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New regio-, stereo-, diastereo-, and enantioselective one-pot reactions mediated by organometallic derivatives*

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Abstract: In the first part of the lecture, we will discuss the one-pot preparation of chiral homoallylic alcohol and amine derivatives by a copper-catalyzed four-component reaction. In this process, three new carbon–carbon bonds as well as a quaternary and a tertiary chiral center are created with excellent regio- and diastereoselectivities. When the reaction was performed without adding external electrophiles, a β-elimination reaction took place to give polysubstituted allenes in good overall yields. This strategy of zinc-homologation followed by a β-elimination reaction was also synthetically used for the transformation of sp^3 sulfoxides into olefins with potential application in asymmetric synthesis. Finally, in the second part of this lecture, the stereoselective preparation of metallated dienes in only two chemical steps from commercially available products will be described. This new strategy is based on a tandem allylic C–H bond activation of a remote ω-double bond followed by an elimination reaction.

INTRODUCTION

The complexity of organic target molecules is constantly increasing, and novel strategies allowing the efficient formation of new carbon–carbon bonds between functionalized moieties are needed. The chemist's ability to make targets of utmost complexity, however, must not hide the fact that the reach of synthesis to the practical construction of elaborated products lags far behind. A seemingly trivial, but rather serious limitation in practice is set by the mere number of steps accumulating in linear sequences and by the extensive protecting-group strategies used.

These drawbacks are serious, and by advocating the "economy of steps" as a priority issue, new and more efficient methodologies have to be developed. Despite the progress in this area, a much larger panel of reactions achieving a significant increase in structural complexity per chemical steps is necessary. This is particularly true for transformations, which involve more than one bond-making event, and particularly if functional groups are present in the carbon skeleton. Indeed, the need for preparing complex polyfunctional molecules in the total synthesis of natural products [1] and in pharmaceutical research requires the development of new selective organometallic reagents [2] and catalysts for organic synthesis [3]. Then the chemo-, regio-, diastereo-, and even enantioselective creation of several functionalized carbon–carbon bond in a one-pot reaction in lieu of multiple group manipulations will result

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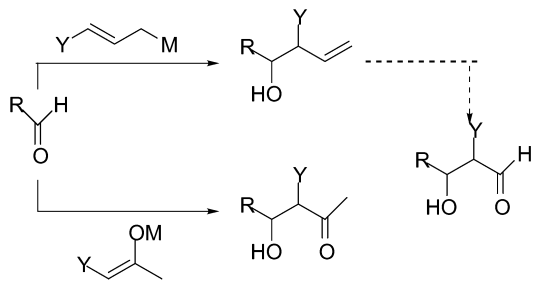
in a better orchestration of retrosynthetic analysis. This relatively new topic of research was recently internationally boosted by the launching of a new journal *Advanced Synthesis and Catalysis* in which Prof. Ryoji Noyori, Nobel Prize Laureate in Chemistry and chairman of the editorial board, stated: "Despite the extraordinary masterworks of total synthesis in the last century, the development of practical and efficient synthetic methodologies is still in its infancy. The need for efficient and practical synthesis remains one of the greatest intellectual challenges with which chemists are faced in the 21st Century".

To meet these challenging problems, we have to develop the synthesis of several new polyreactive and functionalized intermediates, which will be able to create consecutively the same number of carbon–carbon bonds as in a multi-step process, but in a single-pot operation [4]. In this lecture, we will describe some of our results in this field.

DIASTEREO- AND ENANTIOSELECTIVE PREPARATION OF HOMOALLYLIC ALCOHOLS

The enantioselective addition of allylmetal reagents to aldehydes is a powerful method for stereoselective carbon–carbon bond formation [5] and is often employed for the stereoregulated synthesis of conformationally nonrigid complex molecules, such as macrolide- and polypropionate-derived natural products [5a]. Special attention has been paid to aldol reactions, which constitute one of the fundamental bond constructions in biosynthesis. The reaction of allylic organometallic reagents with aldehydes is synthetically analogous to the aldol addition of metal enolates, since the resulting homoallyl alcohol can be easily converted to the aldol product.



Scheme 1

Since the pioneering discovery for the stereocontrol allylation of carbonyl derivatives by Heathcock [6], Hoffmann [7], and Yamamoto [8], the overwhelming majority of examples which proceed with excellent diastereo- and enantioselectivity lead to the creation of chiral tertiary carbon centers in allylic position [5,9]. On the contrary, only very few general methods are available for the stereoselective construction of chiral quaternary carbon centers for the allylation reaction as well as for the aldol condensation [10]. Regarding the allylation reaction, the first problem to be solved is to control the metallotropic equilibrium, and, therefore, most of the efforts were directed toward the preparation of stereochemically pure 3,3-disubstituted allylsilanes, stannanes, or boranes [5,11]. However, these few methods required either several chemical steps for the preparation of geometrically pure 3,3-disubstituted allylmetal reagents [10a–d], or when prepared in a single-pot operation, the control of the asymmetric induction with chiral auxiliaries was achieved only for symmetrically 3,3-disubstituted allylmetal [10a]. Concerning the aldol reaction, the creation of stereochemically pure quaternary center is even more difficult as the control of the stereochemistry of α,α'-disubstituted enolate is a major problem in synthesis [12].

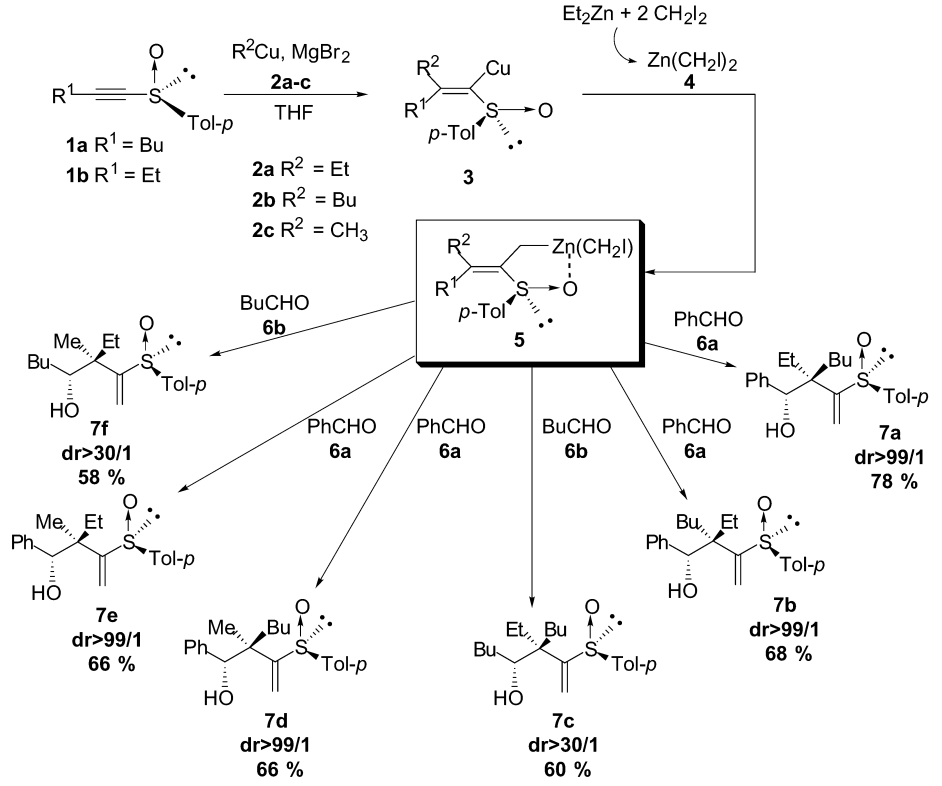
Therefore, the development of new reactions for the creation of several functionalized carbon–carbon bond in a one-pot reaction in lieu of multiple reactions should not only result in a bet-

ter orchestration of the retrosynthetic analysis as stated before, but also opens new synthetic possibilities in organic chemistry.

Herein, we report the first direct entry into enantiomerically pure quaternary centers [12] in a single-pot operation from very common starting materials. Our approach was based on the successive reaction of the readily available racemic or chiral alkynyl sulfoxides **1a,b**, with organocopper reagents **2**, aldehydes or imines and bis(iodomethyl)zinc carbenoid **4**. Chiral 1-hexynyl-*p*-tolyl-(*S*)-sulfoxide **1a,b** are easily prepared by sulfinylation of alkynyl magnesium bromide with (–)-menthyl-(*R*)-*p*-toluenesulfinate [13].

First, the regio- and stereospecific carbocupration reaction of alkynyl sulfoxide **1a,b** with organocoppers **2a–c**, easily prepared from alkylmagnesium halide and CuBr, provides the corresponding metallated β,β-dialkylated α,β-ethylenic sulfoxide **3** in quantitative yield [14]. The reaction mixture is then treated with aldehydes **6a,b** followed by the bis(iodomethyl)zinc carbenoid **4** (Scheme 2) [15]. The vinylic copper reagent **3**, as well as the zinc carbenoid **4**, are not reactive enough to add to the aldehyde derivatives while **3** is, however, readily homologated by a methylene unit with the carbenoid **4**, affording in situ a highly reactive allylic zinc and copper species **5** [16], which react diastereoselectively with the electrophiles, giving after hydrolysis the corresponding adducts in good overall yields with a very high diastereoselectivity (Scheme 2). The zinc carbenoid homologation followed by the allylation reaction occur in less than 5 min at –15 °C. The formation of mainly one diastereomer is in strong contrast with the addition of substituted allylzinc halide to aldehydes, which usually occurs without diastereoselectivity [17].

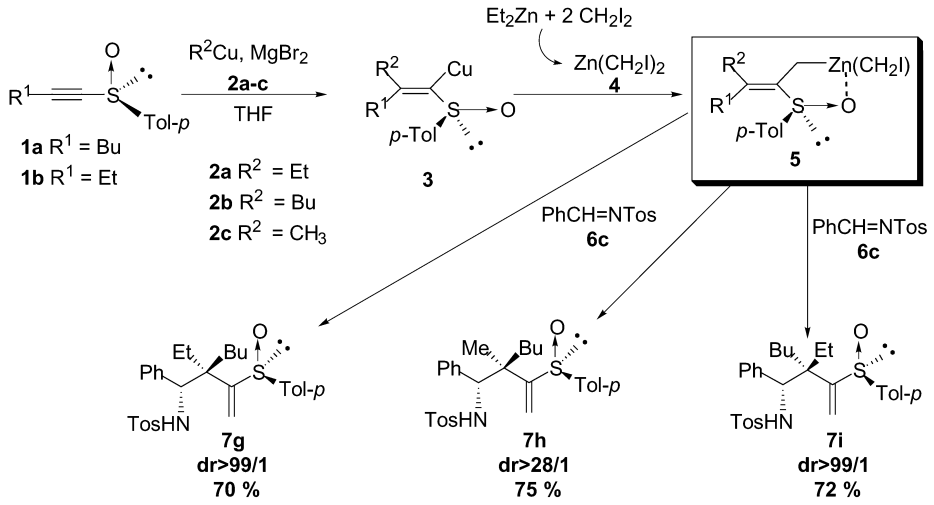
The stereochemistry observed in this one-pot four-component reaction was confirmed by X-ray analysis of **7a** and **7c**, and the configurations of other reaction products were assigned by analogy. Whatever the electrophiles used (aromatic **6a** or aliphatic aldehydes **6b**), excellent diastereo- and



Scheme 2

enantiomeric ratio were obtained in good overall yields as described in Scheme 2. As shown with **7a** (R^1 = Bu, R^2 = Et) and **7b** (R^1 = Et, R^2 = Bu), 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. Even the methyl copper, known to be a sluggish group in the carbocupration reaction [18], adds cleanly to the alkynyl sulfoxide and gives after the homologation-allylation reactions the expected homoallylic alcohol as mainly one isomer.

When the same four-component one-pot reaction was performed with *N*-sulfonyl aldimines instead of carbonyl groups, excellent to complete diastereoselectivities are also obtained as reported in Scheme 3.

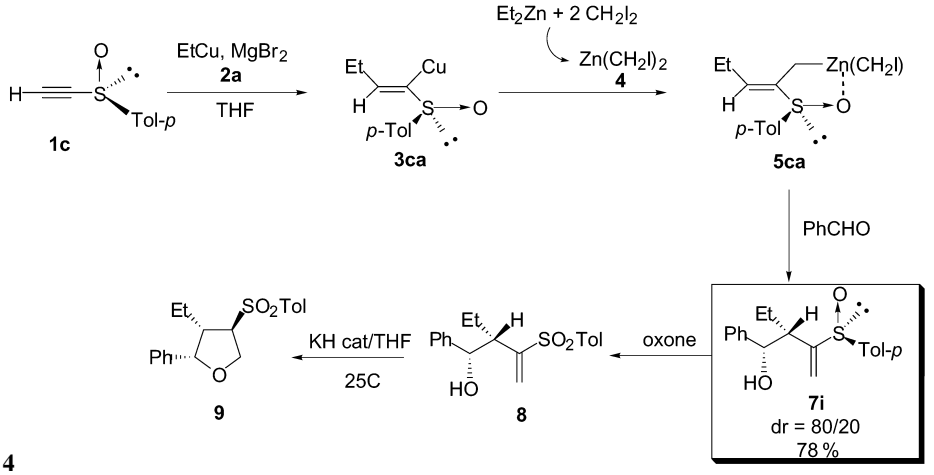


Scheme 3

Here again, both diastereoisomers at the quaternary center are easily prepared by interconverting the starting alkynyl sulfoxide and the alkyl copper reagent (see formation of **7g** and **7i**).

Interestingly, when the same reaction was applied to ethynyl sulfoxide **1c** for the one-pot preparation of two tertiary chiral centers, a mixture of two isomers was obtained in a 80/20 ratio (Scheme 4).

After oxidation of the sulfoxide into sulfone, only one set of diastereoisomers is obtained, indicating that this low diastereoisomeric ratio of 80/20 is due to a moderate diastereofacial choice between



Scheme 4

the 3-substituted allylzinc and the aldehyde. Moreover, treatment of the homoallylic alcohol **8** with catalytic amount of KH led to the polysubstituted tetrahydrofuran ring **9** as single isomer via a 5-*endo*-trig cyclization [19]. The determination of the relative configuration of **9** was deduced from nuclear Overhauser effect (NOE), and, therefore, the stereochemistry of the homoallylic alcohols **8** and **7**i was deduced to be *syn*.

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*-substitution of the carbon–carbon double bond (compare Schemes 2 and 3 with 4 for the diastereoselectivity). It is likely that the additional R^1-substituent causes severe 1,3-allylic strain [20], and the most stable conformer is the one having the lone pair of the sulfoxide eclipsing the double bond. Thus, the combination of this intramolecular chelation with the related allylic strain [20] leads probably to a unique conformation of the allyl zinc derivatives as described in Fig. 1a. Moreover, simple diastereoselection in the reaction of allylic zinc derivatives with aldehydes is usually critically dependent on the configurational stability of the reagent [11]. As a general rule, most substituted allylic zinc reagents are sensitive to sequential 1,3-metal shifts (1,3-metallotropic rearrangement) [21] that result in *E*- to *Z*-olefin isomerization. In this particular case, no isomerization of the primary allyl zinc derivative **5** is observed since the aldehyde, present in the reaction mixture, reacts instantaneously with **5**. Therefore, aldehyde or imine moieties **6a–c** reacts with 3,3-disubstituted allyl zinc **5** with the bulky substituent at the pseudo-equatorial position. In this conformation, one face of the allyl group is shielded by the *p*-tolyl residue at the sulfur. Thus, this level of stereoselectivity is rationalized by the combination of all these parameters (intramolecular chelation—stabilization of the polysubstituted allylzinc—1,3-allylic strain—shielding of one face) in the Zimmerman–Traxler chair-like transition state (Fig. 1b).

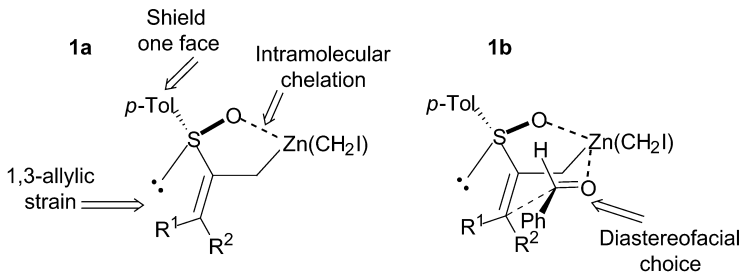
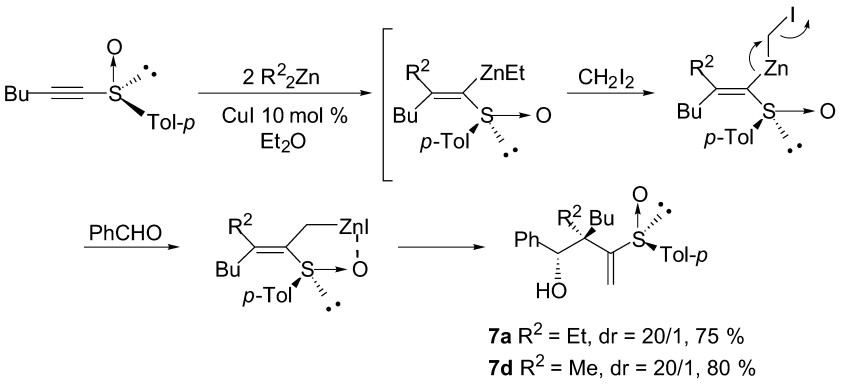


Fig. 1

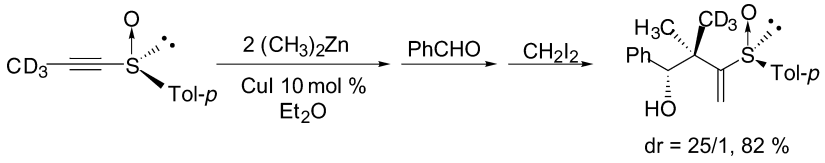
To further increase the efficiency of our new approach, we found an unprecedented catalytic assembly from these four simple precursors: alkynyl sulfoxides, dialkylzinc, aldehyde, and diiodomethane as described in Scheme 5. The copper-catalyzed carbozincation of alkynyl sulfoxide **1a,d** quantitatively leads to the vinyl zinc derivative. In this carbometallation reaction, 2 equiv of R_2Zn are necessary for a fast and reproducible carbozincation reaction [22]. Then, the aldehyde is first added followed by diiodomethane, and after stirring overnight at room temperature, homoallylic alcohols are obtained with a slightly lower diastereomeric ratio of 20/1 in good isolated yields. This lower ratio (20/1 as compared to 99/1) is attributed to the difference of temperature between reactions with preformed zinc carbenoid followed by the allylation (–15 °C as described in Scheme 2) and the in situ generated (overnight at room temperature as described in Scheme 5).

Although we must await further investigations to elucidate completely the mechanism of the in situ carbenoid formation [23], we believe that the rate-determining step of the copper-catalyzed reaction is the formation of the carbenoid.



Scheme 5

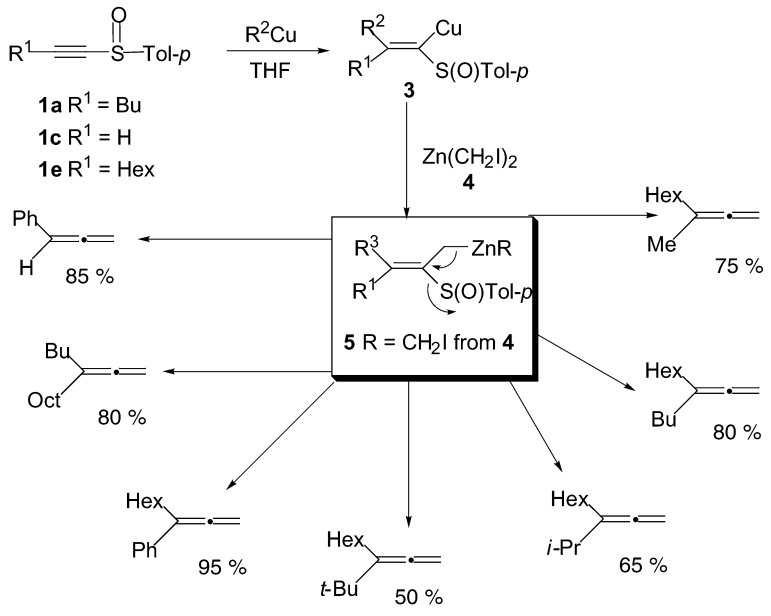
By using this very simple four-component methodology, we were able to prepare the smallest possible difference in the creation of a quaternary center in which a CH_3 vs. CD_3 groups were stereoselectively introduced as described in Scheme 6 [24].



Scheme 6

SYNTHESIS OF POLYSUBSTITUTED ALLENES

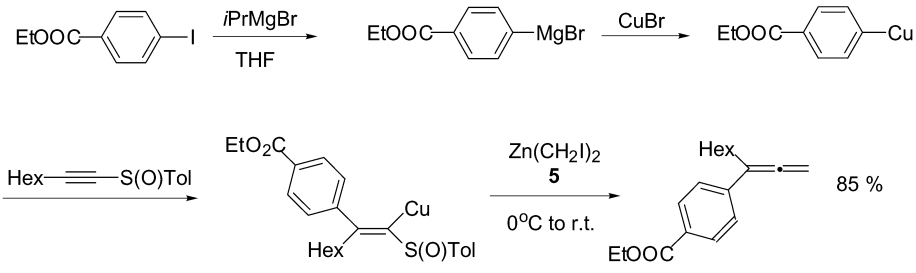
When no external electrophiles were added to the reaction mixture, a β-elimination reaction of the intermediate **5** led to the formation of substituted allenes in good overall yields (Scheme 7) [25]. The



Scheme 7

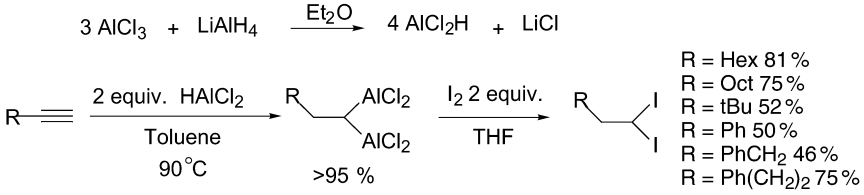
scope of this reaction is broad since primary (Me, Bu, and Oct), secondary (*i*-Pr), and even tertiary alkyl groups (*t*-Bu) all added cleanly to alkynyl sulfoxides to afford first the corresponding vinyl copper species and then the allene through the homologation/β-elimination sequence. Although the yield decreases slightly, as expected, with the degree of substitution of the alkyl copper [18], the reaction proceeds smoothly in all cases. Even aryl copper adds cleanly either to the octynyl or ethynyl sulfoxides to lead to the corresponding allenes in excellent yields.

The recently reported iodine-magnesium exchange reaction for the preparation of functionalized magnesium reagent [26] also enhances the scope of the synthesis of 1,1-disubstituted propadiene. Indeed, treatment of ethyl-4-iodobenzoate with *i*-PrMgBr lead to the corresponding functionalized aryl magnesium halide (Scheme 8). By a transmetallation reaction with copper salt, the organocopper was formed and added to the alkynyl sulfoxide **1**. This is the first example of a carbocupration reaction of an alkyne with a functionalized aryl derivative and it occurred quantitatively. Then, the homologation followed by the β-elimination reaction gave the expected allene in 85 % isolated yield (yield based on the starting 4-ethyl-iodobenzoate after 5 consecutive steps) (Scheme 8).



Scheme 8

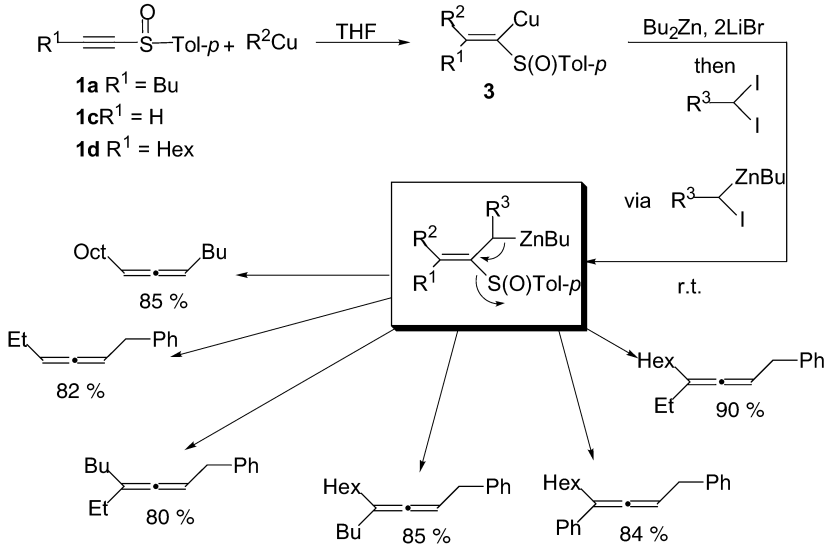
Then, we turned our attention to the synthesis of 1,3-di- and 1,1,3-trisubstituted propadiene. In this context, it was necessary to perform the homologation reaction with a secondary zinc carbenoid. However, their uses in organic synthesis are mainly limited [27] to their in situ preparations for the cyclopropanation reactions [28]. Moreover, secondary carbenoid derivatives are generally prepared from gem-dihaloalkanes by metal-halogen exchange and more specifically from 1,1-diiodoalkanes since they are far more reactive than the corresponding other halogens [29]. Unfortunately, 1,1-diiodoalkanes are also more difficult to prepare because of this high C–I bond reactivity. Indeed, few methods were reported for their preparations and to date, the more versatile approach is based on the alkylation of the diiodomethyl lithium or diiodomethyl sodium with reactive electrophiles [30]. The major drawback of this strategy is that these reactants are unstable at temperature above –95 °C, which preclude the preparation on a large scale. As we needed a more general approach for the preparation of 1,1-diiodoalkanes, we have used the chemistry of 1,1-dialuminioalkane, easily obtained from double hydroalumination of alkynes [4], followed by iodinolysis [31].



Scheme 9

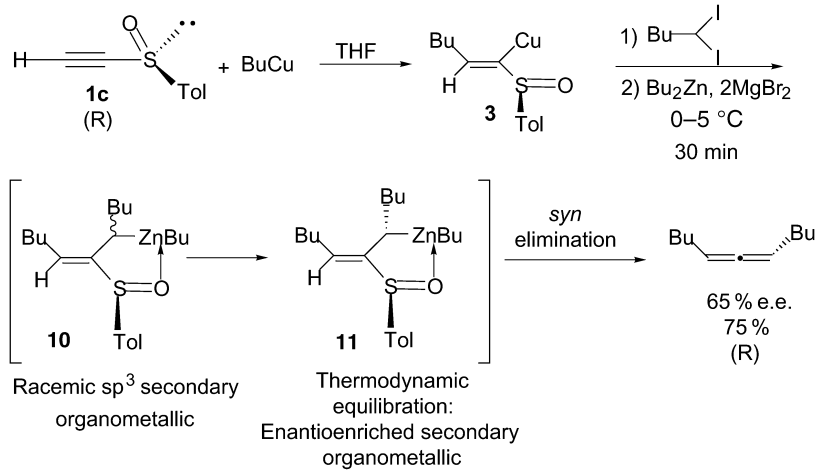
Once large quantity of 1,1-diiodoalkanes in hands, we came back to the preparation of 1,3- and 1,1,3-polysubstituted allenes via our carbometallation-zinc homologation-β-elimination sequence.

We indeed found that the carbocupration reaction on alkynyl sulfoxides, followed by the successive introduction of dibutylzinc (prepared by reaction of 2 equiv of *n*-BuLi to $ZnBr_2$) followed by the 1,1-diiodoalkane at room temperature lead to the expected 1,3-di- and 1,1,3-trisubstituted allenes in excellent yields within 30 min as described in Scheme 10 [32].



Scheme 10

Finally, we wanted to use this new approach for the asymmetric synthesis of allenes. In this case, the critical step is the equilibration of the allylic sp^3 organometallic **10** before the β-elimination reaction (see Scheme 11). An intramolecular chelation between the zinc organometallic and the heteroatom of **10** is then necessary. Thus, via a thermodynamic equilibration [33] (or deracemization if related to an existing chiral center), an *anti* relationship between the *p*-tolyl and the alkyl group should be expected in **11**.



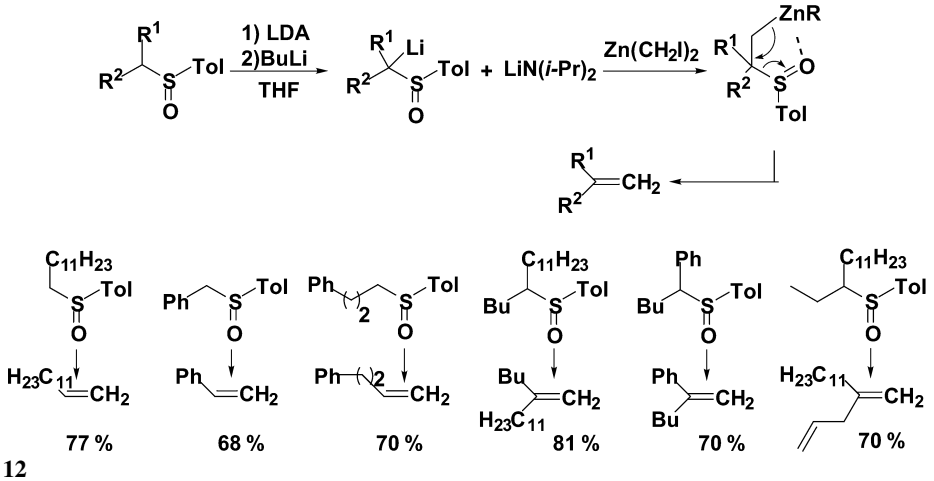
Scheme 11

When chiral sulfoxide **1c** of *R* configuration was reacted with $BuCu{\cdot}MgBr_2$ followed by our standard zinc-homologation β-elimination condition (as described in Scheme 11) optically active 5,6-undecadiene of *R* configuration was obtained in good yield and in 65 % enantiomeric excess. The enantiomeric excess of the allene was determined by gas chromatography analysis with a cyclodextrin-B as stationary phase.

The absolute configuration of the starting material and of the final allene implies that the intermediate allylic zinc derivative **10** undergoes an epimerization into the most stable intermediate in which the *p*-tolyl and the butyl groups are indeed *anti* to each other, followed by a *syn* β-elimination as described in Scheme 11.

SP^3 SULFOXIDES INTO OLEFINS

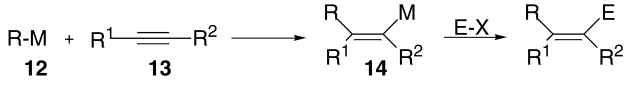
By using this concept of zinc homologation followed by a β-elimination reaction, we have also successfully transformed sp^3 sulfoxides into alkenes in a single-pot operation as described in Scheme 12 [34].



Scheme 12

STEREOSELECTIVE PREPARATION OF METALLATED DIENES

Although dienyl metals are very useful synthetic precursors for various targets, the vinylmetallation of alkynes is still underdeveloped [35]. The principal reason for this lack of development is that the vinylmetallation of unactivated alkyne **13** with **12** (R = alkenyl) should afford a new vinylic organometallic derivative **14**, which has a similar reactivity to that of **12** and therefore can participate also in a subsequent carbometallation reaction. In this case, an oligomerization of the unsaturated substrates results.

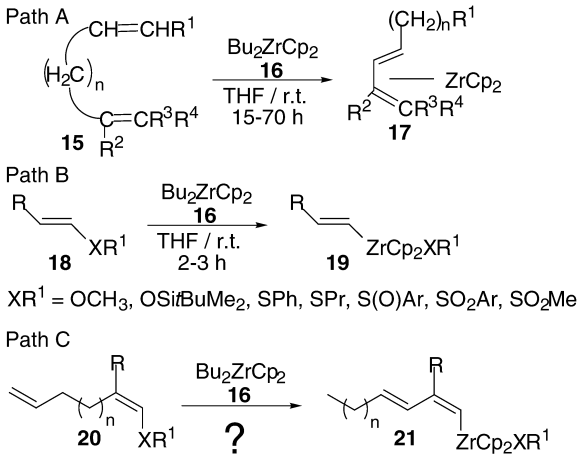


Scheme 13

In the last decade, reactions based on dialkylzirconocene complexes have found tremendous evolution [36]. These achievements have triggered an avalanche of interest, and many elegant applications described in the literature corroborate the notion that zirconocene-based synthesis of complex targets may clearly outperform more conventional approaches [37]. Particularly in the field of metallated dienes, zirconocene derivatives were already successfully used [38], but no general stereo- and regio-

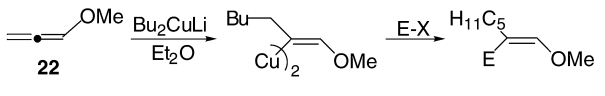
selective method was found. In the context of our study of "economy of steps", we have therefore designed a new strategy for the preparation of metallated dienes as unique stereoisomer.

Transition metal-catalyzed isomerization of terminal olefins into internal olefins has been extensively studied, and in general a mixture of 1-alkenes, (*E*)- and (*Z*)-2-alkenes, reflecting the thermodynamic equilibrium, is obtained [39]. When nonconjugated dienes such as **15** containing one or two substituted vinyl groups are treated with the zirconocene **16** (easily prepared from commercially available Cp_2ZrCl_2 and 2 equiv of *n*-BuLi and called *Negishi reagent*), a regioisomerization of the less-substituted double bond occurs to lead to the formation of the conjugated diene-zirconocene complexes **17** (Scheme 14, path A) [40]. As we have recently developed a new and straightforward stereoselective preparation of vinylic organometallic derivatives **19** from heterosubstituted alkenes **18** such as vinyl enol ethers [41], silyl enol ether, vinyl (alkyl or aryl) sulfides, vinyl sulfoxides, and even vinyl sulfones [42], in a one-pot procedure (Scheme 14, path B), we thought that the combination of the isomerization process with the elimination reaction would lead to an efficient preparation of stereodefined metallated zirconocene complexes **21** from simple enol ether ω-ene **20** (Scheme 14, path C). Indeed, all of these heterosubstituted alkenes **19** [43] smoothly react with the same Negishi reagent Bu_2ZrCp_2 **16** that was used for the isomerization reaction of **15**.



Scheme 14

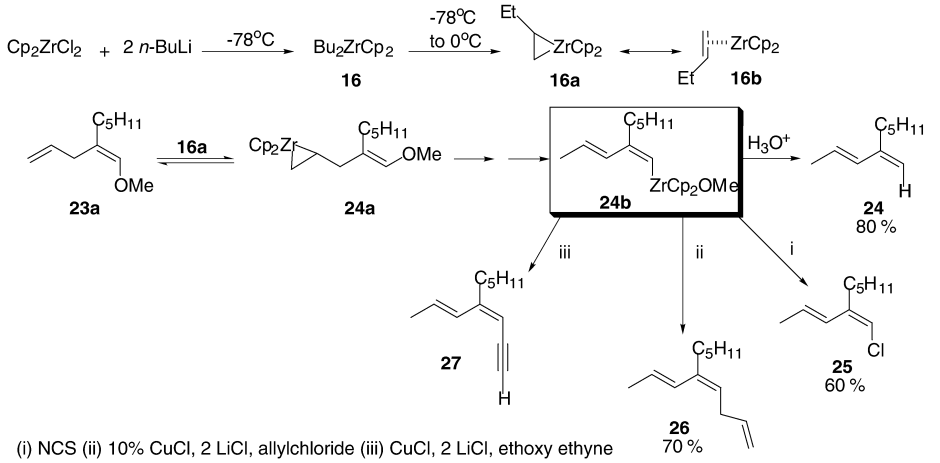
All our starting materials were very easily prepared in a single-pot operation by treatment of the alkoxy-allene **22** with lithium organocuprate and trapping the resulting alkenyl copper with different ω-ene-alkyl halides to give **23a–i** as reported by Normant and Alexakis (Scheme 15) [18].



23a E = $CH_2CH{=}CH_2$
23b E = $(CH_2)_2CH{=}CH_2$
23c E = $(CH_2)_3CH{=}CH_2$
23d E = $(CH_2)_6CH{=}CH_2$
23e E = $CH_2CH{=}CHCH_3$
23f E = $(CH_2)_6CH{=}CH(CH_2)_5CH_3$
23g E = $CH_2C(CH_3){=}CH_2$
23h E = $CH(CH_3)CH{=}CH_2$
23i E = $CD_2CH_2CH{=}CHCH_2CH_3$

Scheme 15

When **23a** was treated with **16** either in THF at +50 °C for 15 min, in Et_2O at +35 °C for 30 min, or in toluene at +65 °C for 15 min, the corresponding diene **24** was constantly obtained with a yield of 80 % (Scheme 16).



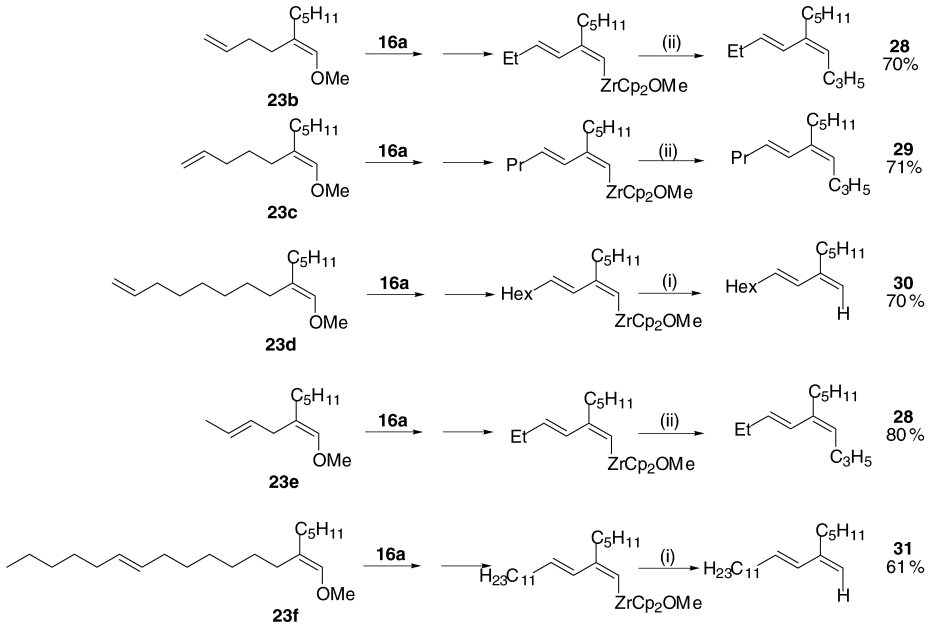
Scheme 16

The presence of a discrete organometallic species as well as the stereochemistry of the metallated diene were first checked by the addition of *N*-chlorosuccinimide, and the corresponding chloro diene **25** was isolated in 60 % yield with an isomeric ratio >98/2. As alternative solution, we have also determined the stereochemistry of the reaction by addition of allyl chloride, in the presence of a catalytic amount of copper salt, to the dienyl zirconocene derivative [44]. **26** was obtained in good overall yield with an isomeric ratio greater than 98/2. The (*E*,*Z*) stereochemistry of the 5-pentyl-octa-1 (4*Z*), (6*E*)-triene **26** was deduced on the basis of differential NOE spectra. After the transmetallation step into vinyl copper derivative, the addition of ethoxy-ethyne led to the carbometallated product, which undergoes an instantaneous β-elimination reaction at the temperature of the reaction. Polysubstituted dienyne can, therefore, be easily prepared in a one-pot operation.

When the same reaction was performed on the opposite isomer of the enol ether, namely, the *E*-isomer (easily obtained from the carbocupration of alkoxy-allene but in THF as solvent instead of Et_2O), the same (*E*,*Z*)-dienyl metal was obtained as determined by the stereochemistry of the resulting product after reaction with allyl chloride [45]. So, whatever the stereochemistry of the starting enol ether, a unique isomer of the dienyl zirconocene is obtained at the end of the process. Furthermore, a mixture of *E*,*Z*-isomers will be used as starting ω-ene-enol ether **23a–h**.

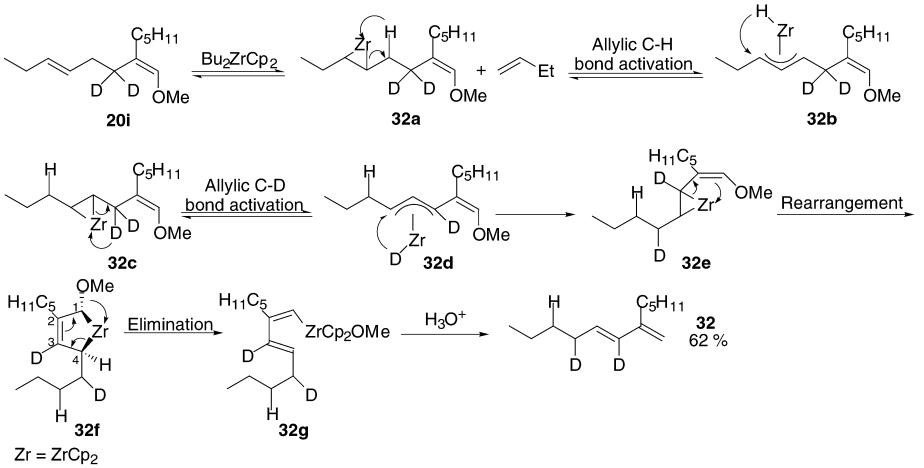
The formation of dienyl zirconocenes is not limited to those dienes with a one-carbon tether (Scheme 17). Interestingly, **23b–d** (with 2, 3, and 6 carbons tether, respectively) also underwent this tandem reaction as fast as **23a** (only 15 min at +50 °C in THF) and in good overall yields. When the migrating double bond is 1,2-disubstituted such as in **23e**, our tandem sequence of isomerization-elimination still proceed very efficiently and after transmetallation of the resulting dienyl zirconocene with copper salt, the allylation reaction gave the (*E*,*Z*)-triene **28** as unique isomer in 80 % isolated yield. By combination of a long tether chain (6 carbons) with a 1,2-disubstituted olefin as in **23f**, diene **31** was isolated in 61 % yield (Scheme 17).

However, when the double bond is 1,1-disubstituted or if an alkyl group is located in the carbon tether such as in **20g** and **20h**, respectively, the reaction proceeds only in very low yield (<10 %).



Scheme 17

To have more insight on the reaction mechanism and on the stereochemical outcome of the reaction, we have performed the following experiment: **20i** was treated with 1.3 equiv of Bu_2ZrCp_2 **16** in THF for 15 min at +50 °C and the corresponding 3,5-dideutero diene **32** was obtained in 62 % isolated yield. The examination of the ^1H and ^{13}C NMR indicates that, indeed, the two deuterium atoms are now located at the vinylic and allylic positions and led us to suggest the following mechanism for the allylic C–H bond activation (isomerization)-elimination reaction (Scheme 18).



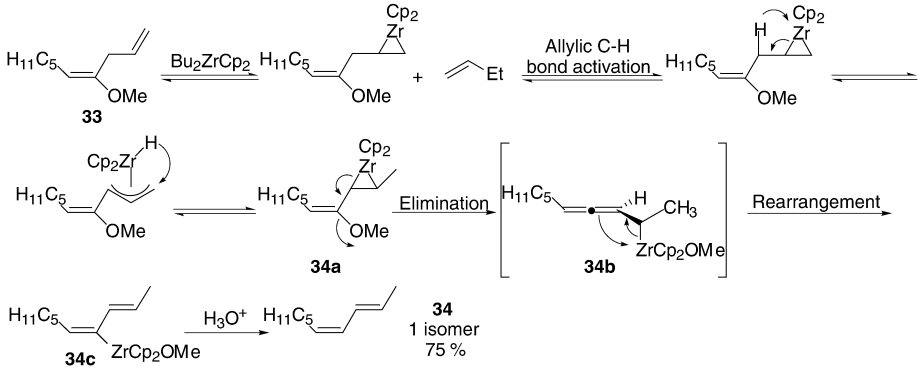
Scheme 18

Bu_2ZrCp_2 **16** reacts first with the remote double bond of **20i** to give the corresponding zirconacyclopropane **32a** and free butene. Then, via an allylic C–H bond activation [46], the η^3-allyl interme-

diate **32b** is generated as transient species and after hydrogen insertion, the new zirconacyclopropane **32c** is formed. By the same sequence, namely, C–D bond allylic activation with deuterium migration (**32c** to η^3-allyl **32d** and then deuterium insertion), the zirconacyclopropane **32e** is produced. As soon as **32e** is formed, an irreversible step occurs, transforming the zirconacyclopropane **32e** into zirconacyclopentene **32f**, which undergoes an elimination reaction to lead to **32g** and then **32** after hydrolysis. Based on this mechanism, we can easily understand that the stereochemistry of the starting enol ether has no effect on the stereochemistry of the dienyl zirconocene; the carbon-heteroatom bond of the metallated center in **32f** can freely epimerize to give the most stable isomer. Such an isomerization could be caused by an interaction between the ether moiety and the zirconium atom, which would weaken the C_1–Zr bond and facilitate the isomerization [47]. In the particular experiment described in Scheme 18, we did not see any scrambling of deuterium atoms along the carbon skeleton, and this can be explained by the initial position of the two deuterium atoms. Indeed, in this C–D bond allylic activation step, as soon as the intermediate **32e** is formed, an irreversible rearrangement-elimination reaction (**32e** to **32g**) occurs and therefore drives the reaction toward the metallated diene **32g**. However, when the two-deuterium atoms are located in a different place in the tether, a scrambling of deuterium is observed along this tether.

The unique stereochemistry of the diene, therefore, results from the elimination step and not from a further isomerization of the dienyl zirconocene with zirconocene derivatives (i.e., Cp_2Zr-catalyzed stilbene stereoisomerization [48]) since the hydrozirconation reaction of several 1*E*-ene-3-yne and 1*Z*-ene-3-yne derivatives with $Cp_2ZrH(Cl)$ lead only to the (*E*,*E*)- and (*Z*,*E*)-isomers, respectively, in good yields [49].

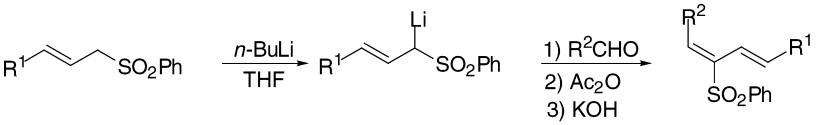
In this new tandem allylic C–H bond activation followed by an elimination reaction, substituted 1-zircono-1*Z*,3*E*-dienes (zirconium moiety at the terminal position of the dienyl system) were easily prepared. With the idea to extend this methodology to the stereoselective synthesis of 3-zircono-1,3-diene (zirconium moiety at the internal position of the dienyl system), we have prepared and investigated the reactivity of **33** with Bu_2ZrCp_2 **16**. When **33** was submitted to the tandem reaction, the diene **34** was isolated after hydrolysis as a unique (*E,Z*)-isomer in 75 % isolated yield (Scheme 19).



Scheme 19

When the migrating group is geminated to the leaving group such as in **33**, the allylic C–H bond activation leads to **34a**, which subsequently undergoes now a β-elimination reaction to lead to the β-metallated allenyl intermediate **34b**. Then, **34b** is isomerized into its more stable dienyl form **34c** in which the alkyl and the organometallic groups are *anti* to each other for steric reasons. After hydrolysis, a unique isomer is observed (determined by NOE). Although this tandem reaction led also to the expected diene as unique isomer in good chemical yield, this methodology had a serious drawback from a preparative point of view since **33** could not be purified by column chromatography due to its instability. The isolated yield obtained from **34** is, therefore, based on the crude starting material **33** used

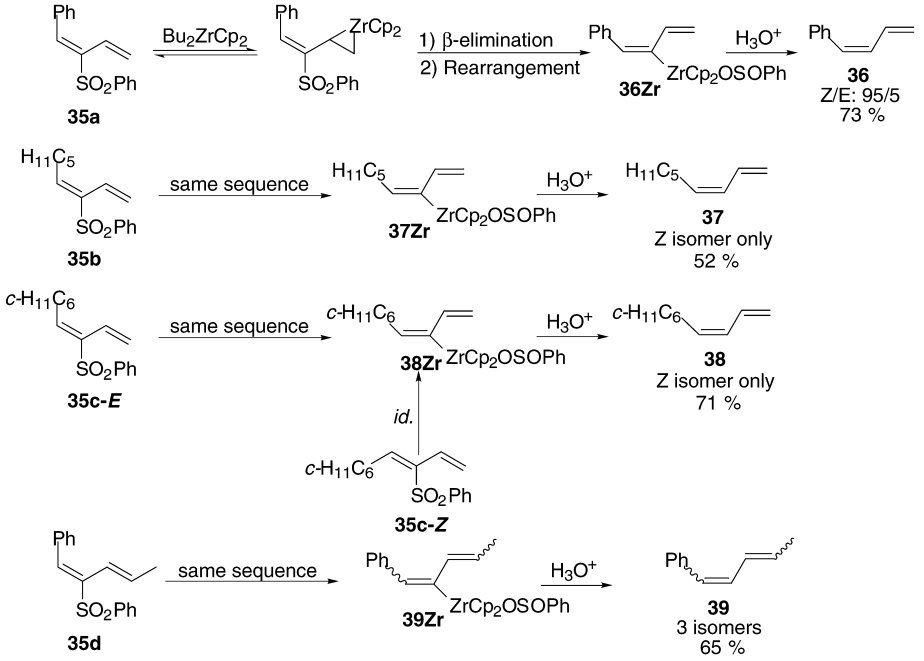
without purification. This very promising route for the preparation of metallated diene such as **34** associated with the problem of stability of α-substituted enol ether **33** led us to consider an alternative starting material. We consequently turned our attention to the preparation of sulfonyl 1,3-dienyls derivatives [50]. As for the enol ether methodology, the main advantage of this approach is the very easy preparation of acyclic 2-arylsulfonyl 1,3-dienes **35a–d** from allylic sulfones and aldehydes in a single-pot operation as described in Scheme 20 [51].



35a R^1 = H, R^2 = Ph, 89 %
35b R^1 = H, R^2 = *n*-Pent, 72 %
35c R^1 = H, R^2 = *c*-Hex, 70 %
35d R^1 = Me, R^2 = Ph, 91 %

Scheme 20

Treatment of **35b–c** with 1.5 equiv of Bu_2ZrCp_2 at room temperature leads only to the *cis*-isomers **37** and **38** whatever the stereochemistry of the starting dienyl sulfones (i.e., ***E*-35c** and ***Z*-35c**, Scheme 21). Even the unstable *Z*-isomer **36** was preferentially formed from **35a** in this process with an excellent *Z*/*E* ratio of 95/5. The low yield obtained for **37** is attributed to the volatility of the resulting diene.

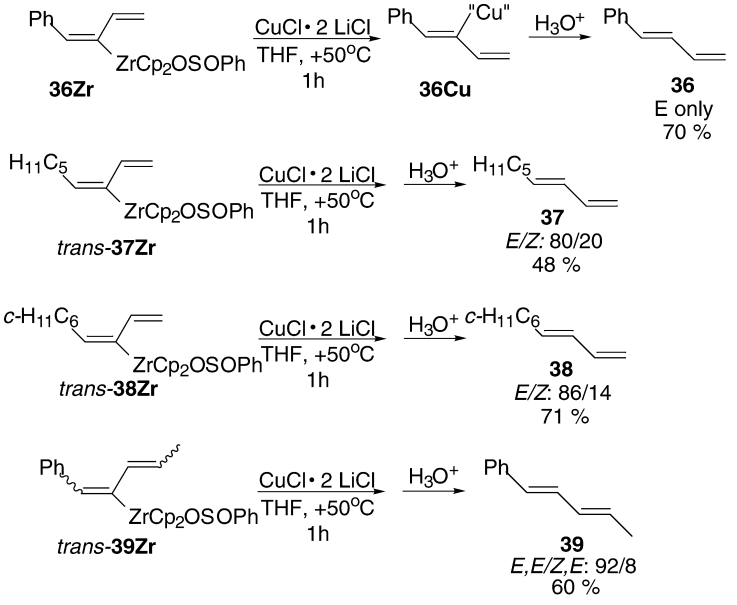


Scheme 21

By analogy with the mechanistic pathway described for the enol ether **33** (Scheme 19), we believe that the transformation of **35a–c** also occurs via the formation of the β-metallated allenyl intermediate generated from the β-elimination of the corresponding zirconacyclopropane and subsequent rearrangement. However, the direct transformation of the vinyl sulfone moieties into dienyl zirconocenes

without intervention of the terminal unsubstituted double bond cannot be ruled out at this stage, particularly that when the more substituted dienyl sulfone **35d** (Scheme 21) was similarly treated with Bu_2ZrCp_2, a mixture of 3 isomers of undetermined geometry was obtained after hydrolysis.

To further increase the scope of the reaction, transmetallation of dienyl zirconium complexes such as **36Zr** into the corresponding dienyl organometallic derivatives was performed. To our surprise, when **36Zr** was transmetallated to copper derivatives by addition of CuCl·2LiCl for 1 h at +45 °C, a complete isomerization of the dienyl system was found; that is, *trans*-**36Zr** is transmetallated into *cis*-**36Cu**, and then after hydrolysis, only the *E*-isomer of **36** is formed in 70 % yield (Scheme 22).

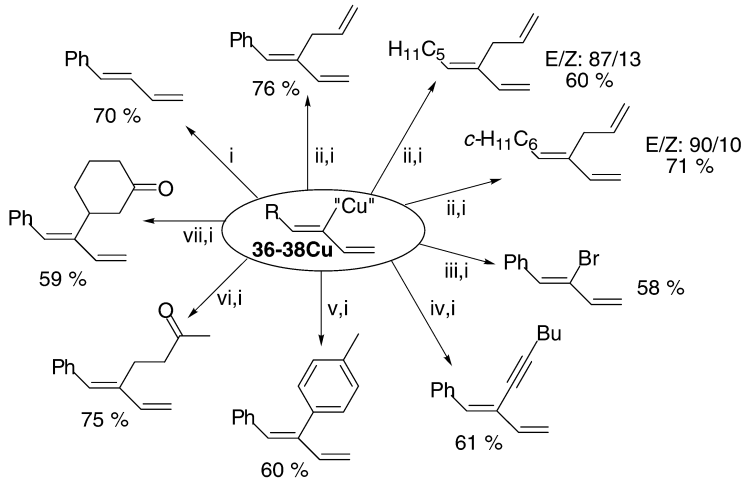


Scheme 22

As nothing is known about the exact nature of organocopper coming from organozirconocene derivatives, we must await further investigations to elucidate completely the mechanism of this transmetallation, but this isomerization was found to be general for all the examined cases.

The synthetic use of this isomerization was also investigated by reaction of the resulting dienyl copper derivatives with several different electrophiles as described in Scheme 23.

36Cu reacts via an S_N2' process with allyl chloride to give a unique *E*-isomer of the triene, and the geometrical mixture of **37** and **38Cu** gave, under the same experimental conditions, the two allylated products with the *E*-isomer as major product (it should be emphasized that although the isomerization occurs at +50 °C, the reactivity of the organocopper remains intact in this process). The addition of methyl vinyl ketone or cyclohexenone in the presence of TMSCl led to the 1,4 adducts in 75 and 59 % yield, respectively, as unique geometrical isomers [53]. The palladium cross-coupling reaction of **36Cu** with alkynyl iodide and aryl iodide opens new routes to further functionalization between two sp^2 and sp^2-sp units as described in Scheme 23.



Scheme 23

In conclusion, we have been able to prepare, in a one-pot procedure, chiral homoallylic alcohol and amine derivatives by a copper-catalyzed four-component reaction. In this process, three new carbon–carbon bonds as well as a quaternary and a tertiary chiral center are created with excellent regio- and diastereoselectivities. When the reaction was now performed without adding external electrophiles, a β-elimination reaction led to the formation of polysubstituted allenes in good overall yields. This strategy of zinc-homologation followed by a β-elimination reaction was also synthetically used for the transformation of sp^3 sulfoxides into olefins with potential application in asymmetric synthesis. Finally, the stereoselective preparation of metallated dienes in only two chemicals steps from commercially available products has been described. This new strategy is based on a tandem allylic C–H bond activation of a remote ω-double bond followed by an elimination reaction. During this study, an unexpected "invertive" transmetallation reaction into organocopper was found.

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