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ASYMMETRIC COUPLING OF ARYLMAGNESIUM BROMIDES WITH ALLYLIC ESTERS

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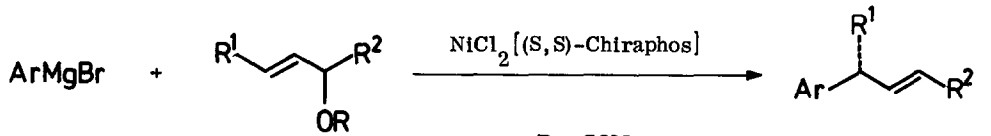
Arylmagnesium bromides were allowed to react with 3-penten-2-yl (or 2-buten-1-yl) acetate (pivaloate, carbonate or methyl ether) in the presence of $NiCl_2$[(S,S)-Chiraphos] catalyst to afford (R)-4-aryl-2-pentene (or 3-aryl-1-butene) in high chemical and optical yields.

In view of anti-inflammatory activity of 2-arylpropanoic acids,[1] efficient synthesis of this class of compounds, particularly optically active ones, has grown problematic, as one enantiomer often exhibits remarkable therapeutic activity.[2] Thus, asymmetric synthesis of 2-arylpropanoic acids became a target of synthetic methodology. Among various approaches,[3,4] asymmetric coupling reaction of aryl moiety with C_3 unit seemed to us most practical with respect to accessibility of starting materials. We report arylmagnesium bromides (1) are alkylated with allylic esters under high asymmetric induction in the presence of $NiCl_2$[(-)-(2S,3S)-2,3-bis(diphenylphosphino)butane], abbreviated as $NiCl_2$[(S,S)-Chiraphos], to afford (R)-3-aryl-1-butene derivatives (6 - 8) which are readily transformed to (S)-2-arylpropanoic acids by oxidative C=C bond cleavage.

In order to reduce the regioselectivity problem, we first employed 3-penten-2-yl acetate (2p), pivaloate (2q), carbonate (2r), and methyl ether (2s) for the reaction with 6-methoxy-2-naphthylmagnesium bromide (1a). Of the esters, the pivaloate 2q generally gave yields 49-67% with 51-67% ee as summarized in Table 1. The acetate 2p and carbonate 2r were less effective. Reduction of the amount of the nickel catalyst from 5 mol% to 1 mol% or addition of magnesium iodide (1 mol%) did not appreciably affect the optical yields of the product (entry 3 vs entry 4; entry 4 vs entry 5). Salt effect



1a: Ar = 6-MeO-2-$C_{10}H_6$ **2:** $R^1 = R^2 = Me$ **p:** R = COMe **6:** $R^1 = R^2 = Me$

1b: Ar = C_6H_5 **3:** $R^1 = Me$, $R^2 = H$ **q:** R = COtBu **7:** $R^1 = Me$, $R^2 = H$

1c: Ar = 4-MeO-C_6H_4- **4:** $R^1 = H$, $R^2 = Me$ **r:** R = COOMe **8:** $R^1 = H$, $R^2 = Me$

s: R = Me

Table 1 Asymmetric Coupling of ArMgBr (1) with Allylic Esters[a]

Entry	ArMgBr	Allylic Esters	Catalyst (mol%)	Solvent	Product (% Yield)[b]	% ee of 6 or 7[c]
1	1a	2p	5	THF	6a (47)	68
2	1a	2p	5	$(MeO)_2CH_2$	6a (24)	60
3	1a	2q	5	THF	6a (49)	67
4	1a	2q	1	THF	6a (59)	56
5	1a	2q	1[d]	THF	6a (65)	51
6	1a	2q	1	THF[e]	6a (67)	64
7	1a	2r	1	THF	6a (24)	41
8	1a	2s	1	THF	6a (52)	58
9	1a	3p	1	THF	7a (16), 8a (11)	--[g]
10	1a	3q	1	THF	7a (47), 8a (28)	83
11	1a	3q	1	THF[f]	7a (50), 8a (25)	89
12	1a	3q	1	Et_2O	7a (48), 8a (24)	89
13	1a	3q	1	$(MeO)_2CH_2$	7a (48), 8a (33)	88
14	1a	4p	1	THF	7a (18), 8a (10)	--[g]
15	1a	4q	1	THF	7a (38), 8a (20)	85
16	1a	4q	1	$(MeO)_2CH_2$	7a (27), 8a (22)	81
17	1a	4q	1	$(MeOCH_2)_2$	7a (10), 8a (14)	76
18	1a	2r	1	THF	6a (24)	41
19	1a	2s	1	THF	6a (52)	58
20	1a	3r	1	THF	7a (28), 8a (23)	64
21	1a	4s	1	THF	7a (41), 8a (26)	67
22	1b	2s	1	THF	6b (47)	47
23	1c	2s	1	THF	6c (55)	30
24	1c	2q	1	THF	6c (40)	68

a) All the reaction was carried out under an argon atmosphere at 0 °C to room temperature for the period of 17 to 20 h unless otherwise stated. The catalyst employed was $NiCl_2$[(S,S)-Chiraphos]. b) All the yields are based on the aryl bromide, precursor of ArMgBr (1). The product ratio was estimated by ^1H NMR. c) Always (R)-configuration. The asymmetric induction was estimated by oxidation of 6 or 7 with $NaIO_4$-$KMnO_4$ to give 2-arylpropanoic acids (ca 60% yields) which were further transformed to the methyl esters with diazomethane. ^1H NMR assay with $Eu(TFC)_3$ (0.3 eq) under clear separation of the ester Me of enantiomers allowed us to estimate % ee.
d) Magnesium iodide (1 mol%) was added. e) The reaction was carried out at -15 °C for 16 h.
f) The reaction was carried out at 0 °C for 17 h. g) Not determined.

with MgI_2 (100 mol%), CuI (1 mol%), or ZnI_2 (1 mol%) turned out completely fruitless. Palladium catalyst, $PdCl_2$[(S,S)-Chiraphos], was totally ineffective for the C-C bond formation.

An experimental procedure for entry 6 is typical: To a mixture of $NiCl_2$[(S,S)-Chiraphos] (5.3 mg, 0.01 mmol), tetrahydrofuran (THF, 1 ml), and 2q (0.204 g, 1.20 mmol) was added the Grignard reagent 1a (0.5 M THF solution, 2.0 ml, 1.00 mmol) at -15 °C drop by drop over a period of 1 h under an argon atmosphere, and the resulting mixture was stirred at -15 °C for 16 h before quenching with saturated ammonium chloride aqueous solution (ca 5 ml). Workup and preparative TLC gave a 4.3 : 1 mixture (0.187 g) of 6a (67% yield) and 2-methoxynaphthalene. These were not separated at this stage and used for the next oxidation. The olefinic configuration of 6a was assigned as (E) by isolation (preparative GLC) followed by IR measurement (965 cm^{-1}). The (Z) isomer was not detected by GLC assay. The product mixture (0.187 g) dissolved in t-butyl alcohol (35 ml) and water (18 ml) along with K_2CO_3 (46 mg) was oxidized with $NaIO_4$ (0.72 g), $KMnO_4$ (25 mg), amd K_2CO_3 (46 mg) dissolved in water (50 ml) (0 °C, 0.5 h). Workup followed by preparative TLC gave (S)-2-(6-methoxy-2-naphthyl)propanoic acid (96 mg, 62% yield), $[\alpha]_D^{20}$ +30.2° (c 0.96, $CHCl_3$); max value: +66°.[2] The optical purity of the acid was estimated to be 64% ee by ^1H NMR study of its methyl ester with $Eu(TFC)_3$ (0.3 mol equiv) in CCl_4.

We next applied the coupling reaction to 2-buten-1-yl and 3-buten-2-yl esters (3 and 4 respectively). The results summarized in Table 1 clearly show the branched product 7a is produced generally in preference to the linear one 8a with the ratio of 1.5 - 2 to 1. Regarding to the chemical yields of 7a, 2-buten-1-yl esters 3 gave better yields than 4. The optical yields were, however, more than 80% for both the substrates. Particularly, 89% ee of 7a was noted for 3q. For this asymmetric coupling reaction, ether solvents such as THF, ether, and dimethoxymethane were equally effective (entries 11 - 13). The configuration of the C=C in 8a was found to be (E) (IR 962 cm^{-1}).

Grignard reagents other than 1a were applied to the coupling reaction. Phenylmagnesium bromide (1b) gave the expected coupling product 6b only by the reaction with 2s. Esters 2p-r afforded no trace of 6b possibly due to rapid nucleophilic attack of 1b at the carbonyl carbons of the esters. 4-Methoxyphenylmagnesium bromide (1c) showed moderate reactivity and gave 6c by the reaction with 2q or 2s.

The asymmetric coupling reaction will reasonably be ascribed to intermediacy of $Ni(R^1CHCHCHR^2)$(Ar)[(S,S)-Chiraphos], which undergoes reductive elimination to give the coupling products as well as "Ni(0)" catalyst species.[4a,4b,5] Actually, $Ni(PPh_3)_4$/(S,S)-Chiraphos also was found to be an effective catalyst system for the reaction.[6,7]

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