

Axial Preferences in Allylation Reactions via the Zimmerman–Traxler Transition State

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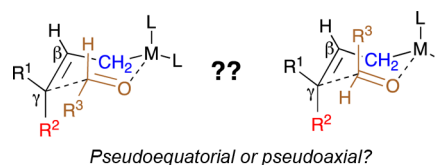
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CONSPECTUS

The reaction of a substituted allylmetal with a prostereogenic carbonyl compound can give rise to up to two racemic diastereomers (*syn* and *anti*). Classically, in such reactions, when pure *E*-isomers have afforded *anti*-selectivity and the *Z*-isomers exhibit *syn*-selectivity, researchers have used the empirical Zimmerman–Traxler model. In this model, chair-like transition states dominate over boat-like arrangements. The incoming aldehyde alkyl (aryl) residue occupies a pseudoequatorial rather than a pseudoaxial position to avoid potential 1,3-diaxial steric interactions. However, the reaction of γ,γ -disubstituted allylzinc species with carbonyl compounds generates two gauche interactions, which may result in a completely different stereochemical outcome. With these two gauche interactions, would a transition state in which the aldehyde substituent occupies a pseudoequatorial position or a pseudoaxial position be preferred?



In this Account, we show that reaction of γ,γ -disubstituted allylzinc species with carbonyl compounds proceeds through a chair-like transition state and the substituent of the incoming aldehyde residue prefers to occupy a pseudoaxial position to avoid these two gauche interactions. Theoretical calculations on model systems support our experimental results. We have extended this new stereochemical outcome to describe the formation of α -alkoxyallylation of aldehydes through the formation of the rather uncommon (*E*)- γ,γ -disubstituted alkoxyallylzinc species. We also used this method to transform aromatic ketones and α -alkoxyaldehydes and ketones into functionalized adducts. In a one-pot reaction and using simple alkynes, three new carbon–carbon bonds and two to three stereogenic centers, including an all-carbon quaternary stereocenter could be created in acyclic systems. Because 1,3-diaxial interactions are now produced with the axial substituent, an increase in the substituent size on the zinc atom decreases the diastereoselectivity.

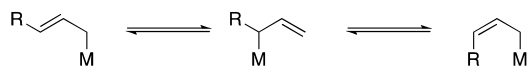
Introduction

The reaction of a substituted allylmetal on a prostereogenic carbonyl compound can give rise to up to two diastereomers (*syn* and *anti*). In this addition, the direction of the *syn/anti* diastereoselectivity is mainly determined by the geometry of the allylic double bond, and its level is influenced by the “cation”, its ligands and the substituents in the allyl part, and the carbonyl compound. Carbanionic species (M = Na, K, Li, MgBr, Cu, Zn, etc.) undergo a rapid and reversible 1,3-metallotropic shift that causes a double bond topomerization and therefore do not usually provide

significantly simple *syn/anti* diastereoselectivities (Scheme 1, path A). Constitutionally more stable allylmetal entities [M = SiR₃, SnR₃, B(OR)₂] lead to highly stereoselective synthesis of homoallylic alcohols. *anti*-Selectivity is usually observed when starting from pure *E*-isomers, while the *Z*-isomers exhibit *syn*-selectivity. This observation finds its empirical rationalization in the Zimmerman–Traxler model, originally created for aldol-type reactions.¹ In this model, chairlike transition states are predicted to dominate over boat-like arrangements. As an illustrative example, in the reaction of an *E*-substituted allylmetal, chair **A** is favored over chair **B**

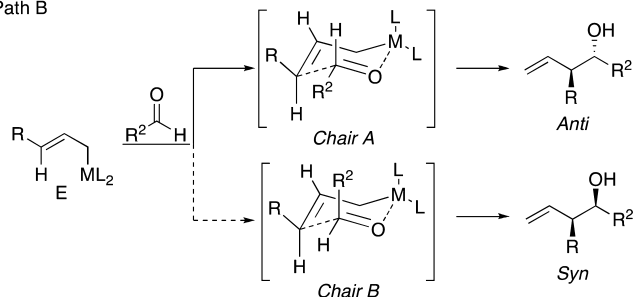
SCHEME 1

Path A



M = Li, MgX, Zn...

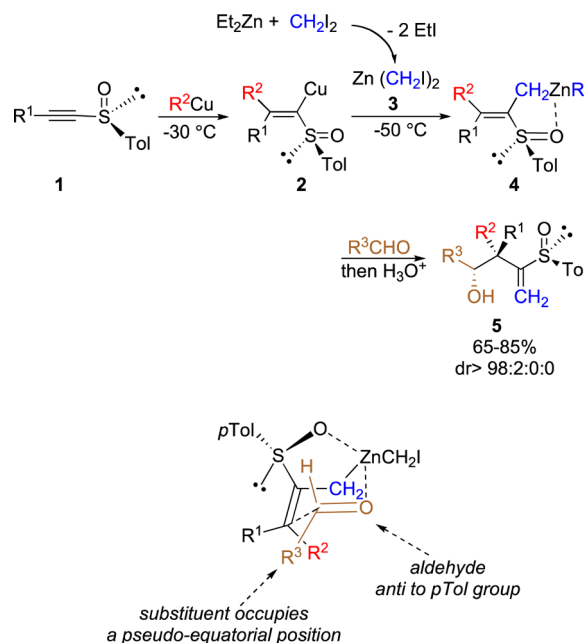
Path B



since, by placing the incoming aldehyde residue R^2 into a pseudoequatorial rather than into a pseudoaxial position, steric interactions with the axial hydrogen and metal ligand are avoided. *Ab initio* molecular orbital calculations point to the validity of this simple model for *E*-2-alkenylmetals.²

In the following years, this model has been implemented for a large majority of the aldol and allylmetal reactions with carbonyl compounds. However, the allylation reaction of prostereogenic carbonyl compounds leading to the creation of an all-carbon quaternary stereocenter is less developed since it required the presence of a stereodefined γ,γ -disubstituted allylmetal species.³ Following the pioneering work of Knochel,⁴ we have used the dual characteristic of zinc carbenoid serving both as an electrophile and as a nucleophile, to prepare various γ,γ -disubstituted allylzinc species that react *in situ* with carbonyl or imine moieties to give homoallyl alcohols and amines, respectively, with very high diastereoselectivity.⁵ For instance, the transformation of alkynyl sulfoxide **1**⁶ into enantiomerically pure homoallyl alcohols **5** was performed in a single-pot operation starting with a regio- and stereoselective carbometalation reaction of alkynyl sulfoxide **1**⁶ that provided the corresponding metalated β,β -dialkylated ethylenic sulfoxide **2** in quantitative yields (Scheme 2).⁷ The defined stereochemistry of the two alkyl groups on the double bond that will be subsequently translated into the γ,γ -disubstituted allylzinc species results from this regio- and stereoselective carbocupration reaction. Subsequently, the *in situ* homologation reaction was performed by the successive addition of aldehyde, Et_2Zn , and CH_2I_2 .⁸ The *in situ* generated zinc carbenoid **3**,⁹ readily homologates the vinylcopper **2** into

SCHEME 2

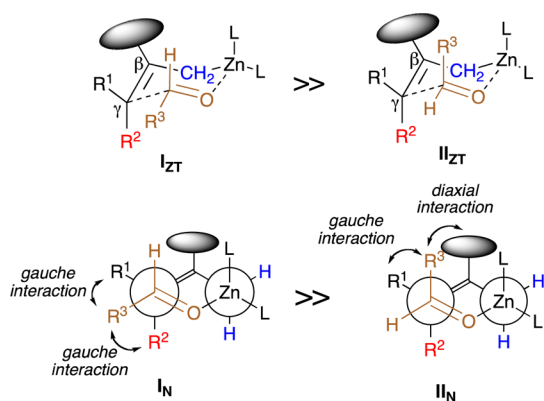


the γ,γ -disubstituted allylzinc species **4**, which reacts diastereoselectively with aldehydes to give the expected homoallyl alcohols **5** in very high diastereoselectivities.¹⁰ The observed final stereochemistry could be rationalized through a Zimmerman–Traxler chairlike transition state in which the oxygen atom of the sulfoxide chelates the zinc atom¹¹ to prevent the metallotropic equilibrium and the aldehyde reacts with the γ,γ -disubstituted allylzinc species **4** from the opposite side of the tolyl group (Scheme 2). Importantly, the R^3 group of the carbonyl moiety occupies a pseudoequatorial position.

When this carbometalation–zinc homologation–allylation of carbonyl compounds sequence was performed on ynamides¹² used in preparing aldol products, analogous stereochemical outcome was obtained, once again consistent with a Zimmerman–Traxler transition state (Scheme 3).¹³ Therefore, when a bulky substituent (represented as a gray ellipse), engaged in a coordinative metallacycle, is present in the β -position of the γ,γ -disubstituted allylzinc species **4** as illustrated in **I_{ZT}** and **II_{ZT}** in Scheme 3, the incoming aldehyde residue R^3 occupies a pseudoequatorial rather than a pseudoaxial position to minimize the 1,3-diaxial interaction despite two gauche interactions (see Newmann projection **I_N** versus **II_N**).

To support this mechanistic hypothesis, theoretical calculations on a model system ($R^1 = R^2 = \text{Me}$) with MO5-2X/6-31G(d) density functional theory have been performed (Scheme 4).¹⁴ Two transition states for the reaction of allylzinc

SCHEME 3

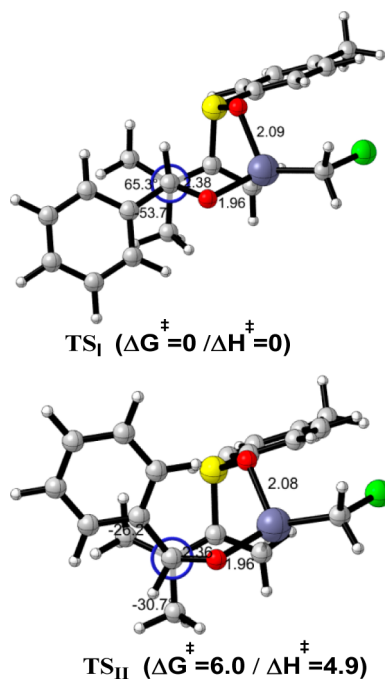


4 with benzaldehyde were located, and as expected, the reaction proceeds through the chairlike transition state **TS_I** in which the aryl group preferentially occupies a pseudo-equatorial position because it is 6.0 kcal/mol more stable than **TS_{II}** where the aryl group occupies a pseudoaxial position.¹⁵ The dihedral angle between the aryl and the two substituents on the allylzinc in **TS_I** shows that two gauche interactions exist. Yet, in **TS_{II}** one substituent has a gauche interaction, and the second substituent has a severe 1,3-diaxial interaction with the sulfoxide group (Scheme 4). It should be, however, noted that these calculations are meant to represent a model system because various salts (such as magnesium, copper, and zinc) are present in the experiments and have an effect on the diastereoselectivity of the reaction (without changing the trend).

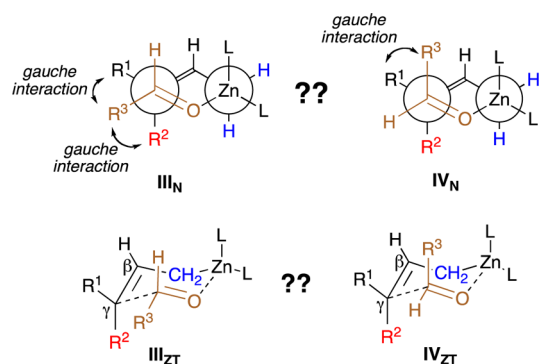
However, we became interested in determining the stereochemical outcome of a reaction where the 1,3-diaxial interaction would not exist anymore, that is, replacing the bulky substituent (gray ellipse) by a hydrogen atom. Would the two gauche interactions present in the transition state **III_N** where the R^3 substituent occupies a pseudoequatorial position be preferred to transition state **IV_N** in which the R^3 substituent of the aldehyde occupies a pseudoaxial position (**III_{ZT}** vs **IV_{ZT}**, Scheme 5). This important stereochemical question can only be solved if one can control the constitutional stability of the η^1 - γ,γ -disubstituted allylzinc species, that is, if the haptotropic rearrangement (metallotropic equilibrium) is slower than the reaction with the aldehyde.¹⁶ Obviously, the potential 1,3-diaxial steric interaction between the R^3 substituent and the ligands on the Zn or any organometallic species should also be considered (**IV_N** or **IV_{ZT}**).

To illustrate this potential 1,3-diaxial steric interaction between the R^3 substituent of the carbonyl compound and the organometallic species, a few examples are described

SCHEME 4



SCHEME 5

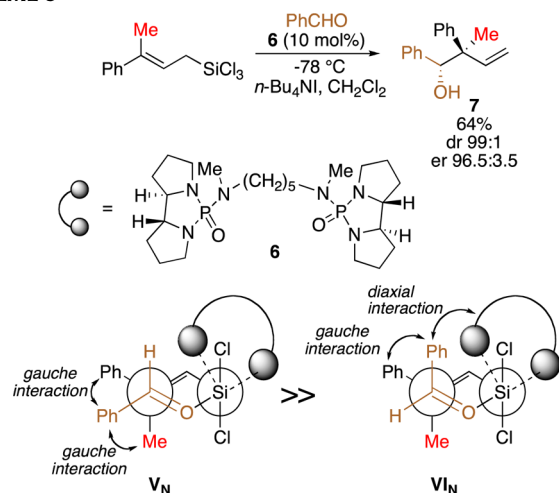


where such interactions have played a major role in the final stereochemical outcome of the reaction.

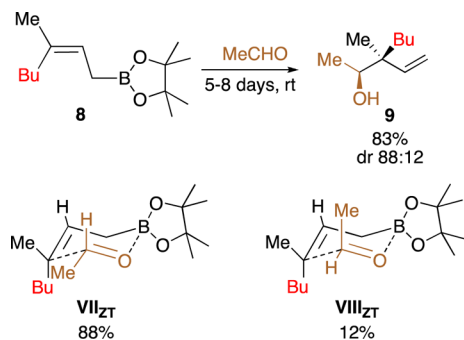
Reaction of Constitutionally Stable γ,γ -Disubstituted Allylmetal Species

S. Denmark has reported, in a series of landmark papers on chiral Lewis bases,¹⁷ excellent diastereo- and enantioselectivities for the reaction of constitutionally stable γ,γ -disubstituted trichloroallylsilane entities with aromatic carbonyl compounds in the presence of a catalytic amount of chiral bidentate phosphoramidate **6** (Scheme 6).¹⁸ Thorough mechanistic studies probed the origins of the activation and stereoselection, and the results can be summarized as a closed chairlike transition state with an octahedral geometry around the silicon center complex.¹⁹ In this case, despite the two gauche interactions, the incoming

SCHEME 6



SCHEME 7

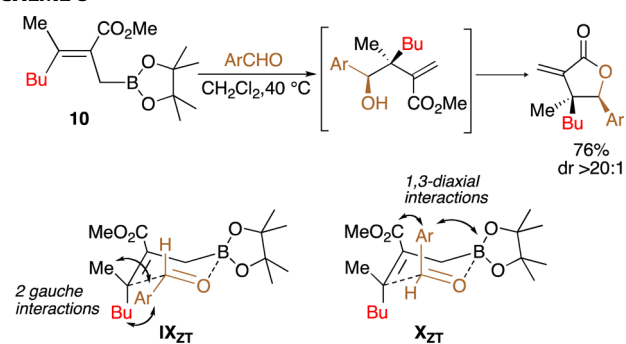


aldehyde residue R^3 ($R^3 = \text{Ar}$) occupies a pseudoequatorial position as described in \mathbf{V}_N due to severe 1,3-diaxial interaction (\mathbf{VI}_N) with the chiral ligand attached to the Si atom when the R^3 substituent occupies a pseudoaxial location.²⁰

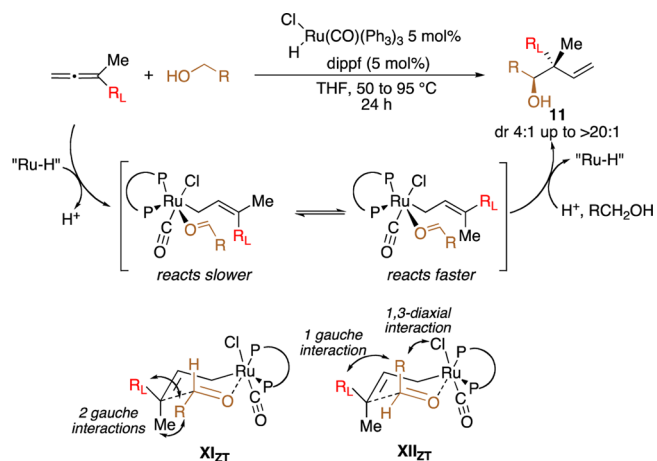
Thus, in the presence of bulky ligands on the silicon, the combined gauche and 1,3-diaxial interactions lead solely to the formation of the homoallylic alcohol **7** through transition state \mathbf{V}_N . However, when a more sterically constrained and less bulky substituent is on the metallic center, a decreased 1,3-diaxial interaction now leads to a certain quantity of the opposite diastereomer. For instance, the reaction of γ,γ -disubstituted allylboronate **8** gives, after 5–8 days, the resulting homoallylic alcohol **9** with a lower diastereoselectivity of 88:12 (Scheme 7). This stereochemical leak was rationalized through a transition state having the substituent residue of the aldehyde in a pseudoaxial arrangement (\mathbf{VIII}_{ZT}).^{21,22}

In contrast to the allylation reaction with γ,γ -disubstituted allylboronate **8**, reactions with β -methoxycarbonyl γ,γ -disubstituted allylboronates **10** do not exhibit any

SCHEME 8



SCHEME 9



stereochemical leakage (Scheme 8).²³ The reason for this improved selectivity is likely that in the competing transition states \mathbf{IX}_{ZT} and \mathbf{X}_{ZT} , the Ar group of the aldehyde presents an unfavorable 1,3-diaxial interaction with the 2-carboethoxyester group in addition to the usual 1,3-interaction between the Ar group and the axial boronate substituent. This additional steric interaction further favors transition state \mathbf{IX}_{ZT} over transition state \mathbf{X}_{ZT} .²⁴

Reaction of Nonconstitutionally Stable γ,γ -Disubstituted Allylmetal Species

Ruthenium-catalyzed transfer hydrogenation of 1,1-disubstituted allene represents a very elegant way to prepare *in situ* nonconstitutionally stable γ,γ -disubstituted allylmetal species (Scheme 9).²⁵ Therefore, from an equilibrating mixture of transient (*Z*-) and (*E*- σ -allylruthenium isomers, a preferential selection of the (*E*- σ -allylruthenium species occurs and the *E*-isomers react with the carbonyl electrophile to give the adduct with good to excellent level of diastereoselectivity.

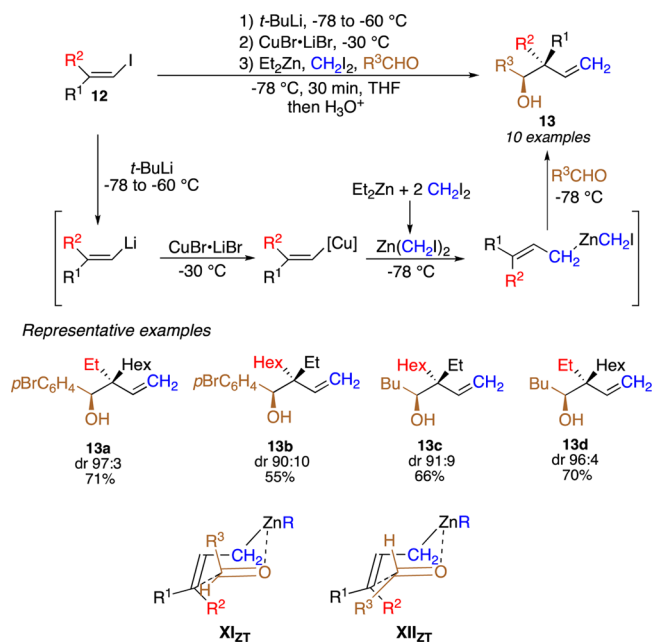
In such processes, carbonyl addition can also be achieved directly from the alcohol oxidation level in the absence of

premetalated nucleophiles.²⁶ As discussed previously, in the presence of bulky ligands on the ruthenium center, the combined gauche and 1,3-diaxial interactions lead to the unique formation of the homoallylic alcohol **11** through transition state **XI_{ZT}**.²⁵ Under the same ruthenium-catalyzed transfer hydrogenation conditions, direct C–C coupling of ethanol with 2-substituted dienes similarly led to the formation of *anti*-configured neopentyl homoallylic alcohols.²⁷

Yet, if one considers a system where bulky substituents would be present neither at the β -position of the allyl system nor at the organometallic center, the presence of two gauche interactions with the aldehyde R^3 substituent in an pseudoequatorial position should be disfavored and force this R^3 substituent to occupy a pseudoaxial position (Scheme 5). In this case, the stereochemistry of the final adduct should be reversed. This very interesting aspect of stereochemistry, never explored to the best of our knowledge, led us to envisage a detailed study on the diastereoselectivity of γ,γ -disubstituted allylzinc species with carbonyl compounds. To this end, we initially tested the allylation reaction by transforming *in situ* vinyl iodides **12**, easily obtained by carbocupration of alkynes,⁷ into γ,γ -disubstituted allylzinc species. The successive treatment of vinyl iodide **12** with *t*-BuLi followed by the subsequent addition of soluble copper salt solution, Et_2Zn , CH_2I_2 , and aldehydes at -80°C leads to the expected homoallylic alcohols **13** in very high diastereomeric ratios (Scheme 10). It should be noted that the zinc homologation reaction needs to proceed at low temperature to avoid the metallotropic equilibrium of the allylzinc species;²⁸ at -80°C , the reaction of γ,γ -disubstituted allylzinc species with aldehydes is faster than its metallotropic equilibrium. Because the permutation of the two alkyl groups (R^1 and R^2 , respectively) on the starting vinyl iodide **12** allows the formation of the two opposite diastereomers at the all-carbon quaternary stereocenter in excellent diastereomeric ratio (compare **13a**, **13b** and **13c**, **13d**), we can rule out the formation of an open transition state and support a cyclic transition state. The reaction is general because it proceeds with aromatic, functionalized aromatic, and aliphatic aldehydes.

The relative configuration, determined by comparison with authentic sample and analyzed by X-ray crystallographic data,¹⁰ shows that the incoming aldehyde residue R^3 occupies a pseudoaxial (**XI_{ZT}**) rather than a pseudoequatorial position (**XII_{ZT}**) as two gauche steric interactions are avoided. Density functional theory calculations point to the validity of this model for γ,γ -disubstituted allylzinc species with aldehydes (Scheme 11). Indeed, three systems were

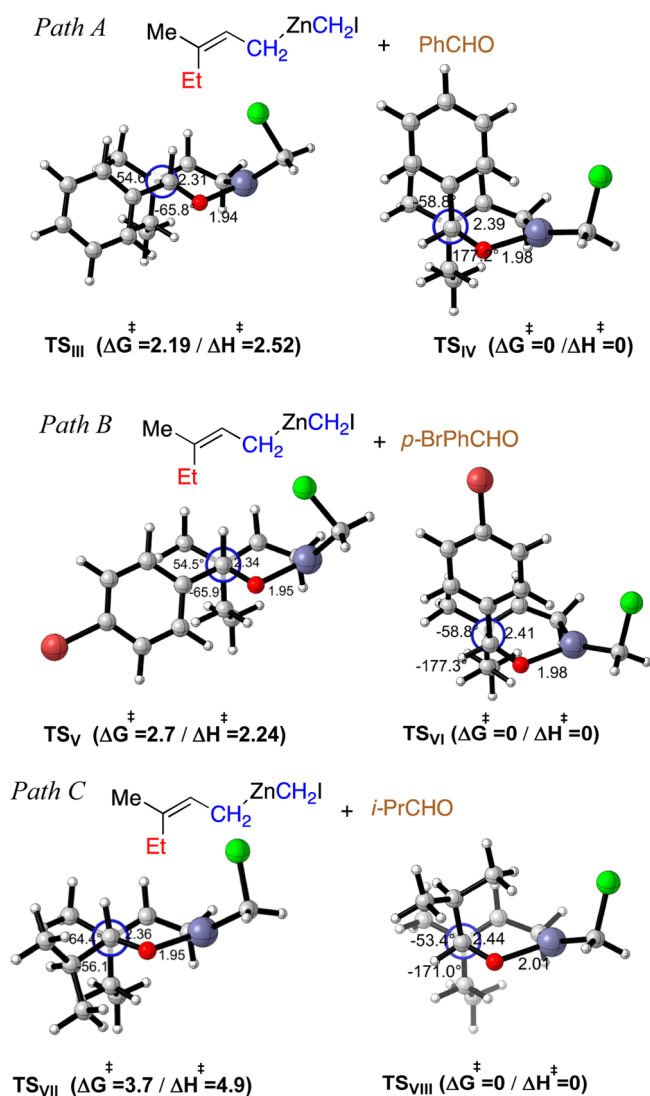
SCHEME 10



calculated, two aromatic (paths A and B, **TS_{III}**–**TS_{VI}**) and one aliphatic (path C, **TS_{VII}**–**TS_{VIII}**) aldehydes. In all cases, an obvious trend toward the energetically favored axial position was observed with a difference of 2.2–3.7 kcal/mol. The dihedral angle between R^3 and one substituent on the allyl system in **TS_{IV}**, **TS_{VI}**, and **TS_{VII}** shows a gauche interaction, and the other show an *anti* interaction. One repulsive interaction is therefore avoided. Several attempts were made to locate boat-like, as well as twist-boat, transition states, but none could be located as stationary points, and the structures always returned to chair geometries.¹⁵ THF as solvent molecules were also incorporated, but transition states could not be located. As raised previously, these calculations are meant to represent only a model system because various salts (such as lithium, copper, and zinc) may be present in the experiments and have an effect on the diastereoselectivity of the reaction (without changing the trend).

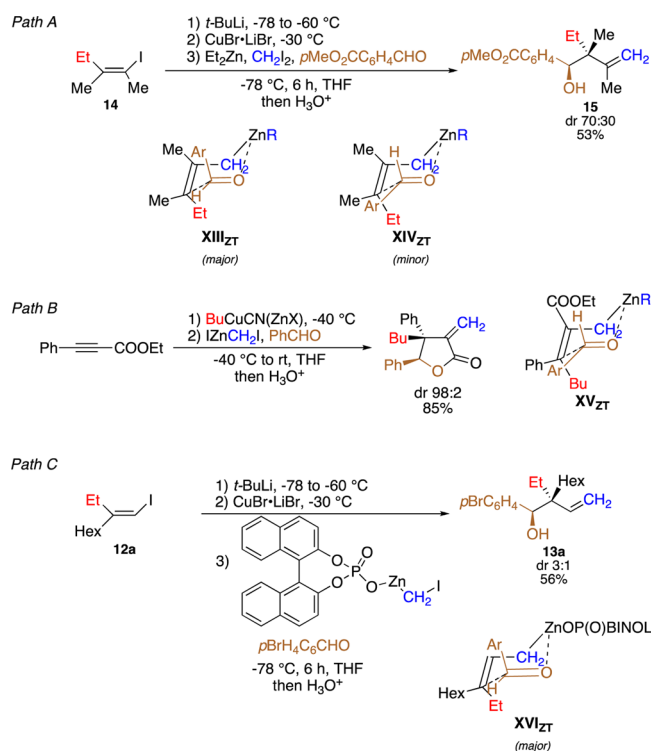
It must be noted that the energy difference with aliphatic aldehyde is much higher than the observed experimental diastereomeric ratio and that could be explained by the higher temperature needed for the reaction to proceed. To get additional support for our mechanistic hypothesis, we experimentally tested two systems where steric 1,3-diaxial interactions were purposely increased. In the first case, β,γ,γ -trialkyl-substituted allylzinc species, *in situ* prepared from the corresponding vinyl iodide **14**,²⁹ were tested in our reaction with aromatic aldehyde (Scheme 12).¹⁵ In this particular

SCHEME 11



case, the methyl group in the β -position of the zinc generates some 1,3-steric interactions with the aromatic substituent of the aldehyde that occupies the pseudoaxial position and a mixture of two diastereoisomers was obtained in a 70:30 ratio (Scheme 12, path A). The configuration of the major diastereoisomer was determined by X-ray crystallographic analysis and still results from a pseudoaxial position of the aromatic substituent in a chairlike transition state. However, when a larger substituent is present on the β -position, the diastereoselectivity of the reaction can be completely reversed. For instance, the carbocupration of acetylenic ester provides selectively the alkenyl copper species when temperature is kept lower than -30 °C. After methylene homologation and reaction with a carbonyl compound, the cis lactone was obtained as the major diastereomer. The stereoselectivity of the reaction results from a Zimmerman–Traxler

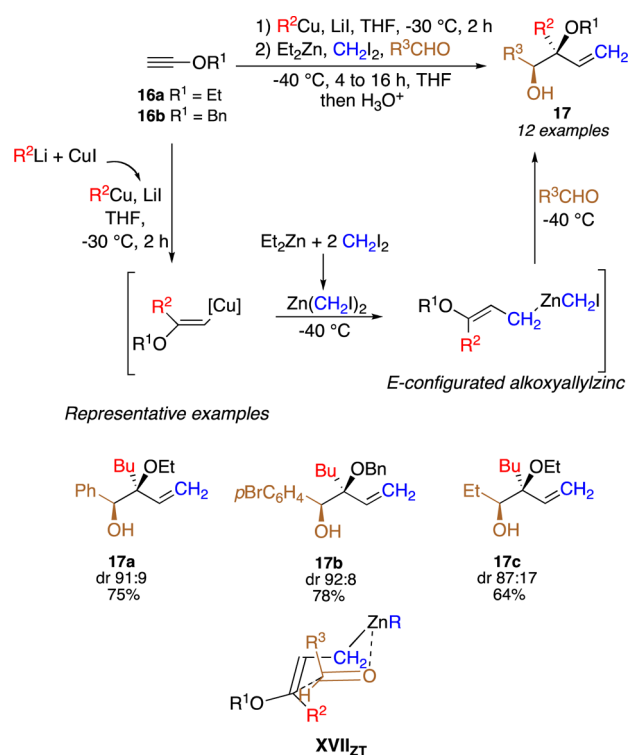
SCHEME 12



transition state in which the substituent of the incoming aldehyde occupies a pseudoequatorial position (Scheme 12, path B).^{4C} In the third system, we increased the 1,3-steric diaxial interaction by adding bulky ligands on the zinc center. Indeed, when vinyl iodide **12a** was transformed *in situ* into the vinyl copper species followed by the addition of phosphate-based carbenoid³⁰ and aromatic aldehyde, the expected adduct was obtained in moderate yield but with a low diastereomeric ratio (Scheme 12, path C). Although we have no evidence on the particular geometry of the Zn-OP(O)BINOL moiety, we can safely assume that it increases the steric environment around the zinc center and, by consequence, increases the 1,3-diaxial interaction with the substituent of the aldehyde in the pseudoaxial position of the chairlike transition state, and therefore results in a lower diastereomeric ratio.

To further extend the idea of having the R substituent in a pseudoaxial position in the Zimmerman–Traxler transition state, we have developed an approach to 1,2-alkenyl diols through α -alkoxyallylation of carbonyl compounds. The carbometalation reaction of commercially available ethoxyacetylene **16a** or easily accessible benzyloxy-substituted acetylene **16b**³¹ followed by a zinc homologation and further allylation reaction was easily performed using our standard procedure to lead to the 1,2-alkenyl diols **17** in

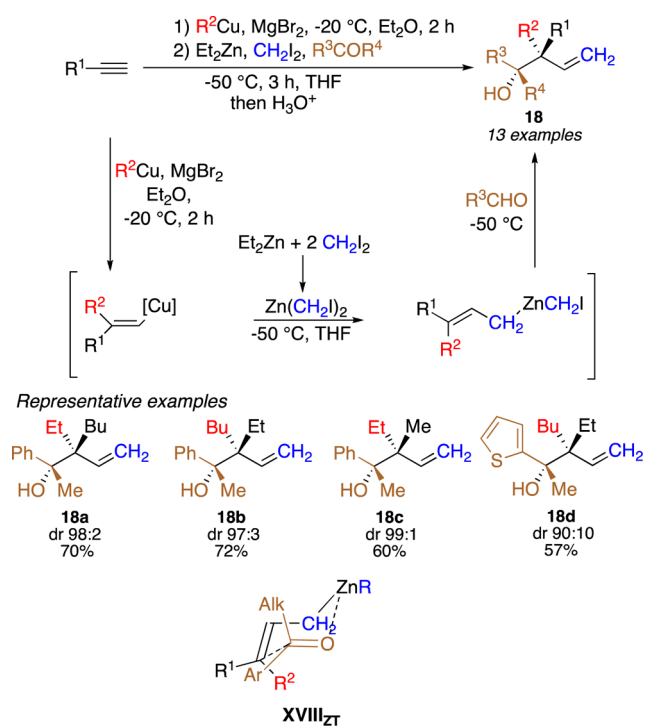
SCHEME 13



good isolated yields and diastereomeric ratios (Scheme 13). The reaction enjoys a large scope because various alkyl groups can be added during the carbometalation step and various functionalized and nonfunctionalized aromatic aldehydes, as well as aliphatic aldehydes, can be used, although in the latter case the ratio is slightly lower.³² Interestingly, the γ,γ -disubstituted alkoxyallylzinc species has a nonclassical *E*-configured geometry.³³

The relative configuration was determined by X-ray crystallographic studies³² and could be rationalized through a Zimmerman–Traxler chairlike transition state in which the bulky R^3 group of the aldehyde occupies again a pseudoaxial position (**XVII_{ZT}**) in order to avoid the two gauche interactions as described previously. It should be noted that the stereochemistry of the major isomer can also be rationalized by a reaction of the fully isomerized *Z*-configured γ,γ -disubstituted alkoxyallylzinc species (thermodynamically more stable due to intramolecular chelation) with an aldehyde in which the substituent would now occupy a pseudoequatorial position in a boat transition state. However, because the zinc homologation proceeds in the presence of the aldehyde and the highest diastereoselectivity is observed at low temperature ($-40 }^\circ\text{C}$, dr 90:10, whereas at $-20 }^\circ\text{C}$ the ratio decreases to 66:33), the outcome of the reaction must be kinetically controlled, and therefore,

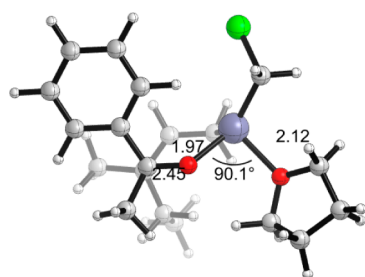
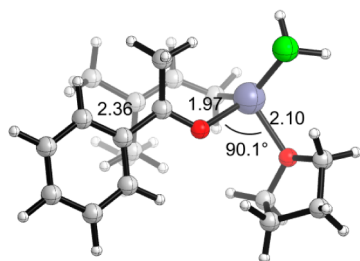
SCHEME 14



the allylation reaction is faster than any haptotropic equilibrium.¹⁶

Then, what would be the stereochemical outcome of this reaction if ketones were to be used as electrophilic partners instead of aldehydes? Would the reaction still be stereoselective? This reaction would allow the construction of two contiguous tetrasubstituted carbon stereocenters in an *acyclic system*, which is an interesting issue to solve. Only a handful of strategies have been devised for directly assembling this structural unit,³⁴ and the most prominent examples originate from sigmatropic rearrangements.³⁵ Therefore, a *syn*-controlled regioselective carbometalation of terminal alkynes, followed by zinc homologation and allylation reaction with ketones was performed at $-50 }^\circ\text{C}$, and the expected homoallylic alcohols were obtained in good yields with excellent diastereomeric ratios (Scheme 14).³⁶ As in the case of the reaction with aldehydes, a simple permutation of the nature of the alkyl groups of the alkyne and of the vinyl copper species allows the independent formation of both diastereoisomers at the quaternary stereocenter with the same level of diastereoselectivity, excluding the possibility of an open transition state (compare **18a** and **18b**). The reaction showed good generality, proceeding well with various alkyl groups in the presence of functionalized and nonfunctionalized ketones. Relative configuration has been determined by X-ray analysis.

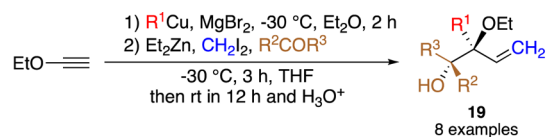
SCHEME 15


 $\text{TS}_{\text{IX}} (\Delta G^\ddagger = 2.03 / \Delta H^\ddagger = 1.72)$

 $\text{TS}_{\text{X}} (\Delta G^\ddagger = 0 / \Delta H^\ddagger = 0)$

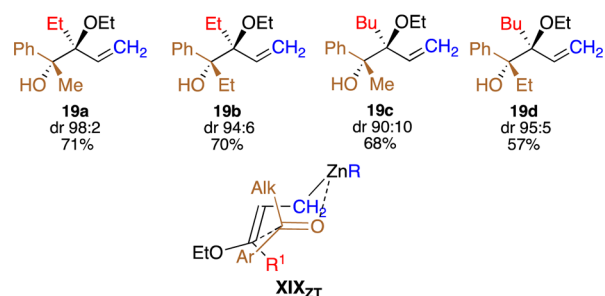
The diastereoselectivity of the reaction can be rationalized using a Zimmerman–Traxler chairlike transition state in which the more sterically demanding alkyl group of the ketone occupies a pseudoaxial position. Although the *A*-value³⁷ is 1.7 for a methyl group and 3 for an aryl group, it is important to note that these *A*-values do not predict the physical size of a group. Because the phenyl ring is planar, it may adopt a position leading to less steric interaction than a nonplanar methyl group. To have more insight on this reaction mechanism, both transition states leading to **18c** were computed with the same MO5-2X/631-G level of theory, and indeed, an energy difference of 2.03 kcal/mol was found between TS_{IX} and TS_{X} . In TS_{X} , the flat aromatic ring is less sterically demanding compared with the methyl group (Scheme 15).

It should be noted that when dialkyl ketones (such as 2-butanone or even 3-methyl-2-butanone) were used, the reaction still proceeds but the two expected diastereomers are formed in equal amount. The γ,γ -disubstituted alkoxyallylzincation of carbonyl species could also be extended to ketones and similar diastereoselectivities and yields were obtained for functional and nonfunctional ketones (Scheme 16).³⁸ The relative configuration was established by X-ray crystallographic studies,³⁸ and let us assume that the substituent alkyl occupies the pseudoaxial position in the Zimmerman–Traxler transition state to avoid the two

SCHEME 16



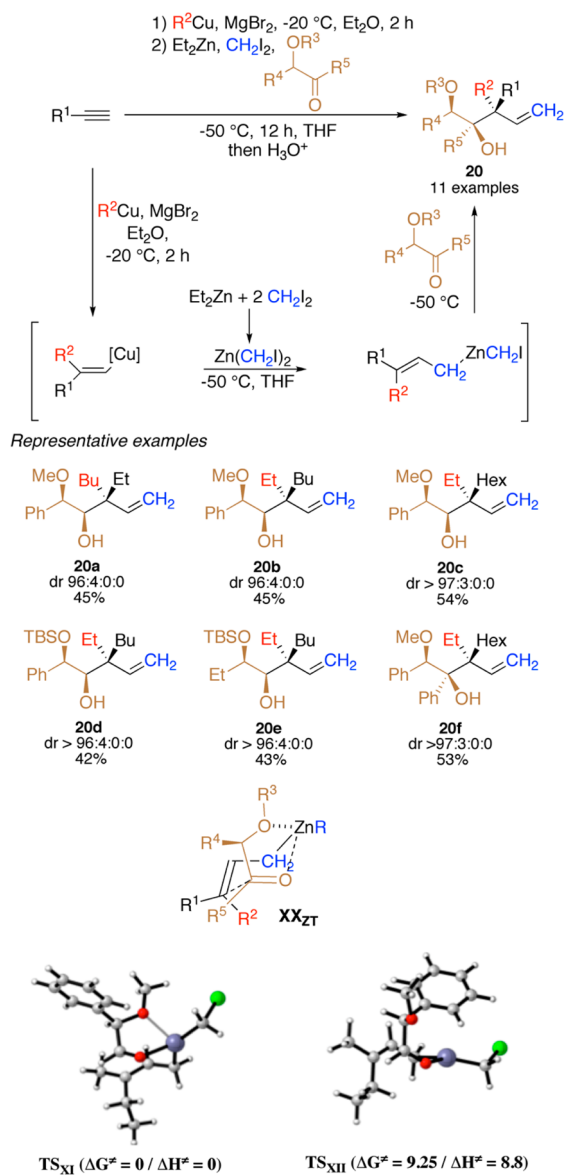
Representative examples



gauche interactions. When the size of the alkyl substituent increases (**19b**, $R^2 = \text{Et}$), diastereomeric ratio and yields are very similar.

With the idea of expanding this new stereochemical outcome to more sophisticated substrates, we were interested in using carbonyl groups possessing an additional stereogenic center. Indeed, an important concept that emanated from the studies of allylation reactions was that of double diastereodifferentiation, which emerges when chiral electrophiles are combined with allylation reactions. In general, α -substituted aldehydes tend to display different facial selectivity with either (*Z*)- or (*E*)- γ -substituted allylmetal species. In all cases, the incoming aldehyde residue possessing the chiral center occupies a pseudoequatorial position and tends to minimize steric interactions with the allylic partner.³⁹ These observations show that the configuration of the reagent and the aldehyde are interdependent in determining the final stereochemical outcome of the reaction. But, what would be the stereochemical outcome for the reaction of γ,γ -disubstituted allylzinc species with carbonyl species possessing an α -chiral substituent since it occupies a pseudoaxial position and no more the pseudoequatorial as described in literature? To answer this interesting question, the combined carbometalation–zinc homologation and reaction with the model 2-methoxy-2-phenylacetaldehyde was initially tested, and we were pleased to obtain the corresponding homoallylic alcohols **20** in moderate yields⁴⁰ (based on the starting alkyne after three consecutive chemical steps) but with outstanding diastereoselectivities (Scheme 17). In this particular reaction, three new carbon–carbon bonds, three consecutive stereocenters including an all-carbon quaternary stereogenic center in acyclic system,⁴¹ are obtained in a single-pot operation from simple and

SCHEME 17



commercially available alkynes. Here again, by permuting the nature of the two alkyl groups (R^1 on the alkyne and R^2 on the organocopper species), both diastereomers are obtained (**20a** and **20b**, respectively) at the all-carbon quaternary stereogenic center suggesting a closed rather than an open transition state. This reaction proceeds similarly for α -silylether (OR^3 group), as well as with an aliphatic R^4 group (**20d** and **20e** respectively) with the same diastereoselectivity. When ketone was used, **20f** has been obtained in 53% yield with an outstanding diastereomeric ratio. The configuration has been established by X-ray analysis. Because the chelation between zinc and heteroatoms in ω -heterosubstituted dialkylzinc reagents has already been shown by NMR studies⁴² and used for the diastereoselective

allylzincation of substituted γ -heterosubstituted vinyl metals,⁴³ we could safely suggest a transition state in which the substituent of the aldehyde occupies again a pseudoaxial position in the chairlike Zimmerman–Traxler transition state in which the alkoxy group chelates intramolecularly the zinc center of the γ,γ -disubstituted allylzinc species. This intramolecular chelation induces a difference between the two prochiral faces of the aldehyde moiety since one is shielded by the R^4 group as described in the transition state **XX_{ZT}** in Scheme 17. To support this experimental work, theoretical calculations have been performed for the two systems (**TS_{XI}** and **TS_{XII}**) where the substituent of the aldehyde occupies a pseudoaxial position and the chelated model **TS_{XI}** is much lower in energy than the nonchelated system **TS_{XII}** (Scheme 17).

In conclusion, the reaction of γ,γ -disubstituted allylzinc species with carbonyl compounds proceeds through a chairlike transition state and the substituent of the incoming aldehyde residue prefers to occupy a pseudoaxial rather than a pseudoequatorial position to avoid two gauche interactions. Our experimental results were supported by theoretical calculations. This new stereochemical outcome has been extended to the α -alkoxyallylation of aldehydes through the formation of the rather uncommon (*E*)- γ,γ -disubstituted alkoxyallylzinc species. This method could also be used to transform aromatic ketones, as well as α -alkoxyaldehydes and ketones, into functionalized adducts in which three new carbon–carbon bonds and two to three stereogenic centers, including an all-carbon quaternary stereocenter, were created in an acyclic systems in a single-pot operation from simple alkynes. Increasing the size of substituents on the zinc atom decreases the diastereoselectivity since 1,3-diaxial interactions are now produced with the axial substituent. This new axial preference in the allylation reaction via the Zimmerman–Traxler transition state will surely find applications in stereoselective synthesis particularly for reactions with α -heterosubstituted carbonyl compounds.

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FOOTNOTES

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