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Cross-Coupling Reaction of Alkenyl Sulfoximines and Alkenyl Aminosulfoxonium Salts With Organozincs by Dual Nickel Catalysis and Lewis Acid Promotion

Irene Erdelmeier,[a][b] Gerd Bülow,[a][c] Chang-Wan Woo,[a][d] Jürgen Decker,[a][e] Gerhard Raabe,[a] and Hans-Joachim Gais*[a]

Abstract: In this article we describe the cross-coupling reaction (CCR) of exocyclic, axially chiral and acyclic alkenyl (*N*-methyl)sulfoximines with alkyl- and arylzincs. The CCR generally requires dual Ni-catalysis and $MgBr_2$ promotion, which is effective in ether but not in THF. NMR spectroscopy revealed a complexation of alkenyl sulfoximines by $MgBr_2$ in ether, suggesting an acceleration of the oxidative addition through nucleofugal activation. The CCR of alkenyl sulfoximines generally proceeds in the presence of Ni(dppp)Cl_2 as precatalyst and $MgBr_2$ with alkyl- and arylzincs with a high degree of stereoretention at both the C and S atom. While CCR of axially chiral alkenyl sulfoximines with Ni$(PPh_3)_2Cl_2$ as precatalyst and $ZnPh_2$ requires no salt promotion and is stereoretentive, that with $Zn(CH_2SiMe_3)_2$ demands salt promotion and is not stereoretentive. CCR of axially chiral α-methylated alkenyl sulfoximines afforded per-substituted axially chiral alkenes with high selectivity. Alkenyl (*N*-triflyl)sulfoximines engage in a stereoretentive CCR with Grignard reagents and Ni$(PPh_3)_2Cl_2$. Ni-Catalyzed and $MgBr_2$ promoted CCR of (*E*)-configured acyclic alkenyl sulfoximines and aminosulfoxonium salts with $ZnPh_2$ and $Zn(CH_2SiMe_3)_2$ is stereoretentive with Ni(dppp)Cl_2 and Ni$(PPh_3)_2Cl_2$. CCR of acyclic alkenyl sulfoximines and alkenyl aminosulfoxonium salts, carrying a methyl group at the α-position, take a different course and give alkenyl sulfinamides under stereoretention at the S and C atom. CCR of acyclic, exocyclic and axially chiral alkenyl sulfoximines has been successfully applied to the stereoselective synthesis of homoallylic alcohols, exocyclic alkenes and axially chiral alkenes, respectively.

Introduction

During synthetic studies of the medicinally important or promising prostacyclin[1] analogs iloprost,[2] cicaprost[3] and *inter-m*-phenylene carbacyclin[4,5] we encountered a challenging stereochemical problem, namely the diastereoselective conversion of the chiral bicyclic ketone **1** to (*E*)-configured alkyl- and aryl-substituted exocyclic alkenes (*E*)-**3** (Scheme 1). This problem is closely related to that of the enantioselective synthesis of the axially chiral alkenes (*aR*)-**6** from achiral cyclohexanone **4**.[6–8] Although both ketones are biased towards the addition of nucleophiles, a chiral reagent or catalyst is required for their diastereo- and enantioselective olefination. In order to find a solution for this problem, we and others had previously studied the *H*orner-*W*adsworth-*E*mmons reaction of ketone **1** and structurally related achiral bicyclo[3.3.0]octanones with chiral lithium phosphonoacetates.[9–11] Although high diastereoselectivity was observed in the *HWE* reaction, it ultimately gave access only to carbonyl-substituted alkenes (*E*)-**3**.[12] The other methods for the enantioselective olefination of **4**, which had been described at the beginning of our studies,[6,7] were unsuitable for the stereoselective conversion of ketone **1** to the required alkenes (*E*)-**3**. Hence, we envisioned a new general stereoselective synthesis of alkenes (*E*)-**3** and (*aR*)-**6** by a two-step route, featuring a conversion of ketones **1** and **4** to the corresponding alkenyl sulfoximines (*E,R*)-**2** and (*aR,R*)-**5** followed by their transition-metal-catalyzed cross-coupling reaction (CCR)[13] with organometallics. We had previously shown that inverse Peterson olefination (*IPO*) of ketones **1** and **4** with lithiomethyl sulfoximine (*R*)-Li-**7a**[14,15] (see Supporting Information) affords the corresponding alkenyl sulfoximines (*E,R*)-**2** and (*aR,R*)-**5** with high diastereoselectivity.[16] Running the *IPO* of **1** with (*S*)-Li-**7a**[14,15] furnished (*Z,S*)-**2** with similar high stereoselectivity.[16] Thus, the conditions were given for an investigation of the CCR of alkenyl sulfoximines with organometallics. Studies of transition-metal-catalyzed alkenyl C–S CCR are limited compared with alkenyl C–halide and C–O CCR.[17] Transition-metal-catalyzed CCR of alkenyl sulfoximines had not been studied. Information about CCR of alkenyl sulfones, which could have served as model, were scarce[18] and CCR of alkenyl sulfoxides was unknown. Only the CCR of alkenyl sulfides had received broader attention.[17,19] Thus, predictions on the feasibility of a CCR of alkenyl sulfoximines and its stereochemical course were difficult to make.

The study of the CCR of the alkenyl sulfoximines (*E,R*)-**2** and (*aR,R*)-**5** was extended to that of the acyclic alkenyl sulfoximines (*E*)-**8**, which are available through reaction of sulfonimidoyl-substituted bis(allyl)titaniums with aldehydes (Figure 1).[20] The purpose of the inclusion of (*E*)-**8** was twofold. First of all, it was of interest to define the scope and limitation of the CCR of alkenyl sulfoximines by also studying acyclic substrates, and second, it seemed desirable to enhance the synthetic potential of (*E*)-**8**[21] through conversion to the substituted homoallylic alcohols (*E*)-**9**, which are a valuable starting material in natural product synthesis.[22] Included into the study of the CCR of the acyclic alkenyl sulfoximines were the corresponding

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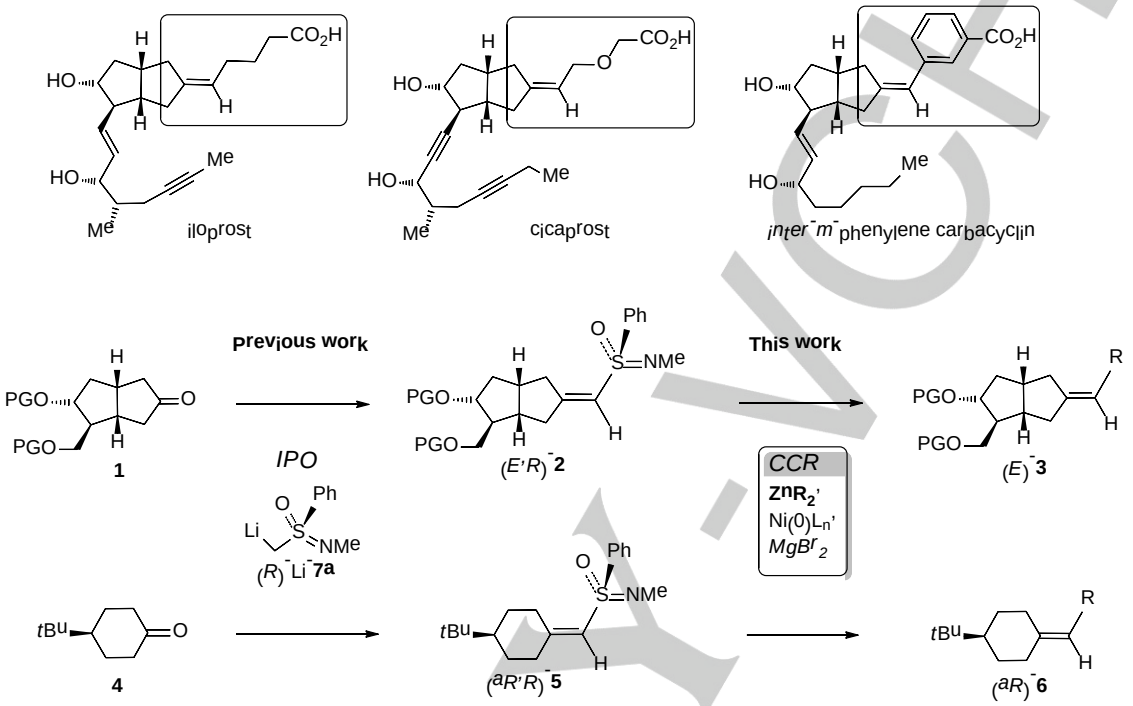
aminosulfoxonium salts (*E*)-**10**, which are readily accessible through methylation[23] of (*E*)-**8**.[21a,24] Alkenyl aminosulfoxonium salts are perhaps more reactive in CCR than alkenyl sulfoximines, because of the higher nucleofugacity of the cationic aminosulfoxonium group.[21a,24] While a few examples of transition metal-catalyzed CCR of alkenyl sulfonium salts had been described,[25,26] nothing was known about the CCR of alkenyl aminosulfoxonium salts.



Scheme 1. Stereoselective synthesis of exocyclic and axially chiral alkenes through IPO of cycloalkanones and CCR of alkenyl sulfoximines (PG = protecting group).

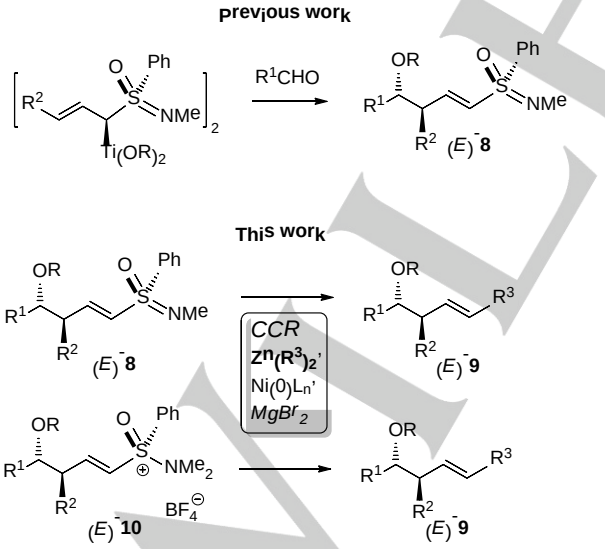


Figure 1. Stereoselective synthesis of homoallylic alcohols through CCR of acyclic alkenyl sulfoximines and alkenyl aminosulfoxonium salts.

In this paper we describe the results of an extended investigation of the nickel-CCR of alkenyl sulfoximines and alkenyl aminosulfoxonium salts with organozincs. It is shown that the CCR generally proceeds through a dual Ni-catalysis and magnesium bromide promotion. The CCR has been successfully applied to the stereoselective synthesis of alkyl- and aryl-substituted exocyclic, axially chiral and acyclic alkenes of the type depicted in Scheme 1 and Figure 1.[27]

Results and Discussion

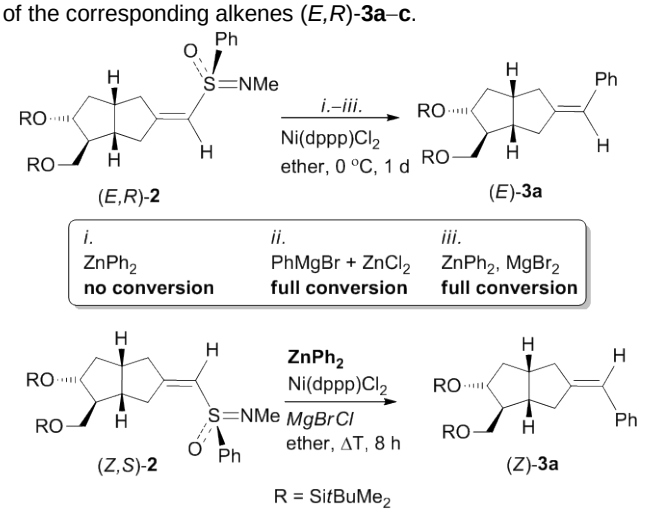
CCR of alkenyl sulfoximines

Organolithiums and Grignard reagents metalate alkenyl sulfoximines (*E,R*)-**2**, (*aR,R*)-**5** and (*E*)-**8**, affording the corresponding α-metalloalkenyl sulfoximines (*E,R*)-M-**2**, (*aR,R*)-M-**5** and (*E*)-M-**8**. The metalloalkenyl sulfoximines are configurationally labile[21,27a,28,29] and engage in a Ni-catalyzed anionic CCR (ACCR) with RLi and RMgX to yield α-alkenylmetals (*E/Z*)-M-**3**, (*aS*)-M-**6** and (*E/Z*)-M-**9**.[27a,29] These observations precluded the application of RLi and RMgX in Ni-catalyzed CCR of the alkenyl sulfoximines and suggested the use of organozincs,[30] which are not capable to metalate alkenyl sulfoximines. We employed $ZnMe_2$, $ZnPh_2$, Zn(*m*-$C_6H_4CH_2OSitBuMe_2)_2$ (**12**), Zn[$(CH_2)_4OSitBuPh_2]_2$ (**14**), $Zn(CH_2SiMe_2OiPr)_2$ (**21**) and $Zn(CH_2SiMe_3)_2$ (**22**) as

diorganozincs, because of synthetic (vide infra) and mechanistic considerations.

Exocyclic alkenyl sulfoximines

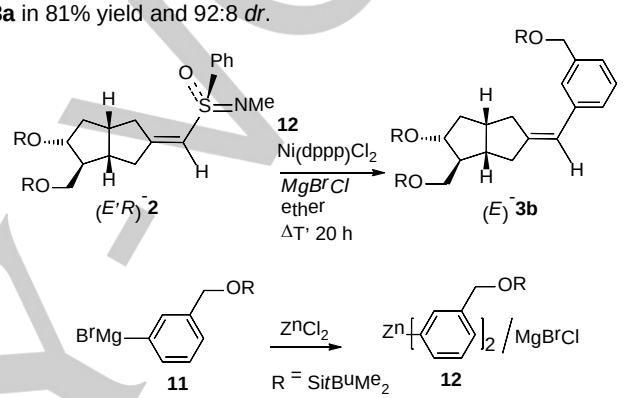
The investigation was begun with the exocyclic alkenyl sulfoximines (*E,R*)-**2** and (*Z,S*)-**2**, because of their relevance for the synthesis of the prostacyclin analogs. A prime goal was the CCR of (*E,R*)-**2** with organozincs **12**, **14** and **21** under formation of the corresponding alkenes (*E,R*)-**3a**–**c**.



Scheme 2. CCR of exocyclic alkenyl sulfoximines (*E,R*)-**2** and (*Z,S*)-**2** with $ZnPh_2$.

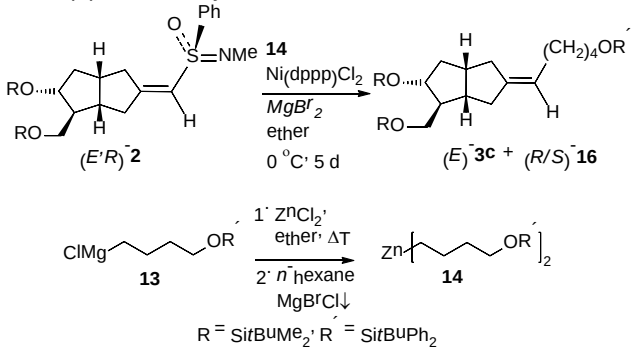
Exploratory experiments were carried out with $ZnPh_2$. Treatment of (*E,R*)-**2** with $ZnPh_2$ (5 equiv) and Ni(dppp)Cl_2 (5 mol%) (dppp = 1,3-bis(diphenylphosphino)propane) as precatalyst in ether even for a prolonged period of time saw no conversion of the alkenyl sulfoximine (Scheme 2). Surprisingly, running a similar experiment with (*E,R*)-**2** (≥98:2 *dr*) and Ni(dppp)Cl_2 (5 mol%) by using $ZnPh_2$ (4 equiv), which had been prepared in situ from $ZnCl_2$ and PhMgBr, resulted in a complete conversion of the substrate and gave alkene (*E*)-**3a** in 83% and ≥98:2 *dr*. Apparently, the presence of the salt MgBrCl in the second experiment had made the difference and caused a promotion of the CCR. Therefore, a third experiment was carried out with (*E,R*)-**2** and Ni(dppp)Cl_2 in ether except that $ZnPh_2$ (5 equiv) was used together with $MgBr_2$/Et_2O (2.5 equiv) as additive. Thereby, alkene (*E*)-**3a** was obtained in 85% yield and ≥98:2 *dr*. The configuration of the alkene was determined by NOE experiments. These findings showed that the Ni-catalyzed CCR of the alkenyl sulfoximine with $ZnPh_2$ requires a promotion by a magnesium salt. Both CCRs took place under homogenous reaction conditions. After the addition of $ZnPh_2$ and $MgBr_2$ or $ZnPh_2$/2MgBrCl to (*E,R*)-**2** and Ni(dppp)Cl_2 in ether, the red crystals of the Ni-complex slowly dissolved and a yellow solution of the Ni(0)-catalyst was formed. In order to find out whether the rate acceleration of the Ni-catalyzed CCR of (*E,R*)-**2** with $ZnPh_2$ is specifically caused by magnesium salts, experiments were run with zinc halides. While no Ni-catalyzed CCR of (*E,R*)-**2** with $ZnPh_2$ (5 equiv) occurred in the presence of 5 equivalents of $ZnCl_2$, the addition of 10 equivalents of $ZnCl_2$ gave a 50% conversion of (*E,R*)-**2** to alkene (*E*)-**3a** of ≥98:2 *dr*. Similar observations were made with $ZnBr_2$ as additive. The addition of 5 equivalents of $ZnBr_2$ resulted in no conversion of the alkenyl sulfoximine, while a 50% conversion of the alkenyl sulfoximine to the alkene occurred with 15 equivalents of the salt. All reactions in the presence of the zinc halides took place under homogeneous conditions.

Finally, the Ni-catalyzed CCR of the isomeric alkenyl sulfoximine (*Z,S*)-**2** was investigated. It was expected that the remote stereogenic centers of the other five-membered ring would exert only a minor effect upon the stereochemistry of the CCR. Treatment of (*Z,S*)-**2** of 96:4 *dr* with $ZnPh_2$/2MgBrCl (4 equiv) and Ni(dppp)Cl_2 (5 mol%) in ether at reflux afforded alkene (*Z*)-**3a** in 81% yield and 92:8 *dr*.



Scheme 3. CCR of exocyclic alkenyl sulfoximine (*E,R*)-**2** with diarylzinc **12**.

The synthesis of *inter-m*-phenylene carbacyclin (cf. Scheme 1) from alkenyl sulfoximine (*E,R*)-**2** demanded as key step a CCR of the later with the functionalized diarylzinc **12** (Scheme 3). The salt-containing diarylzinc was prepared from Grignard reagent **11** and $ZnCl_2$.[31] Treatment of (*E,R*)-**2** with **12**/2MgBrCl (2.5 equiv) and Ni(dppp)Cl_2 (5 mol%) in ether at reflux afforded alkene (*E*)-**3b** in 89% yield and ≥98:2 *dr*.

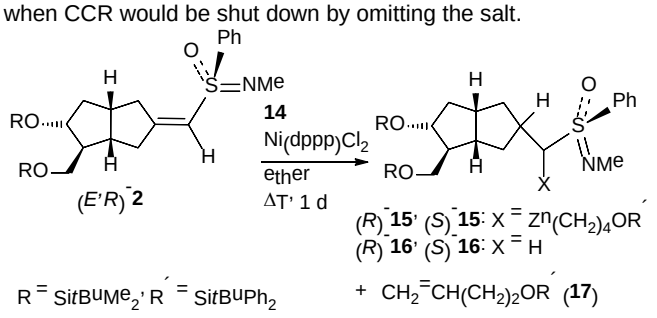


Scheme 4. CCR of exocyclic alkenyl sulfoximine (*E,R*)-**2** with dialkylzinc **14**.

The synthesis of iloprost (cf. Scheme 1) from alkenyl sulfoximine (*E,R*)-**2** asked for a CCR of the later with the functionalized dialkylzinc **14** (Scheme 4). The salt-free dialkylzinc was

synthesized from Grignard reagent **13** and $ZnCl_2$.[31] Treatment of (*E,R*)-**2** with **14** (3.4 equiv), Ni(dppp)Cl_2 (5 mol%) and $MgBr_2$/Et_2O (6.8 equiv) in ether at 0 °C afforded alkene (*E*)-**3c** in 65% yield and 98:2 *dr*. The configuration of the alkene was determined by NOE experiments. Surprisingly, in addition to the alkene a mixture of the diastereomeric alkyl sulfoximines (*R*)-**16** and (*S*)-**16** (Scheme 5) was isolated in 20% yield and 87:13 *dr*.

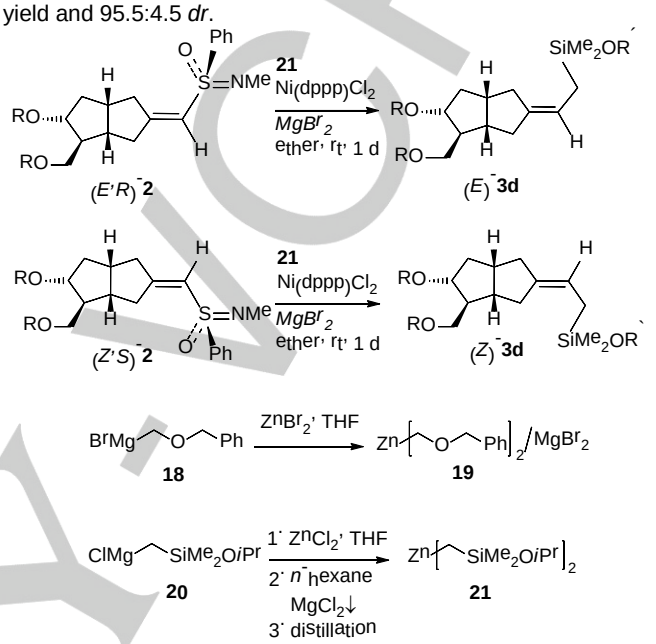
Hydronickelation: formation of alkyl sulfoximines (*R*)-**16** and (*S*)-**16** in the reaction of (*E,R*)-**2** with dialkylzinc **14** in the presence of Ni(dppp)Cl_2 and $MgBr_2$ revealed a competition between hydronickelation and CCR of the alkenyl sulfoximine. Because of the promotion of the CCR by the salt, it was of interest to see whether hydronickelation[32] would be the exclusive path-way when CCR would be shut down by omitting the salt.



Scheme 5. Ni-catalyzed hydronickelation of exocyclic alkenyl sulfoximine (*E,R*)-**2** with dialkylzinc **14**.

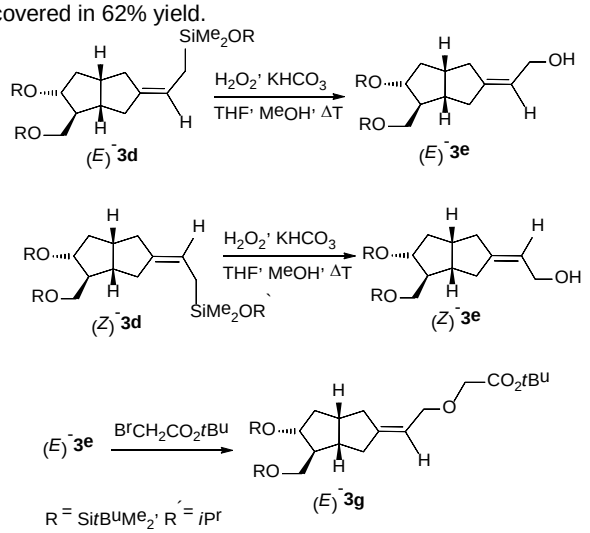
Treatment of (*E,R*)-**2** with dialkylzinc **14** and Ni(dppp)Cl_2 (8 mol%) without $MgBr_2$/Et_2O at reflux gave after aqueous work-up a mixture of the alkyl sulfoximines (*R*)-**16** and (*S*)-**16** in 73% yield and 87:13 *dr*. In addition to the alkyl sulfoximines, butene **17** was formed to a similar extend. Without the Ni-precatalyst formation of the alkyl sulfoximines was not observed and only trace amounts of alkene (*E*)-**3c** were detected. HPLC furnished the pure major diastereomer (*R*)-**16**, the configuration of which was ascertained by NOE experiments. Formation of (*R*)-**16** and (*S*)-**16** most likely involves a hydronickelation of (*E,R*)-**2** followed by a Ni-Zn-exchange and protonation of thus generated alkylzinc sulfoximine (*R*)-**15** and (*S*)-**15** (see Scheme S8, Supporting Information).

The synthesis of cicaprost (cf. Scheme 1) from alkenyl sulfoximine (*E,R*)-**2** required as key step a conversion of the latter to the allylic alcohol (*E*)-**3e** (Scheme 7). Therefore, we planned a CCR of (*E,R*)-**2** with bis(benzyloxymethyl)zinc **19** (Scheme 6), which was prepared from Grignard reagent **18** and $ZnBr_2$ in THF.[33] However, despite several attempts a Ni-catalyzed CCR of (*E,R*)-**2** with **19**/MgBrCl could not be achieved. As an alternative, a step-wise introduction of the hydroxymethyl group of (*E*)-**3e** was envisioned,[34] using bis(alkoxysilylmethyl)-zinc **21**, which was synthesized salt-free from Grignard reagent **20** and $ZnCl_2$.[35] Organozinc **21** is structurally remarkable since it features in the crystal a coordination of the Zn atom by the two C atoms and the O atom of a second molecule in a trigonal planar fashion.[35] It was to be expected that the alkoxy-substituted allylic silane (*E*)-**3d** can be oxidized to the allylic alcohol (*E*)-**3e**.[34] Treatment of (*E,R*)-**2** of 99.5:0.5 *dr* with **21** (2 equiv), Ni(dppp)Cl_2 (20 mol%) and $MgBr_2$/Et_2O afforded the allylic silane (*E*)-**3d** in 92% yield and 98.5:1.5 *dr*. The configuration of the alkene was secured by NOE experiments. A similar CCR of the isomeric alkenyl sulfoximine (*Z,S*)-**2** of 96.4:3.6 *dr* with **21** furnished the isomeric alkene (*Z*)-**3d** in 92% yield and 95.5:4.5 *dr*.



Scheme 6. CCR of exocyclic alkenyl sulfoximines (*E,R*)-**2** and (*Z,S*)-**2** with bis(silylmethyl)zinc **21**.

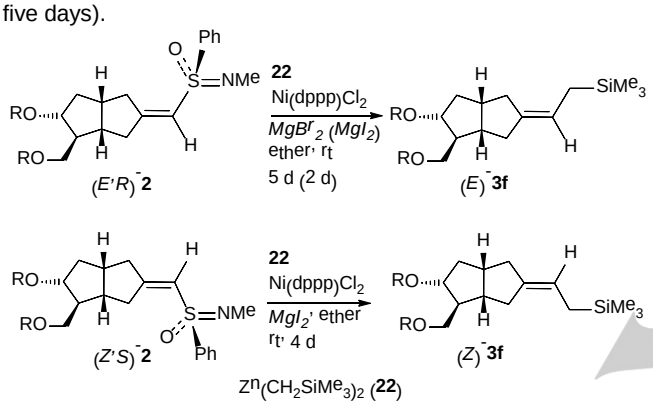
Surprisingly, CCR of (*E,R*)-**2** with **21** in ether in the presence of $MgBr_2$ and Ni$(PPh_3)_2Cl_2$ as precatalyst was unselective and slow, furnishing a mixture of (*E*)-**3d** and (*Z*)-**3d** in 59:41 *dr* and only 21% yield. The alkenyl sulfoximine of unchanged *dr* was recovered in 62% yield.



Scheme 7. Oxidation of exocyclic allylic silanes (*E*)-**3d** and (*Z*)-**3d**.

Oxidation of the allylic silanes (*E*)-**3d** and (*Z*)-**3d** with hydrogen peroxide[34] and purification by HPLC gave the corresponding allylic alcohols (*E*)-**3e** of ≥99:1 *dr* and (*Z*)-**3e** of ≥99:1 *dr* in 69% yield and 64% yield, respectively. Alkylation of the allylic alcohol (*E*)-**3e** with *tert*-butyl bromoacetate gave ether (*E*)-**3g**.

The facile synthesis of the allylic silanes (*E*)-**3d** and (*Z*)-**3d** led us to explore the CCR of (*E,R*)-**2** with bis(silylmethyl)zinc **22**[36] in order to see whether allylic silanes, carrying no functional groups at the Si atom, can also be obtained. CCR of (*E,R*)-**2** of 99.5:0.5 *dr* with salt-free **22** (3 equiv) and Ni(dppp)Cl_2 (10 mol%) in the presence of $MgBr_2$/Et_2O (3 equiv) furnished the allylic silane (*E*)-**3f** in 87% yield and 99.5:0.5 *dr* (Scheme 8). CCR by using MgI_2 as additive gave similar results but the reaction proceeded to completion in much shorter time (two days versus five days).



Scheme 8. CCR of exocyclic alkenyl sulfoximines (*E,R*)-**2** and (*Z,S*)-**2** with bis(silylmethyl)zinc **22**.

CCR of the diastereomeric alkenyl sulfoximine (*Z,S*)-**2** of 96.4:3.6 *dr* with salt-free **22** (3 equiv) and Ni(dppp)Cl_2 (10 mol%) in the presence of MgI_2 (3 equiv) gave the allylic silane (*Z*)-**3f** in 40% yield and 91.1:8.9 *dr*. Alkenyl sulfoximine of unchanged *dr* was recovered in 38% yield.

Because of the many useful synthetic transformations allylic silanes can undergo,[22a,b] (*E*)-**3f** should be an interesting building block for the synthesis of prostacyclin analogs, carrying a side-chain at a di-substituted ring C atom.

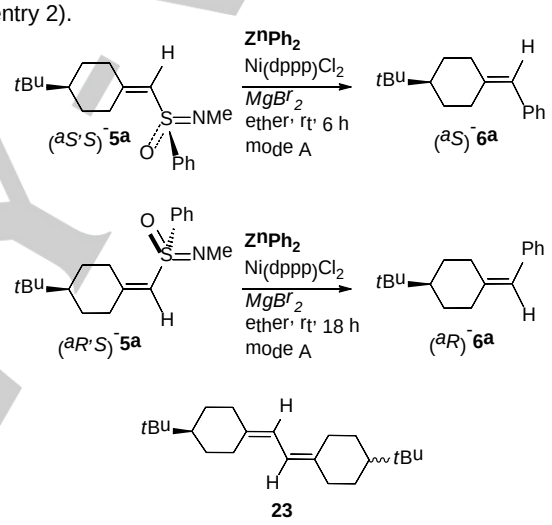
CCR of (*E,R*)-**2** with **22** in the presence of $MgBr_2$ or MgI_2 by using Ni$(PPh_3)_2Cl_2$ (10 mol%) was slower and gave a mixture of the allylic silanes (*E*)-**3f** and (*Z*)-**3f** in only 39% yield and 66:34 *dr*. The alkenyl sulfoximine of unchanged *dr* was recovered in 35% yield.

In summary, CCR of (*E,R*)-**2** with bis(silylmethyl)zincs **21** and **22** by using monophosphine precatalyst Ni$(PPh_3)_2Cl_2$ were not only slower than those with bisphosphine precatalyst Ni(dppp)Cl_2 but also proceeded with a low degree of stereo-retention.

Axially chiral alkenyl sulfoximines

The CCR of the diastereomeric axially chiral alkenyl sulfoximines (*aS,S*)-**5a** and (*aR,S*)-**5a** with alkyl- and arylzincs was studied in more detail under variation of precatalyst, salt additive and solvent. The axially chiral alkenyl sulfoximines have in contrast to the alkenyl sulfoximines (*E,R*)-**2**, (*Z,S*)-**2** and (*E*)-**8** a stereochemically unbiased carbon skeleton, which should make them useful probes for the stereochemistry of the CCR. In addition, the availability of both diastereomeric alkenyl sulfoximines will allow the determination of the influence of the configuration of the sulfonimidoyl group upon the CCR.

Diphenylzinc and Ni(dppp)Cl_2: treatment of a mixture of Ni(dppp)Cl_2 (10 mol%), $MgBr_2$/Et_2O (3 equiv) and salt-free $ZnPh_2$ (3 equiv) in ether with (*aS,S*)-**5a** following an induction period of 15 min (mode A) afforded alkene (*aS*)-**6a** in 72% yield and 92:8 *er* (Table 1, entry 1) (Scheme 9). A similar treatment of a mixture of Ni(dppp)Cl_2 (10 mol%), $MgBr_2$/Et_2O (3 equiv) and $ZnPh_2$ (3 equiv) with diastereomer (*aR,S*)-**5a** (mode A) in ether furnished the enantiomeric alkene (*aR*)-**6a** in 72% yield and 96:4 *er* (entry 2).



Scheme 9. Ni-catalyzed CCR of axially chiral alkenyl sulfoximines (*aS,S*)-**5a** and (*aR,S*)-**5a** with $ZnPh_2$.

The *er* of (*aR*)-**6a** and (*aS*)-**6a** was determined by ^{1}H NMR spectroscopy in the presence of Agfod/Pr(tfc)$_3$[37] (fod = 7,7-dimethyl-1,1,1,2,2,3,3-heptafluoro-octan-4,6-dionato; tfc = (3-trifluoroacetyl-*d*-camphorato) and by GC on a chiral stationary phase. The absolute configuration of (*aS*)-**6a** was assigned based on a comparison of its chirotropic properties with those reported in the literature.[7e]

Diphenylzinc and Ni$(PPh_3)_2Cl_2$: substitution of Ni(dppp)Cl_2 by Ni$(PPh_3)_2Cl_2$ in the CCR of (*aR,S*)-**5a** and (*aS,S*)-**5a** and omitting the induction period (mode B) gave the corresponding alkenes in similar yields and *er* (entries 3 and 4). With Ni$(PPh_3)_2Cl_2$ as pre-catalyst CCR of (*aS,S*)-**5a** was faster than with Ni(dppp)Cl_2. The fastest CCR of (*aS,S*)-**5a** with $ZnPh_2$ in the presence of $MgBr_2$/Et_2O in ether was observed by using a Ni-catalyst, presumably Ni$(PPh_3)_4$,[38a] which was prepared from

$Ni(PPh_3)_2Cl_2$ and MeLi in the presence of PPh_3 (entry 5).[38b,c] Thereby, alkene (*aS*)-**6a** was obtained in 61% yield and 97:3 *er* after a reaction time of only 0.5 h. The use of $Ni(PPh_3)_2Cl_2$ in CCR of (*aR,S*)-**5a** with $ZnPh_2$ was accompanied by a homo-coupling of the alkenyl sulfoximine and gave (*aR*)-**6a** and diene **23** (mixture of diastereomers) in a ratio of 82:18 (entry 4).

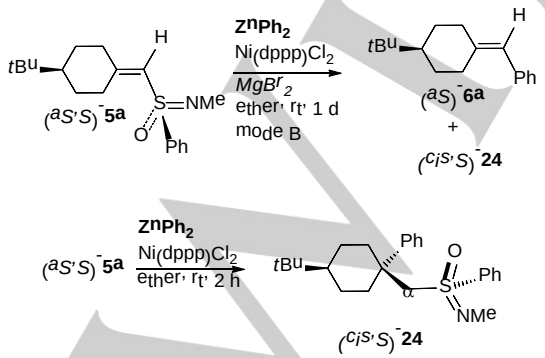
Surprisingly, the alkenyl sulfoximine (*aR,S*)-**5a** also engaged in the absence of $MgBr_2/Et_2O$ according to mode B in an efficient and highly selective CCR with $ZnPh_2$ and the monophosphine precatalyst $Ni(PPh_3)_2Cl_2$ in ether (entry 6). Similarly, the CCR of the diastereomeric alkenyl sulfoximine (*aS,S*)-**5a** also gave in the absence of $MgBr_2$ with $Ni(PPh_3)_2Cl_2$ in ether (mode B) alkene (*aS*)-**6a** in 97:3 *er* (entry 7). However, because of the competing conjugate addition (vide infra), the chemical yield of the alkene was only 29%. The CCR of (*aR,S*)-**5a** with $ZnPh_2$ and $Ni(dppp)Cl_2$ in ether was in the absence of $MgBr_2/Et_2O$ slow and of low selectivity (mode B) (entry 8).

Table 1. Ni-catalyzed CCR of alkenyl sulfoximines (*aS,S*)-**5a** and (*aR,S*)-**5a** with salt-free $ZnPh_2$[a,b].

entry	sulfoximine	mode	precatalyst/ catalyst	salt	solvent	t (h)	**6a**, yield (%)	(*aS*)-**6a**:(*aR*)-**6a**	**5**, **6**, **23**, (*cis,S*)-**24**
1	(*aS,S*)-**5a**	A	$Ni(dppp)Cl_2$	$MgBr_2$	Et_2O	6	72	92:8	-
2	(*aR,S*)-**5a**	A	$Ni(dppp)Cl_2$	$MgBr_2$	Et_2O	18	72	4:96	-
3	(*aS,S*)-**5a**	B	$Ni(PPh_3)_2Cl_2$	$MgBr_2$	Et_2O	2	65	98:2	(*cis,S*)-**24**:(*aS*)-**6a** = 13:87
4	(*aR,S*)-**5a**	B	$Ni(PPh_3)_2Cl_2$	$MgBr_2$	Et_2O	24	67	8:92	(*aR*)-**6a**:**23** = 82:18.
5	(*aS,S*)-**5a**	B	$Ni(PPh_3)_4$[e]	$MgBr_2$	Et_2O	0.5	61	97:3	-
6	(*aR,S*)-**5a**	B	$Ni(PPh_3)_2Cl_2$	-	Et_2O	24	71	3:97	(*aR,S*)-**5a**:(*aR*)-**6a** = 5:95
7	(*aS,S*)-**5a**	B	$Ni(PPh_3)_2Cl_2$	-	Et_2O	24	[c]	97:3	(*cis,S*)-**24**:(*aS*)-**6a:**(*aS,S*)-**5a**=65:29:6
8	(*aR,S*)-**5a**	B	$Ni(dppp)Cl_2$	-	Et_2O	72	[c]	30:70	(*aR,S*)-**5a**:(*aR*)-**6a** = 55:45
9	(*aS,S*)-**5a**	B	$Ni(dppp)Cl_2$	$MgBr_2$	THF	24	[c]	[d]	(*cis,S*)-**24**:(*aS*)-**6a:**(*aS,S*)-**5a**=76:9:15
10	(*aR,S*)-**5a**	B	$Ni(dppp)Cl_2$	$MgBr_2$	THF	24	15	67:33	(*aR,S*)-**5a**:(*aS*)-**6a** = 76:24
11	(*aS,S*)-**5a**	B	$Ni(dppp)Cl_2$	$MgBr_2$	Et_2O	24	67	92:8	(*cis,S*)-**24**:(*aS*)-**6a** = 20:80
12	(*aR,S*)-**5a**	B	$Ni(dppp)Cl_2$	$MgBr_2$	Et_2O	24	87	5:95	-

[a] 0.1 mmol **5a**, 10 mol% precatalyst or catalyst, 3 equiv of $ZnPh_2$ and with or without 3 equiv of $MgBr_2$. [b] **Mode A**: after the mixture of $ZnPh_2$, $Ni(dppp)Cl_2$ and $MgBr_2$ in Et_2O or THF was kept for 15 min at room temperature, **5a** in Et_2O or THF was added and the mixture was stirred at room temperature for the time given. **Mode B**: a mixture prepared through the successive addition of $ZnPh_2$, $Ni(dppp)Cl_2$, $MgBr_2$ and **5a** was stirred in Et_2O or THF at rt for the time given. [c] Not isolated. [d] Not determined. [e] Prepared from $Ni(PPh_3)_2Cl_2$, PPh_3 (2 equiv) and MeLi (2 equiv) in ether.

Conjugate addition: treatment of a mixture of $Ni(dppp)Cl_2$, $MgBr_2/Et_2O$ and salt-free $ZnPh_2$ in ether with alkenyl sulfoximine (*aS,S*)-**5a** without induction period (mode B) furnished a mixture of alkene (*aR*)-**6a** and the phenyl-substituted alkyl sulfoximine (*cis,S*)-**24** in a ratio of 80:20 (entry 11) (Scheme 10). Alkene (*aS*)-**6a** was isolated in 67% yield and 92:8 *er*



Scheme 10. Ni-Catalyzed conjugate addition of $ZnPh_2$ to alkenyl sulfoximine (*aS,S*)-**5a**.

Formation of (*cis,S*)-**24** also occurred with $Ni(PPh_3)_2Cl_2$ in ether or with $Ni(dppp)Cl_2$ in THF as solvent according to mode B (entries 3 and 9). The alkyl sulfoximine (*cis,S*)-**24** was formed as single diastereomer and its configuration was determined by X-ray crystal structure analysis (see Supporting Information).[39] From this result follows that $ZnPh_2$ had undergone in addition to CCR a diastereoselective Ni-catalyzed conjugate addition to the alkenyl sulfoximine (*aS,S*)-**5a**. Formation of (*cis,S*)-**24** indicates a selective equatorial CC-bond formation in accordance with observations made previously in cuprate reactions of (4-*tert*-butyl)cyclohexylidene derivatives.[40] The different results gained in the reactions of (*aS,S*)-**5a** according to modes A and B suggest that in the former case, because of the induction period, most of the Ni(II)-complex had been reduced to the Ni(0)-complex before addition of the alkenyl sulfoximine, while in the latter case both Ni(II)- and Ni(0)-

complexes were present. The Ni(0)-complex catalyzed the CCR, while the Ni(II)-complex catalyzed the conjugate addition.[41] In order to collect further support for this scenario, conjugate addition of $ZnPh_2$ to alkenyl sulfoximine (*aS,S*)-**5a** was probed with catalytic amounts of Ni(II) compounds in the absence of $MgBr_2$ (Table 2), since CCR of (*aS,S*)-**5a** in the absence of the salt is slow. Reactions were carried out by addition of $ZnPh_2$ to a mixture of (*aS,S*)-**5a** and the Ni-precatalyst (mode C). While with complexes Ni(dppp)Cl_2 and Ni$(PPh_3)_2Cl_2$ in ether and THF conjugate addition is the major and CCR the minor path-way (entries 1–3), with Ni$(acac)_2$ and $NiCl_2$ conjugate addition is almost the exclusive path-way (entries 4 and 5). Quenching of the reaction mixtures obtained in conjugate addition with CF_3CO_2D gave the deuteriated alkyl sulfoximine (*cis,S*)-D-**24**, containing 89% D at the α-position, in 77% yield and ≥98:2 *dr*.
In the absence of a nickel compound conjugate addition occurred only to a minor extent (entries 6–8)

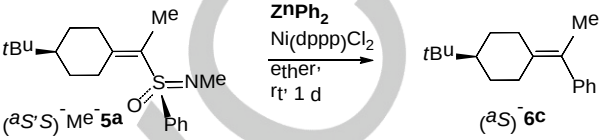
Table 2. Conjugate addition of $ZnPh_2$ to alkenyl sulfoximine (*aS,S*)-**5a** at room temperature in the presence of additives

entry	additive	t (h)	solvent	(*aS,S*)-**5a**: (*cis,S*)-**24**:(*S*)-**6a**	(*S*)-**6a**: (*R*)-**6a**
1	Ni(dppp)Cl_2[a]	24	Et_2O	5:82:13[b]	[c]
2	Ni(dppp)Cl_2[a]	24	THF	3:88:9	[c]
3	Ni$(PPh_3)_2Cl_2$[a]	1	Et_2O	6:65:29	97:3
4	Ni$(acac)_2$[d]	1	Et_2O	2:95:2	[c]
5	$NiCl_2$[d]	1h	Et_2O	2:95:2	[c]
6	$MgBr_2$[d]	48	Et_2O	88:12:0	-
7	-[e]	48	Et_2O	83:17:0	-
8	-[e]	48	THF	100:0:0	-

[a] To a mixture of alkenyl sulfoximine (*aS,S*)-**5a** (.0.10 mmol) and the Ni compound (10 mol%) was added $ZnPh_2$ (3 equiv) (mode C). [b] Sulfoximine (*cis,S*)-**24** was isolated in 77% yield. [c] Not determined. [d] To a mixture of (*aS,S*)-**5a** (0.05 mmol) and the Ni compound or salt (10 mol%) was added $ZnPh_2$ (3 equiv). [e] (*aS,S*)-**5a** (0.05 mmol) was treated with $ZnPh_2$ (3 equiv).

The reactivity of (*aS,S*)-**5a** stands in sharp contrast to that of the diastereomeric alkenyl sulfoximine (*aR,S*)-**5a**, which does not engage in a Ni(II)-catalyzed conjugate addition with $ZnPh_2$ according to modes A–C (Table 1, entries 2 and 12), presumably because of its faster Ni(0)-catalyzed CCR.

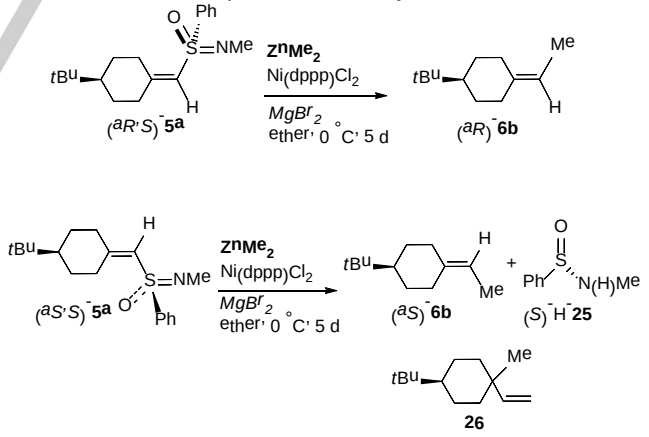
α-Substituted alkenyl sulfoximines: thus far terminal alkenyl sulfoximines were studied. Lithiation of alkenyl sulfoximines (*E,R*)-**2**, (*Z,S*)-**2** and (*aS,S*)-**5a** with MeLi at low temperatures followed by methylation of the corresponding lithioalkenyl sulfoximine (*E,R*)-Li-**2**, (*Z,S*)-Li-**2** and (a*S,S*)-Li-**5a** with MeI in the presence of HMPA at low temperatures gave the corresponding methylated alkenyl sulfoximines (*E,R*)-Me-**2**, (*Z,S*)-Me-**2** and (a*S,S*)-Me-**5a** in high yield and ≥98:2 *dr* (see Supporting Information).[31] This offered the possibility of an enantioselective synthesis of per-substituted axially chiral alkenes, which are otherwise difficult to obtain.[6,7] Treatment of alkenyl sulfoximine (*aS,S*)-Me-**5a** (96:4 *dr*) with salt-free $ZnPh_2$ (3 equiv) in ether with Ni(dppp)Cl_2 (10 mol%) without $MgBr_2/Et_2O$ furnished alkene (*aS*)-**6c** in 82% yield and 96:4 *er* (Scheme 12). Surprisingly, the CCR in the presence of $MgBr_2/Et_2O$ was slower but gave similar results. The *er* of (*aS*)-**6c** was determined by ^1H NMR spectroscopy in the presence of Agfod/Pr$(tfc)_3$[37] and GC on a cyclodextrin phase and the absolute configuration assigned based on comparison of its chirotropic properties with those of alkene (*aS*)-**6a**.



Scheme 12. CCR of the trisubstituted alkenyl sulfoximine (*aS,S*)-Me-**5a**.

Because of the lack of a α-H atom, CCR of alkenyl sulfoximine (a*S,S*)-Me-**5a** with PhMgBr should be possible. Indeed, treatment of (*aS,S*)-Me-**5a** with Ni(dppp)Cl_2 and PhMgBr gave alkene (a*S*)-**6c** in 82% yield and 85:15 *er*.[42]

Dimethylzinc: CCR of alkenyl sulfoximines (*aR,S*)-**5a** and (*aS,S*)-**5a** with salt-free $ZnMe_2$ (4 equiv), Ni(dppp)Cl_2 (4 mol%) and $MgBr_2/Et_2O$ (3 equiv) was much slower than with $ZnPh_2$. It afforded the corresponding alkenes (*aR*)-**6b** in 82% yield and 95:5 *er* and (*aS*)-**6b** in 74% yield and 95:5 *er* (Scheme 13). The *er* of the alkenes was determined by GC on a chiral stationary phase. The absolute configuration of the alkenes was assigned based on a comparison of the chirotropic properties with those reported in the literature.[7c] Alkene **26** of unknown configuration was isolated as a side product in 2–4% yield.

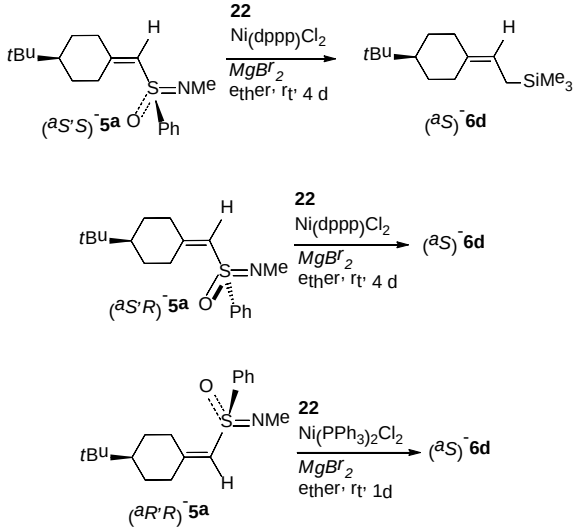


Scheme 13. CCR of alkenyl sulfoximines (*aR,S*)-**5a** and (*aS,S*)-**5a** with $ZnMe_2$.

In all of the CCRs described above the corresponding metallo sulfinamides (*S*)-M-**25** and (*R*)-M-**25** were formed in addition to the alkenes. In the case of the CCR of (*aS,S*)-**5a** sulfinamide (*S*)-H-**25** was isolated, which was obtained in 89% yield and

≥98:2 *er*. Thus, the CCR of the alkenyl sulfoximine had occurred with retention of configuration of the chiral axis and S atom.

Conversion of sulfinamide (*S*)-H-**25** into sulfoximine (*S*)-H-**7a**, the chiral reagent used for the synthesis of (*aS,S*)-**5a**, had already been described.[43]



Scheme 14. CCR of alkenyl (*N*-methyl)sulfoximines (*aR,R*)-**5a** and (*aS,R*)-**5a** with bis(silylmethyl)zinc **22**.

Bis(silylmethyl)zincs: the CCR of alkenyl sulfoximines (*aS,R*)-**5a** and (*aR,R*)-**5a** with bis(silylmethyl)zincs **21** and **22** was investigated in order to obtain further information about their reactivity towards alkylzincs and to explore the synthesis of functionalized axially chiral alkenes (Schemes 14 and 15, Tables 3 and 4).

Ni(dppp)Cl₂ and salt additive: CCR of (*aS,S*)-**5a** with salt-free bis(silylmethy)zinc **22** (3 equiv) in the presence of $MgBr_2/Et_2O$ (3 equiv) in ether by using $Ni(dppp)Cl_2$ (10 mol%) afforded the allylic silane (*aS*)-**6d** in 90% yield and 97:3 *er* (Table 3, entry 1). The *er* of (*aS*)-**6d** was determined by ^{1}H NMR spectroscopy in the presence of Agfod/Pr(tfc)$_3$ and the absolute configuration was assigned based on a comparison of its chirotropic properties with those of alkene (*aS*)-**6b**.

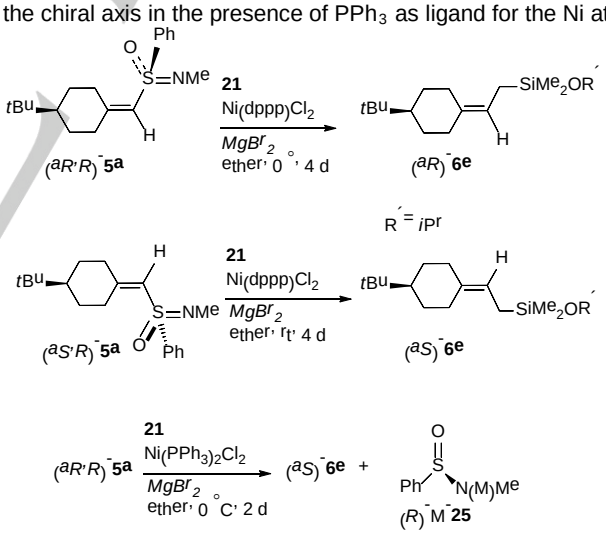
Next the salt additive (3 equiv) was varied in CCR of (*aR,R*)-**5a** with **22** (1.5 equiv) and $Ni(dppp)Cl_2$ (10 mol%) in ether (Table 4). $MgBr_2$ and MgI_2 caused the highest rate acceleration and LiI had an intermediate effect (entries 4, 5 and 2). The *er* of (*aR*)-**6d** was in the case of MgI_2 and LiI only 82:18 and 77:23, respectively (entries 5 and 2). Salts LiBr, $LiClO_4$ and ZnX_2 (X = Cl, Br, I) had only a minor effect upon the rate of the CCR (entries 1, 3 and 6–8).

Interestingly, the amount of $MgBr_2$ used as additive in the CCR of (*aR,R*)-**5a** had a profound influence upon the rate. While with 0.5 equiv no CCR occurred, the use of 1 equiv resulted in the formation of a mixture of (*aR,R*)-**5a** and (*aR*)-**6d** in a ratio of 41:59 and the application of 3 equiv gave the alkene in 90% yield (Table 3, entries 3, 4 and 1).

CCR of the diastereomeric alkenyl sulfoximine (*aS,R*)-**5a** in ether under similar conditions was much slower. Treatment of (*aS,R*)-**5a** with bis(silylmethy)zinc **22** in the presence of $MgBr_2/Et_2O$ in ether by using $Ni(dppp)Cl_2$ afforded the allylic silane (*aS*)-**6d** in only 52% yield and 97:3 *er* (Table 3, entry 5). The alkenyl sulfoximine of unchanged *dr* was recovered in 26% yield.

Rather long reaction times were required for the complete conversion of the alkenyl sulfoximines. Therefore, the time dependency of conversion and alkene formation was determined in the CCR of alkenyl sulfoximine (*aR,R*)-**5a** with **22** in the presence of $MgBr_2$ with $Ni(dppp)Cl_2$ in ether (see Supporting Information, Table S1). The results show that reaction rate slows down more than expected towards the end of the reaction, which could be due to a catalyst deactivation.

Ni(PPh₃)₂Cl₂ as precatalyst: a further surprising observation was made in the CCR of the alkenyl sulfoximines by using $Ni(PPh_3)_2Cl_2$. Treatment of (*aR,R*)-**5a** with bis(silylmethy)zinc **22** in the presence of $MgBr_2/Et_2O$ and $Ni(PPh_3)_2Cl_2$ gave the allylic silane (*aS*)-**6d** in 72% yield and 72:28 *er* (Table 3, entries 6 and 7), while a similar CCR of (*aS,R*)-**5a** furnished (*aR*)-**6d** in 33% yield and 53:47 *er* (entry 8). The CCR of (*aR,R*)-**5a** proceeded with the alleged catalyst $Ni(PPh_3)_4$ in a similar manner (entry 11), while no CCR occurred with alleged complex $Ni(dppp)_2$[38d] (entry 12), which was prepared from $Ni(dppp)Cl_2$, dppp (1 equiv) and MeLi (2 equiv) in ether.[38b,c] Thus, CCR of both alkenyl sulfoximines took place under inversion of the configuration of the chiral axis in the presence of PPh_3 as ligand for the Ni atom.



Scheme 15. CCR of alkenyl (*N*-methyl)sulfoximines (*aR,R*)-**5a** and (*aS,R*)-**5a** with bis(silylmethyl)zinc **21**.

Interestingly, inversion of configuration was also observed when $Ni(dppp)Cl_2$ was used in the presence of PPh_3 (entry 9). A similar result was obtained with precatalyst $Ni(PPh_2Me)_2Cl_2$ (entry 10). Generally, CCRs of the alkenyl sulfoximines with PPh_3 as ligand for the Ni atom were not only less selective but also faster than those with dppp as ligand. Low selectivity and inversion of configuration had also been noted in CCR of alkenyl

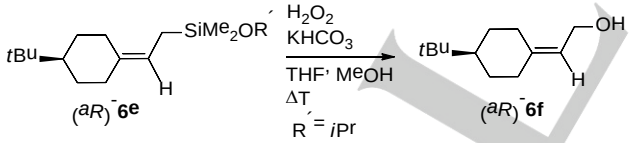
sulfoximine (*E,R*)-**2** with **22** in the presence of $MgBr_2$ and $Ni(PPh_3)_2Cl_2$ (vide supra). These results stand in sharp contrast to the CCR of (*aS,S*)-**5a** and (*aR,S*)-**5a** with $ZnPh_2$ where with $Ni(PPh_3)_2Cl_2$ a high degree of stereo-retention was found (vide supra).

Table 3. Ni-catalyzed CCR of alkenyl sulfoximines (*aR,R*)-**5a** and (*aS,R*)-**5a** with $Zn(CH_2SiMe_3)_2$ (**22**)[a].

entry	sulfoximine	precatalyst/catalyst	salt	solvent	t (d)	**6d**, yield (%)	(*aR*)-**6d**:(*aS*)-**6d**
1	(*aR,R*)-**5a**	$Ni(dppp)Cl_2$	$MgBr_2$	Et_2O	4	90	97:3
2	(*aR,R*)-**5a**	$Ni(dppp)Cl_2$	$MgBr_2$	THF	3	-	-[b]
3	(*aR,R*)-**5a**	$Ni(dppp)Cl_2$	$MgBr_2$[h]	Et_2O	2	-	-
4	(*aR,R*)-**5a**	$Ni(dppp)Cl_2$	$MgBr_2$[i]	Et_2O	2	[j]	[k]
5	(*aS,R*)-**5a**	$Ni(dppp)Cl_2$	$MgBr_2$	Et_2O	4	52	3:97[c]
6	(*aR,R*)-**5a**	$Ni(PPh_3)_2Cl_2$	$MgBr_2$	Et_2O	1	72	28:72[d]
7	(*aR,R*)-**5a**	$Ni(PPh_3)_2Cl_2/PPh_3$	$MgBr_2$	Et_2O	1	78	36:64
8	(*aS,R*)-**5a**	$Ni(PPh_3)_2Cl_2$	$MgBr_2$	Et_2O	4	33	53:47[e]
9	(*aR,R*)-**5a**	$Ni(dppp)Cl_2/PPh_3$	$MgBr_2$	Et_2O	2	86	28:72
10	(*aR,R*)-**5a**	$Ni(PPh_2Me)_2Cl_2$	$MgBr_2$	Et_2O	1	90	40:60
11	(*aR,R*)-**5a**	$Ni(PPh_3)_4$[f]	$MgBr_2$	Et_2O	1	71	40:60
12	(*aR,R*)-**5a**	$Ni(dppp)_2$[g]	$MgBr_2$	Et_2O	1	-	-

[a] 0.2 mmol **5a**, 10 mol% catalyst, 3 equiv of **22** and 3 equiv of salt (mode B). [b] Recovery of 86% (*aR,R*)-**5a**. [c] Recovery of 26% (*aS,R*)-**5a**. [d] Isolation of 5% of **22** as a mixture of diastereomers. [e] Recovery of 61% of (*aS,R*)-**5a.** [f] Prepared from $Ni(PPh_3)_2Cl_2$, PPh_3 (2 equiv) and MeLi (2 equiv) in ether. [g] Prepared from $Ni(dppp)Cl_2$, dppp (1 equiv) and MeLi (2 equiv) in ether. [h] 0.5 equiv. [i] 1 equiv. [j] **5a**:**6d** = 41:59. [k] Not determined.

CCR of the alkenyl sulfoximines (*aR,R*)-**5a** and (*aS,R*)-**5a** with the functionalized bis(silylmethyl)zinc **21** (3 equiv), $MgBr_2/Et_2O$ (3 equiv) and $Ni(dppp)Cl_2$ (10 mol%) afforded the corresponding allylic silanes (*aR*)-**6e** in 96% yield and 97:3 *er* and (*aS*)-**6e** in 97% yield and 97:3 *er*. Again with $Ni(PPh_3)_2Cl_2$ as precatalyst inversion of configuration occurred. Besides the alkenes sulfinamide (*R*)-H-**25** was isolated in 74% yield and ≥98:2 *er*.



Scheme 16. Oxidation of the allylic silanes (*aS*)-**6e** and (*aR*)-**6e**.

Oxidation of the allylic silanes (*aS*)-**6e** and (*aR*)-**6e** gave the corresponding axially chiral allylic alcohols (*aS*)-**6f** and (*aR*)-**6f** in 75% yield and 73% yield, respectively (Scheme 16). The absolute configuration of the allylic alcohols was assigned based on a comparison of its chirotropic properties with those reported in the literature.[44] Conversion of the allylic alcohols to the corresponding acetates (*aR*)-**6h** and (*aS*)-**6h** (see Supporting Information) and GC analysis of the later on a chiral stationary phase gave for both acetates 97:3 *er*.

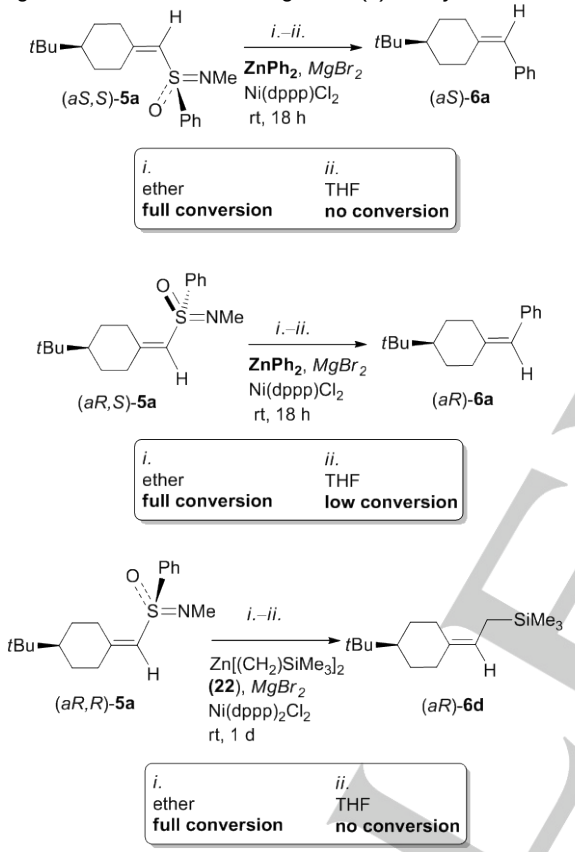
Table 4. Ni-catalyzed CCR of (*aR,R*)-**5a** with $Zn(CH_2SiMe_3)_2$ (**22**) in the presence of salt additives in ether at room temperature[a]

entry	salt	t (d)	(*aR,R*)-**5a**:(*aR*)-**6d**	(*aR*)-**6d**:(*aS*)-**6d**
1	LiBr	3	98:2	[b]
2	LiI	3	64:36	77:23
3	$LiClO_4$	3	90:3	[b]
4	$MgBr_2$	4	5:95	97:3
5	MgI_2	1	5:95	82:18
6	$ZnCl_2$	3	98:2	[b]
7	$ZnBr_2$	3	98:2	[b]
8	ZnI_2	3	96:4	[b]

[a] 0.10 mmol (*aR,R*)-**5a**, 10 mol% $Ni(dppp)Cl_2$, 0.15 mmol of **22**, 0.30 mmol salt (mode B). [b] Not determined.

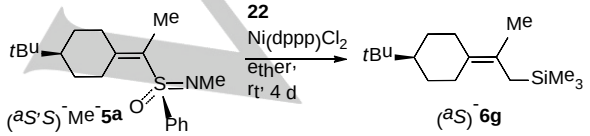
Solvent effect: surprising results were obtained by changing the solvent from ether to THF. CCR of (*aS,S*)-**5a** and (*aR,S*)-**5a** with salt-free $ZnPh_2$ and $Ni(dppp)Cl_2$ in the presence of $MgBr_2/Et_2O$ in ether led to a full conversion of the alkenyl sulfoximines and

gave the corresponding alkenes (*aS*)-**6a** and (*aR*)-**6a** in high yields (Table 1, entries 1 and 2) (Scheme 18). In stark contrast, experiments conducted under similar conditions but using THF as solvent saw a low conversion of the substrates and either no or only minor formation of the alkenes (Table 1, entries 9 and 10). The same solvent dependency was observed in the case of the CCR with an alkylzinc. While treatment of (*aR,R*)-**5a** with salt-free bis(silylmethy)zinc **22** (3 equiv) in the presence of $MgBr_2/Et_2O$ (3 equiv) with $Ni(dppp)Cl_2$ (10 mol%) in ether gave alkene (*aR*)**-6d** in 90% yield (Table 3, entry 1), a similar experiment in THF resulted in no conversion and the alkenyl sulfoximine was recovered in 86% yield (Table 3, entry 2). In both ether and THF the red crystalline Ni(II)-complex was reduced within short time under formation of a yellow-orange homogeneous mixture containing the Ni(0)-catalyst.



Scheme 18. Ni-Catalyzed CCR of alkenyl sulfoximines in ether and THF.

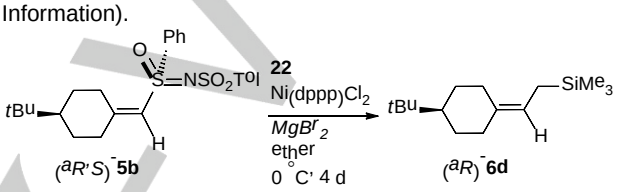
α-Substituted alkenyl sulfoximine: treatment of the non-terminal alkenyl sulfoximine (*aS,S*)-Me-**5a** (96:4 *dr*) with salt-free bis(silylmethyl)zinc **22** (3 equiv) in ether and $Ni(dppp)Cl_2$ (10 mol%) in the absence of $MgBr_2/Et_2O$ furnished alkene (*aS*)-**6g** in only 40% yield and 79:21 *er* (Scheme 19). Alkenyl sulfoximine (*aS,S*)-Me-**5a** was recovered in 40% yield and 96:4 *dr*. CCR in the presence of $MgBr_2$ afforded (*aS*)-**6g** in 55% yield and 61:39 *er*.



Scheme 19. CCR of trisubstituted axially chiral alkenyl sulfoximine (a*S,S*)-Me-**5a** with bis(silylmethyl)zinc **22** .

Interestingly, the CCR with $Ni(PPh_3)_2Cl_2$ occurred under inversion of configuration of the chiral axis and gave (*aR*)-**6g** in 68:32 *er* and 32% yield. The *er* of (*aS*)-**6g** was determined by ^1H NMR spectroscopy in the presence of Agfod/Pr(tfc)$_3$[37] and the absolute configuration was assigned based on comparison of its chirotropic properties with those of alkene (*aS*)-**6d**.

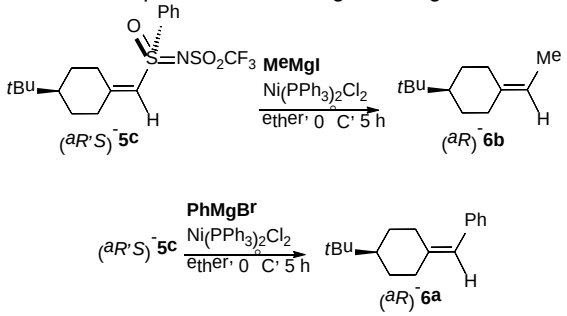
(N-sulfonyl)sulfoximines: in a final set of experiments with axially chiral alkenyl sulfoximines the influence of the substituent at the N atom of the sulfonimidoyl group upon the CCR was probed by using the (*N*-sulfonyl)sulfoximines (*aR,S*)-**5b** and (*aR,R*)-**5c**. Alkenyl sulfoximines (*aR,S*)-**5b** and (*aR,S*)-**5c** were synthesized through sulfonylation of the corresponding alkenyl (*N*-H)sulfoximine (*aR*)-**5d** at the N atom (see Supporting Information).



Scheme 20. CCR of alkenyl (*N*-tosyl)sulfoximine (*aR,S*)-**5b** with bis(silylmethyl)zinc **22**.

CCR of (*N*-tosyl)sulfoximine (*aR,S*)-**5b** with bis(silylmethyl)zinc **22** in the presence of $MgBr_2/Et_2O$ with $Ni(dppp)Cl_2$ gave the allylic silane (*aR*)-**6d** in 70% yield and 92:8 *er* (Scheme 20). As found in the CCR of the alkenyl (*N*-methyl)sulfoximine (*aR,R*)-**5a**, the presence of the salt was crucial for the CCR of the alkenyl sulfoximine to occur.

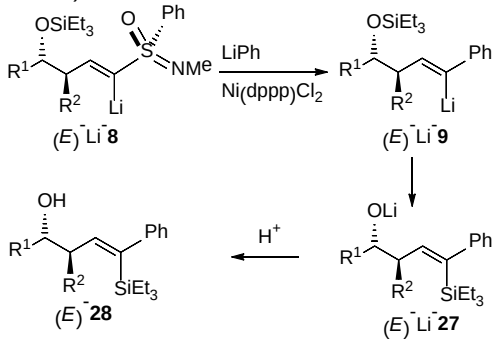
In contrast to alkenyl (*N*-methyl)sulfoximines, the alkenyl (*N*-triflyl)sulfoximine (*aR,S*)-**5c** is not metallated by Grignard reagents at the α-position. This gave reason to study the CCR of (*aR,S*)-**5c** with MeMgI and PhMgBr (Scheme 21). CCR of (*aR,S*)-**5c** with MeMgI (3 equiv) and $Ni(PPh_3)_2Cl_2$ (8 mol%) in ether gave alkene (*aR)*-**6b** in 84% yield and 98:2 *er* under retention of configuration. Under similar conditions the Ni-catalyzed CCR of (*aR,S*)-**5c** with PhMgBr afforded alkene (*aR)*-**6a** in 61% yield and 98:2 *er*. Remarkably, promotion of CCR by $MgBr_2$ was not required with both Grignard reagents.



Scheme 21. CCR of alkenyl (*N*-triflyl)sulfoximine (*aR,S*)-**5c** with Grignard reagents.

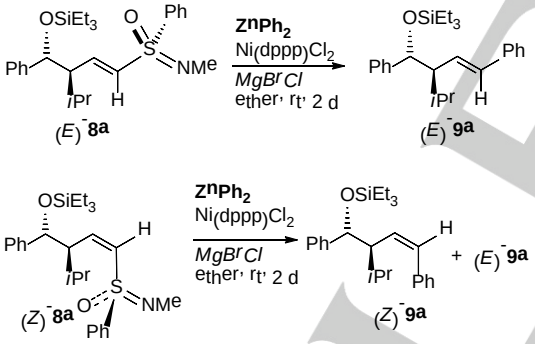
Acyclic alkenyl sulfoximines

The Ni-catalyzed ACCR of lithioalkenyl sulfoximines (*E*)-Li-**8** with PhLi primarily affords the phenyl-substituted alkenyllithiums (*E*)-Li-**9**, which suffer a [1,5]-retro-Brook rearrangement. Protonation of alcoholates (*E*)-Li-**27** furnishes the phenyl- and silyl-substituted homoallylic alcohols (*E*)-**28** (Scheme 22).[29,45] It was therefore of interest to see whether a CCR of (*E*)-**8** would also give access to monosubstituted homoallylic alcohols of type (*E*)-**9**. Gratifyingly, CCR of alkenyl sulfoximine (*E*)-**8a** with $ZnPh_2$ (4 equiv) and $Ni(dppp)Cl_2$ (15 mol%) in ether in the presence of MgBrCl (4 equiv) furnished alkene (*E*)-**9a** in 78% yield and ≥98:2 *dr* (Scheme 23).



Scheme 22. Ni-Catalyzed ACCR of acyclic lithioalkenyl sulfoximines (*E*)-Li-**8** with PhLi.

Interestingly, CCR of the (*Z*)-configured alkenyl sulfoximine (*Z*)-**8a**[20] was much slower and unselective. After a reaction time of 2 d a mixture of (*Z*)-**8a**, (*E*)-**9a** and (*Z*)-**9a** was isolated in a ratio of 80:10:10.



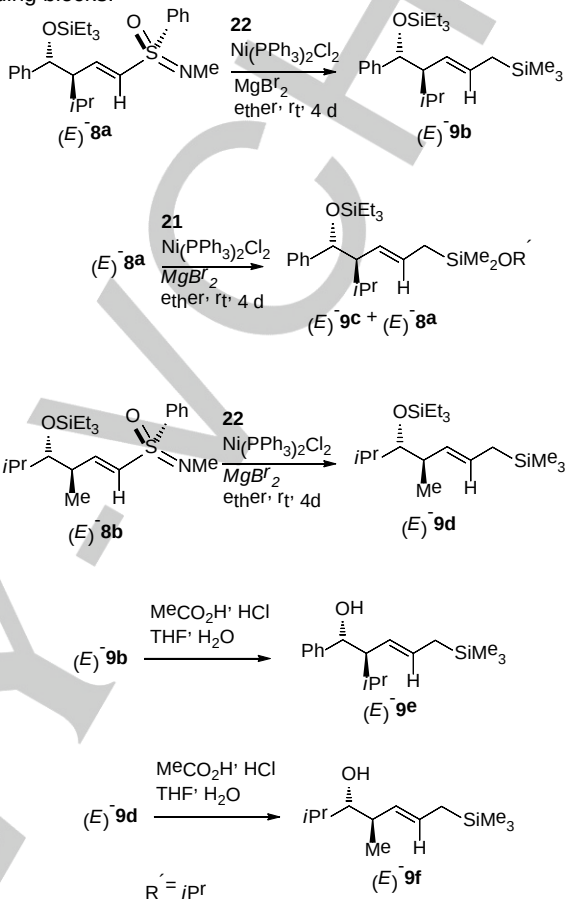
Scheme 23. CCR of acyclic alkenyl sulfoximines (*E*)-**8a** and (*Z*)-**8a** with $ZnPh_2$.

Reaction of (*E*)-**8a** with bis(silylmethyl)zincs **22** and **21**, $Ni(PPh_3)_2Cl_2$ and $MgBr_2/Et_2O$ afforded the corresponding allylic silanes (*E*)-**9b** and (*E*)-**9c** only in 44% yield and 27% yield, respectively, both in ≥98:2 *dr* (Scheme 24). The alkenyl sulfoximine was recovered in 47% yield. In contrast, CCR of alkenyl sulfoximine (*E*)-**8b** with **22**, $Ni(PPh_3)_2Cl_2$ and $MgBr_2/Et_2O$ gave the allylic silane (*E*)-**9d** in 86% yield and ≥98:2 *dr*.

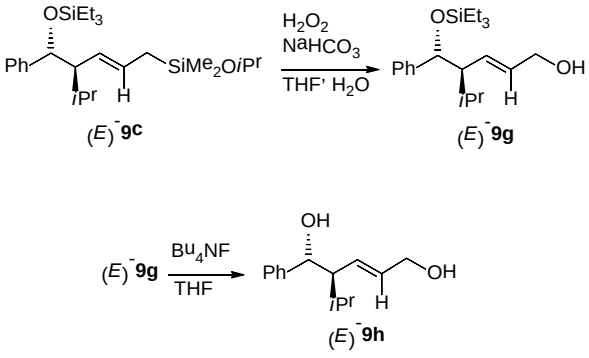
The CCR of the acyclic alkenyl sulfoximines were run in the presence of $MgBr_2$/MgBrCl since without the salt no reaction occurred.

Selective cleavage of the silyl ethers (*E*)-**9b** and (*E*)-**9d** with $MeCO_2H$/HCl gave the corresponding alcohols (*E*)-**9e** and (*E*)-**9f** in 94% yield and 86% yield, respectively.

Homoallylic alcohols of type (*E*)-**9c** and (*E*)-**9d**, having an additional allylic silane moiety, should be interesting synthetic building blocks.[46]



Scheme 24. CCR of acyclic alkenyl sulfoximines (*E*)-**8a** and (*E*)-**8b** with bis(silylmethyl)zincs **21** and **22**.



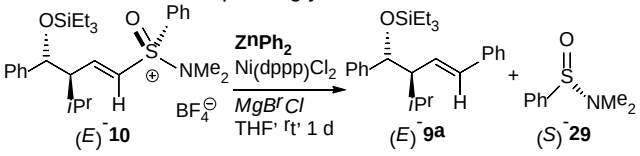
Scheme 25. Oxidation of acyclic allylic silane (*E*)-**9c**.

Oxidation of the allylic silane (*E*)-**9c** furnished the mono-protected allylic diol (*E*)-**9g** in 93% yield and ≥98:2 *dr* (Scheme 25). Homoallylic diols of type (*E*)-**9g** are valuable building block

for polyketide synthesis.[47] Cleavage of silyl ether (*E*)-**9g** with fluoride afforded diol (*E*)-**9h** in 96% yield.

Alkenyl aminosulfoxonium salts

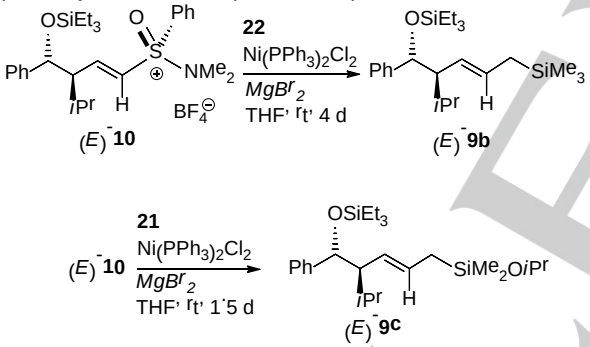
Methylation of alkenyl sulfoximine (*E*)-**8a** with Me_3OBF_4 gives the alkenyl aminosulfoxonium salt (*E*)-**10** in nearly quantitative yield.[24b] Utilization of RMgX or RLi in CCR with alkenyl aminosulfoxonium salts, which carry a H atom at the α-position, is not feasible, because of their ready deprotonation under formation of the corresponding ylides.[21a,24]



Scheme 26. CCR of alkenyl amino sulfoxonium salt (*E*)-**10** with $ZnPh_2$.

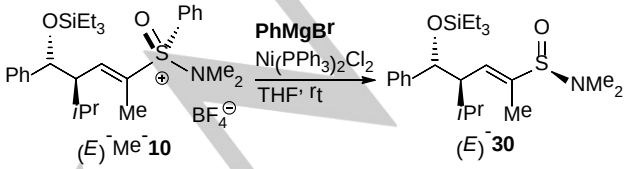
The Ni-catalyzed CCR of salt (*E*)-**10** with $ZnPh_2$/MgBrCl and $Ni(dppp)Cl_2$ was faster than that of the corresponding alkenyl sulfoximine (*E*)-**8a** and afforded alkene (*E*)-**9a** in 85% yield and ≥98:2 *dr* (Scheme 26). In addition, sulfinamide (*R*)-**29**[21a,24] was formed, which was, however, not isolated.

Similarly, CCR of salt (*E*)-**10** with bis(silylmethyl)zincs **22** and **21**, $Ni(PPh_3)_2Cl_2$ and $MgBr_2/Et_2O$ in THF gave the corresponding allylic silanes (*E*)-**9b** and (*E*)-**9c** in 62% yield and 84% yield, respectively and ≥98:2 *dr* (Scheme 27).



Scheme 27. CCR of alkenyl amino sulfoxonium salt (*E*)-**10** with bis(silylmethyl)zins **21** and **22**.

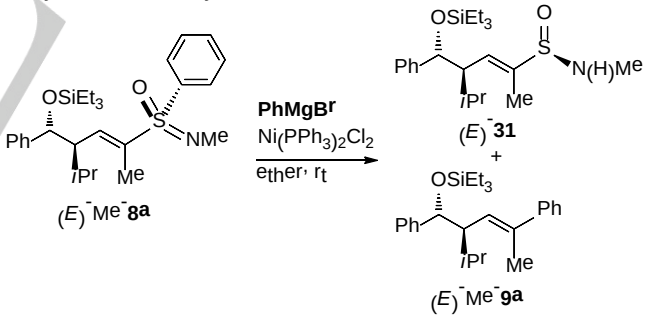
CCR of aminosulfoxonium salt (*E*)-**10** with **22** $Ni(PPh_3)_2Cl_2$ (20 mol%) in THF in the absence of $MgBr_2$ was slow. While conversion of the salt in the presence of $MgBr_2$ was 95% within 4 d, it was only 50% in the absence of magnesium salt under similar conditions.



Scheme 28. CCR of acyclic methyl-substituted aminosulfoxonium salt (*E*)-Me-**10** with PhMgBr.

The Ni-catalyzed reaction of the methylated alkenyl sulfoximine (*aS,S*)-Me-**5a** with $ZnPh_2$ had demonstrated that alkenyl sulfoximines, carrying a substituent at the α-position, can serve as substrates in CCR (vide supra). Therefore, the CCR of the substituted acyclic alkenyl aminosulfoxonium salt (*E*)-Me-**10** (Scheme 28) was investigated. The salt is obtained from alkenyl sulfoximine (*E*)-**8a** in 90% yield in three steps, including lithiation with MeLi to give lithioalkenyl sulfoximine (*E*)-Li-**8a**, followed by treatment with MeI and methylation of thus obtained alkenyl sulfoximine (*E*)-Me-**8a** with Me_3OBF_4.[24b] Because of the absence of a H atom at the α-position of (*E*)-Me-**8a**, a Grignard reagent was used in its CCR. Surprisingly, CCR of the aminosulfoxonium salt (*E*)-Me-**10** with PhMgBr and $Ni(PPh_3)_2Cl_2$ took place with high site-selectivity under reductive dearylation and gave the alkenyl (*N,N*-dimethyl)sulfinamide (*E*)-**30** in 94% yield and ≥98:2 *dr*. It is assumed that the sulfinamide has the (*R*)-configuration since CCR of alkenyl sulfoximines proceeds under retention of configuration at the S atom. Alkenyl sulfinamides are an interesting class of compounds, which have thus far received only scattered attention.[48]

Having obtained this unexpected result, CCR of the parent α-substituted alkenyl sulfoximine (*E*)-Me-**8a**[24b] was studied (Scheme 29). Treatment of (*E*)-Me-**8a** with PhMgBr and $Ni(PPh_3)_2Cl_2$ gave a mixture of the alkenyl (*N*-methyl)sulfinamide (*E*)-**31** and alkene (*E*)-Me-**9a**, both as single diastereomers, in a ratio of 77:23. Chromatography afforded the sulfinamide in 73% yield and ≥98:2 *dr*. Sulfinamide (*E*)-**31** presumably also has the (*R*)-configuration. Thus, two competing CCRs had occurred, reductive dearylation and dealkenylation. While reductive de-alkylation and dealkenylation of sulfoximines has frequently been applied in synthesis,[21a,49] reductive dearylation has rarely been observed.



Scheme 29. CCR of the acyclic methyl-substituted alkenyl sulfoximine (*E*)-Me-**8a** with PhMgBr.

Catalytic cycle

The Ni-catalyzed CCR of alkenyl (*N*-methyl)sulfoximines with organozincs shows the following features: (1) retention of configuration with $Ni(dppp)Cl_2$ (chelating phosphine) as precatalyst and alkyl- and arylzincs and requirement of a promotion by $MgBr_2$, which is efficacious in ether but not in THF, (2) no requirement of salt promotion in the case of α-substituted alkenyl sulfoximines, (3) retention of configuration and no requirement of salt promotion in the case of $Ni(PPh_3)_2Cl_2$ (non-chelating phosphine) and $ZnPh_2$, and (4) loss of configurational integrity in the case of $Ni(PPh_3)_2Cl_2$ and bis(silylmethyl)zincs. We assume a Kumada-Corriu-Negishi (KCN) cycle[13] for the Ni-

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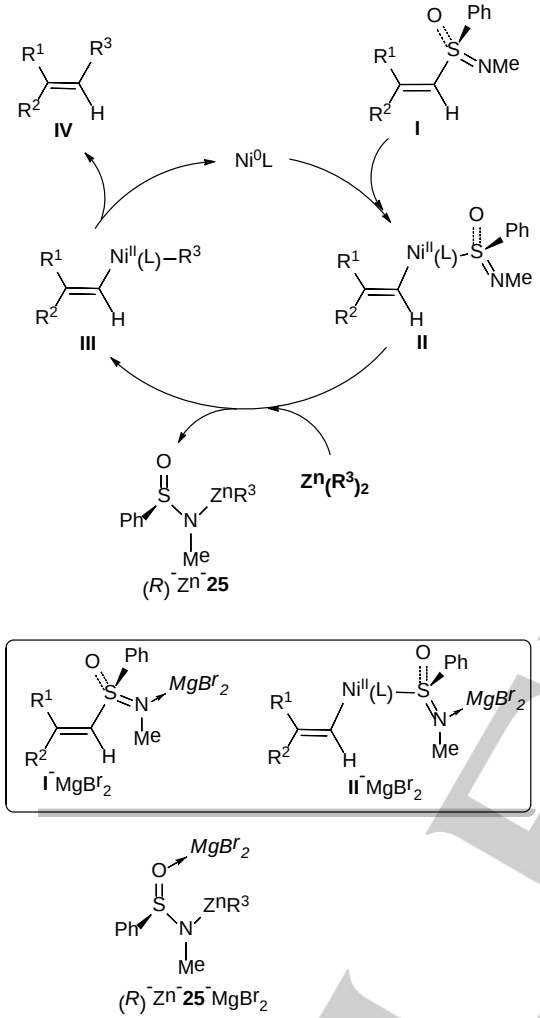
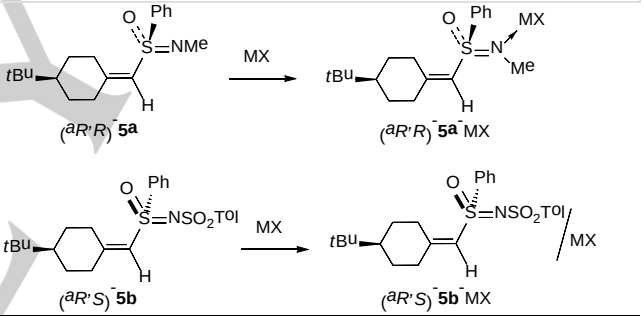
catalyzed CCR of alkenyl sulfoximines and aminosulfoxonium salts with organozincs (Scheme 30, only the KCN cycle of alkenyl sulfoximines is shown). Oxidative addition of the alkenyl sulfoximine **I** to the Ni(0)-catalyst affords the alkenyl Ni(II)-complex **II**. Subsequent transmetallation of **II** with an organozinc yields the alkeny Ni(II)-complex **III** and sulfinamide (*R*)-Zn-**25**. Finally, reductive elimination of **III** furnishes alkene **IV** and the Ni(0)-catalyst.[50]



Scheme 30. Envisioned cycle of the Ni-catalyzed and $MgBr_2$ promoted CCR of alkenyl sulfoximines with organozincs (L = dppp).

Salt promotion: an interesting feature of the CCR of alkenyl sulfoximines is the general necessity of a promotion by $MgBr_2$, which is effective in ether but not in THF. The promotion could be due to a rate enhancement of the oxidative addition[51] through coordination to the nucleofugal sulfonimidoyl group under formation of complex **I**-$MgBr_2$. Rate acceleration of the Ni(0)-catalyzed CCR by Lewis acids had been previously observed and generally ascribed to an acceleration of the oxidative addition through nucleofugal complexation.[13] We had previously observed a complex formation between allylic (*N*-methyl)sulfoximines and BF_3.[52] Hence, the behavior of alkenyl sulfoximine (*aR,R*)-**5a** towards various salts was investigated by ^{1}H NMR spectroscopy. The ^{1}H NMR spectra of (*aR,R*)-**5a** in the presence of $MgBr_2/Et_2O$, MgI_2, $ZnBr_2$ and LiBr (3 equiv) in $[D_{10}]$-ether at room temperature revealed strong down-field shifts of the signals of the α-H atom of the double bond and the *o*-H atoms of the phenyl group (Table 5, entries 1–5). A similar shift variation[53] was observed in $CDCl_3$ as solvent (entries 8 and 9). Notably, no shift variation was observed in the ^{1}H NMR spectrum of a mixture of (*aR,R*)-**5a** and $MgBr_2/Et_2O$ in $[D_8]$-THF (entries 6 and 7). Similar but less strong shift variations were recorded for the alkenyl (*N*-sulfonyl)sulfoximine (*aR,S*)-**5b** in $CDCl_3$ but none in $[D_8]$-THF (entries 10–13). These observations demonstrate a coordination of the Lewis basic sulfonimidoyl group[54] of the alkenyl sulfoximine by $MgBr_2$ in ether and $CDCl_3$ under formation of (*aR,R*)-**5a**-$MgBr_2$ and (*aR,S*)-**5b**-$MgBr_2$. The other salts are expected to form similar complexes with (*aR,R*)-**5a**. While (*aR,R*)-**5a** is expected to be coordinated by $MgBr_2$ at the N atom, (*aR,S*)-**5b** is perhaps coordinated by the salt at the O atoms of the sulfoximine and sulfonyl group.[28] The lack of a shift variation in THF shows the absence of a complexation of the sulfonimidoyl group by $MgBr_2$ in this solvent, because THF forms stronger Lewis acid-base complexes with $MgBr_2$ than ether does.[55] The absence of nucleofugal complexation of alkenyl sulfoximines in THF correlates with the experimental observation that $MgBr_2$ fails to exert a promotion of the CCR in this solvent.

Table 5. ^{1}H NMR spectroscopy of alkenyl sulfoximines in the presence of salts (3 equiv) in different solvents at room temperature.[a]



entry	alkenyl sulfoximine	MX	solvent	δ =CH	δ *N*-Me	δ *o*-Ph
1	**5a**	-	$[D_{10}]$-ether	6.19	2.59	7.89–7.95
2	**5a**	$MgBr_2$	$[D_{10}]$-ether	7.37	2.81	8.33–8.40
3	**5a**	MgI_2	$[D_{10}]$-ether	7.37	2.93	8.37–8.48
4	**5a**	$ZnBr_2$	$[D_{10}]$-ether	7.26	2.70	8.08–8.16
5	**5a**	LiBr	$[D_{10}]$-ether	6.76	-	8.02–8.10
6	**5a**	-	$[D_8]$-THF	6.15	2.54	7.83–7.90
7	**5a**	$MgBr_2$	$[D_8]$-THF	6.16	2.54	7.83–7.90
8	**5a**	-	$CDCl_3$	6.20	2.66	7.88–7.92
9	**5a**	$MgBr_2$	$CDCl_3$	7.13	2.68	8.05–8.15
10	**5b**	-	$CDCl_3$	6.38	-	7.91–7.95
11	**5b**	$MgBr_2$	$CDCl_3$	6.62	-	8.02–8.06
12	**5b**	-	$[D_8]$-THF	6.42	-	7.91–7.95
13	**5b**	$MgBr_2$	$[D_8]$-THF	6.42	-	7.91–7.95

[a] Chemical shifts relative to TMS.

The complexation of alkenyl sulfoximines by $MgBr_2$ points to a promotion of the oxidative addition by the salt. However, the possibility exists that the transmetallation rather than the oxidative addition is affected despite the coordination of the alkenyl sulfoximine by the salt. Reaction of **I**-$MgBr_2$ with the Ni(0)-catalyst will generate the alkenyl Ni(II)-complex **II**-$MgBr_2$, the sulfonimidoyl group of which is also coordinated by $MgBr_2$. This complexation could result in a nucleofugal activation and thus lead to a rate acceleration of the transmetallation.[56] A distinction between both modes of acceleration is not possible on the basis of the data gathered up to now.

Because of the coordination of the alkenyl sulfoximine by $MgBr_2$, transmetallation of **II**-$MgBr_2$ leads to the formation of a Zn-sulfinamide-$MgBr_2$ complex, (*R*)-Zn-**25**-$MgBr_2$ (cf. Scheme 30). This renders the catalytic cycle stoichiometric in $MgBr_2$, a deduction which correlates with the experimental finding.

Whether salt promotion is required in CCR of the axially chiral (*aS,S*)-**5a** and (*aR,S*)-**5a** with $ZnPh_2$ hinges on the phosphine ligand of the precatalyst. While with chelating bisphosphine precatalyst Ni(dppp)Cl_2 salt promotion is necessary, it is not with non-chelating monophosphine precatalyst Ni$(PPh_3)_2Cl_2$. The origin of this finding remains unexplained. Perhaps dissociation of PPh_3 from the Ni(0)-catalyst derived from Ni$(PPh_3)_2Cl_2$ plays a role, giving a more active catalyst.[57]

Zincate formation: although the Lewis acid-base reaction of alkenyl sulfoximines with $MgBr_2$ strongly points to a promotion of the oxidative addition or transmetallation, a completely different mode of promotion of the CCR by the salt has in principle also to be considered. This is the formation of organozincates from organozincs and $MgBr_2$ according to equation (1), exhibiting a higher reactivity in transmetallation than the organozincs. Several studies have appeared, showing that salts generated in the metathesis reaction of ZnX_2 with RM (M = Li, MgX) engage in the formation of mixed metal organozincates with the organozincs, which have a higher reactivity in CCR.[58]

$$ZnR_2 + MgBr_2 \rightleftharpoons [R_2ZnBr]^- [MgBr]^+ \quad (1)$$

There is evidence, however, speaking against a decisive role of organozincates in the CCR of alkenyl sulfoximines. First, promotion by $MgBr_2$ is effective in ether but not in THF, a solvent in which formation of magnesium zincates should be more pronounced, because of the stronger cation solvation. Second, ^{1}H NMR spectroscopy of solutions of bis(silylmethyl)zinc **22** and $ZnPh_2$ with $MgBr_2/Et_2O$ (1 equiv) in $[D_{10}]$-ether at room temperature showed only minor shift differences and no new signals.

Precatalyst and organozinc: difficult to reconcile are the influence of the phosphine ligand (chelating *versus* non-chelating) and organozinc (aryl versus alkyl) on the stereochemical course of the CCR of the axially chiral alkenyl sulfoximines. Examples for such a profound effect of the ligand and organometal upon the stereochemistry of Ni-catalyzed CCR of alkenyl derivatives are rare. One explanation may be a ligand-dependent (*E/Z*)-isomerization of the alkeny Ni(II)-complexes **II** and **III**. Reversible (*E/Z*)-isomerization of alkenyl Ni(II)-complexes had been described.[59] A phosphine-dependent loss of configurational integrity was observed in Pd-catalyzed CCR of alkenyl halides, which was associated with a (*E/Z*)-isomerization of the alkenyl palladium(II)-complexes.[60] In both cases the mechanism of the isomerization and the precise role played by the ligand are unknown.

Summary

Alkenyl (*N*-methyl)sulfoximines undergo a dual Ni-catalyzed and $MgBr_2$ promoted CCR with diaryl- and dialkylzincs, which is with Ni(dppp)Cl_2 as precatalyst generally stereoretentive for both the C and S atom. The promotion of the CCR of alkenyl sulfoximines by $MgBr_2$ takes place in ether but not in THF. Complex formation between alkenyl sulfoximines and $MgBr_2$ in ether may lead to a nucleofugal activation and an acceleration of the oxidative addition of the KCN cycle. With Ni$(PPh_3)_2Cl_2$ as precatalyst the CCR of axially chiral alkenyl sulfoximines with $ZnPh_2$ requires no salt promotion, while with bis(silylmethyl)zincs salt promotion is needed and the configurational integrity of the double bond is lost. (*E*)-Configured alkenyl aminosulfoxonium salts also participate in the Ni-catalyzed CCR with alkyl- and arylzincs in the presence of $MgBr_2$. They show a higher reactivity than the corresponding alkenyl sulfoximines.

The Ni-catalyzed CCR of acyclic alkenyl sulfoximines and aminosulfoxonium salts, carrying a methyl group at the α-position, with PhMgBr takes a different course und delivers through reductive dearylation the corresponding alkenyl sulfinamides under stereoretention at the S atom.

The stereoselective synthesis of axially chiral alkenes and exocyclic alkenes from the corresponding ketones has been achieved in two steps, including a diastereoselective IPO with chiral lithiomethyl sulfoximines and the Ni-catalyzed/salt promoted CCR of the alkenyl sulfoximines with diorganozincs.

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Keywords: Nickel • Cross coupling • Alkenyl sulfoximines • Catalysis • Salt promotion

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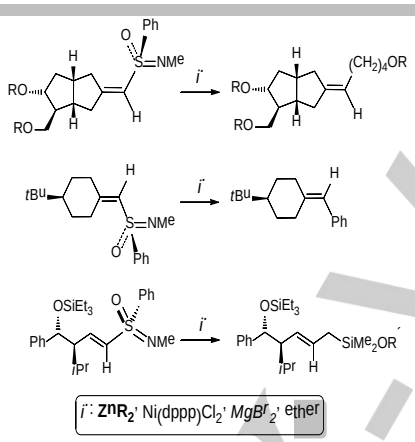
Entry for the Table of Contents

FULL PAPER

Alkenyl sulfoximines undergo a dual Ni-catalyzed and $MgBr_2$ promoted stereoretentive cross-coupling reaction (CCR) with organozincs. Salt promotion is due to a coordination and activation of the sulfonimidoyl group. CCR of alkenyl sulfoximines together with an inverse Peterson olefination of the corresponding ketones with chiral lithiomethyl sulfoximines are key steps of a stereoselective synthesis of exocyclic and axially chiral alkenes.



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Cross-Coupling Reaction of Alkenyl Sulfoximines and Alkenyl Aminosulfoxonium Salts With Organozincs by Dual Nickel Catalysis and Lewis Acid Promotion