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New Multicomponent Approach for the Creation of Chiral Quaternary Centers in the Carbonyl Allylation Reactions

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Abstract: The combined regio- and stereo-controlled carbometalation reaction of alkynyl sulfoxide followed by a zinc homologation and finally an allylation reaction led, in a single-pot operation, to chiral homoallylic alcohols in excellent yields and diastereoselectivities for the creation of chiral quaternary and tertiary centers. The key features in all of the reactions that are described in this article are the high degree of stereocontrol, the level of predictability, and "the ease of execution" which ensures success in the application of such methods. The chiral sulfinyl moiety can be finally removed by simple treatment with alkyllithiums, which allows further functionalizations of the carbon skeleton. By using one of these methods, the creation of chiral quaternary centers with the smallest possible difference, namely CD_3 versus CH_3 and $^{13}CH_3$ versus CH_3, was easily performed.

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 polypropionate-derived natural products, carbohydrates, and other 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 are the semimetallic allylic reagents such as boron, silicon, and tin. This popularity stems mainly from their ease of formation and more particularly from their stability. The reaction of substituted *E*- and *Z*-2-butenylboronates with achiral aldehydes has been used to prepare syn and anti homoallylic alcohols in high diastereoselectivity, respectively.[5] Allyl boronic ester reagents are usually involved in closed, six-membered cyclic chairlike transition states that are characterized by internal activation of the carbonyl group by the boron atom.[6] This high degree of organization in the transition structure led to the development of a myriad of chirally modified allylic boron reagents for asymmetric allylation of carbonyl compounds.[1a] Similarly, the internal stereocontrol of allylic trihalosilanes, which are electrophilic at the silicon center, is also generated through a chairlike transition structure.[7] The use of chiral Lewis bases as promoters for the asymmetric allylation and 2-butenylation of trihalosilane derivatives of aldehydes led to high enantioselectivities.[8] This mechanism contrasts with the allyl trialkylsilane and -stannane analogues, which generally react with aldehydes under the activation of an external Lewis acid by way of open transition structures.[9] More recent examples were reported where external chiral ligands play the role of Lewis acid activators.[10] When more anionic allylic organometallic derivatives are used such as allylic lithium, magnesium, and zinc reagents, the corresponding substituted alkenylmetal reagents are configurationally unstable, existing as mixtures of rapidly equilibrating E- and Z-isomers (Scheme 1), even at very

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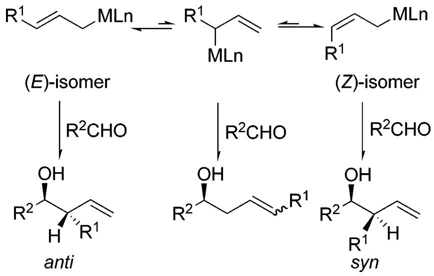
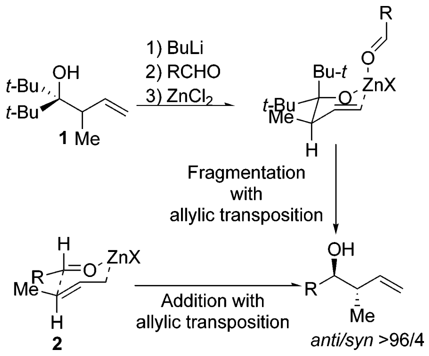
Scheme 1



Scheme 2

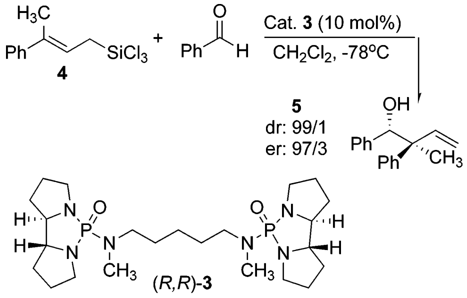


low temperature.[11] Therefore, the diastereoselectivity of such processes is usually very low.

A notable exception is the use of masked allylic zinc reagents. Indeed, as the addition of allylic organozinc reagents to carbonyl derivatives was known to proceed in a reversible manner, the sterically hindered tertiary homoallylic alcohol **1** could, upon generation of a zinc alkoxide, undergo fragmentation to generate the allylic zinc reagent **2**, which could then undergo reaction with a suitable in situ aldehyde.[12] The high diastereoselectivity obtained is attributed to the generation of pure *E*-2-butenylzinc in the presence of the electrophile (Scheme 2).

Despite all these efforts, if one needed to construct chiral quaternary carbon centers[13] by using one of these methods, major problems still arose. With respect to stereogenic quaternary centers, Hoffmann and Schlapbach were the first to show that 3,3′-disubstituted allylboronates could be used to generate stereodefined quaternary carbon centers.[14] Although these allylboronates reacted with aldehydes in the expected Zimmerman−Traxler transition structure, these reactions required 5−8 days to reach completion and the diastereoisomeric purity of the homoallylic alcohol products was lower than the initial purity of the initial allylboronates. Suzuki et al. reported a comparable stereochemical problem a few years later in similar studies.[15] More recent investigations revealed that the reaction could be sped up (12−16-h reaction time) by the presence of certain metallic salts.[16] However, the homoallylic alcohols can be obtained enantiomerically enriched only by using a dual auxiliary approach in the thermal condition (reaction time of 14 days).[17] A single-pot tandem catalytic diene diboration/carbonyl allylation[18] or hydroboration of allene/carbonyl allylation[19] reactions were recently described as new methods for the creation of quaternary stereocenters. Although racemic, a notable exception is the addition 3,3′-disubstituted allylchromium(III) reagents to aldehydes, which proceeds in a stereodivergent manner. This method allows the preparation of a variety of homoallylic alcohols bearing a quaternary center of defined relative configuration in the α-position.[20]

Scheme 3



The "state of the art" in this field belongs to Denmark and Fu, who reported the first catalytic enantioselective addition of 3,3′-disubstituted allylic trichlorosilanes **4** to aromatic aldehydes by the use of chiral 2,2′-bispyrrolidine-based bisphosphoramide **3** (Scheme 3).[21]

However, all of these previously described methods required several chemical steps for the preparation of the desired 3,3-disubstituted allylmetal species. One of the major challenges in synthesis nowadays is to assemble target molecules (here, namely homoallylic alcohols such as **5** from the reaction of 3,3′-disubstituted allylic organometallic derivatives and aldehydes) from readily available starting materials in a one-step synthesis,[22] and in a simple and straightforward manner. Therefore, we thought to develop a totally different retrosynthetic approach based on a four-component reaction.[23] Although allylzinc species were unknown for the enantioselective preparation of chiral quaternary centers due to the metallotropic equilibrium described in Scheme 1, we envisaged that these 3,3-disubstituted allylzinc derivatives should be the best candidates in synthesis if we could combine all the chemical steps in a single-pot operation. Indeed, it was recently reported by Knochel et al. that the homologation reaction of alkenyl compounds **6** with (iodomethyl)zinc iodide represents a unique method for the direct conversion of

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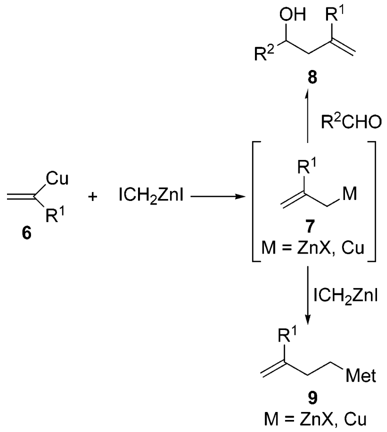
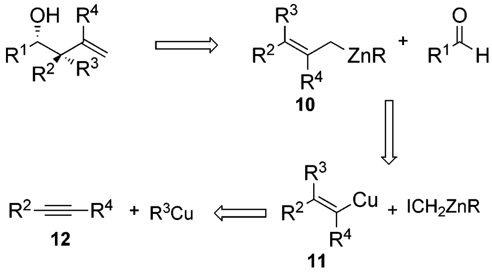
Scheme 4



Scheme 5

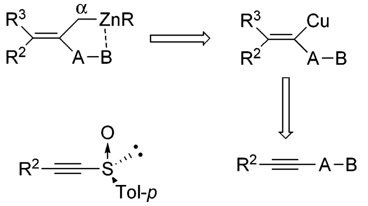


alkenylcopper derivatives into allylic zinc (or -copper) compounds **7**.[24] Moreover, the reaction has to be performed in the presence of an electrophile, to trap efficiently the intermediate **7** and to furnish the corresponding homoallylic alcohols **8** in good yields (Scheme 4).

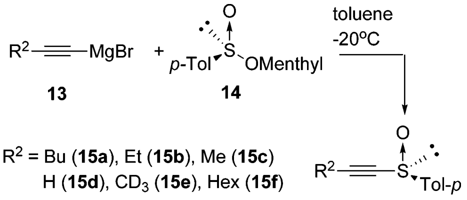
Without the presence of this in situ electrophilic partner, the allylic species **7** undergo further reactions with (iodomethylzinc) iodide to lead to the double homologated product **9** (the reactivity of allylzinc is higher than vinylcopper toward the zinc carbenoid and should be therefore trapped in situ). On the basis of these results, we reasoned that the homologation allylation reactions of alkenylmetal species such as **11** (Scheme 5) should be the most convenient in situ preparation of homoallylic alcohol derivatives **10**. With respect to quaternary centers, one has to start with stereodefined β,β-disubstituted alkenylmetal compounds **11**, which may easily come from a controlled carbometalation reaction of substituted alkynes **12** (Scheme 5).

However, even by following this new retrosynthetic approach, we still have to avoid the potential metallotropic equilibrium of 3,3-disubstituted allylzinc species **10**. Therefore, we thought to (1) increase the stability of the allylic organometallic species in its α-position by an intramolecular chelation of the zinc atom by an A−B unit (Scheme 6) and (2) use this A−B chelating moiety as a source of chirality and as a regiocontrol element for the carbocupration reaction (to lead only to a species with copper geminated to the A−B unit). By combining all of these parameters, we designed our lead starting materials as alkynyl sulfoxides (Scheme 6), easily available in large quantities.

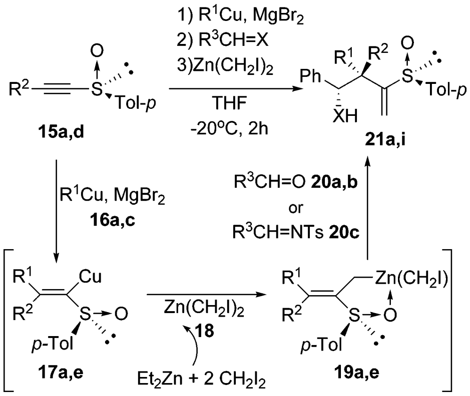
Scheme 6



Scheme 7



Scheme 8



Results and Discussion

Various alkynyl sulfoxides were easily prepared, in the range of 70−80% yields, by the Andersen synthesis[25] using (−)-menthyl (−)-(S)-*p*-toluenesulfinate[26] **14** in toluene with a solution of alkynylmagnesium bromide **13** in Et_2O at −20 °C.[27] The absolute configuration of these acetylenic sulfoxides **15a**−**f** were assigned on the basis that the Grignard reaction with sulfinate esters proceeds stereospecifically with inversion of configuration at the sulfur atom and the enantiomeric excess was determined to be of 98% for **15a** by high-performance liquid chromatography analysis on a chiral stationary phase (chiralpak AD-H Daicel) and assigned by analogy for **15b**−**f** (Scheme 7).[28]

Our first investigation concerned the regio- and stereospecific carbocupration of **15** with organocopper derivatives **16** (easily obtained from 1 equiv of alkylmagnesium halide and 1 equiv of CuX; X = Br, I), which provides the corresponding metalated β,β-dialkylated α,β-ethylenic sulfoxide **17** in quantitative yields (Scheme 8).[29] Then, to the reaction mixture, benzaldehyde was added followed by bis(iodomethyl)zinc carbenoid **18**, indepen-

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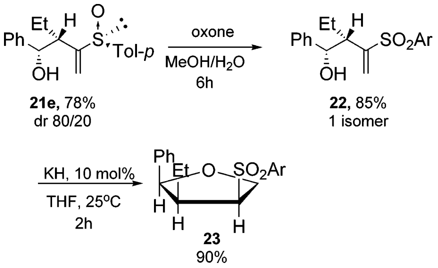
Table 1. Stereocontrol in the Allylation Reaction

entry	R^1	R^2	R^3	Pdts	de %[a]	yield, %[b]
1	Et **16a**	Bu **15a**	Ph **20a**	**21a**	>98	78
2	Bu **16b**	Et **15b**	Ph **20a**	**21b**	>98	68
3	Me **16c**	Bu **15a**	Ph **20a**	**21c**	>98	66
4	Me **16c**	Et **15b**	Ph **20a**	**21d**	>98	66
5	Et **16a**	H **15d**	Ph **20a**	**21e**	60	78
6	Et **16a**	Bu **15a**	Ph **20c**	**21f**	>98	72
7	Bu **16b**	Et **15b**	Ph **20c**	**21g**	>98	70
8	Et **16a**	Bu **15a**	Bu **20b**	**21h**	94	60
9	Me **16c**	Et **15b**	Bu **20b**	**21i**	94	60

[a] Determined on the crude ^{1}H and ^{13}C NMR. [b] Determined after purification by chromatography on silica gel.

Scheme 9



dently prepared from 1 equiv of Et$_2$Zn and 2 equiv of CH$_2$I$_2$.[30] Neither the vinylic organocopper **17**[31] (the nucleophilicity of organocopper reagents is strongly influenced by the nature of the organocopper itself[32] and particularly organocopper bearing sulfur functionality at the α-position[33]) nor the zinc carbenoid is reactive enough to add to aldehydes or imines; however, **17** is readily homologated by a methylene unit with the zinc carbenoid. The in situ reactive chelated allylzinc species **19** reacts diastereoselectively with benzaldehyde **20a** to give after hydrolysis the corresponding adducts **21a**−**d** in good overall yields and in excellent diastereoselectivities (Scheme 8, Table 1, entries 1−4).[34]

The stereochemistry observed in this one-pot reaction was confirmed by X-ray analysis of **21a** and **21c**, and the configurations of other reaction products were assigned by analogy. As shown with **21a** ($R^1 = $ Et, $R^2 = $ Bu; Table 1, entry 1) and **21b** ($R^1 = $ Bu, $R^2 = $ Et; Table 1, entry 2), permutation of the alkyl groups of the alkyne and the organocopper reagent allows the independent formation of the two isomers at the quaternary carbon center, respectively.[35] Even the methylcopper, known to be a sluggish group in carbocupration reaction,[36] adds cleanly to the alkynyl sulfoxide **15a** and gives after the homologation allylation reactions the expected homoallylic alcohol as only one isomer (**21c**; see Table 1, entry 3). By using this simple methodology, a chiral quaternary carbon center with two sterically very similar alkyl groups such as ethyl and methyl can be easily prepared as a single isomer

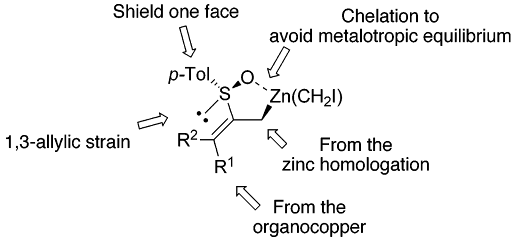


Figure 1.

(**21d**; Table 1, entry 4). Interestingly, when a tertiary carbon center is created (**21e**, $R^1 = $ Et, $R^2 = $ H; Table 1, entry 5), the diastereoselectivity was eroded and two isomers were formed in a 80/20 ratio. To understand the origin of this lower diastereoselectivity, we first removed the chirality at the sulfoxide center of **21e** by simple oxidation with oxone and the corresponding sulfone **22** was obtained as a unique isomer (Scheme 9).

Thus, we can conclude that the enantiofacial choice of the allylation reaction was not completely controlled when the R^2 substituent on the alkyne was a hydrogen[37] (the cis relationship between the ethyl and phenyl substituents in the tetrahydrofuran ring **23** was obtained by a 5-endo-trig cyclization of **22** and determined by NOE experiments).[38] 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)[39] of the carbon−carbon double bond (compare entries 1−4 with 5, Table 1).[40] Thus, for an allylic system **19** having a Z-substituent at the double bond, a unique conformation should be favored, avoiding 1,3-allylic strains as described in Figure 1. 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.[41] Thus, the combination of this intramolecular chelation with the related allylic strain leads to a unique conformation of the allylzinc derivatives as described in Figure 1.

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 prevents the metallotropic equilibrium),[42] 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 benzaldehyde (aryl groups occupies a pseudoequatorial position) in a Zimmerman−Traxler chairlike transition state (Figure 2).

Imine **20c** can also be used as an electrophilic partner in this one-pot transformation (see Table 1, entries 6 and 7); both diastereomers of the homoallylic amines **21f**,**g** are easily obtained with very high diastereoselectivities. Finally, aliphatic

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(35) Both diastereomers at the carbinols centers are different by ^{1}H NMR; both of them were independently prepared by oxidation of the benzylic alcohol into phenyl ketone followed by further nonselective reduction.

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(37) The hydrometalation of **15a** does not lead to the opposite stereoisomer. See: Huang, X.; Duan, D.; Zheng, W. *J. Org. Chem.* **2003**, *68*, 1958.

(38) Auvray, P.; Knochel, P.; Normant, J. F. *Tetrahedron Lett.* **1985**, *26*, 4455.

(39) Hoffmann, R. W. *Chem. Rev.* **1989**, *89*, 1841.

(40) Tietze, L. F.; Schuffenhauer, A.; Schreiner, P. R. *J. Am. Chem. Soc.* **1998**, *120*, 7952.

(41) For examples of 1,3-allylic strains controlling diastereoselective reactions of vinyl sulfoxides, see: (a) Koizumi, T.; Hakamada, I.; Yoshii, E. *Tetrahedron Lett.* **1984**, *25*, 87. (b) Posner, G. H. *Acc. Chem. Res.* **1987**, *20*, 72. (c) Pyne, S. G.; Griffith, R.; Edwards, M. *Tetrahedron Lett.* **1988**, *29*, 2089.

(42) When the same reaction was repeated on terminal alkyne (without the chiral sulfoxide as chelating unit), the reaction proceeds but leads to two diastereomers in a 1:1 ratio.

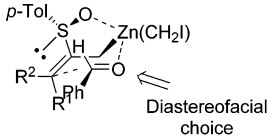
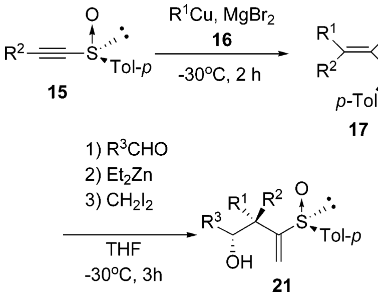


Figure 2.

Scheme 10



aldehydes were tested in this reaction, but the reaction was found to be more difficult to control. Although the diastereoselectivity is usually excellent (see Table 1, entries 8 and 9; dr 30/1; 94% de), the reaction is very dependent on the experimental conditions, and more studies are currently underway to extend the scope with aliphatic aldehydes.

Although these carbometalation−homologation−allylation reactions led, with very high diastereoselectivity, to the corresponding homoallylic alcohol and amine derivatives, we had to prepare independently the bis(iodomethyl)zinc carbenoid and further transferred it into the reaction mixture at low temperature. To improve our reaction sequence, we developed an easier and more straightforward procedure described as follows.

The first step, namely the regio- and stereoselective carbocupration of alkynyl sulfoxides **15** with organocopper derivatives **16**, still provides the corresponding metalated β,β-dialkylated α,β-ethylenic sulfoxide **17** in quantitative yields as originally described in Scheme 8, but now aldehydes Et_2Zn and CH_2I_2 are all added to the reaction mixture at −20 °C (Scheme 10). As discussed previously, neither vinylcopper **17** 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 **18**. This carbenoid readily homologates the vinylcopper **17** into the allyl species **19**, which reacts diastereoselectively with aldehydes to give the expected homoallylic alcohols in very high diastereoselectivities (Scheme 10 and Table 2).

This improved in situ procedure led to identical diastereoselectivities as compared to the one previously described (compare entry 1 of Tables 1 and 2) in slightly better yields. Several different alkyl groups were easily introduced in the carbocupration reaction, which shows the flexibility of the described method (Table 2, entries 1−3). Functionalized aldehydes can also be used in this allylation reaction, such as 4-chlorobenzaldehyde **20d**, 4-carbomethoxybenzaldehyde **20e**, and even 4-acetylbenzaldehyde **20f**. In the last two cases, the reaction proceeds chemoselectively on the aldehyde (no trace of reaction either on the ester or on the ketone moieties).

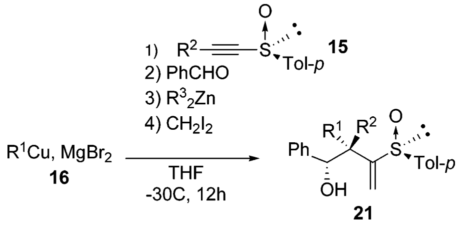
Control of the absolute configuration of remote stereocenters is also a topic of considerable interest,[43] and when the quaternary centers possess two identical alkyl groups (Table 2, entries 5, 6, and 10, $R^1 = R^2 =$ Me), a useful level of 1,4-stereocontrol is obtained (de 96−98%). The absolute configuration was determined by X-ray analysis of **21m** and **21r** and assigned by analogy for **21n**. Finally, even heteroaromatic aldehydes can be used as electrophilic partners in this reaction (Table 2, entries 9−11). This new approach for the allylation reaction can be even further simplified by a real four-component reaction. In this case, one only needs to prepare an alkylcopper derivative. Indeed, alkynyl sulfoxide, benzaldehyde, dialkylzinc, and CH_2I_2 are added simultaneously to the organocopper species in the flask as described in Scheme 11.

Table 2. Allylation Reaction with in Situ Preparation of Zinc Carbenoid

Entry	R^1	R^2	R^3	Pdts	d.e.%[a]	Yield,%[b]
1	Et **16a**	Bu **15a**	Ph **20a**	**21a**	98	81
2	Et **16a**	Hex **15f**	Ph **20a**	**21j**	98	82
3	Me **16c**	Hex **15f**	Ph **20a**	**21k**	98	78
4	Et **16a**	Bu **15a**	p-Cl-C_6H_4 **20d**	**21l**	>98	70
5	Me **16c**	Me **15c**	Ph **20a**	**21m**	98	76
6	Me **16c**	Me **15c**	p-MeOOC-C_6H_4 **20e**	**21n**	94	60
7	Et **16a**	Me **15c**	p-MeOOC-C_6H_4 **20e**	**21o**	96	60
8	Et **16a**	Me **15c**	p-MeOC-C_6H_4 **20f**	**21p**	94	60
9	Et **16a**	Bu **15a**	 **20g**	**21q**	98	83
10	Me **16**	Me **15c**	 **20h**	**21r**	98	75
11	Et **16a**	Bu **15a**	 **20h**	**21s**	98	70

[a] Determined on the crude ^1H and ^{13}C NMR and correlated by chiral HPLC (chiralpak AD-H). [b] Determined after purification by chromatography on silica gel.

Scheme 11



Initially, we checked that this four-component reaction proceeds well with identical alkyl groups such as alkylcopper and dialkylzinc ($R^1 = R^3 =$ Bu) in order to avoid crossover reactions. The chiral homoallylic alcohol **21t** was isolated in 84% yield and 94% diastereomeric excess for the remote 1,4-induction (see Table 3, entry 1). When the same reaction with the same two organometallic species (BuCu, $MgBr_2$, and Bu_2Zn) was performed on a different alkynyl sulfoxide such as **15c** ($R^2 =$ Me), the corresponding chiral homoallylic alcohol **21u** was obtained in good yield and diastereomeric ratio (see Table 3, entry 2). Then, both alkyl groups of the alkylcopper and alkynyl sulfoxide were identical ($R^1 = R^2 =$ Bu), whereas the nature of the alkyl group on the dialkylzinc was different (R^3 = Et). Even in this condition, the reaction leads to **21t** in

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(43) (a) Donnelly, S.; Thomas, E. J.; Arnott, E. A. *Chem. Commun.* **2003**, 1460. (b) Mikami, K.; Shimizu, M.; Zhang, H.-C.; Maryanoff, B. E. *Tetrahedron* **2001**, *57*, 2917 and references therein.

Table 3. Four-Component Carbonyl Allylation Reaction

entry	R^1	R^2	R^3	Pdts	de %[a]	yield, %[b]
1	Bu **16b**	Bu **15a**	Bu	**21t**	94	84
2	Bu **16b**	Me **15c**	Bu	**21u**	90	74
3	Bu **16b**	Bu **15a**	Et	**21t**	96	78
4	Et **16a**	Bu **15a**	Et	**21a**	>98	80
5	Et **16a**	Me **15c**	Et	**21v**	95	75

[a] Determined on the crude ^{1}H and ^{13}C NMR. [b] Determined after purification by chromatography on silica gel.

Scheme 12

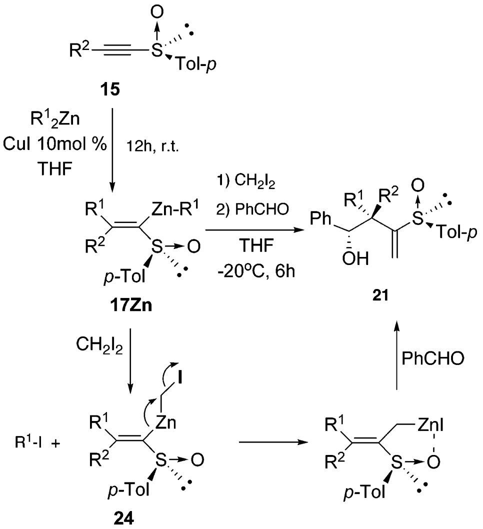

Table 4. Copper-Catalyzed Allylation Reaction

entry	R^1	R^2	Pdts	de %[a]	yield, %[b]
1	Et **16a**	Bu **15a**	**21a**	95	80
2	Et **16c**	Hex **15f**	**21j**	>98	65
3	Me **16c**	Bu **15a**	**21c**	96	81[c]
4	Bu **16b**	Hex **15f**	**21w**	>98	57[d]

[a] Determined on the crude ^{1}H and ^{13}C NMR. [b] Determined after purification by chromatography on silica gel. [c] Et_2Zn was added after the copper-catalyzed carbozincation. [d] BuZnBr was used as initial organometallic species.

excellent yield and diastereomeric excess (Table 3, entry 3) without any crossover addition products having an ethyl group on it. However, when Et_2Zn was used instead of Bu_2Zn, a higher diastereomeric ratio was obtained (de 96% instead of 94%, compare entries 3 and 1, Table 3). This discrepancy may be rationalized by a faster in situ preparation of zinc carbenoid with Et_2Zn than with Bu_2Zn. Therefore, we can conclude from this experiment that the carbocupration of alkynyl sulfoxide **15** with an organocopper is faster than any copper to zinc transmetalation (no formation of EtCu which would have led to the formation of the homoallylic alcohol **21a**). Only when methylcopper was used for the carbometalation reaction, some crossover reactions were detected in trace amounts (not reported in Table 3), due to the very slow carbocupration reaction. Then, in the last two experiments (Table 3, entries 4 and 5), two different alkyl groups for the organocopper and the alkynyl sulfoxide were used with Et_2Zn as a precursor for the zinc carbenoid; in both cases, chiral quaternary and tertiary centers were created with excellent diastereoselectivities and in good overall yields.

Thus, each of these reagents reacts specifically in the appropriate order with its specific "partners", without any crossover reactions (with the exception of MeCu); the organocopper reagent reacts first and only with alkynyl sulfoxide, R_2-Zn 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.

To further increase the efficiency of this new approach, we finally developed an unprecedented catalytic assembly from these four simple precursors: alkynes, dialkylzinc, aldehyde, and diiodomethane as reported in Scheme 12. The copper-catalyzed carbozincation of alkynyl sulfoxide[44] proceeds quantitatively with dialkylzinc to lead to the corresponding vinyl alkylzinc species **17Zn**. Subsequently, benzaldehyde and CH_2I_2 were added to **17ZN**, and the corresponding homoallylic alcohols **21** were obtained in good yields and excellent diastereomeric ratio, as shown in Scheme 12 and Table 4.

Mechanistically, we can rationalize the formation of **21** by an insertion of CH_2I_2 into the sp^3 carbon−zinc bond of **17Zn** to lead to the corresponding vinyl(iodomethyl)zinc carbenoid **24** with concomitant formation of R−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 adds to the benzaldehyde already present in the reaction mixture.[45] This type of rearrangement has been already used in the tandem zirconocene homologation−aldimine allylation reaction.[46]

When Et_2Zn was used for both the copper-catalyzed carbozincation and the in situ formation of the vinyl(iodomethyl)zinc **24**, yields were moderate to good and the diastereoselectivities were excellent (see Table 4, entries 1 and 2). On the other hand, when Me_2Zn was used, the carbozincation of **15a** still led to **17Zn** but the transformation into the carbenoid intermediate **24** (with formation of MeI) was sluggish and yields in homoallylic alcohols were therefore low (vinyl sulfoxide **17** coming from the hydrolysis of **17Zn** was isolated in 40% yield, not represented in the table). To have a better transformation, Et_2Zn should be also added to transform the vinyl methylzinc into the corresponding vinyl ethylzinc, via the Schlenk equilibrium, which then leads to the vinyl(iodomethyl)zinc **24** and then to the corresponding allylzinc derivative (Table 4, entry 3). Finally, alkylzinc halide such as BuZnBr can also be used for the carbometalation reaction (Table 4, entry 4), but Et_2Zn needs to be added for the homologation reaction. Even in this condition, yields are only moderate.

Four different protocols are described herein for the one-pot preparation of homoallylic alcohols for the creation of quaternary and tertiary chiral centers. In all these methods, very high diastereoselectivities were usually obtained due to the unique combination of (1) stereocontrolled carbometalation reaction, (2) homologation into allylzinc species without scrambling the stereochemistry of the double bond, and (3) diastereoselective

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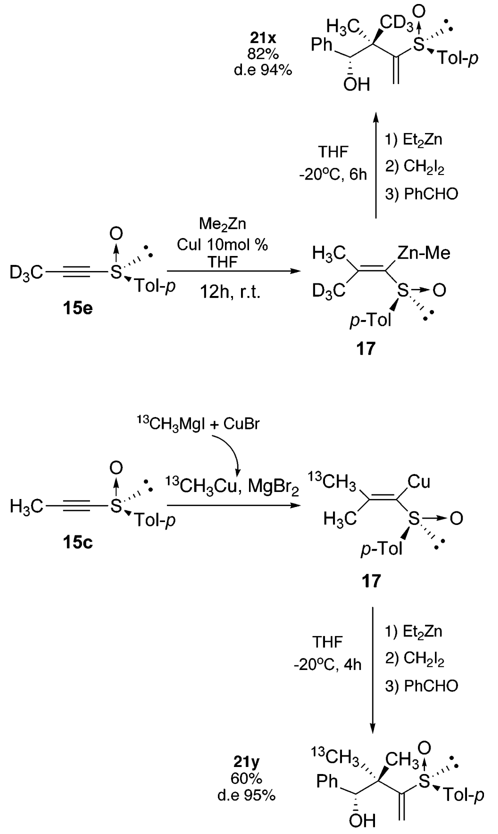
(44) Maezaki, N.; Sawamoto, H.; Yoshigami, R.; Suzuki, T.; Tanaka, T. *Org. Lett.* **2003**, *5*, 1345.

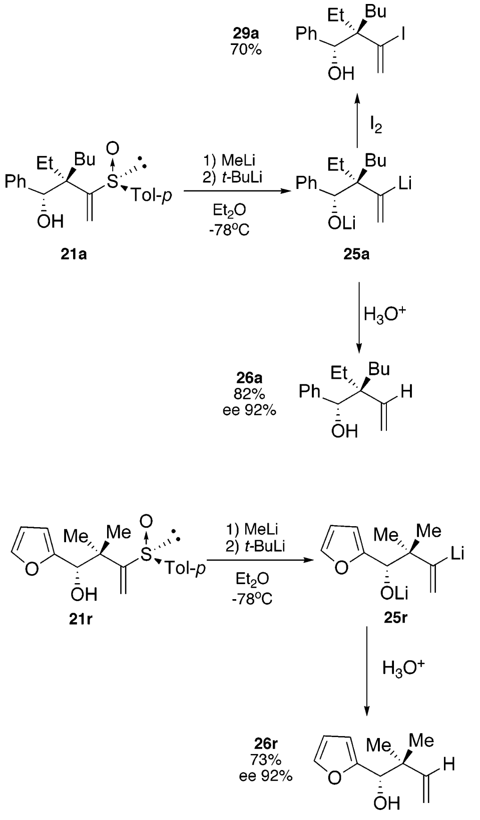
(45) (a) Marek, I. *Tetrahedron* **2002**, *58*, 9463. (b) Charette, A. B.; Marcoux, J. F. *J. Am. Chem. Soc.* **1996**, *118*, 4539. (c) McWilliams, J. C.; Amstrong, J. D.; Zheng, N.; Bhupathy, M.; Volante, R. P.; Reider, P. J. *J. Am. Chem. Soc.* **1996**, *118*, 11970. (d) Shibli, A.; Varghese, J. P.; Knochel, P.; Marek, I. *Synlett* **2001**, 818.

(46) (a) Wipf, P.; Kendall, C. *Org. Lett.* **2001**, *3*, 2773. (b) Wipf, P.; Kendall, C.; Stephenson, C. R. *J. Am. Chem. Soc.* **2001**, *123*, 5122. (c) Wipf, P.; Kendall, C.; Stephenson, C. R. J. *J. Am. Chem. Soc.* **2003**, *125*, 761. (d) Wipf, P.; Pierce, J. G. *Org. Lett.* **2005**, *7*, 3537. (e) Wipf, P.; Stephensom, C. R. J. *Org. Lett.* **2005**, *7*, 1137. (f) Wipf, P.; Werner, S.; Woo, G. H. C.; Stephenson, C. R. J.; Walczak, M. A. A.; Coleman, C. M.; Twining, L. A. *Tetrahedron* **2005**, *61*, 11488.

Scheme 13



Scheme 14



allylation reaction of aldehydes controlled by the stereogenic center of the homochiral sulfoxide. Having in hands these methods, we thought to apply them for the diastereoselective preparation of a chiral quaternary centers with the smallest possible difference between the two alkyl groups. For this purpose, we initially prepared 1,1,1-trideuteriopropynylsulfoxide **15e** and submitted it to our copper-catalyzed methylzincation reaction as originally described in Scheme 12. Once the carbometalated product **17Zn** was obtained, Et_2Zn, CH_2I_2, and benzaldehyde were subsequently added in the reaction mixture to lead to the expected homoallylic alcohol **21x** with very high diastereoselectivity (de 94% in 82% yield) as described in Scheme 13. An even smaller difference for the creation of a quaternary center was achieved by the following labeled experiment: $^{13}CH_3MgI$, easily prepared from iodomethane−^{13}C and Mg°, was transformed into its corresponding organocopper reagent $^{13}CH_3Cu$ and added to propynyl sulfoxide **15c**. To the vinylcopper **17** was subsequently added Et_2Zn, CH_2I_2, and benzaldehyde to give the corresponding product in 60% yield and 95% diastereomeric excess (Scheme 13). The diastereoselectivity of these reactions can be easily determined on the crude NMR (the two parents Me groups of **21m** are diastereotopics), but the absolute configurations were deduced by analogy from all our previously prepared homoallylic alcohols.

In all the examples cited above, the chiral sulfinyl group plays a unique role as chiral auxiliaries for the creation of two new stereogenic centers. However, for further applications, sulfoxide should only be a chiral synthetic tool and must be disposed of at the end of the sequence.[47] Among all the possible methods, the ligand exchange reaction of sulfoxides with alkylmetals is one of the most interesting transformations, although the sulfoxide cannot be reused, since further functionalization may increase the complexity of the carbon skeleton.[48] In this context, we[49] and others[50] have recently described the unique preparation of vinylmetal derivatives from vinyl sulfoxides. When **21a** and **21r** were first treated with MeLi and then with *t*-BuLi in Et_2O at −78 °C, the corresponding vinyllithium species **25a**,**r** were obtained, via a sulfoxide−lithium exchange reaction, in excellent yields as determined after acidic hydrolysis (Scheme 14). The enantiomeric ratio (er = 96/4) of **26a** and **26r** was determined by chiral HPLC (chiral column Chiralpak AD-H) and was found to be similar to the starting alkynyl sulfoxide **15a**,**c** (er = 96/4).

The sulfoxide−lithium exchange reaction leading to **25a** can be used for further functionalization; for instance, the addition

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(47) For a review, see: Posner, G. H. *The Chemistry of Sulphones and Sulphoxides*; Patai, S., Rappoport, Z., Stirling, C. J. M., Eds.; Wiley: Chichester, 1988.

(48) (a) Leroux, F.; Schlosser, M.; Zohar, E.; Marek, I. The Preparation of Organolithium Reagents and Intermediates. In *The Chemistry of Organolithium Compounds*; Rappoport, Z., Marek, I., Eds.; Wiley: New York, 2004; p 435. (b) Cohen, T.; Doubleday, M. D. *J. Org. Chem.* **1990**, *55*, 4784. (c) Cohen, T.; Bhupathy, M. *Acc. Chem. Res.* **1989**, *22*, 152. (d) Yus, M. Arene-Catalyzed Lithiation. In *The Chemistry of Organolithium Compounds*; Rappoport, Z., Marek, I., Eds.; Wiley: New York, 2004; p 647.

(49) (a) Farhat, S.; Marek, I. *Angew. Chem., Int. Ed.* **2002**, *41*, 1410. (b) Farhat, S.; Zouev, I.; Marek, I. *Tetrahedron* **2004**, *60*, 1329. (c) Abramovitch, A.; Varghese, J. P.; Marek, I. *Org. Lett.* **2004**, *6*, 621. (d) Varghese, J. P.; Zouev, I.; Aufauvre, L.; Knochel, P.; Marek, I. *Eur. J. Org. Chem.* **2002**, 4151. (e) Chinkov, N.; Chechik, H.; Majumdar, S.; Marek, I. *Synthesis* **2002**, 2473. (f) Chinkov, N.; Majumdar, S.; Marek, I. *J. Am. Chem. Soc.* **2002**, *124*, 10282. (g) Chinkov, N.; Majumdar, S.; Marek, I. *J. Am. Chem. Soc.* **2003**, *125*, 13258.

(50) For some representative examples of sulfoxide−Li exchange, see: (a) Satoh, T. *Chem. Rev.* **1996**, *96*, 3303. (b) Satoh, T.; Itoh, N.; Watanabe, H.; Koide, H.; Matsuno, H.; Matsuda, K.; Yamakawa, K. *Tetrahedron* **1995**, *51*, 9327. (c) Satoh, T.; Hanaki, N.; Kumarochi, Y.; Inoue, Y.; Hosaya, K.; Sakai, K. *Tetrahedron* **2002**, *58*, 2533. (d) Satoh, T.; Yamada, N.; Asano, T. *Tetrahedron Lett.* **1998**, *39*, 6935.

of iodine to **25a** gave the corresponding vinyl iodide **29a** in 70% yield.

Conclusions

The combination of the (1) regio- and stereoselective carbometalation reaction, (2) in situ homologation of the resulting organocopper with the zinc carbenoid, (3) 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 centers in a single-pot operation from common alkynyl precursors. Even when four components were added at the beginning on organocopper derivatives, each organometallic species present in the flask reacts with a single partner to give the expected product at the end of the sequence. The key features in all of these reactions are the high degree of stereocontrol, the level of predictability, and the ease of execution. Finally, a simple sulfoxide−lithium exchange allows further functionalization of these sulfoxide-free chiral substrates.

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Supporting Information Available: Experimental procedure, spectra data of all compounds, as well as X-ray analysis of selected compounds (CIF, PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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