Directed Reactions

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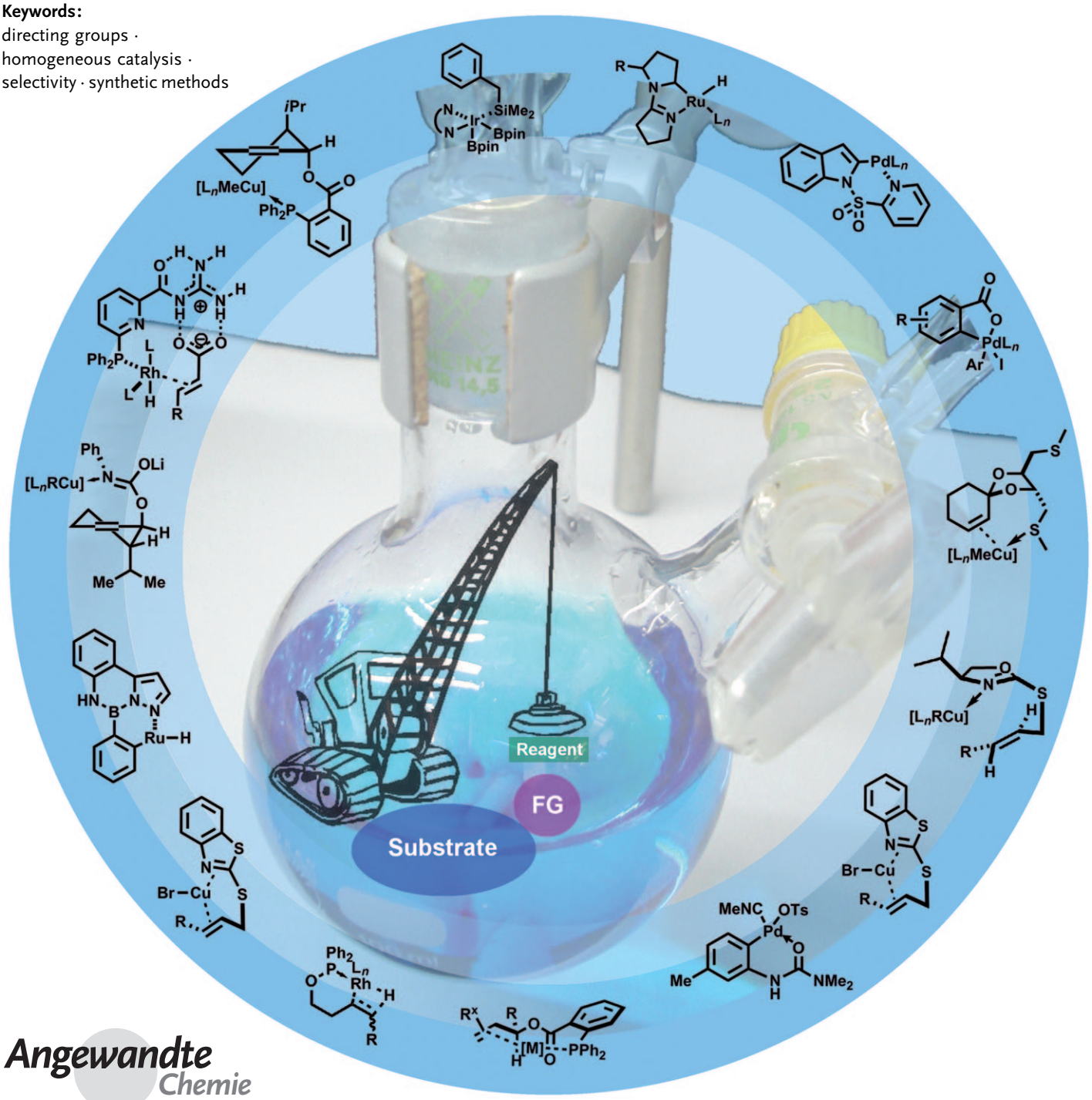
Removable Directing Groups in Organic Synthesis and Catalysis

*Géraldine Rousseau and Bernhard Breit**

Keywords:
directing groups · homogeneous catalysis · selectivity · synthetic methods



Directing groups have been widely used in recent years to achieve control over all aspects of reaction selectivity in a wide range of transformations involving transition-metal catalysis and organometallic reagents. In cases when the existing functional group within a substrate is unsuited to achieve efficient intramolecular delivery of a reagent or catalyst, the specific introduction of an appropriately designed removable reagent-directing group can be a solution to this problem. In this Review we give an overview of the state of the art in this area, including the stoichiometric and catalytic use of directing groups.

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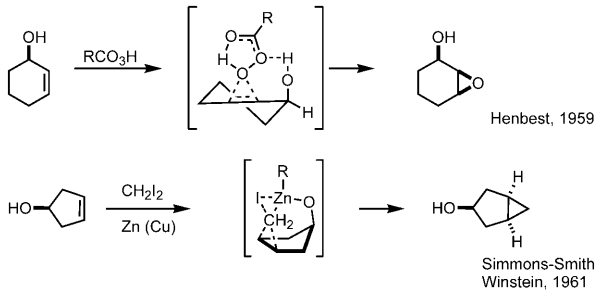
1. Introduction

Control of all aspects of reaction selectivity still stands as one of the major challenges in both organic synthesis and homogeneous catalysis. Selectivity control originating from the reagent or catalyst is usually referred to as reagent or catalyst control of selectivity. Alternatively, one may use inherent structural information to control the trajectory of the incoming reagent; this has been designated as substrate control of selectivity. In cases where repulsive substrate–reagent interactions dominate (steric effects), which may be modulated by stereoelectronic effects, it is generally termed as passive substrate control. Conversely, attractive substrate–reagent interactions may be used to control the reagent trajectory, which is termed active substrate control of selectivity or, more frequently, a substrate-directed reaction. To generate attractive reagent–substrate interactions one has to rely on polar functional groups in the substrate in the vicinity of the reaction center which undergo either hydrogen bonding, covalent interactions, or Lewis acid–base interactions with the corresponding reagent. This enforces a preassociation of the reaction partners, which is maintained in the corresponding transition state of the selectivity-determining reaction step. As a consequence, this transition state is cyclic or polycyclic and, therefore, if properly designed, highly ordered, and allows for an efficient energetic discrimination of competing reaction pathways. In this case the rate- and selectivity-determining step becomes intramolecular in nature, thus leading to a significant rate acceleration that results primarily from a reduction of the activation entropy.

This effect of rate acceleration and selectivity control through intramolecularity is a general phenomenon known from enzyme catalysis.[1] The term effective molarity (EM) has been defined ($EM = k_{intra}/k_{inter}$) to describe and quantify this phenomenon.[2] The EM has the dimensions of concentration. Thus, an EM corresponds to a theoretical concentration of a reagent that would be required to render the bimolecular reaction as fast as the intramolecular process. In enzyme catalysis, EM values between 10^5 to 10^8 M are frequently observed, but values up to 10^{13} have been reached in extreme cases. The rate accelerations seen in substrate-directed reactions have only occasionally been quantified, but are typically lower than in enzyme catalysis. However, rate enhancement is indeed a typical feature of a substrate-directed reaction compared to the nondirected process. Alternative terms which are in use to describe the same phenomenon are the complex-induced proximity effect (CIPE), which is mainly in use in the field of directed deprotonation reactions,[3] as well as the term chelation control of selectivity.[4]

Two classical examples of such reactions are the hydroxy-directed epoxidation with peracids and the alkoxy-directed Simmons–Smith cyclopropanation (Scheme 1).[5] In 1959 Henbest and Wilson reported on the reaction of 2-cyclohexenol with a peracid which led to the formation of the *cis*-epoxide preferentially going through a highly ordered polycyclic transition state with an additional hydrogen-bonding interaction. Two years later Winstein and Sonnenberg described an alkoxide-directed Simmons–Smith cyclopropanation of 3-cyclopenten-1-ol to form the *cis* product as a single stereoisomer. Winstein had already noted that precoordination of the zinc reagent through formation of a zinc–alkoxide

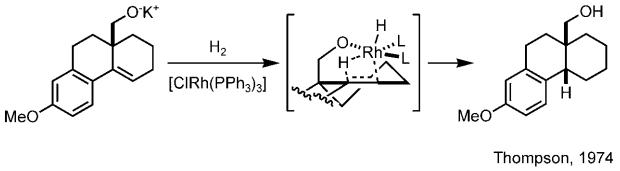


Scheme 1. Substrate-directed reactions.

[*] Dr. G. Rousseau, Prof. Dr. B. Breit
Institut für Organische Chemie und Biochemie
Freiburg Institute for Advanced Studies (FRIAS)
Albert-Ludwigs-Universität Freiburg
Albertstrasse 21, 79104 Freiburg i. Brsg. (Germany)
Fax: (+49) 761-203-8715
E-mail: bernhard.breit@chemie.uni-freiburg.de

bond results in an overall rate enhancement, since the corresponding cyclopentenyl acetate reacted significantly slower (3% conversion).[6]

The first substrate-directed catalytic reaction dates back to a report from Thompson and McPherson on an alkoxide-directed rhodium-catalyzed hydrogenation (Scheme 2).[7]



Scheme 2. Substrate-directed catalytic hydrogenation.

Here, a new property of a successful catalyst-directing group was required—a reversible catalyst binding—which avoids product inhibition and enables turnover and catalysis.

Subsequent to these initial reports, a large number of directed reactions have been discovered and developed which today occupy a prominent position in organic synthesis as a result of their ability to install new functionality as well as stereochemistry in a predictable and reliable fashion, while avoiding expensive chiral reagents and catalysts. These reactions, which rely on the directing effects of classical functional groups in organic molecules, have been summarized in a review by Evans, Hoveyda, and Fu in 1993.[8]

Of course, selectivity control through substrate control also suffers from limitations. A major one occurs when the existing functional groups within a given substrate are either not in the appropriate position to allow for an energetically favorable reaction pathway and/or the nature of the functional groups present is not suited to generate efficient attractive interactions with the reagent or catalyst. This is particularly valid for late-transition-metal catalysts and organometallic reagents, which do not interact efficiently with typical oxygen-containing functional groups such as hydroxy and carboxylic acid groups. In such cases this intrinsic limitation can be overcome by specifically installing a reagent- or catalyst-directing group (RDG/CDG) into the substrate, by either modification of the original functionality or by de novo installation.

Such a group would have to precoordinate to the desired reagent and enable an intramolecular delivery of the reagent (Figure 1). In the case when the reagent is a catalyst,

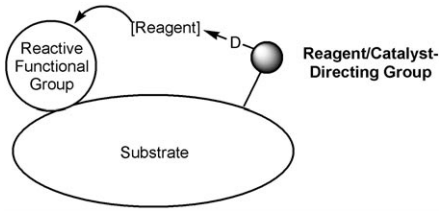


Figure 1. Concept of a reagent- or catalyst-directing group.

reversibility of the catalyst coordination has to be ensured to allow for turnover. Important criteria for the efficency of such reagent-/catalyst-directing groups are:

- Ease of installation of the directing group
- Efficient control over the reactivity/selectivity
- Ease of removal from the substrate.

A number of removable reagent-/catalyst-directing groups have been developed in recent years for a wide range of reactions, including C–H and C–C bond activations, hydro- and carbometalations, as well as transition-metal-catalyzed reactions, nucleophilic additions, and substitutions with organometallic reagents. This Review summarizes these achievements, but will exclude all directed reactions which employ nonremovable directing groups (at least not in a synthetically easy manner) or which rely on standard functional groups. Reactions involving directed metalations have been reviewed previously and have not been included either.[3,9]

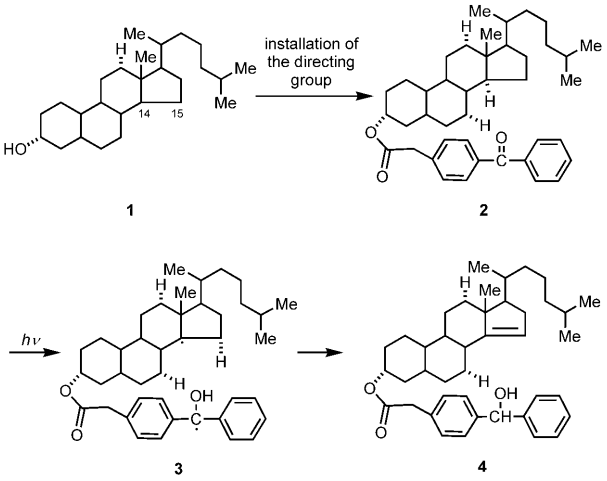
Directing groups have to be installed and removed from the substrate, which requires two additional nonproductive synthetic steps. However, in some cases, the directing group can also be a leaving group and, thus, only the installation step is required. These examples will be discussed in Section 3. Other approaches to overcome this limitation have been developed and are discussed in Sections 4 and 5. Among them

Géraldine Rousseau studied chemistry at the University of Bordeaux, France. She completed her PhD under the supervision of Professor Yannick Landais in 2008, working on the desymmetrization of cyclohexadienes. She is currently a postdoctoral researcher in the group of Professor Bernhard Breit at the Albert-Ludwigs-Universität Freiburg, Germany. Her research focuses on the design of new cooperative catalysts that act through supramolecular interactions.

Bernhard Breit studied chemistry at the University of Kaiserslautern, Germany, where he obtained his PhD in 1993 with Professor Regitz. After postdoctoral research with Professor Trost at Stanford University, he completed his habilitation in 1998 in Marburg with Professor R. W. Hoffmann. In 1999 he was appointed as an Associate Professor at the University of Heidelberg. Since 2001 he has been a Full Professor of Organic Chemistry at the Albert-Ludwigs-Universität Freiburg. His current research interests include the development of new concepts and methods for organic synthesis, including organometallic reagents and homogeneous catalysis.

is the multiple use of one directing group for a sequence of directed reactions, followed by the traceless removal and recovery of the directing group. Furthermore, supramolecular directing groups as well as first reports on covalent but reversibly bound directing groups are included, which allow for the use of catalytic amounts of the directing group.

A stimulating early contribution to this topic was Breslow's position-selective CH abstraction in a steroidal skeleton (Scheme 3).[11] A benzophenone chromophore was tethered through an ester linkage to the hydroxy function of



Scheme 3. Position-selective CH activation in a steroid skeleton: an early example of the use of a removable reagent-directing group.

3α-cholestanol (**1**). Photolysis led to excitation of the carbonyl chromophore to the T^1 state, which was followed by a position-selective hydrogen atom abstraction from C14 with subsequent formation of the C14–C15 double bond in 65% yield. Hence, covalent anchoring of the benzophenone chromophore controlled the trajectory by which the steroid core was attacked and made the position-selective C–H activation possible. Thus, the benzophenone system may be regarded as a removable reagent-directing group, with light taking the role of the reagent.

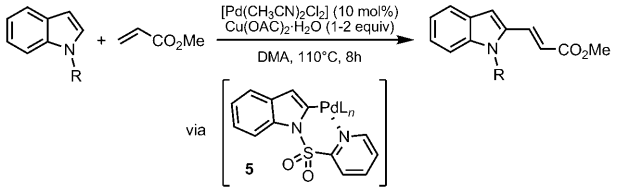
2. Stoichiometric Use of Removable Directing Groups

2.1. Directed Activation of Unreactive Bonds

2.1.1. C–H Bond Activation

The (2-pyridyl)sulfonyl group has been used as a protecting and directing group by Carretero and co-workers to achieve an efficient and general palladium-catalyzed C2-alkenylation of indoles and pyrroles.[10] The role of the (2-pyridyl)sulfonyl group has been explored by changing the nature of the N-indole substituent. Thus, alkenylation occurred regioselectively in 75% yield at position 3 in the case of the unsubstituted indole (Table 1, entry 1). The Boc derivative led to a 68:32 mixture of C2/C3 alkenylation

Table 1: Effect of N-substitution in the C2-alkenylation of indole with methyl acrylate.[a]



Entry	R	C2/C3	Yield [%][b]
1	H	<2:98	75 (66)
2	Boc	68:32	10
3	Ts	87:13	45 (30)
4	(2-pyridyl)SO_2	>98:2	100 (75)
5	(3-pyridyl)SO_2	76:24	27

[a] DMA = *N*,*N*-dimethylacetamide, Boc = *tert*-butyloxycarbonyl, Ts = *p*-toluenesulfonyl. [b] Conversion (yield of isolated products).

products with low conversion (Table 1, entry 2). Switching from Boc to a tosyl group enhanced both the yield and the regiocontrol, although still at a suboptimal level. Pleasingly, the *N*-(2-pyridyl)sulfonyl group provided complete conversion and regioselectivity for the C2 regioisomer (Table 1, entry 4). The low conversion and regiocontrol observed for the *N*-(3-*p*yridyl)sulfonyl group (Table 1, entry 5) indicates that the high selectivities observed for the *N*-(2-*p*yridyl)sulfonyl group are unlikely to originate from electronic effects. The key role of the *N*-(2-*p*yridyl)sulfonyl group is likely to induce CH activation through formation of the palladacycle **5** and, thus, act as a directing group in the course of this reaction.

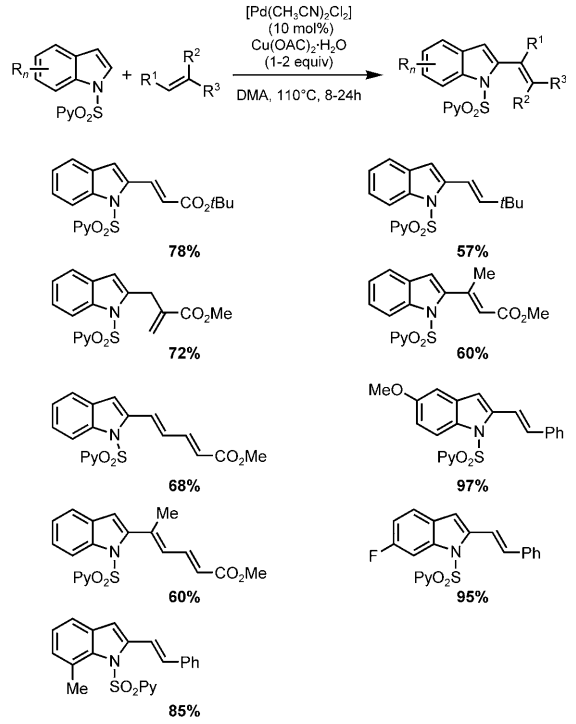
Electron-poor and non-activated alkenes could also be used, with the participation of 1,2-disubstituted alkenes being particularly noteworthy (Scheme 4). Electron-withdrawing or -donating substituents are tolerated at the C5-, C6-, and C7-positions of the indole core.

This method was also applicable to the functionalization of pyrroles. Monosubstituted, disubstituted, as well as unsymmetrical 2,5-disubstituted pyrroles could be obtained by small variations in the reaction conditions (temperature and reaction time, Scheme 5)

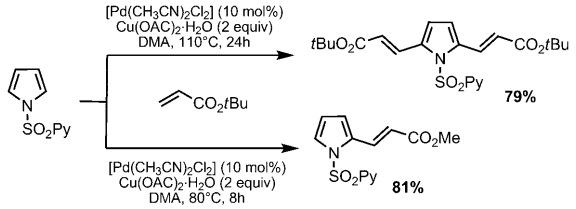
Removal of the *N*-(2-*p*yridyl)sulfonyl group from indoles and pyrroles was readily achieved by reductive cleavage with Zn or Mg to give 2-alkenyl- or alkyl-substituted indoles and pyrroles, respectively (Scheme 6).

A carboxylic acid functionality was shown to act as an in situ traceless removable directing group for a C2-selective alkenylation of indoles with acrylic esters.[11] The reaction presumably proceeds through the palladacycle **6**, which is responsible for the regiochemical control (Scheme 7).

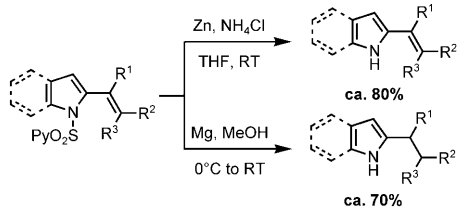
The method could also be applied to 2-carboxylic acid functionalized heterocycles. In this case, highly regioselective alkenylation with acrylic esters occurred in the 3-position. While perfect regioselectivities were found with the corresponding indole, pyrrole, and benzofuran system, the selectivity was lower for benzothiophene, furan, and thiophene derivatives (Table 2).



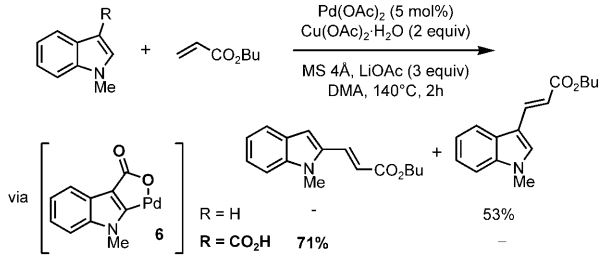
Scheme 4. Scope of indole alkenylation.



Scheme 5. Regioselective C2- and C2/C5-alkenylation of pyrrole.

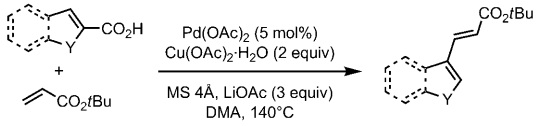


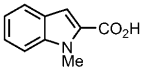
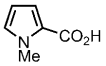
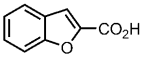
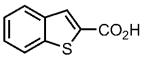
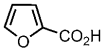
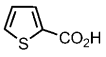
Scheme 6. Removal of the directing (2-pyridyl)sulfonyl group.



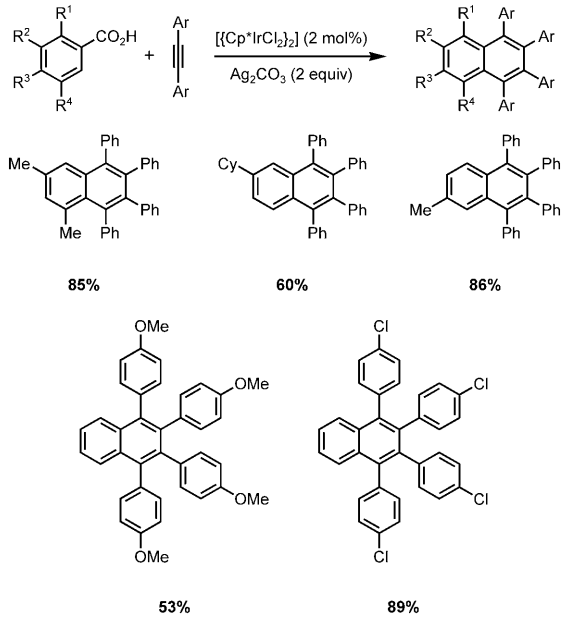
Scheme 7. Effect of the presence of the carboxylic acid on the regioselectivity of the vinylation.

Table 2: Reaction of heteroarene carboxylic acids with butyl acrylate.



Entry	Substrate	*t* [h]	Yield [%]	C3/C2
1		1	85	100:0
2		1	74	100:0
3		4	51	>95:5
4		4	48	7:1
5		5	39	≈1:1
6		8	65	5:1

Interestingly, 1,3-diaryl-functionalized alkynes could also be coupled to benzoic acid derivatives by a decarboxylative CH activation to furnish highly substituted naphthalenes in the presence of an iridium catalyst (Scheme 8).[12]

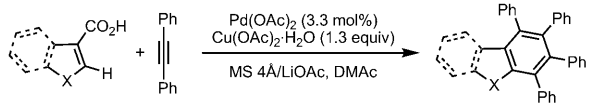


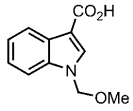
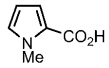
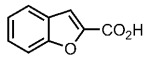
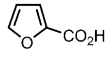
Scheme 8. Reaction of benzoic acids with diaryl acetylenes by dehydrogenation and decarboxylation. Cp* = C_5Me_5.

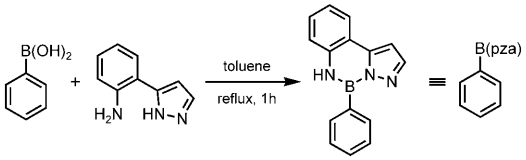
By employing a palladium(II) catalyst the same reaction could be applied to various heteroarene carboxylic acids to furnish the corresponding annulated products in moderate to good yields (Table 3).[13]

2-Pyrazol-5-yl-aniline ($pzaH_2$) has been used as an easily attachable and detachable directing group for the *ortho* C–H functionalization of organoboronic acids (Scheme 9).[14]

Table 3: Reaction of heteroarene carboxylic acids with diphenylacetylene.



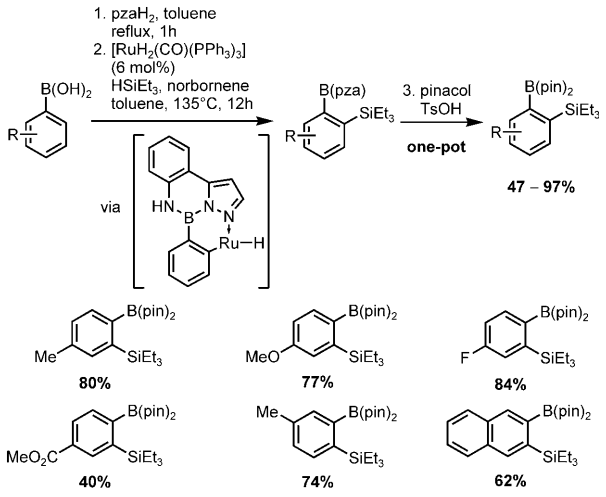
Entry	Substrate	Atmosphere	*t* [h]	Yield [%]
1		N_2	8	72
2		N_2	10	61
3		air	10	70
4		air	6	44



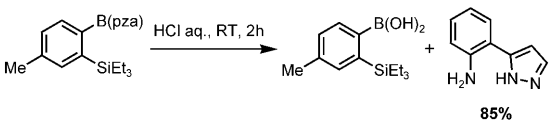
Scheme 9. Introduction of the directing pza group.

Ruthenium-catalyzed *ortho*-silylation was carried out with triethylsilane in very good yields and complete regiocontrol. The *ortho*-directing agent is introduced by condensation of a boronic acid with 2-pyrazol-5-ylaniline (Table 3, Scheme 9).

A one-pot procedure starting with the introduction of pza, followed by *ortho*-CH silylation and transformation to the corresponding pinacolate allowed the formation of a variety of *ortho*-silylated boronic esters in moderate to very good yields (Scheme 10). The reaction is applicable to arene systems with either electron-donating or -electron withdrawing substituents.



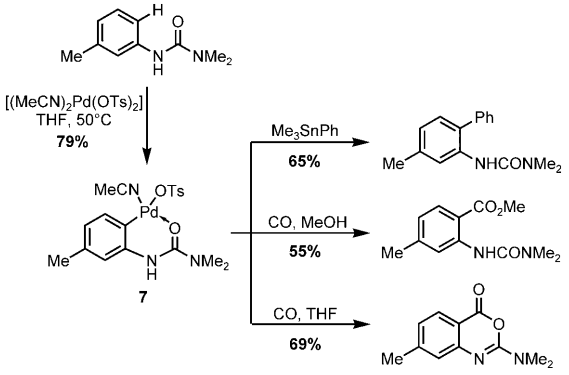
Scheme 10. One-pot *ortho*-silylation of aryl boronic acids.



Scheme 11. Removal of the directing pza group.

The directing pza group can be removed under acidic conditions in good yields and is easily recovered (Scheme 11).

Booker-Millburn and co-workers reported one of the first examples of palladium(II)-mediated carbonylative *ortho*-C–H activation.[15,16] A urea function served as the directing group, thus allowing the formation of biologically and synthetically useful anthranilic acid derivatives and heterocycles (Scheme 12). Initially, stoichiometric amounts of



Scheme 12. Formation and reaction of complex **7**.

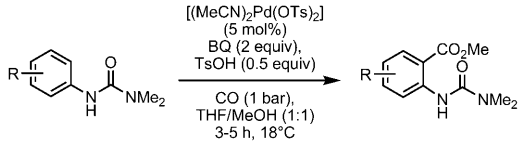
palladium were employed, which allowed for the isolation and characterization of the pallada(II)cycle **7**. This complex could undergo Stille-type arylation as well as methoxycarbonylation and carbonylation reactions.

A reaction variant with catalytic amounts of a palladium(II) salt was developed.[15] A range of substituted urea derivatives were subjected to carbonylation conditions (5 mol% $[Pd(OTs)_2(MeCN)_2]$, 2 equiv benzoquinone (BQ), 1 equiv TsOH, and 1 bar CO in CH_2Cl_2 for 3–8 h at 18°C). The corresponding cyclic imidates were obtained in moderate to good yields (34–81%, not shown) by internal nucleophilic capture of the intermediate acyl palladate. However, anthranilates were produced in moderate to high yields when the reaction was conducted in a 1:1 mixture of MeOH and THF (Table 4).

Removal of the diisopropylurea moiety occurred under mild conditions. Thus, **8** was deprotected after 18 h of heating in H_2O without notable hydrolysis of the ester. The anthranilic acid **9** can also be obtained in good yield by exposure of **8** to NaOH (1M; Scheme 13).

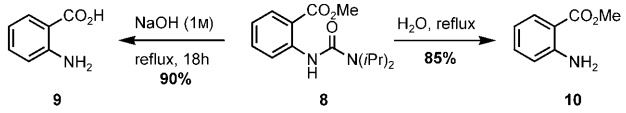
A dimethylhydrosilyl function was used as a directing group for an iridium-catalyzed *ortho*-CH-borylation of arenes, phenols, and *N*-alkylanilines.[16] It was shown that benzyldimethylsilanes undergo exclusive *ortho*-borylation under the conditions depicted in Scheme 14. The mechanism implies the formation of an Ir–Si bond rather than the formation of a silaborane intermediate.

Table 4: Palladium(II)-catalyzed methoxycarbonylation.

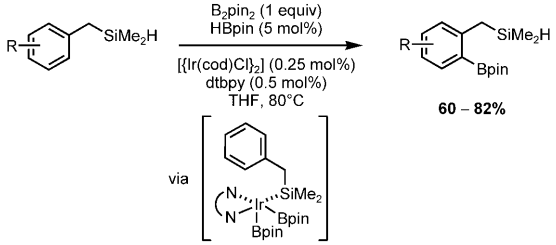


Entry	R	Yield [%][a]
1	H	88
2	*o*-Me	88
3	*m*-Me	84
4	*p*-Me	78
5	*p*-CF_3	5 (30)
6	*o*,*p*-Me	56
7	*p*-CO_2Me	36 (46)

[a] In brackets: reaction conducted at 50 °C.

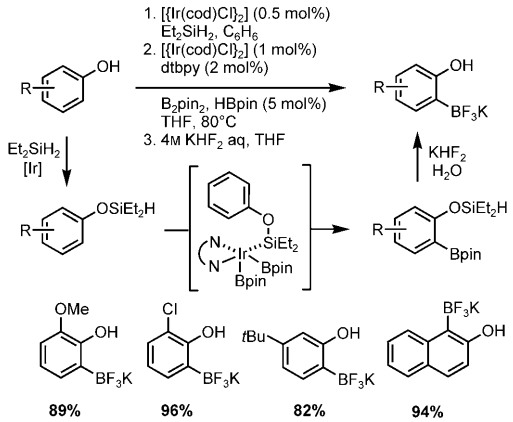


Scheme 13. Hydrolysis of the aryl diisopropylurea **8**.



Scheme 14. Regioselective *ortho*-borylation of benzylic hydrosilanes. cod = cyclooctadiene, dtbpy = 4,4′-di-*tert*-butyl-2,2′-bipyridine.

Benzylsilanes are good directing groups but they are not easy to remove from the substrate. They can only be transformed into methylarenes after cleavage with fluoride or oxidized to form phenols.[17] Boebel and Hartwig have developed an alternative approach that focuses on the installation of a removable, directing silicon agent for the *ortho*-borylation of phenols and anilines (Scheme 15).[18]

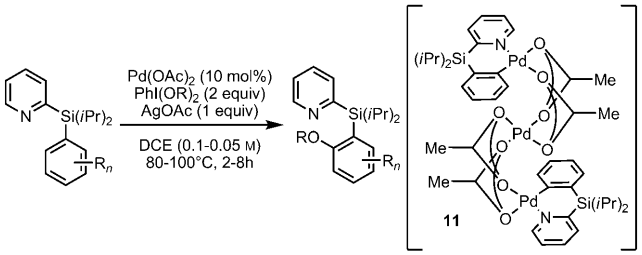


Scheme 15. One-pot *ortho*-borylation of phenols.

Thus, a silyl ether was installed upon reaction of a phenol with diethylsilane, and an iridium-catalyzed borylation was carried out in the same pot to furnish the corresponding *ortho*-borylated products. Subsequent transformation to trifluoroborate salts can also be accomplished in the same reaction vessel. Both electron-withdrawing and electron-donating substituents on the phenol core are tolerated in this method.

A directing 2-pyridylsilyl group has been used for a directed palladium(II)-catalyzed C–H hydroxylation of arenes by employing stoichiometric amounts of a hypervalent iodine reagent and silver acetate as the oxidants.[19] This method allowed the selective monoacyloxylation of a wide range of arenes (Table 5). The mechanism of this reaction has been studied, and a trinuclear palladium aryl species **11** was proposed as the key intermediate.

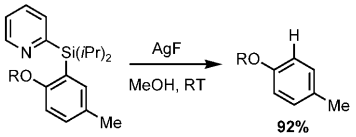
Table 5: Palladium-catalyzed *ortho*-acyloxylation of aryl silanes.



Entry	R_n	R	Yield [%][a]
1	–	Ac	80
2	–	Piv	80
3	*m*-MeO	Piv	60
4	*p*-MeO	Ac	84
5	*p*-Ph	Piv	79
6	*m*,*p*-Me	Piv	90
7	*p*-F	Piv	82
8	*p*-Br	Piv	77
9	*p*-Cl	Piv	74
10	*p*-CO_2Et	Piv	67
11	*p*-$CON(iPr)_2$	Piv	79

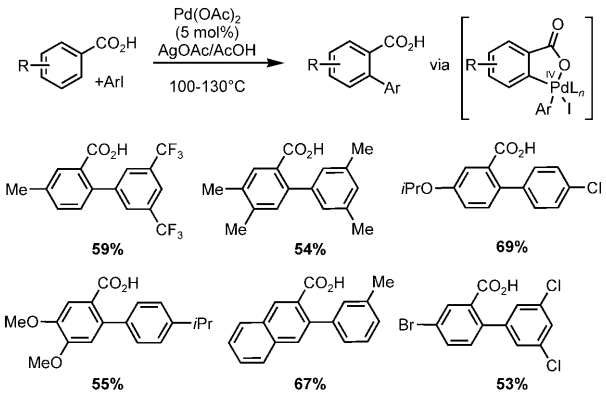
The directing group can be removed upon exposure to silver fluoride in methanol (92%, Scheme 16), or it can also be converted into an iodide (AgF, NIS). Borodesilylation, as well as a Hiyama–Denmark cross-coupling are further potential modifications for these substrates.

Daugulis et al. developed a method for the *ortho*-CH-arylation of benzoic acid derivatives.[20] The carboxylic acid function served as the directing group. The coupling of benzoic acid derivatives with aryl iodides was achieved by employing a ligand-free palladium(II) catalyst in the presence



Scheme 16. Removal of the directing 2-pyridylsilyl group.

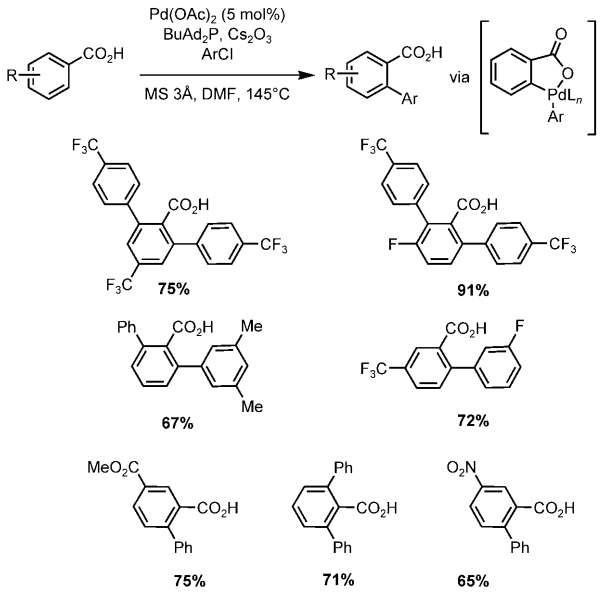
of stoichiometric amounts of silver acetate as the oxidant, presumably proceeding through a Pd^{II}/Pd^{IV} cycle. The coupling of electron-rich and moderately electron poor benzoic acids are well tolerated, as well as bromide and chloride functions on both coupling partners. However *ortho*-substituted aryl iodides are unreactive under these conditions. (Scheme 17).



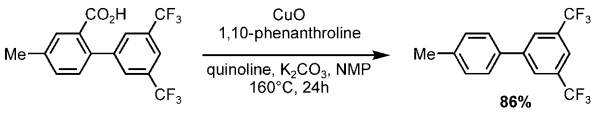
Scheme 17. Arylation of benzoic acids with aryl iodides.

Changing to a palladium/bulky phosphine catalyst system allowed for *ortho* arylation, with aryl chlorides used as the substrates. Here, electron-poor as well as electron-rich benzoic acids can be coupled with electron-poor or electron-rich aryl chlorides. Nitro and ester functions are compatible with the reaction conditions, but halogens other than fluorine are not. In this case, a Pd^{0}/Pd^{II} mechanism is most likely involved (Scheme 18).

Removal of the directing carboxylate group is possible by using a protocol developed by Goossen et al., which involves treating the arylated benzoic acid with CuO/quinoline in NMP; these reaction conditions are rather harsh (Scheme 19).[20b]

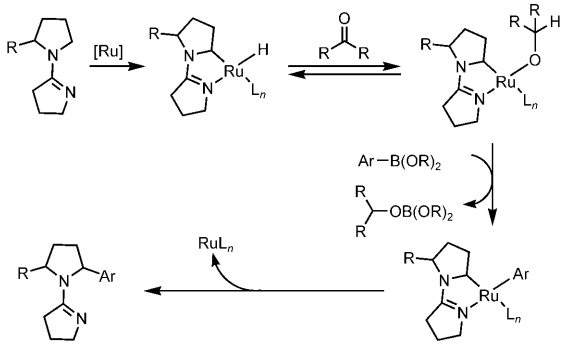


Scheme 18. Arylation of benzoic acids with aryl chlorides.



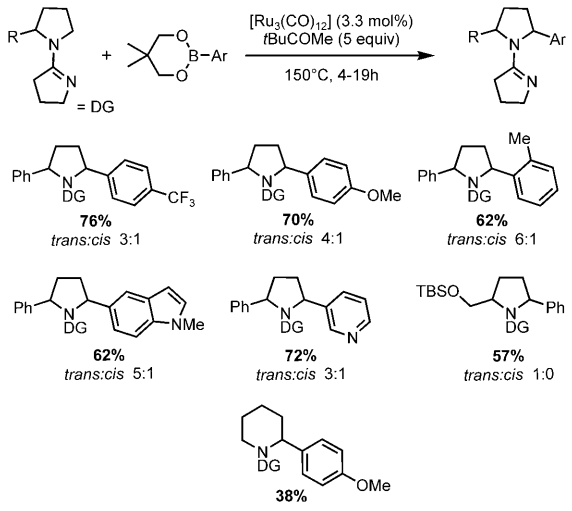
Scheme 19. Removal of the carboxylate group. NMP = *N*-methylpyrrolidine.

In 2006 Sames and co-workers described a ruthenium-catalyzed α-arylation of 2-substituted pyrrolidines and piperidines based on the use of a directing amidine group.[21] The directing group facilitates the insertion of the ruthenium fragment into the C–H bond. The metal hydride is then transformed into the corresponding metal aryl species via a metal–alkoxide intermediate.[22] The final reductive elimination generated the C–C bond in the product and regenerated the ruthenium catalyst (Scheme 20).

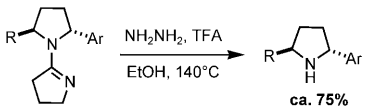


Scheme 20. Directed sp^3-CH arylation.

A wide range of aryl and heteroaryl boronic esters were compatible with the reaction conditions employed. Good yields and diastereoselectivities were obtained with pyrrolidine substrates; extension of this method to piperidine systems was less successful (Scheme 21).



Scheme 21. α-Arylation of pyrrolidines and piperidine.

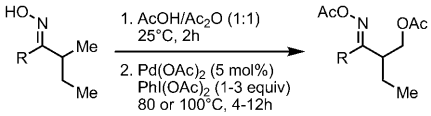


Scheme 22. Removal of the directing amidine group. TFA = trifluoroacetic acid.

Removal of the amidine function from the product was possible; however, rather harsh conditions proved necessary (Scheme 22).

In situ generated *O*-acetyloximes were employed as versatile and readily transformable directing groups to allow for palladium-catalyzed sp^3- and sp^2-CH oxidation.[23] While dialkyl-substituted oximes were selectively acetoxylated at the β-carbon atom, arylmethyl-substituted oximes underwent a chemo- and regioselective *ortho*-aryl acetoxylation (Tables 6 and 7).

Table 6: sp^3-CH functionalization of dialkyloximes.



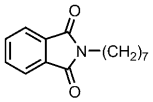
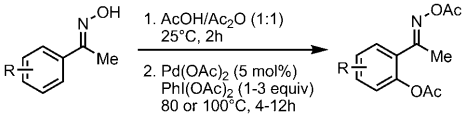
Entry	R	Yield [%]
1	$Ph(CH_2)_3$	49
2	CH_3	61
3	$Cl(CH_2)_7$	33
4		65

Table 7: CH functionalization of arylmethyloximes.

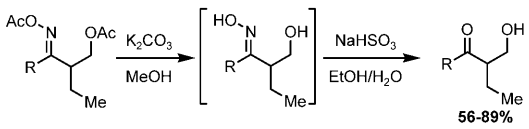


Entry	R	Yield [%]
1	*m*-CF_3	61
2	*m*-Br	86
3	*m*-Me	72
4	*m*-MeO	77
5	*m*-TBDPS[a]	79
6	*p*-*t*Bu	80

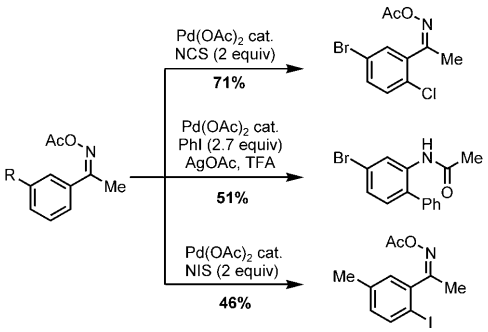
[a] TBDPS = *tert*-butyldiphenylsilyl.

Removal of the directing group is readily achieved in two steps, which may be performed as a one-pot operation. The acetate is first saponified under mild basic conditions (K_2CO_3 in MeOH), which is then followed by cleavage of the oxime under mild acidic conditions to furnish the β-hydroxy ketones in moderate to good yields (Scheme 23).

Initial results on oxime-directed *ortho*-halogenation and arylation have been reported (Scheme 24).



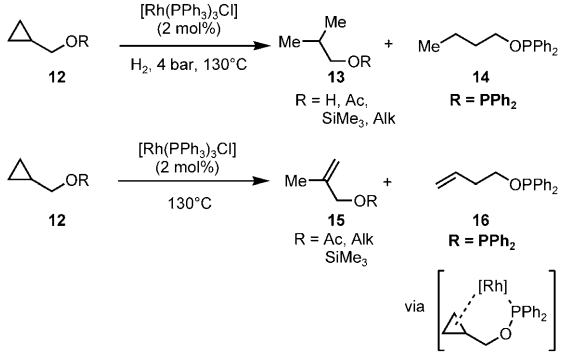
Scheme 23. Removal of the directing oxime group.



Scheme 24. Other palladium-catalyzed CH functionalization reactions with *O*-acetyloximes. NCS = *N*-chlorosuccinimide.

2.1.2. *C–C Bond Activation*

A phosphinite group served as an efficient directing group for a selective and catalytic carbon–carbon bond-cleaving reaction.[24] Treatment of cyclopropyl-substituted carbinol derivatives with the Wilkinson catalyst under the conditions of a rhodium-catalyzed hydrogenation furnished the corresponding hydrogenated and C–C bond-cleavage products **13** and **14**. In the case of the trimethylsilyl- and acetate-protected derivatives, cleavage of the sterically more accessible distal cyclopropane bond occurred to furnish the branched product **13**. The use of a diphenylphosphite substituent reversed the regiochemistry and led, through cleavage of the proximal cyclopropane bond, to the linear product **14**, possibly via the chelate intermediate shown in Scheme 25. In the absence of hydrogen the same catalyst induced an isomerization reaction with C–C bond cleavage to furnish the branched and linear alkenic products **15** and **16**. Nondirecting groups such as trimethylsilyl (TMS) and acetate also allow for the selective cleavage of the distal cyclopropane C–C bond to furnish the branched methallyl product **15**. In contrast, the corresponding diphenylphosphinite switched the regiochemistry completely



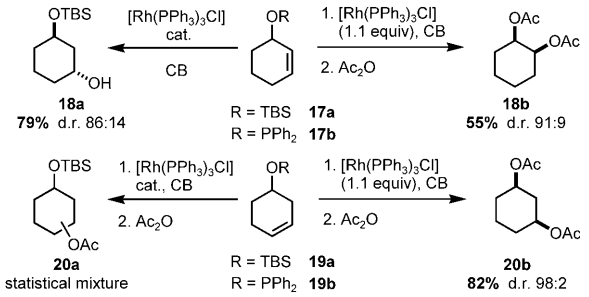
Scheme 25. Directed C–C bond activation.

towards the linear product **16** through a chelation-controlled selective cleavage of the proximal cyclopropane bond.

2.2. Directed Hydro- and Carbometalations

2.2.1. Hydroboration

In 1988 Evans et al. reported the use of phosphinites as effective functional groups to direct the stereochemical course of the rhodium-mediated hydroboration reaction with catecholborane (CB).[25] While hydroboration of the allylic phosphinite **17b** furnished the *syn*-1,2-diol, the hydroboration of the corresponding silyl ether **17a** gave predominantly the 1,3-*anti* diastereomer (Scheme 26). Even the homoallylic phosphinite **19b** reacted with very good stereocontrol. Conversely, the corresponding silyl ether **19a** led to a statistical mixture of products. A drawback of this reaction is the requirement of stoichiometric amounts of rhodium, since the phosphinite does not show turnover at the rhodium center. An iridium-catalyzed directed hydroboration has also been developed in which amides are used as directing groups. However, since amides cannot be removed in subsequent steps, this chemistry will not be discussed herein.[25]



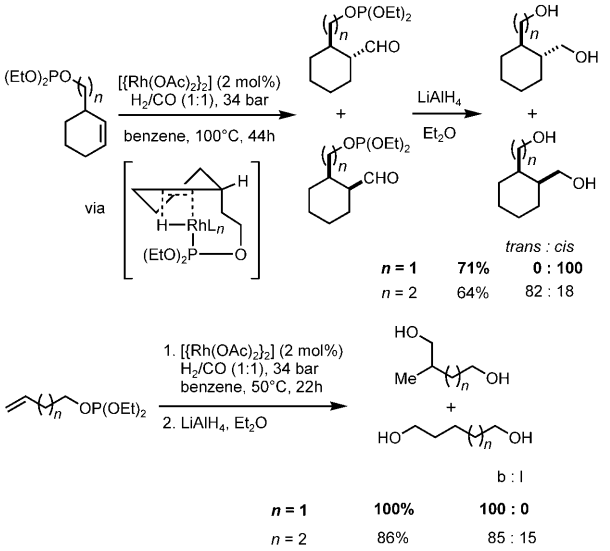
Scheme 26. Directed rhodium-mediated hydroboration and nondirected rhodium-catalyzed hydroboration.

2.2.2. Hydroformylation

2.2.2.1. Regioselective Hydroformylation

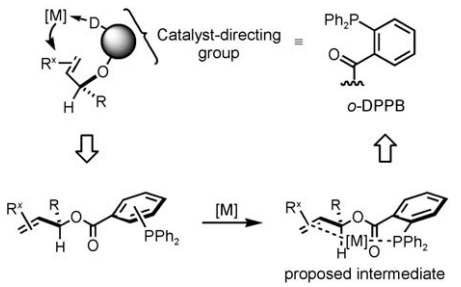
In 1938 Otto Roelen discovered the hydroformylation of alkenes, which is the addition of carbon monoxide and hydrogen across the π bond of the alkene to give saturated C_1-elongated aldehydes.[26] Today, the reaction has become one of the most important applications of homogeneous catalysis in industry, with approximately 9 million tons of oxo products produced per year.[27] Hydroformylation is a catalytic addition reaction, which fulfils all the criteria of atom economy.[28] In addition, the synthetically valuable aldehyde function is formed, which renders hydroformylation products as ideal precursors for subsequent carbon–carbon and carbon–heteroatom bond formation. Hydroformylation should be an appealing reaction for application in modern organic synthesis, but its application has remained scarce.[29] This is certainly due to the difficulty in controlling all aspects of the reaction selectivity simultaneously. While certain catalysts provide regiocontrol to obtain the linear regioisomer, a general solution to furnish branched aldehyde isomers and to obtain useful levels of stereocontrol primarily rely on the use of phosphorus-based directing groups.[30] Such tightly binding directing groups are essential to compete with the strongly ligating carbon monoxide, which is present in large excess. Furthermore monodentate phosphine-type ligands are known to undergo rapid reversible exchange under hydroformylation conditions, which ensures turnover of the phosphine-containing substrate at the rhodium center and should avoid product inhibition.[31]

Phosphites were used by Jackson et al. in 1990 to control the regioselectivity in the hydroformylation of cyclic and acyclic homoallylic olefins.[32] In each case, only the branched regioisomer was obtained, which results from the coordination of the phosphite function to the rhodium catalyst and the preference for a 6-*exo*-trig over a 7-*endo*-trig hydrometalation transition state. A significant chelation control is operative even with a longer chain system ($n = 2$, Scheme 27), although with erosion of the regio- or diastereoselectivity. The phosphite function can be cleaved upon reduction with $LiAlH_4$ to furnish the corresponding diols.



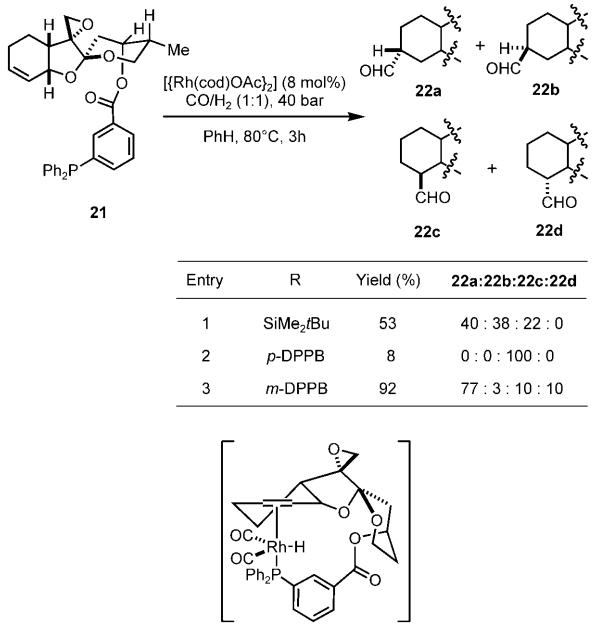
Scheme 27. Phosphite ester directed hydroformylation.

ortho-Diphenylphosphanylbenzoic acid (*o*-DPPBA) has become one of the most useful directing groups to be employed in hydroformylations. The *o*-DPPB group contains a triarylphosphine donor, which allows for an efficient and reversible binding of the rhodium catalyst under the hydroformylation conditions. An ester linkage permits the easy introduction to as well as the straightforward removal from the product. Additionally, the ester linkage sets limitations on the conformational space that is available for the substrate and is, therefore, expected to limit the number of competing transition states (Scheme 28). Finally, the geometry of the *o*-DPPB group has been specifically designed to allow for reversible transition-metal binding and subsequent delivery of the metal into the allylic or homoallyl position of a corresponding allyl- or homoallyl-*o*-DPPB ester.



Scheme 28. Development of the catalyst-directing *o*-DPPB group.

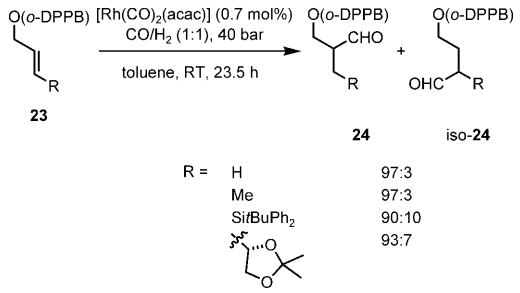
The *meta* variant (*m*-DPPB) has also proved to be efficient in the hydroformylation of 1,2-disubstituted olefins. Burke et al. used it in the course of the total synthesis of (+)-phylanthocin (Scheme 29).[33] The regio- and stereoselective functionalization of the olefin in **21** was found to be problematic. Any attempt to functionalize the alkene (hydrometalation/carbonylation, hydroboration/carbonylation, oxymercuration/demercuration), as well as nondirected hydroformylation led to mixtures of regio- and stereoisomers. While the introduction of the *p*-DPPB group gave very low conversion, it was found that the introduction of the *m*-DPPB group resulted in the formation of the desired aldehyde in good yield and with high regio- and stereoselectivity. The *m*-DPPB ester was subsequently removed by saponification with aqueous NaOH in MeOH at 75 °C.



Entry	R	Yield (%)	22a:22b:22c:22d
1	$SiMe_2tBu$	53	40 : 38 : 22 : 0
2	*p*-DPPB	8	0 : 0 : 100 : 0
3	*m*-DPPB	92	77 : 3 : 10 : 10

Scheme 29. *m*-DPPB-directed hydroformylation.

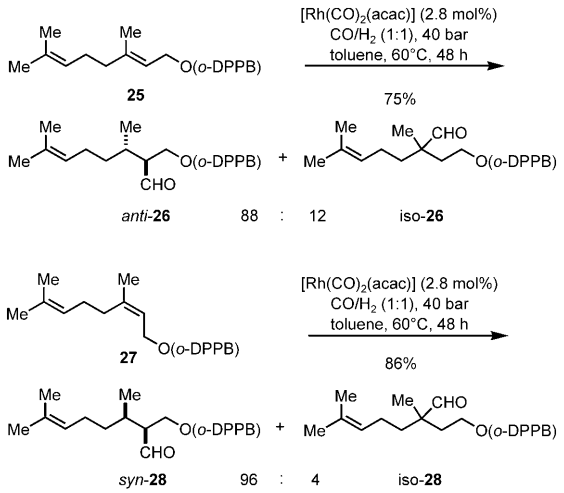
The hydroformylation of terminal alkenes, in general, furnishes two regioisomeric aldehydes. While catalysts exist to allow for the selective formation of the linear aldehyde, no catalyst is known for the selective formation of the branched regioisomer in synthetically useful levels. Even more difficult is the control of the regiochemistry during the hydroformylation of 1,2-disubstituted unsymmetric alkenes. However, subjecting allylic-*o*-DPPB esters **23** to hydroformylation conditions provided the branched regioisomeric aldehydes **24** in good yields and regioselectivities (Scheme 30).[34]



Scheme 30. Directed hydroformylation of allyl *o*-DPPB esters with mono- and disubstituted alkenes. acac = acetylacetonate.

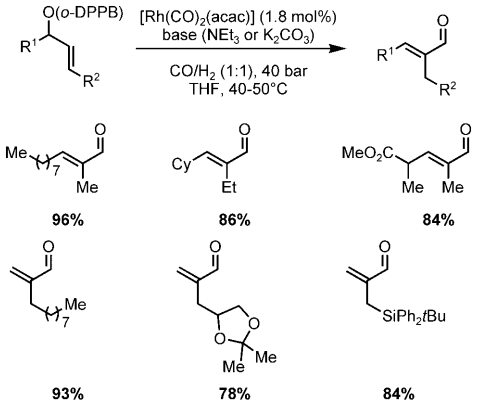
In general, trisubstituted alkenes are considered difficult substrates for hydroformylation because the rate of hydroformylation decreases exponentially with the number of substituents on the alkene functionality. One could expect that the intramolecular pathway for a directed hydroformylation should provide significant rate acceleration as a consequence of a reduction of the activation entropy. In fact, the efficient hydroformylation of trisubstituted alkene functions in allylic positions is even possible when the directing *o*-DPPB group is employed. The rate-accelerating effect exerted by the internal metal delivery through the directing function is shown in the hydroformylation of geranyl- and neryl-*o*-DPPB esters. A position-, regio-, and stereoselective hydroformylation of the trisubstituted allylic alkene function of the geranyl- and neryl-*o*-DPPB esters **25** and **27** occurs in the presence of a remote trisubstituted alkene function (Scheme 31).[34]

A practical synthesis of α,β-unsaturated aldehydes was also developed by a directed tandem hydroformylation/β-



Scheme 31. Position-, regio-, and diastereoselective hydroformylation of geranyl- and neryl-*o*-DPPB esters.

elimination reaction of *o*-DPPB allylic esters.[35] The *o*-DPPB group served as an effective controller for the regioselectivity in the hydroformylation step towards the desired aldolate isomer, and was subsequently eliminated in situ by mild bases. The reaction is general for the preparation of 1,1-disubstituted and trisubstituted enals, and is compatible with many functional groups (Scheme 32).

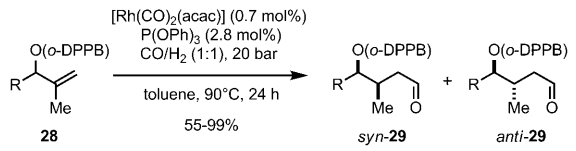


Scheme 32. Tandem *o*-DPPB-directed hydroformylation/β-elimination of allylic *o*-DPPB esters.

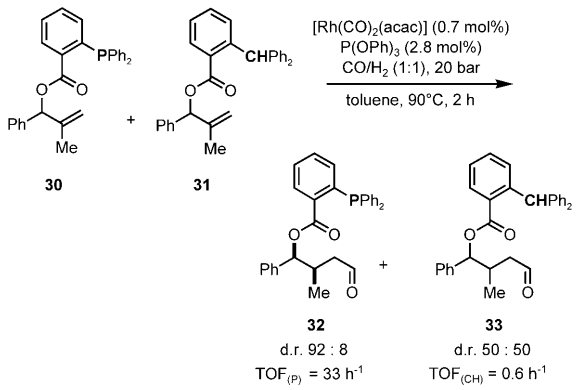
2.2.2.2. *Diastereoselective Hydroformylation*

The diastereoselective hydroformylation of 1,1-disubstituted alkenes has been reported by using *o*-DPPB as the directing group.[36–38] According to Keuleman's rule,[39] which states that the formation of quaternary carbon centers is avoided, only the linear aldehydes can be formed in the case of the methallylic substrate **28** (Table 8), and consequently only the diastereoselectivity has to be controlled. It was first shown that hydroformylation of methallylic substrates having either a free hydroxy function or standard silyl or acyl protecting groups occurred in an almost stereorandom fashion.[40] Conversely, introduction of the *o*-DPPB group allowed the hydroformylation to proceed smoothly to give

Table 8: Diastereoselective hydroformylation of methallylic *o*-DPPB esters.



Entry	R	Yield [%]	d.r. *syn*/*anti*
1	Et	83	73:27
2	*i*Pr	97	96:4
3	Cy	81	95:5
4	Bn	75	80:20
5	Ph	99	92:8
6	CO_2Me	80	90:10
7		90	96:4

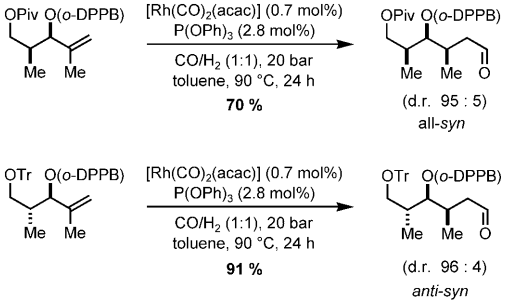


Scheme 33. Role of the *o*-DPPB group in diastereoselective hydroformylation.

rise to high levels of stereocontrol in favor of the corresponding *syn* aldehydes **29** (Table 8).

Further insight into the role of the *o*-DPPB group were garnered with the experiment described in Scheme 33. A 1:1 mixture of *o*-DPPB substrate **30** and the phosphine-free benzoate **31** were subjected to hydroformylation conditions. While **30** underwent a smooth and diastereoselective hydroformylation, the reaction of substrate **31** was significantly slower, and furnished both *syn* and *anti* aldehydes **33** in a 1:1 ratio. This confirms the role of the *o*-DPPB group as a catalyst-directing group.

This method has been applied successfully to the construction of all-*syn* and *anti-syn* stereotriads, which are major building blocks in polypropionate syntheses (Scheme 34).[41,42]

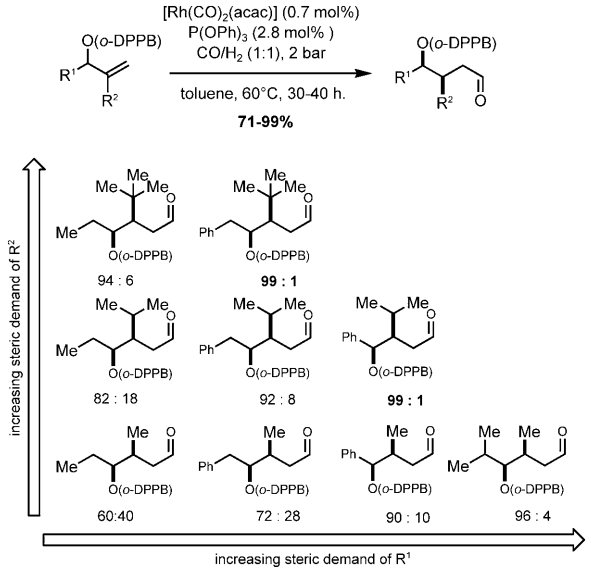


Scheme 34. Diastereoselective hydroformylation for the construction of stereotriads. Piv = pivaloyl, Tr = trityl.

High levels of diastereoselectivity were obtained, regardless of the relative configuration (*syn* or *anti*) in the methallylic *o*-DPPB esters.

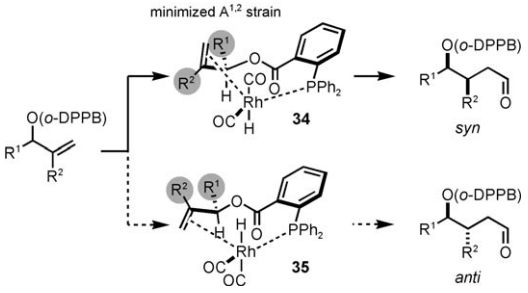
In further studies it was observed that diastereoselectivity is a function of the steric demand of the substituent at the controlling stereocenter (R^1) as well as the substituent at the 2-position of the allylic system (R^2). Increasing the size of both substituents increases the diastereoselectivity (Scheme 35).[43]

To rationalize the diastereoselectivity as well as the factors governing the 1,2-asymmetric induction observed in this reaction one has to compare the starting trigonal



Scheme 35. Influence of the steric demand of substituents R^1 and R^2 on the diastereoselectivity of the hydroformylation of 2-substituted allylic *o*-DPPB esters.

pyramidal hydridoalkene complexes, since it is accepted that the rate- and selectivity-determining step in the hydroformylation reaction is the hydrometalation. Additionally, this step is known to be exothermic. Thus, following Hammond's postulate, the transition state is early, which makes complexes **34** and **35** good models for the corresponding and competing diastereomorphic transition states (Scheme 36). Hence, a repulsive $A^{1,2}$ interaction between R^1 and R^2 in complex **35** and the corresponding transition state strongly disfavors the formation of the *anti* product.

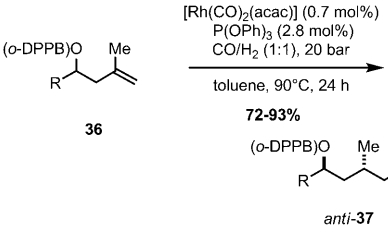


Scheme 36. Proposed model for the 1,2-asymmetric induction.

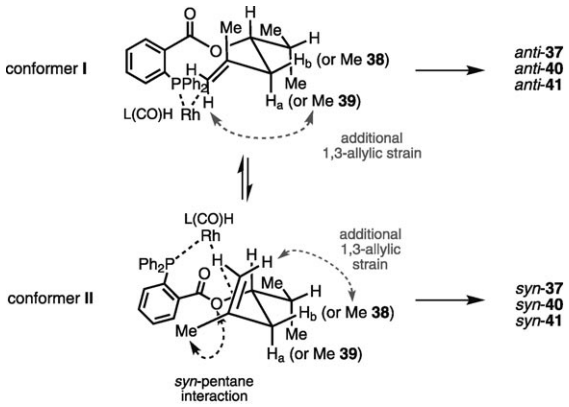
Not only 1,2- but also 1,3-asymmetric induction can be effected by employing the *o*-DPPB group. Thus, homomethallylic *o*-DPPB esters **36** were hydroformylated to give the *anti* aldehydes **37** in good yields and diastereoselectivities (Table 9).[44,45] As for the methallylic substrates, the hydroformylation of the phosphine-free benzoate resulted in low yields and selectivities, thus demonstrating the directing and activating effect of the *o*-DPPB group.

The model proposed to explain the *anti* selectivity is shown in Scheme 37. The conformations of the two different

Table 9: Directed diastereoselective hydroformylation of homomethallylic *o*-DPPB esters.



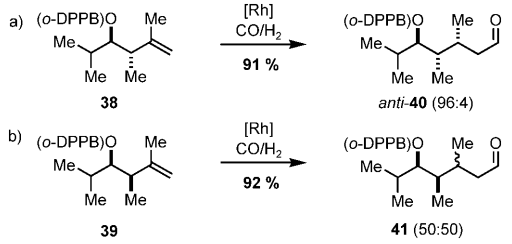
Entry	R	Yield [%]	d.r. *syn*/*anti*
1	*i*Pr	93	91:9
2	Cy	90	91:9
3	Ph	72	90:10
4	*o*-$MeOC_6H_4$	76	90:10
5		99	92:8



Scheme 37. Proposed model for the origin of 1,3-asymmetric induction.

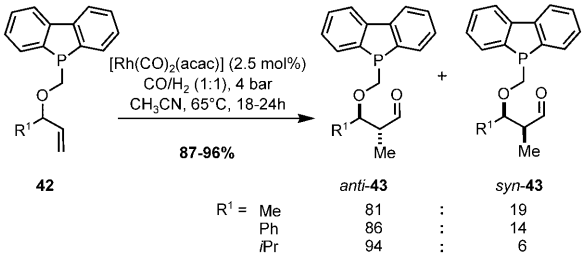
rhodium-alkene-hydrido complexes (**I** and **II**) have to be analyzed. According to experimental and theoretical conformational analysis, homomethallylic *o*-DPPB ester **36** possesses the preferred conformation **I**; conformer **II** suffers from an additional *syn*-pentane interaction. Delivery of the rhodium catalyst via the catalyst-directing *o*-DPPB group from **I** provides the experimentally observed *anti* diastereomer (Scheme 37).

The influence of an additional tertiary stereocenter in an allylic position has been explored to probe this model. Exchanging H_b with a methyl substituent would disfavor conformation **II**, since an additional $A^{1,3}$ strain would arise and shift the equilibrium toward conformer **I** and consequently improve the diastereoselectivity. Indeed, a 96:4 mixture of diastereomers was obtained in the hydroformylation of **38** (Scheme 38a). H_a was also exchanged with a methyl group. In this case, both conformers suffer from an additional $A^{1,3}$ strain. Thus, neither the formation of the *anti* nor the *syn* diastereomer should be favored. This prediction is again congruent with the experiment with derivative **39**, which occurred in a completely stereorandom fashion (Scheme 38b).



Scheme 38. Influence of a second stereocenter on the 1,3-asymmetric induction.

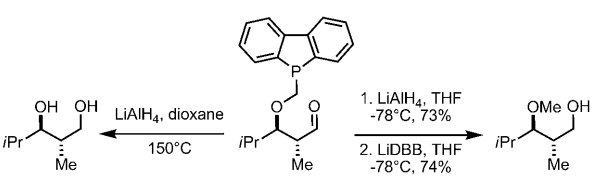
A more difficult problem is the hydroformylation of allylic alcohol derivatives with a terminal alkene function. In this case, simultaneous control of the regio- and diastereoselectivity would be required. Most interesting would be a branched-selective hydroformylation, since propionate aldol products would be formed. Leighton and co-workers showed that employing a dibenzophosphol-1-ylmethyl function as the catalyst-directing group, which is attached through an ether function to allylic alcohol substrates **42**, allows a regio- and stereoselective hydroformylation to give the *anti*-aldol propionates **43** in good yields (Scheme 39).[46] The diastereoselectivity is best when R^1 is a secondary alkyl substituent.



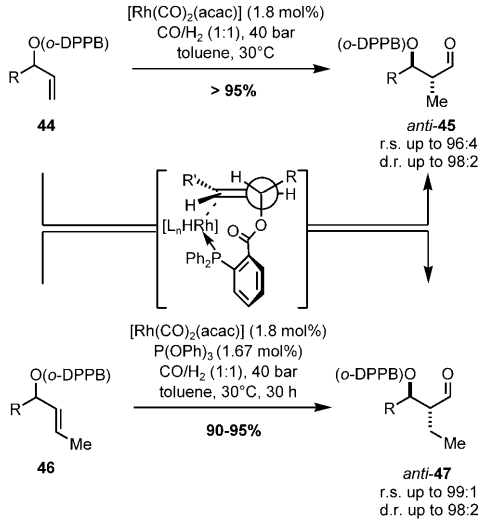
Scheme 39. A dibenzophosphol-1-ylmethyl substituent as a catalyst-directing group for regio- and diastereoselective hydroformylation of allylic alcohols.

The catalyst-directing group is installed from the corresponding methoxymethyl (MOM) ether of the allylic alcohol by successive treatment with Me_2BBr and lithiodibenzophospholide. Removal of the directing group requires rather harsh conditions, such as treatment with LiDBB or reduction with $LiAlH_4$ in dioxane at 150 °C (Scheme 40).

Improved selectivities were obtained by using the *o*-DPPB group as the catalyst-directing function.[47] Starting from the allylic ester **44**, the *anti*-propionate aldolates **45** were obtained in very good yield and high regio- and diastereoselectivity. These products are rather difficult to prepare by traditional aldol or allylmetal addition reactions. Similarly, allylic alcohols with a 1,2-*trans*-disubstituted alkene function **46** were hydroformylated to give similar *anti*-aldols **47** in good regio- and diastereoselectivity (Scheme 41). Minimization of the $A^{1,3}$ strain in the course of the selectivity-determining hydrometalation step accounts for the observed diastereoselectivity.[48]



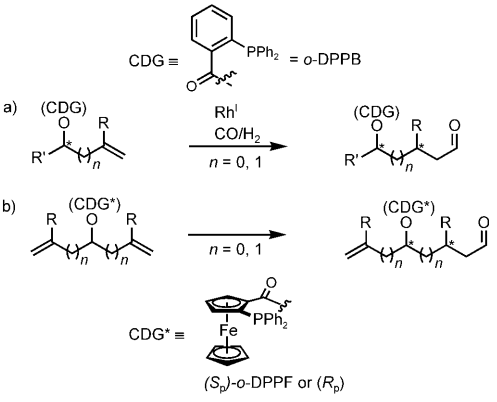
Scheme 40. Removal of the dibenzophospholyl group. LiDBB = lithium-di-*tert*-butylbiphenylide.



Scheme 41. *o*-DPPB-directed regio- and diastereoselective hydroformylation of allylic esters with mono- and 1,2-disubstituted alkenes.

2.2.2.3. *Desymmetrizing Hydroformylation*

The controlling stereocenter was an integral part of the substrate in the diastereoselective hydroformylation presented in the previous section (Scheme 42a). However, for prochiral substrates, the chiral information has to reside in the catalyst-directing group. For this purpose, the *ortho*-diphenylphosphanyl ferrocenoate (*o*-DPPF) group was developed, as a chiral variant of the *o*-DPPB group, and hydroformylations of dialkenylcarbinols ($n = 0$) as well as diallylcarbinols ($n = 1$) were studied (Scheme 42). Interestingly, a stereoselective monohydroformylation could set two stereogenic

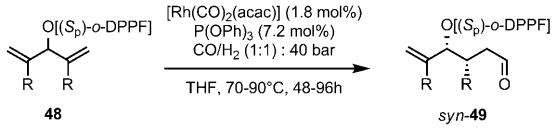


Scheme 42. Diastereoselective as well as desymmetrizing hydroformylation with directing groups.

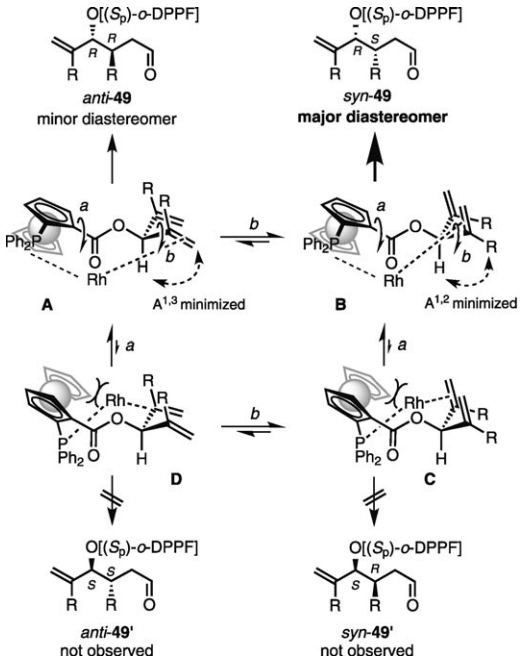
centers simultaneously to give interesting building blocks for polyketide synthesis. However, in this case, control over the selectivity is challenging, as discrimination of the diastereotopic alkene groups as well as the diastereotopic alkene faces has to be managed simultaneously.

Dialkenyl carbinol *o*-DPPF esters were synthesized and subsequently subjected to hydroformylation conditions (Table 10).[49–51] *Syn*-aldehydes were formed predominantly in good to excellent diastereoselectivity and in enantiomerically pure form. Thus, of the four possible diastereomers, only *syn*-**49** is obtained with high selectivity. This means that the hydroformylation occurs with good discrimination of the diastereotopic faces and perfect discrimination of the diastereotopic groups.

Table 10: Desymmetrizing hydroformylation of dialkenylcarbinol *o*-DPPF esters **48**.



Entry	R	Yield [%]	d.r. *syn*/*anti*	*ee* [%]
1	Me	90	88:12	>99
2	Et	80	93:7	>99
3	*i*Pr	80	>98:2	>99
4	*t*Bu	82	>99:1	>99
5	CH_2SiMe_3	71	>99:1	>99

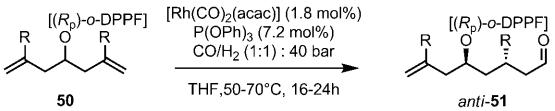


Scheme 43. Stereochemical rational for the desymmetrizing hydroformylation of *o*-DPPF ester **48**.

Discrimination of the diastereotopic faces increases with the size of the R substituent (Table 10), which parallels the observations made in the course of the *o*-DPPB-directed hydroformylation of chiral 2-substituted allylic alcohols (Scheme 35). A model similar to the one presented in that case (Scheme 36), modified by exchanging the *o*-DPPB group with the planar chiral *o*-DPPF, has been proposed (Scheme 43). Comparison of the relative stability of the chelating rhodium–alkene complexes **A**–**D**, which serve as models for the competing rate- and selectivity-determining hydrometalation transition states, allows for prediction of the stereochemistry observed in the reaction. For (S_p)-*o*-DPPF ester **48**, the relative stabilities of the two diastereomeric complexes **A** and **B** determine the facial diastereoselectivity of the reaction. Minimization of the $A^{1,2}$ strain in the alkene moiety leads via **B** to the major diastereomer *syn*-**49**. Reaction through chelation mode **A**, in which the alkene conformation minimizes the $A^{1,3}$ strain, leads to the minor diastereomer *anti*-**49**. Since $A^{1,2}$ strain is a function of the steric demand of the substituent R, it is clear that the diastereoselectivity of the reaction increases as the size of R increases. To understand the stereodiscrimination of the diastereotopic alkene groups, one should compare the stability of complexes **C** and **D** versus **A** and **B**. However, coordination of the opposite diastereotopic alkene moiety requires a bond rotation (*a*; Scheme 43). Such a chelating mode is prohibited because of severe steric hindrance between the ferrocene moiety and the rhodium center. This explains the observed perfect diastereoselection of the alkenic group.

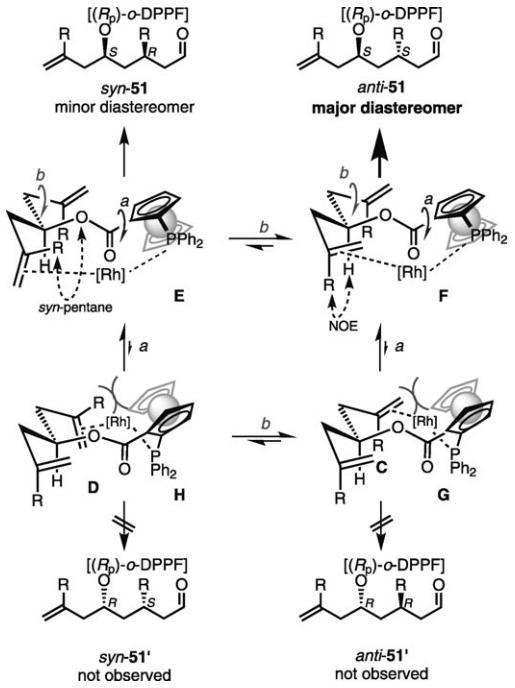
Diallylcarbinol-*o*-DPPF esters **50** are also excellent substrates for desymmetrizing *o*-DPPF-directed hydroformylation. The corresponding *anti*-aldehydes **51** were obtained in good yields, excellent diastereoselectivities, and in enantiomerically pure form (Table 11).[52]

Table 11: Desymmetrizing hydroformylation of diallylcarbinol *o*-DPPF esters **50**.



Entry	R	Yield [%]	d.r. *syn*/*anti*	*ee* [%]
1	Me	83	96:4	>99
2	Et	85	95:5	>99
3	*i*Pr	84	86:14	>99
4	Ph	90	94:6	>99
5	CH_2OTBS	80	96:4	>99

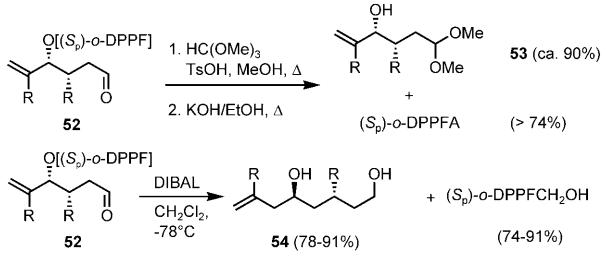
Similar to the previous case, a rationale for the stereochemical course of the *o*-DPPF-directed hydroformylation of diallylcarbinols was proposed by comparison of the four diastereomeric chelating rhodium–alkene complexes **E**–**H** (Scheme 44). Thus complexes **E** and **F** compete for facial diastereoselection, while comparison of the stabilities of complexes **G** and **H** versus **E** and **F** can explain the discrimination of the diastereotopic groups. Minimization of the *syn*-pentane strain in complex **F** leads to the major diastereomer *anti*-**51**. Similar to the previous case, complexes



Scheme 44. Stereochemical rationale for the desymmetrizing hydroformylation of *o*-DPPF esters **50**.

G and **H** are less stable than **E** and **F** because of steric hindrance between the ferrocene group and the rhodium center, and neither diastereomer *syn*-**51′** nor *anti*-**51′** were formed.

Removal of the substrate-bound catalyst-directing *o*-DPPF group can be achieved through saponification after protection of the aldehydes as dimethylacetal functions. The alcohols **53** were obtained in good yields, and the *o*-DPPFA could be recovered. Alternatively, clean reductive removal of the *o*-DPPF group can be achieved upon reduction with DIBAL to furnish 1,5-diols **54** (Scheme 45).

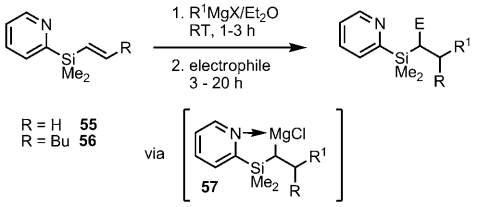


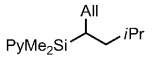
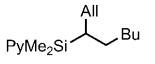
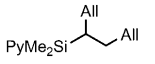
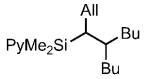
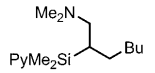
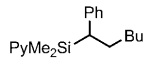
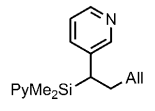
Scheme 45. Removal and recovery of the catalyst-directing *o*-DPPF group. DPPFA = *o*-diphenylphosphanyl ferrocene carboxylic acid, DIBAL = diisobutylaluminum hydride.

2.2.3. *Carbomagnesiation*

An efficient carbomagnesiation of vinylsilanes has been developed by Yoshida et al. by employing the directing 2-PySiMe$_2$ group.[53] The primary carbomagnesiation product—the Grignard compound **57**—could be trapped efficiently with various electrophiles (allyl bromide, iminium salt) or employed directly in a subsequent Kumada coupling with

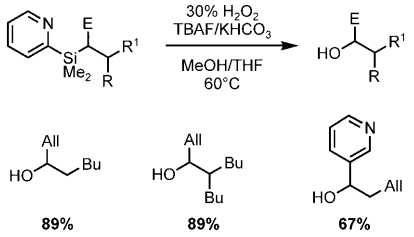
Table 12: Three-component coupling of vinylsilanes, Grignard reagents, and electrophiles.



Entry	Vinyl-silane	Grignard reagent	Electrophile	Product	Yield [%]
1	**55**	*i*PrMgCl	AllylBr		91
2	**55**	*n*BuMgCl	AllylBr		93
3	**55**	AllylMgBr	AllylBr		91
4	**56**	*n*BuMgCl	AllylBr		90
5	**55**	*n*BuMgCl	$H_2C{=}NMe_2^+I^-$		91
6	**55**	*n*BuMgCl	PhI [Pd(PPh$_3$)$_4$] (5 mol%)		77
7	**55**	AllylMgBr	3-bromopyridine [Pd(PPh$_3$)$_4$] (5 mol%)		91

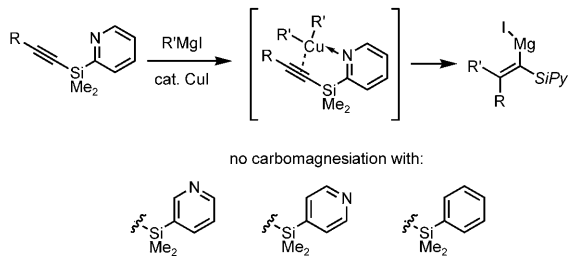
aryl or heteroaryl halides in the presence of a palladium catalyst to yield the corresponding three-component coupling products in high yields (Table 12).

Subjecting the silane products to the conditions of a Tamao–Fleming oxidation furnished the corresponding secondary alcohols after removal of the directing group (Scheme 46).[54]



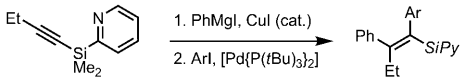
Scheme 46. Oxidative cleavage of the directing group. TBAF = *tert*-butylammonium fluoride.

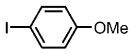
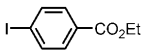
A related copper-catalyzed carbomagnesiation of 2-pyridylsilyl-substituted alkynes furnished the corresponding alkenylmagnesium reagents, which were used directly in subsequent Kumada coupling reactions.[55] Control experiments with 3- and 4-pyridylsilyl derivatives and phenyl-substituted substrates proved that the directing group controls both the reactivity and regioselectivity (Scheme 47, Table 13).



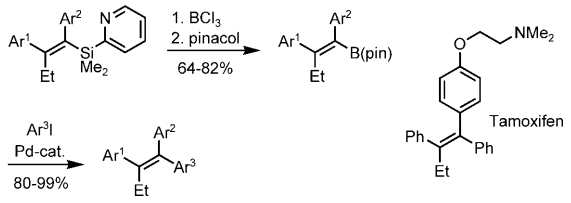
Scheme 47. Carbomagnesiation of 2-pyridylsilyl-substituted alkynes.

Table 13: Directed carbomagnesiation of alkynes.



Entry	ArI	Yield [%]	*E*/*Z*
1	PhI	80	92:8
2		60	92:8
3		58	94:6

The utility of this reaction sequence was illustrated through preparation of a series of tamoxifen-type, tetrasubstituted alkenes (Scheme 48). Conversion of 2-pyridylsilyl function into a boronic ester was achieved in an efficient one-pot protocol. Subsequent Suzuki–Miyaura coupling with aryl iodides enabled the introduction of the third aryl substituent.[56,57]

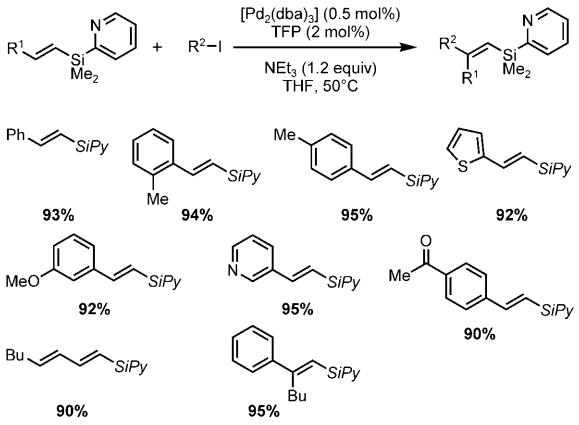


Scheme 48. Synthesis of tamixofen-type tetrasubstituted alkenes.

2.2.4. *Mizoroki–Heck Reactions*

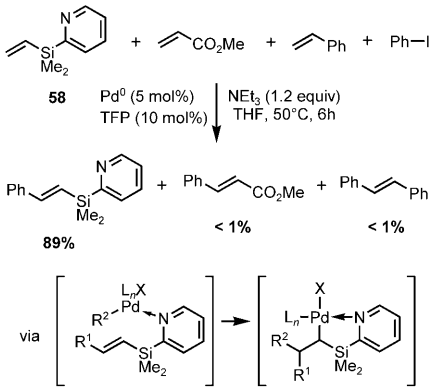
The Mizoroki–Heck coupling has been established as a powerful method for the preparation of substituted olefins.[58] However, the chemoselectivty and regioselectivity of the carbometalation step can be problematic for certain substrate types. For example, the Heck reaction of vinylsilanes is problematic, since cleavage of the C–Si bond is a typical side reaction. Application of the pyridyldimethylsilyl function as a directing group allows for a clean Heck coupling with a number of electronically and structurally diverse aryl and heteroaryl iodides to furnish di- and trisubstituted vinylsilanes in high yields and with complete stereoselectivity (> 99 % *E* for each case, Scheme 49).[59a]

A competition experiment between silylpyridyl-functionalized substrate **58**, methyl acrylate, and styrene in the presence of phenyl iodide was performed. Under these



Scheme 49. Mizoroki–Heck coupling with pyridyl-substituted vinylsilanes. dba = *trans*,*trans*-dibenzylideneacetone, TFP = tri-2-furylphosphine.

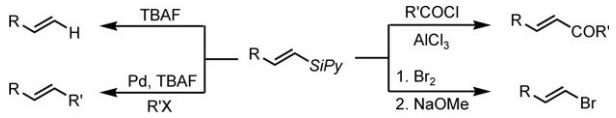
conditions substrate **58** reacted exclusively to furnish the corresponding Heck product, thus demonstrating the strong rate-accelerating effect of the directing pyridyl group (Scheme 50).



Scheme 50. Evidence for the role of the pyridylsilyl group as a directing group in the Heck reaction.

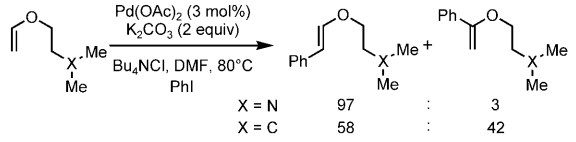
In addition to its role as a directing group, the pyridylsilyl function can act as a "phase tag" to allow for an easy purification of the products.[59b] A simple acid/base treatment allows the isolation of the products in more than 95 % purity. Notably, this process also enables recovery of the palladium catalyst. Removal of the directing pyridylsilyl group can be achieved by protodesilylation with TBAF. The vinylsilane products can be further functionalized by Hiyama coupling reactions, or upon reaction with various electrophiles: Exposure to acid chloride in the presence of $AlCl_3$ affords enones, while reaction with bromine and subsequent treatment with NaOMe gives the corresponding alkenyl bromides (Scheme 51).

Heck reactions of vinyl ethers show low regioselectivity. However, attaching an appropriate donor function such as an amine in the 5-position allows for the highly regioselective β-arylation of enol ethers with aryl iodides, bromides, and triflates.[60,61]



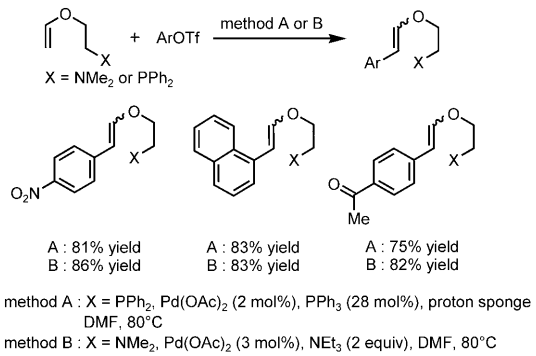
Scheme 51. Removal of the 2-PyMe$_2$Si group.

A comparison of the reactivity of the nitrogen-functionalized substrate with that of the carbon analogue demonstrates the strong directing effect of the amine function (Scheme 52).



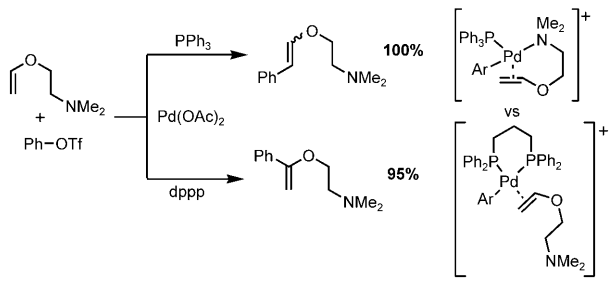
Scheme 52. Influence of the amine function on the regioselectivity of the Heck reaction.

Both a tertiary amine and a phosphine can serve as the directing function. Thus, β-arylation with functionalized aryl triflates was achieved in good yields and excellent regioselectivity (Scheme 53).



Scheme 53. Selective β-arylation of enol ethers.

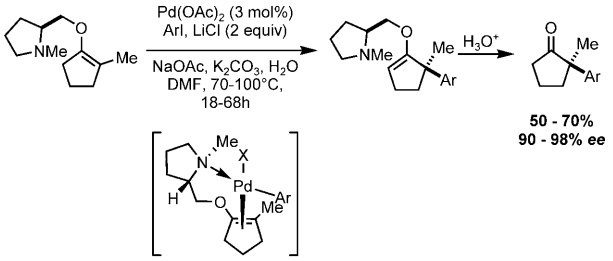
The regioselectivity of the carbometalation can be altered through the choice of the phosphine ligand employed. While the palladium/triphenylphosphine system allowed for selective β-arylation, the use of the bidentate dppp ligand switched the regioselectivity towards the α-arylated product, which was also obtained in high yield (Scheme 54). The enol ether can be



Scheme 54. Switch in the regioselectivity through ligand control.

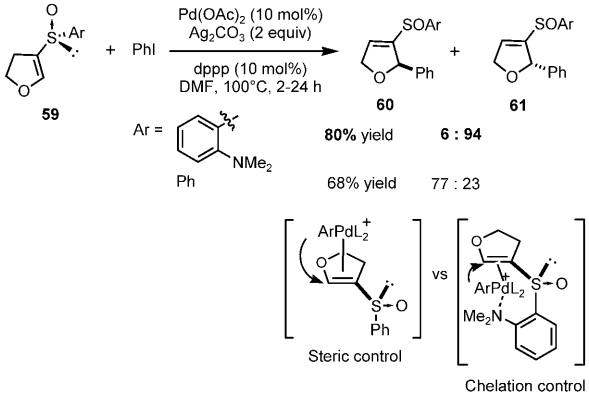
further hydrolyzed easily by treatment with acid to give the corresponding carbonyl derivatives. It is reasonable to assume that the directing amine group can efficiently compete as a ligand in the case of the monodentate phosphine, and thus a directed carbometalation favors the β-arylation product. However, the intrinsic preference (primarily steric reasons) seems to be for the α-arylation pathway. Thus, the use of the bidentate dppp ligand prohibits the amine group from acting as a directing function and shuts off the β-arylation pathway.

This coordinating system was also used to develop an asymmetric intermolecular Heck arylation to yield α-aryl cyclopentanones.[62] The nitrogen atom, in this case, is part of a chiral tertiary amino group (prolinol derivative), which provided efficient regio- and stereocontrol of the selectivity-determining carbometalation step. Acid-mediated hydrolysis of the enol ether furnished enantiomerically enriched α-arylated cyclopentanones with a quaternary stereocenter. The reaction was also successful with o*rtho*, *meta*, as well as *para*-substituted aryl iodides as electrophiles (Scheme 55).



Scheme 55. Chelation-controlled asymmetric Heck-type arylation.

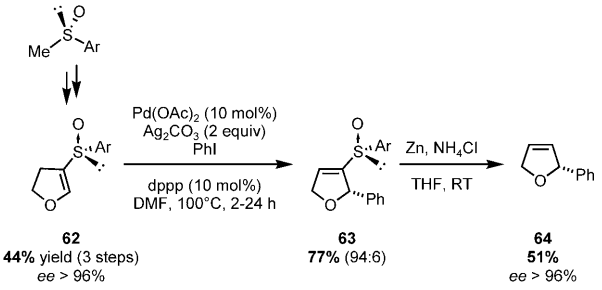
Alternatively, a chiral sulfoxide group equipped with an *N*,*N*-dimethylaminophenyl group has been shown to control the stereochemistry of the Heck reaction efficiently.[63] Thus, after subjecting the chiral sulfoxides **59** to the conditions of the Mizoroki–Heck reaction in the presence of aryl iodides, it was found that the *ortho*-dimethylaminophenyl group afforded the 2-aryl-2,5-dihydrofuran **61** with remarkable stereocontrol (Scheme 56). The use of the corresponding chiral sulfoxide with a phenyl substituent furnished the



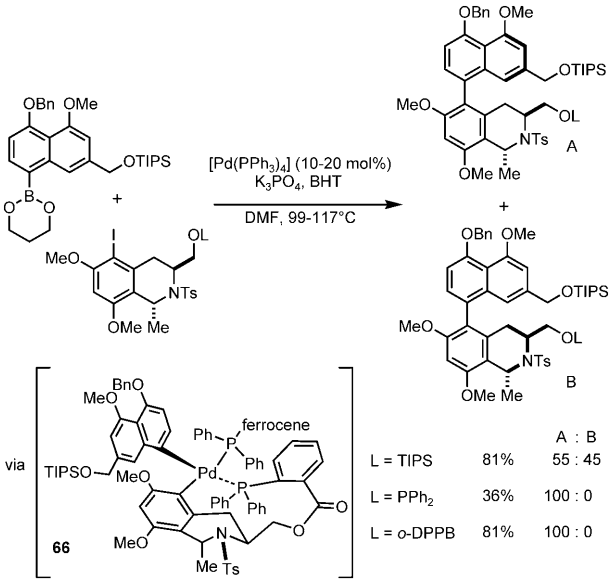
Scheme 56. Directing chiral sulfoxide groups in stereoselective Mizoroki–Heck reactions.

opposite stereoisomer preferentially, thus highlighting the role of the dimethylamino group as a directing function.

To obtain optically pure compounds enantiopure sulfoxide **62** was prepared (44% yield, >96% *ee*) and subjected to the conditions of a Heck reaction in the presence of iodobenzene (Scheme 57). Subsequent cleavage of the directing sulfoxide group under reductive conditions furnished the 2-phenyl-2,5-dihydrofuran **64** (51% yield, >96% *ee*).



Scheme 57. Synthesis of enantiopure 2,5-dihydrofurans.

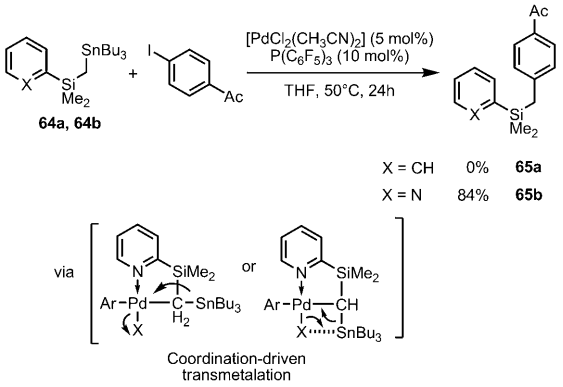


Scheme 59. Diaryl coupling assisted by the directing *o*-DPPB group. TIPS = triisopropylsilyl, BHT = butylated hydroxytoluene.

2.3. Directed Cross-Coupling Reactions

2.3.1. Stille Coupling

Stille coupling reactions with alkyl stannanes are usually unfavorable reactions because the transmetalation step is slow. However, the use of the 2-PyMe$_2$Si-functionalized alkylstannane **64b** results in a clean Stille cross-coupling reaction with aryl iodides (Scheme 58). Replacing the potentially coordinating 2-pyridyl group with a phenyl substituent gave no reaction product at all. Hence, the 2-PyMe$_2$Si group acts as a directing group, most likely by accelerating the rate-limiting transmetalation step of the Stille reaction.[64]



Scheme 58. Directed Stille cross-coupling.

2.3.2. Suzuki Coupling

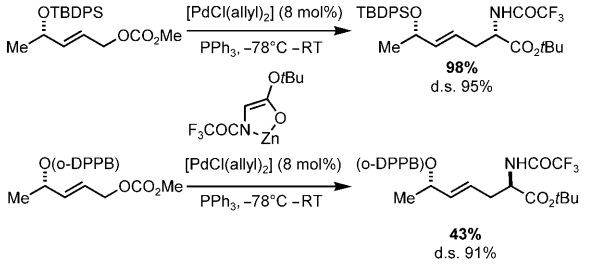
An atropo-diastereoselective Suzuki biaryl cross-coupling was developed by Lipshutz and Keith by using *o*-DPPB as the removable directing group to access korupensamine A, an alkaloid that possesses high antiviral activity.[65] Preliminary attempts with the TIPS-substituted aryl iodide showed that simple steric factors are not sufficient to achieve useful levels of atropo-diastereoselectivity in the cross-coupling step (Scheme 59). Switching from TIPS to a diphenylphosphine unit allowed for complete atropo-diastereoselectivity, but low chemical yield. However, the use of the *o*-DPPB group attached as the corresponding ester furnished the desired cross-coupling product in good yield and excellent diastereoselectivity. Reductive elimination from the highly ordered chelate intermediate **66** has been proposed as the selectivity-determining step (Scheme 59).

2.4. Miscellaneous Directed Transition-Metal-Catalyzed Reactions

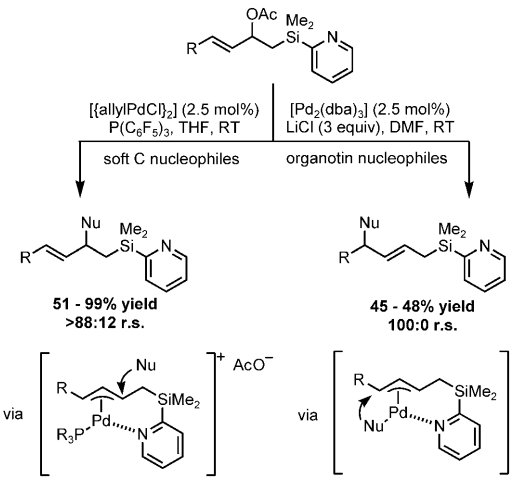
2.4.1. Palladium-Catalyzed Allylic Alkylation

Based on earlier work by the research groups of Kraft and Kocovsky,[66] Kazmaier and Lindner have developed a substrate-directed allylic alkylation in which chelated zinc enolates are employed as nucleophiles. Thus, a 1,5-stereoinduction was observed from the O-protecting group in the presence of allylic electrophiles. While the corresponding OTBDPS derivative led to a 1,5-*syn* stereoinduction, exchanging the silyl group with the directing *o*-DPPB group reversed the stereochemical course of the allylic substitution reaction. Conversely, high levels of *anti* diastereoselectivity were observed as a consequence of chelation control (Scheme 60).[67]

Regioselective allylic alkylation can also be achieved using the directing 2-PyMe$_2$Si group.[68] Depending on the nature of the nucleophile, both regioisomers can be obtained selectively (Scheme 61). Soft carbon nucleophiles, such as malonates, add exclusively to the most hindered position. This occurs as a result of a *trans* influence or chelation-induced allyl distortion,[69] which renders this position more reactive. Organotin nucleophiles add to the opposite allyl terminus



Scheme 60. Diastereoselective allylation with and without a directing group.

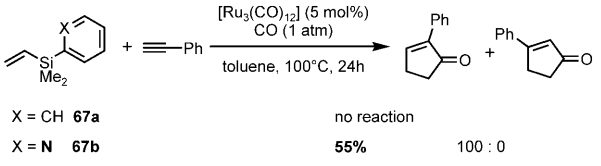


Scheme 61. 2-PyMe$_2$Si-induced regioselectivity in palladium-catalyzed allylic substitution.

through a different mechanism. Here, the first step is a transmetalation of the allyl nucleophile from tin to palladium, which upon reductive elimination transfers the allyl nucleophile to the sterically less hindered C1-position (Scheme 61).

2.4.2. *Pauson–Khand Reactions*

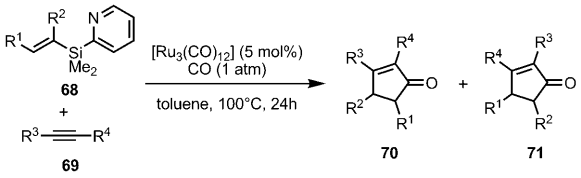
While numerous intramolecular Pauson–Khand reactions are known, the corresponding intermolecular variant is difficult to perform chemo- and regioselectively. Itami, Yoshida et al. showed that the use of the directing pyridylsilyl group resulted in a ruthenium-catalyzed Pauson–Khand reaction of vinylsilane **67b** with phenylacetylene, with complete regioselectivity towards the 2-phenyl-substituted cyclopentenone.[70] A control experiment with the phenyl-substituted silane **67a** confirmed the role of the pyridylsilyl group as a catalyst-directing group in the course of this reaction (Scheme 62). Interestingly, the directing group is removed under the reaction conditions.



Scheme 62. Effect of the directing group on the intermolecular Pauson–Khand reaction.

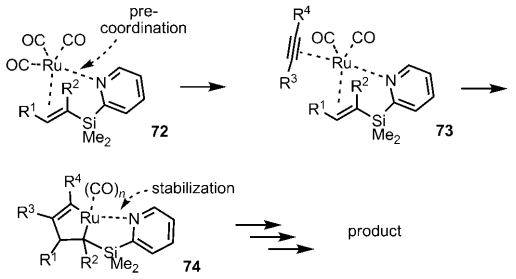
The use of substituted vinylsilane derivatives enabled cyclopentenones to be obtained with good levels of regioselectivity. Interestingly, these products cannot be prepared by classical Pauson–Khand reactions (Table 14).

Table 14: Catalytic intermolecular Pauson–Khand reactions of substituted vinylsilanes and alkynes.



Entry	R^1	R^2	R^3	R^4	Yield [%]	**70/71**
1	H	H	Ph	Ph	88	–
2	H	H	Me	Ph	75	100:0
3	C_4H_9	H	H	Ph	41	100:0
4	H	Me	H	$C6H_{13}$	40	62:38

The difference in reactivity between substrate **67a** and **67b** was explained by the suitably positioned pyridyl group, which should assist the reacting C=C bond to coordinate to the metal center through a chelation effect between the pyridyl nitrogen atom and the ruthenium catalyst (complex **72**, Scheme 63). This chelation effect enables the alkene to compete efficiently with CO as a ligand. In a second step, coordination of the alkyne occurs to furnish complex **73**. Oxidative cyclization via metallaycycle **74**, subsequent migratory insertion into a CO ligand, and final reductive elimination provide the observed product.



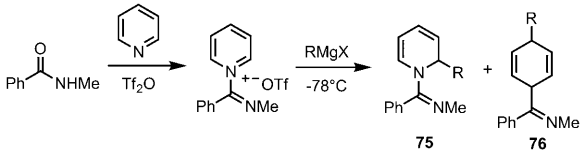
Scheme 63. Effect of the directing group on the reaction mechanism of the Pauson–Khand reaction.

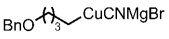
2.5. *Directed Reactions with Organometallic Nucleophiles*

2.5.1. *1,2-Additions*

The directed regio- and stereoselective synthesis of 2-substituted dihydropyridines was reported in 2001 by Charette et al. In this study, *N*-pyridinium imidates were used as substrates, in which the lone pair of electrons on the imidate is located in the proper position to direct the addition of an organometallic reagent towards the C2-position of the pyridine ring. These substrates are readily prepared by reaction of *N*-benzylamide with triflic anhydride in the presence of pyridine.[71] A variety of organomagnesium and

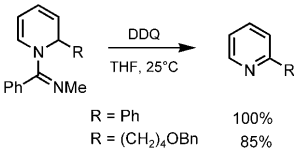
Table 15: Addition of organomagnesium and organocopper reagents to pyridinium imidates.



Entry	RMgX	**75**/**76**	Yield [%]
1	MeMgBr	>95:5	83
2	PhMgBe	>95:5	84
3		>95:5	86
4	EtMgBr	90:10	74
5	EtCuCNMgBr	92:8	65
6	2-furylMgBr	>95:5	96
7		94:6	76

organocopper reagents could be employed as nucleophiles to furnish the desired 1,2-dihydropyridines in good yields and high regioselectivities (Table 15).

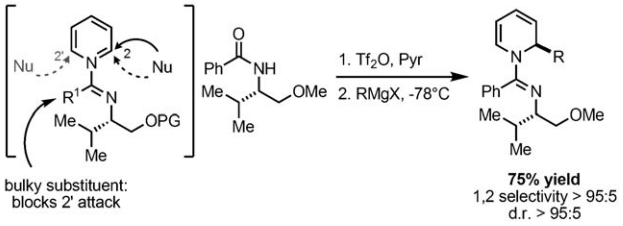
Oxidation of the dihydropyridines and concomitant removal of the directing group with DDQ gave the corresponding substituted pyridine derivatives (Scheme 64).



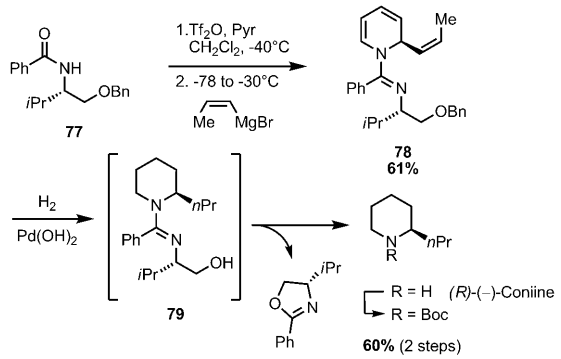
Scheme 64. Oxidation of 1,2-dihydropyridines. DDQ = 2,3-dichloro-5,6-dicyano-1,4-benzoquinone.

Enantiomerically enriched 2-substituted piperidines could be prepared by employing an (*S*)-valinol-derived chiral directing group. Of the two possible positions of nucleophilic attack (Scheme 65) position 2′ is blocked by the R^1 substituent, while position 2 is ideally located to allow an N-directed nucleophile transfer via the imidate function. The nucleophile will attack preferentially from the upper face, thus avoiding repulsive steric congestion with the isopropyl substituent of the auxiliary.

The practicality of this method was illustrated in the total synthesis of (−)-coniine, which was obtained in two steps



Scheme 65. Diastereoselective addition by employing a directing chiral imidate group.

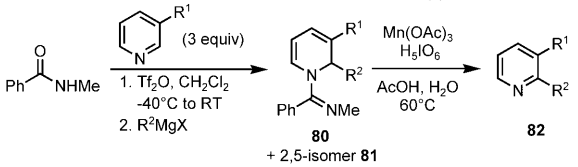


Scheme 66. Synthesis of (*R*)-(−)-coniine.

from **77** (Scheme 66).[72] Introduction of the chiral auxiliary was followed by addition of a propenyl Grignard reagent. Subjecting the intermediate product to the conditions of a catalytic hydrogenation gave intermediate **79**, which was found to eliminate the auxiliary spontaneously as the corresponding oxazoline to furnish (*R*)-coniine in 60% yield.

The same type of reaction was applied in the synthesis of 2,3-disubstituted pyridines starting from 3-substituted pyridinium salts.[73] Both the strong directing effect of the imidate nitrogen atom and stereoelectronic effects led to the formation of 2,3-disubstituted dihydropyridines in good yields and regioselectivities (Table 16). In this case the oxidation step turned out to be problematic. Finally, it was discovered that treatment with a substoichiometric amount of manganese triacetate and periodic acid in acetic acid afforded the desired pyridines **82** in good yields.

Table 16: Directed addition of Grignard reagents to 3-substituted pyridinium salts and oxidation to 2,3-disubstituted pyridines.



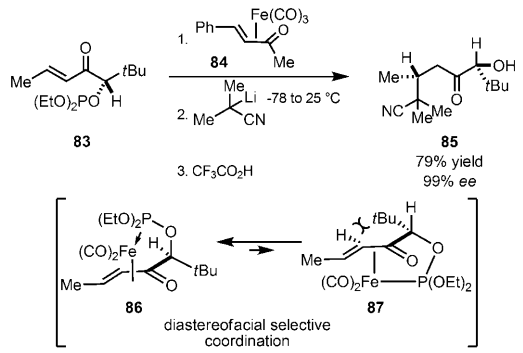
Entry	R^1	R^2	**80**/**81**	Yield **80** [%]	Yield **82** [%]
1	Me	Me	89:11	80	81
2	Me	Ph	79:21	72	80
3	OMe	Me	>95:5	100	–
4	OMe	Ph	>95:5	94	94
5	Cl	Me	95:5	85	63
6	Cl	Ph	78:22	66	91
7	Br	Me	92:8	80	57

A diastereoselective version of this reaction has been applied to the enantioselective synthesis of (−)-L-733,061 and (−)-CP-99,994, two members of a new class of highly potent, nonpeptide, substance P antagonists.[74]

2.5.2. *1,4-Additions*

Helquist and co-workers developed a directed conjugate addition, in which they used the chelation effect to induce

diastereofacial selective coordination of the alkene.[75] Investigations were carried out with α,β-unsaturated compounds because of their known ability to form reasonably stable and characterizable metal complexes. Reaction of phosphite-functionalized enone **83** with the iron complex **84** under substitution of benzylidene acetone led to the corresponding iron complex. Coordination of the metal can occur either on the upper or lower face of the enone. However, coordination on the lower face induces unfavorable interactions between the sterically demanding *tert*-butyl substituent and the alkenyl portion of the enone. Hence, coordination occurs on the upper alkene face to form complex **86** exclusively in 71% yield. Subjecting this complex to the conditions of a Michael reaction with α-lithioisobutyronitrile as the nucleophile furnished the conjugate adduct **85** in good yield and in diastereo- and enantiomerically pure form after acidic hydrolysis of the phosphite function (Scheme 67).



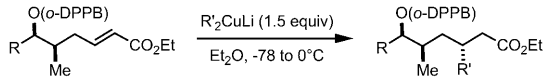
Scheme 67. Phosphite-directed conjugate addition to enone **83**.

Conjugate addition of cuprates to acyclic enoates directed by the *o*-DPPB group were also explored.[76] Enoates of type **88** were synthesized efficiently by combining the previously described *o*-DPPB-directed stereoselective hydroformylation and a subsequent Horner–Wadsworth–Emmons olefination. Chiral δ-methyl-substituted enoates are generally known to react nonselectively upon addition of dimethylcuprate.[77] Conversely, conjugate addition of enoates **88** with dialkyl cuprates gave the corresponding *anti*-1,4-addition products **89** in good yields and diastereoselectivities (Table 17).[78]

tert-Butylsulfinylimines also proved to be efficient directing groups for the conjugate addition of cuprates to α,β-unsaturated systems.[79] Substrates **90** were obtained after titanium-mediated condensation of the α,β-unsaturated aldehyde or ketone with a chiral sulfonamide. The enantiomerically pure *tert*-butylsulfinylimines obtained were subjected to the 1,4-addition conditions, and Yamamoto and Gilman cuprates were added in high yield and diastereoselectivity to both cyclic and acyclic derivatives (Table 18).

The facial selectivity of this 1,4-addition can be rationalized as depicted in Scheme 68. 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.[80]

Table 17: *o*-DPPB directed conjugate addition of cuprates to acyclic enoates.



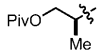
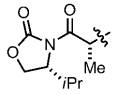
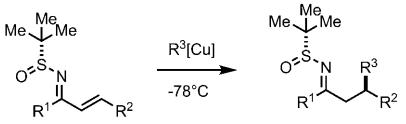
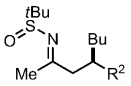
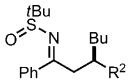
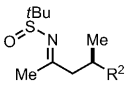
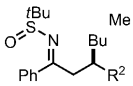
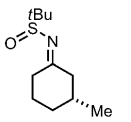
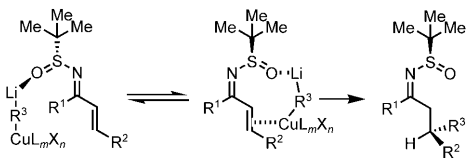
Entry	R	R′	Yield [%]	d.r.
1	*i*Pr	Me	93	95:5
2	*i*Pr	*n*Bu	68	95:5
3	*i*Pr	$CH{=}CH_2$	61	80:20
4		Me	68	95:5
5		Me	71	86:14
6		Me	60	85:15
7		Me	75	95:5

Table 18: Conjugate addition to chiral α,β-unsaturated sulfinylimines.



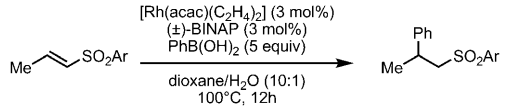
Entry	R^3[Cu]	Solvent	Product	Yield [%]	d.r.
1	Bu_2CuCN $BF_3{\cdot}OEt_2$	THF		68	93:7
2	Bu_2CuCN $BF_3{\cdot}OEt_2$	THF		76	92:8
3	Me_2CuLi	Et_2O		70	85:15
4	Me_2CuLi	Et_2O		91	96:4
5	Me_2CuLi	Et_2O		55	87:13



Scheme 68. Model for the facial diastereoselectivity.

Rhodium-catalyzed conjugate addition of aryl boronic acids to α,β-unsaturated sulfones was reported on using a chelated 2-pyridyl sulfone function.[81] The rate-accelerating effect of this directing group was proven since neither the

Table 19: Rhodium-catalyzed reaction of substituted propenyl sulfones with phenyl boronic acid.

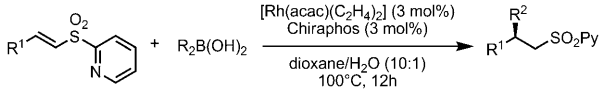


Entry	Ar	Conv [%]
1	Ph	< 2
2		> 98
3		< 2

corresponding phenyl nor the 4-pyridyl derivative gave any addition product (Table 19).

Conjugate addition products were obtained in high yield and good enantioselectivity on using the chiral ligand (*S*,*S*)-chiraphos (76–92 % *ee*, Table 20).

Table 20: Enantioselective rhodium-catalyzed addition of boronic acids to α,β-unsaturated-2-pyridyl sulfones.



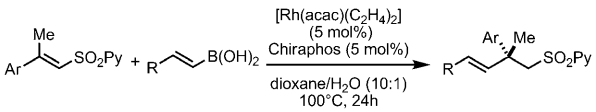
Entry	R^1	R^2	Yield [%]	*ee* [%]
1	Me	Ph	97	81
2	Me	*p*-F-C_6H_4	98	84
3	Me	*p*-MeO-C_6H_4	89	77
4	*n*-Pent	Ph	98	84
5	*n*-Pent	*p*-F-C_6H_4	94	87
6	*n*-Pent	*p*-MeO-C_6H_4	92	81
7	*i*Pr	Ph	93	78
8	*i*Pr	*p*-F-C_6H_4	93	85
9	*i*Pr	*p*-MeO-C_6H_4	74	76
10	β-Naph	Ph	96	87
11	β-Naph	*p*-F-C_6H_4	97	92
12	β-Naph	*p*-MeO-C_6H_4	84	85

Furthermore, the enantioselective construction of quaternary carbon centers could be realized by starting from β,β-disubstituted α,β-unsaturated sulfones and alkenyl boronic acid derivatives (Table 21).[82]

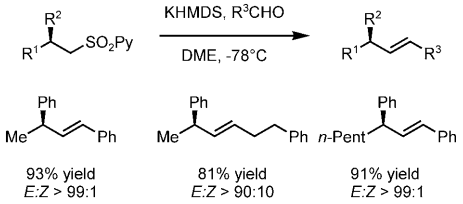
Sulfones with a stereocenter at the β position are highly versatile synthons in organic chemistry because of their ease of derivatization and they provide access to a wide range of building blocks. For example, the pyridylsulfonyl group was eliminated during the course of a Julia–Kocienski olefination, and the corresponding *E* alkenes were obtained in generally good diastereoselectivity without racemization at the β stereocenter (Scheme 69).

2-Pyridyl-functionalized α,β-unsaturated sulfones also underwent an efficient and enantioselective copper-catalyzed conjugate reduction with phenylsilane as the reducing agent (Scheme 70, Table 22).[83] The substrate scope is rather large,

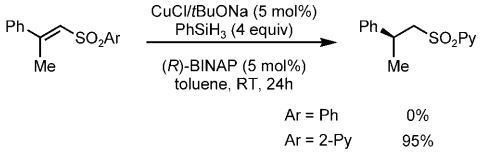
Table 21: Rhodium-catalyzed conjugate addition of alkenyl boronic acids to β,β-disubstituted α,β-unsaturated pyridyl sulfones.



Entry	R^1	R^2	Yield [%]	*ee* [%]
1	Ph	Ph	60	94
2	Ph	Me	41	89
3	Ph	Bn	43	> 99
4	*p*-Cl-C_6H_4	Ph	55	92
5	*p*-Cl-C_6H_4	Me	59	90
6	*p*-Cl-C_6H_4	Bn	71	88

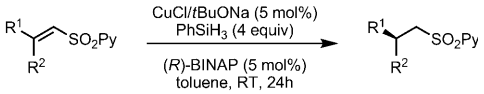


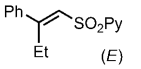
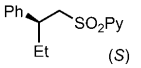
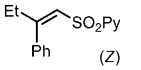
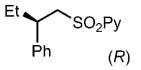
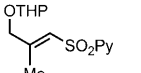
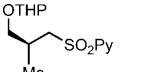
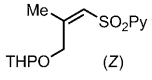
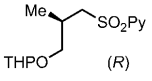
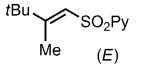
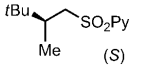
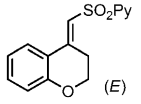
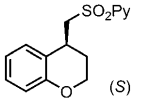
Scheme 69. Elimination of the pyridylsulfonyl group by Julia–Kocienski olefination.



Scheme 70. Reactivity of the phenyl- and 2-pyridylvinyl sulfones in the copper-catalyzed conjugate reduction.

Table 22: Enantioselective conjugate reduction of α,β-unsaturated 2-pyridyl sulfones.

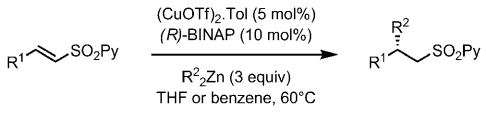


Entry	Substrate	Product	Yield [%]	*ee* [%]
1	 (*E*)	 (*S*)	92	93
2	 (*Z*)	 (*R*)	92	91
3	 (*E*)	 (*S*)	89	91
4	 (*Z*)	 (*R*)	91	91
5	 (*E*)	 (*S*)	93	91
6	 (*E*)	 (*S*)	93	90

with *E* and *Z* stereoisomers of the same vinyl sulfone furnishing opposite enantiomers.

A copper/binap catalyst proved efficient to achieve enantioselective conjugate addition of dialkyl zinc reagents to 2-pyridyl-functionalized α,β-unsaturated sulfones (Table 23).[84] Control experiments confirmed the necessity of the directing 2-pyridyl function for this transformation to occur.

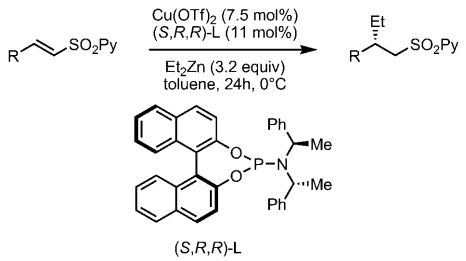
Table 23: Copper-catalyzed addition of diorgano zinc reagents to β-substituted α,β-unsaturated 2-pyridyl sulfones.



Entry	R^1	R^2	Yield in benzene (in THF) [%]	*ee* in benzene (in THF) [%]
1	Ph	Et	93 (72)	92 (98)
2	*p*-MeO-C_6H_4	Et	80 (61)	91 (98)
3	*p*-CF_3-C_6H_4	Et	83 (57)	84 (94)
4	2-Naph	Et	77 (63)	88 (97)
5	*i*Pr	Et	67 (55)	93 (96)
6	Me	Et	92 (93)	93 (88)
7	Ph	*n*Bu	53	90
8	Ph	$PhCH_2CH_2$	72	90

By employing the monodentate phosphoramidite ligand L Feringa and co-workers found the same type of addition under milder conditions (Table 24).[85]

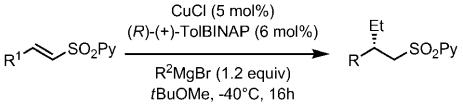
Table 24: Asymmetric conjugate addition of diethylzinc to α,β-unsaturated 2-pyridyl sulfones.



Entry	R	Yield [%]	*ee* [%]
1	Ph	70	92
2	*o*-Cl-C_6H_4	85	70
3	*m*-Cl-C_6H_4	66	84
4	*p*-MeC_6H_4	46	92
5	*p*-CF_3-C_6H_4	84	96
6	*p*-Br-C_6H_4	86	96
7	2-Naph	83	93

A complementary copper-catalyzed addition of Grignard reagents to vinyl sulfones has also been reported.[86] The reaction was applied to a set of α,β-unsaturated sulfones, and high yields and enantioselectivities were obtained by using (*R*)-(+)-TolBinap as the chiral ligand (Table 25). Again, the presence of the 2-pyridyl group was found to be crucial in terms of reactivity and enantioselectivity.

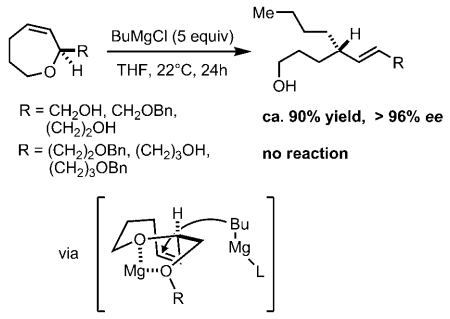
Table 25: Asymmetric conjugate addition of various Grignard reagents to α,β-unsaturated 2-pyridyl sulfones.



Entry	R^1	R^2	Yield [%]	*ee* [%]
1	*n*-Pent	Et	97	93
2	*i*Bu	Et	88	94
3	*i*Pr	Et	93	88
4	Cy	Et	94	94
5	$TBDPSOC_2H_4$	Et	91	92
6	$PhCH_2CH_2$	Et	91	93
7	*n*-Pent	Me	80	89
8	*n*-Pent	*n*Bu	88	93
9	*n*-Pent	$PhCH_2CH_2$	87	87
10	*n*-Pent	but-3-enyl	95	94

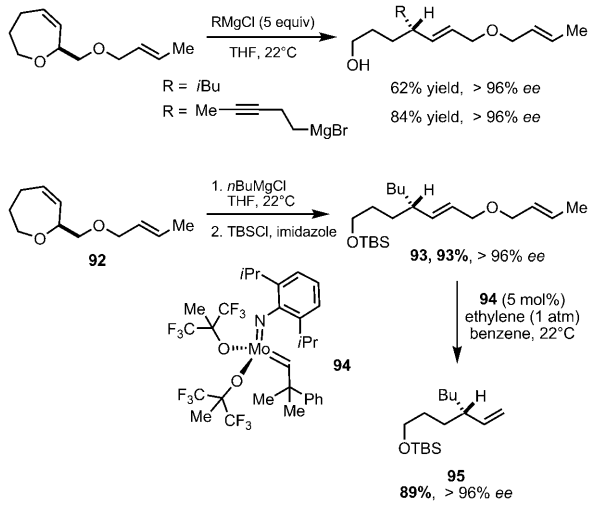
2.5.3. *Allylic Substitution*

Diastereoselective allylic substitutions of cyclic allylic ethers such as unsaturated oxepins and oxocenes were promoted by an appropriately positioned Lewis basic directing group (Scheme 71).[87] This pendant chain at the C2-position is necessary to achieve good levels of selectivity and can be easily removed at the end of the process. The addition of Grignard reagents to these cyclic allylic ethers occurred when both the C2 side chain and the ring system contain Lewis basic heteroatoms that are available for coordination to the Mg center. Very good yields and selectivities were obtained for different side chains. The proposed mode of addition is a two-point chelation, which facilitates the cleavage of the ring C–O bond through activation by the bound Lewis acidic Mg^{2+} center (Scheme 71).



Scheme 71. Diastereoselective allylic substitution of oxepins.

As the Lewis basic site required for the substitution reaction may not be desired in the final product, a method was developed to remove the directing group. For this purpose, a crotyl ether substituent was employed as the directing group, and good results were obtained with various Grignard reagents (Scheme 72). The advantage of the crotyl ether group is its ease of removal through subsequent ring-closing metathesis by using the molybdenum catalyst **94** to furnish the α-chiral olefinic product **95** in high yield and enantiomeric purity.



Scheme 72. Removal of the chelating group by ring-closing metathesis.

3. Stoichiometric Use of Directing Leaving Groups

One major disadvantage of removable directing groups in organic synthesis is the need for additional steps for their installation and removal. One way to minimize these steps is to use the directing group simultaneously as a leaving group, which in turn may influence the stereo- and regiochemical course of the corresponding reaction. This strategy has been used successfully for allylic and propargylic substitution reactions in the presence of transition-metal catalysts and organometallic reagents.

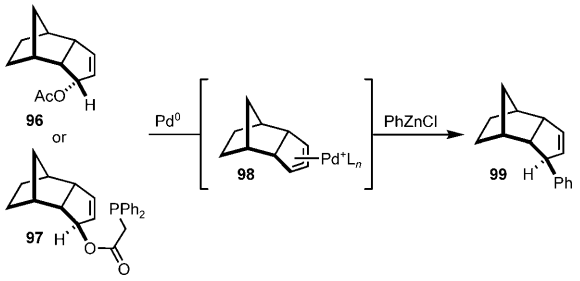
3.1. Allylic Substitution

3.1.1. Palladium-Catalyzed Allylic Substitutions

Palladium-catalyzed allylic substitution in the presence of a "hard" organometallic nucleophile usually occurs through an *anti-syn* mechanism with overall inversion of configuration. Thus, the palladium(0) catalyst attacks the allylic electrophile *anti* to the leaving group. Subsequently, the organometallic nucleophile adds to the palladium center and is transferred *syn* to the palladium to the allylic terminus by reductive elimination. However, the use of an acetate leaving group equipped with a phosphine donor allowed this original stereochemical course to be reversed. Thus, reaction of the sterically biased *endo* allyl acetate **96** with phenylzinc chloride proceeded with overall inversion of configuration. The phosphine-functionalized *exo* acetate **97** furnished the same product with retention of configuration. Thus, the directing phosphine leaving group forces the palladium catalyst to approach *syn* relative to the leaving group (Scheme 73).[66,88]

3.1.2. Copper-Mediated Allylic Substitutions

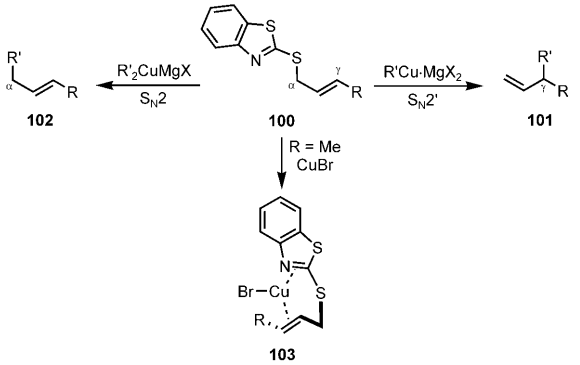
The intrinsic stereochemical course for an allylic substitution with organocopper reagents is an *anti* substitution with respect to the leaving group. This can be overruled in favor of a *syn*-substitution pathway in the case where directing leaving



Scheme 73. Nondirected and directed formation of π-allylpalladium complexes.

groups are employed. Suitable directing groups are equipped with donor atoms, such as nitrogen or phosphorus(III), which are capable of coordinating to organocopper reagents. An additional advantage is that the use of appropriate directing leaving groups may solve the intrinsic regioselectivity problem of S_N versus S_N' pathways for copper-mediated allylic substitution in favor of the S_N' products.[89]

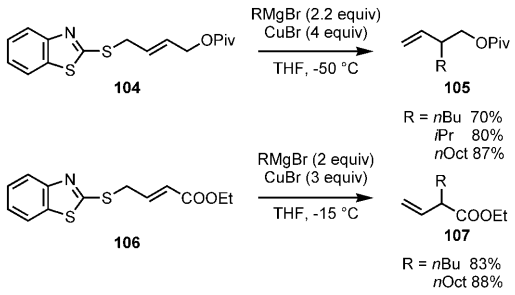
Heterocyclic carbonic acid derivatives proved to be useful directing leaving groups in allylic substitution reactions, and have been investigated by Calò et al.[90] The reaction of benzothiazoles **100** with an organocopper reagent obtained from R′MgBr and an excess of a copper(I) salt furnished S_N2' products **101** in high regioselectivity (Scheme 74). The less electrophilic cuprates R_2CuMgX gave the S_N2 products **102**



Scheme 74. Regioselectivity of the allylic substitution depending on the copper reagents.

selectively, which is proposed to be due to their reduced affinity for additional coordination. The organocopper species is presumed to coordinate to the substrate, with intramolecular transfer of the C nucleophile. The crotyl derivative **100** (R = Me) formed a stable complex **103** with CuBr (Scheme 74).[91] IR spectroscopic investigation of **103** suggested a coordination of the C=N and C=C π systems to the copper(I) center. Exchange of bromine with the corresponding carbon nucleophile allows for an intramolecular nucleophile delivery, which would be responsible for the high chemo- and regioselectivity of the reaction.

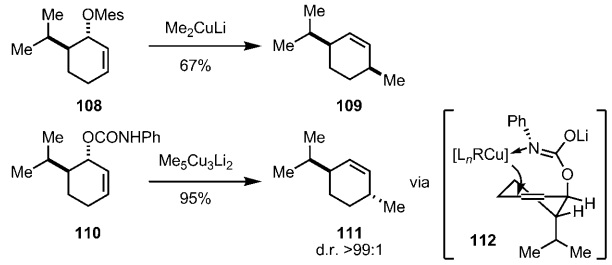
Allylic substitution of benzothiazole **104** with organocopper reagents afforded homoallylic pivalates **105** as single regioisomers (Scheme 75).[92] This result shows the directing



Scheme 75. Allylic substitutions with benzothiazoles.

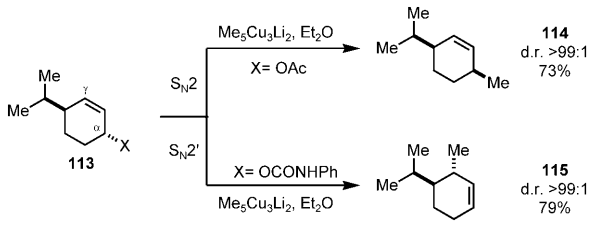
benzothiazole to be a much better leaving group than the competing pivaloate.[93] Equally, when enoates **106** were employed, high chemo- and regioselectivity toward S_N' products **107** were noted.[94]

Carbamates have also been identified as powerful reagent-directing leaving groups. While the reaction of cyclic mesylate **108** gave the *anti* S_N2' product **109** only, the corresponding carbamate **110** reversed the stereochemical course of the reaction and provided the *syn*-substitution product **111** exclusively (Scheme 76).[95] It was assumed that the cuprate reagent is coordinated by the carbamate nitrogen atom (reactive conformation **112**, Scheme 76), which renders the attack of the C nucleophile intramolecular in nature and consequently highly regioselective.



Scheme 76. Nondirected and carbamate-directed allylic substitution.

This is nicely illustrated by the reaction behavior of cyclic substrate **113** (Scheme 77). For this substrate, γ attack is sterically hindered, and the nondirected reaction of the acetate with a higher-order methyl cuprate gave S_N2-type product **114** exclusively. The carbamate on the other hand is able to invert the stereochemistry and allows the exclusive formation of S_N2' product **115** by overruling steric effects.[96] Similar results were obtained upon treatment of **113** with silyl

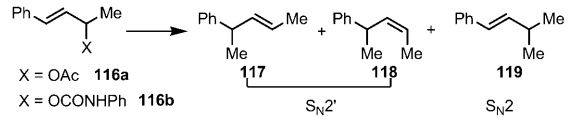


Scheme 77. Regioselectivity with sterically hindered substrates.

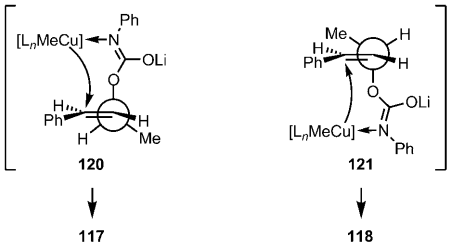
cuprates.[97] Hence, the generalization can be made that carbamate leaving groups induce high γ selectivity upon allylic substitution with organocuprates and can overrule steric hindrance at the γ position in the allylic framework.

The situation is more complex for acyclic substrates. A larger number of reactive conformations become available and the corresponding transition states compete. Thus, upon treatment with lithium dimethylcuprate, methylcinnamyl-derived acetate **116a** gave mainly S_N2 product **119** (Table 26, entry 1).[98] Preference for the S_N2 product is

Table 26: Reaction of acyclic allylic substrates with organocopper reagents.

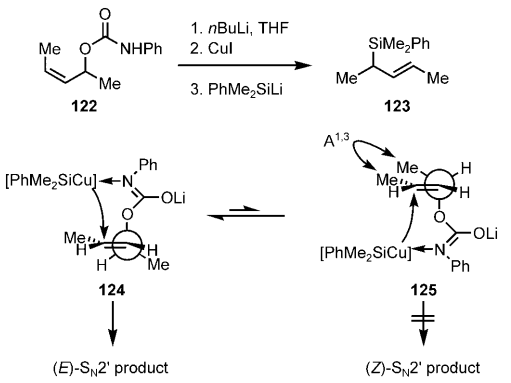


Entry	X	Conditions	117/118/119	Yield [%]
1	OAc	MeCuLi, Et_2O	4:0:96	>99
2	OCONHOPh	1. MeLi, THF 2. CuI 3. MeLi	89:11:0	not determined



expected, since deconjugation of the alkenic system is electronically unfavorable. Conversely, exclusive γ-alkylation was observed on employing carbamate **116b** (Table 26, entry 2).[99] However, the alkene configuration could only be maintained partially to furnish a 89:11 mixture of the *E* and *Z* isomers **117** and **118**.

The formation of both alkene isomers can be rationalized through the two competing transition states **120** and **121**. Minimization of the $A^{1,3}$ strain should favor transition state

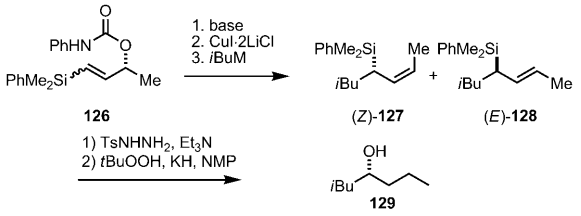


Scheme 78. Improvement of selectivity with *Z* olefins.

120 to form the *trans*-alkene **117**. Since, the $A^{1,3}$ strain in a *cis*-alkene is significantly pronounced, it is thus reasonable that the reaction of (*Z*)-allylic carbamate **122** with the mixed silyl cuprate led to the exclusive formation of *E* alkene **123** via **124** (Scheme 78).

Generally, both (*E*)- and (*Z*)-allylic carbamates furnish, either exclusively or preferentially, the (*E*)-alkenic product upon allylic substitution with organocopper reagents. Conversely, it was found that silyl-substituted allylic carbamates (*E*)-**126** (Table 27) unexpectedly furnished *Z* selectivity in the

Table 27: Allylic substitution with *Z* selectivity.

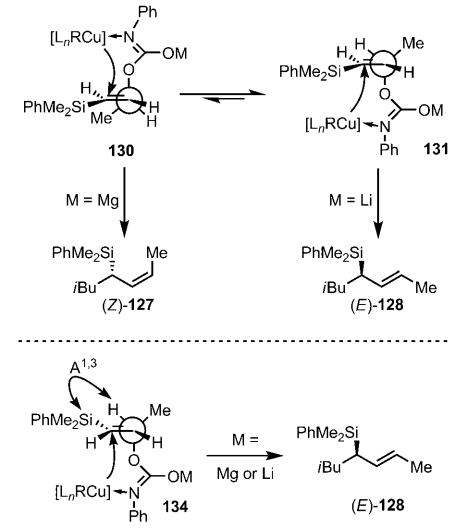


Entry	Substrate	Base	M	**127**/**128**	Yield [%]	*ee* **129** [%]
1	(*E*)-**126**	*n*BuLi	MgCl	94:6	90	88
2	(*E*)-**126**	*n*BuLi	Li	9:91	69	–
3	(*Z*)-**126**	MeLi	MgCl	3:97	93	92
4	(*Z*)-**126**	MeLi	Li	<1:99	93	94

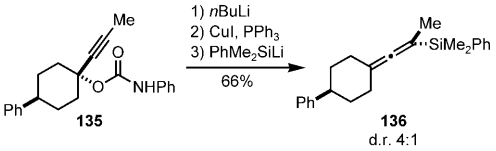
presence of mixed organomagnesium/copper reagents.[100] Enantiomerically pure carbamate (*E*)-**126** furnished (*Z*)-allylsilane **127** in high yield in the presence of an organocopper reagent prepared from isobutylmagnesium chloride (Table 27, entry 1). However, treatment of carbamate (*E*)-**126** with the isobutyl organocopper reagent prepared from the corresponding organolithium reagent furnished (*E*)-allylsilane **128** (Table 27, entry 2). On the other hand, both reagent types reacted with the *Z* isomer of **126** to give (*E*)-allylsilane **128** stereoselectively (Table 27, entries 3 and 4).

The transition-state models depicted in Scheme 79 were suggested as a rationale for these results. Allylic substitution of (*E*)-silanes **126** proceeds via either one of the two rotamers **130** and **131**. In this way, the stereochemical outcome in the presence of the lithium reagent is easily understood through reactive conformation **131**, which has minimized $A^{1,3}$ strain. Reaction via reactive conformation **130** is preferred in the presence of a magnesium counterion to give *Z* alkene **127**. However, for *Z* silane **126**, the pronounced $A^{1,3}$ strain dictates that the reaction in both cases (M = Mg or Li) proceeds via reactive conformation **134** to furnish *E*-allylic silane **128**.[100b]

Related to the allylic substitution reaction is the substitution of propargylic derivatives, which leads 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.[101,102] 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 a reagent-directing carbamate was installed, reaction with a silyl organocopper reagent furnished the corresponding *syn*-substitution product, allene **136**, in good yield and diastereoselectivity (Scheme 80).[103] 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.

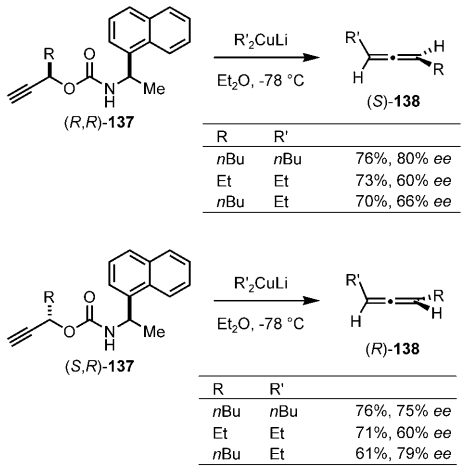


Scheme 79. Rationale for the reagent- and substrate-dependent diastereoselectivity in the allylic substitution with carbamate **126**.



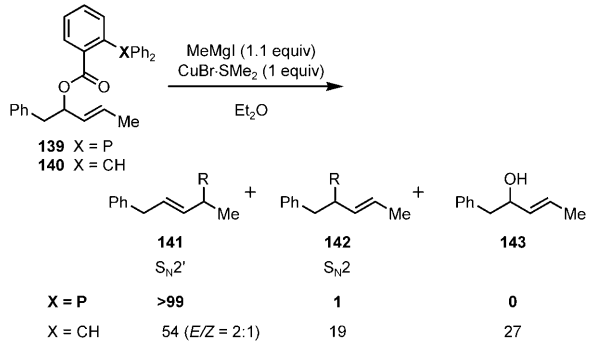
Scheme 80. Propargylic substitution.

Enantiomerically enriched allenes can be accessed by using diastereomeric carbamates (*R*,*R*)-**137** and (*S*,*R*)-**137**.[104] Propargylic substitution of different substrates with Gilman cuprates afforded chiral allenes **138** in good yields and moderate enantioselectivities (60 to 80% *ee*; Scheme 81).



Scheme 81. Propargylic substitution of chiral carbamates.

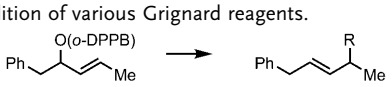
The geometry of the *o*-DPPB group is ideal for directing a metal center into the allylic or homoallylic position of an organic substrate. This group can be expected to serve as a directing leaving group for allylic substitution with organocopper reagents. Indeed, the copper-mediated allylic substitution of allylic *o*-DPPB ester **139** afforded the S_N2' product **141** with high chemo- and regioselectivity (Scheme 82).[105] A control experiment with CH ester **140** revealed a significantly reduced rate and dramatically reduced chemo-, regio-, and diastereoselectivity. These findings underline the role of the *o*-DPPB group as a reagent-directing leaving group.



Scheme 82. Regioselectivity of the *o*-DPPB-directed allylic substitution.

Excellent regio- and stereoselectivity was observed when primary and secondary alkyl and aryl Grignard reagents were used (Table 28). Even better results were obtained in the presence of 0.5 equivalent of a copper salt (Table 28, entries 3 and 4). This finding suggests that phosphine-coordinated organocopper species are the reactive organometallic intermediates.

Table 28: Addition of various Grignard reagents.



Entry	$CuBr\cdot SMe_2$ (equiv)	Grignard reagent	Yield [%]	*E*/*Z*
1	1	*n*BuMgCl	98	>99:1
2	1	*i*PrMgCl	84	97:3
3	1	PhMgBr	94	88:12
4[a]	0.5	PhMgBr	94	97:3

[a] Et_2O/CH_2Cl_2 as solvent.

The coordination behavior of allylic *o*-DPPB esters towards copper(I) salts was studied, and a 2:1 complex (*o*-DPPB ester/CuBr) with a trigonal-planar coordination geometry at the copper center was isolated and analyzed crystallographically (Figure 2). The selected formation of the 2:1 complex suggested that application of 0.5 equivalent of copper salt should be sufficient for a stoichiometrically directed process, which in fact proved to be ideal for most directed allylic substitution reactions of *o*-DPPB esters (Table 28, entry 4).

The optimized reaction conditions for directed allylic substitutions were applied to a series of *o*-DPPB esters

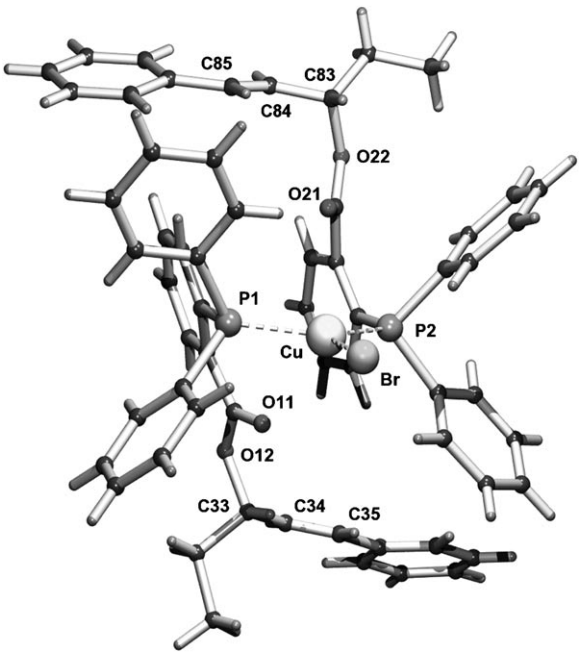
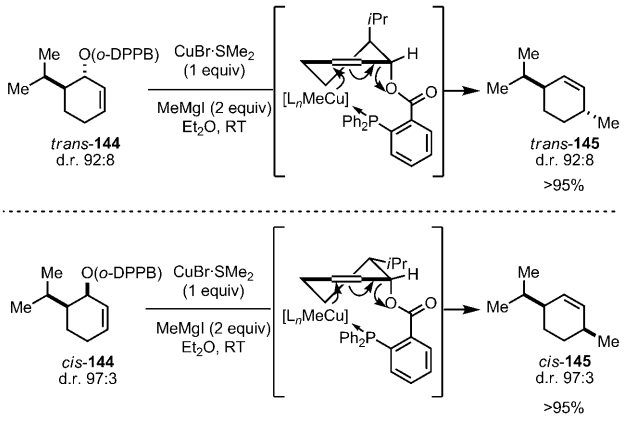


Figure 2. Complex formed between the *o*-DPPB allyl ester and copper bromide.

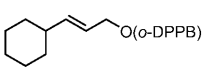
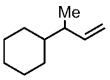
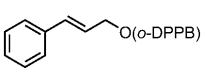
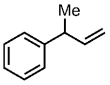
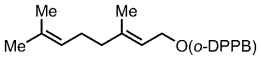
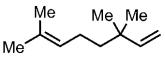
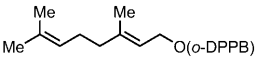
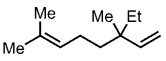
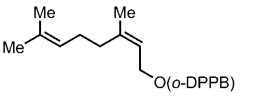
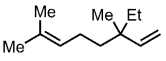
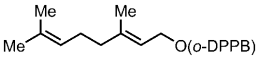
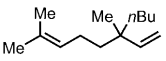
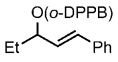
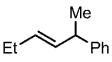
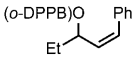
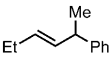
(Table 29). In general, excellent yields and S_N2' regioselectivity were observed. Excellent regioselectivity with concomitant construction of quaternary carbon centers was observed, irrespective of the double bond geometry. Excellent levels of regioselectivity were also reached with secondary allylic *o*-DPPB esters, and the yields of the corresponding isolated S_N2' products were generally high (Table 29, entries 7 and 8).

The stereochemistry of substitution reactions with *o*-DPPB esters upon subjecting the cyclic substrates *cis*-**144** and *trans*-**144** to the conditions of the directed allylic substitution with methylmagnesium bromide was determined. In both cases, a completely *syn*-selective nucleophile transfer was observed to give *cis*- and *trans*-menthene (**145**), respectively (Scheme 83). A complete 1,3-chirality transfer was observed, even for *trans*-**144**, although in this case the substrate has to



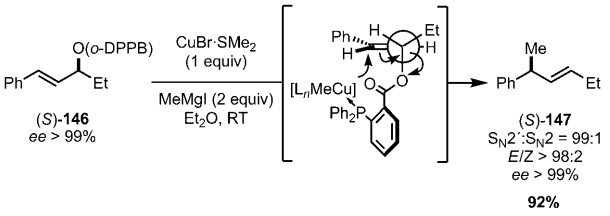
Scheme 83. Stereochemistry of the *o*-DPPB-directed allylic substitution with cyclic substrates **144**.

Table 29: Regioselectivity of the copper-mediated *o*-DPPB-directed allylic substitution (reaction conditions as for Table 28, entries 1–3).

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

pass through a reactive conformation which places the isopropyl substituent in a sterically unfavorable pseudoaxial position to fulfill the stereoelectronic requirements of optimal overlap between the π orbital of the alkene and the σ*-(C-O) orbital of the leaving group.

Copper-mediated allylic substitution of acyclic substrate (*S*)-**146** (>99% *ee*) with methylmagnesium iodide furnished the corresponding S_N2' product (*S*)-**147** in high yield as well as high regio- and stereoselectivity (Scheme 84). This result proves that the reaction of acyclic substrates follows a *syn*-S_N2' pathway to give a perfect 1,3-chirality transfer.



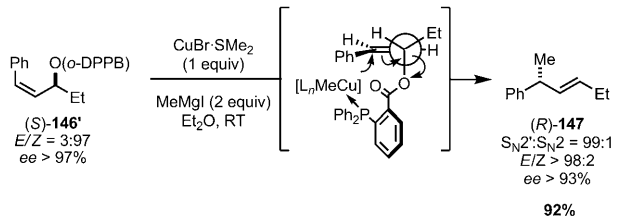
Scheme 84. Stereoselectivity of the *o*-DPPB-directed allylic substitution with acyclic substrate **146**.

According to the transition-state model, a switch of the alkene geometry in the starting allylic ester **146** from the *E* to *Z* configuration should furnish the optical antipode (*R*)-**147**. Indeed, subjecting the *Z* substrate (*S*)-**146′** with the same absolute configuration to the conditions of the directed allylic substitution afforded (*R*)-**147**, with perfect 1,3-chirality transfer, according to the directed *syn*-substitution pathway (Scheme 85).

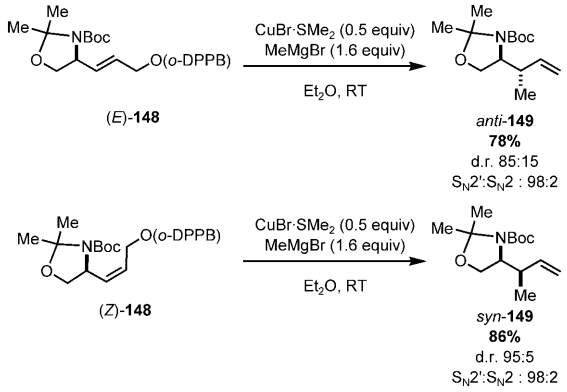
The directed allylic substitution with *o*-DPPB esters of secondary allylic alcohols occurs with perfect 1,3-chirality transfer for both structurally defined cyclic systems and conformationally more flexible acyclic derivatives. In the latter case, the reaction enables the stereospecific construction of a tertiary stereogenic carbon center as a function of the alkene geometry.

In all of the previously discussed cases, the directing *o*-DPPB group was directly attached to a stereogenic tertiary alcohol function, and perfect 1,3-chirality transfer was realized for acyclic and cyclic systems. Conversely, with substrates (*E*)- and (*Z*)-**148**, the stereochemical information is not part of the allylic alcohol system, but resides in the δ position (Scheme 86).[106] Nevertheless, the reaction of (*E*)-allylic *o*-DPPB ester **148** with methylmagnesium bromide in the presence of a copper(I) salt furnished *anti*-substitution product **149** in good diastereoselectivity. Even better results were obtained for *Z*-allylic *o*-DPPB ester **148**, which furnished *syn* product **149**.

Other aliphatic Grignard reagents (Table 30) can be used, and in all cases high yields and regioselectivities were observed. Excellent diastereoselectivities were found with (*Z*)-**148** (Table 30, entries 4–6). For the corresponding (*E*)-*o*-DPPB ester **148**, the *anti* selectivity toward **149** was high when a secondary alkyl Grignard reagent was used (Table 30,

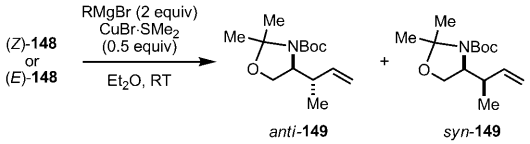


Scheme 85. (*Z*)-*o*-DPPB esters lead to products with opposite absolute configuration.



Scheme 86. Allylic substitution with substrates bearing the stereochemical information in the δ position.

Table 30: Directed allylic substitutions with *o*-DPPB esters (*E*)-**148** and (*Z*)-**148**.



Entry	Substrate	R	S_N2'/S_N2	*syn*/*anti*	Yield [%]
1	(*E*)-**148**	Et	96:4	15:85	91
2	(*E*)-**148**	*n*Bu	98:2	17:83	97
3	(*E*)-**148**	*i*Pr	98:2	7:93	97
4	(*Z*)-**148**	Et	99:1	97:3	98
5	(*Z*)-**148**	*n*Bu	98:2	98:2	96
6	(*Z*)-**148**	*i*Pr	95:5	95:5	98

entry 3), but dropped upon reaction with primary organometallic reagents (Table 30, entries 1 and 2).

A rationale for the stereochemical outcome is depicted in Figure 3. For (*E*)-**148**, both reactive conformations **150** and **151** are plausible for the high *anti* selectivity. The allylic $A^{1,3}$ strain is minimized in these conformations, and the

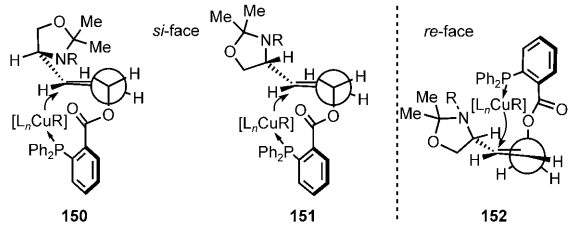
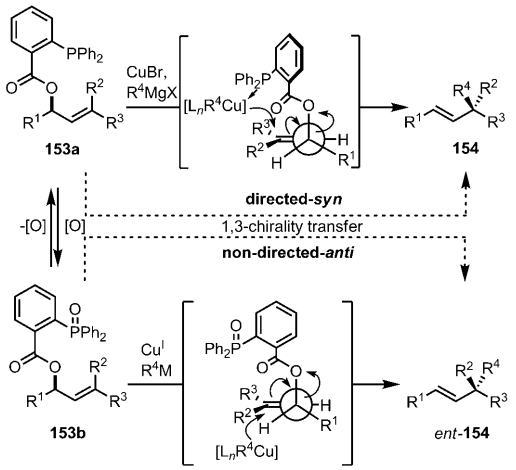


Figure 3. Proposed reactive conformations in the allylic substitution of *o*-DPPB esters (*E*)- and (*Z*)-**148**.

directed attack of the nucleophile can occur from the least hindered *si* alkene face to give the *anti* diastereomer preferentially. In the case of (*Z*)-**148**, reactive conformation **152** explains the predominating formation of the *syn* product, which results 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*)-**148**. This method allowed the synthesis of a naturally occurring amino acid isolated from the mushroom *Amanita castanopsidis hongo*.[107]

Interestingly, the directing power of the *o*-DPPB group can be controlled by an oxidative on/off switch.[108] This allows the preparation of both optical antipodes of the substitution product starting from a single substrate enantiomer (Scheme 87). To gain access to both enantiomeric substitution products, starting from the same *o*-DPPB ester substrate, the mechanism 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 phosphanyl ester **153a** gives phosphine oxide ester **153b**, in which the directing ability of the phosphorus is suppressed. Additionally, changing the *o*-phosphanyl group to a phosphane oxide increases the leaving group capability of the benzoate significantly. Hence, the

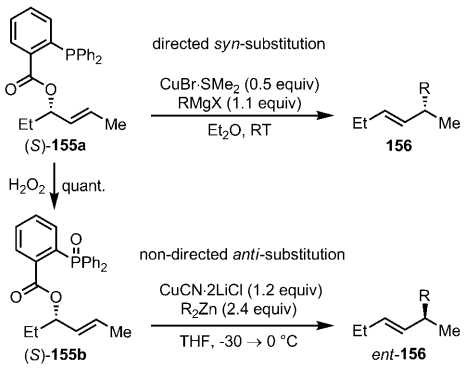


Scheme 87. Oxidative on/off switch.

chirality of the allylic alcohol is transferred to substitution-product **154** and can be easily switched between *syn* and *anti* selectivity.

The viability of the method was examined by using *o*-DPPB esters (*S*)-**155a** and (*S*)-**155b** as the substrates for allylic substitutions (Table 31). In directed substitution reac-

Table 31: Directed and nondirected allylic substitutions with esters (*S*)-**155a** and (*S*)-**155b**.

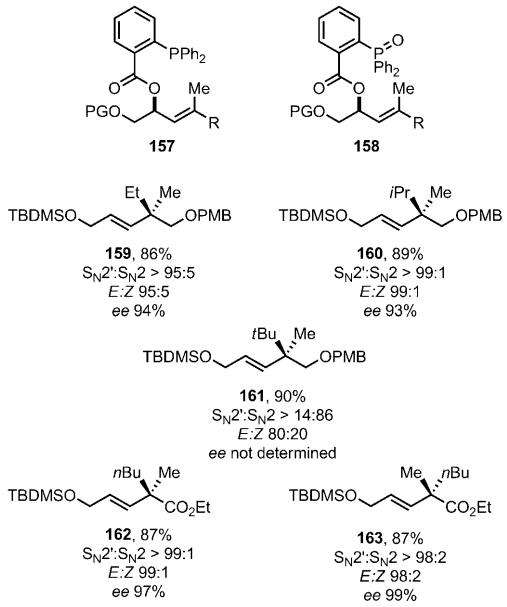


Entry	Substrate	R	S_N2'/S_N2	*ee* [%]	Yield [%]
1	(*S*)-**155a**	*n*Bu	98:2	97	96
2	(*S*)-**155a**	3-Pent	97:3	95	90
3	(*S*)-**155a**	*t*Bu	97:3	80	96
4	(*S*)-**155a**	Ph	98:2	94	94
5	(*S*)-**155a**	Bn	97:3	93	97
6	(*S*)-**155b**	*n*Bu	94:6	97	92
7	(*S*)-**155b**	*t*Bu	75:25	74	68
8	(*S*)-**155b**	Ph	93:7	94	86

tions with alkyl, aryl, and benzyl Grignard reagents, high levels of regio- and stereoselectivity were constantly observed (Table 31, entries 1–5). However, a limitation is the sterically demanding *tert*-butyl reagent, which reacted with diminished chirality transfer (Table 31, entry 3). Treatment of substrate (*S*)-**155a** with hydrogen peroxide gave the corresponding phosphanoxide (*S*)-**155b**. The allylic substitution of (*S*)-**155b**

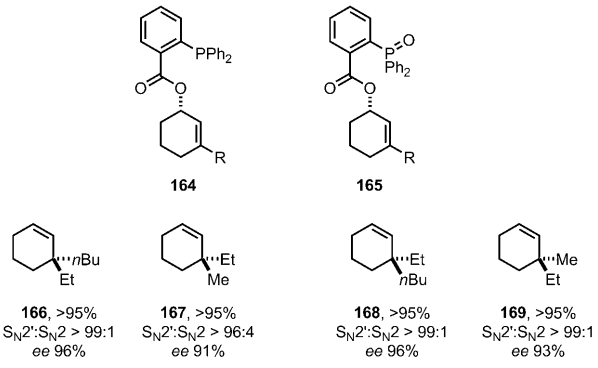
occurred cleanly when employing alkyl and aryl zinc reagents in combination with copper cyanide to furnish the *anti* S_N2' products, generally with excellent chirality transfer.

The stereoselective construction of a quaternary carbon center is also feasible by the directed and nondirected allylic substitution strategy. Thus, from highly functionalized *o*-DPPB esters **157** or phosphane oxides **158**, which are readily accessible from the chiral pool (D-mannitol), *syn*- or *anti*-substitution products were obtained in excellent regio- and stereoselectivities in the presence of different carbon nucleophiles (Scheme 88). In the case of the large *tert*-butyl group, the competing S_N2 reaction became significantly favored for steric reasons.

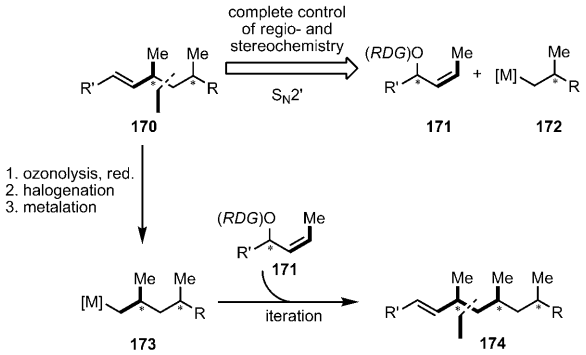


Scheme 88. Construction of a quaternary carbon center.

The on/off switch of the reagent directing group was further explored with cyclic substrates **164** and **165**, and again excellent results were obtained for both the directed and nondirected allylic substitution (Scheme 89).



Scheme 89. Directed and nondirected allylic substitution with cyclic substrates **164** and **165**.

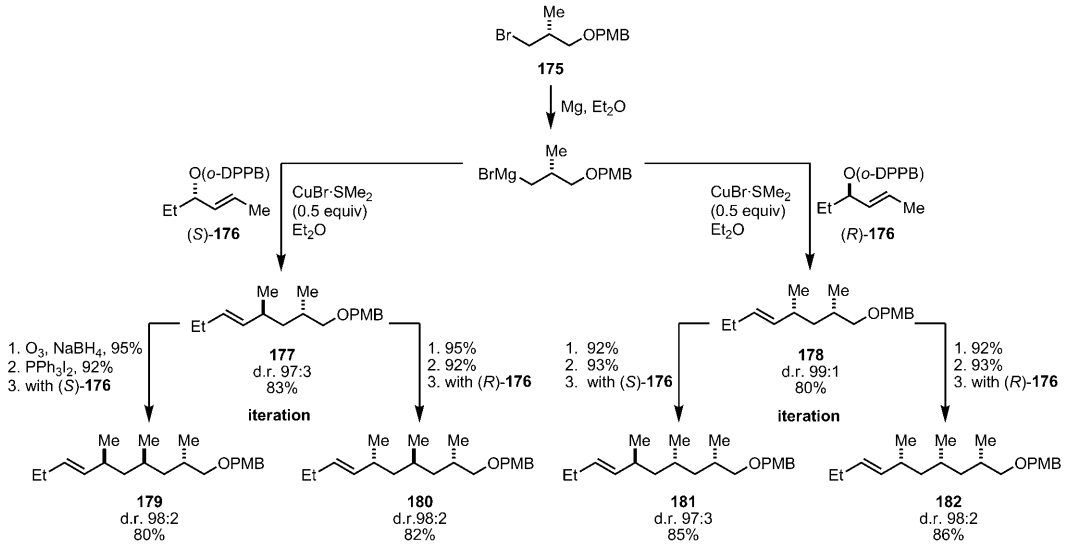


Scheme 90. Iterative process to access deoxypropionate units.

The allylic substitution method with *o*-DPPB esters such as **171** was applied in an iterative fashion for the construction of the 1,3,*n*-methyl substitution pattern of deoxypropionates (Scheme 90).[109] A directed S_N2' reaction of esters **171** with organometallic reagents is the key step of this sequence, and gives access to alkenes **170**. Cleavage of the double bond through ozonolysis followed by a reductive workup gives the corresponding alcohol. Halogenation and consecutive metalation furnish a new organometallic nucleophile **173**, which can be applied in a further directed allylic substitution with **171** to give the trideoxypropionate. After two cycles, highly complex structures such as building block **174** are already accessible, thus allowing for functionalization either on the R group derived from the originally employed organometallic reagent **172** or on the alkene terminus generated in the course of the allylic substitution.

The method allows for the preparation of all four possible diastereomers of a deoxypropionate stereotriad in an enantiomerically pure form (Scheme 91). Thus, starting from the bromide **175**, allylic substitution with enantiomerically pure *o*-DPPB esters (*S*)-**176** and (*R*)-**176** gave dideoxypropionates **177** and **178** in good yields and diastereoselectivity. Formation of the *syn* diastereomer appears to represent a matched case, while substitution reactions producing the *anti* isomer represent a mismatched case. Iteration of this sequence was achieved starting with an oxidative alkene cleavage of dideoxypropionate derivatives **177** and **178** through ozonolysis and reductive workup followed by iodination under standard conditions. Transformation into the organometallic reagent occurred upon halogen–metal exchange with *tert*-butyllithium followed by transmetalation to magnesium. Directed allylic substitution with allyl electrophiles (*S*)-**176** and (*R*)-**176** in the presence of copper bromide furnished all four possible trideoxypropionates in good yields, perfect regioselectivities, and excellent stereoselectivities. The utility of this iterative method was demonstrated in the formal total synthesis of borrelidin[109] as well as in the total synthesis and determination of the absolute and relative configuration of 4,6,8,10,16,18-hexamethyldocosane (Figure 4).[110]

This strategy was also employed for the flexible and stereospecific preparation of propionate, acetate propionate, and acetate deoxypropionate structural motifs (Scheme 92).[111] In this case, the key building block **183** is again an allylic *o*-DPPB ester which contains an additional



Scheme 91. Synthesis of all four diastereomers of a deoxypropionate stereotriad.

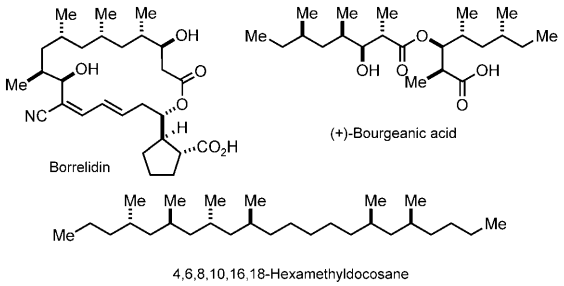
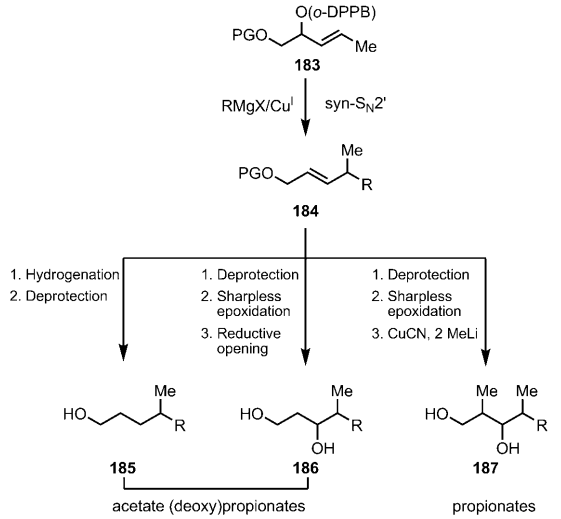
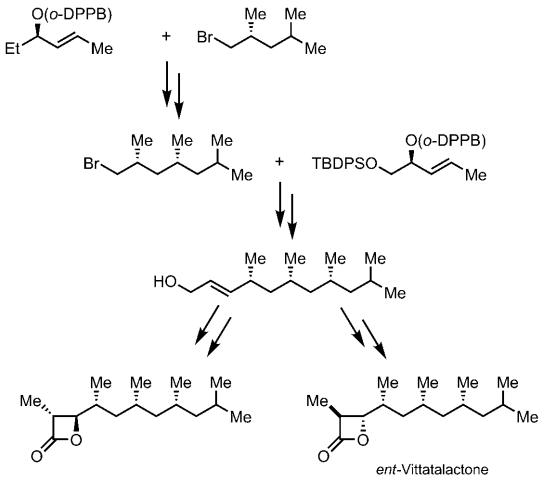


Figure 4. Application of the iterative directed allylic substitution method for the total synthesis of natural products.

oxygen functionality in the homoallylic position. After the first directed allylic substitution, an allylic alcohol function is generated and, depending on the further functionalization, a variety of polyketide motives can be accessed. A hydrogenation step furnishes acetate deoxypropionate **185**. Alternatively, either acetate propionates **186** or propionates **187** can be formed by applying a Sharpless epoxidation followed by nucleophilic opening of the epoxide ring. The utility of this method was demonstrated in the total synthesis of the lichen metabolite (+)-bourgeanic acid, which was obtained in 12 steps and an overall yield of 10% (Figure 4).[112] Furthermore, the absolute configuration of vittatalactone, the sex pheromone of the striped cucumber beetle, was determined through total synthesis of two diastereoisomers (Scheme 93).[113]



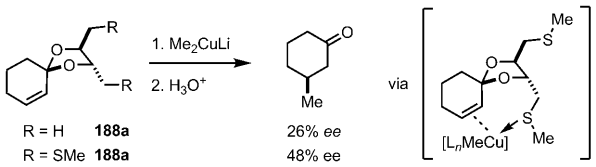
Scheme 92. Iterative strategy for the stereospecific construction of propionates and acetate propionates through a directed allylic substitution.



Scheme 93. Synthesis of vittatalactone and its diastereomer.

3.1.3. Chiral Directing Groups

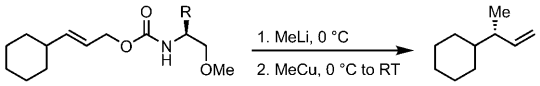
Chiral reagent-directing leaving groups can also be used to achieve enantioselective allylic substitution of a prochiral allylic substrate. A first example was reported by Alexakis et al., who used chiral acetals derived from α,β-unsaturated aldehydes and ketones and chiral C_2-symmetric glycol derivatives.[114] Good results were obtained with nondirecting acetal groups in the case of acyclic compounds (80–95% *ee*). However, for cyclic substrates, such as **188**, the introduction of a chelating sulfur atom was needed to achieve better enantioselectivity (Scheme 94).



Scheme 94. Enantioselective allylic substitution with directing chiral acetals.

Chiral carbamates derived from amino alcohols were also investigated in the course of directed allylic substitution (Table 32).[115] The presence of the methoxy group was found to be crucial for asymmetric induction, presumably because of a chelation to the metal center. The best result was obtained for R = naphthyl, which gave an excellent 1,7-chirality transfer of 98% (Table 32, entry 6).

Table 32: Allylic substitution with chiral carbamates as directing leaving groups.

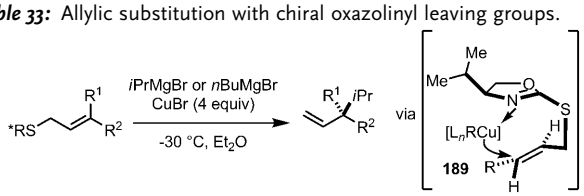


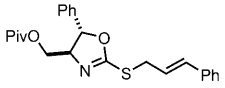
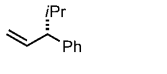
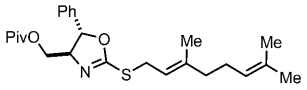
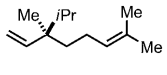
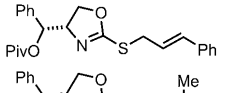
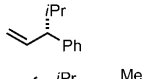
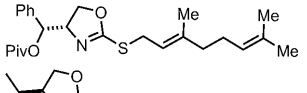
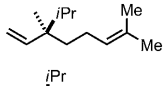
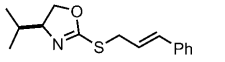
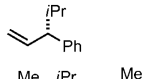
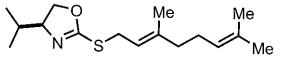
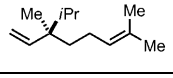
Entry	R	Yield [%]	*ee* [%]
1	*i*Pr	75	31
2	*t*Bu	52	32
3	$PhCH_2$	64	63
4	Ph	62	82
5	4-Anisyl	57	82
6	1-Naphth[a]	56	95

[a] Substrate with 97% *ee*.

As a chiral variant of the use of benzothiazole as a directing leaving group (see above), chiral oxazolinyl groups were examined in allylic substitution (Table 33).[116] A large excess of CuBr proved essential to ensure high levels of S_N2' selectivity. The enantioselectivity depends on both the nature of the oxazoline substituents and the substrate structure. The best result was obtained with a geraniol-derived system (Table 33, entries 2, 4, and 6). Notably, a quaternary carbon center was formed in 98% *ee* (Table 33, entry 4). Control experiments with thiazolines and azolines indicated that only

Table 33: Allylic substitution with chiral oxazolinyl leaving groups.

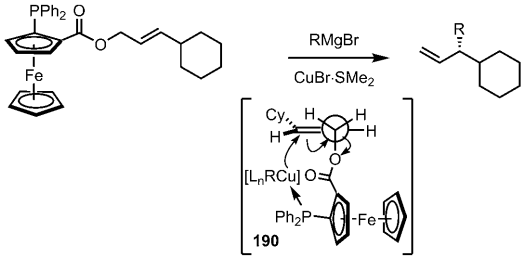


Entry	Substrate	Product	*ee* [%]
1			58 (*S*)
2			73
3			78 (*R*)
4			98
5			50 (*S*)
6			83

the nitrogen atom has a directing effect, and **189** was proposed as the transition state.

The *o*-DPPB group was replaced by its chiral version, the *o*-DPPF group, so as to achieve enantioselective allylic substitution, as in the case of hydroformylation.[117] Allylic substitutions were carried out with several Grignard reagents in good yields, with high regioselectivity and enantioselectivity of up to 95% *ee* being achieved (Table 34). However, lower selectivity was obtained with aryl Grignard reagents. The observed stereochemistry could be rationalized via reactive conformation **190**, in which the σ^* orbital of the leaving group is aligned to overlap efficiently with the π system of the alkene. Minimization of the $A^{1,3}$ strain and an internal delivery of the copper nucleophile through phosphane coordination install the *S* absolute configuration in the substitution products (Table 34, entries 1–3).

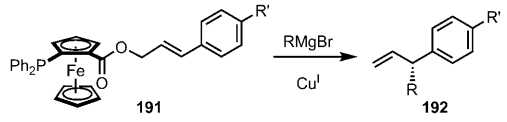
Table 34: Allylic substitution with a planar chiral leaving group.



Entry	RMgX	S_N2'/S_N2	*ee* [%]	Yield [%]
1	MeMgI	93:7	82 (*S*)	56
2	*n*BuMgBr	93:7	95 (*S*)	77
3	*i*PrMgBr	98:2	81 (*S*)	82
4	PhMgBr	75:25	28 (*R*)	n.d.

Cinnamyl *o*-DPPF esters **191** were examined under similar reaction conditions. Slightly lower regio- and stereoselectivities were obtained, probably because of the deconjugation of the π system in the substitution products (Table 35). The enantioselectivity of the reaction was influenced neither by a donor nor by an acceptor substituent attached to the aromatic system.

Table 35: Allylic substitution with cinnamyl alcohol derivatives.

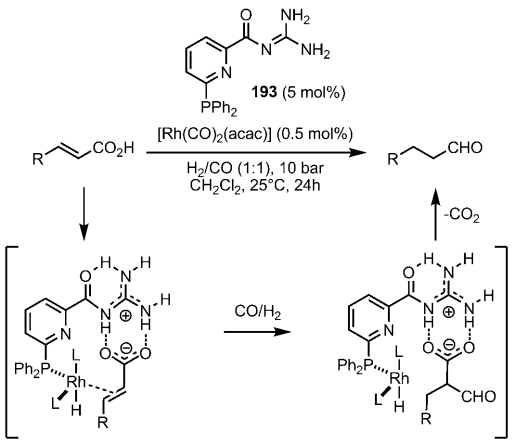


Entry	R′	R	S_N2'/S_N2	*ee* [%]	Yield [%]
1	H	*n*Bu	87:13	78	86
2	H	Cy	98:2	71	100
3	OMe	*n*Bu	84:16	65	60
4	Br	*n*Bu	94:6	68	37

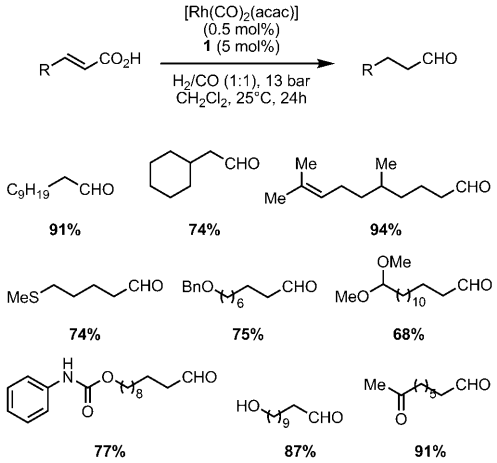
3.2. Hydroformylation

A catalytic method for the reduction of α,β-unsaturated carboxylic acids to aliphatic aldehydes by decarboxylative hydroformylation in the presence of a supramolecular catalyst system was reported.[118] In the course of this reaction the carboxylic acid acts as a temporary directing group which orientates the introduction of the aldehyde in the α position. This becomes possible through an enzyme-like geometric organization of the substrate–catalyst complex, mediated by the guanidinium-functionalized phosphine ligand. The directing group is then eliminated in situ by decarboxylation. (Scheme 95).

Various α,β-unsaturated carboxylic acids were converted into the corresponding aliphatic aldehydes in excellent yields (Scheme 96). Linear unfunctionalized acids as well as those substituted in the 4- and 5-positions gave good results. Additional internal alkene functions were not affected during the process. Protected alcohols as well as free hydroxy



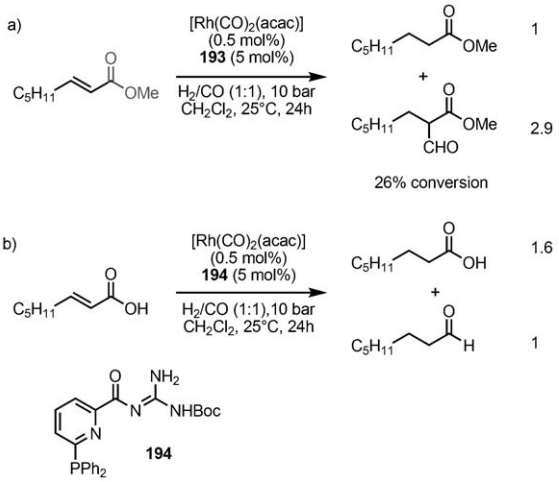
Scheme 95. Decarboxylative hydroformylation of α,β-unsaturated acids.



Scheme 96. Reduction of α,β-unsaturated acids to aliphatic aldehydes.

functions, ketones, alkyl sulfides, ethers, and acetals were found to be compatible with the reaction conditions.

Control experiments were carried out to determine the role of each component of the reaction. First, a methyl ester was used instead of the carboxylic acid. In this case, very low conversion was observed (26%) and only a 1:2.9 mixture of the hydrogenation and hydroformylation products were obtained (Scheme 97a). The use of the Boc-protected guanidine as ligand instead of **193** resulted in only low chemoselectivity (Scheme 97b). These results suggest that the interaction of the guanidine moiety with the carboxylic acid function is crucial for the catalyst performance.



Scheme 97. Control experiments.

4. Sequential Use of Removable Directing Groups

To render the reagent-directing group strategy more efficient it would be interesting to use the same directing group to control not only one but a sequence of transformations before its removal from the product (Figure 5). Ideally, the removal step would be incorporated during the

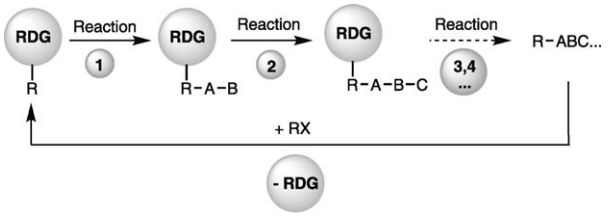
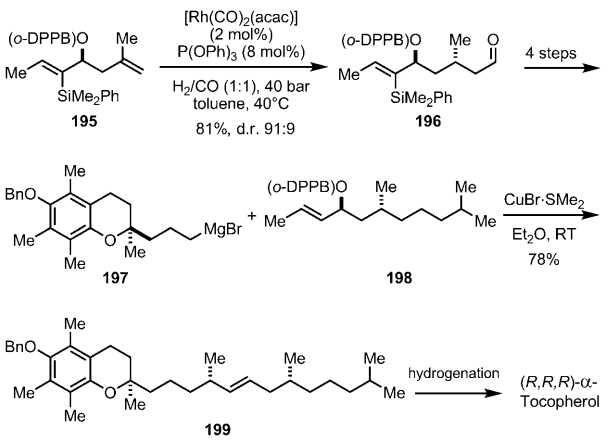


Figure 5. Concept of sequential synthesis by using reagent-directing groups (RDGs): RDG-controlled organic synthesis.

course of a further skeleton-expanding step, which should deliver the RDG in such a way as to recycle and reuse it directly for introduction into a new substrate. The overall process would make very efficient use of substrate control and could be termed RDG-controlled organic synthesis. Although the directing group is used stoichiometrically in each reaction step, the overall process is catalytic in the directing group and shows similarities to biosynthetic pathways used in nature, for example, polyketide construction. There, the coenzyme A plays the role of the covalently attached (as a thioester) directing group that delivers the corresponding enzyme for construction of the polyketide chain.

4.1. The *o*-DPPB Directing Group

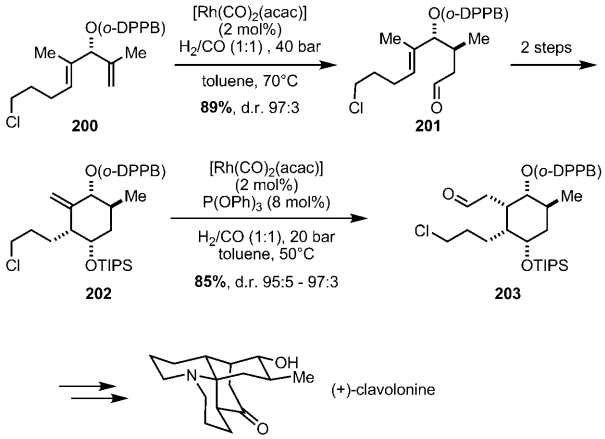
An RDG-controlled organic synthesis with an *o*-DPPB directing group has already shown its feasibility in the course of natural product synthesis. For example, α-tocopherol, which is the most active member of vitamin E compounds, has been synthesized successfully by using this strategy (Scheme 98).[119] First, the reagent-directing group (*o*-



Scheme 98. Total synthesis of (*R*,*R*,*R*)-α-tocopherol by *o*-DPPB-directed hydroformylation and allylic substitution.

DPPB) served to control the diastereoselectivity during the course of the rhodium-catalyzed hydroformylation of the homomethallylic precursor **195**. The *anti* aldehyde **196** was obtained in 81% yield as a 91:9 mixture of diastereomers, which were separated after a reduction step. The same *o*-DPPB group subsequently acted as a reagent-directing leaving group during the course of a directed copper-mediated allylic substitution between the Grignard reagent **197** and the allylic electrophile **198**. This fragment-coupling step led to the protected (*R*,*R*,*R*)-α-tocopherol in 78% yield with concomitant removal of the *o*-DPPB group, which can be recovered during the work-up process. A final simultaneous one-pot cleavage of the benzyl ether and reduction of the alkene furnished the natural product in 13 steps and in 30% overall yield.

Another example of RDG-controlled organic synthesis using the *o*-DPPB as the directing group was reported in the total synthesis of three lycopodium alkaloids (Scheme 99).[120]



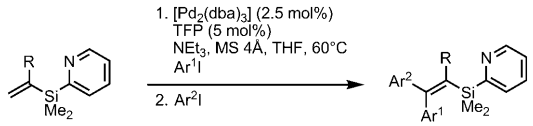
Scheme 99. Total synthesis of (+)-clavolonine by two successive *o*-DPPB-directed hydroformylations.

In the course of this synthesis, the first stereogenic center was generated by asymmetric catalysis, while the remaining five or six stereogenic centers were all constructed exclusively by substrate control. A first directed rhodium-catalyzed hydroformylation of the 1,1-disubstituted alkene **200** furnished the *syn* aldehyde **201** in very good yield and high diastereoselectivity. After subsequent carbonyl-ene cyclization to form the cyclohexanol and TIPS protection, a second directed rhodium-catalyzed hydroformylation of the highly functionalized methylene cyclohexane **202** could be used to furnish aldehyde **203** in good yield and diastereoselectivity (85%, 96:4). Notably, under the same conditions, the corresponding benzyl ether and benzoate gave no product, thus demonstrating the role of *o*-DPPB as a directing group. Aldehyde **203** was subsequently transformed into (+)-clavolonine, (−)-deacetylfawcettiine, and (+)-acetylfawcettiine

4.2. The Pyridyldimethylsilyl Group

Yoshida, Itami, and co-workers have developed a diversity-oriented synthesis of multisubstituted olefins by using their removable 2-PyMe$_2$Si group. A sequential one-pot double Mizoroki–Heck reaction furnished tri- or tetrasubstituted olefins.[121] Good yields were obtained for unsubstituted vinylsilanes (Table 36, entries 1–4), while the reaction is less

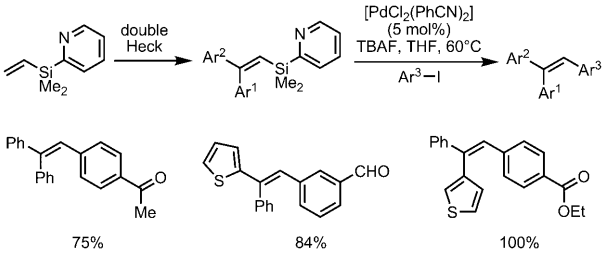
Table 36: One-pot double Mizoroki–Heck reaction for the synthesis of tri- and tetrasubstituted olefins.



Entry	R′	Ar^1I	Ar^2I	Yield [%]
1	H	PhI	PhI	74
2	H	PhI		68
3	H	PhI		67
4	H			69
5	Ph	PhI	PhI	48
6	Ph			28

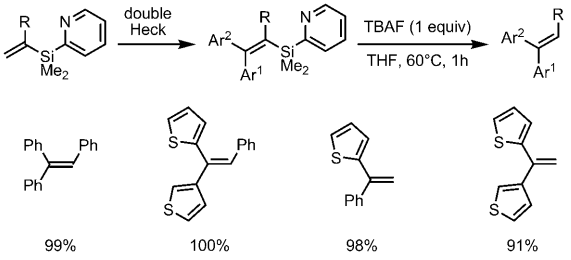
efficient in the case of β-substituted vinylsilanes (Table 36, entries 5 and 6).

Two strategies for the removal of the directing pyridylsilyl group have been developed. Subjecting the products to the conditions of a Hiyama reaction produced triarylethenes stereoselectively and in high yields (Scheme 100).



Scheme 100. Stereoselective synthesis of trisubstituted olefins by double Mizoroki–Heck and Hiyama reactions.

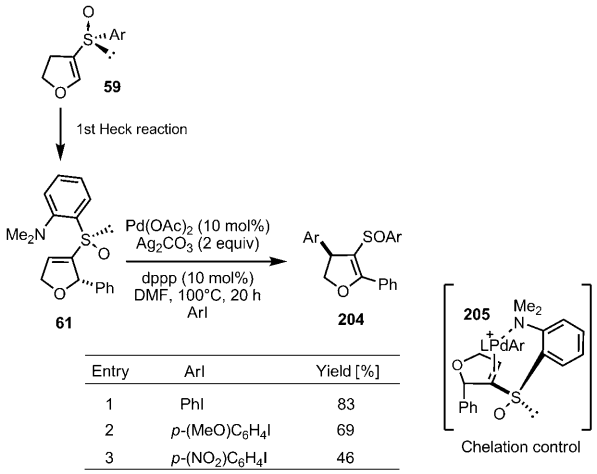
Alternatively, a protodesilylation could be carried out to liberate the corresponding di- and triarylethenes in very good yields (Scheme 101). By altering the order of aryl iodide addition, the method allows for the rapid preparation of any desirable di- and triarylsubstituted olefin in a regio- and stereocontrolled manner.



Scheme 101. Stereoselective synthesis of di- and trisubstituted olefins by double Mizoroki–Heck reaction followed by protodesilylation.

4.3. The Sulfoxide Directing Group

The directing sulfoxide group developed by Carretero and co-workers has also been employed in sequential Mizoroki–Heck reactions.[63] After the first Heck reaction (see Section 2.2.4), the arylated dihydrofuran **61** was obtained with excellent stereocontrol (Scheme 102). This could undergo a



Entry	ArI	Yield [%]
1	PhI	83
2	*p*-(MeO)C_6H_4I	69
3	*p*-(NO_2)C_6H_4I	46

Scheme 102. Sequential Mizoroki–Heck reactions directed by a sulfoxide group.

second Heck reaction under otherwise similar conditions, but requiring longer reaction times, to furnish the bisarylated dihydrofurans **204** stereoselectively in moderate yields. To rationalize the observed stereochemistry a chelation model was proposed, in which both the steric effect induced by the phenyl-substituted stereogenic center and the coordination of the dimethylamino group would favor insertion of the Ar group on the face opposite to the previously installed phenyl substituent.

5. Catalytic Directing Groups

A major drawback of the directing group strategy is the requirement for stoichiometric amounts of the directing group, which has to be installed and removed in extra synthetic steps. The use of catalytic amounts of a directing group would be ideal. For this goal, one might design a catalyst-directing group that could bind the substrate in a covalent but reversible manner (Figure 6).

5.1. Branched-Selective Hydroformylation

Regiocontrol in the course of hydroformylation is a difficult problem of industrial and academic importance.[122] Many catalysts exist which allow for the linear-selective hydroformylation of terminal alkenes. Conversely, only a few catalysts have been developed for the branched-selective hydroformylation of terminal and internal alkenes. Recently, two phosphorus-based catalyst-directing groups were

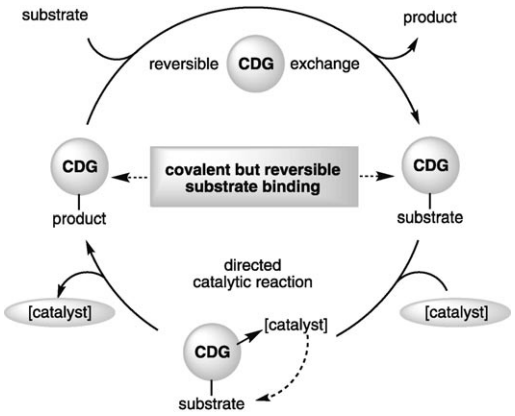


Figure 6. Concept of a catalyst-directing group (CDG) needed only in catalytic amounts because of reversible covalent substrate binding.

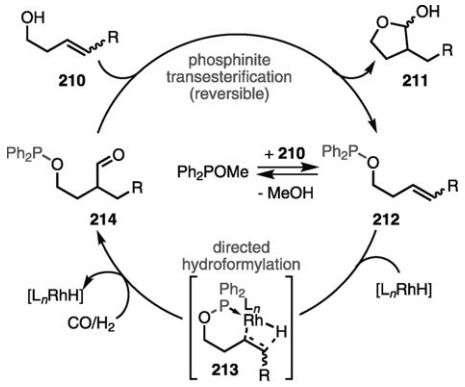
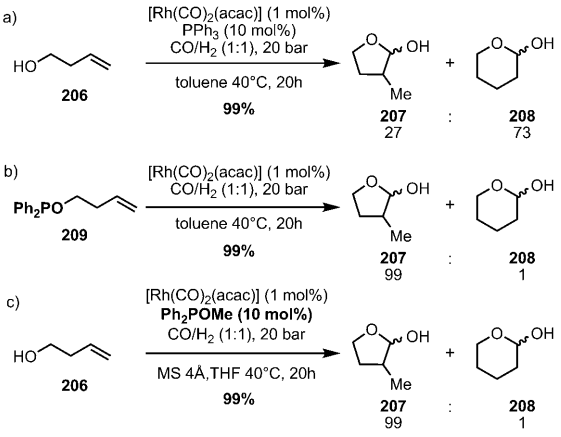


Figure 7. Proposed mechanism of directed hydroformylation with the ligand Ph_2POMe.

reported that could be used in substoichiometric amounts for the branched-selective hydroformylation of alcohols.[30e,123] The success of this strategy resides in the ability of these ligands to simultaneously and reversibly bind hydroxy-functionalized substrates as well as a metal-based catalyst, and thus directed reactions can be performed with a catalytic amount of the ligand.

Phosphinites have been reported to be general catalyst-directing groups for the branched-selective hydroformylation of homoallylic alcohols.[30e] It was first established in orientating experiments that, contrary to the hydroxy function in **206** (Scheme 103a), the covalently bound phosphinite **209** was



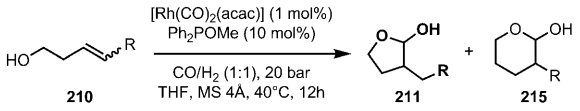
Scheme 103. Hydroformylation of homoallylic alchohols with and without a directing phosphinite group.

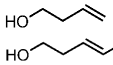
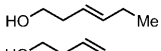
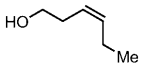
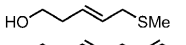
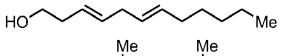
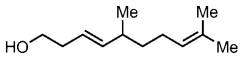
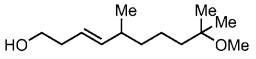
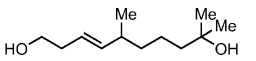
able to direct the hydroformylation reaction to furnish the branched product exclusively (Scheme 103b). Only 10 mol% Ph_2POMe was necessary in the presence of molecular sieves for the hydroformylation of the homoallylic alcohol **206** to obtain lactol **207** with complete conversion and branched regioselectivity (Scheme 103c).

The reaction pathway depicted in Figure 7 was proposed. First a transesterification of the homoallylic alcohol by methyl phosphinite occurs to furnish phosphinite **212**, which undergoes a regioselective hydroformylation in favor of the 6-*exo*-trig hydrometalation over that of the 7-*endo*-trig alternative to give the phosphinite-containing product **214**. Subsequent transesterification with the substrate liberates the γ-lactol **211** and regenerates phosphinite **212**, which enters a new hydroformylation catalytic cycle (Figure 7).

Terminal as well as internal alkenes were hydroformylated efficiently (Table 37). Remarkably, reactions with substrates containing an additional alkene function displayed a

Table 37: Branched-selective directed hydroformylation of homoallylic alcohols.

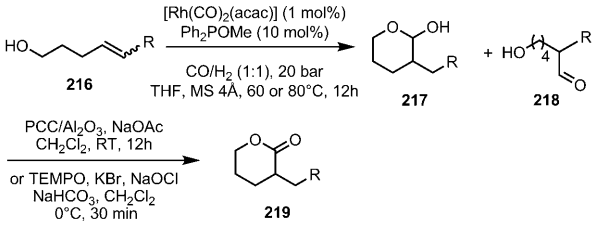


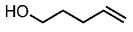
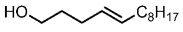
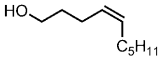
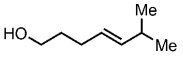
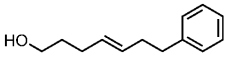
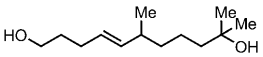
Entry	Substrate	Conv. [%]	Regioselectivity **211/215**
1		100	99:1
2		100	>99:1
3		100	>99:1
4		75	97:3
5		83	97:3
6		93	99:1
7		98	99:1
8		99	99:1

completely regio- and position-selective hydroformylation of the homoallylic olefin. Thioether, free hydroxy, and ether functions are compatible with the reaction conditions.

The reaction can be extended to bishomoallylic alcohols **216**. In this case the hydroxy function to which the directing group is reversibly attached and the reacting alkene function are in a remote 1,4-relation. Thus, the δ-lactols **217** were obtained with excellent regioselectivity by applying similar reaction conditions, but with slightly increased reaction

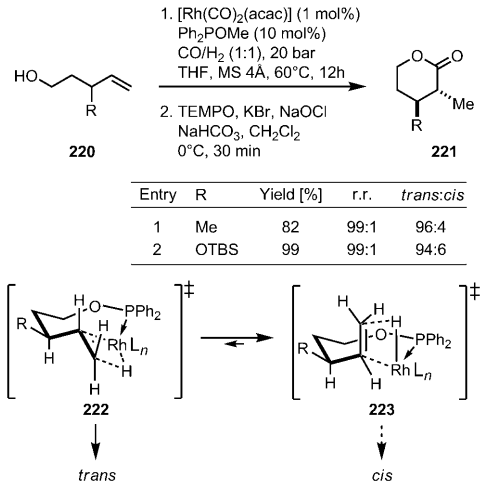
Table 38: Directed hydroformylation of various bishomoallylic alcohols.



Entry	Substrate	Conv. [%]	Regioselectivity **217/218**
1		86	97:3
2		84	99:1
3		87	99:1
4		77	99:1
5		88	98:2
6		69	97:3

temperatures (Table 38). These lactols were then oxidized to furnish the corresponding δ-lactones **219**.[30f]

Good levels of acyclic stereocontrol could be achieved for bishomoallylic alcohols **220** with a stereogenic center in the 3-position (R = Me, OTBS; Scheme 104). A rationale for the



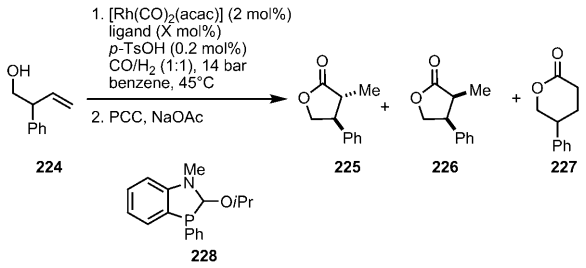
Entry	R	Yield [%]	r.r.	*trans*:*cis*
1	Me	82	99:1	96:4
2	OTBS	99	99:1	94:6

Scheme 104. Acyclic stereocontrol upon hydroformylation of 3-substituted bishomoallylic alcohols. TEMPO = 2,2,6,6-tetramethyl-1-piperidinoxyl, r.r. = regioisomeric ratio.

observed stereochemical outcome is provided by evaluation of the competing diastereomorphic transition states **222** and **223** for the 7-*exo*-trig hydrometalation. Thus, transition state **222**, in which the $A^{1,3}$ allylic strain is minimized, leads to the experimentally observed *trans* product **221**, while transition state **223**, in which the $A^{1,2}$ allylic strain is minimized, furnishes the *cis* minor diastereomer.

Control experiments with triphenylphosphine as the ligand instead of Ph_2POMe as well as reactions with the corresponding methyl ether substrates clearly proved the role of the phosphinite as that of a catalyst-directing group operating through reversible substrate binding.

The phosphane-functionalized aminal **228** has been found to allow for the branched-selective hydroformylation of 2-substituted homoallylic alcohols **224**, while the use of PPh_3 as the ligand results in a mixture of both regioisomers (Scheme 105).[123] Slightly elevated ligand and catalyst loadings were necessary to maintain the reaction selectivity.



Entry	Ligand	Yield [%]	r.r.	d.r. **225:226**
1	PPh_3 (4 mol%)	>98	25:75	42:58
2	**228** (20 mol%)	>98	84:16	88:12

Scheme 105. Nondirected and directed hydroformylation of homoallylic alcohol **224**. PCC = pyridinium chlorochromate.

As in the former example, this reaction is feasible because a rapid transacetalization at the ligand aminal function occurs to allow a covalent and reversible attachment of the substrate to the catalyst-directing group (Figure 8).

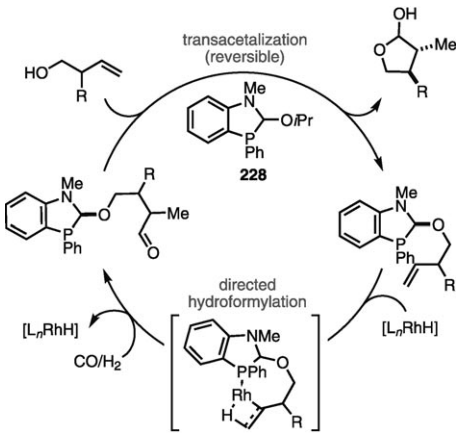
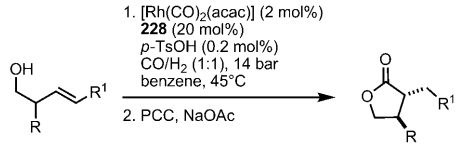


Figure 8. Proposed mechanism of directed hydroformylation with the ligand **228**.

Various 2-substituted homoallylic alcohols **229** were subjected to the reaction conditions (Table 39), and the corresponding γ-lactones **230** were obtained in good yields and with *trans* diastereoselectivities. Also 1,2-disubstituted alkene functions underwent reaction. The level of diastereoselectivity correlates with the size of the substituent at the allylic position. The *trans* diastereoselectivity was rationalized

Table 39: Substrate scope for the directed hydroformylation with **228**.



229 **230**

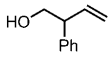
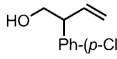
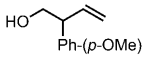
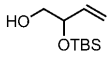
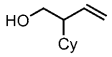
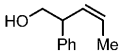
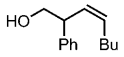
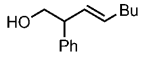
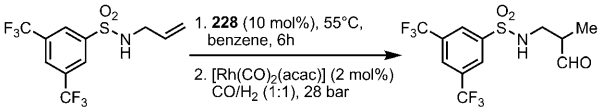
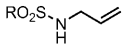
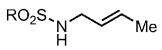
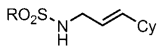
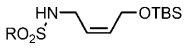
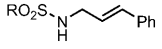
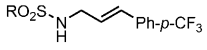
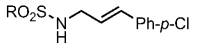
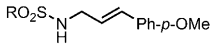
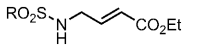
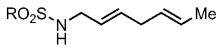
Entry	Substrate	Yields [%]	r.r	d.r.
1		94	86:14	89:11
2		>98	82:18	87:13
3		86	84:16	88:12
4		75	88:12	80:20
5		86	65:35	87:13
6		88	98:2	>98:2
7		70	95:5	92:8
8		69	94:6	78:22

Table 40: Regioselective hydroformylation of allylic sulfonamides.



Entry	Substrate	Regioselectivity	Yields [%]
1		96:4	80
2		99:1	85
3		99:1	84
4		94:6	83
5		99:1	86
6		98:2	92
7		99:1	69
8		97:3	87
9		87:4:9[a]	79
10		>95:5	75

[a] Branched:linear:hydrogenated product.

on the basis of a minimization of the $A^{1,3}$ strain in the selectivity-determining hydrometalation step. Consequently, when *Z*-disubstituted olefins were applied, higher diastereoselectivities were achieved (Table 39, entries 6–8).

Notably, the reaction with the methyl ether of **224** gave a 76:24 linear to branched mixture, thus demonstrating the necessity of a free hydroxy function for branched selectivity.

The same catalyst system allowed for a highly regioselective hydroformylation of allylic sulfonamides to furnish the corresponding β-amino aldehydes in good yields (Table 40).[124]

Furthermore, the same catalyst system was also found to be efficient for the directed branched-selective hydroformylation of 1,1-disubstituted olefins to furnish quaternary carbon centers.[125] Conversely, the linear product was obtained selectively when triphenylphosphine was used as the ligand (Table 41).

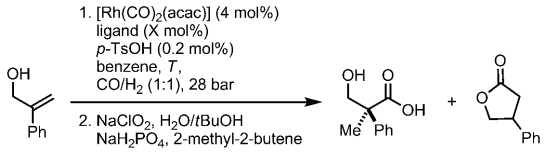
A variety of 2-aryl- and 2-heteroaryl-substituted allylic alcohols could be transformed into quaternary products with good regioselectivity and high yields (Table 42). However, a 2-alkyl substituent gave significantly reduced regioselectivity (Table 42, entry 10).

5.2. *Rhodium-Catalyzed* ortho-*Arylation of Phenols*

A catalytic intermolecular *ortho*-selective arylation of phenols by direct CH activation was reported, which avoided the use of a tin or boron reagent as used in Stille or Suzuki coupling reactions (Scheme 106).[126]

Good results were obtained by using the Wilkinson catalyst combined with a phosphinite co-catalyst directing

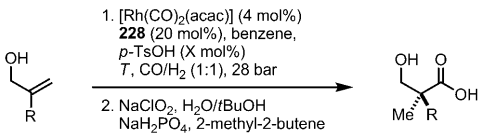
Table 41: Nondirected and directed hydroformylation of 1,1-disubstituted olefin **231**.



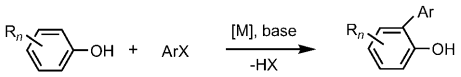
231 **232** **233**

Entry	Ligand	*p* [bar]	*T* [°C]	Yield [%]	Branched/linear
1	PPh_3 (8 mol%)	28	75	66	<2:98
2	**228** (20 mol%)	28	45	73	97:3

Table 42: Substrate scope of the directed hydroformylation of 2-substituted allylic alcohols with **228**.



Entry	R	*T* [°C]	*p*-TsOH (mol%)	Branched/linear	Yield [%]
1	*p*-CF_3Ph	45	0.2	96:4	85
2	*p*-MeOPh	35	0.2	>98:2	66
3	*p*-BrPh	35	0.05	94:6	71
4	*m*-ClPh	35	0.2	>98:2	77
5	*p*-CO_2MePh	45	0.05	>98:2	74
6	2-naphthyl	35	0.05	95:5	85
7	3-thienyl	45	0.2	95:5	70
8	3-pyridyl	45	0.2	98:2	68
9	3-furyl	55	0.05	>98:2	64
10	methyl	45	0.2	76:24	49



Scheme 106. Catalytic *ortho*-arylation of phenols.

group. The strategy relies on the catalytic transesterification of a phenol **234** with a catalytic amount of aryl phosphinite **236**. This aryl phosphinite then coordinates to the Rh^{III} center, and a directed *ortho*-metalation occurs. The product is formed after reductive elimination and transesterification with the phenol substrate (Figure 9).

Various substituted phenols were coupled with different aryl bromides. Activated, non-activated, or deactivated aryl bromides, with respect to oxidative addition, were compatible with the reaction conditions. Even sterically hindered *ortho*-substituted aryl bromides could be employed (Table 43, entry 7), while aryl chlorides were less reactive (entry 8). However, it turned out that a bulky *ortho*-substituent at the phenol is needed for the reaction to be efficient (Table 43, entries 2 and 9).

This method has been used for the direct *ortho*-arylation of protected racemic 2-*tert*-butyltyrosine with a variety of aryl bromides (Scheme 107).[127]

A limitation of this method is the need to prepare the corresponding phosphinite co-catalyst from the respective phenolic substrate first for use as a reversible directing group.

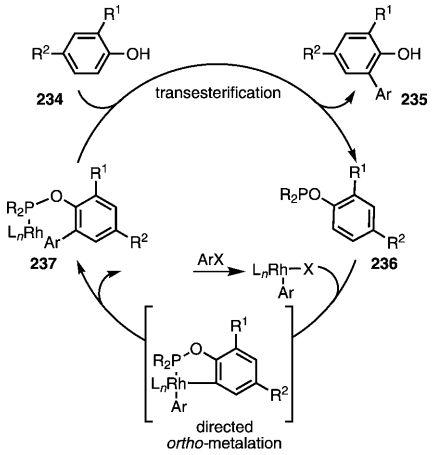
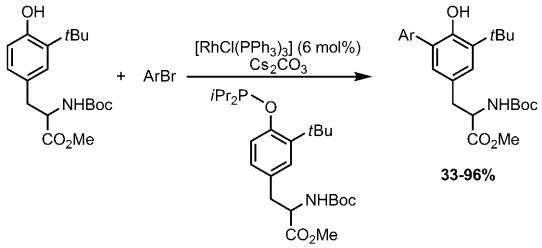
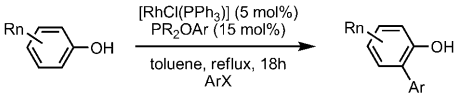


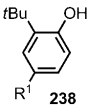
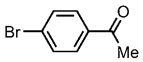
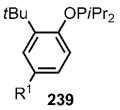
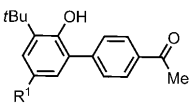
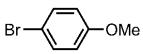
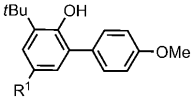
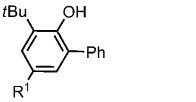
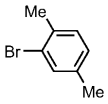
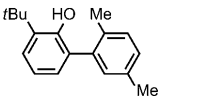
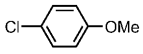
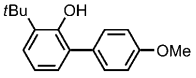
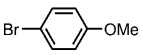
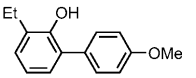
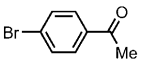
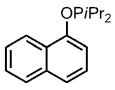
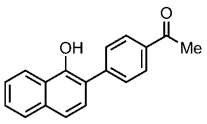
Figure 9. Proposed catalytic cycle for phosphinite-directed *ortho*-arylation of phenols.



Scheme 107. *ortho*-Arylation of protected racemic 2-*tert*-butyltyrosine.

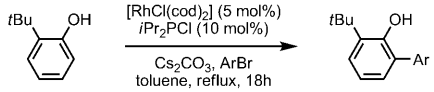
Table 43: Catalytic *ortho*-arylation of phenols.

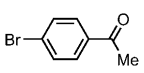
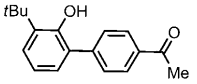
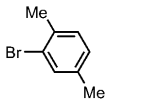
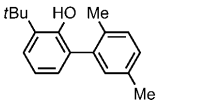
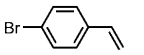
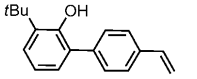
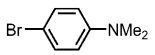
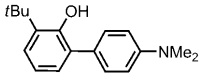
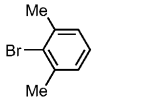
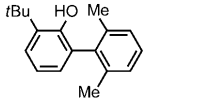


Entry	Phenol	Aryl halide	Phosphinite co-catalyst	Product	Yield [%]
1 ($R^1 = t$Bu) 2 (R^1 = H)	 **238**		 **239**		96 96
3 ($R^1 = t$Bu) 4 (R^1 = H)	**238a** **238b**		**239a** **239b**		86 79
5 ($R^1 = t$Bu) 6 (R^1 = H)	**238a** **238b**		**239a** **239b**		81 84
7	**238b**		**239b**		100
8	**238b**		**239b**		15
9			**239b**		9
10					71

To circumvent these problems, the reaction was carried out with a commercially available chlorophosphine, which allows the in situ formation of the phosphinite.[128] Thus, almost the same results were obtained with a combination of commercially available $[RhCl(cod)_2]$ and iPr_2PCl (Table 44). However, the method remains restricted to *ortho*-substituted phenols, and a desirable mono-*ortho*-arylation of *ortho*-unsubstituted phenols remains a challenge.

Table 44: Coupling of **238b** with various aryl bromides.



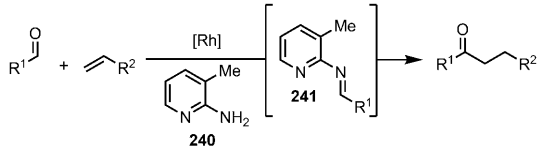
Entry	ArBr	Product	Yield [%]
1			89
2			94
3			74
4			77
5			91

5.3. Intermolecular Rhodium-Catalyzed Hydroacylation

An efficient catalytic system for intermolecular hydroacylation assisted by chelation was reported by Jun et al. (Scheme 108).[129] 2-Aminopicoline (**240**) is used as a co-catalyst to form the intermediate imine **241**. This allows suppression of the aldehyde decarbonylation, which is the major side reaction in hydroacylations. Additionally, it enables coordination towards the catalytically active rhodium center through the pyridine nitrogen atom and thus, facilitates the difficult CH activation step.

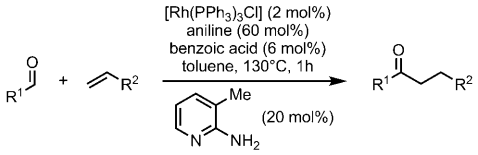
The addition of catalytic amounts of benzoic acid as well as aniline allowed for a more general substrate scope and higher yields (Table 45).

The proposed reaction mechanism starts with the condensation of aldehyde **242** with 2-aminopicoline (**240**) to generate the aldimine **241** (Scheme 109). Chelation-assisted



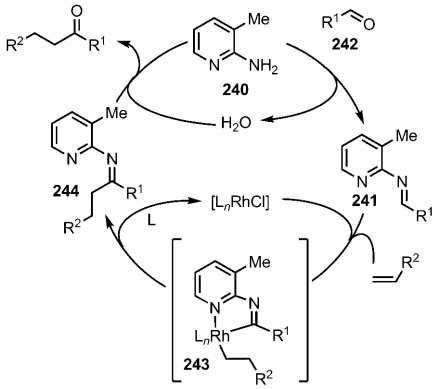
Scheme 108. Chelation-assisted intermolecular hydroacylation.

Table 45: Intermolecular hydroacylation of different 1-alkenes with various aldehydes.



Entry	R^1	R^2	Yield [%]
1	Ph	n-C_4H_9	98
2	Ph	n-C_3H_7	83
3	Ph	n-C_6H_{13}	99
4	Ph	*t*Bu	84
5	Ph	Me_3Si	95
6	Ph	C_6F_5	98
7	Ph	$PhOCH_2$	95
8	p-Meo-C_6H_4	n-C_4H_9	79
9	p-CF_3-C_6H_4	n-C_4H_9	71
10	p-Me_2N-C_6H_4	n-C_4H_9	60
11	$PhCH_2CH_2$	n-C_4H_9	71

CH activation followed by alkene hydrometalation furnished the rhodium(III) intermediate **243**. Reductive elimination allows the product to reversibly exchange with the starting material imine **244**. Hydrolysis of the imine furnishes the ketone product and regenerates the aminopyridine catalyst-directing group. The role of benzoic acid and aniline, which are added in catalytic amounts, is presumably to act as a buffered proton source to catalyze the transimination, which is presumed to be the rate-limiting step.

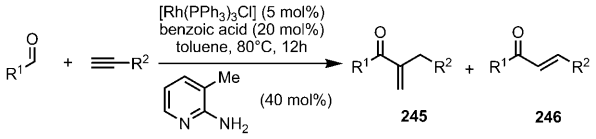


Scheme 109. Proposed catalytic cycle for ligand-assisted hydroacylation.

Alkynes also undergo hydroacylation with this catalyst system.[130] The reaction occurs in high regioselectivity in favor of the branched enone **245**. The best regioselectivities were obtained for aromatic aldehydes, while aliphatic aldehydes were less selective (Table 46, entries 9 and 11). However, complete regioselectivity in favor of the linear regioisomer was noted when *tert*-butyl alkynes were used as the substrate, presumably because of a minimization of the steric repulsion.

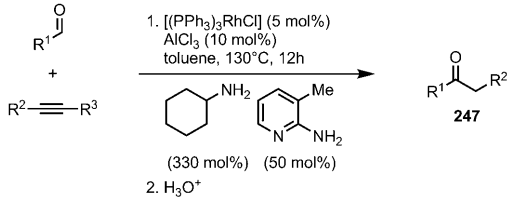
Internal alkenes could be treated with aldehydes in the presence of cyclohexylamine as an additive to obtain ketones

Table 46: Rhodium-catalyzed hydroacylation of various aldehydes and 1-alkynes.



Entry	R^1	R^2	**245/246**	Yield [%]
1	Ph	*n*Bu	100:0	92
2	Ph	*n*Bu	100:0	93
3	Ph	$PhCH_2$	100:0	66
4	*p*-CF_3-C_6H_4	*n*Bu	100:0	95
5	*p*-MeO-C_6H_4	*n*Bu	100:0	76
6	naphthyl	*n*Bu	100:0	83
7	3-thiophenyl	*n*Bu	100:0	96
8	3-pyridyl	*n*Bu	100:0	79
9	*n*-pent	*n*Bu	78:22	85
10	*n*-pent	*t*Bu	0:100	74
11	cyclohexyl	*n*Bu	81:19	98
12	cyclohexyl	*t*Bu	0:100	63

Table 47: Hydroacylation with internal alkynes.

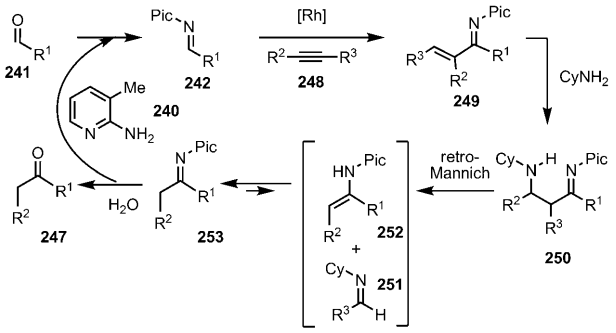


Entry	R^1	R^2, R^3	Yield [%]
1	$PhCH_2CH_2$	Me, Me	90
2	$PhCH_2CH_2$	Et, Et	91
3	$PhCH_2CH_2$	Pr, Pr	94
4	$PhCH_2CH_2$	Me, *t*Bu	33
5	C_5H_{11}	Pr, Pr	91
6	$PhCH_2$	Et, Et	82
7	*p*-MeO-C_6H_4	Et, Et	54

247 in moderate to good yields (Table 47).[131] The regioselectivity and reactivity of the reaction is largely dependent of the steric demand of the alkyne substituents when unsymmetrical alkynes are used. For example (Table 47, entry 4), only 1-phenyl-pentan-3-one was obtained in 33% yield along with the corresponding α,β-unsaturated ketone, the hydrolysis product of the intermediate ketimine (**249**, see Scheme 110).

The proposed mechanism involves first a chelation-assisted hydroacylation to generate the α,β-unsaturated ketimine **249**. This is followed by a conjugate addition of cyclohexylamine to furnish **250**, which undergoes a retro-Mannich fragmentation to afford aldimine **251** and enamine **252**. Isomerization of enamine **252** to ketimine **253** followed by hydrolysis yields the ketone **247** (Scheme 110).

Several related transformations with this catalyst are known, and have been summarized recently. However, in many cases a stoichiometric amount of the 2-aminopicoline as a catalyst-directing group was required.[132,133]



Scheme 110. Suggested reaction mechanism for the hydroacylation with internal alkynes.

6. Summary and Outlook

Substrate control of reaction selectivity becomes extremely efficient when attractive substrate–reagent/catalyst interactions are involved, because of the intramolecular nature of the rate- and selectivity-determining reaction steps. In the case that existing functional groups are insufficient to enable the required reagent–substrate interactions, appropriately designed removable directing groups can be applied to solve the problem. A number of stoichiometrically attachable groups are now known to transform formal unselective reactions into highly chemo-, regio-, and stereoselective variants, which overcome the disadvantage of additional installation and removal steps for such functions.

However, strategies involving the multiple use of one directing group to control the selectivity of a series of transformations have been demonstrated to render the use of directing groups more efficient. Even more attractive is the use of catalytic directing groups which bind to the substrate in a covalent but reversible fashion. Initial examples of this strategy have appeared and more will certainly continue to be developed in the near future.

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