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KINETIC RESOLUTION OF RACEMIC GRIGNARD REAGENTS BY NICKEL-CATALYZED ASYMMETRIC GRIGNARD CROSS-COUPLING

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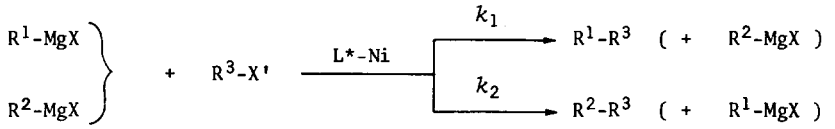
Summary: Racemic Grignard reagents, 2-phenylpropylmagnesium chloride and 2-norbornylmagnesium chloride were kinetically resolved by asymmetric cross-coupling with vinyl bromides in the presence of chiral phosphine-nickel catalysts to give optically active coupling products (~37% ee) and carboxylic acids after carbonation with carbon dioxide.

We have previously reported that nickel complexes with optically active (aminoalkyl)phosphine ligands catalyzed the asymmetric cross-coupling of secondary alkyl Grignard reagents such as 1-phenylethylmagnesium chloride with vinyl bromide to give coupling products of high optical purity (eq. 1).[1] This asymmetric induction is due to kinetic resolution of the racemic secondary alkyl Grignard reagent which, probably, always exists in a racemic form since the inversion of the Grignard reagent is relatively fast as compared with the coupling reaction. In the present paper, we report an asymmetric reaction of Grignard reagents which do not undergo racemization.

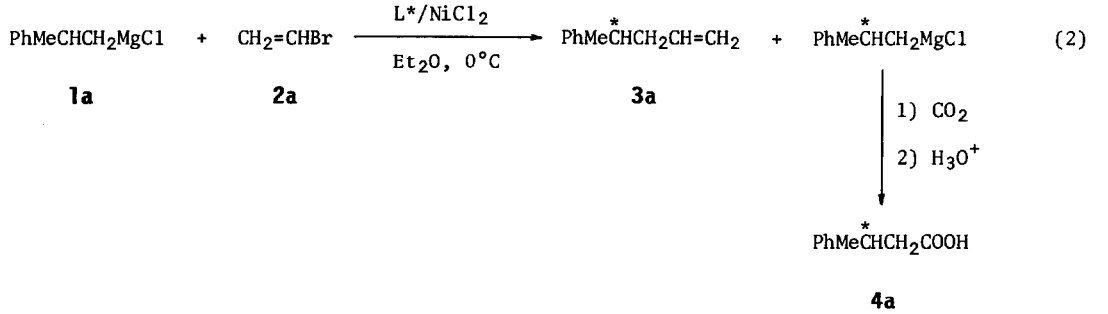
$$PhMeCHMgCl + CH_2{=}CHBr \xrightarrow{L^*\text{-}Ni} PhMe\overset{*}{C}HCH{=}CH_2 \qquad (1)$$

When an optically active nickel catalyst is used for the reaction of a racemic Grignard reagent with a halide, one of the enantiomers of the Grignard reagent reacts faster than the other enantiomer giving rise to an optically active coupling product and an optically active unreacted Grignard reagent (Scheme I: R^1 and R^2 are a pair of enantiomeric groups). Their optical purity is dependent upon the ratio k_1/k_2 and the conversion of the Grignard reagent, and the stereoselectivity can be evaluated by k_1/k_2.[2]

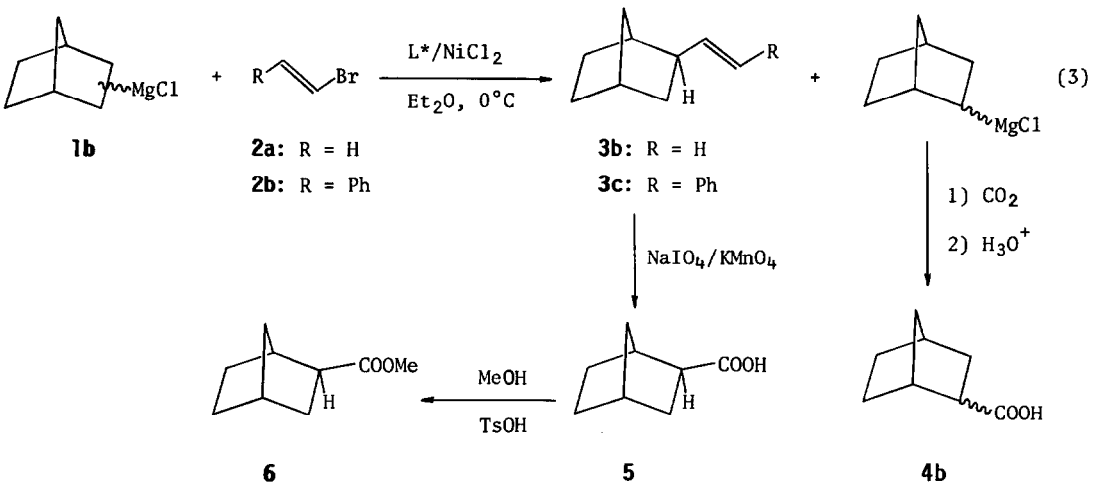
Scheme I.



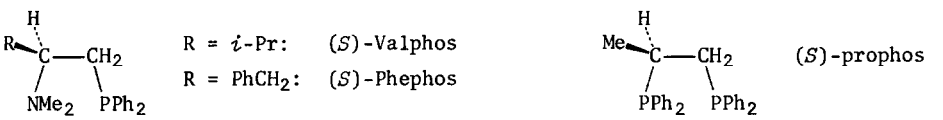
An ether solution of racemic 2-phenylpropylmagnesium chloride (**1a**) was allowed to react with less than one equivalent of vinyl bromide (**2a**) in the presence of (*S*)-Valphos[1a] and nickel



1a **2a** **3a** **4a** (2)



1b **2a:** R = H **2b:** R = Ph **3b:** R = H **3c:** R = Ph **6** **5** **4b** (3)



chloride (eq. 2). Carbonation of the reaction mixture by bubbling carbon dioxide through the solution followed by acid hydrolysis gave 4-phenyl-1-pentene (**3a**) (7.7% ee *S*)[3] and 3-phenylbutanoic acid (**4a**) (5.8% ee *R*).[4] These data indicate that the Grignard reagent **1a** of *R* configuration reacted faster than the *S* isomer and k_1/k_2 is calculated to be 1.23-1.25. The use of (*S*)-prophos[5] as a ligand resulted in the formation of **3a** and **4a** of very low optical purity.

The Grignard reagent (**1b**) from racemic *exo*-2-chloronorbornane was more effectively resolved. The reaction of **1b** with vinyl bromide (**2a**) in the presence of (*S*)-Valphos-$NiCl_2$ catalyst gave *exo*-vinylnorbornane (**3b**)[6] with $[\alpha]_D^{20}$ +14.5° (neat), at 38% conversion. The configuration and optical purity of the coupling product **3b** were determined to be (1*S*, 2*S*, 4*R*) and 31% ee by converting it into *exo*-2-norbornanecarboxylic acid (**5**)[7] and its methyl ester **6**,[8] of which the maximum rotations have been reported.[9] Carbonation of the unreacted Grignard reagent yielded 2-norbornanecarboxylic acid (**4b**) which was a one-to-one mixture of the *exo* and *endo* isomers

Table 1. Kinetic Resolution of Racemic Grignard Reagents 1 by Asymmetric Cross-Coupling.

Grignard reagent 1	Halide 2	Ligand L*	Conversion[a] (%)	Coupling product 3			Acid 4		
				$[\alpha]_D$	% ee[b]	k_1/k_2[c]	$[\alpha]_D$	% ee[d]	k_1/k_2[c]
1a	**2a**	(*S*)-Valphos	41	+1.24[e]	7.7 (*S*)	1.23	-3.33[e]	5.8 (*R*)	1.25
1a	**2a**	(*S*)-prophos	38	-0.31[e]	1.9 (*R*)	0.95	+1.08[e]	1.9 (*S*)	0.93
1b	**2a**	(*S*)-Valphos	38	+14.5[f]	31 (1*S*,2*S*,4*R*)	2.27	-4.5[g]	15 (1*R*,4*S*)	1.9
1b	**2a**	(*S*)-Valphos	19	+17.6[f]	37 (1*S*,2*S*,4*R*)	2.36	-2.1[g]	7 (1*R*,4*S*)	2.0
1b	**2a**	(*S*)-Phephos	24	+12.8[f]	27 (1*S*,2*S*,4*R*)	1.89	——	——	——
1b	**2b**	(*S*)-Valphos	26	+13.2[h]	31 (1*S*,2*S*,4*R*)	2.11	——	——	——

[a] (mol of produced coupling product **3**)/(mol of used Grignard reagent **1**) × 100. Determined by GLC analysis. [b] Maximum optical rotations of the coupling products **3a** and **3b** are as follows: (*S*)-**3a**: α_D^{25} +16.1° (1 dm, neat), (calculated value), ref. 3. (1*S*,2*S*,4*R*)-**3b**: $[\alpha]_D^{20}$ +47° (neat) (calculated value), see text. [c] See ref. 2. [d] (*R*)-**4a**: α_D^{25} -57.3° (1 dm, neat), ref. 4. (1*R*,2*R*,4*S*)-*exo*-**4b**: $[\alpha]_D$ -27.8° (95% ethanol). (1*R*,2*S*,4*S*)-*endo*-**4b**: $[\alpha]_D$ -30.6° (95% ethanol), see ref. 9 and 10. [e] α_D^{25} (1 dm, neat). [f] $[\alpha]_D^{20}$ (neat), d_4^{20} 0.8781∿9, ref. 6. [g] $[\alpha]_D^{25}$ (*c* 2, 95% ethanol). [h] $[\alpha]_D^{25}$ (*c* 1, benzene).

having $[\alpha]_D$ -4.5° (95% ethanol), and estimated[10] to be enriched in (1*R*, 4*S*) isomers over (1*S*, 4*R*) isomers by about 15%. It is of interest that the reaction gave only the *exo* isomer **3b** (>95% pure) as the coupling product while the acid **4b** obtained by carbonation was a mixture of *exo* and *endo* isomers. A possible rationale is that only the *exo* isomer of the Grignard reagent is subject to cross-coupling due to steric reasons, on the assumption that the cross-coupling proceeds with net retention at C-2 of the norbornyl group.[11]

A lower conversion of the Grignard reagent **1b** led to a higher optical purity of the coupling product **3b** and a lower optical purity of the acid **4b**, as expected from the k_1/k_2 value kept constant during the reaction. Product **3b** of 37% optical purity was obtained at 19% conversion. (*S*)-Phephos[1b] was a little less effective than (*S*)-Valphos in connection with the enantioselective ability for the present asymmetric cross-coupling.

(*E*)-2-Bromostyrene (**2b**) could be also used for the cross-coupling, the stereoselectivity being almost the same as that with vinyl bromide (**2a**).[12]

Although the stereoselectivity observed is not satisfactorily high at present, the kinetic resolution of racemic Grignard reagents by the catalytic asymmetric cross-coupling provides a new efficient route to the synthesis of optically active Grignard reagents, whose absolute configuration and enantiomeric purity can be estimated from the optical data of the coupling products.[13]

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(2) The value k_1/k_2 is calculated from the following equation using the enantiomeric excess value of the coupling product (P) or the recovered Grignard reagent (G): $k_1/k_2 = \ln[1-(1+P)X]/\ln[1-(1-P)X] = \ln(1+G)(1-X)/\ln(1-G)(1-X)$, X = (mol of produced coupling product)/(mol of used Grignard reagent).

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(7) $[\alpha]_D^{25}$ +8.69° (95% ethanol), 31% ee.[9]

(8) $[\alpha]_D^{25}$ +9.48° (95% ethanol), 28% ee.[9] The enantiomeric purity determined by ^{1}H NMR spectrometry using chiral shift reagent tris(3-trifluoroacetyl-*d*-camphorato)europium(III) [Eu(facam)$_3$] was 32(±3)%.

(9) (a) J. A. Berson and D. A. Ben-Efrain, *J. Am. Chem. Soc.*, **81**, 4083 (1959); (b) J. A. Berson, J. S. Walia, A. Remanick, S. Suzuki, P. Reynolds-Warnhoff, and D. Willner, *J. Am. Chem. Soc.*, **83**, 3986 (1961).

(10) The specific rotations of the acids (1*R*,2*R*,4*S*)-*exo*-**4b** and (1*R*,2*S*,4*S*)-*endo*-**4b** have been reported to be nearly equal.

(11) The norbornyl Grignard reagent is known to exist in *exo-endo* dynamic equilibrium and undergo electrophilic substitution with retention of configuration. See, (a) N. G. Krieghoff and D. O. Cowan, *J. Am. Chem. Soc.*, **88**, 1322 (1966); (b) F. R. Jensen and K. L. Nakamaye, *J. Am. Chem. Soc.*, **88**, 3437 (1966); (c) E. A. Hill, *J. Org. Chem.*, **31**, 20 (1966).

(12) The coupling product **3c** was converted into the methyl ester **6** and the optical purity was established by ^{1}H NMR spectrometry using Eu(facam)$_3$.

(13) Partial kinetic resolution of a Grignard reagent by the reaction with chiral ketones has been reported: J. D. Morrison, A. Tomash, and R. W. Ridgway, *Tetrahedron Lett.*, 565 (1969).

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