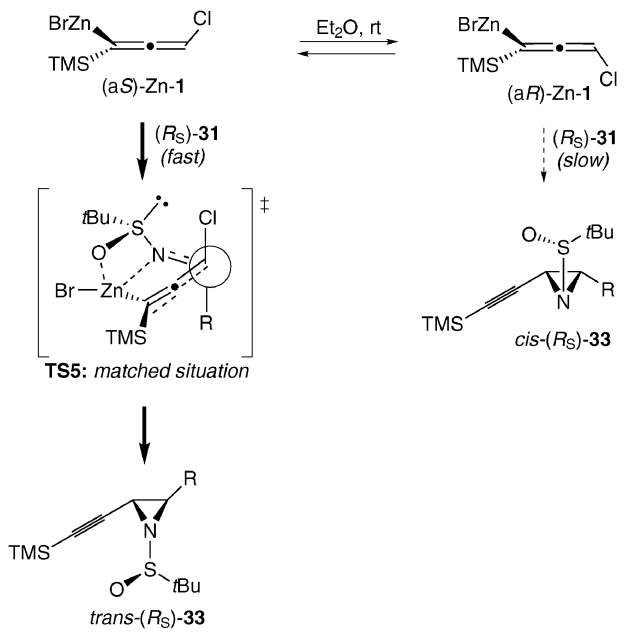


Scheme 20 Synthesis of *trans*-acetylenic *t*BS-aziridines (R_S)-**33**.

ratio predicted by the kinetic resolution process and obtained with the racemic imine (±)-**31**. The same reaction conditions were applied to other enantiopure *t*BS-aldimines (R_S)-**31** giving the corresponding aziridines (R_S)-**33** with *trans* : *cis* stereoselectivities close to those observed with the series of racemic aziridines **33** (Scheme 20).[139]

After chromatography over silica gel, *trans*-acetylenic aziridines **33** are then isolated as diastereomerically (>98 : 2 dr) and enantiomerically (>99% ee) pure compounds in good isolated yields ranging from 50% to 69%. Under the same conditions, a symmetrical ketimine gives the corresponding aziridine in excellent yield (87%) and as a single isomer.

The high *trans*-selectivity cannot reasonably be explained through a thermodynamic process as *cis*-sulfonylaziridines have been described to be thermodynamically favored.[140,141] In fact, overall these results strongly suggest that the *trans*-isomers (R_S)-**33** could result from the matched (R_S)-**31**–(a*S*)-Zn-**1** pairs *via* the six-membered ring chelate type transition state **TS5** containing a four-membered metallacycle as postulated by others in the addition of lithium or titanium enolates and of potassium dialkyl phosphites onto sulfinimines[105,108,142–145] (Scheme 21).



Scheme 21 Origin of the *trans*-stereoselectivity in the addition of (±)-Zn-**1** onto *t*BS-imines.

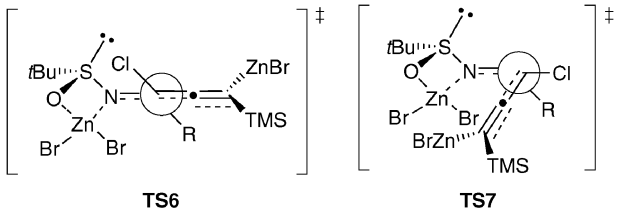


Fig. 1 Plausible open transition states **TS6** and **TS7** for the formation of minor *cis*-acetylenic *t*BS-aziridines (R_S)-**33**.

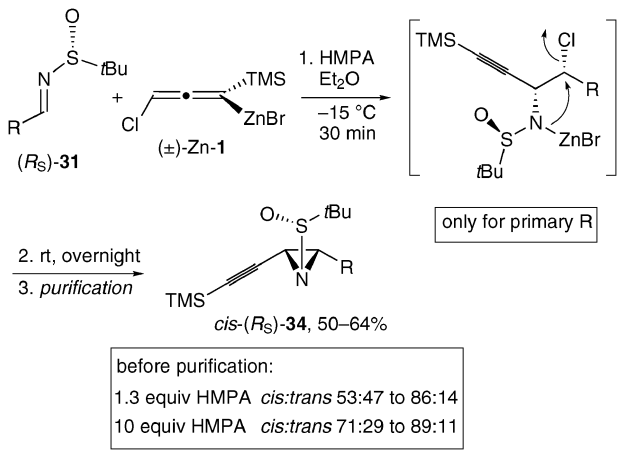
Similarly, the *cis*-isomers (R_S)-**33** could result from the mismatched (R_S)-**31**–(a*R*)-Zn-**1** pairs. Three different transition states can be envisaged for the formation of the *cis*-isomers, *i.e.* one chelate type transition state similar to **TS5**, and two open transition states **TS6** (antiperiplanar) and **TS7** (synclinal) (Fig. 1).

In the course of our study, we have shown that running the reaction at 0 °C (instead of room temperature) with the *t*BS-imine (±)-**31** with R^1 = Pr results in a decreased *trans* : *cis* ratio of 62 : 38 (instead of 90 : 10). This drop in selectivity was explained by *trans*- and *cis*-isomers being entropically and enthalpically driven, respectively.[146,147] This is consistent with the formation of the *cis*-isomer through an open transition state (**TS6** or **TS7**) rather than a chelate one. Moreover, with reference to our further work in the presence of HMPA (see part 2.2.1.3), the synclinal transition state **TS7** might be preferred.

However, whatever might be the preferred open transition state (**TS6** or **TS7**), it is worthy of note that the minor *cis*-*t*BS-aziridines seem to be formed through a S_E2' suprafacial process, which is uncommon, the addition of allenylmetals to carbonyl derivatives or imines being reported to be antarafacial.

2.2.1.3 Stereoselective synthesis of enantioenriched cis-acetylenic aziridines. In all the above cases, the high *trans*-stereoselectivity was then assumed to be due to good kinetic resolution of (±)-Zn-**1** through the chelate type transition state **TS5** in which the zinc atom of (±)-Zn-**1** is coordinated by both the nitrogen and the oxygen atoms of the imine in a four-membered metallacycle. Under the assumption that the coordination of the zinc was responsible for the formation of **TS5**, we first reasoned that using a Lewis acid could have some influence on the stereoselective outcome of the reaction. Indeed, the coordination of an extra Lewis acid by both the nitrogen and oxygen atoms of the imine could perhaps prevent the formation of **TS5**. Under these conditions, we even envisaged the formation of *cis*-acetylenic aziridines as major products through an open transition state with reference to our previous work on the addition of (±)-Zn-**1** onto *N*-sulfonylimines or aromatic aldehydes.[44,91] In preliminary work, the pre-coordination of *t*BS-imines by $ZnBr_2$ or $BF_3 \cdot Et_2O$ in CH_2Cl_2 or methylaluminium bis(2,6-di-*tert*-butyl-4-methylphenoxide) (MAD) in toluene was proven to afford the *trans*-aziridines as major products. These results were explained by a decoordination of the Lewis acid and the subsequent coordination of (±)-Zn-**1** giving the *trans*-isomer through **TS5**. On the other hand, the use of $TiCl_4$ in CH_2Cl_2

only led to unidentified by-products. We then proceeded under the assumption that HMPA (hexamethylphosphoric triamide) would be able to coordinate the zinc atom of reagent (±)-Zn-**1** as observed for various metal ions.[148–152] At first, 1.3 equiv. of HMPA (with respect to the 6.0 equiv. of reagent (±)-Zn-**1**) were used.[153] These conditions allowed the reaction to be complete with non-α-branched (R_S) *t*BS-aldimines, *i.e.* with primary R. While no starting imine remained after 30 min stirring at –15 °C, the reaction needed to be continued overnight at room temperature to reach the end of the aziridine ring closure from the α-chloro *N*-zincated sulfinamide intermediates. On the other hand, no reaction occurred with α-branched aldimines. As expected,[154] HMPA was proven to have a dramatic influence on the stereochemical outcome of the reaction since the corresponding *t*BS-aziridines (R_S)-**34** were obtained as *cis* : *trans* isomeric mixtures with fair to high selectivities in favor of the *cis*-isomers. Moreover, single *cis*-isomers are formed indicating that here again the *t*BS-auxiliary has fully played the role of a good chiral directing group (Scheme 22).



Scheme 22 Synthesis of *cis*-acetylenic *t*BS-aziridines (R_S)-**34**.

To our great surprise, the *cis*-aziridines thus formed were different from those obtained, as minor products, when performing the reaction without HMPA. When running the reaction between the *t*BS-aldimine (R_S)-**31**, with R = Pr and only 1.0 equiv. of (±)-Zn-**1**, 36% of the starting imine was recovered while an equimolar mixture of *cis*- and *trans*-aziridines was obtained. This result could be explained by the configurational stability of (±)-Zn-**1** with respect to the time scale defined by the reaction rate under these conditions and strongly suggests that each enantiomer of (±)-Zn-**1** gives only one isomer (*cis* or *trans*). Furthermore, since the reaction of 6.0 equiv. of (±)-Zn-**1** with the above enantiopure (R_S) imine leads to a *cis* : *trans* ratio of 75 : 25 very close to that obtained with racemic imine (*i.e.* 78 : 22), we have postulated that almost the highest kinetic resolution was attained under these conditions.

The amount of HMPA was also shown to have an influence on the level of the stereoselectivity of the addition of (±)-Zn-**1** to non-α-branched *t*BS-aldimines (R_S)-**31**.[153] Indeed, using larger amounts of HMPA allows the stereoselectivity to be improved in all cases. In fact, the best results are obtained with 10.0 equiv. of HMPA. All imines give the corresponding aziridines with better *cis* : *trans* ratios, ranging from 71 : 29 to 89 : 11. Moreover, *t*BS-aziridines could be isolated in good yields (50–64%) as diastereo- and enantiopure compounds (dr > 98 : 2 and ee > 99%) by flash chromatography on silica gel (Scheme 22). When carrying out the reaction between the *t*BS-imine (R_S)-**31**, with R = Pr, and only 1 equiv. of (±)-Zn-**1**, 55% of the starting imine was recovered while a 66 : 34 *cis* : *trans* ratio is obtained. This result, significantly different from 51 : 49 (obtained in the presence of 1.3 equiv. of HMPA, see above), could be explained by the partial configurational lability of (±)-Zn-**1** with respect to the time scale defined by the reaction rate under these conditions. Thus, everything proceeded as planned though the rate of racemization of (±)-Zn-**1** was higher in the presence of 10 equiv. of HMPA than in the presence of 1.3 equiv. This apparent faster racemization of (±)-Zn-**1** can well explain the increase in the *cis* : *trans* ratio when using 10 equiv. of HMPA.

The stereoselectivity of the reaction cannot be explained only by an antiperiplanar transition state, but also by a synclinal transition state **TS8** or **TS9**. In such transition states the imine adopts the lowest in energy conformation **C1** due to a stabilizing negative $\sigma^*_{S-O} \rightarrow n_N$ hyperconjugative interaction.[155–157] In addition, we have conducted semiempirical calculations which have shown that the conformation **C1** of the imine (R_S)-**34**, with R = (*E*)-cinnamyl, in **TS8/9** is more stable than the one (**C2**) in **TS5**; it is preferred by 5.23 kJ mol^{-1} and 24.34 kJ mol^{-1} by MM2 and AM1 calculations, respectively. Moreover, with respect to that previously reported for the reaction without HMPA, **TS8**, which corresponds to a suprafacial S_E2' process, would certainly be preferred (Fig. 2).

Subsequently, such a transition state was postulated in the stereoselective allylzincation of *t*BS-imines in the presence of HMPA.[128]

Like the major *cis*-aziridines, the minor *trans*-isomers (R_S)-**34** are formed as single diastereomers. The latter are different from those which had been obtained earlier as the major

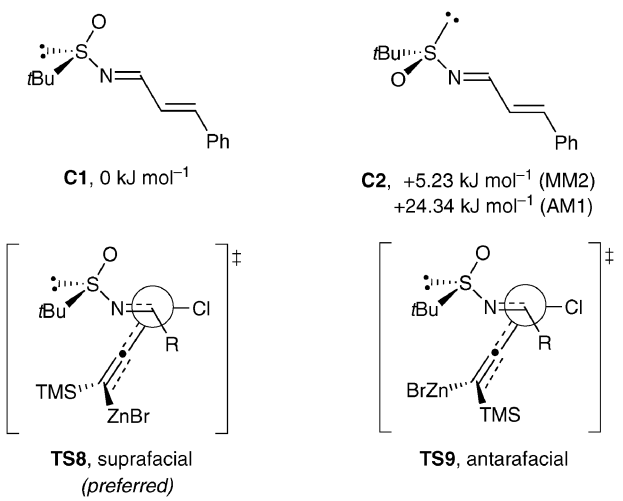
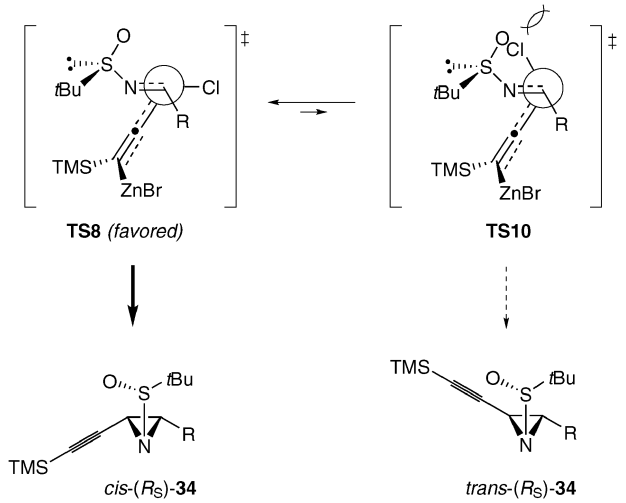


Fig. 2 Postulated synclinal suprafacial transition state **TS8** for the formation of *t*BS-aziridines *cis*-(R_S)-**34**.



Scheme 23 Origin of the *cis*-stereoselectivity in the addition of (±)-Zn-**1** onto *t*BS-aldimines in the presence of HMPA.

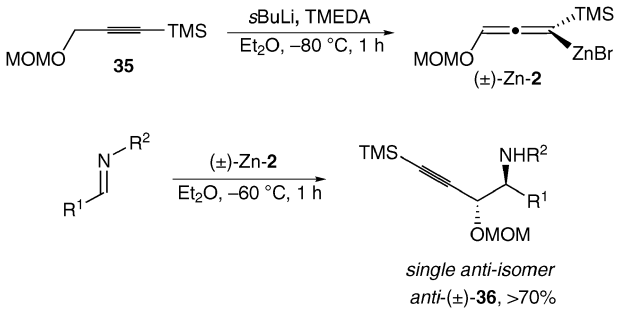
compounds in the absence of HMPA. By analogy with **TS8**, only the suprafacial synclinal transition state **TS10** (disfavored because of steric interactions between the chlorine atom and the sulfinyl moiety) could reasonably be invoked to explain the formation of *trans*-aziridines (R_S)-**34** (Scheme 23).

Thus, **TS8** and **TS10**, wherein (±)-Zn-**1** is approaching onto the less hindered *Re* face of the imine (opposite to the very bulky *tert*-butyl substituent at the sulfur center) correspond to the matched and mismatched situations, respectively. These competitive transition states allow the increase in the *cis* : *trans* ratio to be explained when the steric demand of the substituent R on the imine becomes greater. Indeed, the bulkier the substituent R on the imine, the higher the steric interactions with the chlorine atom in the synclinal transition states **TS8**. On the other hand, the bulkiness of R should have only a little influence on the synclinal transition states **TS10** since the allenyl moiety can be regarded as very little hindered (Scheme 23). Then, making the substituent R more sterically demanding should render **TS8** less favored relative to **TS10** leading to a drop in the *cis*-selectivity. Moreover, with the very bulky α,α-dibranched *t*BS-aldimine, with R = *t*Bu, no reaction at all occurs, neither through **TS8** nor through **TS10**. This is in agreement with our earlier work showing that such an imine exhibits low reactivity towards (±)-Zn-**1**.

2.2.2 Stereoselective synthesis of acetylenic 1,2-amino alcohols

2.2.2.1 Initial works. Encouraged by our work on the synthesis of acetylenic aziridines, we then thought to elaborate a new synthetic approach to acetylenic 1,2-amino alcohols. The synthesis of the latter was still challenging since only a few methods of stereoselective preparation had been reported in the literature.[158–163] As for us, we envisaged obtaining these 1,2-amino alcohols through the condensation of the analogous 3-alkoxy allenylzinc reagent (±)-Zn-**2** with imines.

Reagent (±)-Zn-**2**, generated *in situ* by the lithiation of (methoxymethyl) (3-trimethylsilylprop-2-ynyl) ether (**35**) with *s*BuLi in the presence of TMEDA, was then rapidly shown to react efficiently with various achiral imines

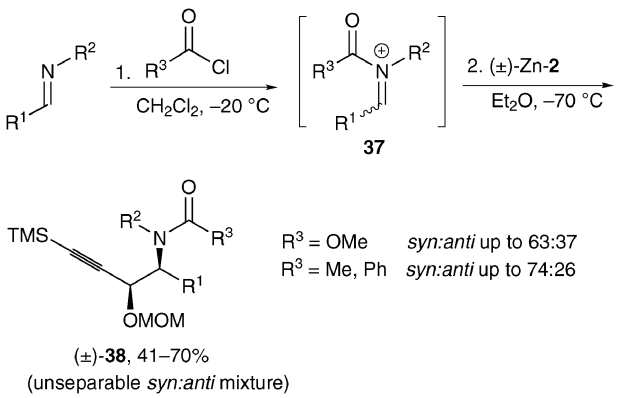


Scheme 24 Addition of (±)-Zn-**2** onto achiral imines.

(R^2 = Pr, *c*Hex, Bn), at −60 °C within 1 h, to give the corresponding *anti*-1,2-amino ethers **36** as single isomers and in high yields (Scheme 24).[164]

The *anti*-stereoselectivity of the reaction can be explained by a transition state analogous to **TS4** in Scheme 18 wherein the chlorine atom is replaced with the MOM group.

We further reasoned that the *syn*-isomers could perhaps be obtained through the reaction of (±)-Zn-**2** with iminium ions. After several attempts, we found that the optimized conditions correspond to reaction of the *in situ* formed iminium species **37** (R^2 = PMB, Pr, *c*Hex, allyl) with (±)-Zn-**2**, affording, within 2 h at −70 °C, the (±)-*syn*-1,2-amino ethers **38** as the major products (Scheme 25).[164]

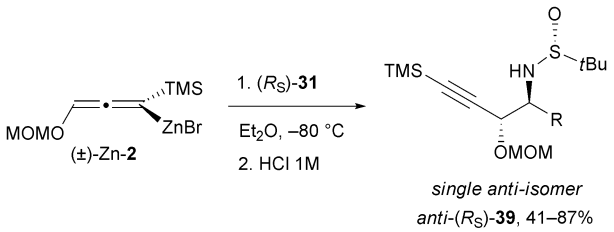


Scheme 25 Addition of (±)-Zn-**2** to iminium ions.

Unfortunately, under these conditions, only fair to modest selectivities are attained, the best results being obtained with *N*-methyl- or phenylcarbonyl iminium species (R^3 = Me or Ph). Moreover, in most cases, the major *syn*-ethers are inseparable from their *anti*-isomers, precluding the synthetic usefulness of this method.

2.2.2.2 Synthesis of enantioenriched acetylenic 1,2-amino alcohols from tBS-imines. Following our preliminary work, we envisaged the stereoselective synthesis of enantioenriched acetylenic 1,2-amino alcohols *via* the addition of (±)-Zn-**2** onto *t*BS-imines (R_S)-**31**. We found that (±)-Zn-**2** exhibits a much higher reactivity than the analogous 3-chloro species (±)-Zn-**1**. Indeed, the former reacts rapidly with *t*BS-imines (R_S)-**31** at −80 °C in Et_2O whereas the latter only reacts smoothly at room temperature in the same solvent. Thus,

performing the reaction within 1 h at −80 °C allows the corresponding *anti*-1,2-sulfinamido alkyl ethers **39** to be obtained as the major products with a high level of stereoselectivity (Scheme 26).[165]



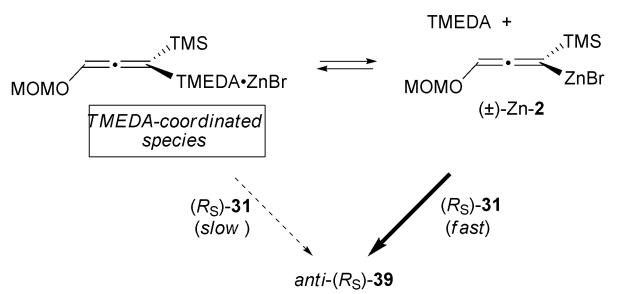
Scheme 26 Addition of (±)-Zn-**2** onto *t*BS-imines

The fact that in each case only one major *anti*-compound is formed indicates again that the *t*BS-group fully plays its role of a chiral auxiliary. Further purification by flash chromatography over silica gel allows major *anti*-ethers (R_S)-**39** to be isolated in diastereo- and enantiomerically enriched forms in excellent yields ranging from 41 to 87% (Scheme 26).

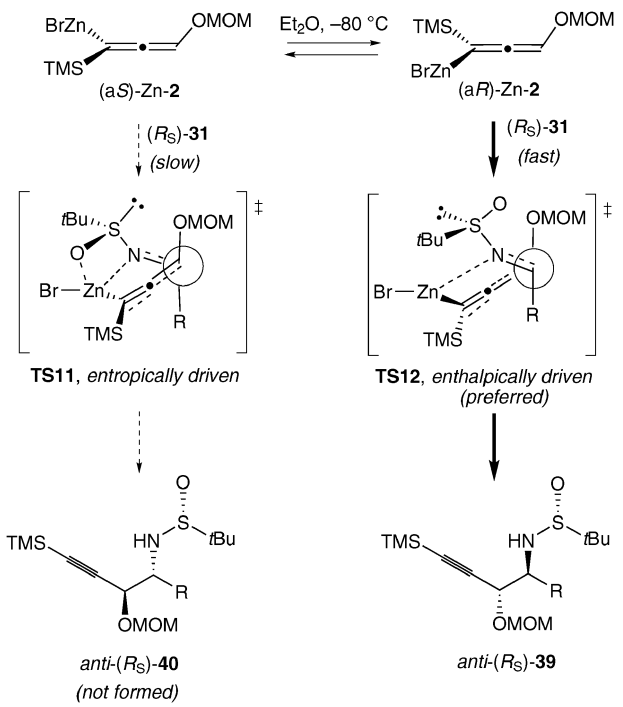
TMEDA, which is needed for the *in situ* formation of (±)-Zn-**2**, was proven to exert a dramatic influence upon both the kinetics and the stereoselectivity of the reaction. For instance, in the presence of 1 equiv. of TMEDA (with respect to (±)-Zn-**2**), the rapid addition (over a period of 2 min) of the aldimine (R_S)-**31** (with R = Pr) to (±)-Zn-**2** gives the corresponding 1,2-sulfinamido alkyl ether with only 47% conversion within 3 h at −80 °C, albeit with a high *anti* : *syn* ratio > 95 : 5. However, carrying out the reaction with only 0.1 equiv. of TMEDA results in complete conversion only after 1 h of stirring at −80 °C but with a lower *anti* : *syn* stereoselectivity of 89 : 11. This striking difference in reactivity and diastereoselectivity seems to come from an apparent lower reactivity of the allenyl (±)-Zn-**2** in the presence of 1 equiv. of TMEDA than in the presence of only 0.1 equiv. of TMEDA. Although the exact role of TMEDA is not clear, it can be assumed to coordinate the 3-alkoxy allenylzinc (±)-Zn-**2** giving a poorly reactive TMEDA-coordinated species. So, only the 3.6 equivalents of (±)-Zn-**2** that are not coordinated by TMEDA seem to react with the imine (Scheme 27).

Finally, the best result was obtained by the slow dropwise addition (over a period of 45 min *via* a syringe-pump) of the imine to (±)-Zn-**2** in the presence of 0.1 equiv. of TMEDA. By this process, complete conversion is attained with excellent stereoselectivity. This result suggests that the 3-alkoxyallenylzinc (±)-Zn-**2** is not completely configurationally stable (on the time scale defined by the rate of its reaction with the imine) at −80 °C in Et_2O. Indeed, on the hypothesis of a racemization rate of (±)-Zn-**2** comparable to the reaction rate, the addition of the imine over a period of 45 min should result in a higher dynamic kinetic resolution by giving more time to the mismatched enantiomer (a*S*)-Zn-**2** to racemize into the matched enantiomer (a*R*)-Zn-**2** (Scheme 28). As a matter of fact, under the same conditions, with less reactive α-substituted or unsaturated aldimines or with ketimines (R_S)-**31** no slow addition is needed to obtain *anti*-1,2-sulfinamido alkyl ethers as single isomers after 1 h of stirring at −80 °C. This seems to be in accordance with an apparently greater racemization rate of the (±)-Zn-**2** relative to its condensation with these less reactive imines that is recognized to result in a better dynamic kinetic resolution (Scheme 28).[136–138]

The configurations of the two newly formed stereogenic carbons were unexpected as they could not be explained by the chelate transition state **TS11** in Scheme 28, similar to **TS5** postulated with the 3-chloroallenylzinc (±)-Zn-**1**. This chelate transition state would give the *anti*-diastereoisomeric ethers (R_S)-**40** which are not observed. The stereoselectivity was then assumed to result from the high kinetic resolution of (±)-Zn-**2** through a mono-coordinated transition state **TS12** wherein the zinc atom of the allenylzinc reagent is coordinated only by the nitrogen of the imine. **TS12** has been postulated as a consequence of the higher reactivity of (±)-Zn-**2**: the mono-coordination of the zinc by the nitrogen could sufficiently activate the imine to allow the reaction to take place. In **TS12**, the imine reacts through the lowest energy conformation (see above), and the substituent on the imine and the



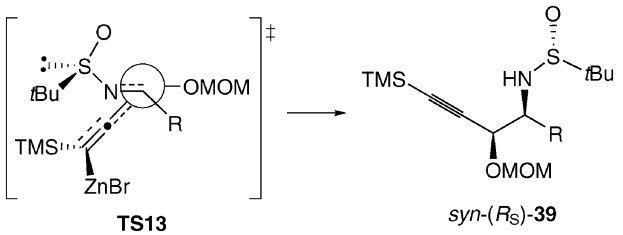
Scheme 27 Possible role of TMEDA in the addition of (±)-Zn-**2** onto *t*BS-imines.



Scheme 28 Postulated mono-coordinated transition state **TS12** for the formation of ethers *anti*-(R_S)-**39**.

(methoxymethyl) ether moiety of the zinc species adopt an *anti*-relationship to minimize steric interactions.

When the imine (R_S)-**31**, with R = *c*Hex, is reacted with (±)-Zn-**2** at 20 °C, the formation of the corresponding ether *anti*-**39** is observed with an *anti*-**39** : *anti*-**40** ratio of 49 : 51 whereas it is >95 : 5 at −80 °C. This variation in the stereoselectivity of the reaction according to the temperature may reflect the competition between transition states **TS11** and **TS12** which can be regarded as entropically and enthalpically driven, respectively.[146,147] Thus, **TS12** corresponds to the matched situation in which the (a*R*) enantiomer of (±)-Zn-**2** approaches the less hindered face of (R_S) imines, *i.e.* the *Re*-face opposite the bulky *tert*-butyl group. On the other hand, **TS11** corresponds to a mismatched situation wherein the (a*S*) enantiomer of (±)-Zn-**2** approaches the *Si*-face of (R_S)-*t*BS-imines. Furthermore, when the imine (R_S)-**31** (with R = *c*Hex) is reacted with (±)-Zn-**2** in THF at −80 °C, an *anti* : *syn* stereoselectivity of 87 : 13 was observed whereas it was >95 : 5 in Et_2O. This drop in selectivity in THF could be due to the higher basicity of this solvent which certainly weakens the coordination of the zinc atom by the nitrogen atom of the *t*-BS-imine. This makes **TS12** less favored relative to the very entropically disfavored synclinal transition state **TS13** (Scheme 29), leading to a greater amount of the corresponding *syn*-isomer **39**. **TS13** thus corresponds to another mismatched situation, *i.e.*, the reaction of the (a*S*)- enantiomer of (±)-Zn-**2** on the *Re*-face of the (R_S)-*t*BS-imines *via* a suprafacial process.

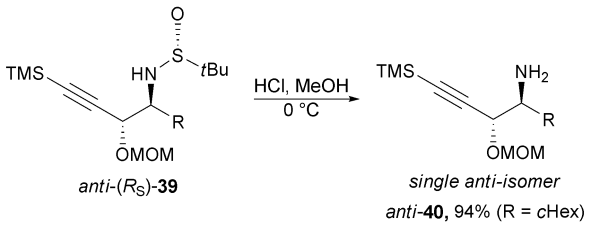


Scheme 29 Postulated synclinal transition state **TS13** for the formation of ethers *syn*-(R_S)-**39**.

At this time, we reasoned that using HMPA as a cosolvent could result in switching of the stereoselectivity of the reaction in favor of the *syn*-isomer as with the 3-chloro allenylzinc (±)-Zn-**1** (see above). Nevertheless, under such conditions, with the 3-alkoxy allenylzinc (±)-Zn-**2**, *t*BS-imines (R_S)-**31** give the corresponding *anti*-1,2-sulfinamido alkyl ethers **39** with *anti* : *syn* ratios >95 : 5. This surprising difference between (±)-Zn-**1** (X = Cl) and (±)-Zn-**2** still remains unclear to us and indicates that the *syn*-**40** isomers could not be readily prepared from (±)-Zn-**2**.

The high yielding selective deprotection of the nitrogen of ethers *anti*-**39** can be achieved by acidic removal of the *t*BS-auxiliary with dry methanolic HCl within 1 h at 0 °C as illustrated in Scheme 30.[166]

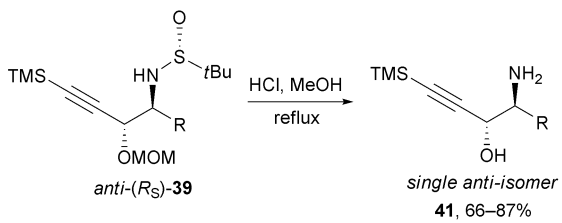
All attempts to deprotect selectively the oxygen atom by removal of the methoxymethyl ether moiety failed. Conditions involving the use of Lewis acids such as $BF_3 \cdot Et_2O$ or $MgBr_2 \cdot Et_2O$ in Et_2O or CH_2Cl_2 in the presence of an excess of ethanethiol were tested. Under such conditions no reaction



Scheme 30 Selective removal of the *t*BS-auxiliary.

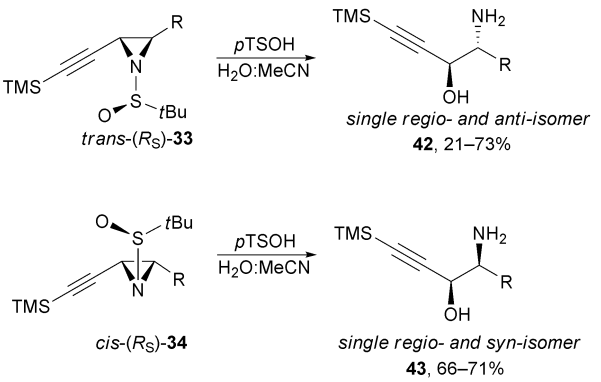
is observed at room temperature and only full deprotection occurs at reflux.

On the other hand, acetylenic *anti*-1,2-sulfinamido alkyl ethers **39** can be converted into the corresponding *anti*-1,2-amino alcohols **41** in one pot, by the treatment with dry methanolic HCl at reflux. Under these acidic conditions, the removal of the *t*BS-group on the nitrogen occurs first, followed by the deprotection of the methoxymethyl ether moiety (Scheme 31). In all cases, only traces (<5%) of 1,2-amino ethers were observed and crude acetylenic *anti*-1,2-amino alcohols **41** are obtained with high purity (>90%). They can be further isolated in good to excellent yields (66–87%) as diastereo- and enantioenriched products after flash chromatography over silica gel.



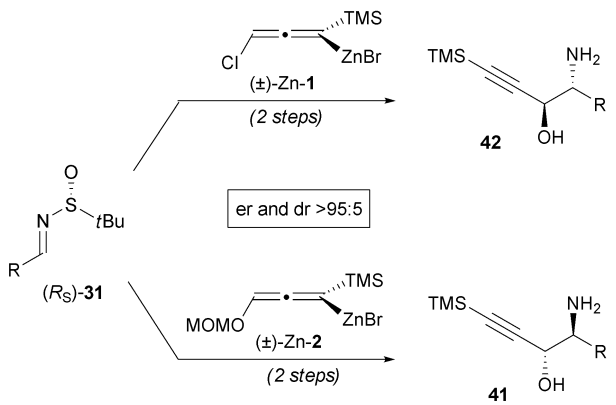
Scheme 31 Conversion of ethers *anti*-(R_S)-**39** into acetylenic *anti*-1,2-amino alcohols **41**.

2.2.2.3 Synthesis of enantioenriched acetylenic 1,2-amino alcohols through the ring-opening of tBS-aziridines. Despite their great synthetic potential, relatively little investigation has been undertaken of the reactivity of acetylenic aziridines.[10] For instance, acetylenic aziridines can be regarded as valuable precursors for the preparation of 1,2-amino alcohols through aziridine ring opening.[167] After many attempts, we have shown that acetylenic *t*BS-aziridines react with water under acidic conditions (*p*TsOH in MeCN–H_2O) to yield the corresponding 1,2-amino alcohols.[168] The ring opening reaction occurs through the nucleophilic attack of water at the propargylic carbon, followed by deprotection of the nitrogen atom by removal of the *t*BS-group. Under these conditions, *anti*-1,2-amino alcohols **42** and **43** are obtained in a highly regio- and stereoselective fashion from *trans*-**33** and *cis*-**34** aziridines, respectively (Scheme 32). This method appears to be efficient with a wide variety of *t*BS-aziridines. Moreover, although it is applicable neither with aziridines bearing unsaturated side-chains (with R = vinyl or phenyl) nor with 3,3-disubstituted aziridines derived from ketimines, it allows various acetylenic *syn*-1,2-amino alcohols to be obtained.



Scheme 32 Ring-opening of *t*BS-aziridines.

Interestingly, both enantiomers of the *anti*-acetylenic 1,2-amino alcohols can be obtained, in a highly stereoselective manner, from the same enantiopure *t*BS-imines. Indeed, the reaction of *t*BS-imines with (±)-Zn-**1** affords, in two steps *via* *trans*-*t*BS-aziridines, *anti*-1,2-amino alcohols **42** which are enantiomeric to those obtained, *i.e.* **41**, through the reaction of the same imines with (±)-Zn-**2**. In other words, the sense of the induction simply depends on the nature of the heteroatom in the allenylzinc species (Scheme 33).



Scheme 33 Formation of both enantiomers of *anti*-acetylenic 1,2-amino alcohols from *t*BS-imines (*R*S)-**31**.

2.2.3 Conclusions and perspectives: *en route* to the stereoselective synthesis of natural compounds. The addition of 3-hetero-substituted allenylzinc species (±)-Zn-**1** and **2** to enantiopure *t*BS-imines constitutes an efficient method for the preparation of acetylenic 1,2-amino alcohols. The latter are of great synthetic interest since they are found in a number of bioactive naturally occurring products[169,170] such as alkaloids,[171–173] amino-sugars,[174] enzyme inhibitors[175–178] and antibiotics.[179,180] Also, they are frequently employed in asymmetric synthesis as chiral auxiliaries or chiral catalysts.[181] The biological importance of numerous compounds presenting the 1,2-amino alcohol pattern has meant that methods for their stereoselective preparation have been the subject of frequent publications.[182] Our methodology can thus be applied to the synthesis of naturally occurring compounds of biological interest such as sphingosines, phytosphingosines and sphinganines, which represent the three main classes of the sphingoid bases of sphingolipids, all containing an 1,2-amino alcohol unit[183] (Fig. 3).

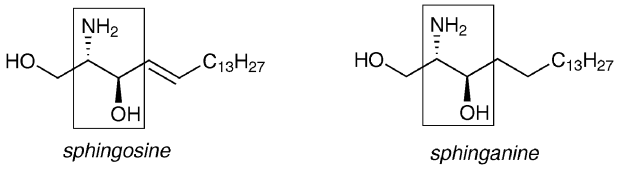
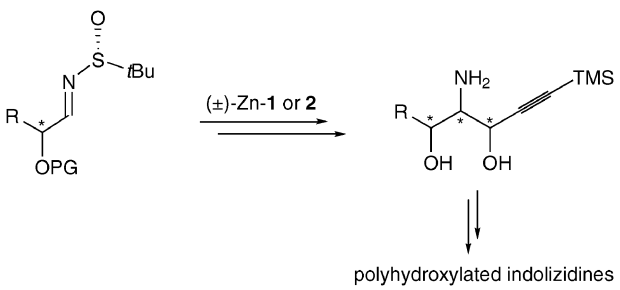


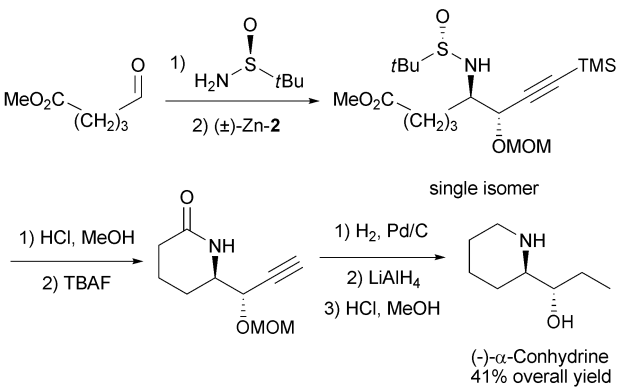
Fig. 3 Possible synthetic targets.

The reaction of reagents (±)-Zn-**1** or **2** with α-chiral *t*BS-imines can also be regarded as a valuable means of obtaining 2-amino-1,3-diols in a highly stereoselective manner. This could give access to the synthesis of nitrogen-containing heterocyclic compounds, and more particularly, the synthesis of polyhydroxylated indolizidines and quinolizidines and related compounds,[184] among which alkaloids such as (−)-swainsonine and (+)-castanospermine could be envisaged (Scheme 34).



Scheme 34 Access to polyhydroxylated indolizidines *via* 2-amino-1,3-diols.

An example of the synthetic interest of the methodologies described above is our recent straightforward synthesis of (−)-α-conhydrine.[185] Conhydrine is one of the alkaloids in hemlock *Conium maculatum* L, isolated from the seeds and leaves of this poisonous plant.[186] We have reported recently a highly stereoselective and efficient total synthesis of this natural product as depicted in Scheme 35. (−)-α-Conhydrine was obtained in seven steps and in 41% overall yield; this strategy represents the most rapid and efficient synthesis reported to date.[187]



Scheme 35 Total synthesis of (−)-α-conhydrine.

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