Review

Directed Reactions of Organocopper Reagents

Bernhard Breit, and Yvonne Schmidt

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1. Introduction

Among the variety of organometallic reagents, organocopper reagents are the most widely used and powerful tools in synthetic organic chemistry, delivering carbon, hydrogen, and heteroatom nucleophiles. Because of the low polarity of the copper−carbon bond, a unique reactivity profile ranging from conjugate addition and S_N- and S_N'-type displacement reactions to carbometalation of alkynes is observed. A wide range of different organocopper reagents with their special application ranges exists, and their regio- and stereoselective reactions have been summarized in general reviews of organocopper chemistry.[1] More recently, a wide range of useful chiral copper catalysts has been developed, which has been reviewed recently.[2]

As it holds for all organic reactions, also in organocopper chemistry, selectivity control can originate either from the reagent or catalyst itself (reagent control of selectivity) or, alternatively, from the substrate (substrate control). In this case, the structural information inherent in the substrate is used to control the trajectory of the incoming reagent. If repulsive substrate reagent interactions are involved, this is generally termed passive substrate control. Alternatively, attractive substrate−reagent interactions may be used to control the reagent trajectory, which is coined as active substrate control of selectivity or, alternatively, as a substrate-directable reaction.[3] This type of selectivity control has been demonstrated to provide high levels of selectivity, since highly ordered cyclic transition states are passed, which allow for an efficient energetic differentiation of competing reaction pathways. During the past decade, this type of selectivity control has been found to be a valuable tool in controlling chemo-, regio-, and stereoselectivity in copper-mediated and -catalyzed transformations. The goal of this review is to summarize substrate-directed reactions of organocopper reagents, giving emphasis to synthetically useful transformations.

Attractive substrate−reagent interactions rely most frequently on polar functional groups which are either removable or an integral part of the substrate. Such functional groups may be termed reagent-directing groups (RDG). In general, attractive substrate−organocopper reagent interactions are provided by Lewis basic donor atoms within these groups, which allow for coordinative interaction with the copper center of the organocopper reagent. Two general cases may be distinguished: First, the reagent-directing group remains unchanged in the substrate. The obvious advantage is the possibility of further use of the directing group in synthesis. In a second scenario, the reagent-directing group simultaneously acts as a leaving group, the domain of displacement reactions. The latter approach enables the stereospecific construction of highly functionalized tertiary and quaternary carbon centers which cannot be easily accessed by other means (vide infra) concomitant with a traceless removal of the reagent-directing group.

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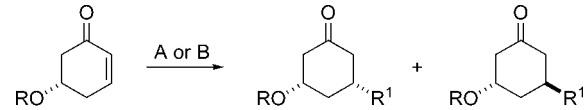
Yvonne Schmidt was born in 1982 in Reutlingen, Germany. She studied chemistry at the Albert-Ludwigs-Universität Freiburg, where she obtained her diploma degree in 2006. For her diploma thesis under the supervision of Professor Breit she was awarded the Steinhofer prize 2006 from the Steinhofer Foundation. In 2007 she was granted a research fellowship from the Fonds der Chemischen Industrie and pursued her scientific career as a Ph.D. student in the group of Professor Breit. Her research is focused on the copper-mediated *o*-DPPB-directed allylic substitution and its application to natural product synthesis.

2. Conjugate Addition

2.1. Passive versus Active Substrate Control in Cyclic Systems

Conjugate addition of organocopper reagents to Michael acceptors is a fundamental and synthetically valuable C−C bond forming reaction, which may generate a new stereocenter in the β-position with respect to the acceptor function. For cyclic systems, high levels of diastereoselectivity have been observed due to the preference for distinct reactive conformations. Thus, minimization of repulsive substrate−reagent interactions coupled with stereoelectronic requirements allows for a diastereoselecive and predictable installation of a carbon nucleophile via conjugate addition.[4]

Table 1. Conjugate Addition of Organocopper Reagents to Enones 1 and 2



entry	substrate	R^1	method[a]	*cis*:*trans*	yield (%)
1	**1**	*n*Bu	B	10:90	87
2	**1**	*n*Bu	A	>98:2	80
3	**2**	*n*Bu	A[b]	>99:1	92
4	**2**	*n*Bu	B	2:98	92
5	**2**	Me	A	>99:1	83
6	**2**	Me	B	3:97	83

[a] Et_2O, −78 °C, 2.4 equiv of cuprate reagent A [$R^4Cu(CN)Li$] or B [$(R^4)_2Cu(CN)Li_2$]. [b] With 1.2 equiv of cuprate reagent.

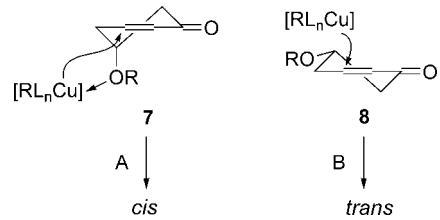
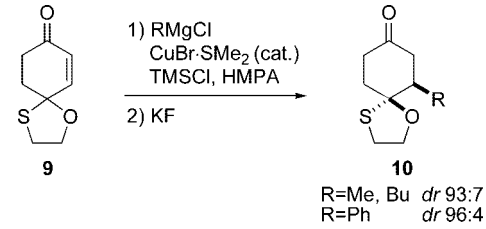


Figure 1. Directed and nondirected conjugate addition on cyclic substrates.

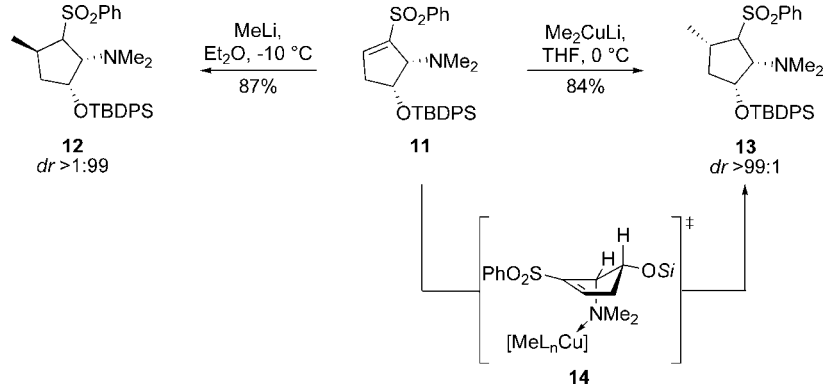
Scheme 1



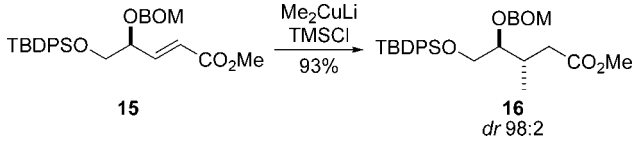
The disadvantage of this mode of stereocontrol is that only one stereoisomer is available. However, this inherent passive stereocontrol observed for cyclic substrates can be overruled by a reagent-directing or -coordinating group. In the conjugate addition reaction of 5-substituted cyclohexenones, both diastereomeric products can be formed selectively with a change of cuprate reagent (Table 1).[5] Thus, reaction of 5-oxygen-substituted cyclohexenones **1** and **2** with a higher-order cyanocuprate gave the expected *trans* addition products **5** and **6**, respectively [entries 1, 4, and 6 (Table 1)]. Conversely, when the corresponding lower-order cyanocuprate was employed, diastereoselectivity was reversed and the *cis* addition products **3** and **4** were formed in high selectivities (entries 2, 3, and 5). A most reasonable explanation for this result is a benzyloxy- or silyloxy-directed cuprate addition via transition state **7** on the one hand, and passive substrate control via the less biased transition state **8** (Figure 1) on the other.[6] So the higher-order cuprate is not capable of further coordinative interaction with the substrate due to its more saturated coordination sphere.[6,7]

Another cyclohexenone derivative, the S,O-acetal **9** features two possible directing groups, one sulfur and one oxygen atom (Scheme 1). The results of the copper-catalyzed conjugate addition with Grignard reagents indicate the

Scheme 2



Scheme 3



coordinating ability of the alkoxy group to be far stronger than that of the sulfide moiety. High diastereoselectivities favoring the *cis* adducts **10** (with respect to oxygen) were achieved with various sp^2 and sp^3 nucleophiles.[8]

Also in five-membered ring systems interesting stereocomplementarity can be achieved upon switching between passive (repulsive) and active (attractive) substrate control. Thus, cyclopentenyl sulfone **11** (Scheme 2) reacts with the hard nucleophile methyllithium from the sterically less hindered face to give *trans* product **12** in excellent diastereoselectivity and yield.[9] The corresponding Gilman cuprate, Me_2CuLi, reacts with this highly substituted substrate diastereoselectively in favor of *cis* adduct **13**.[10] This complete reversal of the inherent stereofacial selectivity has been explained by coordination of the copper source by the amine function, as depicted in transition state **14**, directing the organometallic reagent onto the more crowded face of the molecule.

2.2. Acyclic Systems

In contrast to the passive substrate control in cyclic systems, which can afford excellent selectivities, the less rigid open chain α,β-unsaturated carbonyl compounds are more challenging substrates in copper-mediated 1,4-additions. For some γ-alkoxy-substituted unsaturated esters like **15** in Scheme 3,[11] high levels of *anti* selectivity upon conjugate addition of Me_2CuLi have been achieved (→**16**). However, the method remains limited.

Thus, only the different properties of the substituents in the γ-position (represented by S, M, and L in Figure 2), with L being the largest substituent, more precisely the one possessing the lowest σ* orbital, determine the stereochemistry. This so-called "modified" Felkin−Anh model has been proposed[12] in analogy to the classical model used for

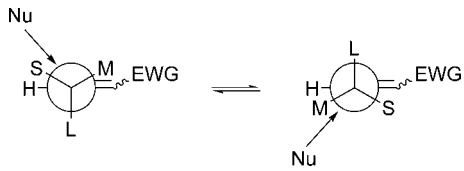
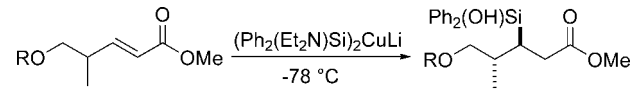


Figure 2. Modified Felkin−Anh model for conjugate additions.

Table 2. Conjugate Addition to δ-Substituted α,β-Unsaturated Esters 17



entry	substrate	R	product	*anti*:*syn*	yield (%)
1	**17a**	Bn	**18a**	50:50	95
2	**17b**	TBS	**18b**	50:50	45
3	**17c**	CONHPh	**18c**	89:11	77
4	**17d**	COOMe	**18d**	>95:5	80
5	**17e**	COOBn	**18e**	>95:5	85

prediction of the stereochemical outcome of nucleophilic additions to α-substituted aldehydes.[13]

2.2.1. Carbonates and Carbamates

Substrates with more remote substituents or with substituents of similar size lose their ability to control the stereochemistry in the addition reaction. In agreement with this general trend, benzyloxy and silyloxy derivatives **17a** and **17b** reacted with a silyl cuprate nonselectively to give conjugate adducts **18a** and **18b**, respectively (entries 1 and 2, respectively, in Table 2).[14] For the corresponding carbamate **17c**, by contrast, high levels of diastereoselectivity were noted, and even better results were obtained for carbonates **17d** and **17e** to give the *anti* esters **18c**−**e** as the major diastereomers (entries 3−5, respectively).[14]

It was proposed that coordination of the cuprate reagent by a carbamate or a carbonate as the reagent-directing group may account for the stereochemical result of these reactions (see models **19** and **20** in Figure 3).[3,14]

Even with the acyclic substrate **21** having the controlling stereogenic center in the δ-position, good levels of acyclic stereocontrol could be achieved in the course of the conjugate addition with silylcuprate reagent (Scheme 4) to furnish ester **22**.

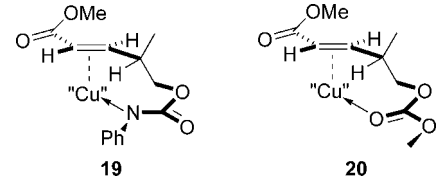
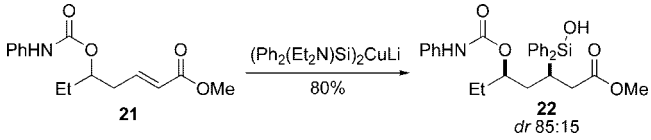


Figure 3. Carbamate- and carbonate-directed conjugate addition.

Scheme 4

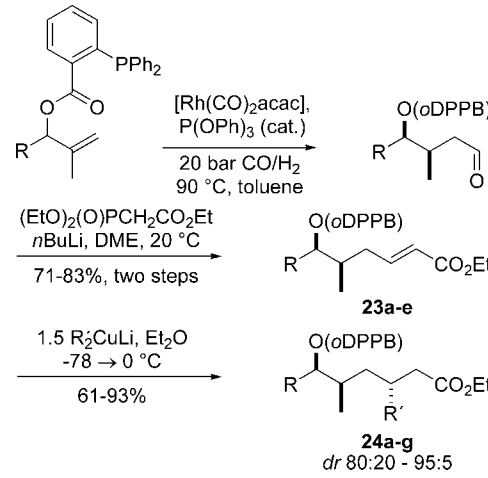


2.2.2. o-Diphenylphosphanylbenzoates

A new concept employing a specifically introduced reagent-directing group[15] allowed application of the substrate direction to conjugate addition of cuprates to acyclic enoates more efficiently.[16] Thus, as an appropriate directing group, the *o*-diphenylphosphanylbenzoyl (*o*-DPPB) function was identified. Like the corresponding carbamates (section 2.2.1), this group is easily attached to the substrate through a hydroxyl or amine function. Notably, this group has a multifunctional character since the phosphorus moiety can act as an efficient directing group for a number of late transition metal-mediated or -catalyzed reactions. So far, directed hydroformylations,[17] rhodium-catalyzed domino-type processes,[18,19] and a palladium-catalyzed atropselective biaryl coupling[20] have been described.

Enoates **23** were prepared efficiently combining an *o*-DPPB-directed stereoselective hydroformylation followed by HWE olefination (Scheme 5). Generally, chiral δ-methyl-substituted enoates are known to react nonselectively upon addition of dimethylcuprate.[21] Conversely, conjugate addition of enoates **23** with dialkyl cuprates gave the corresponding *anti* 1,4-addition products **24** in good yield and diastereoselectivity (Table 3).[16]

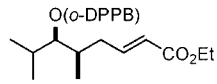
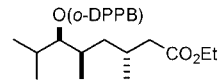
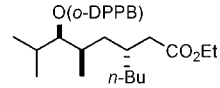
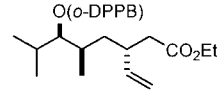
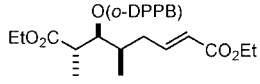
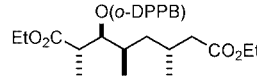
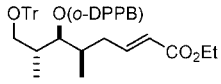
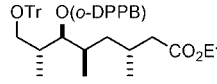
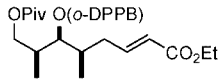
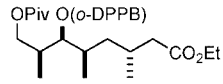
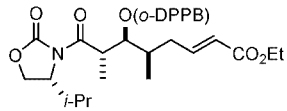
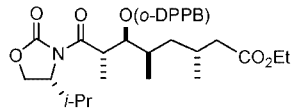
Scheme 5



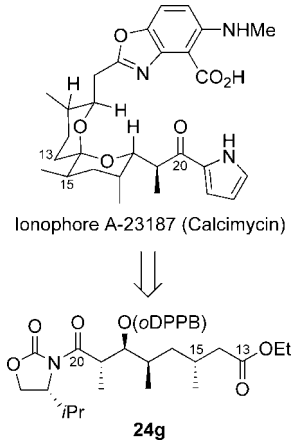
Therefore, a combination of *o*-DPPB-directed hydroformylation and *o*-DPPB-directed cuprate addition provided useful building blocks for polyketide synthesis with up to four stereogenic centers (**24**; see Scheme 5 and Table 3).[16b]

Comparison of the ionophore calcimycin with **24g** (entry 7 in Table 3) reveals the utility of this combination of substrate-directed methods. This conjugate addition product, **24g**, is equipped with the absolute and relative configuration of the four consecutive stereocenters found in the alkyl chain of calcimycin (Scheme 6). Additionally, with the different functional groups on both sides of the molecule, it represents a reasonable intermediate for total synthesis.[22]

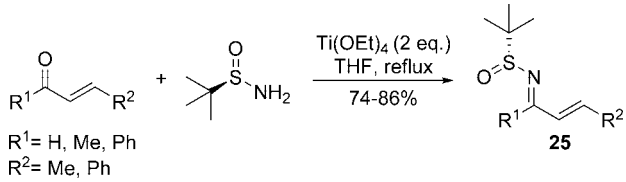
Table 3. *o*-DPPB-Directed Conjugate Addition to Acyclic Substrates

entry	enoate	product	yield [%]	*dr*
1	 **23a**	 **24a**	93	95:5
2	**23a**	 **24b**	68	95:5
3	**23a**	 **24c**	61	80:20
4	 **23b**	 **24d**	68	95:5
5	 **23c**	 **24e**	71	86:14
6	 **23d**	 **24f**	60	85:15
7	 **23e**	 **24g**	75	95:5

Scheme 6



Scheme 7



2.2.3. tert-Butylsulfinyl Imines

As removable chiral directing groups, *tert*-butylsulfinyl imines have been successfully employed. This directing group is introduced upon condensation of α,β-unsaturated aldehydes or ketones with a chiral sulfinamide producing enantiomerically pure *tert*-butylsulfinyl imines of the general structure **25**, and this reaction proceeds in good yield using 2 equiv of $Ti(OEt)_4$ as a Lewis acid and water scavenger (Scheme 7).[23]

These sulfinyl imines **25** were employed in the 1,4-addition with Yamamoto (entries 1 and 2 in Table 4) and Gilman (entries 3−5) cuprate reagents. High yields and diastereoselectivities were realized for both acyclic and cyclic derivatives.

The facial selectivity of this 1,4-addition can be rationalized as depicted in Scheme 8. Thus, coordination and delivery of the cuprate reagent by the oxygen atom of the sulfinyl imine function occur on the side opposite from the bulky *tert*-butyl substituent.[7]

3. Allylic Substitution

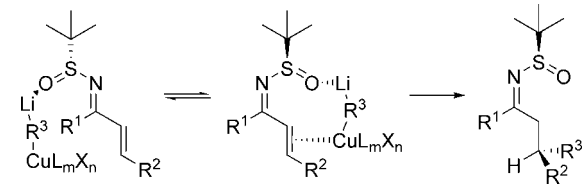
3.1. General Remarks on Regioselectivity and Stereoselectivity

Reaction of allylic substrates **27** equipped with an adequate leaving group X in the allylic position with organocopper reagents may occur either as an S_N2-type process (α-attack) or alternatively in an S_N2' fashion (γ-attack) to give substitution product **28** or **29**, respectively (Scheme 9).[24,25]

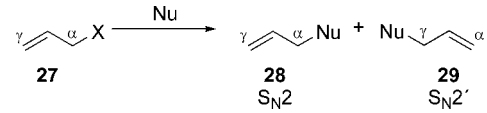
The ratio of α-attack to γ-attack is a subtle function of substrate structure (steric, electronic situation), the leaving group, and the nature of the organocopper reagent employed. Similar to the S_N2 process, the S_N2' reaction with organocopper reagents occurs generally with inversion of configuration which results from the attack of the organocopper reagent *anti* to the leaving group in the allylic position.

A simple stereoelectronic model based on frontier molecular orbital considerations has been proposed to explain the

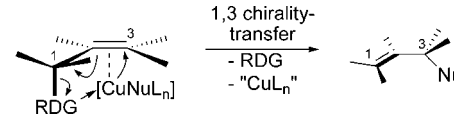
Scheme 8



Scheme 9



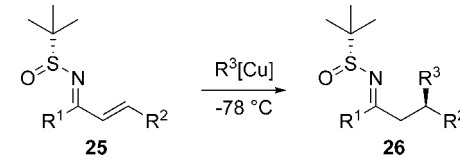
Scheme 10

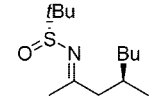
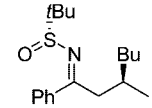
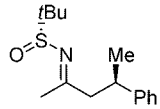
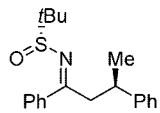
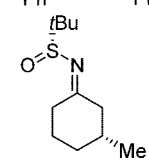


stereochemistry of the allylic substitution reaction [**30** (Figure 4)]. Thus, in contrast to C nucleophiles, organocopper reagents possess filled d orbitals (d^{10} configuration), which can interact with both the π*-(C═C) orbital at the γ-carbon and to a minor extent with the σ*-(C−X) orbital as depicted in Figure 4.[26] To achieve an optimal orbital overlap, the σ*-orbital of the C−X bond should be aligned coplanar to the alkenic π-system.

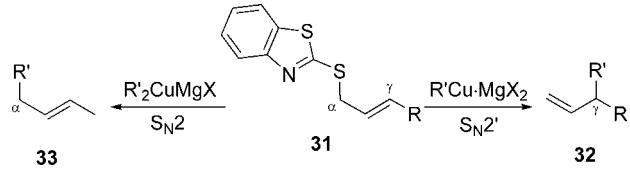
This intrinsic stereocontrol can then be overruled in favor af a *syn* substitution pathway if a reagent-directing leaving group (RDG in Scheme 10) is employed. Suitable directing leaving groups are equipped with donor atoms capable of

Table 4. Conjugate Addition to Chiral α,β-Unsaturated Sulfinyl Imines



entry	R^3[Cu]	solvent	product	yield [%]	*dr*
1	Bu_2CuCN $BF_3{\cdot}OEt_2$	THF		68	93:7
2	Bu_2CuCN $BF_3{\cdot}OEt_2$	THF		76	92:8
3	Me_2CuLi	Et_2O		70	85:15
4	Me_2CuLi	Et_2O		91	96:4
5	Me_2CuLi	Et_2O		55	87:13

Scheme 11



coordination to the organocopper reagents such as nitrogen (benzothiazoles[27,28] and carbamates[29,30]) or phosphorus (*o*-diphenylphosphanyl esters[31]).

3.2. Benzothiazoles

Heterocyclic leaving groups proved to be useful auxiliaries in allylic substitution reactions and have been investigated by Calò et al.[32] Thus, the reaction of benzothiazoles **31** with an organocopper reagent obtained from R′MgBr and an excess of copper(I) salt gave S_N2' products **32** in high regioselectivity (Scheme 11). The less electrophilic cuprates R_2CuMgX furnished the S_N2 products **33** selectively, which is suggested to be due to their reduced affinity for additional coordination. The organocopper species is supposed to coordinate to the substrate, with intramolecular transfer of the C nucleophile.

The crotyl benzothiazol derivative **34** formed a stable complex **35** with CuBr (Figure 5).[33] IR spectroscopic investigation of **35** suggested coordination of the C═N and C═C π-systems to the copper(I) center. Exchange of bromine via the corresponding carbon nucleophile allows for an intramolecular nucleophile delivery, which should be responsible for the high chemo- and regioselectivity of the reaction.

Allylic substitution with organocopper reagents using benzothiazole **36** as a substrate afforded homoallylic pivalate **37** as a single regioisomer (Scheme 12).[34] Hence, the directing benzothiazole is a much better leaving group than a competing pivaloate.[35] Equally, when enoates **38** were employed, high chemo- and regioselectivity toward S_N2' product **39** was noted.[36]

3.3. Carbamates

As an alternative to benzothiazoles, carbamates have been identified as powerful reagent-directing leaving groups.

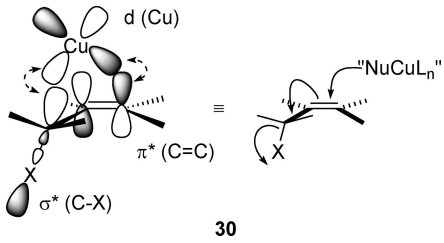


Figure 4. Orbital interactions in copper-mediated allylic substitutions.

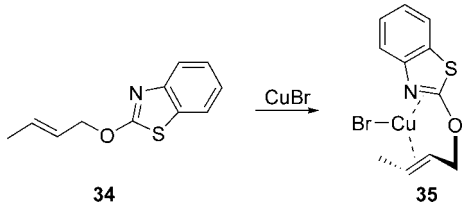
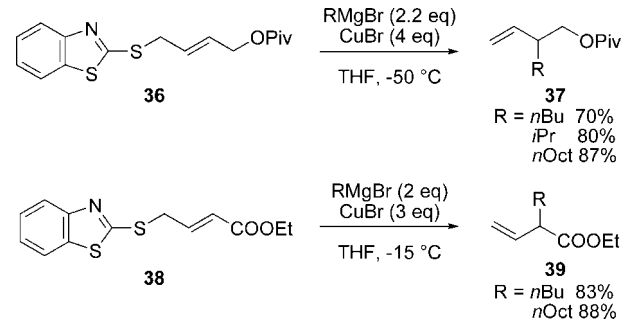
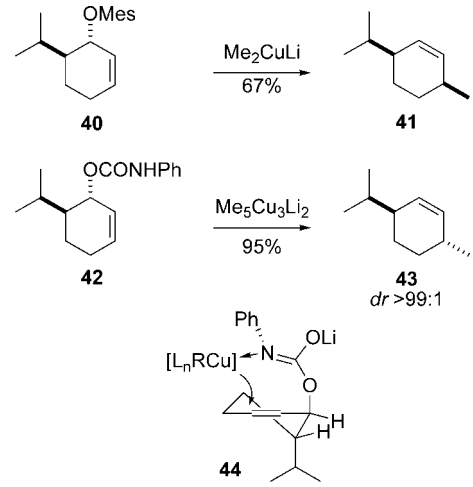


Figure 5. Formation of stable chelation complex **35**.

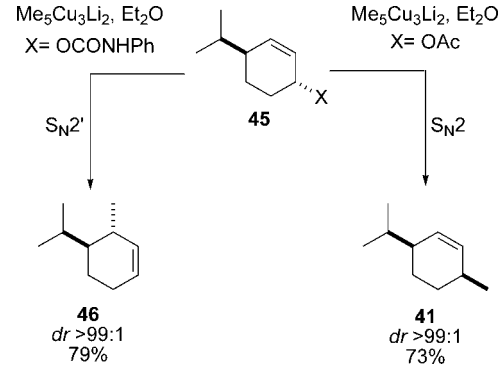
Scheme 12



Scheme 13



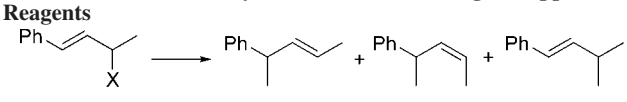
Scheme 14



While reaction of cyclic mesylate **40** gave the *anti* S_N2' product **41** only,[37] the corresponding carbamate **42** furnished *syn* substitution product **43** exclusively (Scheme 13). It was assumed that the cuprate reagent is coordinated by the carbamate nitrogen (see reactive conformation **44**) which renders the attack of the C nucleophile intramolecular in nature.

Associated with this intramolecular delivery of organocopper reagent is the benefit of high regioselectivity, since an intramolecular trajectory prohibits the alternative α-attack. This is nicely illustrated by the reaction behavior of cyclic substrate **45** in Scheme 14. For this substrate, γ-attack is sterically hindered, and the nondirected reaction of the acetate of **45** with a higher-order methyl cuprate gave exclusively S_N2-type product **41**. The carbamate of **45** on the other hand not only is able to invert stereochemistry but also allows the exclusive formation of S_N2' product **46**.[29] Similar results were obtained upon treatment of **45** with silylcuprates.[38] Therefore, the generalization can be made that carbamate

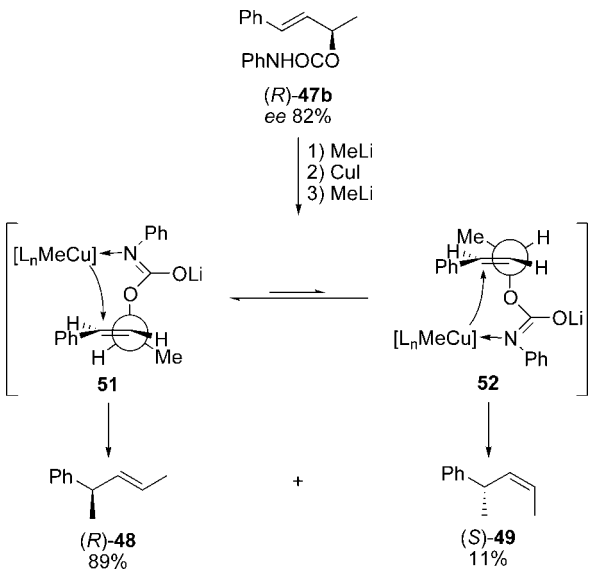
Table 5. Reaction of Allylic Substrates with Organocopper Reagents



entry	X	solvent	**48**:**49**:**50**	yield (%)
1	OAc	Et_2O[a]	4:0:96	>99
2	OCONHPh	THF[b]	89:11:0	not determined

[a] Me_2CuLi. [b] (1) MeLi, (2) CuI, (3) MeLi.

Scheme 15



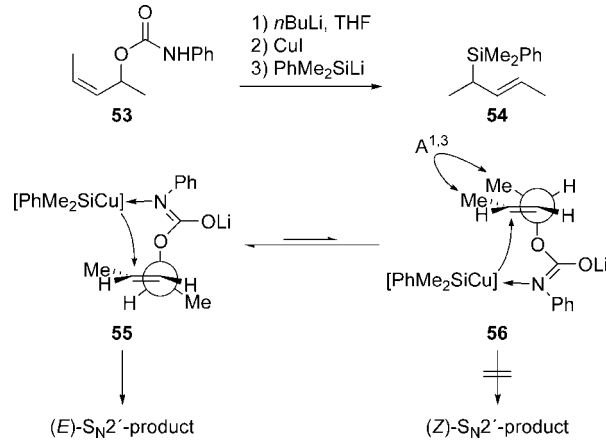
leaving groups induce high γ-selectivity upon allylic substitution with organocuprates and can overrule steric hindrance at the γ-position in the allylic framework.

In the case of acyclic substrates, the situation is more complex. A larger number of reactive conformations become available and the corresponding transition states compete. Thus, upon treatment with lithium dimethylcuprate, methyl cinnamyl-derived acetate **47a** gave mainly S_N2 product **50** (entry 1 in Table 5).[39] The preference for the S_N2 product is expected since deconjugation of the alkenic system is electronically unfavorable.

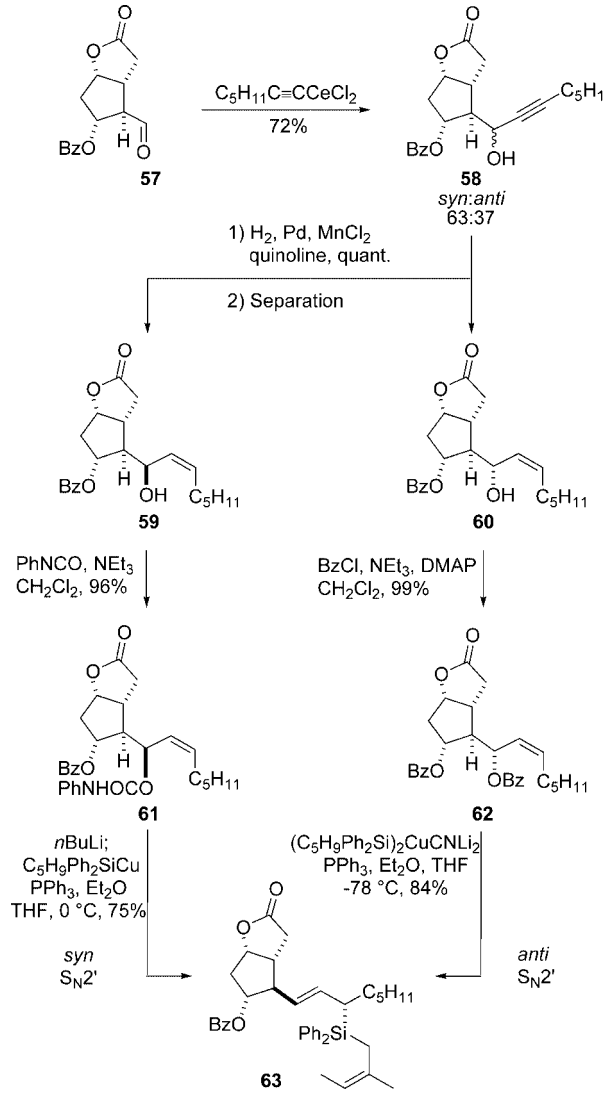
Conversely, employing carbamate **47b** (entry 2), exclusive γ-alkylation was observed. However, the double bond configuration could be maintained only partially to give **48** and **49** in a ratio of 89:11.[30,39] The formation of both alkene isomers is rationalized via the two competing transition states, **51** and **52** (Scheme 15). Minimization of $A^{1,3}$ strain[12] should favor transition state **51** to some extent. The proposed *syn* attack of the organocopper nucleophile could be confirmed by employing the enantiomerically enriched carbamate (*R*)-**47b** [82% enantiomeric excess (*ee*)] as the starting material. The obtained ratio of the two diastereomers, (*R*)-**48** and (*S*)-**49**, is therefore solely due to an unsatisfactory energetic differentiation of competing transition states **51** and **52** (Scheme 15).[30]

As a consequence of this model, one would predict that increasing $A^{1,3}$ strain, for example, with a (*Z*)-alkenic system, should favor transition state **51** even more, giving higher levels of *E* selectivity for the corresponding allylic substitution product. Accordingly, reaction of (*Z*)-allylic carbamate **53** with the mixed silyl cuprate led to the exclusive formation

Scheme 16



Scheme 17



of (*E*)-alkene **54** (Scheme 16).[40] This result is rationalized by comparison of the two rotamers, **55** and **56**, in Scheme 16. Thus, the severe allylic $A^{1,3}$ strain in conformation **56** suppresses the alternative pathway to the (*Z*)-alkene, and (*E*)-alkene **54** is obtained as a single isomer.[12]

These results were applied elegantly in a stereoconvergent synthesis of prostaglandins (Scheme 17). Starting from a diastereomeric mixture of propargylic alcohols **58** obtained

Scheme 18

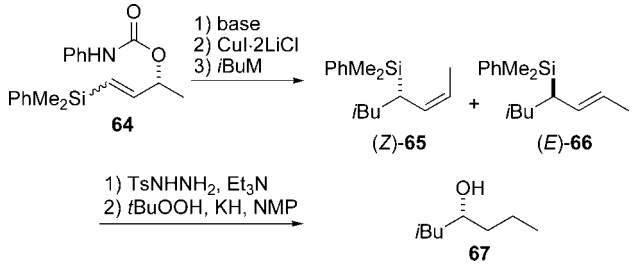


Table 6. Allylic Substitutions of (*E*)- and (*Z*)-Silanes 64

entry	substrate	base[a]	M	**65**:**66**	yield[b] (%)	*ee* of **67** (%)
1	(*E*)-**64**	*n*BuLi	MgCl	94:6	90	88
2	(*E*)-**64**[c]	*n*BuLi	Li	9:91	69	–
3	(*Z*)-**64**[d]	MeLi	MgCl	3:97	93	92
4	(*Z*)-**64**[d]	MeLi	Li	<1:99	93	94

[a] THF, 0 °C. [b] Yield of **65** and **66**. [c] Racemic starting material was employed. [d] A 96% *ee*; 3:97 *E*:*Z* ratio.

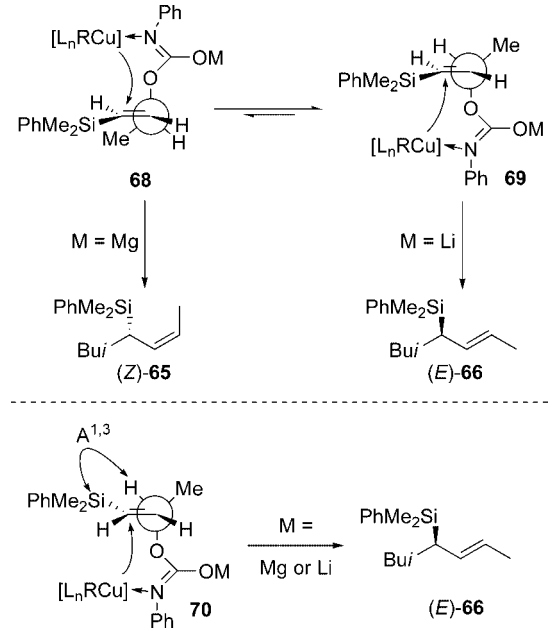
from a nonselective 1,2-addition of an alkinylcerium reagent to aldehyde **57** and subsequent *cis* hydrogenation with a palladium catalyst gave diastereomeric (*Z*)-allylic alcohols **59** and **60**. Both diastereomers were separated and transformed into carbamate **61** and benzoate **62**, respectively. Allylic substitution of both substrates with a phosphine-modified silylcuprate reagent merged into the formation of a single allylic silane **63**. The combination of these two pathways produced a high overall yield and excellent stereoselectivity.[41]

Generally, both (*E*)- and (*Z*)-allylic carbamates furnish upon allylic substitution with organocopper reagents either exclusively or preferentially the (*E*)-alkenic product. Conversely, it was found by Woerpel et al. that silyl-substituted allylic carbamates (*E*)-**64** (Scheme 18) provided remarkable *Z* selectivities under reaction conditions involving mixed organomagnesium/copper reagents.[42]

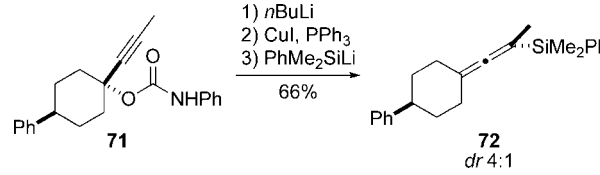
Thus, enantiomerically pure carbamate (*E*)-**64** furnished (*Z*)-allylsilane **65** in high yield and *Z* selectivity, employing an organocopper reagent prepared from *iso*-butylmagnesium chloride. After transformation to saturated alcohol **67**, an enantiomeric excess of 88% was determined, which is consistent with the *E*:*Z* ratio of the allylsilane with respect to the *ee* of the starting compound (entry 1 in Table 6). However, when the switch to an *iso*-butyl organocopper reagent prepared from the corresponding *iso*-butyllithium was made, carbamate (*E*)-**64** furnished (*E*)-allylsilane **66** (entry 2). On the other hand, both reagent types reacted with the *Z* isomer of **64** to give (*E*)-allylsilane **66** stereoselectively (entries 3 and 4). To explain the inverted stereochemical course in the allylic substitution of (*E*)- versus (*Z*)-vinylsilane **64** with the magnesium/copper and lithium/copper reagents, respectively, the transition state models in Scheme 19 were suggested.

Thus, allylic substitution of (*E*)-silanes **64** proceeds via either one of the two rotamers, **68** and **69**. In this way, the stereochemical outcome with the lithium reagent is easily understood via reactive conformation **69** with minimized $A^{1,3}$ strain. In the case of the presence of a magnesium counterion, reaction via reactive conformation **68** is preferred to give (*Z*)-alkene **65**. However, for (*Z*)-allylic silane **64**, the pronounced $A^{1,3}$ strain dictates the reaction in both cases (M = Mg or Li) to pass reactive conformation **70** to furnish (*E*)-allylic silane **66**.[42b]

Scheme 19



Scheme 20



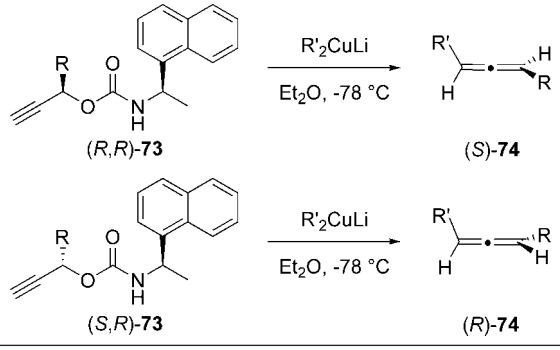
Related to the allylic substitution reaction is the propargylic substitution, leading to substituted allenes. Since propargylic alcohols are readily available in enantiomerically pure form from a number of processes, this reaction becomes a useful synthetic entry toward chiral allenes.[43,44] As in the case of allylic substitution, the intrinsic stereochemical pathway is an *anti* attack of the organometallic nucleophile with respect to the leaving group. However, when the switch to a reagent-directing carbamate as the leaving group as realized in substrate **71** was made, reaction with a silyl organocopper reagent furnished the corresponding *syn* substitution product, allene **72**, in good diastereoselectivity and yield (Scheme 20).[45] In analogy to the allylic substitution, the stereochemistry in the course of the propargylic substitution is reversed by a carbamate-directed attack of the organocopper nucleophile.

Enantiomerically enriched allenes can be accessed using diastereomeric carbamates (*R*,*R*)-**73** and (*S*,*R*)-**73**.[46] These substrates were obtained from addition of the racemic propargylic alcohol to an enantiomerically pure isocyanate and subsequent chromatographic separation of the diastereomers. Propargylic substitution of different substrates with Gilman cuprates was examined (Table 7). Thus, chiral allenes **74** were obtained in enantioselectivities ranging from 60 to 80% *ee* and in good yields.

3.4. *o*-Diphenylphosphanylbenzoates

The *o*-diphenylphosphanylbenzoyl (*o*-DPPB) group is a multifunctional reagent-directing group. Several late transition metal-catalyzed and -mediated processes such as hydroformylation, rhodium-catalyzed domino processes, palladium-catalyzed atropselective biaryl coupling, palladium-catalyzed allylic substitution, and conjugate addition of

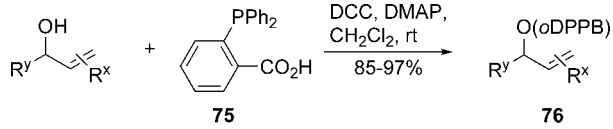
Table 7. Propargylic Substitution of Chiral Carbamates



entry	substrate	R	R′	*ee* (%)	yield (%)
1	(*R*,*R*)-**73**	*n*Bu	*n*Bu	80 (*S*)	76[a]
2	(*S*,*R*)-**73**	*n*Bu	*n*Bu	75 (*R*)	76[a]
3	(*S*,*R*)-**73**	*n*Bu	Et	61 (*R*)	79[b]
4	(*R*,*R*)-**73**	Et	Et	60 (*S*)	73[b]
5	(*S*,*R*)-**73**	Et	Et	60 (*R*)	71[b]
6	(*R*,*R*)-**73**	*n*Bu	Et	66 (*S*)	70[b]

[a] Addition of carbamate to cuprate. [b] Inverse addition.

Scheme 21



organocopper processes (see section 2.2.3) are known. Thus, the geometry of this group is ideal for directing a metal center into the allylic or homoallylic position of an organic substrate. Hence, this group can be expected to serve as a directing leaving group for allylic substitution with organocopper reagents. Allylic *o*-DPPB esters **76** are readily available through esterification employing standard protocols (Scheme 21).

The required *o*-diphenylphosphanylbenzoic acid **75** is commercially available. Alternatively, it may be obtained in multigram scale in a one-pot operation starting from *o*-chlorobenzoic acid upon reaction with sodium diphenylphosphide generated under Birch conditions from triphenylphosphine.[47]

3.4.1. Chemo- and Regioselectivity

Orienting experiments aimed at identifying ideal conditions for establishing a directed allylic substitution were performed with allylic *o*-DPPB ester **77**.[31] This substrate was chosen since it is structurally not biased toward a preference for either α-attack or γ-attack to give alkene **79** or **80**, respectively (Scheme 22). To clarify the role of the phosphine, control reactions with CH derivative **78** were undertaken. Thus, with Gilman cuprates similar and low regioselectivities were observed with substrates **77** and **78**, ruling out a directed reaction pathway in this case (entries 1 and 2 in Table 8).

Conversely, a directed and highly chemo- and regioselective process was observed when the copper(I) salt was precomplexed by *o*-DPPB ester **77** prior to generation of the organocopper reagent by addition of a Grignard reagent (entry 3). A control experiment with CH-ester **78** revealed a significantly reduced rate, and dramatically reduced chemo-, regio-, and diastereoselectivities, which underline the role of the *o*-DPPB group as a reagent-directing leaving group. Employing primary and secondary alkyl Grignard reagents,

Scheme 22

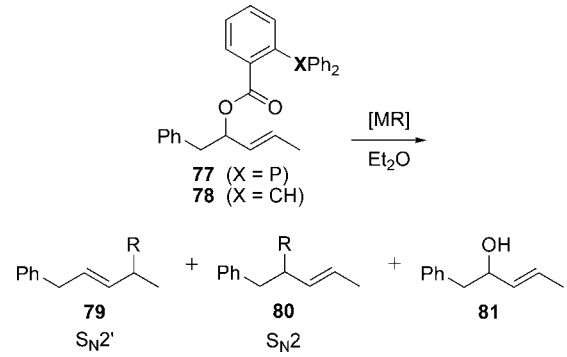


Table 8. Regioselectivity of Directed versus Nondirected Allylic Substitution

entry	X	reagent (equiv)	**79**:**80**:**81**
1	P	$Me_2CuLi\cdot LiI$	74:26:0
2	CH	$Me_2CuLi\cdot LiI$	78:22:0
3	P	MeMgI (1.1), $CuBr\cdot SMe_2$ (1.0)	>99:1:0
4	CH	MeMgI (1.1), $CuBr\cdot SMe_2$ (1.0)	42[a]:15:21

[a] At a 64:36 *E*/*Z* ratio.

Table 9. Directed Allylic Substitution with *o*-DPPB Ester 77

entry	$CuBr\cdot SMe_2$ (equiv)	Grignard reagent	yield (%)	*E*:*Z*
1	1	*n*BuMgCl	98	>99:1
2	1	*i*PrMgBr	84	97:3
3	1	PhMgBr	94	88:12
4	0.5	PhMgBr	90	93:7
5[a]	0.5	PhMgBr	94	97:3

[a] Et_2O/CH_2Cl_2 as a solvent.

excellent regio- and stereoselectivity were observed (entries 1 and 2 in Table 9). However, the less nucleophilic aryl Grignard reagents gave high regioselectivities only when the Grignard reagent was added slowly. Even better results were obtained employing 0.5 equiv of copper salt (compare entry 3 vs entries 4 and 5). This suggests that phosphine-coordinated organocopper species are the reactive organometallic intermediates. Thus, adjusting the Grignard addition rate to the rate of the directed allylic substitution prevents formation and accumulation of a corresponding cuprate reagent which has been shown to follow a nondirected unselective pathway (see entry 1 in Table 8).[48]

Coordination behavior of copper(I) salts with allylic *o*-DPPB esters was studied, and a 2:1 complex (*o*-DPPB ester−CuBr) with a trigonal-planar coordination geometry at the copper center was isolated and crystallographically analyzed (Figure 6). This suggested that application of 0.5 equiv of copper salt should be enough for a stoichiometrically directed process which in fact proved to be ideal for most directed allylic substitution reactions of *o*-DPPB esters (entries 4 and 5 in Table 9).

The optimized reaction conditions for directed allylic substitutions were applied to a series of *o*-DPPB esters (Table 10). In general, excellent S_N2' regioselectivities and yields were observed. Irrespective of double bond geometry [compare geraniol and nerol *o*-DPPB esters (entries 4 and 5)], excellent regioselectivity with concomitant construction of quaternary carbon centers was observed.

Secondary allylic *o*-DPPB esters starting from acyclic secondary allylic alcohols were subjected to the conditions of the directed allylic substitution as well (Table 10, entries

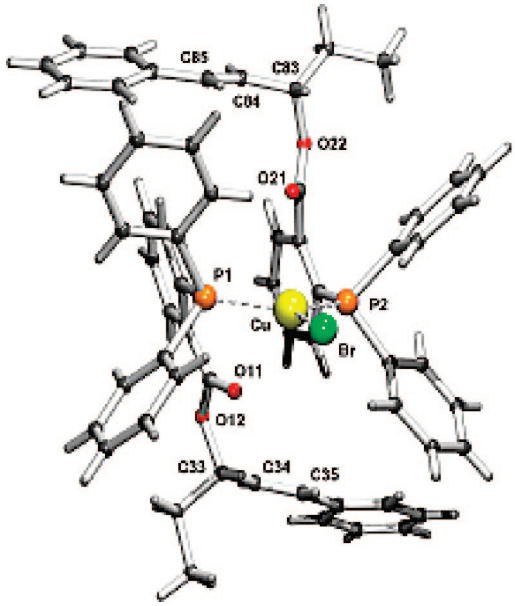


Figure 6. Complex of the *o*-DPPB ester and CuBr.

7−10). Again, excellent levels of regioselectivity were achieved, and isolated yields of the corresponding S_N2' products were generally high.

3.4.2. Stereochemistry

The stereochemistry of substitution reactions with *o*-DPPB esters was determined upon subjection of cyclic substrates *cis*-**82** and *trans*-**82** to the conditions of the directed allylic substitution with methyl magnesium bromide. In both cases, a completely *syn*-selective nucleophile transfer was observed to give *cis*- and *trans*-menthene (**83**), respectively (Scheme 23). Even for *trans*-**82** a complete 1,3-chirality transfer was observed, although in this case the substrate has to pass a reactive conformation which places the isopropyl substituent in a sterically unfavorable pseudoaxial position (Scheme 23) to fulfill stereoelectronic requirements [optimal π-(C═C)/σ*-(C−O) overlap].[26,49]

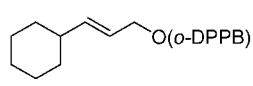
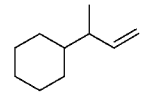
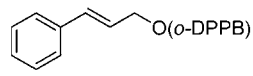
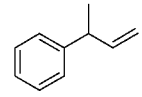
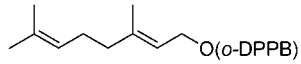
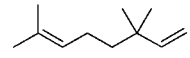
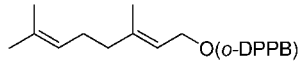
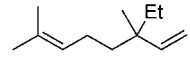
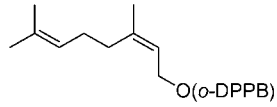
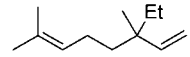
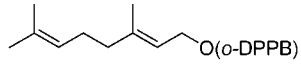
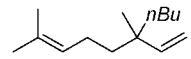
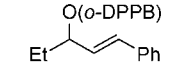
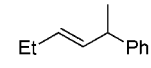
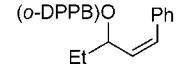
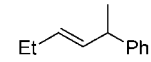
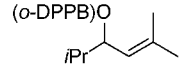
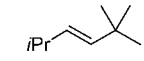
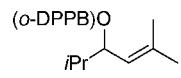
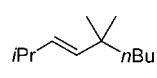
Copper-mediated allylic substitution of acyclic substrate (*S*)-**84** (99% *ee*) with methylmagnesium iodide furnished the corresponding S_N2' product, (*S*)-**85**, in high yield and regio- and stereoselectivity (Scheme 24). This proves that also for acyclic cases the reaction follows a *syn*-S_N2' pathway to give a perfect 1,3-chirality transfer. This can be rationalized by comparing the two stereoelectronically available reactive conformations, **86** and **87**. Thus, **87** should be energetically favored due to minimization of $A^{1,3}$ strain.

Interestingly, inspection of the *o*-DPPB ester conformation in the 2:1 copper complex (Figure 6) reveals that the organic substrate adopts a conformation which is very similar to postulated reactive conformation **87** (Figure 7).

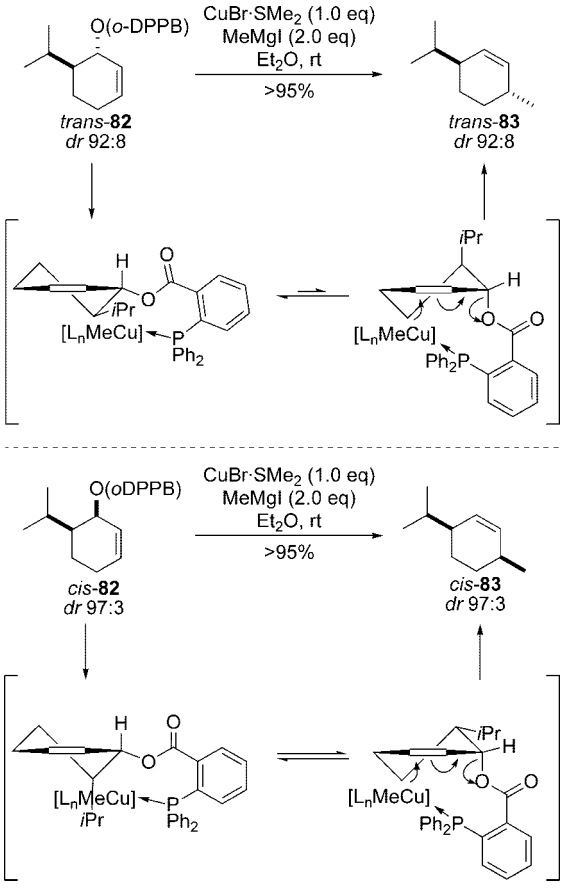
According to this transition state model, a switch of the alkene geometry in the starting allylic ester **84** from the *E* to *Z*-configuration should give access to the optical antipode, (*R*)-**85**. Indeed, subjection of corresponding *Z* substrate (*S*)-**88** with the same absolute configuration to the conditions of the directed allylic substitution furnished (*R*)-**85**, with perfect 1,3-chirality transfer, according to the directed *syn* substitution pathway (Scheme 25).

Hence, the directed allylic substitution employing *o*-DPPB esters of secondary allylic alcohols occurs with perfect 1,3-chirality transfer for both structurally defined cyclic systems and conformationally more flexible acyclic derivatives. In the latter case, the reaction enables the stereospecific

Table 10. *o*-DPPB-Directed Allylic Substitution

entry	substrate	RMgX	product	S_N2'/S_N2 (S_N2' *E*/*Z*)	yield [%]
1		MeMgI		>99:1	99
2		MeMgI		92:8	99
3		MeMgI		95:5	91
4		EtMgBr		>98:2	80
5		EtMgBr		>98:2	95
6		*n*BuMgBr		>99:1	87
7		MeMgI		97:3 (96:4)	84
8		MeMgI		>99:1 (98:2)	88
9		MeMgI		>99:1 (>99:1)	68
10		*n*BuMgBr		>99:1 (>99:1)	99

Scheme 23

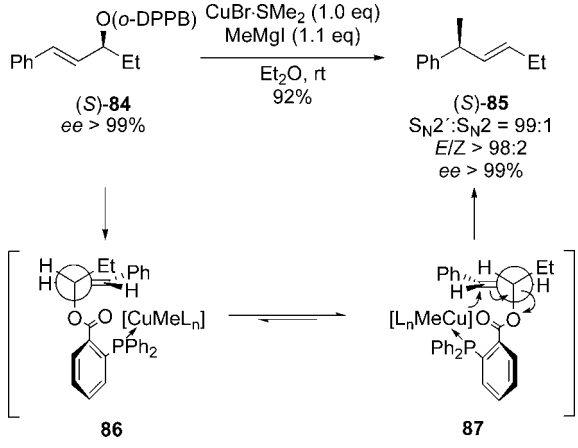


construction of a tertiary stereogenic carbon center as a function of alkene geometry.

In all previous cases of stereospecific *o*-DPPB-directed allylic substitution reactions, the directing *o*-DPPB group was directly attached to a stereogenic tertiary alcohol function, and excellent levels of 1,3-chirality transfer were realized for acyclic and cyclic systems.

Conversely, with substrates (*E*)- and (*Z*)-**89**, the stereochemical information is not part of the allylic alcohol system but in the δ-position relative the primary allylic substrate (Scheme 26).[50] Nevertheless, reaction of (*E*)-allylic *o*-DPPB ester **89** with methylmagnesium bromide in the presence of a copper(I) salt furnished *anti* substitution product **90** in good diastereoselectivity. Even better results were obtained for (*Z*)-allylic *o*-DPPB ester **89**, furnishing *syn* product **90**.

Scheme 24



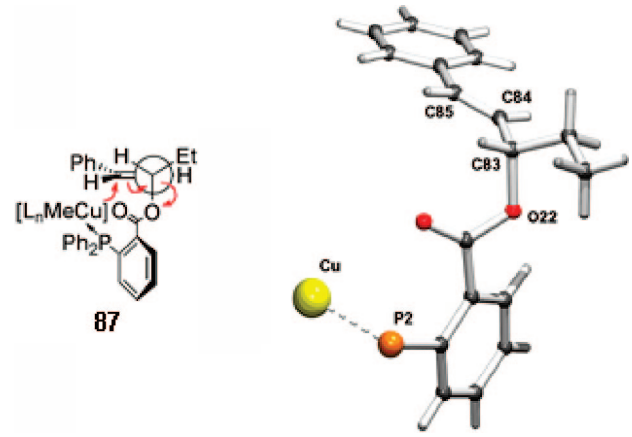
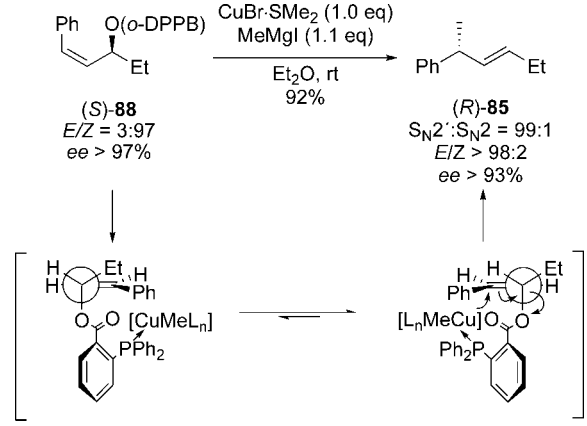
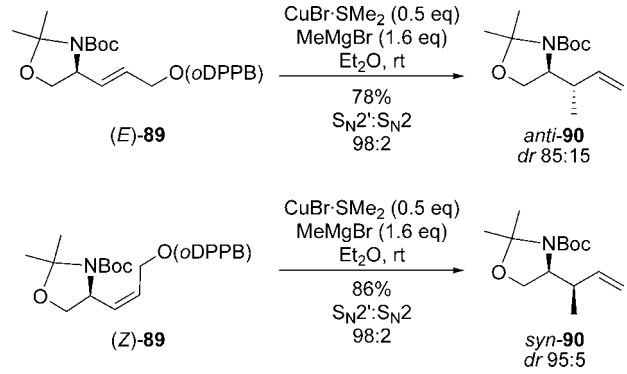


Figure 7. Comparison of reactive conformation **87** with the copper complex crystal structure.

Scheme 25



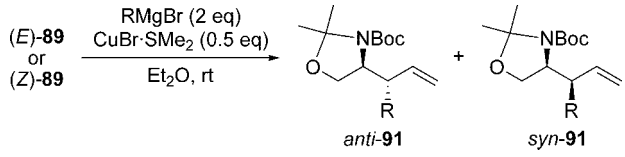
Scheme 26



The scope of the reaction was examined using different aliphatic Grignard reagents (Table 11). In all cases, high regioselectivities and yields were observed. With *Z* substrate **89**, excellent diastereoselectivities were noted (entries 4−6). Conversely, employing (*E*)-*o*-DPPB ester **89** the *anti* selectivity toward **91** was high using a secondary Grignard reagent (entry 3) but dropped upon reaction with primary organometallic reagents (entries 1 and 2).

The rationale for the stereochemical outcome is depicted in Figure 8. Thus, for (*E*)-allylic substrate **89**, both reactive conformations **92** and **93** are plausible for the high *anti* selectivity. The allylic $A^{1,3}$ strain is minimized in these conformations, and the directed attack of the nucleophile can occur from the least hindered *si* alkene face to give preferentially the *anti* diastereomer. In the case of *Z* substrate **89**, reactive conformation **94** explains the predominating

Table 11. Directed Allylic Substitutions with *o*-DPPB Esters (*E*)-89 and (*Z*)-89



entry	substrate	R	S_N2':S_N2	*syn*:*anti*	yield (%)
1	(*E*)-**89**	Et	96:4	15:85	91
2	(*E*)-**89**	*n*Bu	98:2	17:83	97
3	(*E*)-**89**	*i*Pr	98:2	7:93	97
4	(*Z*)-**89**	Et	99:1	97:3	98
5	(*Z*)-**89**	*n*Bu	98:2	98:2	96
6	(*Z*)-**89**	*i*Pr	95:5	95:5	98

formation of the *syn* product, resulting from attack on the *re* face. The increased $A^{1,3}$ strain in (*Z*)-alkenes may account for the higher diastereoselectivities observed with *o*-DPPB ester (*Z*)-**89**.

Therefore, the products of allylic substitution employing substrates (*E*)-**89** and (*Z*)-**89** represent precursors of β-branched α-amino acids, which could be obtained in two steps upon deprotection and oxidation of the alcohol. This methodology was applied in the synthesis of naturally occurring amino acid **97**, isolated from the mushroom *Amanita castanopsidis hongo* (Scheme 27).[51] Cyclopropanation of *anti*-**90** was accomplished quantitatively with diazomethane and catalytic palladium acetate to give protected amino acid precursor **95**. Subsequent deprotection and oxidation furnished the corresponding N-protected amino acid **96**. Final cleavage of the Boc protecting group yielded natural amino acid **97** (*dr* 9:1) in quantitative yield.

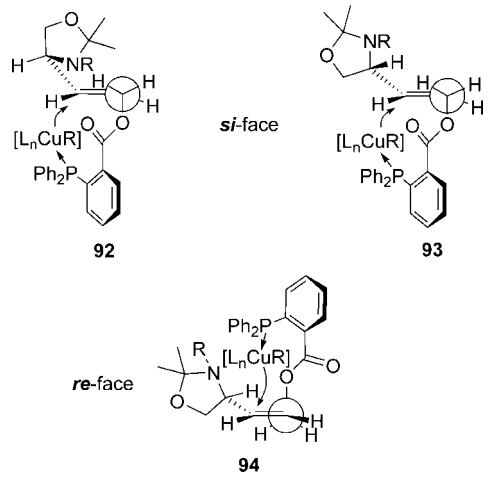
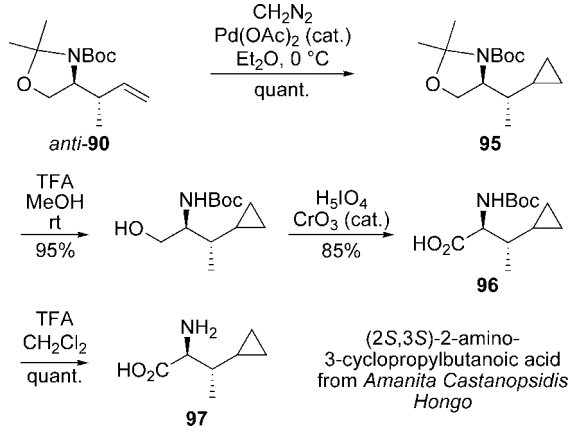
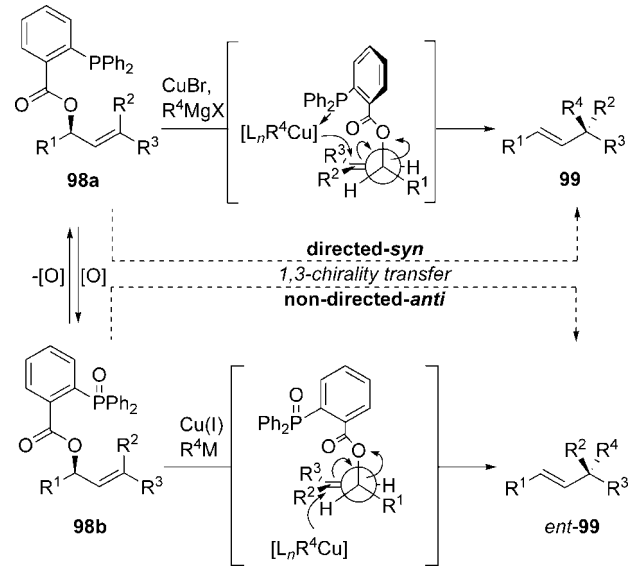


Figure 8. Reactive conformations in allylic substitution of *o*-DPPB esters (*E*)-**89** and (*Z*)-**89**.

Scheme 27



Scheme 28

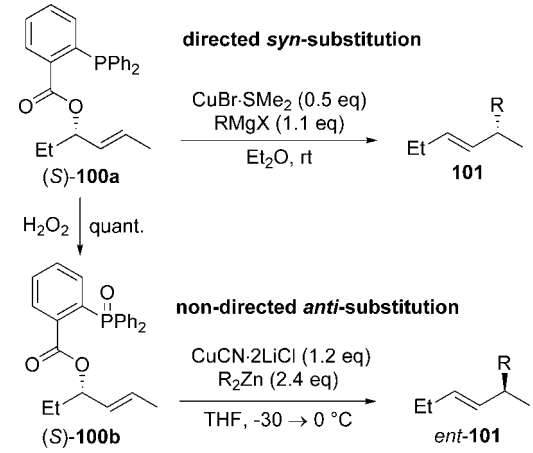


3.4.3. Stereodivergency

Interestingly, the directing power of the *o*-DPPB group can be controlled by an oxidative on−off switch.[52] This allows the preparation of both optical antipodes of the substitution product starting from a single substrate enantiomer (Scheme 28).

To gain access to both enantiomeric substitution products, starting from the same *o*-DPPB ester substrate, the mecha-

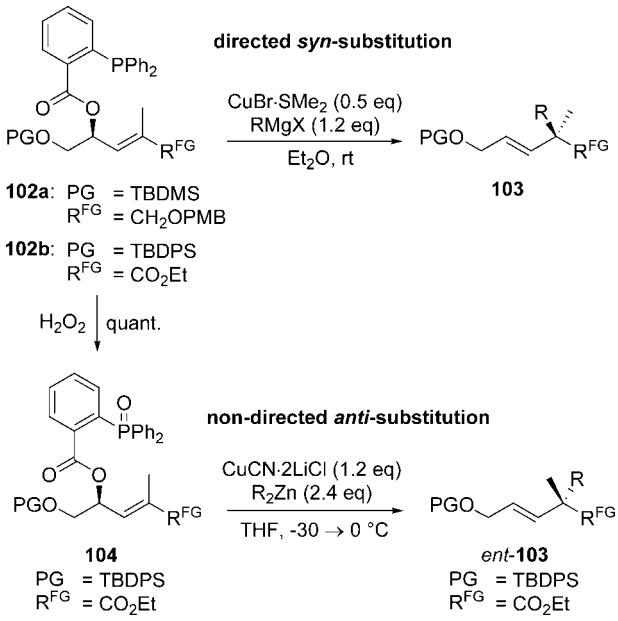
Table 12. Directed and Nondirected Allylic Substitution with Esters (*S*)-100a and (*S*)-100b



entry	substrate	R	S_N2':S_N2[a]	product	*ee* (%)	CT[b] (%)	yield (%)
1	(*S*)-**100a**	*n*Bu	98:2	(*S*)-**101a**	97	99	96
2	(*S*)-**100a**	3-Pent	97:3	(*S*)-**101b**	95	99	90
3	(*S*)-**100a**	*t*Bu	97:3	(*S*)-**101c**	80	82	96
4	(*S*)-**100a**	Ph	98:2	(*R*)-**101d**	94	97	94
5	(*S*)-**100a**	Bn	97:3	(*S*)-**101e**	93	96	97
7	(*S*)-**100b**	*n*Bu	94:6	(*R*)-**101a**	97	100	92
8	(*S*)-**100b**	*t*Bu	75:25	(*R*)-**101c**	74	76	68
9	(*S*)-**100b**	Ph	93:7	(*S*)-**101d**	94	97	86

[a] Determined by GC. The *E*:*Z* ratio was >99:1 in all cases as determined by GC. [b] CT, chirality transfer calculated on the basis of 99% *ee* and an *E*:*Z* ratio of 99:1 of the starting material [(*S*)-**100a** and (*S*)-**100b**] determined by HPLC.

Table 13. Directed and Nondirected Allylic Substitution with Functionalized Esters 102 and 104



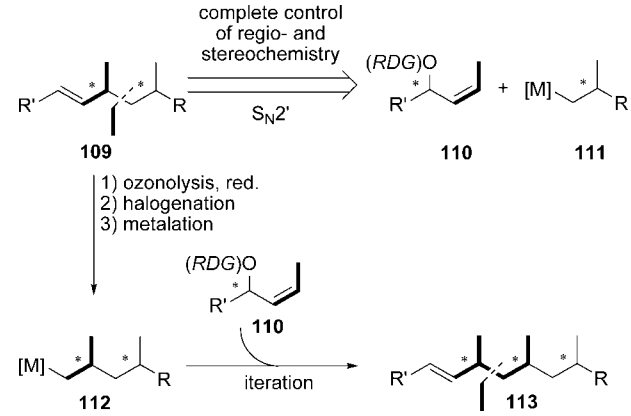
entry	substrate	R	S_N2':S_N2[a]	*E*:*Z*[a]	product	*ee* (%)	CT[b] (%)	yield[c] (%)
1	**102a**	Me	>95:5	>95:5	**103a**	—	—	72
2	**102a**	Et	>99:1	>99:1	**103b**	94	100	86
3	**102a**	*n*Bu	>99:1	>99:1	**103c**	93	100	99
4	**102a**	*i*Pr	>99:1	>99:1	**103d**	93	100	89
5	**102a**	Bn	>99:1	>99:1	**103e**	85	91	53
6	**102a**	*t*Bu	14:86	80:20	**103f**	*d*	*d*	90
7	**102b**	Et	>99:1	>99:1	**103g**	98	98	84
8	**102b**	*n*Bu	>99:1	>99:1	**103h**	97	98	87
9	**102b**	*i*Pr	>99:1	>99:1	**103i**	97	98	84
10	**104**	Et	>99:1	>99:1	*ent*-**103g**	99	100	85
11	**104**	*n*Bu	>98:2	>98:2	*ent*-**103h**	99	100	87
12	**104**	*i*Pr	97:3	>95:5	*ent*-**103i**	>99	100	94

[a] Determined by ^{1}H NMR or HPLC analysis. [b] The chirality transfer (CT) was calculated as [*ee*(**103**)/*ee*(**102** or **104**)] × 100. [c] Isolated yield after chromatographic purification. [d] Not determined.

nism of the allylic substitution has to be reversed from a directed *syn* substitution pathway to a nondirected *anti* attack of the nucleophile with respect to the leaving group. Quantitative oxidation of phosphinoester **98a** gives phosphanoxide ester **98b** in which the directing ability of the phosphorus is suppressed. Additionally, changing the *o*-phosphino group to a phosphanoxide increases the leaving group capability of the benzoate significantly. In summary, the chirality of the subjacent allylic alcohol is transferred to substitution product **99** and can be easily switched between *syn* and *anti* selectivity.

The liability of the method was examined using *o*-DPPB ester (*S*)-**100a** as substrate for allylic substitutions (Table 12). In directed substitution reactions with alkyl, aryl, and benzyl Grignard reagents, constantly high levels of regio- and stereoselectivity were observed (entries 1−5). Only in case of the sterically demanding *tert*-butyl reagent was the enantiomeric excess slightly decreased (entry 3). Substrate (*S*)-**100a** was then oxidized by hydrogen peroxide to the corresponding phosphanoxide (*S*)-**100b** and subjected to allylic substitution. In this case, the use of organozinc reagent in combination with copper cyanide proved to be favorable. The *anti* S_N2' reaction proceeded with alkyl- and arylzinc reagents with excellent chirality transfer, while with tBu_2Zn, a decrease in selectivity occurred.

Scheme 29



To explore the possibility for stereoselective construction of quaternary carbon centers, highly functionalized *o*-DPPB esters **102a** and **102b** were chosen (Table 13). These substrates are synthetically interesting for two reasons. First, they are readily available from the chiral pool (D-mannitol),[53] and second, the resulting allylic substitution products are equipped with the appropriate functionalities to allow a flexible incorporation of the quaternary stereocenter into a desired carbon skeleton. Thus, allylic substitution with substrate **102a** using Grignard reagents was investigated. The *syn* substitution products **103** were obtained with different carbon nucleophiles in excellent regio- and stereoselectivity (entries 1−5). In case of the large *tert*-butyl group, the competing S_N2 reaction became significantly favored for steric reasons (entry 6).

For enoate substrate **102b**, the problem of a thermodynamically unfavorable enoate deconjugation is combined with a chemoselectivity problem caused by the additional ethyl ester functionality (allylic substitution vs conjugate addition).[4,54,55] However, the directed allylic substitution occurred with complete chemo-, regio-, and stereoselectivity and with excellent chirality transfer to give substitution products **103g−i** (Table 13, entries 7−9). After oxidation, the corresponding phosphane oxide **104** was treated with a zinc/copper reagent to furnish the *anti* S_N2' products *ent*-**103g−i** in good yield with perfect regioselectivity and excellent 1,3-*anti* chirality transfer.

The on−off switch of the reagent-directing group was further explored with cyclic substrates **105** and **106** (Table 14). After *syn* substitution producing cyclohexenes **107** (entries 1−3) and **108** (entries 5−7), respectively, a constantly high chirality transfer was observed with alkyl Grignard reagents. Reaction of *o*-DPPB ester **105a** with PhMgBr exhibited low regioselectivity, while the *syn* selectivity was still high (entry 4). For the *anti* S_N2 reaction, the substrates were oxidized to phosphanoxide esters **105b** and **106b**. In all cases, excellent transfer of chirality was noted (entries 7−13).

3.4.4. Iterative Deoxypropionate Construction

The allylic substitution methodology with *o*-DPPB esters such as **110** was applied in an iterative fashion for the construction of the 1,3,*n*-methyl substitution pattern of deoxypropionates (Scheme 29).[56]

A directed S_N2' reaction of esters **110** with organometallic reagents is the key step of this sequence and gives access to alkenes **109**. Cleavage of the double bond through ozonolysis

Scheme 30

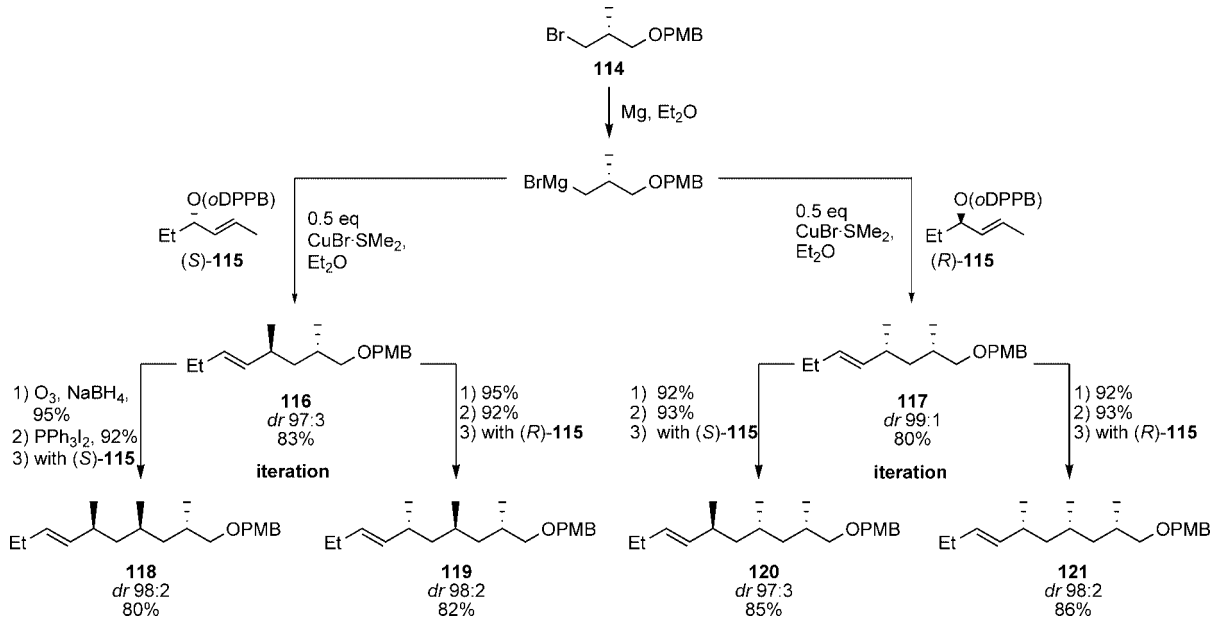
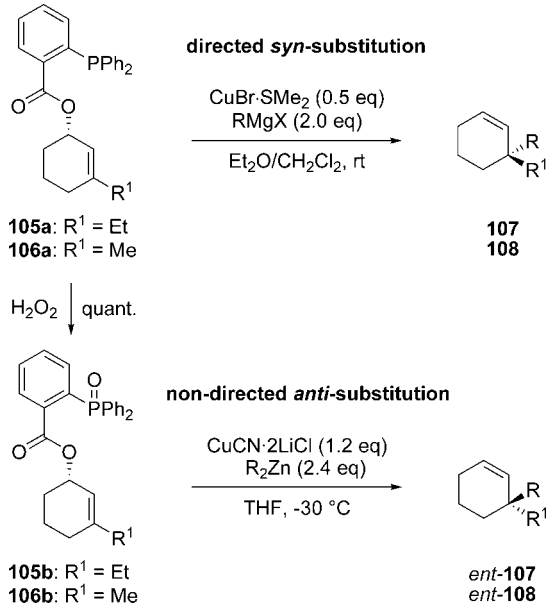


Table 14. Directed and Nondirected Allylic Substitution with Cyclic Esters 105 and 106



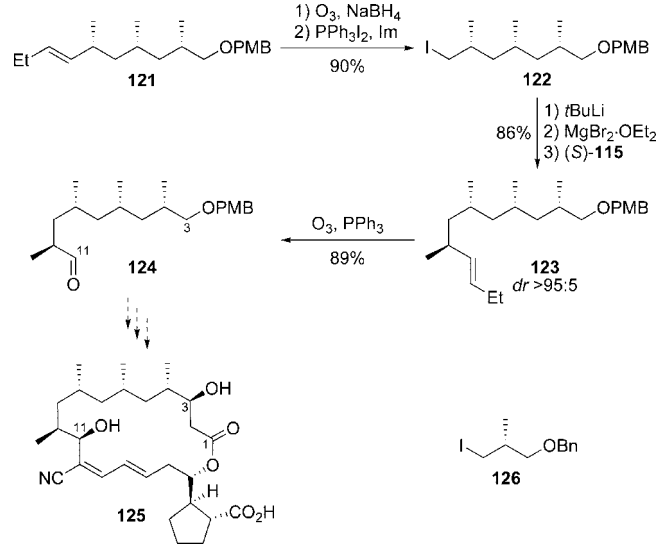
entry	substrate	R	$S_N2':S_N2$[a]	product	*ee* (%)	CT[b] (%)	yield[c] (%)
1	**105a**[d]	Me	99:1	(*S*)-**107a**	96	99	>95
2	**105a**	*n*Bu	>99:1	(*S*)-**107b**	96	99	>95
3	**105a**	*i*Pr	98:2	(*R*)-**107c**	96	99	>95
4	**105a**	Ph	40:60	(*R*)-**107d**	92	95	>95
5	**106a**[e]	Et	96:4	(*R*)-**107a**	91	97	>95
6	**106a**	*n*Bu	98:2	(*S*)-**108a**	94	100	>95
7	**106a**	*i*Pr	96:4	(*S*)-**108b**	91	97	>95
8	**105b**[d]	Me	99:1	(*R*)-**107a**	93	96	>95
9	**105b**	*n*Bu	>99:1	(*R*)-**107b**	96	99	>95
10	**105b**	*i*Pr	97:3	(*S*)-**107c**	94	97	>95
11	**106b**[e]	Et	>99:1	(*S*)-**107a**	93	99	>95
12	**106b**	*n*Bu	99:1	(*R*)-**108a**	94	100	>95
13	**106b**	*i*Pr	99:1	(*R*)-**108b**	93	99	>95

[a] Determined by ^{1}H NMR and GC analysis. [b] The chirality transfer (CT) was calculated as [*ee*(**107**)/*ee*(**105** or **106**)] × 100. [c] GC yield. [d] In 97% *ee*. [e] In 94% *ee*.

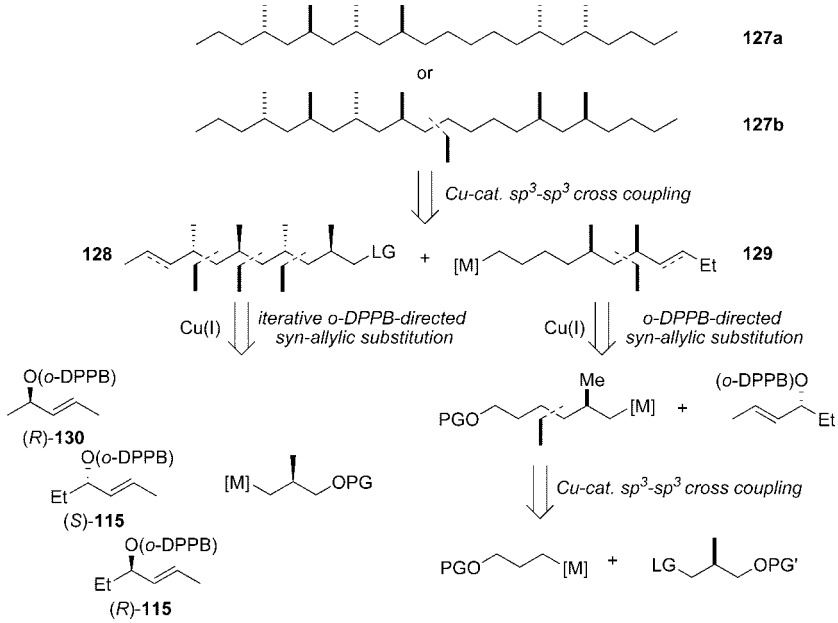
followed by a reductive workup gives the corresponding alcohol. Halogenation and consecutive metalation furnish a new organometallic nucleophile **112** which can be applied in a further directed allylic substitution. Already after two cycles, highly complex structures such as building block **113** are accessible, bearing inherent possibilities of functionalization either on the R group derived from the originally employed organometallic reagent **111** or on the side of the alkene terminus generated in the course of the allylic substitution.

To demonstrate the stereochemical diversity which can be achieved employing this methodology, all four possible diastereomers of a desoxypropionate stereotriad were prepared in enantiomerically pure form (Scheme 30). Starting from the bromide **114**, allylic substitution with enantiomerically pure *o*-DPPB esters (*S*)-**115** and (*R*)-**115** gave dideoxypropionates **116** and **117** in good yields and diastereoselectivities. Formation of the *syn* relative configuration appears to represent a matched case, while substitution reactions producing the *anti* configuration represent a mismatched case. Iteration of this sequence started with oxidative alkene cleavage of dideoxypropionate derivatives **116** and **117** through ozonolysis and reductive workup followed by

Scheme 31



Scheme 32



iodination under standard conditions. Transformation into the organometallic reagent was achieved in all cases by halogen−metal exchange with *tert*-butyllithium followed by transmetalation to magnesium. Directed allylic substitution with allyl electrophiles (*S*)-**115** and (*R*)-**115** in the presence of copper bromide dimethyl sulfide furnished all four possible trideoxypropionates in good yields, perfect regioselectivities, and excellent stereoselectivities as essentially single stereoisomers.

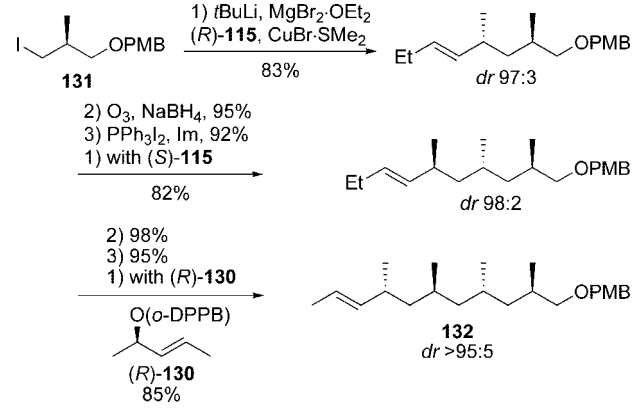
3.4.5. Natural Product Synthesis

The utility of this iterative method for deoxypropionate synthesis was demonstrated in natural product synthesis. A first target was aldehyde **124** which has been used as a building block for the total synthesis of Borrelidin by Theodorakis (Scheme 31).[57] This aldehyde has been prepared employing a conventional iterative enolate alkylation strategy developed by Myers et al.[58] in 13 steps starting from iodide **126** in 36% overall yield.

Synthesis of aldehyde **124** commenced from all-*syn*-trideoxypropionate **121** which was subjected to ozonolysis and reductive workup to give after Mukaiyama redox condensation iodide **122** in excellent yields.[56] Transformation of this iodide to the corresponding Grignard reagent and subjection to the conditions of the directed allylic substitution with (*S*)-**115** gave tetradeoxypropionate **123** in excellent yield and stereoselectivity. Ozonolysis followed by reductive workup with triphenylphosphine furnished known aldehyde **124**, thus representing a formal total synthesis of Borrelidin (**125**). This alternative synthesis required eight steps from bromide **114** in a global yield of 41% and thus compares favorably with the previous approach toward **124**.

The absolute and relative configuration of the hexamethyldocosane (**127**) isolated from the cuticula of the Australian sugar cane bug[59] was determined upon total synthesis of both diastereomers **127a** and **127b** in enantiomerically pure form with the result that **127b** is identical with the natural product in all physical properties measured (Scheme 32).[60] The synthesis features a copper-catalyzed sp^3-sp^3 cross coupling reaction as the fragment coupling step. Construction of the

Scheme 33



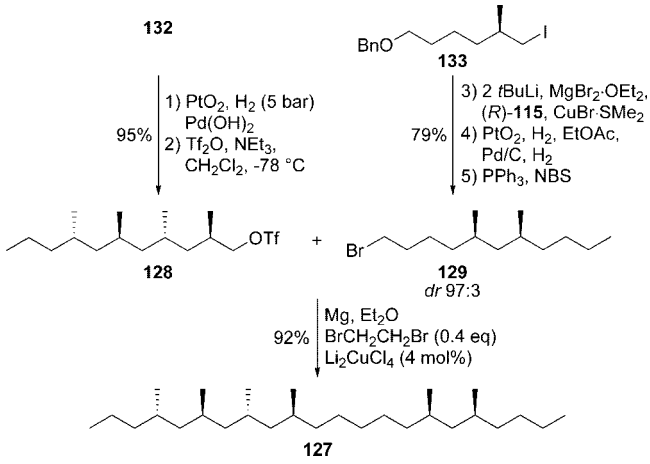
tetradeoxypropionate as well as the dideoxypropionate relies on the *o*-DPPB-directed allylic *syn* substitution for iterative deoxypropionate construction.

Synthesis of tetradeoxypropionate building block **128** is depicted in Scheme 33. Thus, starting from iodide **131**, which is derived from the commercially available Roche ester in three steps employing three iterations of directed allylic substitution, alkene-functionalized tetradeoxypropionate **132** was obtained.

Building block **128** synthesis was completed by simultaneous reduction of the alkene function to the alkane and PMB ether cleavage employing catalytic hydrogenation. The alcohol was activated as the triflate prior to the fragment coupling reaction (Scheme 34). The second building block, **129**, was assembled in three steps starting from iodide **133**. Allylic substitution to build the second stereocenter was followed by hydrogenation and the transformation of the alcohol into Grignard precursor **129**. The sp^3-sp^3 coupling of both molecule fragments was then accomplished using Kochi's catalyst Li_2CuCl_4 to give **127** in 92% *ee* and in an overall yield of 41% starting from iodide **131**.[61]

A total synthesis of α-tocopherol exemplified the efficiency of the *o*-DPPB ester as a multifunctional directing group.[62] In this synthesis, the copper-mediated allylic substitution was used as the fragment coupling step of two complex mol-

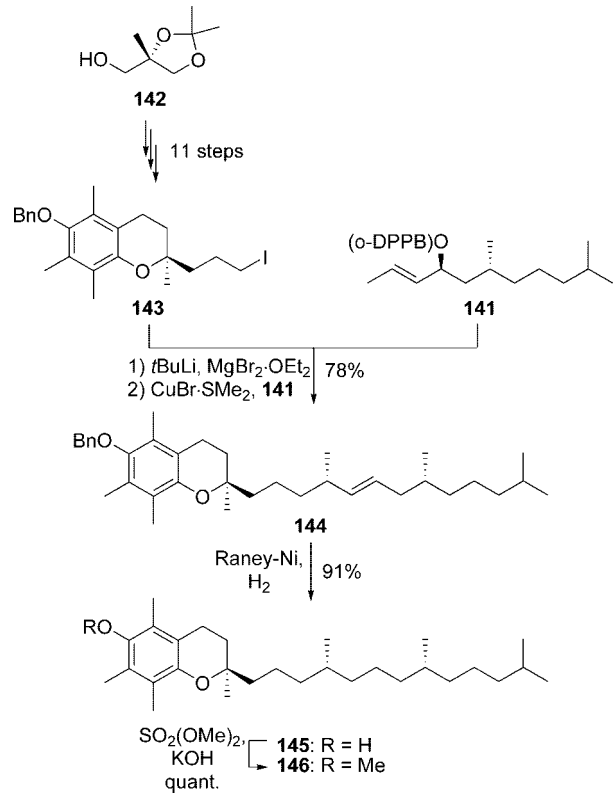
Scheme 34



ecules. Thus, synthesis of the C_{16}-isoprenoid side chain of tocopherol began with trapping of lithiopropyne with chlorodiphenylmethylsilane to give alkyne **134** (Scheme 35). Regioselective hydro-alumination with DIBAL-H followed by activation as the corresponding ate complex through reaction with methyllithium allowed for C_1-chain elongation with paraformaldehyde. Oxidation with the Dess-Martin reagent furnished aldehyde **135**. The first stereogenic center was introduced efficiently by applying asymmetric catalytic methallylation of aldehyde **135** with a silver/BINAP catalyst,[63] yielding homomethallylic alcohol **136** in 85% yield and >97% *ee*. Next, the reagent-directing *o*-DPPB group was installed to furnish substrate **137** for an *o*-DPPB-directed rhodium-catalyzed hydroformylation.[64] Thus, the corresponding *anti*-aldehyde, **138**, was obtained in good yield and high diastereoselectivity. Reduction of the aldehyde function led to alcohol **139**, and transformation into the corresponding iodide allowed installation of the remaining isobutyl side chain through a copper-catalyzed sp^3-sp^3 cross coupling reaction with isobutylmagnesium chloride.[63] Desilylation of the vinyl silane then generated fragment coupling precursor **140** in good yield.

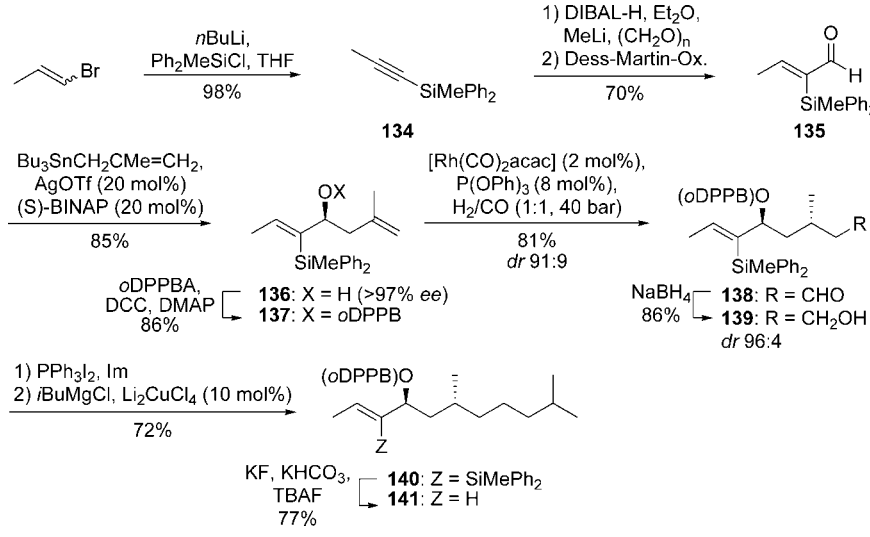
The final fragment coupling step was accomplished by an *o*-DPPB-directed allylic substitution. Since only stoichiometric amounts of organometallic reagent are required to achieve complete conversion, this reaction is suitable

Scheme 36



for the coupling of valuable metalorganic building blocks with allylic *o*-DPPB esters. As the metalorganic coupling partner of *o*-DPPB ester **141** served chromanyl iodide **143** (Scheme 36). This chromane system was prepared in 11 steps from C_4-building block **142**, whose quarternary stereogenic center originated from enzymatic hydrolysis.[65] Reaction with allylic electrophile **141** initiated a clean and highly selective directed allylic *syn* substitution to give coupling product **144** in 78% isolated yield. For the completion of synthesis, benzyl ether deprotection and alkene reduction were accomplished in one pot to give (*R*,*R*,*R*)-α-tocopherol (**146**) in 13 steps referring to the longest linear sequence and 30% overall yield.

Scheme 35



3.5. Chiral Reagent-Directing Groups

To achieve an enantioselective allylic substitution starting from a prochiral allylic substrate, one could make use of chiral leaving groups.

3.5.1. Chiral Acetals

The first report in this field by Alexakis and co-workers[66] reports on chiral acetals derived from α,β-unsaturated aldehydes and ketones and chiral C_2-symmetrical glycol derivatives. In the case of acyclic derivatives, good results (85−95% *ee*) were obtained with nondirecting acetal leaving groups. However, in the case of cyclic substrates such as ketal **147**, stereoselectivities were low (Scheme 37). Better results were obtained upon introduction of a bis-thioether-functionalized ketal leaving group to substrate **148**. It is proposed that the improved stereoselectivities result from a directing effect of the thioether function.

3.5.2. Chiral Carbamates

Denmark and co-workers have explored chiral carbamates as directing leaving groups for enantioselective allylic substitution.[67] Thus, a series of carbamates **149** derived from chiral amino alcohols has been prepared and investigated in the course of the directed allylic substitution (Table 15). The best results were obtained for R = 1-naphthyl, giving an excellent 1,7-chirality transfer of 98%. Additionally, it was found that a methoxy substituent is essential for asymmetric induction presumably due to additional chelation to the metal center.

3.5.3. Chiral Oxazolines

As a chiral variant of the benzothiazole directing leaving groups (section 3.2), chiral oxazolinyl leaving groups were examined in allylic substitution (Table 16).[68] To ensure high levels of S_N2' selectivity, a large excess of CuBr had to be employed. Furthermore, the reaction has to be performed in diethyl ether as the solvent, since in THF the competitive S_N2 pathway was preferred. Enantioselectivities depend on both the nature of the oxazoline substituents and the substrate structure. The best results were obtained with a geraniol-derived system. Notably, a quarternary carbon center was formed in 98% *ee* (entry 4).

Some control experiments with thiazolines and azolines indicated that the nitrogen atom of the oxazoline is the source of the directing effect, which is in charge of selectivity control (Table 17, entries 3 and 4). A transition state model has been proposed and is depicted in Scheme 38. The model can account for the formation of opposite stereoisomers as a function of alkene geometry (see entries 1 and 2).[69]

3.5.4. Chiral Esters

As a planar chiral analogue of the *o*-DPPB system (section 3.4), the *o*-diphenylphosphanylferrocene carboxylate (*o*-DPPF) group, **152**, has been developed as directing leaving group in allylic substitutions (Scheme 39). An efficient synthesis of both optical isomers of the corresponding carboxylic acid is available starting from ferrocene.[70] Attachment of this group to a prochiral allylic alcohol is readily achieved by standard esterification protocols.[71]

Optimization of reaction conditions for the allylic substitution with allylic *o*-DPPF esters led to a system using $CuBr \cdot SMe_2$ as the copper source and dichloromethane as the solvent at room temperature. In this way, allylic substitution with several aliphatic Grignard reagents was accomplished in good yields, with high regioselectivities and enantioselectivities of up to 95% *ee* (Table 18, entries 1−3). Unfortunately, in the case of aryl Grignard reagents regio- and enantioselectivities were lower. Interestingly, the chiral auxiliary is cleaved during the course of the reaction and can be recovered quantitatively during workup.

A rationale which may account for the observed stereochemistry is depicted in Figure 9. Thus, reactive conformation **153** in which the σ*-orbital of the leaving group is aligned to overlap efficiently with the alkene π-system is most reasonable. Minimization of $A^{1,3}$ strain and an internal delivery of the copper nucleophile through phosphane coordination (in accord with previous observations)[31,52] install the *S* absolute configuration in the substitution products (Table 18, entries 1−3).

Furthermore, cinnamyl-*o*-DPPF esters **154** were examined under similar reaction conditions (Table 19). Regio- and stereoselectivity were slightly lower compared to those of the cyclohexyl-substituted allylic system (compare Table 18), which can be anticipated due to deconjugation of the π-system in substitution products **155**. The enantioselectivity of the process was influenced neither by a donor nor by an acceptor substituent attached to the aromatic system.

Scheme 37

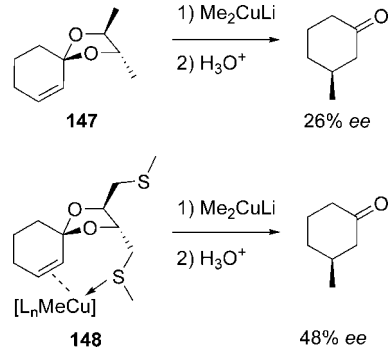


Table 15. Allylic Substitutions with Chiral Carbamate Leaving Groups

entry	R	yield (%)	*ee* (%)
1	*i*Pr	75	31
2	*t*Bu	52	32
3	$PhCH_2$	64	63
4	Ph	62	82
5	4-anisyl	57	82
6	1-naphthyl[a]	56	95

[a] Substrate with 97% *ee*.

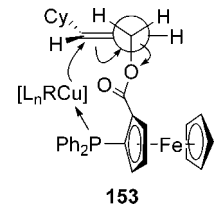
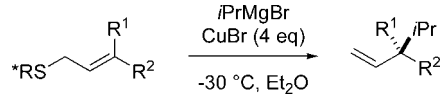


Figure 9. Reactive conformation in *o*-DPPF-directed allylic substitutions.

Table 16. Allylic Substitution with Chiral Oxazolinyl Leaving Groups



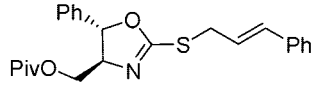
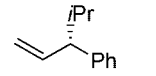
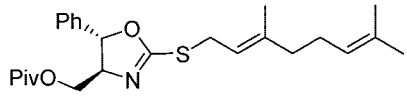
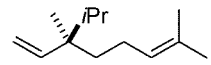
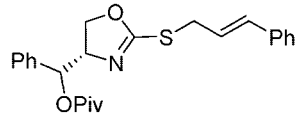
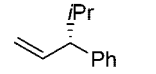
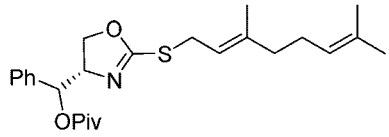
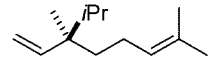
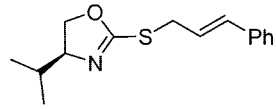
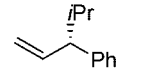
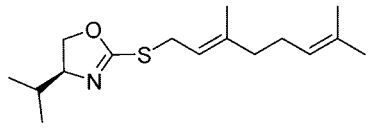
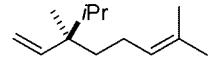
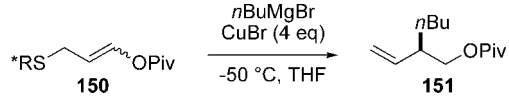
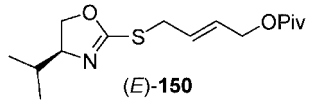
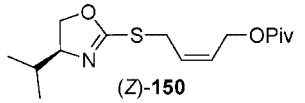
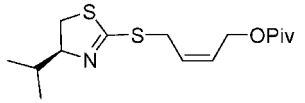
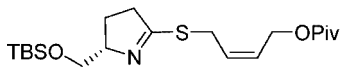
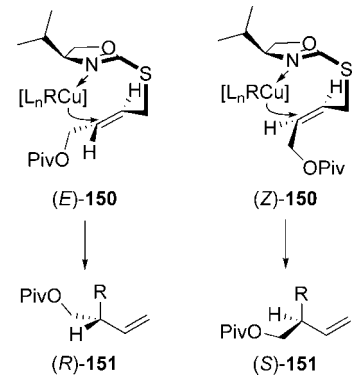
entry	substrate	product	*ee* [%]
1			58 (*S*)
2			73
3			78 (*R*)
4			98
5			50 (*S*)
6			83

Table 17. Stereoselectivity of Substitutions with Several Allylic Oxazolinyl Substrates

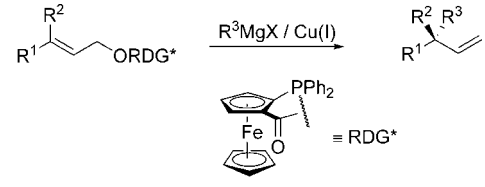


entry	substrate	product	yield [%]	*ee* [%]
1	 (*E*)-**150**	(*R*)-**151**	85	>98
2	 (*Z*)-**150**	(*S*)-**151**	90	>98
3		(*S*)-**151**	93	90
4		(*R*)-**151**	94	91

Scheme 38



Scheme 39



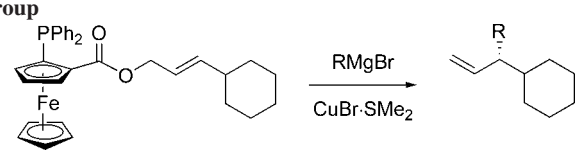
4. Carbometalation of Alkynes

4.1. Tethered Alkoxy and Sulfide Groups

Carbometalation of alkynes with organocopper reagents, derived from either Grignard reagents or organolithium species, is a powerful entry for the stereoselective construction of di- and trisubstituted alkenes.[72] A strong regiochemical preference of the carbocupration step for a Markovnikov-like addition is observed, and the so-called "branched" products, **156**, are formed in good yield and high selectivities (see, for example, entry 1 in Table 20). Conversely, introduction of reagent-directing groups into the alkynic substrate allows reversal of the regiochemistry, giving access to the so-called "linear" alkenic products, **157** (Scheme 40).

The best results were obtained employing a thioether-directing function attached with a three-carbon tether which allows the sample to pass a six-membered chelation inter-

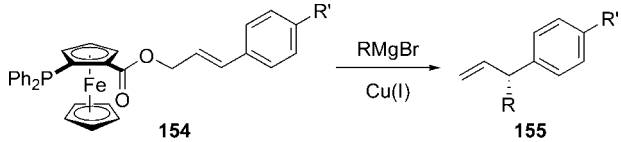
Table 18. Allylic Substitution with a Planar Chiral Leaving Group



entry	RMgX	$S_N2':S_N2$	*ee* (%)	yield (%)
1	MeMgI	93:7	82 (*S*)	56
2	*n*BuMgBr	97:3	95 (*S*)	77
3	*i*PrMgBr	98:2	81 (*S*)	82
4	PhMgBr	75:25	28 (*R*)[a]	not determined

[a] The opposite enantiomer of *o*DPPF ester was employed.

Table 19. Allylic Substitution with Cinnamyl Alcohol Derivatives



entry	R′	R	$S_N2':S_N2$	*ee* (%)	yield (%)
1	H	*n*Bu	87:13	78	86
2	H	Cy	98:2	71	>100
3	OMe	*n*Bu	84:16	65	60
4	Br	*n*Bu	94:6	68	37

Table 20. Carbometalation with Heteroatom-Substituted Alkynes

entry[a]	X	n	yield [%]	linear/branched ratio
1	H	2	90%	0:100
2	NEt_2	2	89%	40:60
3	SEt	2	75%	52:48
4		2	81%	55:45
5	SEt	3	78%	95:5
6	OMe	2	64%	19:81
7	OMe	1	65%	97:3
8[b]	OMe	1	42%	10:90

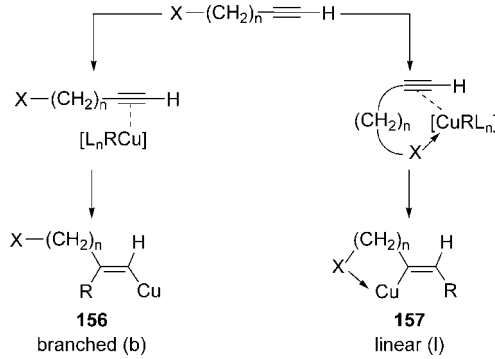
[a] $BuCu\cdot MgBr_2$ in ether. [b] $BuCu\cdot MgBr_2$ in THF.

mediate (entry 5). On the other hand, five-membered chelates seem to be less favorable (entries 2−4).[73]

Further evidence for a directed process came from studying carbocupration of *trans*- and *cis*-enynes **158a** and **158b** (Scheme 41). For geometrical reasons, only in the case of *cis* derivative **158b** is a thioether-directed process possible. Accordingly, linear carbocupration product **161** is formed via chelated intermediate **160** selectively. Conversely, *trans* derivative **158a** displayed the standard Markovnikov selectivity with formation of branched diene product **159**.

Besides thioethers even ether functions can serve as directing groups. However, a subtle influence of the solvent environment is observed. Thus, carbocupration of propargylic ethers in diethyl ether as a solvent (see entry 7 in Table 20) followed the directed reaction pathway and furnished the

Scheme 40



Scheme 41

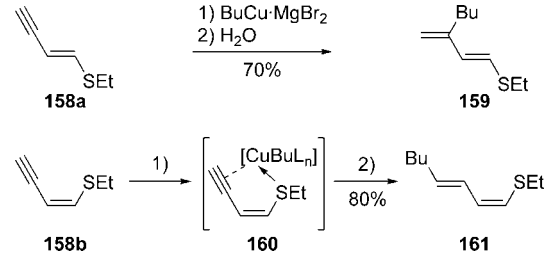
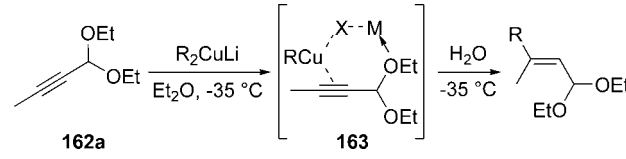
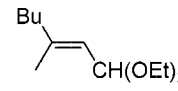
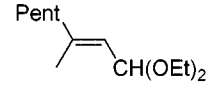
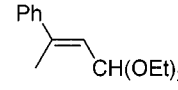
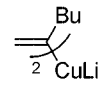
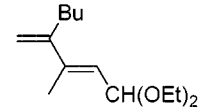
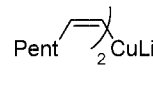
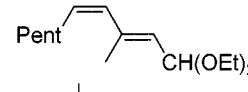
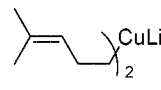
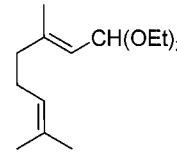


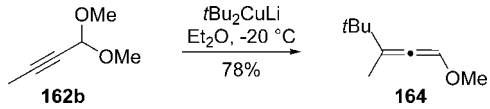
Table 21. Directed Carbocupration with Different Organocopper Reagents



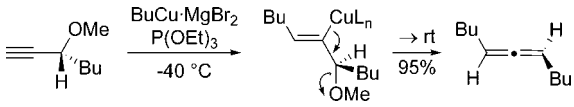
entry	R_2CuLi	product	yield [%]
1	Bu_2CuLi		94
2	$Pent_2CuLi$		91
3	Ph_2CuLi		65
4			80
5			76
6			92

linear regioisomer. However, employing the stronger coordinating THF as the solvent, regioselectivity was reversed (entry 8). Thus, THF competes successfully with the methoxy function of the substrate for the available coordination site(s) at the metal center and thus supresses the directed linear-selective reaction pathway. A bimetallic chelate intermediate (compare **163** in Table 21) has been suggested to account for the experimental observations.

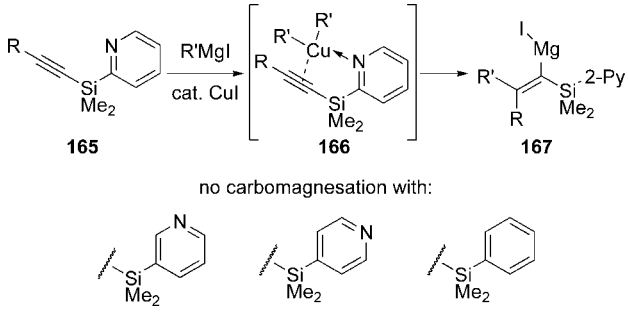
Scheme 42



Scheme 43



Scheme 44



Additions to methyl-substituted propargylic acetals displayed a remarkable substrate-directed regioselectivity (Table 21).[74] Acetal **162a** reacted smoothly with a variety of alkylorganocopper reagents (entries 1−3) but also gave a vinylic adduct and a sterically hindered *cis*-alkene in high yields (entries 4 and 5). The last example represents a rapid and effective synthesis of the natural product Geranial, which can be obtained from the acetal in entry 6 by deprotection in quantitative yield.

The primarily formed alkenic organocopper intermediates may undergo β-elimination at temperatures above −20 °C. If appropriate electrophiles are unavailable, these eliminations can be turned into a practical allene synthesis as depicted in Scheme 42. Thus, if one starts from achiral propargylic acetal **162b**, allene **164** is obtained in good yield as a racemate.[74]

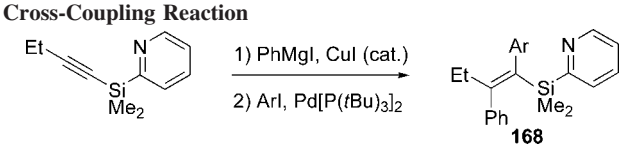
Employing enantiomerically enriched propargylic ethers, excellent central to axial chirality transfer was observed (96%, Scheme 43).[75] The stereochemical result is explained best as a consequence of a directed carbocupration followed by elimination through an antiperiplanar reactive conformation.[76]

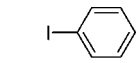
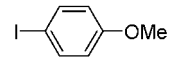
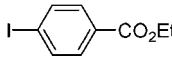
4.2. 2-Pyridylsilanes

The 2-pyridylsilyl group represents a versatile removable directing group for many metal-mediated and metal-catalyzed reactions.[77] Advantages of the 2-pyridylsilyl group are the excellent coordinating ability of the pyridine moiety and the stability of the carbon−silicon bond in association with a facile introduction and removal of the directing group.

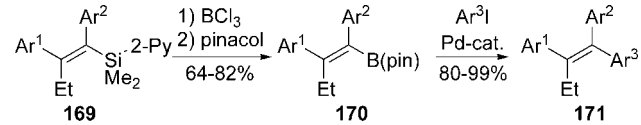
In the copper-catalyzed carbometalation, of alkynes with Grignard reagents, 2-pyridylsilyl-substituted substrates **165** yield cleanly the carbomagnesation products, **167** (Scheme 44).[78] As a rationale for the observed regioselectivity, chelate intermediate **166** has been proposed. Transmetalation from copper to magnesium then furnishes the corresponding Grignard reagents, **167**. To prove the involvement of the pyridyl coordination, 3- and 4-pyridylsilyl- and phenylsilyl-substituted substrates were prepared and subjected to similar reaction conditions. In all cases, carbomagnesation did not proceed at all, which proves that the directing group assistance is essential for both reactivity and regioselectivity.

Table 22. One-Pot Directed Carbometalation and Cross-Coupling Reaction



entry	ArI	yield [%]	*E*/*Z*
1		80	92:8
2		60	92:8
3		58	94:6

Scheme 45



Subsequent trapping of the carbomagnesation intermediates with various electrophiles allows for preparation of highly functionalized alkenes. The one-pot process of carbomagnesation and Pd-catalyzed cross-coupling reaction with aryl halides gives access to the silanes, **168** (Table 22). Reactions with both activated and deactivated aromatic halides were accomplished in good yields and excellent *E*:*Z* selectivity.

The utility of this reaction sequence was demonstrated upon synthesis of a series of tamoxifen-type, tetrasubstituted alkenes (Scheme 45). Conversion of 2-pyridylsilyl-substituted alkenes **169** to boranes **170** was achieved in a one-pot procedure in high yields. Subsequent Suzuki−Miyaura coupling with aryl iodides furnished the tetrasubstituted olefins, **171**.[79] Tamoxifen itself (Figure 10) was synthesized in this way together with an array of differently substituted olefins.[80,81]

5. Allylation of Carbonyl Compounds

Another variant of substrate activation through application of the 2-pyridylsilyl group is observed in the course of a copper-catalyzed carbonyl allylation employing 2-pyridyl-functionalized allylsilanes. In these reactions, pyridyl-directed transmetalation to give the corresponding copper-allyl intermediates has been proposed.[82] The assistance of the pyridyl substituent proved to be crucial for the reaction, since with the corresponding allyl-trimethoxysilane or -trimethylsilane no reaction occurred. Furthermore, reaction of

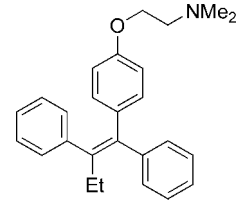


Figure 10. Anti-breast cancer drug tamoxifen.

Scheme 46

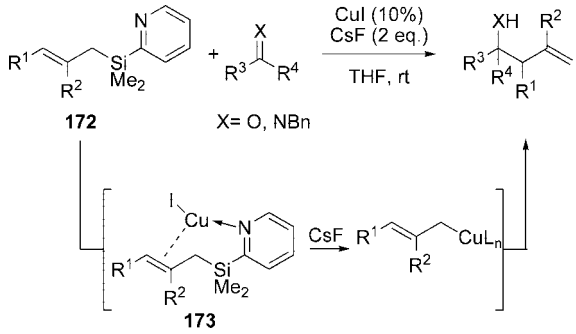
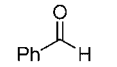
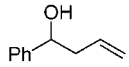
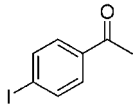
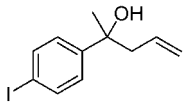
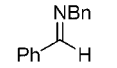
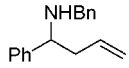
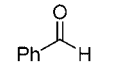
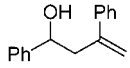
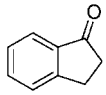
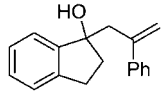
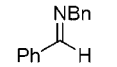
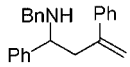
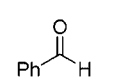
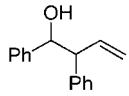
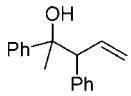
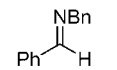
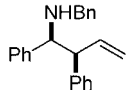


Table 23. Copper-Catalyzed Allylation of Carbonyl Compounds

entry	R^1,R^2	carbonyl-compound	product	yield [%]
1	H,H			86
2	H,H			95
3	H,H			76
4	H,Ph			99
5	H,Ph			93
6	H,Ph			93
7	Ph,H			77 *syn*/*anti* 48:52
8	Ph,H			46 *syn*/*anti* 34:66
9	Ph,H			77 *syn*/*anti* >99:1

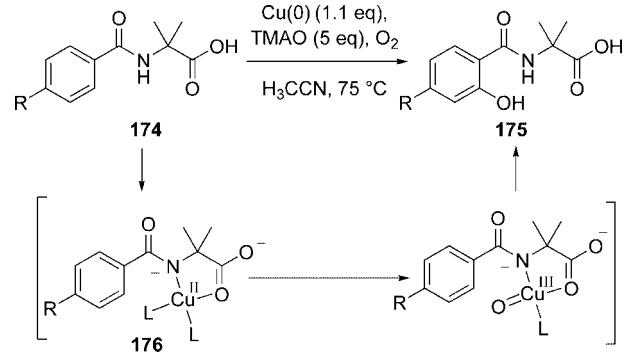
allylpyridylsilane **172** with a quantitative amount of copper salt led to formation of chelation complex **173** which could be analyzed crystallographically (Scheme 46). When this complex was mixed with carbonyl compounds, no reaction occurred until CsF was added, activating the silicon for the necessary Si-to-Cu transmetalation.

The reaction scope includes aryl aldehydes and ketones as well as imines. The corresponding homoallylic alcohols and amines were obtained in good to excellent yields (Table 23, entries 1−6). Also, γ-substituted allyl 2-pyridylsilanes reacted with a carbonyl compound highly regioselective at the γ-position of the allylsilane (entries 7−9). Excellent diastereoselectivity in favor of the *syn* product was observed for addition to an imine. Conversely, diastereoselectivity upon addition to aldehydes and ketones was low.

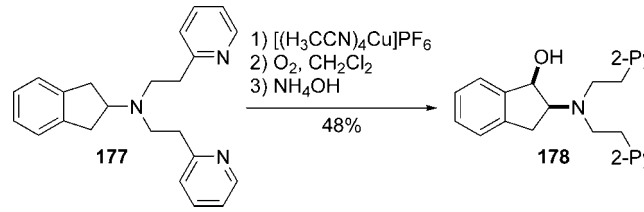
6. Oxidation of Nonactivated C−H Bonds

The activation of C−H bonds in organic reactions is one of the most promising and intriguing topics in actual organic chemistry research. It promises to solve many problems, especially concerning the demands of green chemistry, providing reactions with minimized waste production. Additionally, it supersedes the synthesis of adequate coupling partners like halides, which are often accomplished using hazardous reagents.[83]

Scheme 47



Scheme 48



6.1. Directed *Ortho* Hydroxylation of Aromatic Carboxylic Acids

A synthetically useful approach to salicylic acids was introduced by Reinaud et al.[84] Oxidation of benzoic acid derivatives in classical syntheses often requires harsh reaction conditions associated with low yields. However, transformation of the carboxylic acid function into the amide with 2-methylalanine furnished substrate **174** that could be readily oxidized upon reaction with 1.1 equiv of copper(0) and excess trimethylamine *N*-oxide (TMAO) under an oxygen atmosphere to hydroxylation product **175** (Scheme 47).

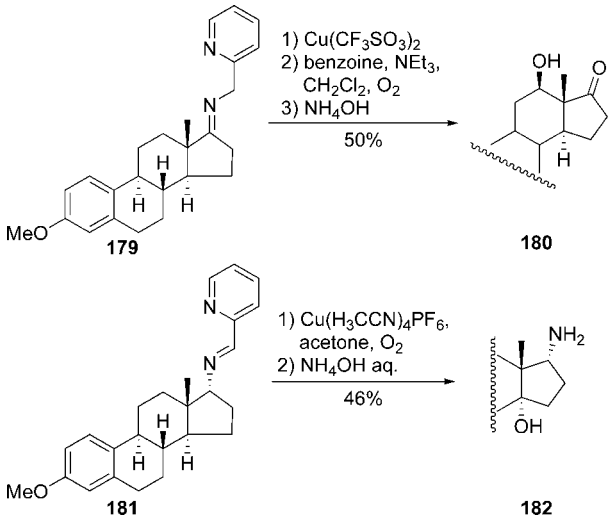
The mechanism proposed for this reaction includes the formation of copper complex **176**, which places the copper in proper distance for intramolecular and completely *ortho*-selective hydroxylation. Regardless of the electronic properties of the aryl substituents in the para position, generally high yields of salicylic acid derivatives **175** were obtained (Table 24).

6.2. Directed Hydroxylation of Steroid Derivatives

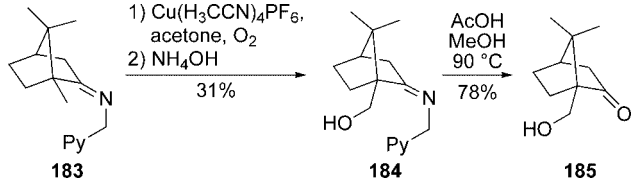
Direct reactions of nonactivated sp^3 C−H bonds are even more challenging. In substrate **177**, the benzylic C−H bonds are of course electronically activated (Scheme 48). Nevertheless, direct hydroxylation requires the presence of an appropriately positioned pyridyl-directing group. As a result of the directed process, the *syn* product **178** was formed stereoselectively.[85]

Directed copper-mediated oxidative C−H bond activation has been applied to position-selective and stereoselective steroid hydroxylation.[86] As a removable directing group, an imino-pyridyl system (IMPY) in **179** and alternatively the related amino-pyridyl system (AMPY) in **181** were installed

Scheme 49



Scheme 50



in the D ring of a steroid skeleton (Scheme 49). With the IMPY system, the highly regio- and diastereoselective hydroxylation of the 12β position of the steroid core was achieved using 1.2 equiv of copper(II) triflate (reduced in situ with benzoine/triethylamine) and molecular oxygen. After workup with aqueous ammonia to cleave the directing group, hydroxylated product **180** was obtained in 50% yield. Conversely, employing the AMPY directing group under the same reaction conditions, 14α-hydroxylation was detected. If one starts from steroid derivative **181**, *syn* hydroxylation product **182** was obtained with again complete regio- and stereocontrol in 45% yield.

The IMPY reagent-directing group was also successfully applied in the hydroxylation of camphor (Scheme 50). Camphor derivative **183** was regioselectively hydroxylated in the β-position, furnishing imine **184** in 31% yield. Cleavage of the directing group through hydrolysis furnished β-hydroxycamphor **185**. The reaction mechanism is proposed to involve a binuclear copper complex as shown in Figure 11. With the simple indanyl substrate, **177** (Scheme 48), the crystal structure of a similar complex was identified.[85]

Hence, with the aid of the reagent-directing imino- and aminopyridyl-directing groups, regio- and stereoselective C−H bond activation becomes possible. However, thus far,

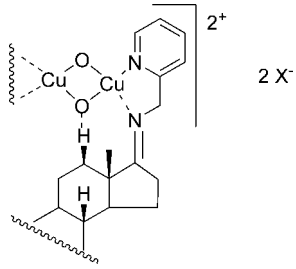


Figure 11. Bimetallic dioxygen complex in hydroxylation of steroids.

Table 24. Directed *Ortho* Hydroxylation to Salicylic Amides

entry	R	product	yield (%)
1	H	**175a**	79
2	Me	**175b**	95
3	NO_2	**175c**	88
4	Cl	**175d**	87

the method is restricted to conformationally locked rigid carbon backbones. Nevertheless, with this approach it is possible to imitate the function of natural β-monooxygenases, which selectively hydroxylate organic substrates.[87] In nature, it is the enzyme which orients the substrate and the copper/dioxygen system in the active site to allow C−H bond activation.[88] Here, the role of the enzyme is taken over by the directing group system, which temporarily connects the reaction partners in a covalent fashion. The result is an intramolecular process passing a highly ordered bicyclic transition state which ensures a high level of regio- and stereoselectivity.

7. Conclusions

The selectivity of reactions involving organocopper reagents can be controlled efficiently upon use of attractive substrate−reagent interactions. These substrate-directable reactions offer in many cases complementary regio- and stereoselectivity compared with their nondirected counterparts, in which steric and electronic substrate factors dominate. On the other hand, the intramolecular nature of the selectivity-determining step of the directed reaction pathway and the associated fixed trajectory of the copper reagent dictates the overall outcome of the reaction.

Temporarily installed removable directing groups with soft-donor functions capable of coordination to a copper(I) center have proven to be of particular use. Especially, the use of reagent-directing leaving groups such as the *o*-diphenylphosphanyl benzoate group (*o*-DPPB) in allylic substitution reactions has turned this once capricious transformation into a reliable synthetic method with perfect control over all aspects of reaction selectivity, including a perfect 1,3-chirality transfer. Application in deoxypropionate construction and in total synthesis as a fragment coupling step underlines its synthetic utility.

Hence, if a reliable and predictable transformation of an organocopper reagent is in demand, substrate direction involving reagent-directing groups might be a good first choice for the practitioner in organic synthesis.

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