Pergamon

Tetrahedron Letters, Vol. 37, No. 18, pp. 3161-3164, 1996

0040-4039/96 $15.00 + 0.00

S0040-4039(96)00517-5

Enantioposition-Selective Alkynylation of Biaryl Ditriflates by Palladium-Catalyzed Asymmetric Cross-Coupling

Takashi Kamikawa, Yasuhiro Uozumi, and Tamio Hayashi*

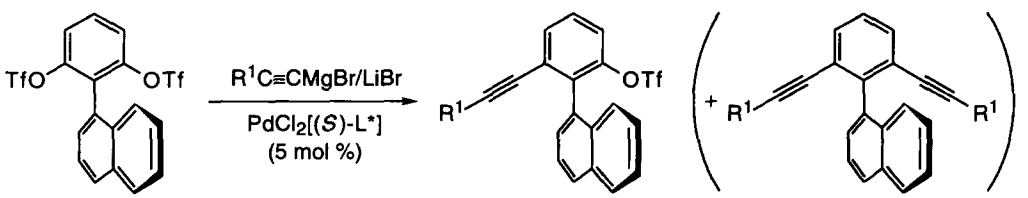
Department of Chemistry, Faculty of Science, Kyoto University, Sakyo, Kyoto 606-01, Japan

Abstract: Asymmetric cross-coupling of prochiral biaryl ditriflate, 1-[2,6-bis[[(trifluoromethyl)sulfonyl]oxy]phenyl]naphthalene (**1**) or 1,3-bis[[(trifluoromethyl)sulfonyl]oxy]-2-(biphenyl-2-yl)benzene (**4**) with triphenylsilylethynylmagnesium bromide in the presence of lithium bromide and 5 mol % of palladium catalyst, $PdCl_2$[(*S*)-Alaphos], proceeded with high enantioposition selectivity to give high yields of the corresponding axially chiral monoalkynylated biaryls, **2a** or **2d**, of high enantiomeric purity (up to >99% ee).

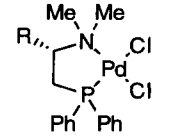
We have previously reported[1] a new type of catalytic asymmetric synthesis of axially chiral biarys which is realized by enantioposition-selective monoarylation of achiral ditriflates with aryl Grignard reagents in the presence of palladium catalyst coordinated with a chiral β-aminoalkylphosphine ligand. Biaryl molecules of high enantiomeric purities were conveniently obtained by a kinetic resolution of monoarylation product at the second arylation step forming bisarylation product, though the enantioselectivity in the monoarylation step is not higher than 85%. Here we wish to report that alkynyl groups can be introduced with higher enantioposition-selectivity by use of alkynyl Grignard reagents.

For the asymmetric monosubstitution of enantiotopic ditriflates in 1-[2,6-bis[[(trifluoromethyl)sulfonyl]-oxy]phenyl]naphthalene (**1**)[2] with an alkynyl group, several reaction conditions were examined. Attempts with Sonogashira method[3] were not successful. The highest enantioselectivity was merely 20%, which was obtained with 1-heptyne, cuprous iodide, diisopropylamine, and 5 mol % of $PdCl_2$[(*S*)-Phephos][4] in THF at 40 °C. It was found that the substitution with alkynyl Grignard reagents proceeds[5] with much higher enantioselectivity

Scheme 1

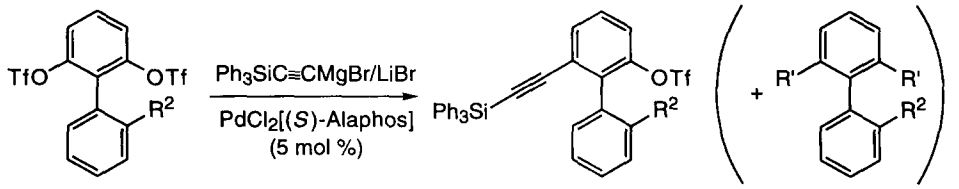


1 **2a**: $R^1 = Ph_3Si$ **3a-c**
2b: R^1 = Ph
2c: $R^1 = n\text{-}C_5H_{11}$



R = CH_3: $PdCl_2$[(*S*)-Alaphos]
R = $PhCH_2$: $PdCl_2$[(*S*)-Phephos]
R = $(CH_3)_2CH$: $PdCl_2$[(*S*)-Valphos]
R = $(CH_3)_3C$: $PdCl_2$[(*S*)-*t*-Leuphos]

Scheme 1 (continued)



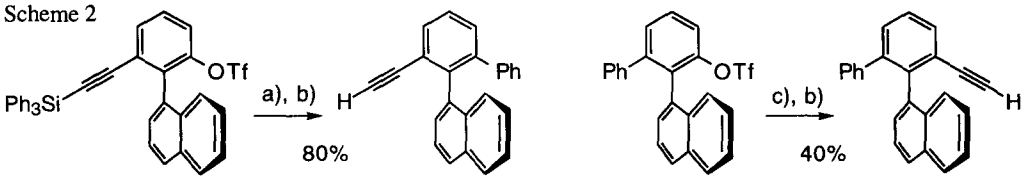
4: R^2 = Ph
5: R^2 = Me

2d: R^2 = Ph
2e: R^2 = Me

3d,e

(Scheme 1). Thus, the reaction of **1** with 2.1 equiv of triphenylsilylethynylmagnesium bromide,[6] which was generated from triphenylsilylethyne and ethylmagnesium bromide, in the presence of 1.0 equiv of lithium bromide[7] and 5 mol % of $PdCl_2$[(*S*)-Alaphos][4] in ether/toluene at 20 °C for 6 h gave 88% yield of axially chiral monoalkynylated biaryl **2a** ($[\alpha]_D^{20}$ –80.3 (*c* 1.0, chloroform)) and 10% yield of dialkynylated biaryl **3a** (entry 2 in Table 1). Removal of triphenylsilyl group in **2a** with TBAF followed by alkaline hydrolysis of triflate with aq NaOH in methanol gave 1-(2-ethynyl-6-hydroxyphenyl)naphthalene, whose enantiomeric purity was determined to be 92% ee by HPLC analysis with chiral stationary phase column, Sumichiral OA-4700 (hexane/1,2-dichloroethane/ethanol = 250/20/1). The absolute configuration of (–)-**2a** was assigned to be (*S*) by comparison of the optical rotation value of 1-(3-ethynylbiphenyl-2-yl)naphthalene (**6**) obtained by palladium-catalyzed phenylation of the remained triflate on **2a** with that obtained by palladium-catalyzed ethynylation of (*S*)-**7**[1] (Scheme 2).[8]

Scheme 2



(*S*)-(–)-**2a** (*S*)-(+)-**6** (*S*)-(–)-**7** (*R*)-(–)-**6**

a) PhMgBr, LiBr, $PdCl_2[Ph_2P(CH_2)_2NMe_2]$ (5 mol %). b) Bu_4NF. c) $Ph_3SiC{\equiv}CH$, CuI, $PdCl_2(PPh_3)_2$ (5 mol %).

A little lower enantioselectivity was observed in the reaction with Phephos[4] and Valphos[4] ligand, which gave **2a** of 82% ee and 86% ee, respectively (entries 5 and 7). The palladium catalyst coordinated with *t*-Leuphos,[4] which is one of the most effective ligands for the nickel-catalyzed asymmetric cross-coupling of 1-phenylethylmagnesium chloride, was much less catalytically active and less enantioselective for the present enantioposition-selective alkynylation (entry 8).

Higher enantiomeric purity of monoalkynylation product **2a** in the reaction forming higher yield of bisalkynylation product **3a** was observed in the asymmetric alkynylation of **1** (entries 1-6). Enantiomerically pure **2a** was obtained in the reaction carried out with $PdCl_2$[(*S*)-Alaphos] catalyst for a prolonged reaction time, where 43% yield of **3a** was formed together with 53% yield of **2a** (entry 4). The higher enantiomeric purity of **2a** at the higher conversion to **3a** can be accounted for by a kinetic resolution at the second cross-coupling forming **3a**. Thus, the minor enantiomer, that is (*R*)-**2a**, formed at the first asymmetric alkynylation is consumed preferentially at the second asymmetric alkynylation, which causes an increase of enantiomeric purity of (*S*)-**2a** as the amount of bisalkynylation product **3a** increases. The kinetic resolution was confirmed by the

Table 1. Asymmetric Cross-Coupling of Ditriflates with Alkynyl Grignard Reagents[a]

entry	ditriflate	Grignard reagent	catalyst	reaction time (h)	recovered ditriflate (%)[b]	yield of **2** (%)[b]	yield of **3** (%)[b]	% ee of **2**[c]
1	**1**	$Ph_3SiC{\equiv}CMgBr$	$PdCl_2$[(*S*)-Alaphos]	4	4 (**1**)	91 (**2a**)	0 (**3a**)	88 (*S*)
2	**1**	$Ph_3SiC{\equiv}CMgBr$	$PdCl_2$[(*S*)-Alaphos]	6	0 (**1**)	88 (**2a**)	10 (**3a**)	92 (*S*)
3[d]	**1**	$Ph_3SiC{\equiv}CMgBr$	$PdCl_2$[(*S*)-Alaphos]	10	0 (**1**)	83 (**2a**)	13 (**3a**)	92 (*S*)
4	**1**	$Ph_3SiC{\equiv}CMgBr$	$PdCl_2$[(*S*)-Alaphos]	17	0 (**1**)	53 (**2a**)	43 (**3a**)	>99 (*S*)
5	**1**	$Ph_3SiC{\equiv}CMgBr$	$PdCl_2$[(*S*)-Phephos]	4	7 (**1**)	89 (**2a**)	0 (**3a**)	82 (*S*)
6	**1**	$Ph_3SiC{\equiv}CMgBr$	$PdCl_2$[(*S*)-Phephos]	17	0 (**1**)	60 (**2a**)	38 (**3a**)	92 (*S*)
7	**1**	$Ph_3SiC{\equiv}CMgBr$	$PdCl_2$[(*S*)-Valphos]	17	0 (**1**)	86 (**2a**)	7 (**3a**)	86 (*S*)
8	**1**	$Ph_3SiC{\equiv}CMgBr$	$PdCl_2$[(*S*)-*t*-Leuphos]	17	48 (**1**)	54 (**2a**)	0 (**3a**)	4 (*S*)
9	**1**	$PhC{\equiv}CMgBr$	$PdCl_2$[(*S*)-Alaphos]	20	0 (**1**)	84 (**2b**)	2 (**3b**)	86
10[e]	**1**	$PhC{\equiv}CMgBr$	$PdCl_2$[(*S*)-Alaphos]	70	11 (**1**)	83 (**2b**)	0 (**3b**)	87
11[e]	**1**	$PhC{\equiv}CMgBr$	$PdCl_2$[(*S*)-Valphos]	120	3 (**1**)	79 (**2b**)	0 (**3b**)	85
12	**1**	$n\text{-}C_5H_{11}C{\equiv}CMgBr$	$PdCl_2$[(*S*)-Valphos]	70	0 (**1**)	79 (**2c**)	15 (**3c**)	64
13	**4**	$Ph_3SiC{\equiv}CMgBr$	$PdCl_2$[(*S*)-Alaphos]	24	31 (**4**)	60 (**2d**)	0 (**3d**)	96
14	**4**	$Ph_3SiC{\equiv}CMgBr$	$PdCl_2$[(*S*)-Alaphos]	48	0 (**4**)	88 (**2d**)	4 (**3d**)	99
15	**5**	$Ph_3SiC{\equiv}CMgBr$	$PdCl_2$[(*S*)-Alaphos]	10	3 (**5**)	87 (**2e**)	4 (**3e**)	85

[a] The cross-coupling was carried out with 2.1 equiv of the Grignard reagent in ether/toluene (1/1) in the presence of 1.0 equiv of LiBr and 5 mol % palladium catalyst at 20 °C. [b] Isolated yield by silica gel chromatography. [c] Determined by HPLC analysis of phenols obtained by desilylation of **2** followed by alkaline hydrolysis (see text): For entries 1-12, Sumichiral OA-4700 (hexane/1,2-dichloroethane/ethanol = 250/20/1); for entries 13-14, Chiralcel OD-H (hexane/2-propanol = 95/5); for entry 15, Chiralcel OB-H (hexane/2-propanol = 95/5). **2a** in entry 1; $[\alpha]_D^{20}$ –80.3 (*c* 1.0, chloroform). **2a** in entry 5; $[\alpha]_D^{20}$ –90.0 (*c* 1.1, chloroform). **2b** in entry 10; $[\alpha]_D^{20}$ –202 (*c* 1.0, chloroform). **2d** in entry 14; $[\alpha]_D^{20}$ –77.0 (*c* 1.1, chloroform). **2e** in entry 15; $[\alpha]_D^{20}$ –23.5 (*c* 1.4, chloroform). [d] Reaction with 2 mol % of catalyst. [e] Reaction at 0 °C.

asymmetric alkynylation of racemic **2a** under similar reaction conditions. At 21% conversion to bisalkynylation product **3a**, the recovered **2a** was an (*S*)-isomer with 14% ee, indicating that the (*R*)-**2a** undergoes the second alkynylation about 3 times faster than (*S*)-**2a** ($k_{(R)}/k_{(S)}$ = 3/1).

Asymmetric substitution of ditriflate **1** with phenylethynyl group also proceeded with high enantioselectivity (entries 9-11). Monoalkynylation product **2b** of 87% ee was obtained under the conditions where bisalkynylation product was not formed. The enantioselectivity was much lower in the reaction with 1-heptynylmagnesium bromide, which gave monoalkynylation product **2c** of 64% ee (entry 10). It is interesting that the enantioselectivity is strongly dependent on the substituent on the ethynyl Grignard reagents. If the stereochemistry in the present asymmetric substitution were determined at attack of a chiral palladium(0) species on one of the enantiotopic triflate groups on aryl ditriflate **1**, the total stereochemical outcome would be all the same irrespective of the Grignard reagents used.

The asymmetric substitution with an alkynyl group was also successful for 1,3-bis[[(trifluoromethyl)-sulfonyl]oxy]-2-(biphenyl-2-yl)benzene (**4**)[2] and its 2-methylphenyl analog **5**[2] (entries 13-15). The highest enantioselectivity was observed in the reaction of **4** with triphenylsilylethynylmagnesium bromide catalyzed by

$PdCl_2$[(*S*)-Alaphos]. Monoalkynylation product **2d** of 96% ee was formed in the reaction where the formation of bisalkynylation product **3d** was not observed (entry 13), indicating that the enantioposition-selectivity at the first alkynylation step is 96%. In the reaction which is accompanied by a small amount (4%) of **3d**, the enantiomeric purity of **2d** was significantly increased by the kinetic resolution at the second alkynylation to give **2d** of 99% ee in 88% yield (entry 14).

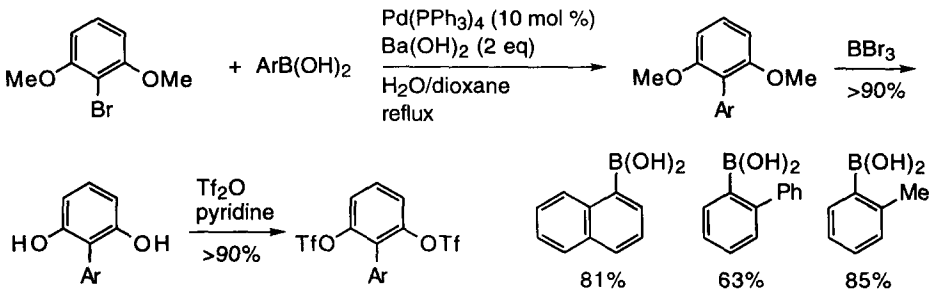
Acknowledgment:

We thank the Ministry of Education, Science, Sports and Culture, Japan, for a Grant-in-Aid for Scientific Research, for partial financial support of this work.

References and Notes:

1 Hayashi, T.; Niizuma, S.; Kamikawa, T.; Suzuki, N.; Uozumi, Y. *J. Am. Chem. Soc.* **1995**, *117*, 9101.

2 The starting ditriflates **1**, **4**, and **5** were prepared by Suzuki coupling of 2,6-dimethoxyphenyl bromide with aryl boronic acids follwed by conversion of the methoxy groups into triflate groups.



3 (a) Tsuji, J. *Palladium Reagents and Catalysts;* Wiley: New York, 1995. (b) Heck, R. F. *Palladium Reagents in Organic Syntheses*; Academic Press: New York, 1985. (c) Sonogashira, K.; Tohda, Y.; Hagihara, N. *Tetrahedron Lett.* **1975**, 4467. (d) Weir, J. R.; Patel, B. A.; Heck, R. F. *J. Org. Chem.* **1980**, *45*, 4926.

4 (a) Hayashi, T.; Konishi, M.; Fukushima, M.; Kanehira, K.; Hioki, T.; Kumada, M. *J. Org. Chem.* **1983**, *48*, 2195. (b) Hayashi, T.; Fukushima, M.; Konishi, M.; Kumada, M. *Tetrahedron Lett.* **1980**, *21*, 79.

5 To our best knowledge, this is the first example for the palladium-catalyzed cross-coupling of aryl triflates with alkynyl Grignard reagents.

6 Other silylethynyl Grignard reagents such as $Me_3SiC{\equiv}CMgBr$, $PhMe_2SiC{\equiv}CMgBr$, and $Et_3SiC{\equiv}CMgBr$ can not be used because of their insolubility in the reaction solvent (ether/toluene = 1/1).

7 In the absence of lithium bromide, the present cross-coupling reaction is very slow. For the effects of lithium bromide, see ref 1.

8 The specific rotations of 1-(3-ethynylbiphenyl-2-yl)naphthalene (**6**) derived from (–)-**2a** (92% ee) and (*S*)-**7** (>99% ee) are $[\alpha]_D^{20}$ +88 (*c* 0.9, chloroform) and $[\alpha]_D^{20}$ –104 (*c* 0.2, chloroform), respectively.

(*Received in Japan* 19 *February* 1996; *revised* 8 *March* 1996; *accepted* 15 *March* 1996)