Asymmetric Cross-coupling of Organozinc Reagents with Alkenyl Bromides Catalyzed by a Chiral Ferrocenylphosphine–Palladium Complex

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(Received July 12, 1982)

Synopsis. Organozinc reagents, prepared from secondary alkyl Grignard reagents (ArRCHMgCl: Ar=Ph, *p*-Tol; R=Me, Et) and excess zinc halides, were allowed to react with vinyl bromide and (*E*)-*β*-bromostyrene in the presence of dichloro[(*R*)-*N*,*N*-dimethyl-1-[(*S*)-2-(diphenylphosphino)ferrocenyl]ethylamine]palladium(II) as a catalyst to give the corresponding coupling products of up to 86% enantiomeric excess.

It has been well recognized that asymmetric synthesis catalyzed by chiral phosphine-transition metal complexes is one of the most useful methods for preparation of optically active compounds, and intense interest is now aroused by asymmetric carbon-carbon bond forming reactions with chiral transition metal catalysts.[1] Nickel- or palladium-catalyzed asymmetric Grignard cross-coupling has been reported by us and other research groups to afford optically active olefins of moderate to high enantiomeric excess: 3-Phenyl-1-butene obtained from reaction of 1-phenylethylmagnesium chloride has 68, 81, 67, and 15% ee with nickel catalysts for phosphine ligands, PPFA, Valphos, Norphos, and DIOP, respectively.[2–5] We report here that coupling products of higher enantiomeric purities can be obtained by use of organozinc reagents instead of Grignard reagents.

Results and Discussion

The secondary alkyl zinc reagents **1** were prepared *in situ* by mixing corresponding Grignard reagents with excess zinc halides. Preparation from alkyl halides and zinc metal was less convenient due to low yield and poor reproducibility. For the reaction of 1-phenylethylzinc halide (**1a**) with vinyl bromide, several nickel and palladium complexes with chiral phosphine ligands have been examined. Dichloro[(*R*)-*N*,*N*-dimethyl-1-[(*S*)-2-(diphenylphosphino)ferrocenyl]ethylamine]palladium(II) ($PdCl_2$[(*R*)-(*S*)-PPFA])[2,6] was found to be the most effective catalyst giving rise to high yield of optically active 3-phenyl-1-butene (**2a**) in THF at 0 °C for 20—40 h. It is noteworthy that the coupling reaction of the zinc reagents proceeded successfully only in THF,[7] although ether is usually the best solvent for the reaction of Grignard reagents.[2] Palladium complexes with other phosphine ligands were less catalytically active. Nickel complexes were almost inactive under the reaction conditions.

Results obtained for the asymmetric cross-coupling of **1** in the presence of $PdCl_2$[(*R*)-(*S*)-PPFA] catalyst are summarized in Table 1, which also contains data obtained for the reaction of organomagnesium and -aluminium reagents for comparison. The organozinc reagent **1a** prepared from 1-phenylethylmagnesium chloride and zinc chloride or iodide gave the olefin **2a** of 85—86% ee (*S*) in quantitative yield (entries 1 and

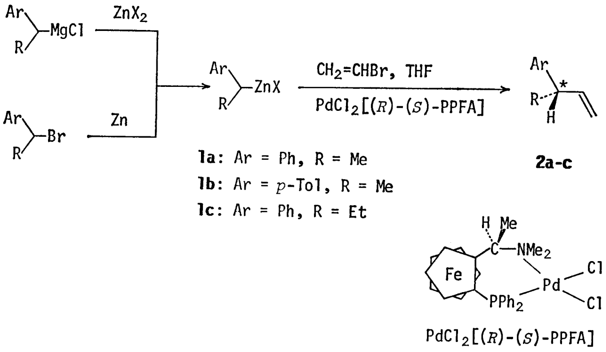

Table 1. Asymmetric cross-coupling of organozinc reagents with vinyl bromide catalyzed by $PdCl_2$[(*R*)-(*S*)-PPFA]

Entry	Organometallics	Solvent	Reaction condition		Yield[a]	$[\alpha]^{22}_D$/°	% ee
			Temp/°C	Time/h	%	(neat)	(Confign.)
1	**1a** PhMeCHMgCl/$ZnCl_2$ (1/2)	THF/Et_2O	0	40	>95	+5.05	85[b] (*S*)
2	**1a** PhMeCHMgCl/ZnI_2 (1/2)	THF/Et_2O	0	21	>95	+5.08	86[b] (*S*)
3	**1a** PhMeCHZnBr	THF	10	70	51	+5.10	86[b] (*S*)
4	PhMeCHMgCl	Et_2O	0	21	>95	+3.86	65[b] (*S*)
5	PhMeCHMgCl/$AlCl_3$ (1/2)	Et_2O	5	22	>95	+2.52	43[b] (*S*)
6	**1b** *p*-TolMeCHMgCl/ZnI_2 (1/2)	THF/Et_2O	0	44	>95	+6.97	86[c] (*S*)
7	**1c** PhEtCHMgCl/ZnI_2 (1/2)	THF/Et_2O	0	22	57	+35.0[d]	61[e] (*S*)
8[f]	**1a** PhMeCHMgCl/$ZnCl_2$ (1/2)	THF/Et_2O	0	22	88	−31.7[g]	60[h] (*S*)

a) Yields based on vinyl bromide were determined by GLC analysis using an internal standard. Isolated yields were usually over 70%. b) (*R*)-3-Phenyl-1-butene (**2a**) has $[\alpha]^{22}_D$ −5.91±0.04° (neat), d^{22}_4 0.8809 (Ref. 2). c) (*R*)-3-*p*-Tolyl-1-butene (**2b**) has $[\alpha]^{22}_D$ −8.15° (neat), d^{22}_4 0.885 (Ref. 8). d) $[\alpha]^{20}_D$ (*c* 6, benzene). e) The olefin **2c** was oxidized into the known (*R*)-(−)-2-phenylbutyric acid; $[\alpha]^{21}_D$ −60.0° (*c* 3, benzene) (Ref. 9). f) Reaction with (*E*)-*β*-bromostyrene. g) $[\alpha]^{20}_D$ (*c* 3, benzene). h) (*R*)-(*E*)-1,3-Diphenyl-1-butene has $[\alpha]^{20}_D$ +52.9° (*c* 3, benzene) (Ref. 2).

2). The reagent **1a** from 1-phenylethyl bromide and zinc metal also gave (*S*)-**2a** of 86% ee, though the reaction was slower (entry 3). The stereoselectivity attained here is the highest for the asymmetric cross-coupling. The olefin **2a** of lower enantiomeric purity was obtained in a similar reaction of 1-phenylethylmagnesium chloride or organoaluminium reagent prepared *in situ* from the Grignard reagent and aluminium chloride (entries 4 and 5). The palladium complex $PdCl_2$[(*R*)-(*S*)-PPFA] also catalyzed effectively the reaction of other zinc reagents, (*S*)-3-*p*-tolyl-1-butene (**2b**) (86% ee) and (*S*)-3-phenyl-1-pentene (**2c**) (61% ee) being produced from the corresponding *in situ* organozinc reagents **1b** and **1c** (entries 6 and 7).

Experimental

Asymmetric Cross-coupling. The results are summarized in Table 1. The following experimental procedure for entry 2 is typical. To a mixture of 31 mg (0.05 mmol) of $PdCl_2$-[(*R*)-(*S*)-PPFA] and 19.2 g (60 mmol) of ZnI_2 were added successively 70 ml of THF, 42 ml (30 mmol) of 0.7 M 1-phenylethylmagnesium chloride in ether (1 M=1 mol dm^{-3}), and 1.07 g (10 mmol) of vinyl bromide under argon at −78 °C. The mixture was stirred at 0 °C for 21 h and hydrolyzed with 10% hydrochloric acid. GLC analysis of the organic layer indicated the formation of quantitative yield of 3-phenyl-1-butene (**2a**). The organic layer and ether extracts from the aqueous layer were combined, washed with saturated $NaHCO_3$ and then 10% $Na_2S_2O_3$, and dried over anhydrous Na_2SO_4. Distillation under reduced pressure (65 °C/20 mmHg) (1 mmHg=133.322 Pa) and purification by preparative GLC (Silicone DC550) gave 1.05 g (80%) of pure **2a**: $[\alpha]^{22}_{D}$ +5.08° (neat).

Oxidation of **2c** into 2-phenylbutyric acid was effected with sodium periodate and potassium permanganate in *t*-butyl alcohol according to a reported procedure.[10]

We thank the Ministry of Education, Science and Culture Japan for the Grant-in-Aid for Scientific Research No. 00547080 serving as a partial financial support for this work.

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