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Preliminary communication

NICKEL CATALYZED ASYMMETRIC CROSS-COUPLING REACTION BETWEEN C_6H_5X AND s-BuMgX. THE INFLUENCE OF THE NATURE OF THE HALOGENS OF THE TWO REAGENTS

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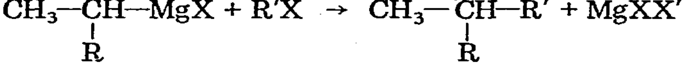
Summary

The asymmetric cross-coupling reaction between phenyl halides and sec-butylmagnesium halides has been carried out in the presence of [(+)(*R*)-1,2-bis(diphenylphosphino)propane]nickel(II) chloride. The optical purity and the absolute configuration of the 2-phenylbutane were dependent on which halogen was present in the organic and the organometallic moieties.

In the cross coupling reaction between aryl or vinyl halides and chiral sec-alkylmagnesium halides in the presence of $NiCl_2[(-)(R,R)\text{-DIOP}]$ (Scheme 1), enantiomer differentiation [1] with up to 17% optical yield can take place, as we have previously shown [2].



$$CH_3-\underset{R}{CH}-MgX + R'X \rightarrow CH_3-\underset{R}{\overset{*}{C}H}-R' + MgXX'$$

(X, X' = halide; R = C_6H_5, R' = $CH_2{=}CH$; R = CH_3, R' = C_6H_5, $CH_2{=}CH$)

SCHEME 1

Pursuing our interest in the mechanistic and synthetic aspects of this stereodifferentiating reaction [1], we have synthesized $NiCl_2[(+)(R)\text{-Prophos}]$ [3], where Prophos is 1,2-bis(diphenylphosphino)propane [4].

We report in this paper some preliminary results obtained in the asymmetric cross-coupling reaction, carried out in the presence of the above catalyst precursor, between phenyl halides and sec-butylmagnesium halides, which leads to the formation of optically active 2-phenylbutane (Table 1). The optical yield

TABLE 1

CROSS-COUPLING BETWEEN C_6H_5X AND s-BuMgX IN THE PRESENCE OF $NiCl_2$[(+)(*R*)-Prophos] IN DIETHYL ETHER SOLUTION[a]

C_6H_5X X =	s-BuMgX X =	Reaction time (h)	Reacted C_6H_5X (%)	Reduction[b] to C_6H_6 (%)	Isomerization[c] (%)	2-Phenylbutane Isolated yield (%)	2-Phenylbutane α_D^{25} (l = 1)
Cl	Cl	17	82	3	3.4	70	+5.33
Cl	Br	19	95	3	3.2	80	−6.17
Cl	I	24	97	2	4.3	85	−1.02
Br	Cl	20	~100	6	4.7	85	+2.38
Br	Br	10	97	4	4.0	82	−11.03
Br	I	24	93	11	5.7	70	−8.21
I	Cl	2	~100	7	3.7	85	+4.12
I	Br	3	~100	8	4.5	80	−9.05
I	I	3	~100	7	5.0	75	−5.31

[a] At the boiling point (~34°C) of a 65 ml solution containing: 0.05 mol C_6H_5X, 0.07 mol s-BuMgX and 0.16—0.17 × 10^{-3} mol catalyst. [b] Percentages based on the C_6H_5X reacted. [c] Refers to the sum of the cross-coupling products formed.

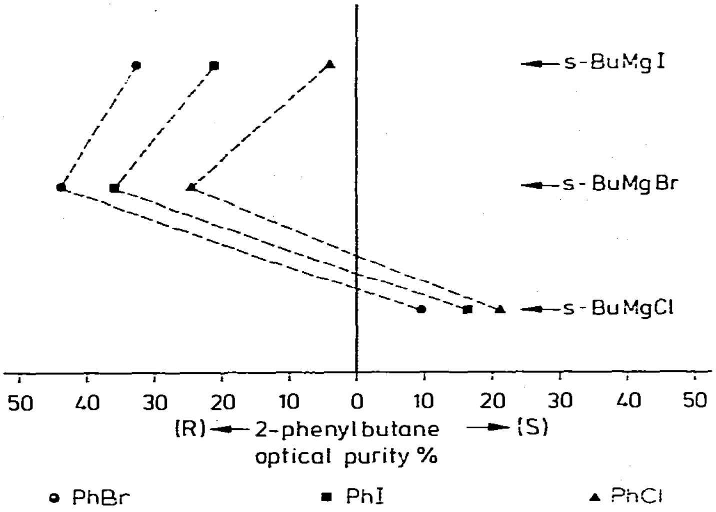


Fig. 1. Absolute configuration and optical purity of 2-phenylbutane from cross-coupling reaction between C_6H_5X and s-BuMgX catalyzed by $NiCl_2$[(+)(*R*)-Prophos].

data are presented in the Fig. 1, where the dotted lines joining the experimental points have no physical meaning, but only illustrate that trends are similar for the various halides. The data were calculated on the basis of the maximum rotatory power ($[\alpha]_D^{25}$ +29.26 (neat)) reported for (+)(*S*)-2-phenylbutane [5].

$NiCl_2$[(+)(*R*)-Prophos] has a much higher catalytic activity for the cross-coupling than does $NiCl_2$[(−)(*R*,*R*)-DIOP]. With the former, by-products arising from rearrangement of the alkyl group of the Grignard reagent (leading to the formation of 1-phenylbutane) [2,6] or from the reduction of C_6H_5X to benzene [6] are formed in rather small amounts. Moreover, the highest optical yield obtained (~44%) is one of the best ever observed in an enantiomer-discriminating reaction catalyzed by a chiral transition metal complex in solution [7]. In this case the ratio between the reaction rates for both enantiomers is at least 2.6 [8].

The absolute configuration of 2-phenylbutane can be reversed by changing the halogen of the Grignard reagent: the (*S*) enantiomer is prevailingly formed when starting with s-BuMgCl, whereas the (*R*) enantiomer predominates when s-BuMgBr or s-BuMgI is used. Inspection of Fig. 1 reveals also similar influences of the halogens of the phenyl moiety when used with the same Grignard reagent: the optical purity of 2-phenylbutane, obtained from C_6H_5I, is always intermediate between those observed with C_6H_5Br or C_6H_5Cl; this behaviour is not a reflection of the reactivity of C_6H_5X, which decreases in the order $C_6H_5I > C_6H_5Br > C_6H_5Cl$. Furthermore, the range in values for optical yield obtained with the three phenyl halides decreases with the Grignard reagent used in the order s-BuMgI > s-BuMgBr > s-BuMgCl.

It has been already noted in the cross-coupling reaction catalyzed by $NiCl_2$[(−)(*R*,*R*)-DIOP] that the optical yield can be affected by the type of halogen in the halobenzene [8], although in that case the observed differences were rather small. This is the first instance in which the dramatic influence of the halogen of the Grignard reagent, which can reverse the absolute configuration of the reaction product, is recognized. Furthermore similar trends, shown in Fig. 1, suggest that the influences of the halogens of the two moieties may be additive.

Many mechanistic possibilities have been envisaged for the nickel catalyzed cross-coupling reaction [9]. All the proposed mechanisms, however, involve a reductive elimination of the two organic moieties, leading to formation of the cross-coupling product. The appreciable optical yields obtained for both enantiomers of 2-phenylbutane indicate that the reductive elimination must occur with a high stereospecificity, very probably with retention of configuration. Retention of stereochemistry at the vinylic centers in *cis*- and *trans*-β-bromostyrene during cross-coupling with phenylmagnesium bromide has, indeed, been observed [10].

The limited formation of the achiral isomer and the change in the prevailing configuration we observed, suggest that possible epimerization at the asymmetric carbon atom bound to nickel (e.g., via a π-olefin complex formation) does not play an important role.

Experiments are in progress to improve understanding of the mechanistic aspects of the cross coupling reaction and to extend the observations to other substrates.

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