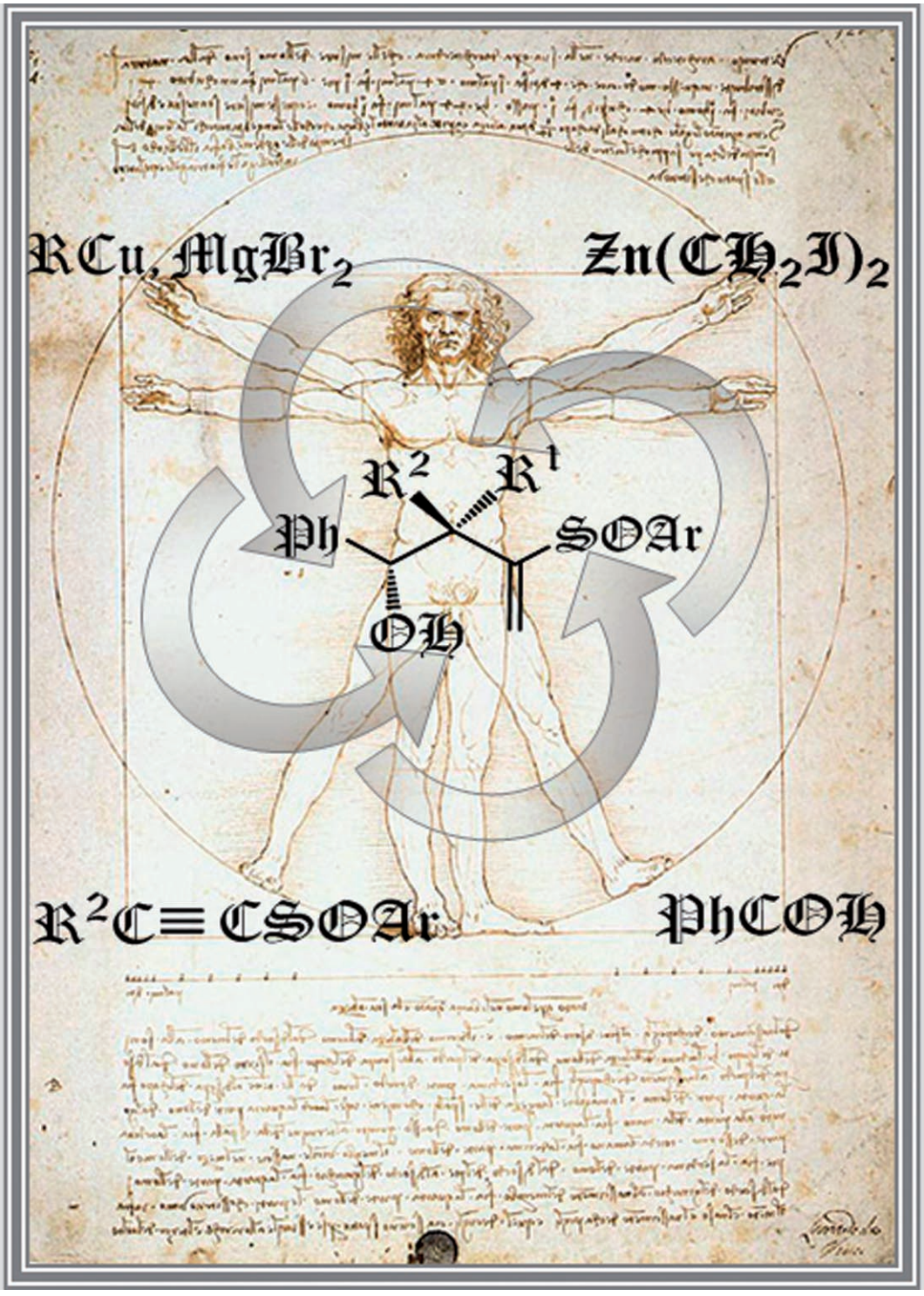
CHEMISTRY
A EUROPEAN JOURNAL

DOI: 10.1002/chem.200800580

A Shift in Retrosynthetic Paradigm

Ilan Marek*[a]

Dedicated to Professor Sason Shaik on the occasion of his 60th birthday

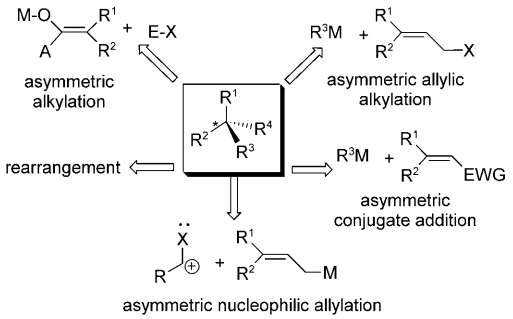


Abstract: The current state-of-the-art synthesis for the formation of enantiomerically enriched all-carbon quaternary stereocenters in acyclic system relies on the formation of a single carbon–carbon bond per chemical step by asymmetric catalysis. These extraordinary sophisticated methods were logically classified among the most powerful and innovative ones. In this concept article, we are proposing a new retrosynthetic paradigm to solve differently such challenging problems. These new synthetic pathways lead to the diastereo- and enantiomerically pure formation of three new carbon–carbon bonds in acyclic system, in a one-pot reaction, including the formation of all-carbon quaternary stereocenters by using classical reagents and experimental conditions and from common starting materials.

Keywords: allylation · carbometalation · synthetic methods · zinc carbenoids

Introduction

Our field of research, synthetic organic chemistry, has now reached a situation where major changes are needed. We would like to illustrate this provocative statement by focusing on one of the major achievements of the last few decades, namely asymmetric synthesis. The development of new and highly enantioselective processes for the creation of carbon–carbon or carbon–heteroatom bonds was, and still is, one of the main problems of chemical synthesis. In contrast to tertiary stereocenters, where a wide variety of chiral auxiliaries, reagents and catalysts nowadays form the basis for modern asymmetric synthesis and are a guarantee for high selectivity, the construction of a quaternary stereocenter, that is carbon centers with four different non-hydrogen substituents, represents the most challenging and dynamic area in organic synthesis and still remains the touchstone of every enantioselective procedure.[1] The state-of-the-art would be the asymmetric construction of quaternary all-carbon stereocenters (all-carbon substituted excluding therefore tertiary alcohols, ethers, amines, etc.).[2] To understand why this field needs major changes, we should briefly review the different synthetic approaches for the construction of quaternary all-carbon stereocenters. The methods that have been successfully employed for the formation of cyclic quaternary all-carbon stereocenters include the Heck reaction, alkylation, arylation, and Michael addition,[1,2] whereas for the creation of all-carbon quaternary centers in non-cyclic system (more complicated due to the number of degrees of freedom associated with these structures), the most promising results are either the asymmetric allylic alkylations,[3] asymmetric conjugate addition,[4] sigmatropic[5] and Jung epoxide rearrangements,[6] asymmetric alkylation,[7] and asymmetric nucleophilic allylation[8] (Scheme 1). The last route to products with quaternary all-carbon stereocenters—nucleophilic allylation of electrophilic species—results from a combination of a cationic synthon with an ambident nucleophile provided that the latter is 1) configurationally stable (no metallotropic equilibrium) and 2) attacked at the γ-carbon atom (Scheme 1).[8]



Scheme 1. General methods for the creation of all-carbon quaternary stereocenters in acyclic system.

These methods are currently the state-of-the-art in our field (all by asymmetric catalysis). However, one can easily see that only a single carbon–carbon bond is formed in the reaction sequence between two components. Despite this obvious lack of efficiency, the synthetic challenge imposed by the inherent difficulties in the creation of all-carbon quaternary centers in acyclic system led logically the synthetic community to classify them among the most powerful and innovative ones. This clearly shows that synthetic organic chemistry reached nowadays an extraordinary levels of sophistication for the creation of *one* carbon–carbon bond but the development of more efficient synthetic methodologies (i.e., more than one enantioselective carbon–carbon bond created per reaction), is still in its complete infancy. Indeed, a seemingly trivial but rather serious limitation in practice in our field is set by the mere number of chemical steps accumulating in linear sequences. This challenging goal of efficiency (step economy) can be achieved only through the use of reactions that allow a great increase in complexity or through operations that incorporate many steps that collectively achieve the same high complexity increase. Therefore, the invention of new reactions, reaction sequences, reagents or strategies that allow this complexity increase in a one-pot reaction are critical to the realization of step economical syntheses. Surprisingly, multicompo-

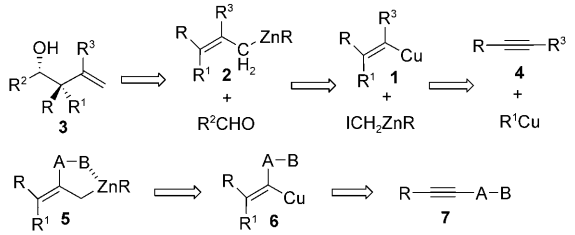
[a] Prof. I. Marek
Contribution from the Mallat Family Laboratory of Organic Chemistry
Schulich Faculty of Chemistry and
the Lise Meitner-Minerva Center for Computational Quantum Chemistry
Technion-Israel Institute of Technology, Haifa 32 000 (Israel)
Fax: (+972) 4-829-3709
E-mail: chilanm@tx.technion.ac.il

nent[9] and domino reactions[10] are well known concepts in organic synthesis but as soon as the synthetic transformation is getting more challenging, that is, all-carbon quaternary stereocenters in non-cyclic system, the more classical way of creating carbon–carbon bonds in chemistry prevail.

Thus, diastereo- and enantioselective reactions that form multiple carbon–carbon bonds in acyclic system, including the formation of all-carbon quaternary stereocenters and in a one-pot reaction from easily accessible starting materials are still extremely challenging and therefore rare despite its exciting promises.

Asymmetric Nucleophilic Allylation

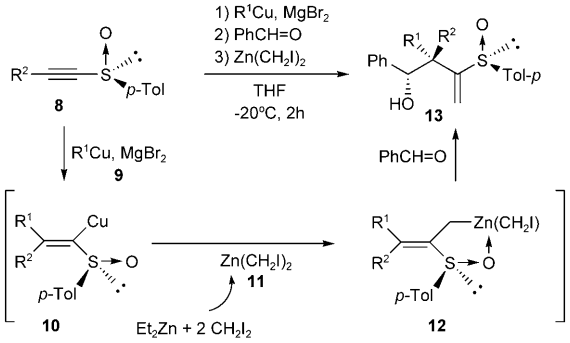
To illustrate this concept, we initially concentrated our efforts to develop a new route to enantiomerically pure homoallylic alcohols **3** in a one-pot reaction possessing this all-carbon quaternary stereocenters from common starting materials (alkynes). We reasoned that the most convenient preparation of in situ allyl metal species **2** would be the homologation reaction of alkenyl compounds such as **1** with (iodomethyl)zinc.[11] With respect to all-carbon quaternary stereocenters as in the final product **3**, one has to start with stereodefined β,β-disubstituted alkenylmetal compounds **1**, which may easily come from a controlled carbometalation reaction of substituted alkynes **4** (Scheme 2).[12]



Scheme 2. Requisite for the one-pot formation of homoallylic alcohol derivatives.

However, even by following this new retrosynthetic approach, the potential metalotropic equilibrium of 3,3-disubstituted allylzinc species **2** has to be avoided.[13] 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 of **5** by an A–B unit and 2) use this A–B chelating moiety as a source of chirality and as a regiocontrol element for the carbocupration reaction of **7**.[14] By combining all of these parameters, alkynyl sulfoxide **8**, easily available in large quantities by the Andersen synthesis,[15] were designed as potential starting materials (Scheme 3). The regio- and stereospecific carbocupration of **8** with organocopper derivatives **9** (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 **10** in quantitative yields (Scheme 3).[16]

Then, aldehyde was added followed by bis(iodomethyl)-zinc carbenoid **11**, independently prepared from 1 equiv of Et_2Zn and 2 equiv of CH_2I_2.[17] Neither the vinylic organocopper **10** nor the zinc carbenoid is reactive enough to add to aldehydes, however, **10** is readily homologated by a methylene unit with the zinc carbenoid **11**. The in situ reactive chelated allylzinc species **12** reacts diastereoselectively with aldehydes, to give after hydrolysis the corresponding adducts **13** in good overall yields and in excellent diastereoselectivities (Scheme 3).[18]



Scheme 3. One procedure for the preparation of homoallyl alcohol possessing all-carbon quaternary stereocenters.

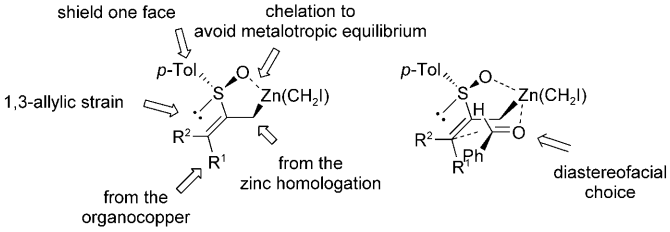
As shown in Table 1, entry 1 versus 2, permutation of the alkyl groups of the alkyne and the organocopper reagent allows the independent formation of the two isomers at the quaternary stereocenter, respectively.[18] Even the methylcopper, known to be a sluggish group in carbocupration reaction,[16a] adds cleanly to alkynyl sulfoxide and gives after the homologation–allylation reactions, the expected homoallylic alcohol as only one isomer (Table 1, entry 3). 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 (dr 30:1, Table 1, entries 5 and 6), the reaction is more difficult to control and yields are lower. 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), the presence of the *p*-tolyl group (shields one face) and the 1,3-allylic strain[19] leads to very high diastereoselectivity when the allylzinc reacts with aldehydes (aryl/alkyl groups occupies a pseudo-equatorial position) in a Zimmerman–Traxler chair like transition state (Scheme 4). Although this new carbometalation–homologation–allylation one-pot reaction led, with very high diastereoselectivity, to the corresponding homoallylic alcohols **13**, the bis(iodomethyl)zinc carbenoid **11** 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 carbocupra-

Table 1. Formation of homoallyl alcohols.

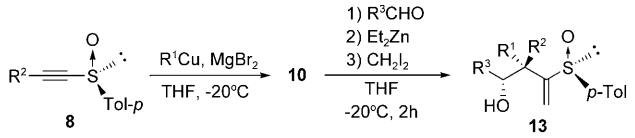
Entry	R^1	R^2	RCHO	dr[a]	Yield[b]
1	Et	Bu	PhCHO	99:1	78
2	Bu	Et	PhCHO	99:1	68
3	Me	Bu	PhCHO	99:1	66
4	Me	Et	PhCHO	99:1	68
5	Bu	Et	BuCHO	30:1	60
6	Me	Et	BuCHO	30:1	58

[a] Diastereoisomeric ratio determined on crude ^{1}H NMR spectroscopy. [b] Isolated yield after purification by column chromatography.



Scheme 4. Rationalization for the diastereoselectivity.

tion of alkynyl sulfoxide **8** with organocopper derivatives still provides the corresponding metalated β,β-dialkylated ethylenic sulfoxide **10** in quantitative yields as originally described in Scheme 3, but now aldehydes, Et_2Zn and CH_2I_2 are all added to the reaction mixture at −20 °C (Scheme 5).



Scheme 5. Improved one-pot procedure for the formation of homoallyl alcohols possessing all-carbon quaternary stereocenters.

As discussed previously, neither vinylcopper **10** 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 **11**. This carbenoid readily homologates the vinylcopper **10** into the allyl species **12**, which reacts diastereoselectively with aldehydes to give the expected homoallylic alcohols **13** in very high diastereoselectivities (Scheme 5). This improved in situ procedure led to identical diastereoselectivities (Table 2) as compared to the one previously described (compare entry in 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). Functionalized aldehydes can also be used in this allylation reaction (Table 1, entries 6–8). In these 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,[20] and when the quaternary centers possess two identical alkyl groups

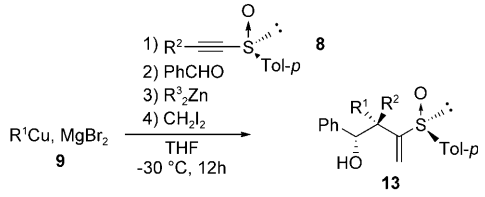
Table 2. Improved formation of homoallyl alcohols.

Entry	R^1	R^2	R^3	dr[a]	Yield[b]
1	Et	Bu	Ph	99:1	81
2	Et	Hex	Ph	99:1	82
3	Me	Hex	Ph	99:1	78
4	Et	Bu	*p*-ClC_6H_4	99:1	70
5	Me	Me	Ph	98:2	80
6	Me	Me	*p*-$MeOCOC_6H_4$	96:4	60
7	Et	Me	*p*-$MeOCOC_6H_4$	98:2	60
8	Me	Me	*p*-$MeCOC_6H_4$	96:4	60
9	Et	Bu		99:1	83
10	Me	Me		99:1	75
11	Et	Bu		99:1	70
12	$^{13}CH_3$	Me	Ph	97:3	60

[a] Diastereoisomeric ratio determined on crude ^{1}H NMR spectroscopy. [b] Isolated yield after purification by column chromatography.

(Table 2, entries 5, 6, 8, 10) an excellent 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 (Table 2, entries 9–11).[21] An elegant application of such method is the diastereoselective preparation of quaternary stereocenters with the smallest possible difference between the two alkyl groups. For this purpose, $^{13}CH_3MgI$, easily prepared from iodomethane-^{13}C and Mg^0, was transformed into its corresponding organocopper reagent $^{13}CH_3Cu$ and added to propynyl sulfoxide **8**. To the vinyl copper **10** was subsequently added Et_2Zn, CH_2I_2 and benzaldehyde to give the corresponding product **13** in 60 % yield and 97:3 diastereomeric excess (Table 2, entry 12).[21]

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 **9**, homoallylic alcohols were obtained in excellent yields and diastereoisomeric ratio as described in Scheme 6.[21] 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 6).



Scheme 6. Four-component reaction for the formation of homoallyl alcohols possessing all-carbon quaternary stereocenters.

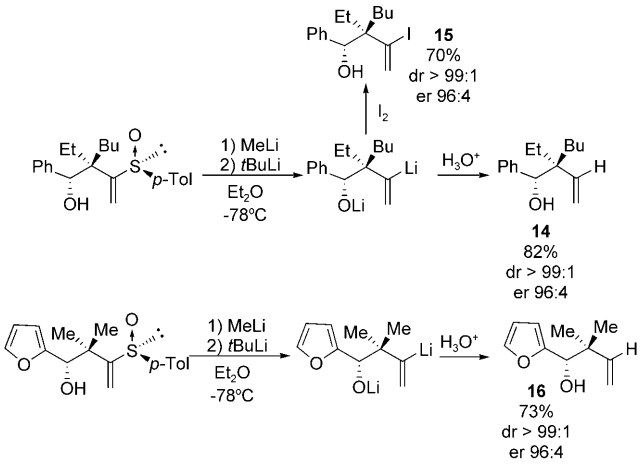
We initially checked that this four-component reaction proceeds well with identical alkyl groups such as alkylcopper and dialkylzinc ($R^1=R^3=Bu$) in order to avoid crossover experiment. The homoallylic alcohol was isolated in 84% yield and a excellent 94% diastereoisomeric excess for the remote 1,4-induction (Table 3, entry 1). Evidently, when the same reaction was performed on a differently substituted alkynyl sulfoxide, the reaction proceeded similarly (Table 3, entry 2). When both alkyl groups of the alkylcopper and alkynyl sulfoxide are identical ($R^1=R^2=Bu$) whereas the nature of the alkyl group on the dialkylzinc was different ($R^3=Et$), the corresponding homoallylic alcohol is also obtained in excellent diastereoisomeric ration and yield (Table 3, entry 3). 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, all-carbon quaternary and tertiary centers were created with excellent diastereoselectivities and in good overall yields.

Table 3. Four-component reaction for the formation of homoallyl alcohols.

Entry	R^1	R^2	R^3	dr[a]	Yield[b]
1	Bu	Bu	Bu	97:3	84
2	Bu	Me	Bu	95:5	74
3	Bu	Bu	Et	98:2	78
4	Et	Bu	Et	99:1	80
5	Et	Me	Et	97:3	75

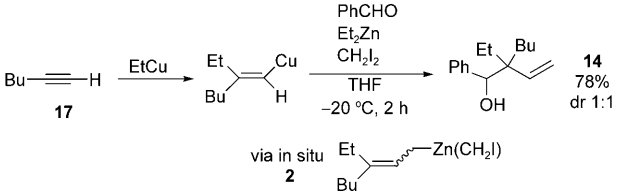
[a] Diastereoisomeric ratio determined on crude ^1H NMR spectroscopy. [b] Isolated yield after purification by column chromatography.

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, and 3) diastereoselective allylation reaction of aldehydes controlled by the stereogenic center of the chiral sulfoxide. The chiral sulfinyl group plays a multiple role as chelating element to slow down the metalotropic equilibrium, activator and regiocontrol element for the carbometalation reaction of the alkynyl moiety as well as a chiral auxiliary 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.[22] 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.[23–25] When the two following homoallylic alcohols (Scheme 7) were first treated with MeLi and then with *t*BuLi in Et_2O at −78 °C, the corresponding vinyl lithium species were obtained, by a sulfoxide–lithium exchange reaction, in excellent yields as determined after acidic hydrolysis (Scheme 7). The enantiomeric ratio (er 96:4) of **14** and **16** were determined by chiral HPLC (chiral column Chiralpak AD-H) and was found to be similar to the starting alkynyl sulfoxide (*ee* 92%). Such sulfoxide–lithium exchange reaction can be used for further functionalization; for instance, addition of iodine to give the corresponding vinyl iodide **15** in 70% yield (Scheme 7).



Scheme 7. Sulfoxide lithium exchange reaction.

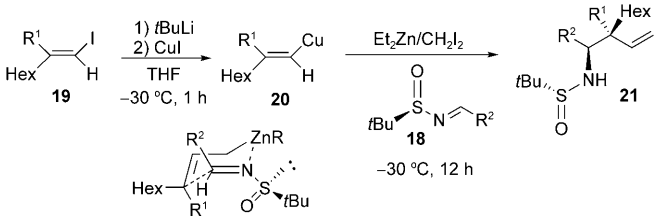
When the same reaction was performed on a non-functionalized alkyne such as 1-hexyne **17**, the reaction still proceeded to give the expected homoallylic alcohol **14** in good yield but as a 1:1 mixture of two diastereoisomers (Scheme 8). In such case, the zinc carbenoid homologation reaction of vinyl copper leads to the in situ generated allylzinc species **2** that is no more configurationally stable[13] and therefore the two geometrical isomers resulting from its metalatropic equilibrium react with the aldehyde.



Scheme 8. Non-stereoselective approach to the carbonyl allylation reactions.

To further extend this new approach for the creation of all-carbon quaternary stereogenic centers, we needed to find an alternative method to slow down the metalotropic equilibrium. This approach shouldn't be based anymore on intramolecular chelation from the substrate but rather on intermolecular chelation through an external ligand. Among all the possible sources of chiral ligands, we were primarily interested to study the case of enantiopure Ellman's (*R*)-*N*-*tert*-butanesulfinimines **18**.[27] Beside the fact that sulfinimines could be utilized as chiral nitrogen intermediates for the preparation of a wide range of chiral amines, we were interested by the potential intermolecular stabilization of the sulfinimines to the allyzinc species. In our first approach, disubstituted vinyl iodides **19**, easily prepared by carbocup-

ration reaction of octyne,[12] were treated with *t*BuLi in THF at −78 °C, followed by addition of one equivalent of CuI to lead to the corresponding vinylcoppers **20** at −30 °C. To the resulting vinylcopper derivatives were consequently added diethylzinc, methylene iodide and various sulfinimines. The reaction between diethylzinc and methylene iodide occurs first to lead to the in situ formation of zinc carbenoid, which readily homologates the vinyl copper into the allyl species, as previously described, which reacts diastereoselectively with (*R*)-*N*-*tert*-butanesulfinimines **18** to give the expected homoallyl sulfinamines **21** with very high diastereoselectivities and in good overall yields as described in Scheme 9 and Table 4.[28]



Scheme 9. Preparation of homoallylic amine derivatives from vinyl iodides.

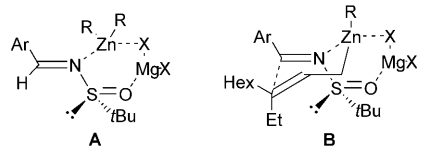
Table 4. Stereocontrol in the allylation reaction from vinyl iodides.

Entry	R^1	R^2	dr[a]	Yield[b]
1	Et	Ph	>98:2	85
2	Me	Ph	>98:2	65
3	*i*Pr	Ph	>98:2	87
4	Et	*p*-Br-C_6H_4	>98:2	81
5	Et	*p*-Ac-C_6H_4	>98:2	77
6	Et	PhCH=CH	95:5	75

[a] Diastereoisomeric ratio determined on crude ^{1}H NMR spectroscopy. [b] Isolated yield after purification by column chromatography.

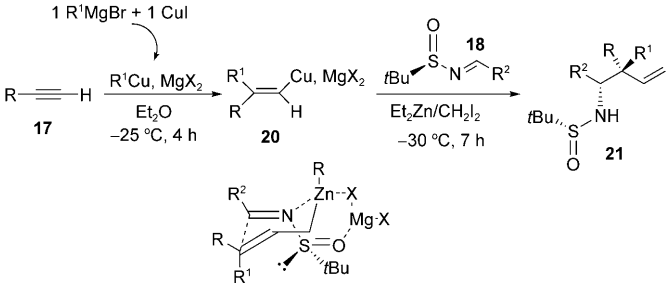
As can be deduced from Table 4, the reaction can be performed by a combination of various sulfinimines and vinylcopper derivatives. The alkyl group R^1 of the vinyl iodide can be primary (Table 4, entries 1, 2 and 4–6), as well as secondary (although in a pseudo axial position in the chair like transition state, see Table 4, entry 3). The reaction could be performed in the presence of various aromatic (Table 4, entries 1 to 3), functionalized aromatic (Table 4, entries 4, 5), and conjugated (Table 4, entry 6) sulfinimines. Only aliphatic sulfinimines lead to poor diastereoisomeric ratio (dr 70:30, not reported in Table 4). Sulfinimine usually prefers to adopt the conformation in which the S−O bond and the lone pair on the nitrogen atom are antiperiplanar, mainly as a result of an important $n_N \Pi S^*_{S-O}$ negative hyperconjugation interaction.[29] Such interaction has a high rotational barrier (41.3 kJ mol^{-1}) and therefore blocks the conformation of sulfinimines. The formation of the homoallylic products is rationalized through a close transition state in which the substituent of the sulfininimes occupies a pseudo axial position (see Scheme 9).[30]

However, nonbonding interactions contributed by substrate substituents may provide the dominant stereochemical control element. In many cases, metals have been documented to pre-associate with polar functional groups in the vicinity of the reaction center and to influence the stereochemical outcome of the process, providing even an opposite stereochemical outcome.[31] Since the S−O bond may operate as an acceptor site for Lewis acids,[32] the conformation of the sulfinimine moiety in the transition state can be influenced by an intramolecular chelation[33] with metallic salts (Scheme 10).[34] If such a case, the addition of metallic salts should lead to a chelated intermediate with consequences that the active and inert volume located on the sulfur atom are now reversed as compared to the transition state depicted in Scheme 10. The facial selectivity should then be opposite.



Scheme 10. Chelated transition state.

Under this assumption, the reaction was performed in the presence of MgX_2. Although MgX_2 could be added to the vinylcopper species **20** the direct carbocupration reaction of alkyne with RCu, $MgBr_2$ (easily prepared from 1 equiv alkylmagnesium halide and 1 equiv CuI)[12] was a more attractive and efficient route. When the carbocupration was performed in Et_2O at −25 °C for 4 h, the corresponding vinyl copper species **20** were formed as described in Scheme 11.



Scheme 11. Preparation of homoallylic amines from alkynes.

Then, Et_2Zn, CH_2I_2 and (*R*)-*N*-*tert*-butanesulfinimines were all added to the vinyl copper at −30 °C and after few hours at the same temperature, the corresponding homoallylic amines **21** were also obtained as a unique diastereoisomer. To our delight, the diastereoisomers **8** obtained in the procedure depicted in Scheme 11 are indeed the opposite diastereoisomers that were obtained in Scheme 9 (see Table 5).

This discrepancy can be rationalized by a cyclic transition state with MgX_2 coordinated to the oxygen of the sulfinyl group and to the zinc atom (as opposite to the antiperiplanar situation described in Scheme 9). The high level of pre-

Table 5. Stereocontrol in the allylation reaction from alkynes.

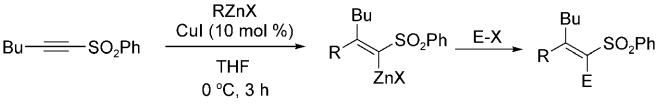
Entry	R	R^1	R^2	dr[a]	Yield[b]
1	Hex	Et	*p*-Br-C_6H_4	>98:2	75
2	Hex	Et	*p*-Ac-C_6H_4	>98:2	67
3	Hex	Et	Bu	>98:2	67
4	Hex	*i*Pr	*p*-Br-C_6H_4	>98:2	62
5	Hex	Bu	*p*-Br-C_6H_4	97:3	70
6	Bu	Hex	*p*-Br-C_6H_4	96:4	60

[a] Diastereoisomeric ratio determined on crude ^{1}H NMR spectroscopy. [b] Isolated yield after purification by column chromatography.

organization presumably contributes to the very high selectivity for attack opposite to the large *t*Bu group. The scope of the reaction is broad since functionalized aromatic (Table 5, entries 1, 2 and 4–6) but also aliphatic sulfinimines (Table 5, entry 3) leads to excellent diastereoselectivities. As shown in Table 5 (entry 5 vs 6), permutation of the alkyl group of the alkyne and the organocopper reagent allows the independent formation of the two isomers at the quaternary carbon center, respectively.

Finally, the sulfinyl group is readily cleaved under mild acidic conditions to provide the free amine derivatives in quantitative yields with an all-carbon quaternary stereogenic center in acyclic system (see Scheme 12).[28]

Clearly, such new strategies are really powerful for the efficient assembly of three new carbon–carbon bonds, two new stereogenic centers including the extremely challenging all-carbon quaternary one, in a one-pot reaction from commercially available alkyne. Nonetheless, one can easily see that such methodologies still requires the need of a full equivalent of chiral auxiliaries attached either on the nucleophile (Schemes 3–6) or on the electrophile (Schemes 9–11). Although these auxiliaries can be easily removed (Scheme 7 and 12), the next challenging issue, far beyond the current state-of-the-art would combines the diastereo- and enantioselective creation of several carbon–carbon bonds with a catalytic amount of chiral ligand in a one-pot reaction from alkynes. However, the beauty of this reaction generates also its own limitation: as magnesium, lithium, zinc and copper salts are coexisting in the reaction mixture, they may also strongly interfere for a specific chelation of any chiral ligands with a given organometallic species. Therefore, to have a better chance to succeed towards asymmetric catalysis, we should first decrease the amount of metallic salts present in the reaction mixture (to promote a selective chelation between the chiral ligand and the intermediate allylzinc species). Consequently, the development of catalytic carbometalation reaction (first step in our sequence) is absolutely needed (Scheme 13). Only very few approaches are



Scheme 13. Copper-catalyzed carbozincation of alkynyl sulfones.

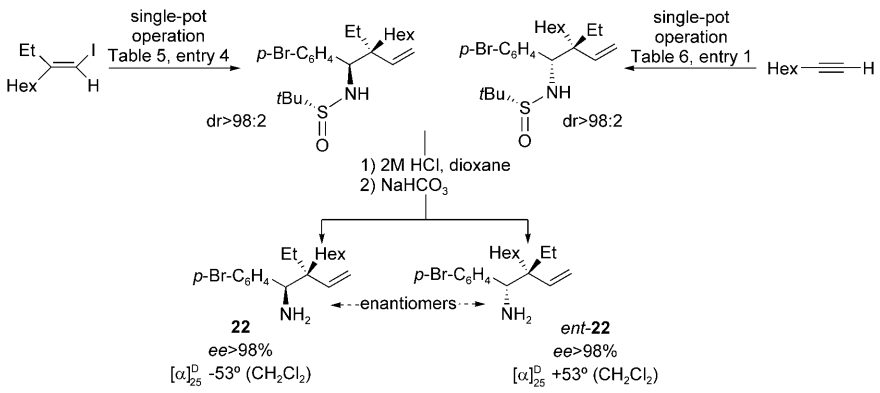
known for such transformations[12] and we concentrated our initial efforts towards the copper-catalyzed carbozincation of alkynyl sulfones, which are known to give two geometrical isomers by carbocupration reactions.[35] We were pleased to observe that alkynyl sulfones (as alkynyl sulfoximines and sulfoxides) also react cleanly with a copper-catalyzed addition of alkylzinc derivatives to lead to a single regio- and stereoisomer in good isolated yields as described in Scheme 13 and Table 6. Primary-, secondary-, functionalized

Table 6. Copper-catalyzed carbozincation reaction.

Entry	RZnX	E-X	E	Yield[a]
1	Bu_2Zn	HCl	H	70
2	Et_2Zn	HCl	H	72
3	*i*PrZnBr[b]	HCl	H	92
4	$MeOCO(CH_2)_3Zn$[c]	HCl	H	55
5	Et_2Zn	I_2	I	65
6	Et_2Zn	allyBr	allyl	60

[a] Yields determined after purification by chromatography on silica gel. [b] Generated from the corresponding Grignard reagent and $ZnBr_2$. [c] Prepared from the corresponding alkyl iodide and zinc dust.

derivatives react regio- and stereoselectively with alkynyl sulfones.[36] The addition is *syn* and the resulting sp^2 organometallic derivatives can easily react with classical electrophiles. Now, the only organometallic species in the reaction mixture is the dialkylzinc species catalyzed by 5 mol% of copper salt. This new catalytic carbozincation reaction opens new horizons for the catalytic assembly of three new carbon–carbon bonds by the method previously described with the creation of the expected all-carbon quaternary stereocenters.



Scheme 12. Cleavage of the sulfinyl group into free homoallylic amines possessing enantiomerically pure quaternary stereogenic centers.

Conclusion

The current state-of-the-art for the formation of enantiomeri-

cally pure all-carbon quaternary stereocenters in acyclic system relies on the formation of a single carbon–carbon bond per chemical step by asymmetric catalysis. These extraordinary sophisticated methods were logically classified among the most powerful and innovative ones. In this concept article, we describe an alternative method that would now rely on the efficient creation of three new carbon–carbon bonds in a one-pot reaction from common and even commercially available starting material through the combination of a 1) regio- and stereoselective carbometalation reaction, 2) in situ homologation of the resulting organocopper with a zinc carbenoid, 3) intra- or intermolecular chelation of the zinc moiety, and 4) diastereoselective allylation reaction. The key features in all these reactions are the high degree of stereocontrol, the level of predictability, and the ease of execution. We believe that such efficient methodologies should find a wide range of applications in synthesis and we are currently extending this concept to asymmetric alkylation reactions. The next challenging step would be to combine this described concept with asymmetric catalysis and efforts towards this goal are currently ongoing in our research group.

Acknowledgements

The author thanks the Israel Science Foundation administrated by the Israel Academy of Sciences and Humanities (grant No 459/04), the German-Israeli Foundation for Scientific Research and Development (GIF Research Grant No. I-871-62.5/2005), the United States–Israel Binational Science Foundation (grant 2005128) and the Technion Research & Development. The author is holder of the Sir Michael and Lady Sobell Academic Chair.

[1] For reviews, see a) E. J. Corey, A. Guzman-Perez, *Angew. Chem.* **1998**, *110*, 402; *Angew. Chem. Int. Ed.* **1998**, *37*, 388; b) J. Christoffers, A. Baro, Wiley-VCH, Weinheim, **2005**; c) B. M. Trost, C. H. Jiang, *Synthesis* **2006**, 369.

[2] For reviews, see a) J. Christoffers, A. Mann, *Angew. Chem.* **2001**, *113*, 4725; *Angew. Chem. Int. Ed.* **2001**, *40*, 4591; b) J. Christoffers, A. Baro, *Adv. Synth. Catal.* **2005**, *347*, 1473.

[3] a) Y. Lee, A. H. Hoveyda, *J. Am. Chem. Soc.* **2006**, *128*, 15604; b) J. van Veldhuizen, J. E. Campbell, R. E. Giudici, A. H. Hoveyda, *J. Am. Chem. Soc.* **2005**, *127*, 6877; c) N. Harrington-Frost, H. Leuser, I. M. Calaza, F. Kneisel, P. Knochel, *Org. Lett.* **2003**, *5*, 2111; d) C. Spino, C. Beaulieu, *Angew. Chem.* **2000**, *112*, 2006; *Angew. Chem. Int. Ed.* **2000**, *39*, 1930.

[4] a) E. Fillion, A. Wilsily, *J. Am. Chem. Soc.* **2006**, *128*, 2774; b) J. Wu, D. M. Mampreian, A. H. Hoveyda, *J. Am. Chem. Soc.* **2005**, *127*, 4584; c) P. Mauleon, J. C. Carretero, *Chem. Commun.* **2005**, 4961; d) M. S. Taylor, D. N. Zalatan, A. M. Lerchner, E. N. Jacobsen, *J. Am. Chem. Soc.* **2005**, *127*, 1313; e) H. Li, J. Song, X. Liu, L. Deng, *J. Am. Chem. Soc.* **2005**, *127*, 8948; f) M. S. Taylor, E. N. Jacobsen, *J. Am. Chem. Soc.* **2003**, *125*, 11204; g) D. O. Jang, D. D. Kim, D. K. Pyun, P. Beak, *Org. Lett.* **2003**, *5*, 4155.

[5] a) Y.-C Qin, C. E. Stivala, A. Zakarian. *Angew. Chem.* **2007**, *119, 7610; Angew. Chem. Int. Ed.* **2007**, 46, 7466; *Angew. Chem. Int. Ed.* **2007**, *46*, 7466; b) K. Wang, C. J. Bungard, S. G. Nelson, *Org. Lett.* **2007**, *9*, 2325.

[6] M. E. Jung, D. C. D′Amico, *J. Am. Chem. Soc.* **1995**, *117*, 7379.

[7] a) A. G. Doyle, E. N. Jacobsen, *Angew. Chem.* **2007**, *119*, 3775; *Angew. Chem. Int. Ed.* **2007**, *46*, 3701; b) A. H. Mermerian, G. C. Fu, *J. Am. Chem. Soc.* **2005**, *127*, 5604; c) A. Zhang, T. V. RajanBabu, *J. Am. Chem. Soc.* **2006**, *128*, 5620; d) S. Mukherjee, B. List, *J. Am. Chem. Soc.* **2007**, *129*, 11336; e) T. Fujimoto, K. Endo, H. Tsuji, M. Nakamura, E. Nakamura, *J. Am. Chem. Soc.* **2008**, *130*, 4492.

[8] a) S. R. Denmark, J. Fu, D. M. Coe, X. Su, N. E. Pratt, B. D. Griedel, *J. Org. Chem.* **2006**, *71*, 1513; b) J. B. Morgan, J. P. Morken, *Org. Lett.* **2003**, *5*, 2573.

[9] D. J. Ramón, M. Yus, *Angew. Chem.* **2005**, *117*, 1628; *Angew. Chem. Int. Ed.* **2005**, *44*, 1602.

[10] L. F. Tietze, *Chem. Rev.* **1996**, *96*, 115.

[11] a) I. Marek, *Tetrahedron* **2002**, *58*, 9463; b) A. Sidduri, P. Knochel. *J. Am. Chem. Soc.* **1992**, *114*, 7579; c) A. Sidduri, M. J. Rozema, P. Knochel, *J. Org. Chem.* **1993**, *58*, 2694; d) P. Knochel, T.-S. Chou, H. G. Chen, M. C. P. Yeh, M. J. Rozema, *J. Org. Chem.* **1989**, *54*, 5202; e) P. Knochel, N. Jeong, M. J. Rozema, M. C. P. Yeh, *J. Am. Chem. Soc.* **1989**, *111*, 6474; f) S. Avolio, C. Malan, I. Marek, P. Knochel, *Synlett* **1999**, 1820; g) V. A. Vu, I. Marek, K. Polborn, P. Knochel, *Angew. Chem.* **2002**, *114*, 361; *Angew. Chem. Int. Ed.* **2002**, *41*, 351.

[12] a) I. Marek, J. F. Normant, in *Metal-Catalyzed Cross-Coupling Reactions* (Eds.: P. J. Stang, F. Diederich), Wiley-VCH, Weinheim, **1998**, p. 271; b) N. Chinkov, D. Tene, I. Marek, *Metal-Catalyzed Cross-Coupling Reactions*, 2nd ed. in (Eds.: F. Diederich, A. de Meijere), Wiley-VCH, Weinheim, **2005**, p. 395; c) D. Tene I. Marek, in *Transition Metals for Organic Synthesis*, 2nd ed. (Eds.: C. Bolm, M. Beller), Wiley-VCH, Weinheim, **2004**, p. 563; d) E. Lorthiois, I. Marek, J. F. Normant, *J. Org. Chem.* **1998**, *63*, 566; e) N. Chinkov, S. Majumdar, I. Marek, *J. Am. Chem. Soc.* **2002**, *124*, 10282.

[13] a) G. Courtois, L. Miginiac, *J. Organomet. Chem.* **1974**, *69*, 1; b) H. Felkin, Y. Gault, G. Roussi, *Tetrahedron* **1970**, *26*, 3761; c) G. Fraenkel, W. R. Winchester, *J. Am. Chem. Soc.* **1989**, *111*, 3794; d) N. Chinkov, A. levin, I. Marek, *Angew. Chem.* **2006**, *118*, 479; *Angew. Chem. Int. Ed.* **2006**, *45*, 465.

[14] a) W. E. Truce, M. J. J. Lusch, *J. Org. Chem.* **1978**, *43*, 2252; b) V. Fiandanese, G. Marchese, F. Naso, *Tetrahedron Lett.* **1978**, *19*, 5131.

[15] a) K. K. Andersen, *Tetrahedron Lett.* **1962**, *3*, 93; b) K. K. Andersen, *J. Org. Chem.* **1964**, *29*, 1953; c) K. K. Andersen, J. Foley, R. Perkins, W. Gaffield, W. Papanikalaou, *J. Am. Chem. Soc.* **1964**, *86*, 5637; d) G. Solladie, J. Hutt, A. Girardin, *Synthesis* **1987**, 173.

[16] a) J. F. Normant, A. Alexakis, *Synthesis* **1981**, 841; b) H. Westmijze, H. Kleijn, J. Meijer, P. Vermeer, *Recl. Trav. Chim. Pays-Bas* **1981**, *100*, 98; c) H. Westmijze, J. Meijer, H. J. T. Bos, P. Vermeer, *Recl. Trav. Chim. Pays-Bas* **1976**, *95*, 299.

[17] a) A. B. Charette, J. F. Marcoux, C. Molinaro, A. Beauchemin, C. Brochu, E. Isabel, *J. Am. Chem. Soc.* **2000**, *122*, 4508; b) S. E. Denmark, S. P. O'Connor, *J. Org. Chem.* **1997**, *62*, 3390.

[18] G. Sklute, D. Amsallem, A. Shibli, J. P. Varghese, I. Marek, *J. Am. Chem. Soc.* **2003**, *125*, 11776.

[19] Interestingly, when a tertiary carbon center is created (**13**, R^1=Et, R^2=H), the diastereoselectivity was eroded and two isomers were formed in an 80:20 ratio.

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

[21] G. Sklute, I. Marek, *J. Am. Chem. Soc.* **2006**, *128*, 4642.

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

[23] a) F. Leroux, M. Schlosser, E. Zohar, I. Marek, in *The Preparation of Organolithium reagents and intermediates in The Chemistry of Organolithium Compounds*, Patai series (Eds.: Z. Rappoport, I. Marek), Wiley, Chichester, **2004**, p. 435; b) T. Cohen, M. D. Doubleday, *J. Org. Chem.* **1990**, *55*, 4784; c) T. Cohen, M. Bhupathy, *Acc. Chem. Res.* **1989**, *22*, 152; d) M. Yus, in *Arene-catalyzed Lithiation in The Chemistry of Organolithium Compounds*, Patai series (Eds.: Z. Rappoport, I. Marek), Wiley, Chichester, **2004**, p. 647.

[24] a) S. Farhat, I. Marek, *Angew. Chem. Int. Ed.*, **2002**, *41*, 1410; *Angew. Chem.* **2002**, *114*, 1468; b) S. Farhat, I. Zouev, I. Marek, *Tetrahedron* **2004**, *60*, 1329; c) A. Abramovitch, J. P. Varghese, I.

Marek, *Org. Lett.* **2004**, *6*, 621; d) J. P. Varghese, I. Zouev, L. Aufauvre, P. Knochel, I. Marek, *Eur. J. Org. Chem.* **2002**, 4151; e) N. Chinkov, H. Chechik, S. Majumdar, I. Marek, *Synthesis* **2002**, 2473.
[25] For some representative example of sulfoxide-Li exchange, see: a) T. Satoh, *Chem. Rev.* **1996**, *96*, 3303; b) T. Satoh, N. Itoh, H. Watanabe, H. Koide, H. Matsuno, K. Matsuda, K. Yamakawa, *Tetrahedron* **1995**, *51*, 9327; c) T. Satoh, N. Hanaki, Y. Kumarochi, Y. Inoue, K. Hosaya, K. Sakai, *Tetrahedron* **2002**, *58*, 2533; d) T. Satoh, N. Yamada, Asano, *Tetrahedron Lett.* **1998**, *39*, 6935.
[26] I. Marek, G. Sklute, *Chem. Commun.* **2007**, 1683.
[27] a) J. A. Ellman, T. D. Owens, T. P. Tang, *Acc. Chem. Res.* **2002**, *35*, 984; b) J. A. Ellman, *Pure Appl. Chem.* **2003**, *75*, 39; c) D. Morton, R. A. Stockman, *Tetrahedron* **2006**, *62*, 8869.
[28] G. Kolodney, G. Sklute, S. Perrone, P. Knochel, I. Marek, *Angew. Chem.* **2007**, *119*, 9451; *Angew. Chem. Int. Ed.* **2007**, *46*, 9291.
[29] a) P. V. Bharatam, P. Uppal, A. Kaur, D. Kaur, *J. Chem. Soc. Perkin Trans. 2* **2000**, 43; b) F. Ferreira, M. Audouin, F. Chemla, *Chem. Eur. J.* **2005**, *11*, 5269; c) L. F. Tietze, A. Schuffenhauer, *Eur. J. Org. Chem.* **1998**, 1629.
[30] a) F. Chemla, F. Ferreira, *J. Org. Chem.* **2004**, *69*, 8244; b) P. Wipf, C. Kendall, C. R. Stephenson, *J. Am. Chem. Soc.* **2003**, *125*, 761; c) D. H. Hua, S. W. Miao, J. S. Chen, S. Iguchi, *J. Org. Chem.* **1991**, *56*, 4; d) D. A. Cogan, G.-C. Liu, J. Ellman, *Tetrahedron* **1999**, *55*, 8883.
[31] A. H. Hoveyda, D. A. Evans, G. C. Fu, *Chem. Rev.* **1993**, *93*, 1307.
[32] L. F. Tietze, A. Schuffenhauer, P. R. Schreiner, *J. Am. Chem. Soc.* **1998**, *120*, 7952.
[33] X.-W. Sun, M.-H. Xu, G. Q. Lin, *Org. Lett.* **2006**, *8*, 4979.
[34] For some examples where metallic salts lead to different stereochemical outcome, see a) S. Samah, I. Marek, *Org. Lett.* **2007**, *9*, 2569; b) A. Alexakis, I. Marek, P. Mangeney, J. F. Normant, *J. Am. Chem. Soc.* **1990**, *112*, 8042.
[35] a) J. Meijer, P. Vermeer, *Recl. Trav. Chim. Pays-Bas* **1975**, *94*, 14; b) V. Fiandanese, G. Marchese, F. Naso, *Tetrahedron Lett.* **1978**, *19*, 5131; c) J. J. Eisch, M. Behrooz, J. E. Galle, *Tetrahedron Lett.* **1984**, *25*, 4851; d) J. J. Eisch, M. Behrooz, S. K. Dua, *J. Organomet. Chem.* **1985**, *285*, 121; e) M. Xie, X. Huang, *Synlett* **2003**, 477; f) M. Xie, J. Wang, X. Gu, Y. Sun, S. Wang, *Org. Lett.* **2006**, *8*, 431.
[36] G. Sklute, C. Bolm, I. Marek, *Org. Lett.* **2007**, *9*, 1259.

Published online: June 18, 2008

