Enantioselective Nickel Catalyzed Grignard Cross Coupling of Allyl Electrophiles. The Influence of the Alkyl Group of the Grignard Reagent

Adriano F. Indolese and Giambattista Consiglio*

Eidgenössiche Technische Hochschule, Laboratorium für Technische Chemie, ETH-Zentrum, CH-8092 Zürich, Switzerland

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The enantioselective cross coupling reactions of 2-cyclopentenyl phenyl ether (**1a**) and 2-cyclohexenyl phenyl ether (**1b**) with methyl-, ethyl-, *n*-propyl-, and isopropylmagnesium bromide were carried out using either [(*R*,*R*)-*trans*-cyclopentane-1,2-diylbis(diphenylphosphine)]-nickel(II) chloride (**5a**) or [(*R*)-(6,6′-dimethylbiphenyl-2,2′-diyl)bis(diphenylphosphine)]nickel-(II) bromide (**5b**) as the catalyst precursor. With both catalytic systems a maximum enantioselectivity was observed for the ethylation reactions leading to 3-ethylcyclopentene (up to 94% ee with **5b**). Enantioselectivities are in general lower in the alkylation of **1b** than in that of **1a**. The results are discussed on the basis of a nickel η^3-allyl intermediate and of the possible change of mechanism going from a small to a bulky alkyl group.

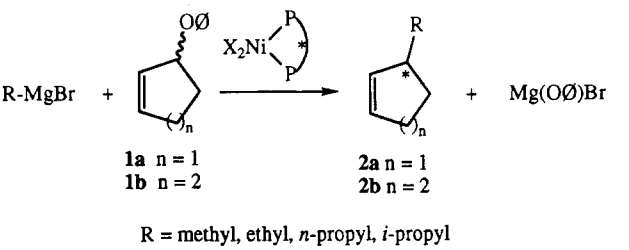
Introduction

Optically active polymers have recently attracted much attention.[1] One approach for the synthesis of chiral polymers is the polymerization of simple chiral olefins.[2] The alkylation of allyl electrophiles with a Grignard reagent in the presence of nickel complexes with optically active phosphine ligands provides a versatile and straightforward access to these olefins.[3-5] However, to date this methodology has provided a high enantiomeric excess in only a few cases.[4,6,7]

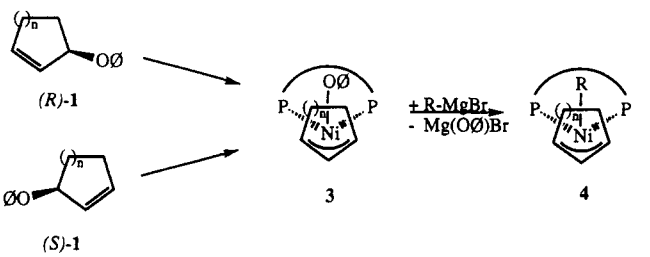
In our initial work[8] we investigated the influence of the electronic and steric factors of ligands on the reaction of cyclic allyl phenyl ethers and ethyl Grignard reagent (Scheme 1, R = ethyl). The products were obtained in good yields and with high enantiomeric excesses (up to 94%). It was shown that the enantioselectivity was only influenced by the steric properties of the ligands. The only effect of increasing the basicity of the phosphorus atoms was to decrease the reaction rate.

We were intrigued to know if it would be possible to extend these good results to reactions with other alkyl Grignard reagents. Herein we report the results obtained from the reactions of 2-cyclopentenyl phenyl ether (**1a**) and 2-cyclohexenyl phenyl ether (**1b**) with methyl-, ethyl-, *n*-propyl-, and isopropylmagnesium bromide.

Scheme 1



Scheme 2



Results

The cyclic allyl phenyl ethers **1** have the advantage that a symmetric allyl ligand is formed during the oxidative addition (Scheme 2). As a consequence, the stereochemical information of the starting material is lost and the enantiomeric excess of the product is only determined by the enantioselectivity of the reductive elimination from the alkyl allyl complex **4**.[9] Therefore, the kinetic resolution of the starting material which may occur does not influence the enantiomeric excess.

On the basis of our previous work,[8] [(*R*,*R*)-*trans*-cyclopentane-1,2-diylbis(diphenylphosphine)]nickel(II) chloride {nickel (*R*,*R*)-cycpenphos dichloride} (**5a**) (which contains a five membered chelate ring) and [(*R*)-(6,6′-dimethylbiphenyl-2,2′-diyl)bis(diphenylphosphine)]nickel(II) bromide {nickel (*R*)-Biphemp dibromide} (**5b**) (which contains a seven membered ring) (Chart 1) were chosen

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(1) (a) Okamoto, Y.; Yashima, E. *Prog. Polym. Sci.* **1990**, *15*, 263. (b) De, B. B.; Sivaram, S.; Dahl, P. K. *Polymer* **1992**, *33*, 1756. (c) Coates, G. W.; Waymouth, R. M. *J. Am. Chem. Soc.* **1993**, *115*, 91.

(2) (a) Wilke, G. *Angew. Chem.* **1988**, *100*, 190. (b) Zambelli, A.; Grassi, A.; Galimberti, M.; Perego, G. *Makromol. Chem., Rapid Commun.* **1992**, *13*, 467 and 269.

(3) (a) Consiglio, G.; Morandini, F.; Piccolo, O. *Helv. Chim. Acta* **1980**, *63*, 987. (b) Consiglio, G.; Morandini, F.; Piccolo, O. *J. Chem. Soc., Chem. Commun.* **1983**, 112.

(4) Consiglio, G.; Piccolo, O.; Roncetti, L.; Morandini, F. *Tetrahedron* **1986**, *42*, 2043.

(5) Cherest, M.; Felkin, H.; Umpleby, J. D.; Davies, S. G. *J. Chem. Soc., Chem. Commun.* **1981**, 681.

(6) Hayashi, T.; Yamamoto, A.; Hojo, M.; Ito, M. *J. Chem. Soc., Chem. Commun.* **1989**, 495.

(7) Iida, A.; Yamashita, M. *Bull. Chem. Soc. Jpn.* **1988**, *61*, 2365.

(8) Consiglio, G.; Indolese, A. *Organometallics* **1991**, *10*, 3425.

(9) Consiglio, G.; Waymouth, R. M. *Chem. Rev.* **1989**, *89*, 257.

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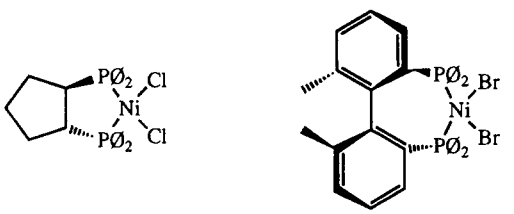
Table 1. Alkylation of 2-Cyclopentenyl Phenyl Ether (1a) and 2-Cyclohexenyl Phenyl Ether (1b) with RMgBr

entry no.	catalyst precursor	substrate	alkyl group R	yield of phenol (%)	yield of rearranged substrate 9 (%)	yield of β-H elimination products 7 + 8 (%)	coupling product 2	
							yield (%)	ee (%)[a]
1	**5a**	**1a**	Me	14.4	85.6	2.6	11.5	41.3
2			Et	99.3	0.7	0.0	91.2	82.7
3			*n*-Pr	95.3	3.9	12.1	80.3	71.2
4			*i*-Pr	10.3	89.0	6.6	3.2	32.8
5		**1b**	Me	8.2	1.5	2.6	5.5	10.1
6			Et	100.0	0.0	0.6	99.4	74.8
7			*n*-Pr	99.1	0.7	75.8	17.3	28.4
8			*i*-Pr	16.6	3.2	15.1	0.5	8.1
9	**5b**	**1a**	Me	56.3	43.7	1.4	53.0	51.4
10			Et	93.6	6.4	3.1	89.6	93.5
11			*n*-Pr	18.5	81.5	8.4	9.5	60.7
12			*i*-Pr	11.5	88.5	3.2	8.2	35.6[a]
13		**1b**	Me	86.4	0.7	1.6	84.8	10.6
14			Et	92.3	1.1	7.7	84.1	83.5
15			*n*-Pr	14.7	2.2	10.8	3.6	16.9
16			*i*-Pr	28.4	3.5	18.7	1.0	50.2

[a] The (*S*)-enantiomer always prevails, but for entry 12 for which the (*R*)-enantiomer was obtained.

Chart 1



5a **5b**

as the catalyst precursors for this study. Both complexes proved to be efficient catalysts, providing the products with high enantiomeric excess.

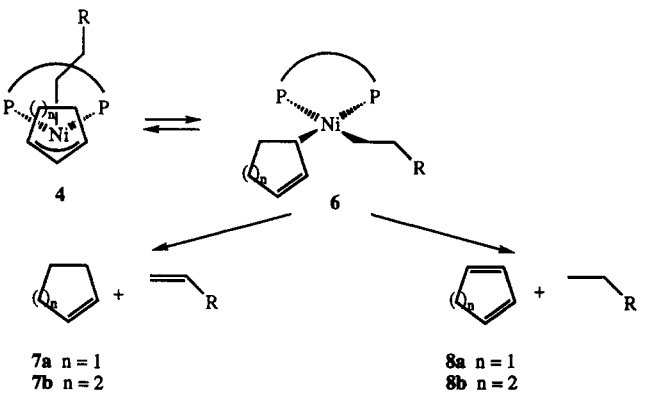
The effect of the solvent, the leaving group, and the halide of the Grignard reagent was previously probed.[4] These factors were shown to have little or no effect on the outcome of the cross coupling reaction. These observations are easily rationalized since neither the solvent, the leaving group, nor the magnesium halide is intimately involved in the enantioselective reductive elimination step. However to exclude these factors diethyl ether as the solvent and the phenoxy group as the leaving group were always used. The Grignard reagent was generated from the corresponding alkyl bromides.

In the present study the reaction mixture was quenched after 23 h with water and acidified, and the organic phase was dried and directly analyzed by GC using a chiral stationary phase (Lipodex C).[10] The enantiomeric excess was determined at 25 °C together with the low boiling side products. The error in determination of the enantiomeric excess was less than 2%, except for 3-*n*-propylcyclohexene and for the isopropyl derivatives, where the separation was worse and the error was about 10%.

The chemoselectivity was defined as the ratio of the desired product to the sum of all observed low boiling products. More than 90% of the low boiling side products was derived from the β-H elimination (Scheme 3) to give cyclopentene (**7a**) or cyclopentadiene (**8a**), and cyclohexene (**7b**) or 1,3-cyclohexadiene (**8b**), respectively. Unfortunately, we were unable to distinguish between the monoenes and the dienes. The other minor byproducts probably arose from the isomerization of the cross coupling

(10) Schurig, V.; Nowotny, H.-P. *Angew. Chem.* **1990**, *102*, 969.

Scheme 3



Scheme 4

products. As these were present in such small amounts, they were not characterized.

By use of a high temperature gas chromatographic run (180 °C), the remaining starting material, phenol, and *o*-(2-cyclopentenyl)phenol (**9a**) or *o*-(2-cyclohexenyl)phenol (**9b**) were measured. The phenol was liberated during the acidic workup from magnesium phenolate which was formed when the allyl phenyl ether underwent oxidative addition to the nickel complex. The *o*-(2-cyclopentenyl)-phenol (**9a**) and *o*-2-(cyclohexenyl)phenol (**9b**) arose from the Claisen rearrangement of the starting material (Scheme 4). In the case of the 2-cyclopentenyl phenyl ether (**1a**), only phenol and **9a** could be observed after 23 h, so the rearrangement was quite fast. In the case of 2-cyclohexenyl phenyl ether (**1b**) about 10% of the remaining starting material after 23 h had rearranged. Since we were interested in the cross coupling reaction, the arrangement reaction was neglected for the calculation of the conversion, which was therefore defined as the ratio of phenol to the sum of the observed high boiling products. With this

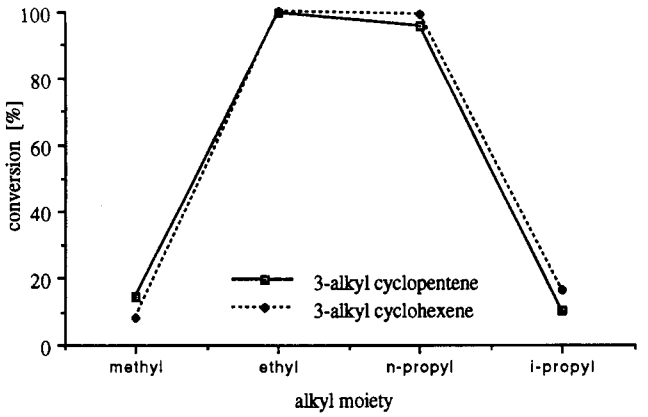


Figure 1. Conversion of the reactions of the Grignard reagent with different alkyl moieties with 2-cyclopentenyl phenyl ether (**1a**) and 2-cyclohexenyl phenyl ether (**1b**) in the presence of nickel (*R,R*)-cycpenphos dichloride (**5a**).

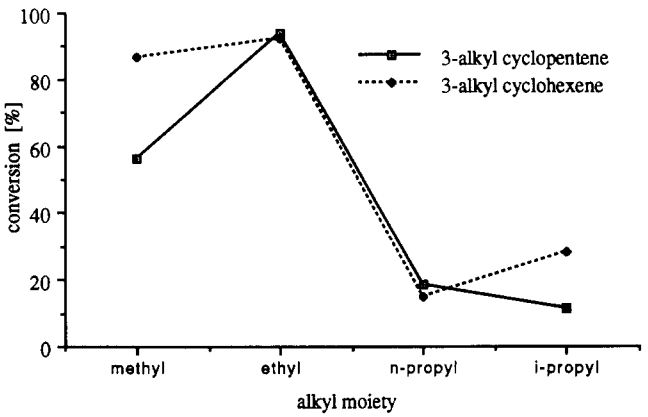


Figure 2. Conversion of the reactions of the Grignard reagent with different alkyl moieties with 2-cyclopentenyl phenyl ether (**1a**) and 2-cyclohexenyl phenyl ether (**1b**) in the presence of nickel (*R,R*)-Biphemp dibromide (**5b**).

definition the conversion becomes a rough measure of the reaction rate; i.e. the higher the conversion the faster the catalytic reaction. The results are summarized in Table 1.

The extents of conversion differed very strongly depending on the Grignard reagent utilized (Figures 1 and 2) but were very similar for both cyclic allyl ethers. In the case of cypenphos complex **5a** as the catalyst, almost complete conversion occurred with ethyl- and *n*-propylmagnesium bromide, whereas in the case of methyl and isopropyl it was very poor (Figure 1). Similarly, with the Biphemp catalyst **5b**, the highest conversion was obtained with the ethyl reagent. For the methyl reagent the conversion was clearly increased in comparison to the cypenphos case, but for *n*-propyl the same low conversion was observed as for isopropyl.

In all reactions, except in the reaction to 3-isopropylcyclohexene catalyzed by the Biphemp complex, the sense of asymmetric induction was the same (Figures 3 and 4). The highest enantiomeric excesses were obtained with the ethyl Grignard reagent (up to 94%) (Figure 3). In all other cases the enantiomeric excess was considerably lower. 2-Cyclohexenyl phenyl ether (**1b**) always gave a lower enantiomeric excess than that obtained with 2-cyclopentenyl phenyl ether (**1a**) in the corresponding reaction.

With the methyl and ethyl Grignard reagents, the observed chemoselectivity was good (Figures 5 and 6). The *n*-propyl Grignard reagent only gave in the reaction with

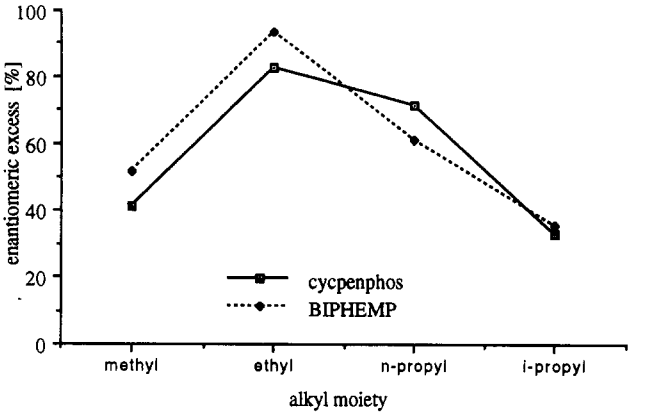


Figure 3. Enantiomeric excess of the 3-alkylcyclopentenes formed in the reactions of the Grignard reagent with different alkyl moieties in the presence of nickel (*R,R*)-cycpenphos dichloride (**5a**) and nickel (*R,R*)-Biphemp dibromide (**5b**).

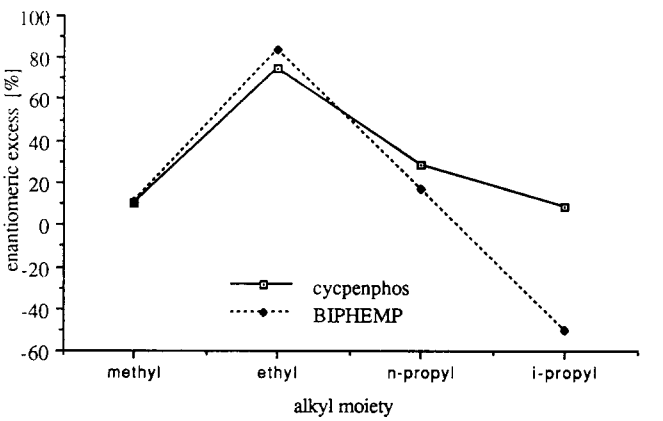


Figure 4. Enantiomeric excess of the 3-alkylcyclohexenes formed in the reactions of the Grignard reagent with different alkyl moieties in the presence of nickel (*R,R*)-cycpenphos dichloride (**5a**) and nickel (*R,R*)-Biphemp dibromide (**5b**).

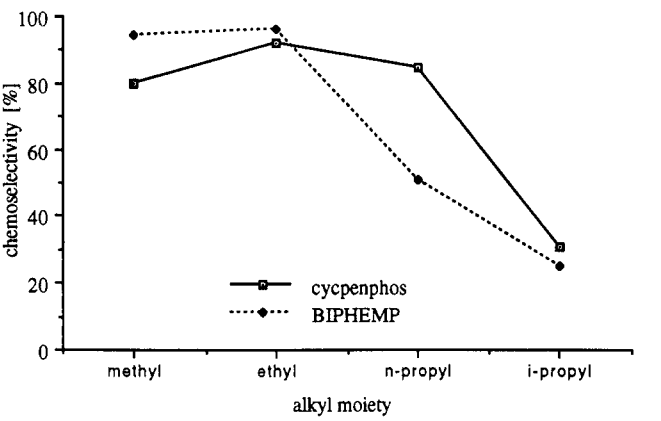


Figure 5. Chemoselectivity to form the 3-alkylcyclopentenes of the reactions of the Grignard reagent with different alkyl moieties in the presence of nickel (*R,R*)-cycpenphos dichloride (**5a**) and nickel (*R,R*)-Biphemp dibromide (**5b**).

cyclopentenyl phenyl ether (**1a**) satisfying chemoselectivity. In all other cases the elimination products rather than the coupling product predominated.

Discussion

The mechanism of the Grignard cross coupling reaction involving allyl electrophiles is reasonably well understood. Mechanistic studies have shown that the reaction proceeds

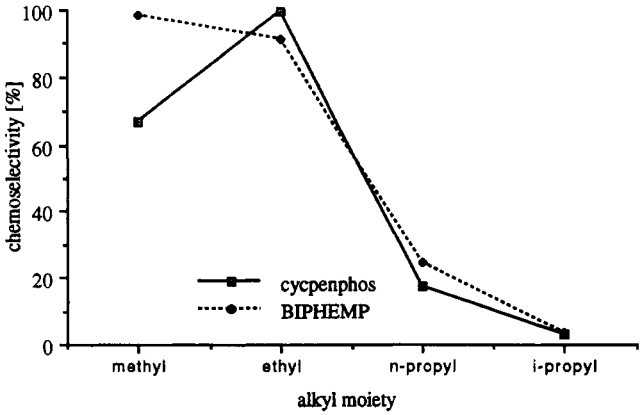
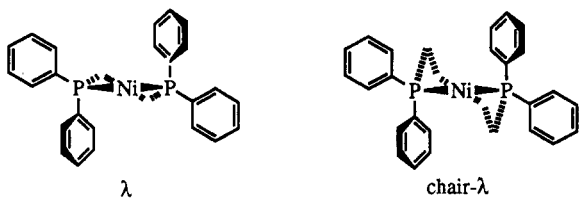


Figure 6. Chemoselectivity to form the 3-alkylcyclohexenes of the reactions of the Grignard reagent with different alkyl moieties in the presence of nickel (*R,R*)-cycpenphos dichloride (**5a**) and nickel (*R,R*)-Biphemp dibromide (**5b**).

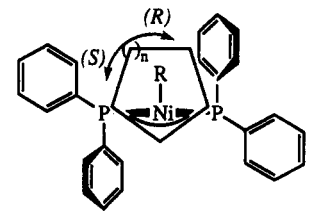
Chart 2



via η^3-allyl intermediate 4 (Scheme 2).[11,12] Not only is 4 a thermodynamically more stable intermediate than η^1-allyl complex 6 (Scheme 3), but it also reductively eliminates much faster.

Using achiral Grignard reagent and cyclic allyl ethers, the reductive elimination from the alkyl η^3-allyl intermediate 4 is the enantioselective step. The enantiodifferentiation seems to be influenced exclusively by the steric interaction of the alkyl and allyl moieties with the four phenyl rings of the diphosphine ligand.[8] The four phenyl rings form a chiral pocket[13] in such a way that two rings are pseudoaxial and two are pseudoequatorial in relation to the chelate ring (Chart 2).[14-16] The arrangement of the phenyl rings is mainly determined by the conformation of the chelate ring.[14a] The λ-conformation of the chelate ring usually leads in our reaction to the (*S*)-enantiomer, whereas the δ-conformation leads to the (*R*)-enantiomer.[17,18] The chelate ring of the nickel (*R,R*)-cycpenphos complex **5a** shows a λ-conformation,[15] and that of the nickel (*R*)-Biphemp complex **5b** a chair λ-conformation[16] (Chart 2); so it was expected that in both cases the (*S*)-enantiomer would be predominantly formed.

Chart 3



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A possible explanation of this empirical rule could be as follows. In order to undergo reductive elimination, it seems very likely to us that the allyl ligand has to be rotated a little bit, making one end more accessible for the attack by the alkyl group. The steric interactions of the allyl ligand with the phenyl rings of the ligand favor the rotation in one direction and disfavors the opposite one. In our specific case the favored counterclockwise motion leads to the (*S*)-enantiomer (Chart 3). A similar model was recently used to rationalize the palladium catalyzed enantioselective synthesis of oxazolidin-2-ones through intermediate allyl complexes.[19]

Changing from methyl to ethyl Grignard reagent increased the enantioselectivity significantly. The difference in the activation energies, which is responsible for the enantioselectivity, must also be enlarged in the case of the ethyl reagent, probably because the steric interactions between the different ligands on the nickel intermediate were larger with the ethyl than with the methyl group. Extension of this result to the more bulky *n*-propyl and isopropyl groups led us to predict that the enantiomeric excess would be even higher. But in any event a lower enantioselectivity was observed, and in one case, the opposite enantiomer was even preferentially formed. This observation suggested that a change in the mechanism occurred, possibly due to a larger steric interaction. The course of the chemoselectivity strongly supports our suggestion. The alkyl η^3-allyl intermediate 4 involved in the reactions with small alkyl groups has no free coordination site that would be necessary for the β-H elimination, and a high chemoselectivity is observed. The extensive formation of β-H elimination products in the reaction with bulky alkyl groups strongly suggests that a different intermediate having a vacant coordination site (e.g. a η^1-allyl intermediate) could be involved.

The lower reaction rate of the methyl group in comparison with that of the ethyl, might be caused by the higher electron donating ability of the ethyl group. Since the reductive elimination is increased with the donor ability,[20,21] the results indicate that the reductive elimination is the rate determining step. However, at this point it is impossible to rule out that steric factors are not responsible for the difference in the reaction rates, since the activation energy of the reductive elimination could be much lower for the ethyl intermediate, as it is more destabilized by the steric interaction of the ligands.

By careful comparison of the results it seems that there was gradual change of the mechanism. In the reactions with *n*-propylmagnesium bromide probably both pathways

(11) Consiglio, G.; Morandini, F.; Piccolo, O. *J. Am. Chem. Soc.* **1981**, *103*, 1846.
(12) Kurosawa, H.; Onishi, H.; Emoto, M.; Chatani, N.; Kawasaki, Y.; Murai, S.; Ikeda, I. *Organometallics* **1990**, *9*, 3038.
(13) Trost, B. M.; Murphy, D. J. *Organometallics* **1985**, *4*, 1143.
(14) For the general significance of this aspect in asymmetric catalysis by transition metal complexes, see, e.g.: (a) Bosnich, B.; Fryzuk, M. D. In *Topics in Inorganic and Organometallic Stereochemistry*; Geoffroy, G., Ed.; Topics in Stereochemistry, Vol. 12; Wiley: New York, 1981; pp 119–154. (b) Brunner, H. *J. Organomet. Chem.* **1986**, *300*, 39. (c) Noyori, R. *CHEMTECH* **1992**, 360. (d) Pavlov, V. A.; Klabunovskii, E. I.; Struchkov, Yu. T.; Voloboev, A. A.; Yanovsky, A. I. *J. Mol. Catal.* **1988**, *44*, 217.
(15) Allen, D. L.; Gibson, V. C.; Green, M. L. H.; Skinner, J. F.; Bashkin, P. D.; Grebenik, P. D. *J. Chem. Soc., Chem. Commun.* **1983**, 895.
(16) Knierzinger, A.; Schönholzer, P. *Helv. Chim. Acta* **1992**, *75*, 1211.
(17) Pavlov, V. A.; Zhorov, E. Yu.; Voloboev, A. A.; Klabunovskii, E. I. *J. Mol. Catal.* **1990**, *59*, 119.
(18) Pavlov, V. A.; Mistryukov, E. A.; Duddeck, H.; Vinogradov, M. G.; Snatzke, G. *J. Mol. Catal.* **1993**, *79*, 55.
(19) Trost, B. M.; Van Vranken, D. L. *Angew. Chem.* **1992**, *104*, 194; *Angew. Chem., Int. Ed. Engl.* **1992**, *104*, 194.
(20) (a) Tatsumi, K.; Hoffmann, R.; Yamamoto, A.; Stille, J. K. *Bull. Chem. Soc. Jpn.* **1981**, *54*, 1857. (b) Tatsumi, K.; Nakamura, A.; Komiya, S.; Yamamoto, A.; Yamamoto, T. *J. Am. Chem. Soc.* **1984**, *106*, 8181.
(21) Komiya, S.; Ozaki, S.; Shibue, A. *J. Chem. Soc., Chem. Commun.* **1986**, 1555.

are available. With the cypenphos catalyst the reaction seemed to proceed more through the alkyl η^3-allyl intermediate, whereas another intermediate was involved if the Biphemp ligand was used.

Our results seem to indicate that the cypenphos complex has a slightly larger chiral pocket than Biphemp. This small difference has, in the case of the *n*-propyl, an impressive influence on the reaction. It should be therefore possible to obtain high enantiomeric excesses with a variety of Grignard reagents by selecting the correct phosphine ligand.

In conclusion we have shown that simple unfunctionalized olefins can be synthesized with very high enantioselectivities by a nickel catalyzed Grignard cross coupling reaction. In order to obtain a high enantiomeric excess the ligand has to be tuned so as to maximize the steric interaction without a change in reaction mechanism. Since the enantioselectivity seems overwhelmingly influenced by steric interactions, it should be possible to test a rationally designed ligand by molecular modeling, prior to investing time in their sometimes quite difficult synthesis. With the data reported herein we have a very good starting point for these types of calculations.

Experimental Section

2-Phenoxycyclopentene[22] and 2-phenoxycyclohexene[22] were synthesized as reported. The Grignard reagents were synthesized from the corresponding bromoalkanes using magnesium turnings activated by dry stirring.[23] Diethyl ether was dried according to standard procedures and distilled under nitrogen. (*R*,*R*)-Cycpenphos was synthesized as previously reported.[15] Alternatively, it can be prepared in a larger scale by resolution of the corresponding oxide, according to published procedures for similar compounds.[24] (*R*)-Biphemp[25] was a generous gift of F. Hoffmann-LaRoche AG (through Dr. E. Broger).

NMR spectra were measured on a Bruker 300WB or a Bruker AC 200 spectrometer. The gas chromatographic analyses were carried out on a Shimadzu GC 8A equipped with a flame ionization detector using a 50-m Lipopdex C capillary column (Macherey Nagel) and hydrogen as the carrier gas. Optical rotations were measured on a Perkin-Elmer 241 polarimeter.

Coupling Reactions. A 2.5-mL aliquot of Grignard reagent (1 M) was added to a mixture of the nickel diphosphine complex (0.01 mmol) and allyl phenyl ether (2.4 mmol) in dry diethyl ether (2.5 mL) under nitrogen. After the reaction mixture was stirred at room temperature for 23 h, it was quenched with ice and acidified with aqueous hydrochloric acid (1 M). The ether phase was dried over sodium sulfate and directly analyzed by GC.

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(22) Frater, G.; Schmid, H. *Helv. Chim. Acta* **1967**, *50*, 255.
(23) Baker, K. V.; Brown, J. M.; Hughes, N.; Skarnulis, A. J.; Sexton, A. *J. Org. Chem.* **1991**, *56*, 698.
(24) Brunner, H.; Pieronczyk, W.; Schönhammer, B.; Streng, K.; Bernal, I.; Korp, J. *Chem. Ber.* **1981**, *114*, 1137.
(25) Schmid, R.; Cereghetti, M.; Heiser, B.; Schönholzer, P.; Hansen, H.-J. *Helv. Chim. Acta* **1988**, *71*, 897.