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Perspective

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All-Carbon Quaternary Stereogenic Centers in Acyclic Systems through the Creation of Several C–C Bonds per Chemical Step

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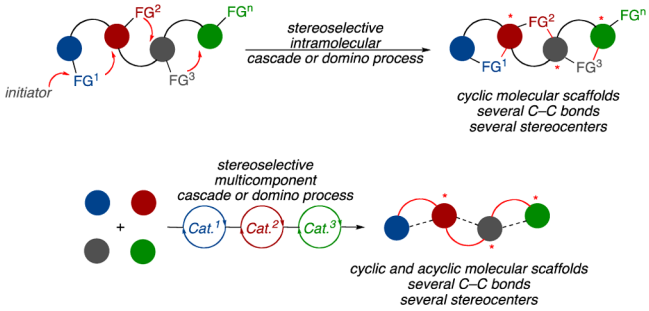
ABSTRACT: In the past few decades, it has become clear that asymmetric catalysis is one of the most powerful methods for the construction of carbon–carbon as well as carbon–heteroatom bonds in a stereoselective manner. However, when structural complexity increases (i.e., all-carbon quaternary stereogenic center), the difficulty in reaching the desired adducts through asymmetric catalytic reactions leads to a single carbon–carbon bond-forming event per chemical step between two components. Issues of efficiency and convergence should therefore be addressed to avoid extraneous chemical steps. In this Perspective, we present approaches that tackle the stimulating problem of efficiency while answering interesting synthetic challenges. Ideally, if one could create all-carbon quaternary stereogenic centers via the creation of several new carbon–carbon bonds in an acyclic system and in a single-pot operation from simple precursors, it would certainly open new horizons toward solving the synthetic problems. Even more important for any further design, the presence of polyreactive intermediates in synthesis (bismetalated, carbenoid, and oxenoids species) becomes now an indispensable tool, as it creates consecutively the same number of carbon–carbon bonds as in a multi-step process, but in a single-pot operation.

INTRODUCTION

Life is three-dimensional, and chirality plays a fundamental role. Therefore, the field of stereoselective synthesis—chemical reactions in which one or more new elements of chirality are formed in a substrate molecule and which produce the stereoisomeric products in unequal amounts—has witnessed tremendous achievements over the past half-century, providing access to sophisticated molecular fragments with high levels of diastereo- and enantioselectivity.[1] Most notably, the advent of catalysis has affected our view toward the creation of carbon–carbon and carbon–heteroatom bonds,[2] and these many advancements have profoundly influenced the art of organic synthesis. In this rapidly evolving field, modern leading strategies therefore take maximum advantage of asymmetric catalysis. Moreover, recent years have witnessed an important change in synthetic approaches, and classical methods involving a single carbon–carbon bond-forming event per chemical step are now evolving into new approaches leading to the creation of more than one bond. For instance, domino and cascade reactions giving access to multiple carbon–carbon bonds and stereocenters with high chemo- and stereoselectivity in a single-pot operation constitute a powerful approach (Scheme 1)[3] and are the subject of intense activities for cyclic and acyclic systems (see a few representative examples in Scheme 2 for acyclic systems).[4]

Scheme 1



Therefore, asymmetric catalysis is now incorporated in many multistep one-pot sequences to provide simple access to structurally complex target molecules in a highly stereoselective fashion (Scheme 2).[3] However, when the structural complexity of the target adducts increases, only a few methods maintain their efficiency. One element of structure that invariably increases the difficulty of a chemical synthesis is the presence of an all-carbon quaternary stereocenter in the target molecule.[5]

Asymmetric construction of quaternary *all-carbon* stereocenters is even more difficult if the target molecules are acyclic—more complicated due to the number of degrees of freedom associated with these structures.[6] The impediment to synthesis presented by such centers arises from the steric congestion imposed by the four attached carbons; therefore, the difficulty in reaching these desired adducts through asymmetric catalytic reactions leads usually to a single carbon–carbon bond-forming event per chemical step between two components. All the current methods available for the preparation of these all-carbon quaternary stereogenic centers are based on enantioselective substitution (nucleophilic allylic substitution and conjugate addition), enantioselective nucleophilic allylation, alkylation, and aldol reactions. Additionally, examples of rearrangements and especially [3,3]-sigmatropic rearrangements leading to a general access to all-carbon stereogenic centers in architecturally complex settings[7] have been reported (Scheme 3, Paths A–E, respectively).[6]

In a conceptually different approach, an elegant stereodivergent dual catalysis was recently reported in which two

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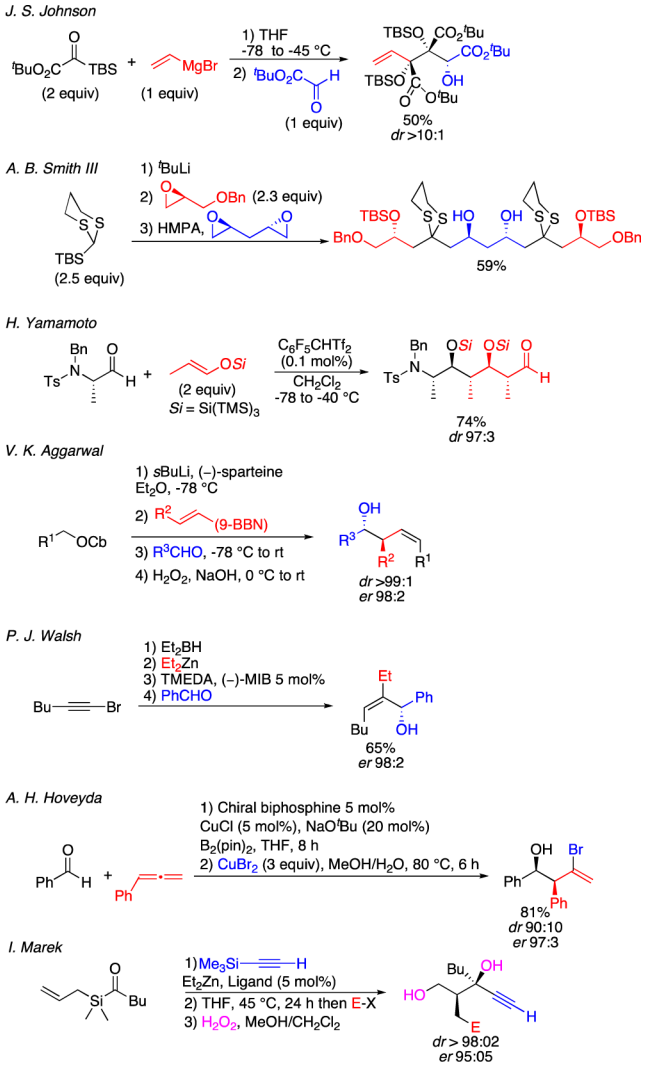
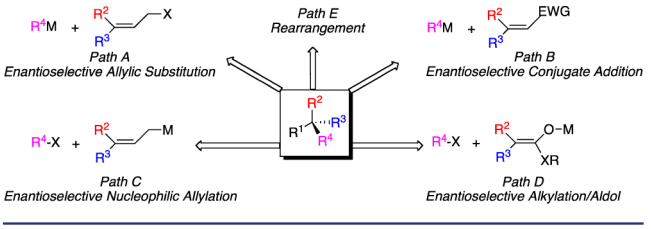
Scheme 2



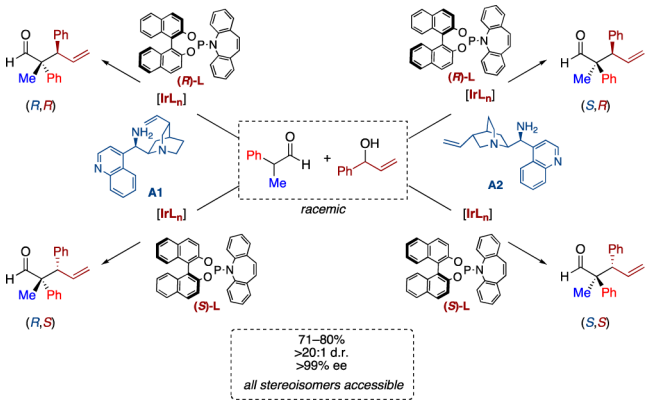
Scheme 3



distinct and highly face-selective catalytic cycles were merged to provide access to all possible stereoisomers of products possessing the quaternary stereocenter, in a vicinal relationship to a tertiary stereocenter, in good yields and with excellent selectivities (Scheme 4).[8] Although these methods represent today the best approaches to compounds possessing quaternary stereocenters in acyclic systems, the creation of more than a single carbon−carbon bond is necessary (even if not through asymmetric catalysis), and therefore issues of efficiency and convergence should also be addressed to avoid these extraneous chemical steps. This challenge is further exacerbated if more than one stereogenic center is created in the final adducts.[9]

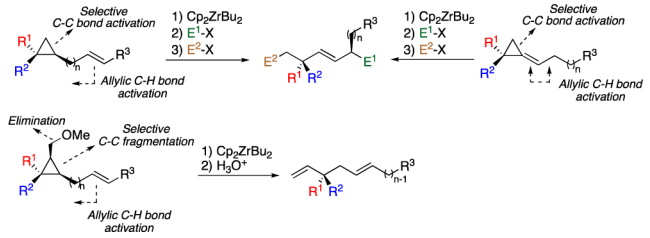
Is the creation of new bonds the only approach that should lead to this expected molecular framework? An alternative and

Scheme 4



unique approach that exploits multifold reactivity of readily accessible substrates with a single organometallic species that furnishes the expected advanced molecular scaffolds through a unique merging of allylic C−H and selective C−C bond activations has recently been reported.[10] The resulting bifunctional nucleophilic species, possessing an all-carbon quaternary stereogenic center, can further be selectively derivatized by the addition of two different electrophiles to give more-complex molecular architectures from these easily available starting materials (Scheme 5).[10]

Scheme 5



In this Perspective, we concentrate on methods toward the formation of all-carbon quaternary stereocenters in acyclic systems through the formation of several new carbon−carbon bonds in a single-pot operation starting from simple precursors. The success of such an approach would certainly open new horizons on our way toward solving synthetic problems and holds great promise, particularly toward the compounds containing stereogenic quaternary carbons that are widespread among natural products.[11]

RESULTS AND DISCUSSION

To meet this stimulating problem, polyreactive intermediates, which are able to create consecutively the same number of carbon−carbon bonds as in a multistep process, but in a single-pot operation, represent a powerful solution. An approach that improves efficiency and illustrates the role of these polyreactive intermediates is the formation of bismetalated species that can formally react selectively with two different electrophiles.[12] In this context, the catalytic enantioselective 1,2-diboration of 1,3-dienes leading to 1,2-bis(boronate) species has been employed for the *in situ* stereoselective allylation reaction (Scheme 6).[13] This approach allows for the preparation of the all-carbon quaternary stereocenter with subsequent formation of an allylborane that can further be manipulated.[14]

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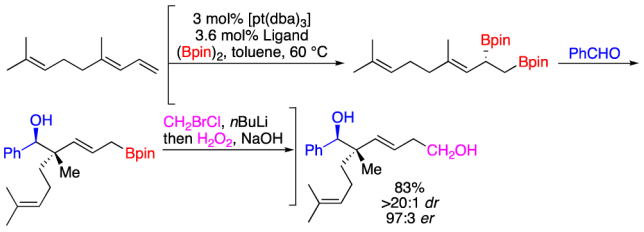
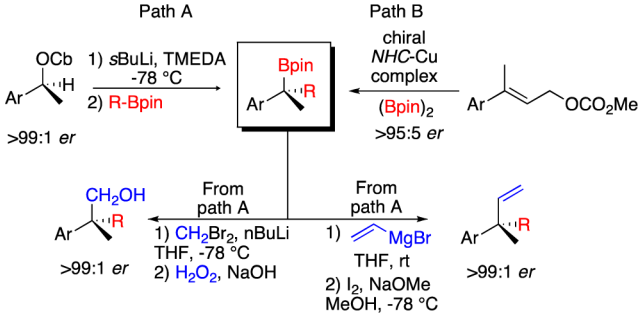
Scheme 6



Alternatively, several carbon−carbon bonds could be created in a single-pot operation through the use of an ambiphilic carbenoid.[15] Indeed, when a nucleophile reacts with a carbenoid, a new carbon−carbon bond is formed, with the concomitant creation of a new organometallic species that can additionally be functionalized. The preparation of quaternary stereocenters that makes use of this ambiphilic nature has recently been explored by Aggarwal using the 1,2-metalate rearrangement of sp^3 boronate complexes.[16] Secondary benzylic boron derivatives can easily be prepared in high enantioselectivity either by the reaction of Hoppe's lithiated carbamates[17] with aryl/alkyl boronic esters (Path A, Scheme 7)[18] or by the enantioselective boronate conjugate addition or

Scheme 7



substitution on trisubstituted alkenyl species (Path B, Scheme 7).[19] Especially noteworthy is the generation of contiguous quaternary and tertiary stereogenic centers with high diastereomeric and enantiomeric ratios.[20]

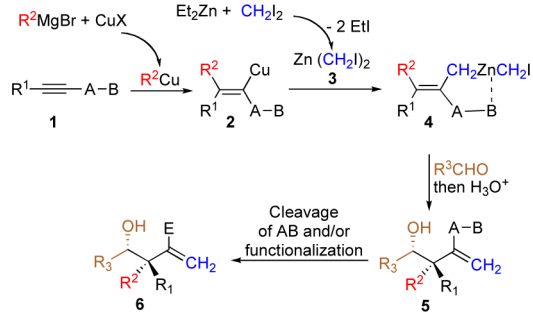
Following the pioneering work of Knochel that showed that zinc carbenoid can be used for the homologation reaction of vinylcopper into allylmetal species,[21] we were interested in combining the carbocupration reaction of alkynes[22] with the zinc homologation reaction as a new route to stereodefined γ,γ'-disubstituted allylzinc species.[23] If one can control the configurational stability of allylmetal species, the subsequent addition of an electrophile would lead to the formation of the all-carbon quaternary stereocenters with high diastereoselectivity. To preserve the geometrical integrity of polysubstituted allylmetal species, our first approach was based on the following chemical steps:

(1) Formation of a stereodefined β,β'-disubstituted vinylmetal **2**, easily obtained through a controlled carbocupration reaction of heterosubstituted alkynes **1** possessing a chelating and electron-withdrawing A-B unit (Scheme 8).[24]

(2) Homologation reaction with a zinc carbenoid **3**, leading to the *in situ* formation of the γ,γ'-disubstituted allylmetal species **4**, stabilized by intramolecular chelation with the A-B unit. This chelation should additionally slow down the metallotropic equilibrium (as compared to the reaction with electrophiles).[25]

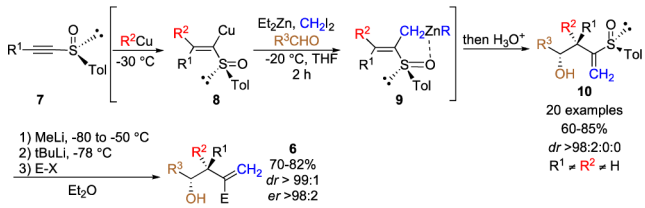
(3) Reaction with carbonyl compounds giving the diastereomerically enriched homoallylic alcohols **5**. A simple cleavage or functionalization of the A-B unit would finally lead to the diastereo- and enantiomerically enriched homoallylic alcohols **6** (Scheme 8).[26]

Scheme 8



Considering these prerequisites, alkynyl sulfoxide **7** was initially designed as a potential substrate,[27] as the regio- and stereospecific carbocupration of **7** provides the required β,β'-dialkylated vinylcopper **8** in quantitative yield (Scheme 9).[28]

Scheme 9



Then aldehyde, Et_2Zn, and CH_2I_2 were all added to the reaction mixture at −20 °C. As neither vinylcopper **8** nor Et_2Zn reacts with aldehydes, and as vinylcopper does not react either with CH_2I_2, the reaction between Et_2Zn and CH_2I_2 occurs first, leading to the *in situ* formation of the zinc carbenoid **3**. Next, **8** is homologated with the zinc carbenoid **3** to generate the *in situ*-reactive chelated allylzinc species **9**. The latter reacts diastereoselectively with the carbonyl group to give, after hydrolysis, the corresponding adducts **10** in good overall yields and with excellent diastereoselectivities (Scheme 9).[29] By using this simple methodology, a chiral quaternary carbon center with two sterically very similar but formally different alkyl groups (R^1 and R^2) can easily be prepared as a single diastereoisomer (dr > 98:2:0:0). The reaction proceeds similarly with aromatic and aliphatic aldehydes (R^3), and permutation of the alkyl groups of the alkyne (R^1) and the organocopper reagent (R^2) allows for the independent formation of the two isomers at the quaternary carbon center, respectively.

The chiral sulfoxide moiety played several roles, directing the regio- and stereoselectivity of the carbometalation reaction, decreasing the rate of metallotropic equilibration of the *in situ* formed γ,γ'-disubstituted allylzinc species through intramolecular chelation, and finally serving as a chiral inductor to differentiate between two prochiral faces in the reaction of the allylzinc with the carbonyl group.[30] Moreover, sulfoxide can easily be disposed at the end of the sequence. In this context, the sulfoxide−metal exchange reaction leading to the formation

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of vinylmetal species that can be further functionalized is of special interest. For instance, *E*- and *Z*-heterosubstituted alkenes such as enol ethers,[31] silylenol ethers,[31] vinylsulfides,[32] vinylsulfoxides,[32] vinylsulfones,[32] and vinyl carbamates[33] are excellent candidates for the stereoselective formation of vinyl-[34,35] and dienylmetal[36] species. In this particular case, the most efficient sulfoxide−metal exchange reaction was achieved when homoallylic alcohol **10** was first treated with MeLi (for the initial deprotonation of the alcohol) and then with *t*BuLi in Et_2O at −78 °C.[37] The corresponding vinyllithium species could further react with electrophiles to give functionalized adducts **6** in excellent yields and enantiomeric ratios. The observed final stereochemistry is rationalized through a sequence of events as summarized below and illustrated in Scheme 9:

(a) The defined stereochemistry of the two alkyl groups on the double bond (R^1 and R^2) results from the regio- and stereoselective carbocupration reaction.[22,24]

(b) The zinc homologation proceeds at low temperature and leads to the corresponding allylzinc species.[21,25]

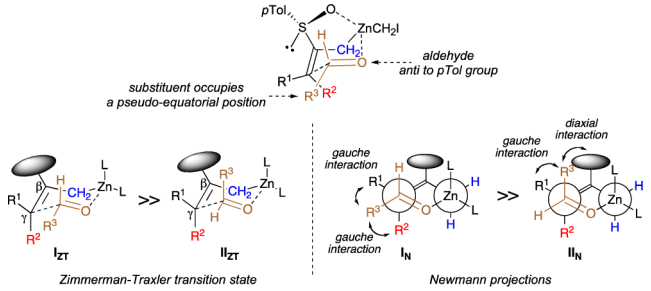
(c) The oxygen atom of the sulfoxide chelates the zinc and prevents the metallotropic equilibrium.[30]

(d) The nonbonding electrons of the sulfoxide group are *syn* to the double bond to minimize the 1,3-allylic strain.[38]

(e) The aldehyde reacts with the γ,γ′-disubstituted allylzinc species **9** through a Zimmerman−Traxler transition state and from the opposite side of the tolyl group.

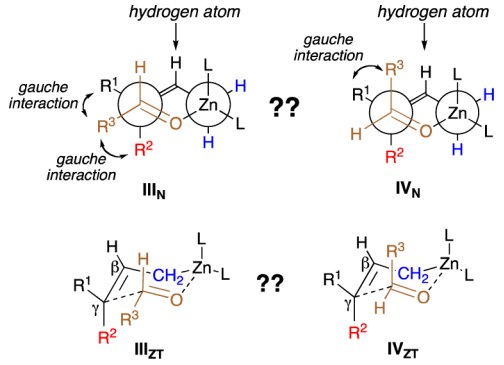
(f) When the bulky substituent (i.e., sulfoxide) is engaged in a coordinative metallacycle at the β-position of the γ,γ′-disubstituted allylzinc species **9**, the incoming aldehyde residue R^3 occupies a pseudoequatorial position, as illustrated in $\mathbf{I}_{ZT}$ versus $\mathbf{II}_{ZT}$ (bulky substituent represented as a gray ellipse), despite two gauche interactions (see Newman projection $\mathbf{I}_N$ versus $\mathbf{II}_N$, Scheme 10).[39]

Scheme 10



Interestingly, despite the presence of two gauche interactions, the incoming aldehyde residue R^3 occupies a pseudoequatorial position to avoid the 1,3-diaxial interaction with the bulky substituent (i.e., sulfoxide, represented as an ellipse). To support this mechanistic hypothesis, theoretical calculations on a model system (R^1 = R^2 = Me) using density functional theory at the MO5-2X/6-31G(d) level were performed, and the two transition states for the reaction of allylzinc **9** with benzaldehyde were located. As expected, the reaction proceeds through a chairlike transition state $\mathbf{I}_{ZT}$, in which the aryl group of the benzaldehyde preferentially occupies a pseudoequatorial position, as it is 6.0 kcal/mol more stable than $\mathbf{II}_{ZT}$, in which the aryl group occupies a pseudoaxial position.[39] However, what would be the stereochemical outcome of a reaction if this 1,3-diaxial interaction did not exist (i.e., replacing the bulky substituent, shown as a gray ellipse, by a hydrogen atom)? Would the two gauche interactions present in the transition state $\mathbf{III}_N$, where the R^3 substituent occupies a pseudoequatorial position, be preferred to transition state $\mathbf{IV}_N$, in which the R^3 substituent of the aldehyde occupies a pseudoaxial position ($\mathbf{III}_{ZT}$ vs $\mathbf{IV}_{ZT}$, Scheme 11)? This very interesting aspect of stereochemistry

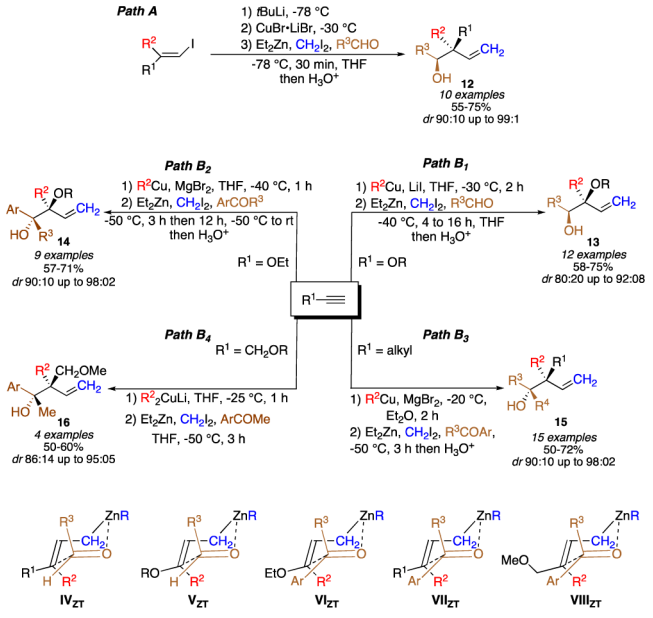
Scheme 11



could be answered only if the constitutional stability of the η^1-γ,γ-disubstituted allylzinc species is higher than that of the reaction with the aldehyde.[40]

To this end, the allylation reaction of carbonyl derivatives was tested through different routes and with different starting materials and carbonyl derivatives (Scheme 12). In Path A, the

Scheme 12



one-pot transformation of vinyl iodide into homoallylic alcohols **12** was performed through the successive treatment of vinyl iodide with *t*BuLi followed by the addition of a copper salt solution, Et_2Zn, CH_2I_2, and aldehydes at −80 °C. The reaction proceeds equally well with aliphatic, aromatic, and functionalized aldehydes, although diastereoselectivity with aliphatic aldehydes is slightly lower. As the permutation of the alkyl groups at the vinyl iodide allows for the independent formation of the two diastereoisomers at the quaternary carbon center, it

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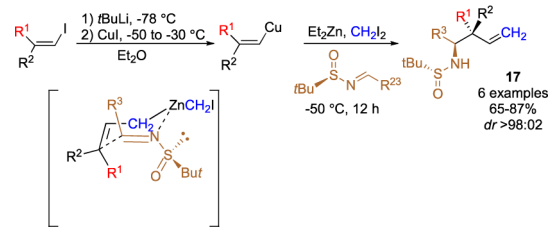
implies not only that the haptotropic rearrangement is slow with respect to the reaction with aldehydes at −78 °C but also that the reaction proceeds through a cyclic transition state (in an open transition state, both isomers of γ,γ′-disubstituted allylzinc would lead to the same diastereoisomer). Several different alkyl groups were easily introduced at the all-carbon stereogenic center, which shows the flexibility of the described method. Importantly, the relative configuration of all homoallylic alcohols **12** indicates that the R^3 group of the aldehyde occupies a pseudoaxial position in a chairlike transition state when it reacts with γ,γ′-disubstituted allylzinc species, as shown in $\mathbf{IV}_{ZT}$ (Scheme 12).[39] Indeed, computational studies show that the existence of two gauche interactions leads to a transition state higher in energy by 2.7 kcal/mol, and the system therefore prefers to have the substituent of the aldehyde R^3 in an axial position.[41] As the haptotropic equilibrium is slower for γ,γ′-disubstituted allylzinc species than the reaction with aldehydes at low temperature, the diastereoselective formation of homoallylic alcohols as well as monoprotected 1,2-alkenyl diols could be performed directly from commercially available alkynes in a single-pot operation through the formation of three new carbon−carbon bonds. For instance, in Path B_1, when the tandem carbocupration of commercially available ethoxyacetylene was performed followed by the zinc homologation and reaction with aldehydes, the corresponding monoprotected 1,2-alkenyl diols **13** were obtained in good isolated yield and diastereoselectivity.[42] The reaction proceeds well using classical organocopper reagents and aromatic and aliphatic aldehydes, albeit with slightly lower diastereoisomeric ratios in the latter case. Importantly, a nonclassical *E*-configured alkoxy-substituted allylmetal reagent is formed as an intermediate,[43] and the substituent of the aldehyde occupies again a pseudoaxial position in a Zimmerman−Traxler transition state, as depicted in $\mathbf{V}_{ZT}$ (Scheme 12, Path B_1).

To further validate this stereochemical concept combined with the approach to create complex molecular fragments in a single-pot operation, the allylation and alkoxyallylation of ketones were investigated. For the alkoxyallylation reaction, commercially available ethoxyacetylene (R^1 = OEt) was employed (Scheme 12, Path B_2),[44] whereas for the allylation reaction, either terminal alkynes (Scheme 12, Path B_3)[45] or propargylic ether (Scheme 12, Path B_4)[44] was engaged in the combined carbometalation reaction, zinc homologation, and addition of various aryl ketones. Adducts **14**−**16** were obtained in good yields with excellent diastereoselectivities, as shown in Scheme 12, Paths B_2−B_4. The relative configurations, established by X-ray crystallography, show that the bulky alkyl substituent always occupies the pseudoaxial position in the Zimmerman−Traxler transition state to avoid the gauche interactions, as described in $\mathbf{VI}_{ZT}$ to $\mathbf{VIII}_{ZT}$ (Scheme 12).[41] Various functionalized aryl ketones were successfully engaged in this reaction, and in all cases, excellent diastereomeric ratios were obtained. For aliphatic ketones, the reaction becomes sluggish with a meaningless diastereoselectivity.

The addition of aromatic and aliphatic enantiomerically pure imines as electrophilic partners (i.e., chiral Ellman's sulfinylimines)[46] was also successfully employed in this multicomponent reaction. In the first approach, disubstituted vinyl iodides were treated with *t*BuLi, followed by the addition of CuI, Et_2Zn, CH_2I_2, and aromatic sulfinimines. The expected homoallylic sulfinylamines **17** (Scheme 13) were obtained in excellent yields and diastereoselectivities in all cases,

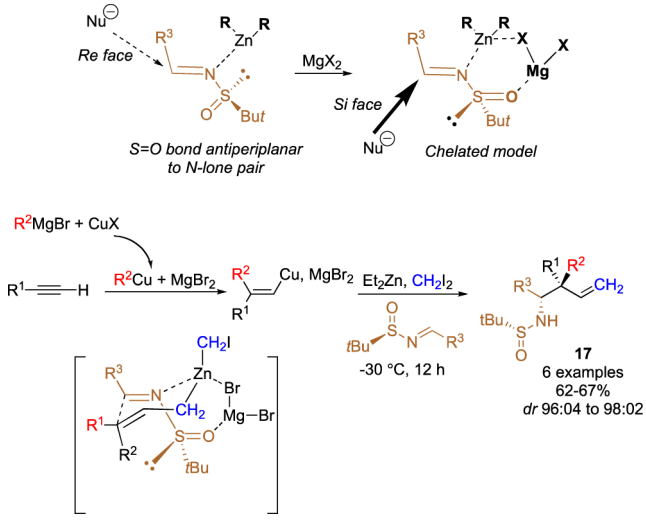
Scheme 13



irrespective of the nature of the aliphatic substituents on the starting alkenes.[47] As the S═O bond of the sulfinylimine should adopt an antiperiplanar conformation with the lone pair of electrons of the nitrogen atom, the γ,γ′-disubstituted allylzinc species react with the imine anti to the bulky substituent *t*Bu.[48] Due to the *E*-conformation of the sulfinylimine, the substituent of the sulfinylimine occupies a pseudoaxial position in the Zimmerman−Traxler transition state, as described in Scheme 13.

However, the lone pair of the sulfinylimine could also be engaged in a chelation mode with organometallic species.[49] In such a case, a change in the stereochemical outcome of the reaction can be expected, and products resulting from chelation control should be obtained. Indeed, from a conformation in which the S═O bond and the lone pair of electrons of the nitrogen atom are antiperiplanar (Scheme 13), addition of metallic salts (i.e., MgX_2) should lead to a chelated model, as represented in Scheme 14.[50] The outcome of this chelated

Scheme 14



model is that, for the same absolute configuration of the sulfinylimine, the bulky *t*Bu group now shields the opposite stereoface, and therefore the diastereoselectivity of the incoming nucleophile (Nu^- = γ,γ′-disubstituted allylzinc species) would be opposite. To test this hypothesis, the direct carbocupration reaction of alkynes with alkylcopper, prepared from alkylmagnesium halide and a copper salt generating *in situ* magnesium salts, was tested. To the resulting vinylcopper species were added Et_2Zn, CH_2I_2, and the same-configuration (*R*)-sulfinylimines at low temperature to give the opposite diastereomer of the homoallylamines **17** as the ones described in Scheme 13, in good isolated yields and excellent diastereomeric ratios (Scheme 14).[47]

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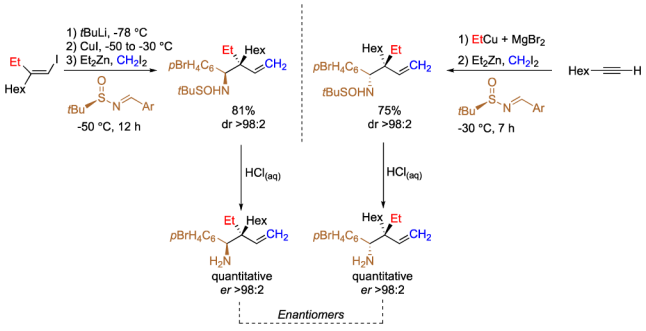
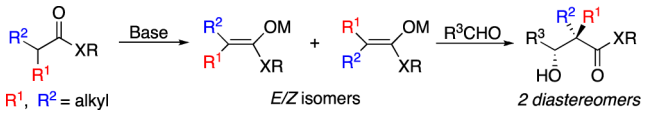
It is important to note that aliphatic sulfinylimine can also be converted into the expected adducts with excellent diastereomeric ratio,[47] and both diastereoisomers could be obtained only by permuting the nature of the two alkyl groups on the alkyne and on the copper species. After acidic hydrolysis of the sulfinamines, both enantiomers can be obtained from the same (*R*)-sulfinylimines (Scheme 15).

Scheme 15



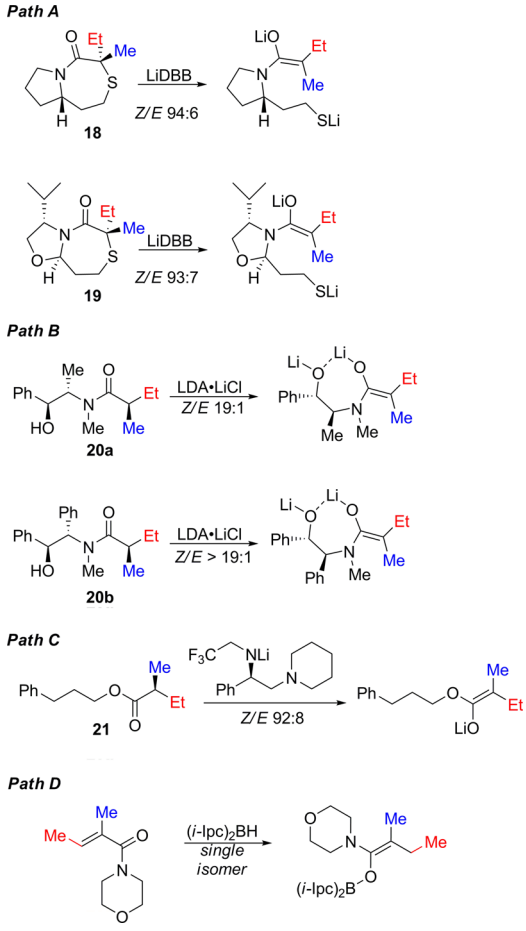
To expand further this approach in chemistry for the one-pot creation of several carbon−carbon bonds including the all-carbon quaternary stereocenters in acyclic systems, the problem of the aldol reaction has also been tackled. Indeed, due to the lack of efficient methods for the preparation of geometrically defined α,α-disubstituted enolates, or enolate equivalents, the preparation of an all-carbon quaternary stereocenter at the α-position to carbonyl groups in aldol compounds represents one of the prototypes of challenging synthetic transformations.[51] Indeed, despite the impressive developments in asymmetric aldol processes, the asymmetric construction of such quaternary carbon stereocenters is hampered by the lack of *E*/*Z* selectivity in the enolization of simple unfunctionalized α,α-disubstituted carbonyl compounds (Scheme 16).[52]

Scheme 16



Any solution allowing for the preparation of geometrically defined α,α-disubstituted enolates not only would automatically empower the aldol reaction but also could provide an easy and straightforward access to the synthesis of a large family of adducts possessing quaternary centers by reactions of these enolates with various electrophiles. Therefore, strategies leading to complete control of the geometry of fully substituted enolates are absolutely needed[53] (alternatively, a selective enolate tautomerization assuming that one isomer would react faster with the electrophile,[54a] or both enolates leading to the same final enantiomer,[54b,c] could also be considered). It should be noted that different approaches that avoid the issues associated with enolate geometry—use of silyl ketene imines[55] and ring-opening of β-lactones[56]—successfully led to aldol surrogates. Proposed solutions for the generation of such substituted acyclic enolates with complete control of the *E*/*Z* selectivity required a resident chirality on the enolizable carbon center. Indeed, Gleason initially proposed an elegant solution using a two-electron reduction of thioglycolate lactams **18** as

Scheme 17



described in Scheme 17, Path A.[57] Carbon−sulfur bond cleavage occurs to form an enolate dianion, and the *E*/*Z* stereochemistry is governed by the relative location of the α-alkyl groups in the starting lactam. Importantly, this method allows for any alkyl groups to be present at the α-positions. To improve on the lengthy synthesis of the starting lactam, a second generation of bicyclic lactam (**19**) was later reported.[58] An alternative method for the stereocontrolled generation of α,α-disubstituted enolates was reported by Myers when diastereomeric α-methylbutyramide **20a** underwent stereospecific enolization with the LDA·LiCl complex (Scheme 17, Path B) and was successfully used in alkylation reactions.[59] A more recent report showed that the chiral auxiliary pseudoephenamine **20b** could be used with a greater efficiency than pseudoephedrine for the selective formation of substituted enolates through either selective enolization or conjugate addition (not represented in Scheme 17).[60] The selective enolization of challenging α-branched ester **21**, based on an original chirality match between a chiral base and a chiral enolate precursor, was developed by Zakarian and allows for a straightforward access to trisubstituted enolates (Scheme 17, Path C).[7]

In addition to these solutions where control of the *E*/*Z* selectivity is based on the resident chirality of the enolizable carbon center, the 1,4-hydroboration reactions of substituted morpholine acrylamides with (diisopinocampheyl)borane provide stereodefined tetrasubstituted enolborinates with exceptional stereochemical control (Scheme 17, Path D), leading to the aldol reactions with a panel of aldehydes with

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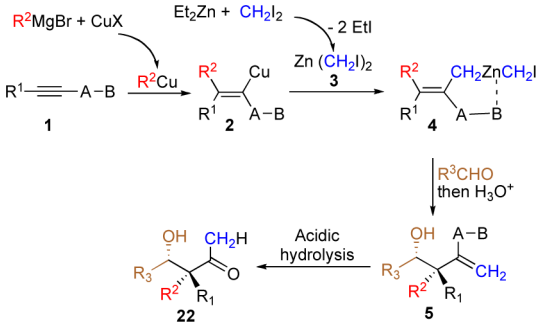
excellent diastereo- and enantioselectivity.[61a] The selective formation of dienolate was also achieved by γ-deprotonation of α,β-unsaturated imides,[61b,c] and a direct enantioselective intermolecular aldol reaction of α,α'-dialkylaldehydes with aryl aldehydes was reported by Barbas and Tanaka,[62] but gave a mixture of two diastereoisomers, reflecting the presence of the two enamine intermediates. The same holds when the chiral ligand is histidine[63] or O-*t*Bu-L-threonine.[64] A few more powerful, stereoselective enamine-mediated alkylations of α,α'-disubstituted aldehydes were reported,[65] although issues of stereochemistry of the reactive intermediates were not always addressed. However, in all of these approaches, a single carbon−carbon bond is formed in the critical event. To answer the problem while creating several new carbon−carbon bonds in a single-pot operation, a retrosynthetic analysis similar to the one discussed in Scheme 8 has been proposed (Scheme 18).[66]

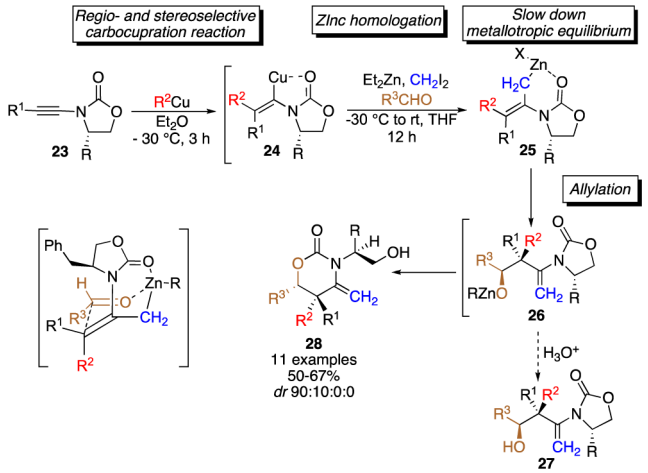
Scheme 18



The target aldol adduct **22**, possessing the expected quaternary stereocenter, would come from a simple acidic hydrolysis of heterosubstituted alkene **5**, which should be easily obtained from a nucleophilic allylation reaction of **4** with a carbonyl compound. The allylmetal **4**, with a defined stereochemistry at the γ,γ'-position, may result from insertion of a methylene unit into the vinylmetal bond of **2**.

Finally, the preparation of **2** may result from a regio- and stereoselective carbometalation reaction of heterosubstituted alkyne **1**.[24] Thus, a possible solution to the synthetic problem under consideration, namely the creation of an all-carbon quaternary stereocenter in an aldol reaction, with concomitant formation of three new carbon−carbon bonds in a single-pot operation, would not hinge on enolizable carbonyl compounds (i.e., Scheme 16) but on multiple *in situ* manipulations of heterosubstituted alkyne **1** (Scheme 18).[66] Following the previous studies on carbocupration reactions of *N*-heterosubstituted alkynes, ynamides **23** (A-B = oxazolidinone, Scheme 19),[24] easily prepared from oxazolidinone and alkynyl derivatives,[67] were chosen as starting materials, as the acidic hydrolysis of enamides **5** (A-B = oxazolidinone) should give the expected ketone (Scheme 18). Although our approach stems from a detailed analysis of all the potential factors governing the reaction, when **23** was subsequently treated with an organocopper, followed by the zinc homologation and allylation reactions, **26** was indeed formed as reactive intermediate, but after acidic hydrolysis, not the aldol surrogate **27** but rather the cyclic enamide **28** was observed.[53,68] This unexpected cyclization of **26** into **28** most probably occurs due to a favorable conformation generated by a Thorpe−Ingold effect (Scheme 19).[69]

Scheme 19



The reaction proceeds nicely for all tested aromatic aldehydes, and the cyclic adducts **28** were obtained in good diastereoselectivity and yields. The minor isomers result from the metallotropic equilibrium of the substituted allylzinc species and have therefore the opposite absolute configuration at the all-carbon quaternary stereocenters.[66] When aliphatic aldehydes are used, the reaction still proceeds, although sluggishly, resulting in much lower yields and diastereoselectivity. The final stereochemistry is rationalized through a Zimmerman−Traxler transition state in which the benzyl group of the oxazolidinone shields one stereoface in this chelated six-membered ring and the aldehyde approaches the substituted allyl moiety *anti* to this benzyl group, with its substituent in a pseudoequatorial position (Scheme 19; oxazolidinone plays the role of the bulky substituent represented as a gray ellipse in Scheme 10). Although cyclic enamides **28** are structurally very close to our expected aldol surrogates **27** (hydrolysis of the cyclic carbamate should give the aldol adducts **22**), hydrolysis of these cyclic carbamates proved to be extremely difficult. Under mild conditions no reactions were observed, whereas harsher conditions led to the cleavage of cyclic carbamates **28** but also instantaneously to the retro-aldol products. Therefore, the strategy needed to be improved, and it became clear that zinc alcoholate **26** must be trapped *in situ* to avoid the cyclization. However, the power of this approach relies on complete control of the reactivity of each component present in this one-pot reaction. Therefore, the additional reactant should react with the formed zinc alcoholate **26** but should not interfere with any of the components present in the reaction mixture. We were pleased to find that the simple addition of R_3SiCl could solve the problem and lead to silyl ethers **29**.[70] Thus, the regio- and stereospecific carbocupration of ynamide **23** with an organocopper derivative led to the corresponding metalated β,β-dialkylated enamide **24** as a single regio- and stereoisomer (Scheme 20). The next step requires the *in situ* formation of the Simmons−Smith−Furukawa zinc carbenoid $[Zn(CH_2I)_2]$,[71] a reaction performed in the presence of the aldehyde and R_3SiCl. However, we found that a slightly improved chemical yield was obtained when a transmetalation of the formed vinylcopper **24** into a vinylzinc was performed (without such zinc transmetalation, direct reaction of **24** with the aldehyde occurs in the range of 10%, most probably due to activation of the aldehyde by the mildly Lewis acid R_3SiCl). Therefore, under these conditions, $ZnBr_2$, R^3CHO, Et_2Zn,

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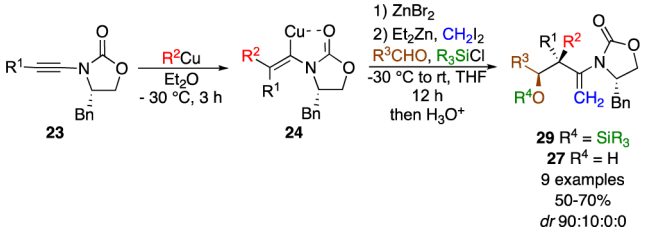
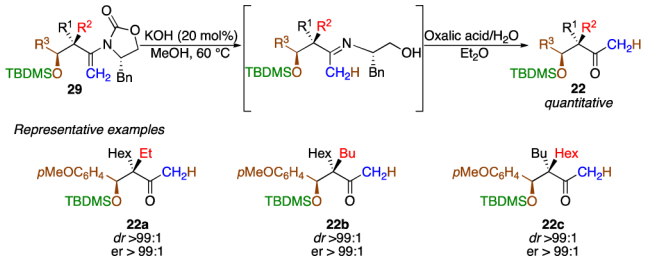
Scheme 20



CH_2I_2, and R_3SiCl were sequentially added to the metalated enamide **24** to give the linear aldol surrogates **29** in good overall yields (based on the starting ynamides) and a diastereoisomeric ratio of 90:10:0:0 (Scheme 20).[66] Both diastereoisomers were easily separated by simple column chromatography on silica gel. The labile silyl ether derivatives **29** have the additional advantage that they are easily cleaved to give the free alcohols **27** either by simple aqueous acidic treatment or during purification using column chromatography on silica gel (without any noticeable cyclization reaction).

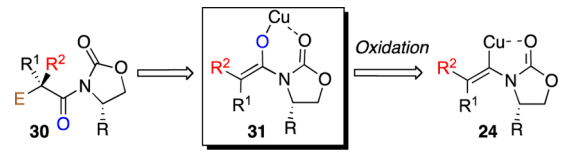
The reaction proceeds smoothly for diverse aromatic, heteroaromatic, and aliphatic aldehydes. Here again, permutation of the alkyl groups of the alkyne and the organocopper reagents allows for the independent formation of the two isomers at the quaternary all-carbon stereocenter. To obtain the desired aldol adducts, diastereoisomerically pure aldol surrogates **29**[72] were treated in basic conditions to give first imines, followed by acidic hydrolysis to give the aldol products **22** in quantitative yields with perfect diastereo- and enantiomeric ratios (Scheme 21). During the hydrolysis of enamides **29**, the presence of silyl ethers avoids the retro-aldol reaction.[66]

Scheme 21



Although we were pleased to find that this new strategy fulfilled our initial research goal[73] (preparation of aldol products **22** possessing the challenging all-carbon quaternary stereogenic center from simple ynamide **23**, with the concomitant formation of three new carbon−carbon bonds in a single-pot operation), through the formation of γ,γ'-disubstituted β-heterosubstituted allylzinc species as reactive intermediates, the intrinsically low reactivity of allylzinc derivatives with electrophiles other than carbonyl groups severely impedes the scope of this reaction. Therefore, the straightforward preparation of stereodefined enolates from simple precursors seemed to be the key to broaden the scope and continued to attract our curiosity. Owing to the attractiveness of chiral oxazolidinone imides in organic synthesis,[74] we decided to find a solution to the preparation of these trisubstituted enolates, as their reactions with various electrophiles would offer an easy and rapid access to the formation of compounds possessing quaternary stereocenters (i.e., **30**, Scheme 22). As we have reported the regio- and stereoselective formation of **24**[24] by carbocupration reaction of

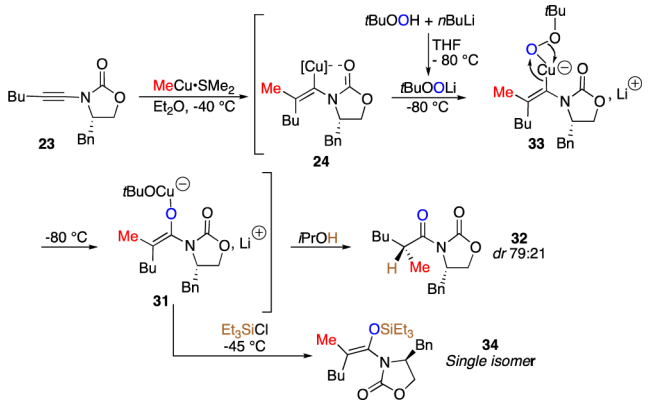
Scheme 22



ynamides **23** (Schemes 19 and 20), the formation of stereodefined enolates **31** could logically result from an oxidation reaction of vinylcopper species **24** (Scheme 22).

However, clean oxidation of sp^2 organometallic species is not a trivial task, particularly when traces of oxygen are present during the preparation of organocopper species: instantaneous degradation (that is, dimerization) of organocopper species through single-electron transfer to dioxygen is observed.[75] Therefore, oxidation of organocopper species requires a different approach, meaning a different mechanistic oxidation pathway.[76] As the best approach to insert a methylene unit was to use the electrophilic nature of carbenoids (Schemes 8−15 and 18−21), we thought that the best method to insert an oxygen atom would be to use the electrophilicity of oxenoid species.[15c] Oxenoids are compounds that bear a metal (M) and a leaving group (X) at the oxygen atom (oxo-analogues of carbenoids). After Müller's discovery that lithiated peroxide was an excellent oxidant for sp^3 organolithium species through a postulated S_N2 reaction,[77] similar observations were made by Whitesides for sp^2 organolithium species.[78] Vinyllithium reacts with *t*BuOOLi with a complete retention of configuration. Not only alkyllithiums but also Grignard reagents could be oxidized with oxenoids as well as lower cyano- and cyano-Gilman cuprates (RCuCNLi and $R_2CuCNLi_2$, respectively).[79] More recently, Ready successfully oxidized vinylmagnesium, -copper, and -aluminum species.[80] The feasibility of this new approach was initially checked by performing a carbocupration reaction of ynamides **23** (R^1 = Bu) with *Me*Cu·SMe_2, followed by oxidation of the resulting vinylcopper **24** by addition of 1.1 equiv of oxenoid *t*BuOOLi, independently prepared by mixing *t*BuOOH with 1 equiv of *n*BuLi in THF at low temperature, to give the corresponding copper enolate **31**. The corresponding imide **32** was obtained after protonation with alcohol as shown in Scheme 23, with a moderate diastereoselectivity (dr = 79:21).[81] We could rationalize this successful transformation by

Scheme 23



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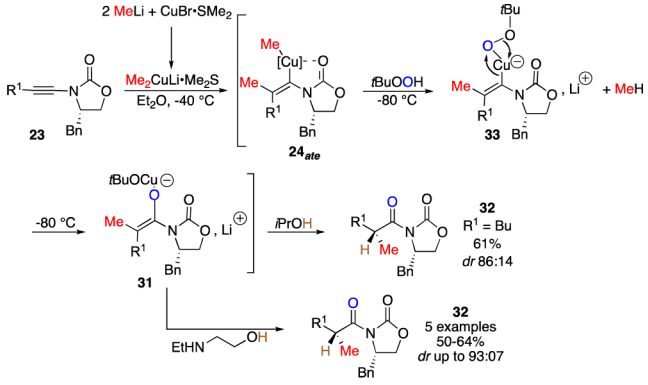
the initial formation of a heterocuprate **33** that would undergo a 1,2-metalate rearrangement,[20,25] leading to the copper enolate **31** (Scheme 23).[82]

To get information on the stereochemistry of the oxidation reaction, copper enolate **31** was trapped with triethylchlorosilane, and a single geometrical isomer of silylenol ether **34** was obtained.[83] Therefore, the oxidation reaction proceeds with complete preservation of the stereochemistry initially obtained during the carbocupration reaction.[24] This combined approach of carbometalation of ynamides followed by stereospecific oxidation with oxenoid leads to the formation of stereodefined trisubstituted copper enolate **31**. Although the diastereoselectivity of the final imide **32** (after hydrolysis) was not initially high, the most important feature of this transformation was that a single isomer of the enolate **31** was obtained. Despite the unique stereochemistry of the enolate, the practicality of the reaction needs to be improved. Indeed, this original protocol required the preparation, in a different flask, of the oxenoid by deprotonation of *t*BuO*O*H by *n*BuLi. This reaction is rather exothermic, and the resulting oxenoid needs to be transferred into the flask containing vinylcopper reagent at low temperature. These inconveniences should be solved if one wants a safe and convenient approach to stereodefined enolates. To achieve this goal, the carbocupration reaction was performed with an organocuprate ($Me_2CuLi{\cdot}SMe_2$) instead of the original organocopper species ($MeCu{\cdot}SMe_2$). Indeed, when 1 equiv of ynamide **23** was added to 1.1 equiv of an organocuprate, the reaction proceeded similarly, but only one alkyl group was added to the alkyne, leading to dissymmetric organocuprate $\mathbf{24}_{ate}$ (Scheme 24). As a hybridized sp^3 is more basic than a sp^2

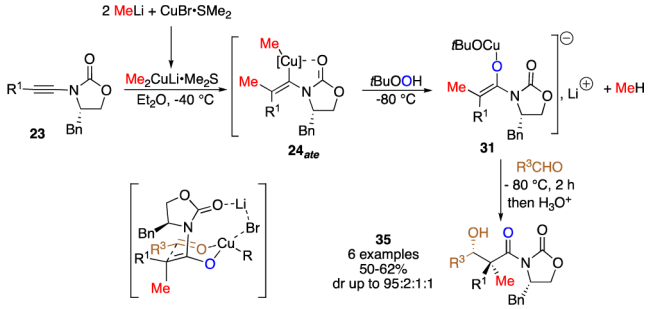
Scheme 24



organometallic species,[84] simple addition of the acidic *t*BuOOH to the reaction mixture led to an *in situ* deprotonation of the acidic hydrogen of the peroxide by the methyl group on the organocuprate, to give the same heterocuprate **33** with liberation of *Me*H. Once **33** was generated, the 1,2-metalate rearrangement proceeded and gave the copper enolate **31**. Addition of *i*PrO*H* gave **32** (R^1 = Bu) in slightly better yields with similar diastereomeric ratio (dr = 86:14).[81]

Now that an easier and safer protocol has been established, the diastereomeric ratio has been improved by adding *N*-ethylaminoethanol as a protic source.[85] As the carbocupration reaction is known not only for its high regioselectivity but also for its chemoselectivity, the smooth addition of various organocuprates to ynamides possessing sensitive functionalities such as esters has also been briefly investigated in this combined sequence of carbometalation−oxidation−hydrolysis. It is important to note that, when trisubstituted enolate **31** is warmed to room temperature and stirred at the same temperature for an additional 1 h, the same diastereomeric ratio was obtained after hydrolysis. Enolate **31** shows remarkable stereochemical stability, and no observable epimerization was detected under our experimental conditions. Similarly, the carbocupration followed by the oxidation reaction can be performed at higher temperature (i.e., 0 °C) without any erosion in chemical yield as well as selectivity. Finally, the preparation of the aldol adducts possessing the expected all-carbon quaternary stereocenter was achieved to validate this new approach to stereodefined polysubstituted enolates. When 1 equiv of ynamide **23** was treated with 1.1 equiv of organocuprate, followed by the addition of 1.1 equiv of *t*BuOOH and then 1.1 equiv of aldehydes, the aldol adducts were obtained in good overall yields (based on the starting ynamide after three consecutive chemical steps) and excellent diastereomeric ratios, as described in Scheme 25.[81,86] The

Scheme 25



major diastereoisomer could easily be separated by simple column chromatography on silica gel. The stereochemistry of the major isomer could be rationalized by a Zimmerman−Traxler transition state in which the oxazolidinone chelates the copper (or more probably its associated salts) and the benzyl group shields one stereoface. The incoming aldehyde reacts with the enolate from the stereoface opposite to the benzyl group, and the aldehyde residue R^3 occupies a pseudoequatorial rather than a pseudoaxial position to avoid steric interactions with the axial oxazolidinone and the metal ligands. When aliphatic aldehydes and ketones are added, much lower yields and diastereomeric ratios of the final products are obtained. In these cases, longer reaction time (overnight) and higher temperatures (−40 °C instead of −80 °C) were necessary.

For instance, *n*-heptanal and isobutyraldehyde resulted in 60% and 50% conversion with a moderate diastereomeric ratio of 60:40, while methyl phenyl ketone did not show any reactivity toward enolate **31**, even in the presence of Lewis acids (e.g., $BF_3{\cdot}Et_2O$, $TiCl_4$). However, it is important to note that 10-fold scale-up of the aldol reaction with aromatic aldehydes (for example, 2-naphthaldehyde successfully reacted both on 0.5 and 5.0 mmol scales referring to the starting ynamide) worked well without erosion of the diastereomeric ratios and yields, and that the reaction conditions are mild enough to avoid retroaldol reactions.[86] Similarly, the addition of imines after our sequence of carbometalation−oxidation gave the Mannich adducts in good isolated yields and impressive diastereoisomeric ratios (Scheme 26).[81]

The stereochemistry of **36** is consistent with a Zimmerman−Traxler transition state with approach of the imine from the back face of the bulky benzyl group of the oxazolidinone. As the

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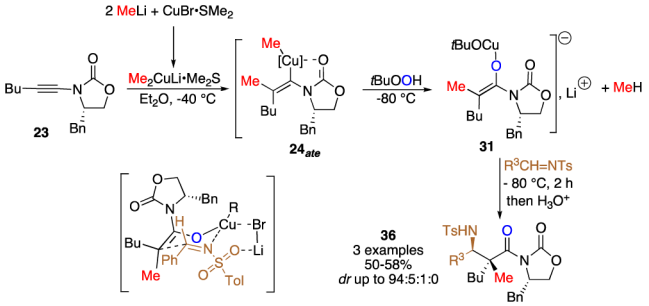
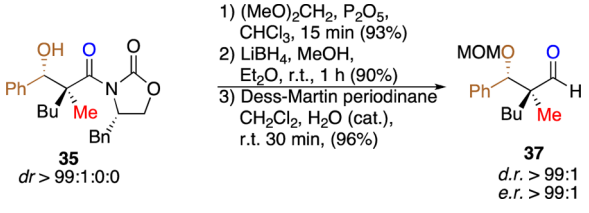
Scheme 26



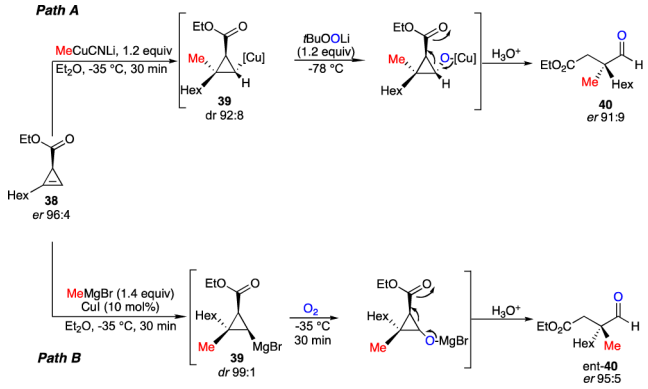
barrier of planar inversion of *N*-sulfonyl imines (*E* to *Z*) is low, steric factors may account for the formation of the *Z*-isomer in the six-membered transition state.[48a] The reaction sequence described above allows the preparation of the aldol **35** and Mannich adducts **36** possessing the oxazolidinone chiral moiety, with the creation of three new bonds and two new stereogenic centers, including the all-carbon quaternary stereocenter, in a single-pot procedure from easily accessible ynamides **23**. Cleavage of the oxazolidinone moiety of diastereomerically pure **35**, obtained after purification by column chromatography, could be performed using standard and reliable high-yielding transformations[87] (with recovery of the chiral oxazolidinone-based chiral auxiliaries), and the aldehyde **37** could be obtained diastereomerically and enantiomerically pure, as shown in Scheme 27.[81,86]

Scheme 27



It is now clear that the real question is no longer "Can we synthesize all-carbon quaternary stereogenic centers?" but rather "How can we synthesize them efficiently through the creation of several C−C bonds in a single-pot operation?" How can we improve synthetic efficiency to such an extent that even challenging acyclic molecular frameworks could be prepared through the formation of several C−C bonds in a single-pot operation? One of the solutions illustrated in this Perspective is to use polyreactive intermediates such as bismetalated, carbenoid as well as oxenoids species that are able to create consecutively the same number of carbon−carbon bonds as in a multistep process, but in a single-pot operation. Particularly promising is the chemistry of oxenoids as electrophilic oxidant leading to the formation of stereodefined trisubstituted enolate from simple precursors.[88] This remarkable selectivity and efficiency of oxidation processes was illustrated by the diastereodivergent formation of all-carbon quaternary stereocenters in α-branched acyclic aldehydes through the sequential carbometalation−oxidation−fragmentation of cyclopropenylcarboxylic acid esters **38** (Scheme 28).[89] Indeed, when the carbocupration was performed with R^2CuCNLi, the diastereomerically enriched cyclopropylcopper species **39** was generated through an *anti*-directed carbometalation reaction with an excellent diastereomeric ratio. Next, **39** was oxidized with an

Scheme 28



equimolar amount of oxenoid reagent *t*BuO*O*Li to promote the selective fragmentation of the cyclopropane ring, leading to the formation of **40** after hydrolysis (Scheme 28, Path A). The formation of the opposite enantiomer could be achieved from the same precursor through a *syn*-directed copper-catalyzed carbomagnesiation−aerobic oxidation−selective fragmentation (Scheme 28, Path B).

Focusing on the allylation as well as the aldol reactions, these new approaches led the authors to the preparation of stereodefined γ,γ′-substituted allylmetal and trisubstituted enolates in acyclic systems. The key features in all of these reactions are the high degree of stereocontrol, the level of predictability, and the simplicity of experimental manifolds that ensure success in the application of such methods. Moreover, the reaction of γ,γ′-disubstituted allylzinc species with carbonyl compounds generated two gauche interactions, which led the authors to refine the Zimmerman−Traxler transition state. This study illustrates that even the most challenging problems can be efficiently addressed when new and powerful synthetic tools are provided. However, one should emphasize that, except in Morken's works (Scheme 6),[13,14] the selectivity control was always based on chiral auxiliaries. Among the challenges facing this field, the combination of asymmetric catalysis with the creation of several new C−C bonds in acyclic systems and in a single-pot operation (i.e., toward the formation of quaternary stereocenters) stands out. Clearly, if one could design synthetic approaches in which a catalytic amount of a chiral ligand would trigger the formation of several carbon−carbon or carbon−heteroatom bonds in a single-pot operation and in acyclic systems, including the all-carbon quaternary stereocenter, it would surely impact our approach to solving synthetic problems. There is no doubt that the power of polyreactive intermediates in stereoselective synthesis will continue to flourish and lead to beautiful new transformations.

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Notes

The authors declare no competing financial interest.

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