Creation of quaternary stereocenters in carbonyl allylation reactions

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Despite the advances in stereoselective carbonyl allylation reactions, the creation of quaternary stereocenters in the addition of 3,3′-disubstituted allylmetals to aldehydes is still a challenging issue. This feature article describes the most powerful approaches that have been devised to address this problem.

Introduction

The reaction of allylmetal reagents and carbonyl compounds is an important transformation in organic synthesis.[1] Advances in stereoselective carbonyl allylation reactions have been spurred by interest in the stereoregulated synthesis of conformationally nonrigid complex molecules such as polyhydroxylated compounds.[1b] This widespread stereocontrolled use of allylic organometallics in organic synthesis appears to have been triggered by the original articles from Buse and Heathcock,[2] Hoffmann and Zeiss,[3] and Yamamoto *et al.*[4] Since then, the most powerful reagents in synthesis for such transformations are the semimetallic allylic reagents such as those containing boron, silicon and tin. This popularity stems mainly from their ease of formation, their stability and more particularly from the predictable final relative configurations.[5] The relative stereoselection of such reactions relates to the geometry of the double bond; the *syn*/*anti* ratio reflects the *Z*/*E* ratio of the starting material. When more anionic allylic organometallic derivatives are used such as allylic lithium, magnesium and zinc reagents, the corresponding substituted allylmetal reagents are configurationally unstable, existing as mixtures of rapidly equilibrating *E*- and *Z*-isomers, even at very low temperature.[6] Therefore the relative stereoselection of such processes is usually very low. A notable exception is the use of masked allylic zinc reagents in which the high diastereoselectivity obtained is attributed to the generation of pure *E*-2-butenylzinc in the presence of the electrophile.[7]

The chiral induction in the carbonyl allylation reactions may follow several conceptually distinct routes. When the newly formed stereocenters are created under the influence of covalently bound subunits, the process is referred to as *internal stereoselection*. The resident stereocenter can be anywhere in the reactants such as:

(1) Reagent-induced stereoselectivity (chiral allyl units bearing stereogenic centers on the allyl unit)
(2) Chirally-modified allylating reagents that bear controller groups on the metal
(3) Substrate-induced stereoselectivity (chiral aldehydes).

When the allylmetal aldehyde addition operates under the influence of stereocontrolled reagents such as chiral catalysts, *external stereoselection* will be used to describe the enantiofacial outcome at the newly stereogenic centers (Scheme 1).

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Ilan Marek

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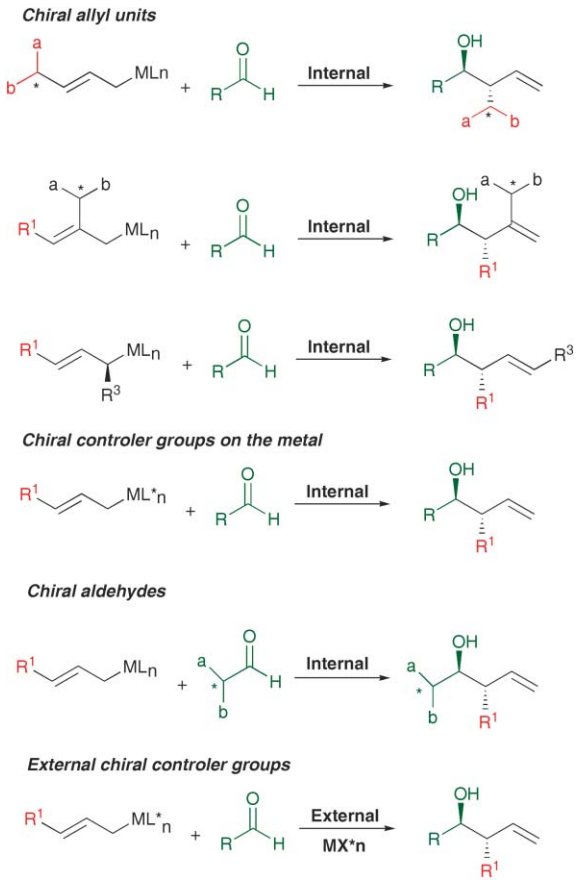


Scheme 1

However, and despite all these efforts, if one needs to construct quaternary stereocenters[8] by using one of these methods (diastereoselective reaction of 3,3′-disubstituted allylmetal with aldehydes), major problems still arose ($R^1 \neq R^2 \neq H$, Fig. 1).[9] To solve this challenging problem, two critical issues have to be solved: the first is the stereocontrol formation of geometrically defined 3,3′-disubstituted allyl organometallic reagents and the second is the chiral induction in the allylation reaction.

In this feature article, we will review the most pertinent contributions from our research group and others to this significant research area. The most logical organization of this manuscript will be by metal. In each of these subsections, stereochemical issues will be discussed.[10]

Allylic boron reagents

Following his pioneer work on chirality transfer from chiral α-substituted allylboronates to homoallylic alcohols,[11]

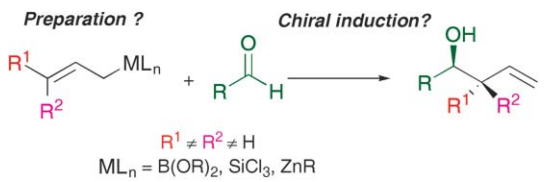


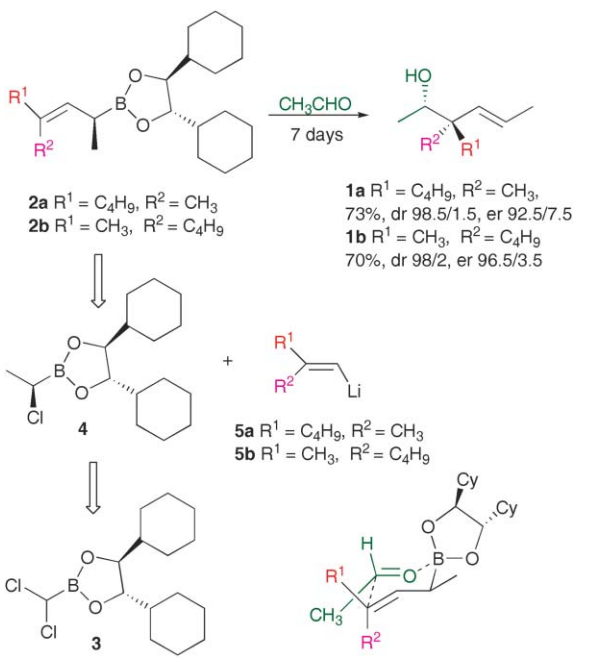
Fig. 1

Hoffmann was the first to prepare enantiomerically enriched alcohols **1a,b** possessing quaternary stereocenters from 1,3,3′-trisubstituted allylboronates **2a,b** (Scheme 2).[12] The preparation of **2a,b** goes back to Matteson's studies;[13] the dichloromethylboronate **3** was converted first into the α-chloroethylboronate **4** and then to the allylboronates **2a,b** by using vinyllithium compounds[14] **5a,b**.

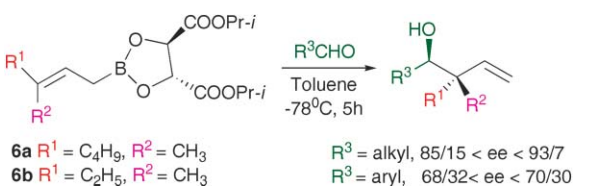
When $R^2 \neq H$, the methyl group in α-position of the allylboronate, occupies a pseudo-equatorial position to avoid any 1,3-allylic strain (see transition structure in Scheme 2).[15] The enantiomeric ratio (er) of the alcohols **1a** and **1b**, (92.5/7.5 and 96.5/3.5 respectively) is mostly related to a slight loss of enantiomeric purity in the preparation of **4**. This strategy was applied to an elegant synthesis of benzoyl-pedamide.[16]

When the resident stereocenter is the metal subunit (auxiliary-induced stereoselection) such as tartrate ester derivatives of 3,3-disubstituted allylborane **6a,b**, *in situ* formed from diisopropoxy derivatives, react with aldehydes, the corresponding homoallylic alcohols is obtained with high diastereoselectivity (generally >95%) but only moderate enantiomeric ratio (see Scheme 3).[17]

To increase the efficiency for the preparation of 3,3′-disubstituted allylboronate, a two-step, one-pot procedure preparation was recently developed.[18] The flexibility in the nature of the appendages R^1 and R^2 on the double bond would



Scheme 2



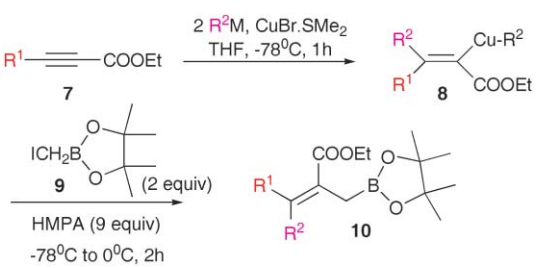
Scheme 3

be provided by the carbometalation reactions of alkynes as originally recognized by Hoffmann.[19] Therefore, the carbocupration of alkynoate esters **7** was performed and the resulting alkenylcopper intermediate **8** was trapped with iodomethane boronate **9**. As the 1-alkoxycarbonylalkenylcopper intermediate **8** is configurationally unstable above −30 °C, the alkylation reaction has to be performed in the presence of 9 equivalents of hexamethylphosphoramide (HMPA). In such case, excellent *E*/*Z* selectivities (>20/1) are observed (Scheme 4).

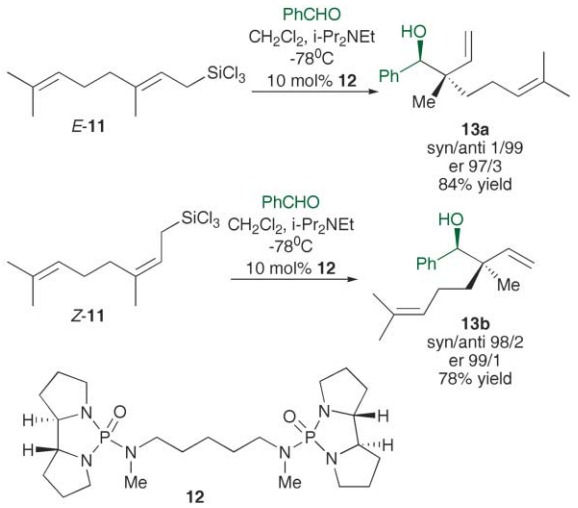
Cuprates derived from either alkyllithium or Grignard reagents may be used. The only limitation resides in the addition of vinyl- and phenylcuprates. Several attempts were made to replace the carcinogenic HMPA, but only DMPU comes the closest and must be used in much larger amounts in order to achieve similar results (40 equivalents). A more recent study of the role of additives in this carbocupration–alkylation sequence shows that HMPA plays a dual role: it stabilizes the alkenylcopper intermediate **8** by sequestering lithium cations from solution and it enhances the alkylation process. Excellent yields and diastereoselectivities are therefore also obtained with as little as 2 equivalents of HMPA provided that 1 equivalent of 12-crown-4 is included in the electrophilic quench.[20] Having in hand an easy preparation of polysubstituted allylboronates **10**, Hall nicely extended his methodology to the enantioselective additions to carbonyl compounds *via* either a carboxyester-based chiral auxiliary[21] or a dual auxiliary approach (chiral auxiliaries on both the carboxyester and boronic ester),[22] but surprisingly, this method was never used for the preparation of quaternary stereocenters, although all the necessary elements were in place to obtain high enantioselectivities.

Allylic trichlorosilane reagents

As opposite to the Lewis acid-catalyzed addition of allyltrimethylsilane to aldehydes, which lead to the *syn*-isomer irrespective of the geometry of the 3-substituted allyl species, the chiral-Lewis base catalyzed enantioselective addition of allylic trichlorosilanes reacts through a closed transition structure.[23] Following pioneering studies,[24] Denmark developed the first catalytic enantioselective additions of allylic trichlorosilanes to aldehydes by the use of chiral phosphoramides.[25] The major breakthrough came when it was found that 2,2′-bispyrrolidine-based bisphosphoramide catalyzes the addition of various allylic trichlorosilanes to aldehydes with excellent diastereo- and enantioselectivity.[26] As regards to the creation of chiral quaternary carbon centers, the two



Scheme 4

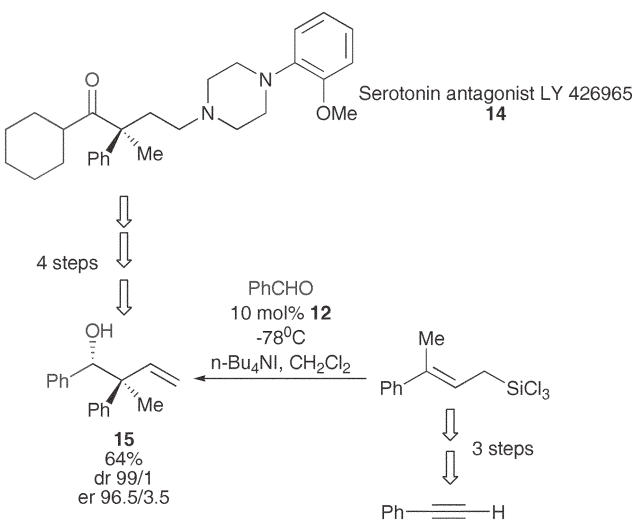


Scheme 5

trichloroallylsilanes *E*-**11** and *Z*-**11**, synthesized from geraniol and nerol respectively, were added to benzaldehyde in the presence of 10 mol% of the catalyst **12** (Scheme 5).

The sense of relative induction clearly supports the intermediacy of a siliconate complex, which reacts through a closed, chair-like transition structure. As a demonstration of such method in synthesis, it was applied to the enantioselective synthesis of serotonin antagonist (LY426965) **14** as described in Scheme 6.[27] Clearly, a more direct approach to LY 426965 would have been the addition to cyclohexanecarbaldehyde instead of benzaldehyde, which needs a further chemoselective reduction. However, when aliphatic aldehydes are used in this allylation reaction, α-chloro silyl ether is obtained.[28]

This allylation reaction of trichloroallylsilanes in the presence of a catalytic amount of phosphorus-based identity legends provides a versatile route for the construction of quaternary centers and the high fidelity between the allyl geometry and product configuration supports the hypothesis of a highly organized chair-like transition structure.[29]



Scheme 6

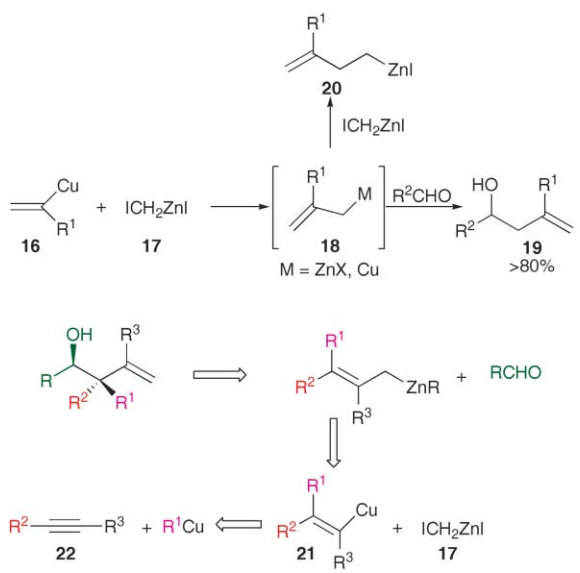
Allylic zinc reagents

Although allylzinc species were unknown for the enantioselective preparation of quaternary stereocenters due to the previously discussed metallotropic equilibrium,[6] it was envisaged that 3,3-disubstituted allylzinc derivatives would be an excellent candidate in synthesis if all the chemical steps could be combined in a single-pot operation. Indeed, it was recently reported by Knochel that the homologation reaction of alkenyl copper **16** with (iodomethyl)zinc iodide **17** represents a unique method for the direct conversion of vinyl metal **16** into allyl species **18**.[30] The reaction has to be performed in the presence of the electrophile to trap efficiently the intermediate **18** and to furnish the corresponding homoallylic alcohols **19** in good yields (Scheme 7).

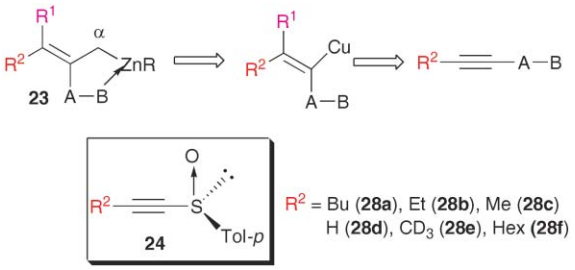
Without the presence of this *in situ* electrophilic partner, the allylic species **18** undergo further reactions with the zinc carbenoid **17** to lead to the double homologation product **20** (the reactivity of the allylzinc is higher than vinyl copper towards the zinc carbenoid).[31] On the basis of these results and with respect to quaternary stereocenters, it was postulated that the homologation reactions of β,β-disubstituted alkenylmetal species such as **21** should be a straightforward route to 3,3-disubstituted allyl zinc derivatives. Obviously, stereodefined β,β-disubstituted alkenyl metal compound **21** would easily come from a controlled carbometalation reaction of substituted alkynes **22** (Scheme 7).[14] However, even by following this new retrosynthetic approach, the metalotropic equilibrium of 3,3′-disubstituted allylzinc species **23** has still to be avoided (Scheme 8). Therefore, few additional parameters were devised to:

(1) Slow down the equilibration process of the allylic organometallic species **23** by an intramolecular chelation of an A–B unit to the zinc atom.

(2) Use this A–B chelating moiety as a source of chirality and as a regiocontrol element for a regioselective carbometalation reaction.



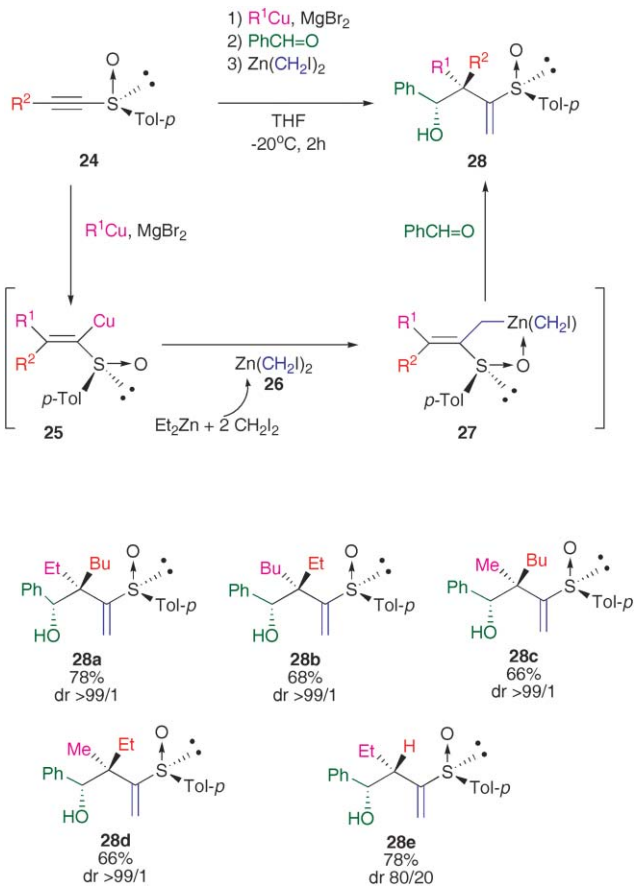
Scheme 7



Scheme 8

By combining all of these parameters, alkynyl sulfoxides **24**, easily available in large quantities by the Andersen synthesis,[32] were designed as potential starting materials (Scheme 8).

The regio- and stereospecific carbocupration of **24** with organocopper derivatives (obtained from 1 equiv. of alkylmagnesium halide and 1 equiv. of copper salt such as CuBr or CuI), provides the corresponding metalated β,β-dialkylated ethylenic sulfoxide **25** in quantitative yields (Scheme 9).[14] Then, benzaldehyde was added followed by bis(iodomethyl)-zinc carbenoid **26**, independently prepared from 1 equiv. of Et_2Zn and 2 equiv. of CH_2I_2.[33] Neither the vinylic organocopper **24** nor the zinc carbenoid **26** is reactive enough to add to aldehydes, however, **25** is readily homologated by a methylene unit with the zinc carbenoid. The *in-situ* reactive chelated allylzinc species **27** reacts diastereoselectively with



Scheme 9

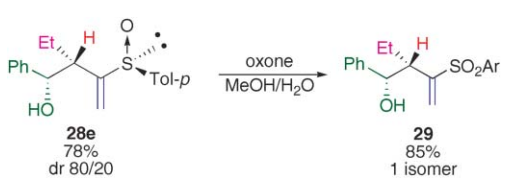
benzaldehyde, to give after hydrolysis the corresponding adducts **28** in good overall yields and in excellent diastereoselectivities (Scheme 9).[34] As shown with **28a** (R^1 = Et, R^2 = Bu) and with **28b** (R^1 = Bu, R^2 = Et), permutation of the alkyl groups of the alkyne and the organocopper reagent allows the independent formation of the two isomers at the quaternary stereocenter, respectively.[35] Even the methylcopper, known to be a sluggish group in carbocupration reaction,[14a] adds cleanly to the alkynyl sulfoxide **24a** and gives after the homologation-allylation reactions, the expected homoallylic alcohol as only one isomer (**28c**). By using this simple methodology, a chiral quaternary stereocenter with two sterically very similar alkyl groups such as ethyl and methyl can be easily prepared as single isomer (**28d**).

Interestingly, when a tertiary carbon center is created (**28e**, R^1 = Et, R^2 = H), the diastereoselectivity was eroded and two isomers were formed in an 80/20 ratio. To understand the origin of this lower diastereoselectivity, the chirality at the sulfoxide center of **28e** was removed by oxidation with oxone and the corresponding sulfone **29** was obtained as a unique isomer (Scheme 10).[36]

Therefore, the lower diastereoselectivity for **28e** (R^1 = Et, R^2 = H), comes from an incomplete diastereofacial choice in the allylation reaction. Since the S–O bond operates as an acceptor site for Lewis acids, the conformation of the sulfoxide is strongly influenced by complexation of the zinc atom and also by the *Z*-substituent (*syn* to the sulfoxide moiety)[37] of the carbon–carbon double bond.[38] Thus, for an allylic system **27** having a *Z*-substituent at the double bond, a unique conformation should be favored, avoiding 1,3-allylic strains as described in Fig. 2. Therefore, the groups on the sulfur atom are disposed in such positions that the difference in their active or inert volume may optimally induce facial selectivity for reactions, which occur at the double bond.[39] Thus, the combination of this intramolecular chelation with the related allylic strain leads to a unique conformation of the allylzinc derivatives as described in Fig. 2.

The combination of the stereoselective carbometalation (introduction of the R^1 substituent), the zinc homologation (introduction of the CH_2 unit of the allylzinc fragment), the intramolecular chelation of the zinc atom by the sulfoxide (which slow down the metalotropic equilibrium),[40] the presence of the *p*-tolyl group (shields one face) and the 1,3-allylic strain leads to very high diastereoselectivity when the allylzinc reacts with aromatic aldehydes (aryl groups occupies a pseudo-equatorial position) in a Zimmerman–Traxler chair-like transition state (Fig. 2).

Aliphatic aldehydes were also tested in this reaction but the reaction was found to be more difficult to control. Although the diastereoselectivity was usually excellent (*i.e.* with valeraldehyde dr 30/1), the reaction is very dependent of the



Scheme 10

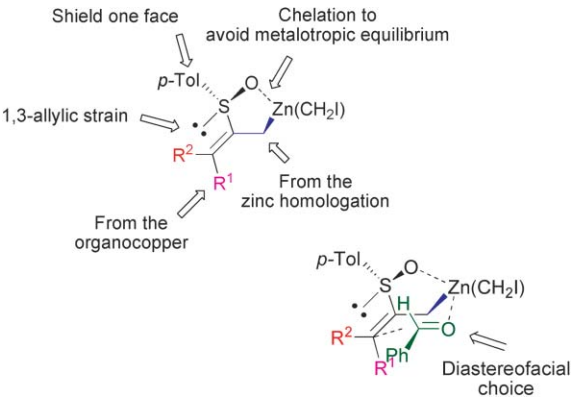


Fig. 2

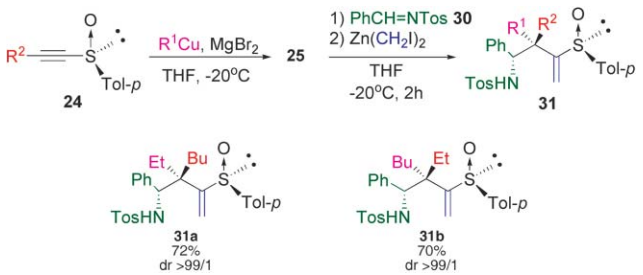
experimental conditions and more studies are currently underway to extend the scope with aliphatic aldehydes.

Imine **30** could also be used as electrophilic partners in this one-pot transformation; both diastereomers of the homoallylic amines **31a,b** were easily obtained with very high diastereoselectivities (Scheme 11). The stereochemistry observed was confirmed by X-ray analysis.

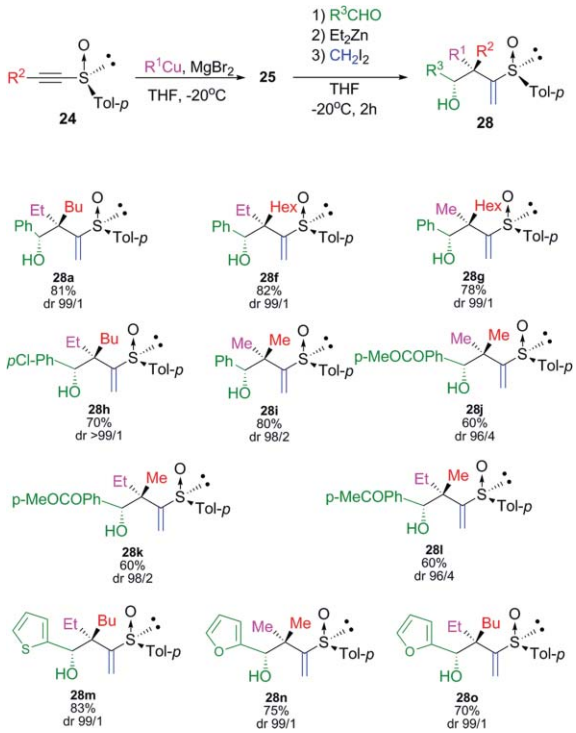
Although these carbometalation–homologation–allylation reactions led, with very high diastereoselectivity, to the corresponding homoallylic alcohols **28** and amines **31**, the bis(iodomethyl)zinc carbenoid **26** had to be prepared independently and further transferred into the reaction mixture at low temperature. To improve the reaction sequence, an easier, safer and even more straightforward procedure was developed.

The first step, namely the regio- and stereospecific carbocupration of alkynyl sulfoxides **24** with organocopper derivatives still provides the corresponding metalated β,β-dialkylated ethylenic sulfoxide **25** in quantitative yields as originally described in Scheme 9, but now aldehydes, Et_2Zn and CH_2I_2 are all added to the reaction mixture at −20 °C (Scheme 12).

As discussed previously, neither vinylcopper **25** nor Et_2Zn reacts with aldehydes, and as the transmetalation from vinylcopper to vinylzinc is a slow process at −20 °C, the reaction between Et_2Zn and CH_2I_2 occurs first to lead to the *in-situ* formation of the zinc carbenoid **26**. This carbenoid readily homologates the vinylcopper **25** into the allyl species **27**, which reacts diastereoselectively with aldehydes to give the expected homoallylic alcohols in very high diastereoselectivities (Scheme 12). This improved *in-situ* procedure led to identical diastereoselectivities as compared to the one previously described (compare **28a** in Schemes 9 and 12) in



Scheme 11

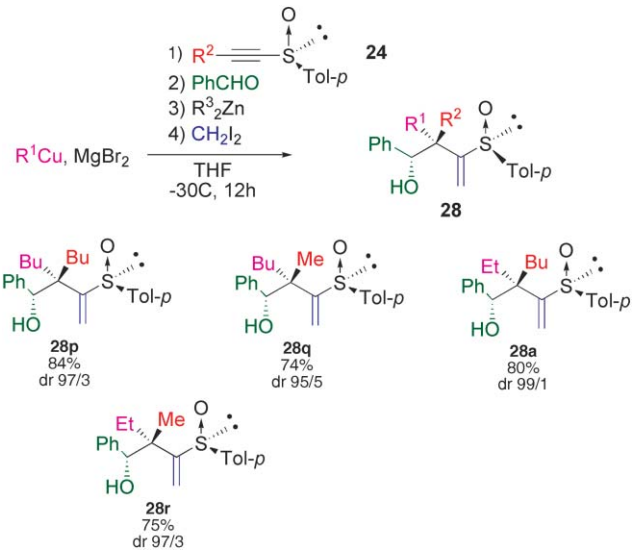


Scheme 12

slightly better yields. Several different alkyl groups were easily introduced in the carbocupration reaction, which shows the flexibility of the described method (Scheme 12). Functionalized aldehydes can also be used in this allylation reaction such as 4-chlorobenzaldehyde, 4-carbomethoxybenzaldehyde and even 4-acetylbenzaldehyde to lead to **28h,k,l**, respectively. In the last two cases, the reaction proceeds chemoselectively on the aldehyde (no trace of reaction neither on the ester nor ketone moieties). Control of the absolute configuration of remote stereocenters is also a topic of considerable interest,[41] and when the quaternary centers possess two identical alkyl groups, (**28i,j,n**, R^1 = Me, R^2 = Me), a useful level of 1,4-stereocontrol is obtained (dr 98/2 to 99/1). Finally, even heteroaromatic aldehydes can be used as electrophilic partner in this reaction (**28m,n,o**).[42]

This new approach for the allylation reaction can be ultimately further simplified by a four-component reaction. In this case, one only needs to prepare an alkylcopper derivative. Indeed, when alkynyl sulfoxide, benzaldehyde, dialkylzinc and CH_2I_2 are added simultaneously to the organocopper species in the flask, homoallylic alcohols were obtained in excellent yields and diastereoisomeric ratio as described in Scheme 13.[42]

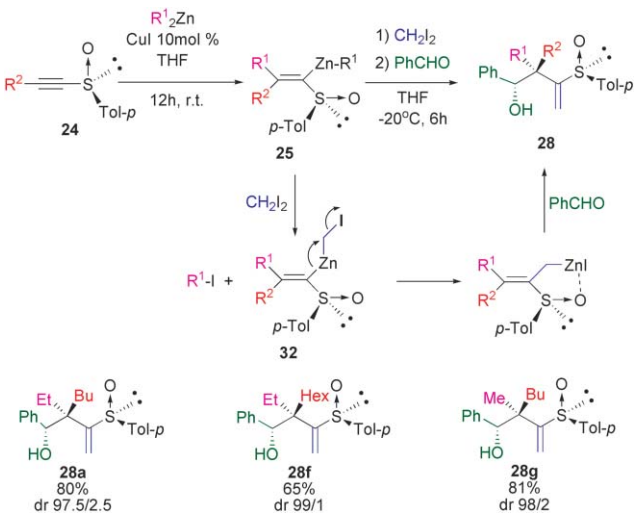
Each of these reagents reacts specifically in the appropriate order with its specific "partners", without any crossover reactions; the organocopper reagent reacts first and only with alkynyl sulfoxide, R_2Zn and CH_2I_2 form only zinc carbenoid, and these two later *in-situ* generated nucleophilic species give the allylzinc derivatives that subsequently allylate the benzaldehyde. In all cases, quaternary and tertiary stereocenters were created with excellent diastereoselectivities and in good overall yields (Scheme 13).



Scheme 13

To further increase the efficiency of this carbometalation–homologation–allylation sequence, a catalytic assembly from four simple precursors; alkynes, dialkylzinc, aldehyde and diiodomethane was also developed as reported in Scheme 14. The copper-catalyzed carbozincation of alkynyl sulfoxide[43] proceeds quantitatively with dialkylzinc to lead to the corresponding vinyl alkylzinc species **25**. Subsequently, benzaldehyde and CH_2I_2 were added to **25** and the corresponding homoallylic alcohols **28** were obtained in good yields and excellent diastereomeric ratio as shown in Scheme 14.

Mechanistically, the formation of **28** can be rationalized by an insertion of CH_2I_2 into the sp^3 carbon-zinc bond of **25** (Zn–R^1) to give the corresponding vinyl(iodomethyl)zinc carbenoid **32** with concomitant formation of R^1–I. The sp^2 carbon ligand bound to the zinc then undergoes a 1,2-shift to the electrophilic carbon attached to the same metal to furnish the new allylzinc species, which finally add to the benzaldehyde already present in the reaction mixture.[44] This type of



Scheme 14

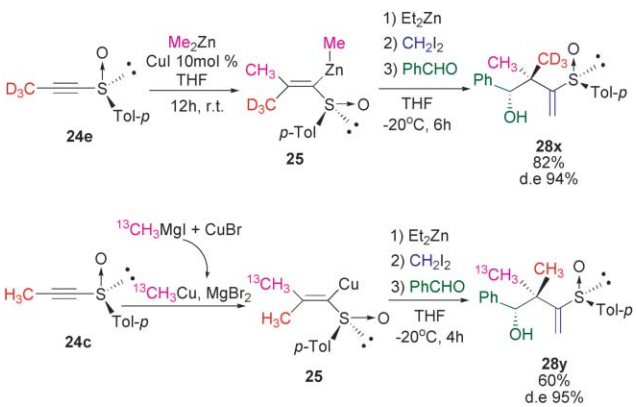
rearrangement has been already used in the tandem zirconocene homologation-aldimine allylation reaction.[45] When Et_2Zn was used both for the copper-catalyzed carbozincation and the *in-situ* homologation of vinyl (iodomethyl)zinc **32**, yields and diastereoselectivities were still excellent. On the other hand, when Me_2Zn was used, the carbozincation of **24** leads to the vinyl zinc **25** but the transformation into the carbenoid intermediate **32** (with formation of MeI), is sluggish and yields in homoallylic alcohols are low. To have a better transformation, Et_2Zn should therefore be added to promote the transformation of vinyl methylzinc into the corresponding vinyl ethylzinc, *via* a Schlenk equilibrium. Finally, alkylzinc halide such as BuZnBr can also be used for the carbometalation reaction but Et_2Zn needs to be added for the homologation reaction. Even under this condition, yields are only moderate. Although catalytic in copper, this process is much less efficient that the reaction developed in Scheme 12, where all the partners were added on the vinyl copper derivatives.[42]

The characteristic features of all these different protocols for the one-pot preparation of homoallylic alcohols are the unique combination of (1) stereocontrolled carbometalation reaction, (2) homologation into allylzinc species without scrambling the stereochemistry of the double bond, (3) diastereoselective allylation reaction of aldehydes controlled by the stereogenic center of the chiral sulfoxide. An elegant application of such methods is the diastereoselective preparation of quaternary stereocenters with the smallest possible difference between the two-alkyl groups. For this purpose, 1,1,1-trideuterioalkynylsulfoxide **24e** was initially prepared and submitted it to the copper-catalyzed methylzincation reaction as originally described in Scheme 14. Once the carbometalated product **25** was obtained, Et_2Zn, CH_2I_2 and benzaldehyde were subsequently added in the reaction mixture to lead to the expected homoallylic alcohol **28x** with very high diastereoisomeric ratio (dr 97/3 in 82% yield) as described in Scheme 15. An even smaller difference for the creation of a quaternary stereocenter was achieved by the following labeled experiment: $^{13}CH_3MgI$, easily prepared from iodomethane-^{13}C and Mg^0, was transformed into its corresponding organocopper reagent $^{13}CH_3Cu$ and added to propynyl sulfoxide **24c**. To the vinyl copper **25** was subsequently added Et_2Zn, CH_2I_2 and benzaldehyde to give the corresponding product **28y** in 60% yield and 97.5/2.5 diastereomeric excess (Scheme 15).[42] The diastereoselectivity of these reactions can be easily determined on the crude NMR (the two parents Me groups of **28i** are diastereotopic) but the absolute configurations were deduced by analogy to all our previous prepared homoallylic alcohols.

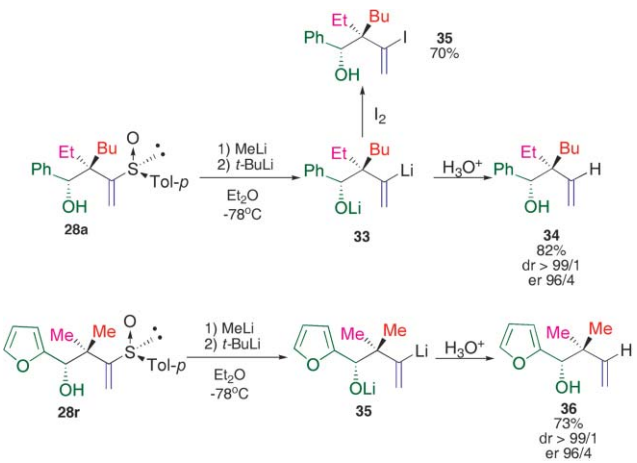
In all the examples described above for zinc allylation reactions, the chiral sulfinyl group plays a dual role as chelating element to slow down the metalotropic equilibrium as well as chiral auxiliaries for the creation of two new stereogenic centers. However, for further synthetic applications, sulfoxide should only be a chiral synthetic tool and must be disposed of at the end of the sequence.[46] Among all the possible methods, the ligand exchange reaction of sulfoxides with alkylmetals is one of the most interesting transformations, since further functionalization may increase the complexity of the carbon skeleton.[47–49] When **28a** and **28r** were first treated with MeLi and then with *t*-BuLi in Et_2O at −78 °C, the corresponding vinyl lithium species **33** and **35** were obtained, *via* a sulfoxide–lithium exchange reaction, in excellent yields as determined after acidic hydrolysis (Scheme 16). The enantiomeric ratio (er = 96/4) of **34** and **36** was determined by chiral HPLC (chiral column Chiralpak AD-H) and was found to be similar to the starting alkynyl sulfoxide **24a,c** (ee = 92%). The sulfoxide–lithium exchange reaction leading to **33** can be used for further functionalization; for instance, the addition of iodine to **33** gave the corresponding vinyl iodide **35** in 70% yield (Scheme 16).

Conclusions

Although the reaction of allylmetal reagents and carbonyl compounds is an important synthetic transformation in stereoselective synthesis, the creation of quaternary stereocenters, by reaction of 3,3′-disubstituted allylmetal with aldehydes, was still a challenging issue. In this feature article, we described the most relevant examples for such transformations. Particularly attractive are 3,3-substituted- allylboronates, bisphosphoramide-catalyzed allyltrichlorosilanes, and allylzinc addition to aldehydes. In the latter case, the combination of (1) regio- and stereoselective carbometalation reaction of heterosubstituted alkynes, (2) *in-situ* homologation of the resulting organocopper with zinc carbenoid, (3)



Scheme 15



Scheme 16

intramolecular chelation of the zinc moiety by the sulfinyl group and (4) diastereoselective allylation reaction led to the preparation of chiral homoallylic alcohol derivatives with quaternary and tertiary stereocenters in a single-pot operation from common alkynyl precursors with excellent diastereoisomeric ratio. Even when four different components are added to an organocopper derivative, the expected product is formed, which shows that each organometallic species present in the flask reacts with a single partner. Finally, a simple sulfoxide–lithium exchange allows further functionalization to give sulfoxide-free chiral substrates.

The key features in all of these described reactions are the high degree of stereocontrol, the level of predictability and the ease of execution.

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