

JOM 23776

Influence of the extent of conversion on enantioselectivity in the nickel-catalyzed cross-coupling reaction

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(Received April 5, 1993)

Abstract

In the cross coupling reaction between 1-phenylethyl magnesium bromide and vinyl chloride to give 3-phenylbut-1-ene in the presence of nickel(II)bromide complexes of optically active *trans*-cyclopentane-1,2-diylbis(diarylphosphine)] as the catalyst precursors, the degree of asymmetric induction depends on the aryl substituent, and is more influenced by steric than by electronic factors. Furthermore, the enantioselectivity of the coupling reaction changes with the extent of conversion, and is substantially influenced by the method of preparation of the reaction mixture.

1. Introduction

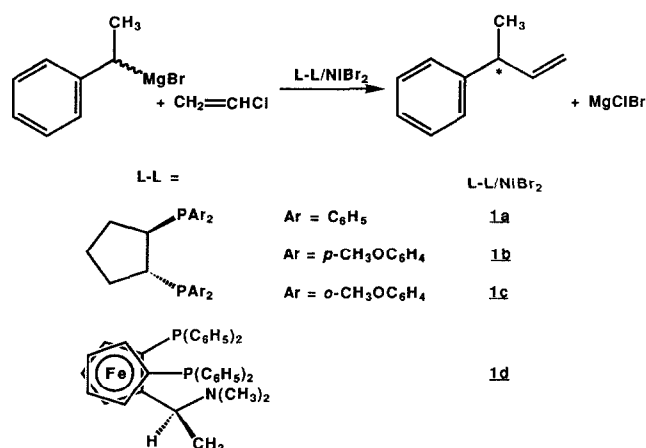
The enantioselective cross-coupling reaction between chiral Grignard reagents (in which the metal atom is directly bound to the asymmetric carbon atom) and vinyl, aryl or allyl electrophiles using either nickel or palladium phosphine complexes as the catalyst precursor has attracted much interest [1]. Many types of chiral ligands have been developed in order to improve the optical yields [2–11]; they were mostly tested for the model reaction between 1-phenylethylmagnesium halides and vinyl halides (Scheme 1). Mechanistic insights into the reaction are still poor [12,13]. It is assumed that the coupling product is formed by reductive elimination from the metal catalyst [13], this reaction probably being stereospecific [13–16]. As a consequence the step responsible for asymmetric induction should be the alkylation of the transition metal catalyst by the Grignard reagent. The stereochemistry of this step is expected to be affected by the nature of the alkylating species and by the enantiomeric composition of the Grignard reagent; low racemization rates of this reaction partner could therefore influence the extent of asymmetric induction [17]. However, epimerization

at the level of the transition metal alkyl intermediate cannot be excluded [18].

It was reported that addition of zinc halide can change the sense of enantioselectivity in the cross-coupling of 1-phenylethyl magnesium chloride with vinyl bromide catalyzed by nickel and palladium complexes of aminophosphines derived from amino acids [19]. This followed the previous observation that all factors that are known to influence the structure of the Grignard reagent in solution also affect the extent of asymmetric induction, at the least for the reaction catalyzed by nickel diphosphine complexes [20]. Owing to the formation of magnesium salts during the reaction, the composition in solution of the magnesium species (*i.e.*, the structure of the species which can alkylate the transition metal catalyst) changes [21]. Therefore, it would be expected that enantioselectivity would also change during the reaction [22*] unless asymmetric induction is determined by the epimerization at the carbon–transition metal bond. However, no data relating to this problem of the coupling reaction have been reported. This aspect of the reaction can be readily investigated by monitoring the change in the enantiomeric excess as a function of the degree of the

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* Reference number with asterisk indicates a note in the list of references.



Scheme 1.

conversion of the substrate by use of enantioselective GLC [7]. We report here some results related to the influence of the extent of conversion on the enantioselectivity in systems involving various chiral ligands and various reaction conditions.

2. Results and discussion

The coupling reaction between 2-phenylethyl magnesium bromide and vinyl chloride (Scheme 1) was studied using as the catalyst precursor the nickel dibromide complexes of (+)-*trans*-cyclopentane-1,2-diylbis(diphenylphosphine) (**1a**) [23], (+)-*trans*-cyclopentane-1,2-diylbis(di-*p*-methoxyphenylphosphine) (**1b**) [24], (+)-*trans*-cyclopentane-1,2-diylbis(di-*o*-methoxyphenylphosphine) (**1c**) [25] and of (*S*)-(*R*)-1-[1-(dimethylamino)ethyl]-1,2-bis(diphenylphosphino)ferrocene ((*S*)-(*R*)-BPPFA) (**1d**) [3]. Each experiment was repeated at least twice and was found to be reproducible. The solution of the Grignard reagent was at least one week old. In a first set of experiments the reaction mixture was prepared by mixing the Grignard reagent, the catalyst precursor, and the vinyl halide at the same time. With a catalyst to substrate molar ratio of ~ 250 in a 0.5 M solution of the Grignard reagent ($\sim 25\%$ excess with respect to vinyl chloride) we observed 50% conversion in *ca.* 12 h. The chemoselectivity of the coupling was quite good, small amounts of styrene being formed as the byproduct. The enantioselectivity of the reaction (Fig. 1) depends on the extent of conversion. For the cyclopentane-based ligands variation in the enantioselectivity during the reaction is particularly evident in the case of catalytic system **1c** (best *ee* $\sim 44\%$). The other systems **1a** and **1b** give lower enantioselectivities (11 and 17%, respectively). This shows that asymmetric induction for this reaction is more strongly influenced by steric than by

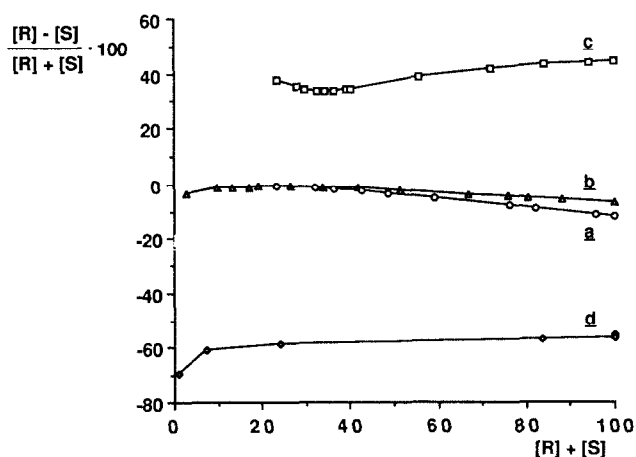


Fig. 1. Enantioselectivity (*ee*, %) in the coupling reaction of $\text{C}_6\text{H}_5\text{CH}(\text{CH}_3)\text{MgBr}$ with $\text{CH}_2=\text{CHCl}$ using different chiral ligands as a function of the conversion. The letters refer to the ligands in Scheme 1; the reactions were carried out by mixing all the components at the same time.

electronic factors. For the (*S*)-(*R*)-BPPFA-containing catalytic system (**1d**) the enantiomeric purity of the produced 3-phenyl-1-butene remains substantially constant at about 60% throughout the reaction; a higher enantioselectivity (70%) is observed only at very low conversion ($\sim 1\%$). When ligand **1c** is used the enantioselectivity of the reaction is not affected by the presence of an olefin such as allylbenzene or cyclopentene (0.5 M), but the reaction rate is lowered.

Particularly interesting is the behaviour of the difference in concentration of the two enantiomers as a function of the sum of their concentrations (Fig. 2). To allow comparison of the various experiments the

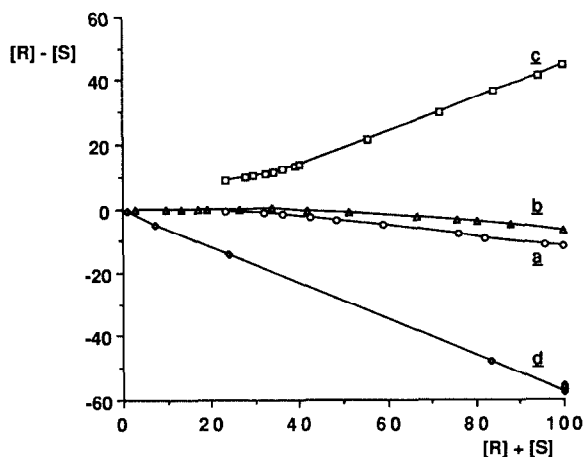


Fig. 2. Normalized *ee* in the coupling reaction of $\text{C}_6\text{H}_5\text{CH}(\text{CH}_3)\text{MgBr}$ with $\text{CH}_2=\text{CHCl}$ using different chiral ligands as a function of the conversion. The letters refer to the ligands in Scheme 1; the reactions were carried out by mixing all the components at the same time.

normalized values of these differences are reported in the Figure. The slope of the curve gives the actual enantioselectivity of the catalytic system at each conversion. The only catalytic system showing essentially linear behaviour is **1d**. Deviation from linearity is mostly evident for **1c** at lower conversion (< 40%). The second part of the plot (conversions > 40%) is linear, and has a slope of 0.521, showing that a steady state has been achieved in which the enantioselectivity of the reaction corresponds to a 52.1% ee and remains constant. The departure from linearity in the first part of the curve can be interpreted as originating from a change in the nature of the alkylating species of the Grignard reagent or from a change in the nature of the catalytic species. In fact, as previously stated, the enantioselectivity of this catalytic system is not changed if the reaction is carried out in the presence of an olefin such as allylbenzene or cyclopentene (0.5 M). For the catalytic system **1c** we have compared the results previously discussed with those obtained by carrying out the reaction at higher dilution (0.1 M solution of the Grignard reagent) under otherwise identical conditions. This substantial dilution should ensure a consistent variation of the association degree of the Grignard reagent [17]. Indeed, we observed an unexpected increase in the reaction rate, which hampered the determination of the enantioselectivity of the reaction at low conversion. Nevertheless, the behaviour of the enantiomeric excess at conversions of > 40% is essentially superimposable on that previously observed (Fig. 1 and 2, curves 1c). The dependence of the normalized enantiomeric excess is linear over the full range of conversions examined. The slope (0.515) shows an enantioselectivity equal within experimental error to that observed in the more concentrated solution. The intercept of the curve has a non-zero value (-0.253); this may be related to the formation of the catalytic species, which then remain unchanged (at least as far as enantioselectivity is concerned) throughout the reaction.

To gain some insight into the reasons for the non-linearity of part of plot 1c in Fig. 2, we allowed the catalyst precursor and the Grignard reagents to react for eight days and then added vinyl chloride. This causes no modification of the structure of the chiral ligand, as demonstrated by a control experiment. Under these conditions styrene formation appears to be somewhat more extensive (~17% *vs.* 6%). The plots related to the enantioselectivity of the reaction are also reported in Figs. 3 and 4, where they are compared with those from similar experiments in which **1b** or **1d** was the catalyst precursor. For **1d** no change in the enantioselectivity is observed relative to that in the previous experiments (Fig. 1 and 2). Curves d in Figs. 2 and 4 are perfectly superimposable. Some difference in

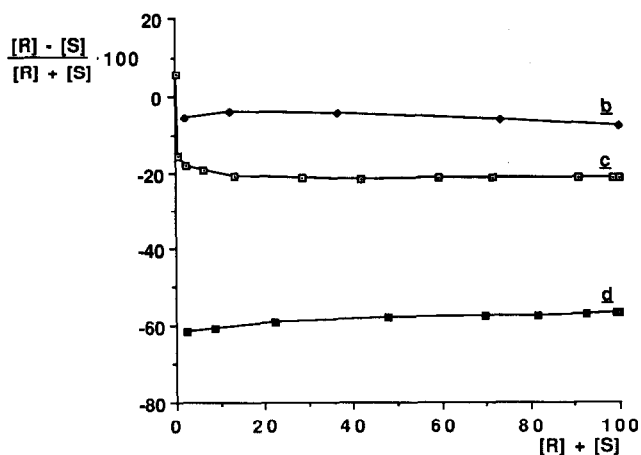


Fig. 3. Normalized ee in the coupling reaction of $C_6H_5CH(CH_3)MgBr$ with $CH_2=CHCl$ using different chiral ligands as a function of the conversion. The letters refer to the ligands in Scheme 1; the reactions were carried out by adding $CH_2=CHCl$ to a one week old solution of the $C_6H_5CH(CH_3)MgBr$ and of the catalyst.

the extent of the asymmetric induction is found for **1b**, for which enantioselectivity is rather low. The largest difference is observed for **1c**. Except for the first observed enantiomeric excess (the extent of conversion at this point corresponds to the molar amounts of the catalyst) the predominant enantiomer formed is opposite in the two sets of experiments. The enantioselectivity as given by the slope of the linear plot (Fig. 4) corresponds to 21.4% ee. The almost zero-value of the intercept is consistent with a very rapid development of the active system to a steady state situation.

As previously found for other coupling reactions the nature of the halide on both the organic and metallor-

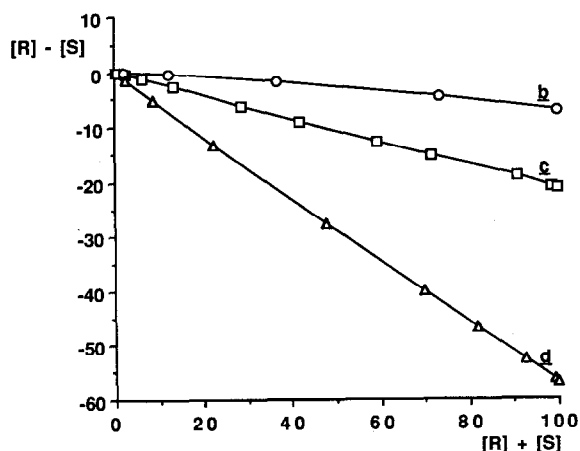


Fig. 4. Normalized ee in the coupling reaction of $C_6H_5CH(CH_3)MgBr$ with $CH_2=CHCl$ using different chiral ligands as a function of the conversion. The letters refer to the ligands in Scheme 1; the reactions were carried out by adding $CH_2=CHCl$ to a one week old solution of the $C_6H_5CH(CH_3)MgBr$ and of the catalyst.

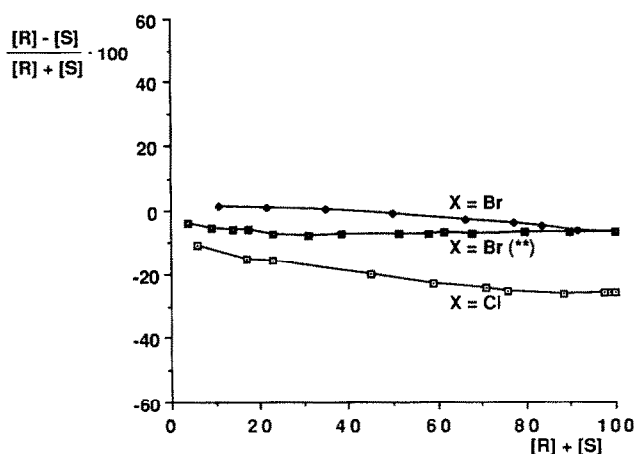


Fig. 5. Enantioselectivity (ee, %) in the coupling reaction of $C_6H_5CH(CH_3)MgX$ with $CH_2=CHX$ using **1b** as the catalyst precursor. The reactions were carried out by mixing all the components at the same time. ** In the presence of an excess of $MgBr_2$.

ganic moiety influences the enantioselectivity of the reaction. Some results obtained with **1b** as the catalyst precursor are shown in Figs. 5 and 6 for the coupling reaction leading to 3-phenyl-1-butene. The final enantioselectivity is $\sim 26\%$ when the chloride are used but only 7% for the bromide. For the latter system the presence of an excess of magnesium bromide does not change the final enantioselectivity (Fig. 5); instead under these conditions the enantioselectivity seems to remain constant throughout the reaction. For the chlorine-containing system the enantioselectivity is not much influenced by the extent of conversion, probably because of the precipitation of insoluble magnesium chloride during the reaction.

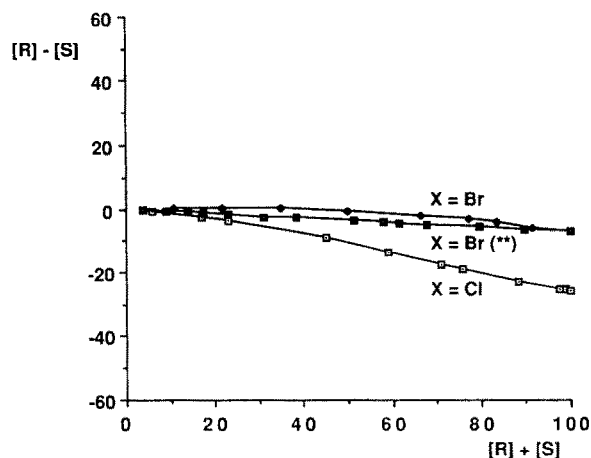


Fig. 6. Normalized ee in the coupling reaction of $C_6H_5CH(CH_3)MgX$ with $CH_2=CHX$ using **1b** as the catalyst precursor. The reactions were carried out by mixing all the components at the same time. ** In the presence of an excess of $MgBr_2$.

3. Conclusions

The reported results show that the enantioselectivity of the cross-coupling reaction depends on the extent of conversion, at least for the systems containing the *trans*-cyclopentane-1,2-diylbis(diarylphosphine) ligands. This effect is possibly related to the variation in the nature of the Grignard reagent as a consequence of the formation of magnesium halides and of the increased dilution. The fact that no change is observed for the system containing the (*S*)-(*R*)-1-[1-(dimethylamino)ethyl]-1,2-bis(diphenylphosphino)ferrocene ((*S*)-(*R*)-BPP-FA) ligand is in agreement with the previous proposal that the dimethyl amino group can interact with the Grignard reagent before alkylation of the transition metal [3]. Therefore the nature of the species responsible for alkylation does not change during the course of the reaction. Particularly puzzling at the moment are the results obtained for catalyst precursor **1b** under the two different sets of reaction conditions used. The reported experiments can be interpreted on the basis of (at least) two different steady state conditions which can be attained during the cross-coupling reaction examined. The difference does not depend on a chemical change of the chiral ligand. Preliminary experiments to identify variations of the catalytic species by NMR spectroscopy have up to now revealed no clear difference in the catalytic species involved.

4. Experimental section

4.1. Starting materials

Vinyl chloride and vinyl bromide were purchased from Fluka. Diethyl ether was dried by standard procedures and distilled under nitrogen. 1-Phenylethyl chloride [26] and 1-phenylethyl bromide [27] were made as previously reported.

Optically pure (+)-*trans*-cyclopentane-1,2-diylbis(diphenylphosphine), (+)-*trans*-cyclopentane-1,2-diylbis(di-*p*-methoxyphenylphosphine), (+)-*trans*-cyclopentane-1,2-diylbis(di-*o*-methoxyphenylphosphine) [25] were obtained by resolution of the corresponding oxides prepared by published procedures [28]. (*S*)-(*R*)-1-[1-(dimethylamino)ethyl]-1,2-bis(diphenylphosphino)ferrocene [(*S*)-(*R*)-BPPFA] (**1d**) was a generous gift from Professor A. Togni.

4.2. General procedures

Gas chromatographic analyses were carried out on a Shimadzu instrument with flame ionization detector and a 50 m Lipodex C capillary column (Macherey-Nagel). Hydrogen was the carrier gas. Optical rotations were measured on a Perkin Elmer 241 polarimeter.

NMR spectra were measured on a Bruker 300WB or AC200 spectrometer.

All coupling reactions were performed under nitrogen with 4 mmol of the vinyl halide, 5 mmol of the Grignard reagent, and 0.02 mmol of the catalyst. The reactions were carried out at 25°C. Samples of the reaction mixtures were hydrolyzed with ice followed by diluted HCl. The ether layer was dried over sodium sulphate and analyzed by GLC with anisole as internal standard.

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