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Nickel-Catalyzed Asymmetric Allylation of Alkyl Grignard Reagents. Effect of Ligands, Leaving Groups and a Kinetic Resolution with a Hard Nucleophile

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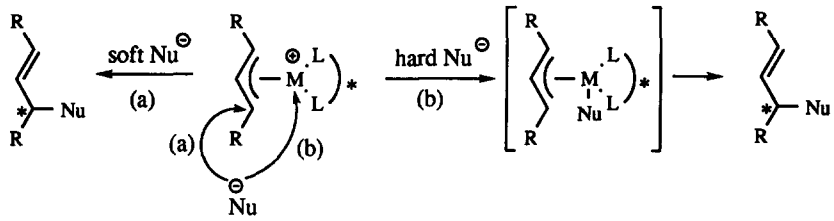
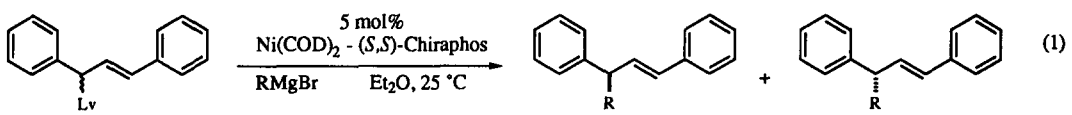
Abstract: Enantioselective addition of Grignard reagents to methyl 1,3-diphenylallyl ether in the presence of Ni(0)-phosphine catalysts is reported. Kinetic resolution (79 %ee) observed in the addition of MeMgBr has important implications for the mechanism and further development of this reaction as a valuable synthetic reaction. © 1997 Elsevier Science Ltd. All rights reserved.

Asymmetric allylation catalyzed by transition metals has been a prolific area of research during the last decade.[1] Excellent selectivity has been achieved using palladium catalysts in the allylation of soft-nucleophiles.[2] It is believed that in this case, the nucleophiles directly attack allyl-terminal carbons from the remote ('anti') side of palladium (Scheme 1 (a)) and considerable literature dealing with the steric and stereoelectronic control of this reaction exists. On the other hand, reaction with a hard-nucleophile is believed to proceed through a different mechanism, where the nucleophile attacks transition metal first (Scheme 1 (b)), and then the M(II)-complex collapses to the product via a reductive elimination. This widely accepted mechanism using hard nucleophiles suggests that the enantio-discrimination should occur within the coordination sphere of the metal, and thus might be a better situation to produce higher ligand-dependent selectivities *vis-à-vis* the path (a). Yet the isolated examples reported in the literature provide only moderate to good enantioselectivity, mostly in the Ni(0)-catalyzed allylation of Grignard reagents.[3-5] In these instances, chemical yield and the selectivity of the reaction are highly dependent on the nucleophiles and the ligands that are used in the process. One has to also address the problems associated with the increased number of possible diastereomers of the penultimate Ni(II) intermediate and β-hydride elimination (and the attendant reduction of the allylic substrate) in case of alkyl Grignard reagents with β-hydrogens. A systematic study of this system would be highly desirable, since the starting components of the reaction viz. Grignard reagents and various allylic derivatives, are among the most readily available organic intermediates. Here we report the results of our first studies in the nickel-catalyzed asymmetric addition of alkyl Grignard reagents to 1,3-diphenylallyl derivatives (eq 1).[6] This system was chosen for model studies because the π-allyl Pd-intermediates derived from this class of substrates have been extensively studied in the context of its reaction with stabilized nucleophiles, and a direct comparison between the Ni- and Pd-mediated reactions is thus possible. To the best of our knowledge, there are no reports of the coupling reactions between Grignard reagents and these substrates.



Scheme 1

Of the various 1,3-diphenylallyl derivatives, the methyl and phenyl ethers were chosen for detailed study since they gave practically no background (uncatalyzed) reaction. The reactions were carried out in ether at 25 °C with 3 equivalents of the Grignard reagent and 0.05 equivalents of the Ni-catalyst. The results are shown in Table 1.



(1)

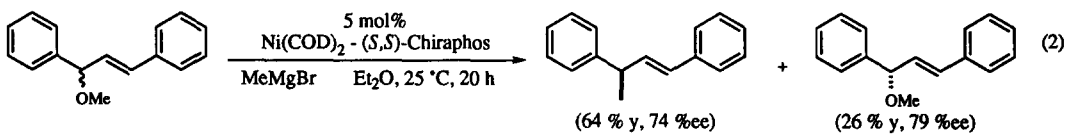
1 2 3

There was no reaction between the methyl ether and MeMgBr at 25 °C without the nickel catalyst, and the starting material was recovered in 99 % yield (entry 1).[7] On the contrary, the reaction proceeded at 25 °C in the presence of a nickel-phosphine complex, which is prepared *in situ* from $Ni(COD)_2$ and the chiral phosphine, (*S,S*)-Chiraphos to give predominantly the product of (*R*)-absolute configuration.[8] The reaction rate was comparable to palladium-catalyzed allylation between the acetate derivative and malonate anion,[9] and it gave moderate enantioselectivity even with MeMgBr (entry 2).[10] The addition of a polar solvent, THF, slightly decelerated the reaction but little effect was observed in the enantioselectivity (entry 3). The ethylation was faster than methylation (reaction was over after 12 h), and a small amount of reduced by-product was formed (entries 4 and 5). The difference of reaction rate between methylation and ethylation did not seem to effect the enantioselectivity when the leaving group was OMe (entries 2 and 5). In sharp contrast to methyl ether, the phenyl ether mainly underwent decomposition upon reaction with MeMgBr without the catalyst (entry 6). The chemical yield was poor even with the nickel catalyst (entry 7), and the enantioselectivity was lower than that of methyl ether derivative (entries 2 and 7). However, ethylation under the same condition gave moderate yield and enantioselectivity (entry 8). (*R, R*)-Me-DuPhos ligand was slightly less effective in the enantioselectivity (entry 9), the absolute configuration of the product being opposite to that obtained from (*S,S*)-Chiraphos. 1,3-Diphenylallyl alcohol reacted with MeMgBr under the same condition, and the product was obtained in 73 %ee (entry 10), although the reaction was very slow (~ 10 % yield after 4 days). The enantioselectivity was the same as that of the methyl ether derivative (entry 2).

Table 1. Asymmetric Allylation Reaction between RMgBr and 1,3-Diphenylallyl Ether[a]

Entry	Ligand	R	Lv	Yield[b] (%)	Op. yield[c] (R/S)
1	No catalyst	Me	OMe	0[d]	-
2	(*S,S*)-Chiraphos	Me	OMe	81	87.0:13.0
3[e]	(*S,S*)-Chiraphos	Me	OMe	51	87.0:13.0
4	(*S,S*)-Chiraphos	Et	OMe	91[f]	86.5: 13.5
5[g]	(*S,S*)-Chiraphos	Et	OMe	78[h]	89.5:10.5
6	No catalyst	Me	OPh	3	-
7	(*S,S*)-Chiraphos	Me	OPh	8	66.0:34.0
8	(*S,S*)-Chiraphos	Et	OPh	56[i]	82.0:18.0
9	(*R,R*)-Me-DuPhos	Me	OMe	88	17.0:83.0
10	(*S,S*)-Chiraphos	Me	OH	10[j]	86.5: 13.5

[a] Reaction was carried out for 24 h using RMgBr (3 equiv.) and methyl 1,3-diphenylallyl ether (1 equiv.). [b] Isolated yield. [c] Determined by HPLC analysis with Daicel Chiralcel OJ and/or OB columns. See footnote 8 for determination of absolute configuration. [d] The starting material was recovered in 99 % yield. [e] THF/Et_2O (5.7/1) was used as solvent. [f] 2 % Reduction product was also observed. Reaction was over after 12 h. [g] Reaction at 0 °C. [h] 8 % Reduction product was also observed. [i] 13 % Reduction product was also obtained. [j] After 4 days at 25°C.



(2)

The stereochemical outcomes of the individual steps in the Ni-catalyzed allylation are far from certain and appear to depend on a variety of factors such as the leaving group, the nucleophile and the nature of the allylic system, even though overall the reaction appears to proceed with inversion at the allylic center.[11] (*S,S*)-Chiraphos-Ni-mediated Grignard additions to isomeric butenyl phenyl ethers and to 3-phenoxy-cyclopentene and -cyclohexene suggest a common allyl metal intermediate.[12] In cases where the difference in reactivity between the enantiomeric substrates were checked, it was found that there was little enantiomer selection in the formation of the allyl-Ni intermediate.[12-14] For example racemic 2-cyclohexen-1-ol was resolved only to the extend of 13.8 %ee after 70 % conversion in a Ni-catalyzed reaction with MeMgBr.[12] Thus there are no successful reports of kinetic resolutions in nickel-catalyzed asymmetric allylation.[15] As a mechanistic probe we decided to investigate the kinetic resolution in the present system. To our surprise, we found that when the reaction between methyl ether derivative **2** and MeMgBr was quenched after 20 h, the starting material was recovered with 79 %ee in addition to the expected formation of the enriched product (eq. 2). This intriguing results mean that in acyclic Ni-allylic systems, the enantioselective ionization mechanism could be exploited for kinetic resolution. Further, the enantioselectivity of the reaction depends on the relative rates of ionization, interconversion of the allyl intermediates and alkylation via the reductive elimination. We are currently investigating the mechanism and the origin of the kinetic selectivity and the asymmetric induction in the present case.

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6. While our study was in progress, Hoveyda reported nickel-catalyzed addition of alkyl Grignard reagents to allylic methyl ethers assisted by a properly positioned Lewis base in the molecule. Didiuk, M. T.; Morken, J. P.; Hoveyda, A. H. *J. Am. Chem. Soc.* **1995**, *117*, 7273.
7. As expected (allyl)PdCl-dimer with (*S,S*)-Chiraphos gave no allylation product. A number of chelating phsophinite ligands which were successfully used in Pd-catalyzed malonate-type additions[2i] were also found to be ineffective in the Ni-chemistry using methyl 1,3-diphenylallyl ether as a substrate.
8. The absolute configuration of the major product was determined as follows: (*E*)-1,3-diphenyl-1-butene was treated with $NaIO_4$ and $KMnO_4$ in acetone/water at 0 °C. The resulting acid was treated with (-)-menthol in the presence of DCC and trace of DMAP to get diastereomeric menthyl esters which were analyzed on a Chirasil-S-Val column (25 m X 0.25 mm from Chrompack Company, 130 °C isothermal run). A base-line separation of the two isomers were observed under these conditions and the major product was identified by comparison of retention time with that of an authentic sample prepared from (-)-menthol and (*S*)-2-phenylpropionic acid purchased from Aldrich. The retention times of the various (*E*)-1,3-diphenylprop-2-enyl derivatives on a Chiralcel OJ column using hexane/i-propanol are also characteristic of the configuration of the benzylic carbon. Replacing the Me group of **2** with OH, OMe, OAc or $CH(CO_2Me)_2$ does not change the relative elution order of the two enantiomers in HPLC.
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