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ASYMMETRIC CROSS-COUPLING REACTION OF *sec*-ALKYL GRIGNARD REAGENTS WITH ORGANIC HALIDES IN THE PRESENCE OF A CHIRAL PHOSPHINE-NICKEL COMPLEX AS A CATALYST

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A racemic secondary alkyl Griganrd reagent in which magnesium attaches to a chiral carbon center may react to form an optically active product if the reaction is conducted in an appropriate chiral environment. One main reason why such asymmetric reactions[1] have little been examined[2] may be a lack of the suitable reaction conditions. The recently recongnized[3] facile cross-coupling reaction of *sec*-alkyl Grignard reagents with aryl and alkenyl halides catalyzed by a phosphine-nickel complex suggests a new type of asymmetric reaction.

The asymmetric cross-coupling reaction (see eq 1),[1] indeed, can be achieved by using Ni-[(-)-diop]Cl_2[4] as a catalyst, where diop stands for 2,3-*O*-isopropylydene-2,3-dihydroxy-1,4-bis(diphenylphosphino)butane.[5] Representative results observed with this catalyst are given in Table I.

$$HR^1R^2C\text{-}MgX \quad + \quad R^3X \quad \xrightarrow[\text{catalyst}]{Ni[(-)\text{-diop}]Cl_2} \quad \underset{\text{optically active}}{HR^1R^2C^*\text{-}R^3} \qquad (1)$$

While the reaction of *sec*-butylmagnesium chloride with an aryl halide gave a mixture of products owing to the alkyl group isomerization accompanying the cross-coupling reaction,[3] the reaction of α-phenylethylmagnesium chloride with vinyl chloride took place under much milder reaction conditions (0°, 10 min *vs.* 35°, 3 days) to form 3-phenyl-1-butene as a sole product. In a typical experiment, the reaction of *sec*-butylmagnesium chloride (1.45 M-ether solution, 81 mmol) with chlorobenzene (4.15 g, 37 mmol) was carried out in the presence of Ni[(-)-diop]Cl_2

Table I. Asymmetric Cross-Coupling Reactions of *sec*-Alkyl Grignard Reagents with Organic Halides in the Presence of Ni[(-)-diop]Cl_2[a]

No.	Grignard reagent[b]	Organic halide	Ratio of $\frac{\text{Grignard reagent}}{\text{organic halide}}$	Product[c]	Yield (%)[d]	$[\alpha]_D^{25}$ deg. of product[e]	Conf. (% ee)[f]
1	EtCHMeMgCl	PhF	2.0	EtC*HMePh	30	-3.74	*R* (13.6)
2	EtCHMeMgCl	PhCl	2.2	EtC*HMePh	31 (14)	-3.00	*R* (10.9)
3	EtCHMeMgCl	PhCl	1.0	EtC*HMePh	35 (35)	-2.81	*R* (10.2)
4	EtCHMeMgCl	PhBr	2.0	EtC*HMePh	20	-4.09	*R* (14.8)
5	EtCHMeMgCl	α-NpBr[g]	2.0	EtC*HMe-Np-α	44	+0.57	[h]
6	PhCHMeMgCl	$H_2C{=}CHCl$	3.85	PhC*HMeCH=CH_2	81 (21)	-0.83	*R* (13.0)[i]
7	PhCHMeMgCl	$H_2C{=}CHCl$	1.75	PhC*HMeCH=CH_2	90 (51)	-0.61	*R* (9.6)
8	PhCHMeMgCl	$H_2C{=}CHCl$	[j]	PhC*HMeCH=CH_2	[j] (63)	-0.50	*R* (7.8)

[a] Catalyst: Grignard reagent = 2.5×10^{-3} for EtCHMeMgCl, 1×10^{-3} for PhCHMeMgCl. Solvent; diethyl ether. Reaction conditions; at 35° for 48 - 72 hr in the case of EtCHMeMgCl, at 0° for 10 - 60 min in the case of PhCHMeMgCl. [b] Concentrations; EtCHMeMgCl 1.45 *M*, PhCHMeMgCl 0.70 *M*. [c] Only chiral products are listed. [d] Based on the organic halide. Yields based on the Grignard reagent is described in parentheses. [e] Neat. [f] Configuration of the predominant isomer. ee = Enantiomeric excess. [g] Np = naphthyl. [h] Maximum rotation is unknown. [i] (*R*)-(-)-3-phenyl-1-butene; $[\alpha]_D^{22}$ -6.39° (neat): D.J. Cram, *J. Amer. Chem. Soc.*, *74*, 2141 (1952). [j] Not determined.

(122 mg, 0.19 mmol) at 35° for 72 hr to give a mixture of sec-butylbenzene, n-butylbenzene, and benzene[3](56 : 28 : 16) in 55% total yield based on the chlorobenzene. The sec-butylbenzene isolated by preparative glpc showed an optical rotation of $[\alpha]_D^{25}$ -3.00° (neat) corresponding to a 10.9% optical purity of the R-isomer.[6]

There are two cases to be considered in the present asymmetric cross-coupling reaction. If the rate of the cross-coupling reaction (r_c) is much slower than that of the inversion at chiral carbon of Grignard reagent (r_{inv}), the optical yield of the product should be independent of the amount of the consumed Grignard reagent, while if $r_c \gtrsim r_{inv}$, the smaller the amount of the consumed Grignard reagent, the higher should be the optical yield.[7] The reaction of sec-butylmagnesium chloride with chlorobenzene (Table I, No. 2 and 3) may be the former case, while the reaction of α-phenylethylmagnesium chloride with vinyl chloride (No. 6 - 8) may represent the latter case.

The present results afford crucial evidence showing that the cross-coupling reaction occurs on a nickel center complexed with a phosphine ligand. A chiral carbon center is transferred from a Grignard reagent to a chiral nickel complex with forming diastereomeric intermediates containing a nickel-carbon σ-bond, from which an optically active cross-coupling product is released.[3] In this respect, it is noteworthy that the optical yield depends on the nature of the halide of halobenzenes (No. 1 - 4).

We anticipate that the present asymmetric cross-coupling reaction may open a facile and wide applicable route to the preparation of optically active hydrocarbons,[11] while optical resolution to obtain such compounds is rather tedious.[12]

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