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

Tom Mejuch[‡], Noga Gilboa[‡], Eric Gayon[‡], Hao Wang[‡], K. N. Houk[†], and Ilan Marek^{‡,*}

Ilán Marek: chilnm@technion.ac.il

[‡]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. Technion City, Haifa 32000 (Israel). Phone/Fax: (+972)-4-8293709

[†]Department of Chemistry and Biochemistry. University of California, Los Angeles. 607 Charles E. Young Drive East, Los Angeles, CA 90095 (USA)

CONSPECTUS

The reaction of substituted allylmethyl on prostereogenic carbonyl compound can give rise to up to two racemic diastereomers (*syn* and *anti*). Classically, when *anti* selectivity was observed from pure *E*-isomers while the *Z*-isomers exhibit *syn*-selectivity, the empirical Zimmerman – Traxler model is used. In this model, chair-like transition states are predicted to dominate over boat-like arrangements and the incoming aldehyde alkyl (aryl) residue occupies a pseudo-equatorial rather than a pseudo-axial position to avoid potential 1,3-diaxial steric interactions. However, the stereochemical outcome of the reaction of γ,γ -disubstituted allylzinc species with carbonyl compounds reaction may be completely different as two gauche interactions are generated. Would the two gauche interactions present in the transition state where the aldehyde substituent occupies a pseudo-equatorial position be preferred to a transition state in which the same substituent of the aldehyde occupies a pseudoaxial position? In this study, we could 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 pseudo-axial rather than into a pseudo-equatorial position to avoid these two gauche interactions. Our experimental results were supported by theoretical calculations on model systems. This new stereochemical outcome has been extended to the formation of 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 ketone 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.

*Corresponding Author: chilnm@technion.ac.il.

Dedicated to Prof. Dieter Seebach for his 75th birthday

Keywords

Zimmerman — Traxler; equatorial; allylation; stereochemistry

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 ($M = \text{Na}, \text{K}, \text{Li}, \text{MgBr}, \text{Cu}, \text{Zn}, \dots$) undergo a rapid and reversible 1,3-metallotropic shift that cause a double bond topomerization and therefore do not usually provide significantly simple *syn/anti* diastereoselectivities (Scheme 1, Path A). Constitutionally more stable allylmetal entities [$M = \text{SiR}_3, \text{SnR}_3, \text{B(OR)}_2$] 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, chair-like transition states are predicted to dominate over boat-like arrangements. As illustrative example, in the reaction of a *E*-substituted allylmetal, chair **A** is favored over chair **B** since, by placing the incoming aldehyde residue R^2 into a pseudo-equatorial rather than into a pseudo-axial 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** into enantiomerically pure homoallylic alcohols **5** was performed in a single-pot operation starting with a regio- and stereoselective carbometalation reaction of alkynyl sulfoxide **1**⁶ that provide 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 the γ,γ -disubstituted allylzinc species **4**, which reacts diastereoselectively with aldehydes to give the expected homoallylic alcohols **5** in very high diastereoselectivities.¹⁰ The observed final stereochemistry could be rationalized through a Zimmerman — Traxler chair-like transition state in which the oxygen atom of the sulfoxide chelates the zinc atom¹¹ to prevent the metalotropic 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 pseudo-equatorial 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 grey 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 pseudo-equatorial rather than a pseudo-axial 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 **4** with benzaldehyde were located and as expected, the reaction proceeds through the chair-like transition state **TS_I** in which the aryl group preferentially occupies a pseudo-equatorial position as it is 6.0 kcal/mol more stable than **TS_{II}** where the aryl group occupies a pseudo-axial position.¹⁵ The dihedral angle between the aryl and the two substituents on the allylzinc in **TS_I** shows that two gauche interactions are existing. 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 as 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 wouldn't exist anymore i.e. replacing the bulky substituent (grey ellipse) by a hydrogen atom. Would the two gauche interactions present in the transition state **III_N** where the R^3 substituent occupies a pseudo-equatorial 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 η^1 - γ,γ -disubstituted allylzinc species, that is, if the haptotropic rearrangement (metalotropic 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 interactions between the R^3 substituent of the carbonyl compound and the organometallic species, few examples are described 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 diastereoand 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 chair-like transition state with an octahedral geometry around the silicon center complex.¹⁹ In this case, despite the two gauche interactions, the incoming aldehyde residue R^3 ($R^3 = \text{Ar}$) occupies a pseudoequatorial position as described in **V_N** due to severe 1,3-diaxial interaction (**VI_N**) with the chiral ligand attached to the Si atom when the R^3 substituent occupies a pseudo axial 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 **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 homoallyl 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 pseudo-axial arrangement (**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 stereochemical leakage (Scheme 8).²³ The reason for this improved selectivity is likely that in the competing transition state **IX_{ZT}** and **X_{ZT}**, the Ar group of the aldehyde present 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 **IX_{ZT}** over transition state **X_{ZT}**.²⁴

Reaction of non-constitutionally stable γ,γ -disubstituted allylmetal species

Ruthenium-catalyzed transfer hydrogenation of 1,1-disubstituted allene represents a very elegant way to prepare *in-situ* non-constitutionally 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 wouldn't 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 R³ substituent in an pseudo-equatorial position should be disfavored and force this R³ substituent to occupy a pseudo-axial 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 *in-situ* transforming 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, Et₂Zn, CH₂I₂ 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 metalotropic equilibrium of the allylzinc species²⁸; at –80 °C, the reaction of γ,γ -disubstituted allylzinc species with aldehydes is faster than its metalotropic equilibrium. As the permutation of the two alkyl groups (R¹ and R² 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 as it proceeds with aromatic, functionalized aromatic as well as 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 R³ occupies a pseudo-axial (**XI_{ZT}**) rather than a pseudo-equatorial 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 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 towards the energetically favored axial position was observed with a difference of 2.2 to 3.7 kcal/mol. The dihedral angle between R³ 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 always returned to chair geometries.¹⁵ THF as solvent molecules were also incorporated but transition states couldn't be located. As raised previously, these calculations are meant to represent only a model system as 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 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 pseudo-axial 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 pseudo-axial position of the aromatic substituent in a chair-like transition state. However, when 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 transition state in which the substituent of the incoming aldehyde occupies a pseudo equatorial 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 *in-situ* transformed 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 increase the 1,3-diaxial interaction with the substituent of the aldehyde in the pseudo-axial position of the chair-like transition state and therefore result in a lower diastereomeric ratio.

To further extend the idea of having the R substituent in a pseudo-axial 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 good isolated yields and diastereomeric ratios (Scheme 13). The reaction enjoys a large scope as various alkyl groups can be added during the carbometalation step, various functionalized and non-functionalized 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 non-classical *E*-configured geometry.³³

The relative configuration was determined by X-ray crystallographic studies³² and could be rationalized through a Zimmerman — Traxler chair-like transition state in which the bulky R^3 group of the aldehyde occupies again a pseudo-axial position (**XVII_{2T}**) 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 pseudo-equatorial position in a boat transition state. However, as the zinc homologation proceeds in the presence of the aldehyde and the highest diastereoselectivity is observed at low temperature ($-40\text{ }^\circ\text{C}$, dr 90:10 whereas at $-20\text{ }^\circ\text{C}$ the ratio decreases to 66:33), the outcome of the reaction must be kinetically controlled and, therefore, 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 number of strategies have been devised for directly assembling this structural unit³⁴ 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 $-50\text{ }^\circ\text{C}$ 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 non-functionalized ketones. Relative configuration has been determined by X-ray analysis.

The diastereoselectivity of the reaction can be rationalized using a Zimmerman — Traxler chair-like transition state in which the more sterically demanding alkyl group of the ketone occupies a pseudo-axial 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. As the phenyl ring is planar, it may adopt a position leading to less steric interaction than a non-planar 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 were found between **TS_{IX}** and **TS_X**. In **TS_X** the flat aromatic ring is less sterically demanding as compared to 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 as well as non-functional 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 pseudo-axial position in the Zimmerman—Traxler transition state to avoid the two 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 pseudo-equatorial 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 a α -chiral substituent since it occupies a pseudo-axial position and no more the pseudo-equatorial 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 system⁴¹ are obtained in a single-pot operation from simple and 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 diastereomer are obtained (**20a** and **20b** respectively) at the all-carbon quaternary stereogenic center suggesting a close rather than an open transition state. This reaction proceeds similarly for α -silylether (OR^3 group) as well as with 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. As the chelation between zinc and heteroatoms in ω -hetero-substituted 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 pseudo-axial position in the chair-like 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 pseudo-axial position and the chelated model **TS_{XI}** is much lower in energy than the non-chelated system **TS_{XII}** (Scheme 17).

In conclusion, the 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 pseudo-axial rather than into a pseudo-equatorial position to avoid two gauche interactions. Our experimental results were supported by theoretical calculations. This new stereochemical outcome has been extended to the formation of 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 ketone 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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Biographies

Ilan Marek is the Sir Michael and Lady Sobell Chair at the Schulich Faculty of Chemistry at the Technion – Israel Institute of Technology. He is interested in the design and development of new and efficient stereo- and enantioselective strategies for the synthesis of important complex molecular structures, and more particularly in developing carbon-carbon bond forming processes, which efficiently create multiple stereocenters in a single-pot operation.

Noga Gilboa, born in 1979 in Moshav Balfuya, Israel, completed her undergraduate studies at Bar-Ilan University in Medicinal Chemistry in 2006 (*Cum Lauda*) and joined the research group of Professor Ilan Marek initially as a Master student and then moved to the direct PhD program. Noga Gilboa graduated as Doctor of Philosophy in Chemistry in 2012 for a thesis on “Preparation and Stereochemistry of Homoallylic Alcohols Containing Quaternary Stereocenters”.

Tom Mejuch was born in 1983. In 2006 he received his B.A degree in Molecular Biochemistry program at the Schulich Faculty of Chemistry at the Technion. In 2008 Tom received his M.Sc. degree (Cum Laude) at the same faculty under the supervision of Prof. Ehud Keinan. In 2008, Tom started his PhD research under the supervision of Prof. Ilan Marek. The title of his doctorate is “New and Efficient Methods for the Preparation of Quaternary Stereocenters”.

Eric Gayon was born in Mourenx, France, in 1984. He completed his undergraduate studies at the University Paul Sabatier (Toulouse, France) and received his Master and PhD degree at the Ecole Nationale Supérieure de Chimie de Montpellier (France) under the supervision of Pr. Jean-Marc Campagne and Dr. Emmanuel Vrancken. During his PhD thesis, he joined the research group of Prof. Marek for a few months. Since January 2013, Eric joined Holis Technologies, a growing young fine chemical company, developing innovative process for the pharmaceutical, agrochemical and cosmetic industry, as a R&D project leader.

WANG Hao received his B.S. in chemistry from Wuhan University, China in 2005. He received his M.S. in organic chemistry from Hong Kong Baptist University in 2007. He is currently a fifth year graduate student, and C.S. Foote Fellow in Prof. Houk's group at UCLA.

K. N. Houk is the Saul Winstein Chair in Organic Chemistry at UCLA. He is an organic computational chemist and Senior Editor of Accounts of Chemical Research.

Path A

$M = \text{Li}, \text{MgX}, \text{Zn} \dots$

Path B

Scheme 1.

Scheme 2.

Scheme 4.

Scheme 5.

Scheme 6.

Scheme 7.

Scheme 8.

Scheme 9.

Scheme 10.

Scheme 11.

Scheme 12.

Scheme 13.

Scheme 14.

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

TS_X ($\Delta G^\ddagger = 0$ / $\Delta H^\ddagger = 0$)

Scheme 15.

Representative examples

Scheme 16.

Scheme 17.