

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

Tamio HAYASHI, Toshiya HAGIHARA, Yoshio KATSURO, and Makoto KUMADA*

Department of Synthetic Chemistry, Faculty of Engineering, Kyoto University, Kyoto 606

(Received July 12, 1982)

Synopsis. Organozinc reagents, prepared from secondary alkyl Grignard reagents (ArRCHMgCl : $\text{Ar}=\text{Ph}$, $p\text{-Tol}$; $\text{R}=\text{Me}$, 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) ($\text{PdCl}_2[(R)-(S)\text{-PPFA}]$)^{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.

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) ($\text{PdCl}_2[(R)-(S)\text{-PPFA}]$)^{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 $\text{PdCl}_2[(R)-(S)\text{-PPFA}]$ catalyst are summarized in Table 1, which also contains data obtained for the reaction of organomagnesium and -aluminum 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

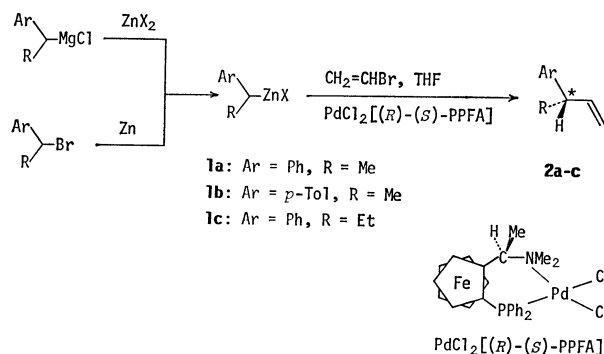


TABLE 1. ASYMMETRIC CROSS-COUPLING OF ORGANOZINC REAGENTS WITH VINYL BROMIDE CATALYZED BY $\text{PdCl}_2[(R)-(S)\text{-PPFA}]$

Entry	Organometallics	Solvent	Reaction condition		Yield ^{a)} %	[α] _D ²⁵ / ^o (neat)	% ee (Confign.)
			Temp/°C	Time/h			
1	1a PhMeCHMgCl/ZnCl_2 (1/2)	THF/ Et_2O	0	40	>95	+5.05	85 ^{b)} (<i>S</i>)
2	1a PhMeCHMgCl/ZnI_2 (1/2)	THF/ Et_2O	0	21	>95	+5.08	86 ^{b)} (<i>S</i>)
3	1a PhMeCHZnBr	THF	10	70	51	+5.10	86 ^{b)} (<i>S</i>)
4	PhMeCHMgCl	Et_2O	0	21	>95	+3.86	65 ^{b)} (<i>S</i>)
5	PhMeCHMgCl/AlCl_3 (1/2)	Et_2O	5	22	>95	+2.52	43 ^{b)} (<i>S</i>)
6	1b $p\text{-TolMeCHMgCl/ZnI}_2$ (1/2)	THF/ Et_2O	0	44	>95	+6.97	86 ^{c)} (<i>S</i>)
7	1c PhEtCHMgCl/ZnI_2 (1/2)	THF/ Et_2O	0	22	57	+35.0 ^{d)}	61 ^{e)} (<i>S</i>)
8 ^{f)}	1a PhMeCHMgCl/ZnCl_2 (1/2)	THF/ Et_2O	0	22	88	−31.7 ^{g)}	60 ^{h)} (<i>S</i>)

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 [α]_D²⁵ −5.91±0.04° (neat), d_4^{25} 0.8809 (Ref. 2). c) (*R*)-3-*p*-Tolyl-1-butene (**2b**) has [α]_D²⁵ −8.15° (neat), d_4^{25} 0.885 (Ref. 8). d) [α]_D²⁵ (*c* 6, benzene). e) The olefin **2c** was oxidized into the known (*R*)-(-)-2-phenylbutyric acid; [α]_D²⁵ −60.0° (*c* 3, benzene) (Ref. 9). f) Reaction with (*E*)- β -bromostyrene. g) [α]_D²⁵ (*c* 3, benzene). h) (*R*)-(*E*)-1,3-Diphenyl-1-butene has [α]_D²⁵ +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 $\text{PdCl}_2[(R)-(S)\text{-PPFA}]$ 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 $\text{PdCl}_2[(R)-(S)\text{-PPFA}]$ 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% $\text{Na}_2\text{S}_2\text{O}_3$, 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**: $[\alpha]_D^{25} + 5.08^\circ$ (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.

References

- 1) Reviews: a) H. B. Kagan and J. C. Fiaud, *Top. Stereochem.*, **10**, 175 (1978); b) B. Bosnich and M. D. Fryzuk, *ibid.*, **12**, 119 (1981).
- 2) a) T. Hayashi, M. Konishi, M. Fukushima, T. Mise, M. Kagotani, M. Tajika, and M. Kumada, *J. Am. Chem. Soc.*, **104**, 180 (1982); b) T. Hayashi, M. Tajika, K. Tamao, and M. Kumada, *ibid.*, **98**, 3718 (1976).
- 3) T. Hayashi, M. Fukushima, M. Konishi, and M. Kumada, *Tetrahedron Lett.*, **21**, 79 (1980).
- 4) H. Brunner and M. Pröbster, *J. Organomet. Chem.*, **209**, C1 (1981).
- 5) a) G. Consiglio and C. Botteghi, *Helv. Chim. Acta*, **56**, 460 (1973); b) Y. Kiso, K. Tamao, N. Miyake, K. Yamamoto, and M. Kumada, *Tetrahedron Lett.*, **1974**, 3.
- 6) T. Hayashi, K. Tamao, Y. Katsuro, I. Nakae, and M. Kumada, *Tetrahedron Lett.*, **21**, 1871 (1980).
- 7) E. Negishi, A. O. King, and N. Okukado, *J. Org. Chem.*, **42**, 1821 (1977).
- 8) K. Tamao, T. Hayashi, H. Matsumoto, H. Yamamoto, and M. Kumada, *Tetrahedron Lett.*, **1979**, 2155.
- 9) R. Weidmann and A. Horeau, *Bull. Soc. Chim. Fr.*, **1967**, 117.
- 10) L. F. Fieser and M. Fieser, "Reagents for Organic Synthesis," Wiley, New York (1967), p. 810.