Pergamon

Tetrahedron Letters 39 (1998) 1773–1776

TETRAHEDRON LETTERS

Synthesis and Evaluation of a New Chiral Ligand: 2-diphenylarsino-2'-diphenylphosphino-1,1'-binaphthyl (BINAPAs)

Suk Young Cho and Masakatsu Shibasaki*

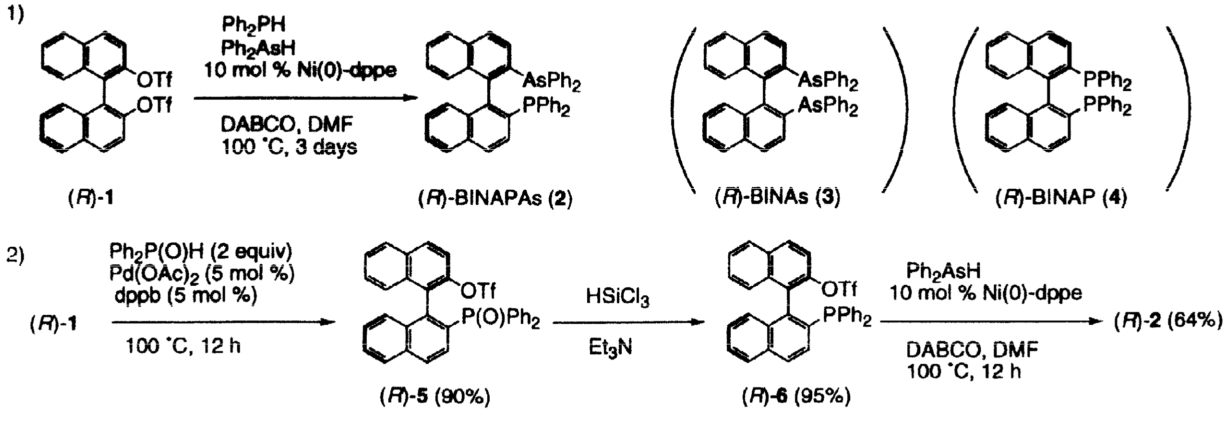
Graduate School of Pharmaceutical Sciences, The University of Tokyo, Hongo, Bunkyo-ku, Tokyo 113, Japan

Received 1 December 1997; accepted 15 December 1997

Abstract : Chiral 2-diphenylarsino-2'-diphenylphosphino-1,1'-binaphthyl (BINAPAs) was synthesized and found to be an effective ligand in an aryl triflate-using asymmetric Heck reaction.

From its modest beginnings in the late 1980s, the asymmetric Heck reaction has developed into a powerful method for the formation of both tertiary and quaternary chiral carbon centers, with enantiomeric excesses typically 80% and in some cases, much higher.[1] The great majority of asymmetric Heck reactions reported to date have utilized the BINAP ligand[2] system, which has proven to be the most effective system in most of the cases in which the performance of different ligands has been assessed. However, in terms of the practical use of asymmetric Heck reactions, there are still several problems, such as low reaction rates and high catalyst loading. Quite recently, we have found that a new chiral arsine ligand, 2,2'-bis(diphenylarsino)-1,1'-binaphthyl (BINAs), is a much more effective ligand in intramolecular asymmetric Heck reactions of alkenyl iodides.[3,4] However, BINAs is a much less satisfactory ligand in intramolecular asymmetric Heck reactions of aryl triflates and/or alkenyl triflates.[3] To overcome this problem, we here report the synthesis and evaluation of a new chiral ligand, 2-diphenylarsino-2'-diphenylphosphino-1,1'-binaphthyl (BINAPAs), and demonstrate that BINAPAs is more effective than BINAP in asymmetric Heck reactions that use aryl triflates.

Scheme 1

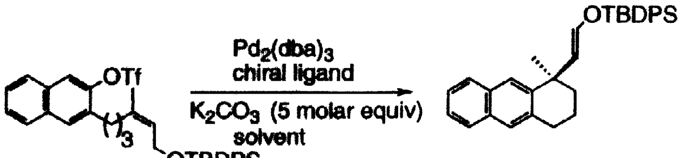


0040-4039/98/$19.00 © 1998 Elsevier Science Ltd. All rights reserved.
PII: S0040-4039(98)00041-0

It was expected that BINAPAs would show a more satisfactory reactivity than BINAs in asymmetric Heck reactions of aryl triflates and/or alkenyl triflates because we had observed earlier that for aryl triflates a phosphine containing ligand was superior to BINAs.[3] Therefore, first an effective synthesis of BINAPAs was attempted. Surprisingly, it was found that treatment of the ditriflate of binaphthol **1** derived from (*R*)-BINOL with 10 mol % bis(1,5-cyclooctadiene)nickel, 11 mol % bis(diphenylphosphino)ethane, diphenylarsine[5] (1 equiv), diphenylphosphine (1 equiv), and 1,4-diazabicyclo[2.2.2]octane (DABCO) (4 molar equiv) in DMF at 100 °C for 3 days provided the desired BINAPAs (**2**) in 30% yield together with a trace amount of BINAP (**3**) and BINAs (**4**).[6] Unfortunately, despite the convenient one-pot preparation and rather good yield of BINAPAs, it was very difficult to achieve perfect purification of BINAPAs and exact reproducibility of the results. Thus, a stepwise synthesis of BINAPAs was next examined. Treatment of **1** with 5 mol % palladium(II) acetate, 5 mol % bis(diphenylphosphino)butane, diphenylphosphite (2 molar equiv), and *N*,*N*-diisopropylethylamine (4 molar equiv) in DMSO at 100 °C for 12 h gave **5** in 90% isolated yield,[7] which underwent reduction on treatment with $HSiCl_3$ (5 molar equiv) and triethylamine (7 molar equiv) in toluene at 100 °C for 12 h[8] to furnish **6** in 90~98% yield. Finally, exposure of **6** to 10 mol % bis(1,5-cyclooctadiene)nickel, 11 mol % bis(diphenylphosphino)ethane, diphenylarsine[5] (1.2 molar equiv), and DABCO (4 molar equiv) in DMF at 100 °C for 12 h[6] afforded BINAPAs (**2**) in 64% isolated yield, $[\alpha]_D^{25}$+145.3 (*c* = 0.28, benzene). The optical purity of the isolated material was >95% ee, as determined by HPLC (DAICEL CHIRALPAK OP(+)) using the dioxide **i**, readily derived from **2**.[9]

With large quantities of optically pure BINAPAs (**2**) in hand, we then evaluated **2** as a chiral ligand in asymmetric Heck reactions of aryl triflates. Toward this end, an intramolecular asymmetric Heck reaction leading to the enantioselective construction of a benzylic quaternary carbon center was first investigated in detail. The aryl triflate **7**, which is known to be best converted to **8** in 87% ee and in 60% yield by treatment with $Pd_2(dba)_3$ (5 mol %), (*R*)-BINAP (20 mol %), and K_2CO_3 (5 molar equiv) in THF at 60 °C for 48 h,[10, 11] was subjected to an asymmetric Heck reaction using $Pd_2(dba)_3$ (5 mol %), (*R*)-BINAPAs (20 mol %), and K_2CO_3 (5 molar equiv) in THF (60 °C, 36 h) to give **8** in 61% ee and in 86% yield.[12] Since the asymmetric Heck reaction using BINAPAs appeared to proceed more speedily than the reaction using BINAP, as a next step solvent effects were carefully examined. We were very pleased to find that, among the solvents examined toluene and 1,2-dichloroethane provided the most exciting results. When an asymmetric Heck

Table 1. Intramolecular Asymmetric Heck Reaction Using BINAPAs and BINAP



7 **8**

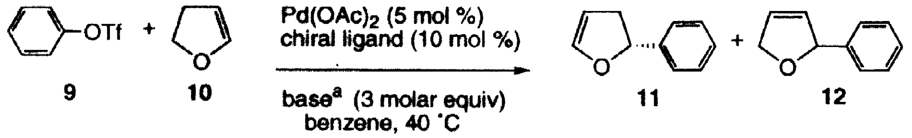
run	chiral ligand	solvent	temp(°C)	time(h)	yield(%)	ee(%)
1[a]	(*R*)-BINAP	THF	60	48	60	87
2[a]	(*R*)-BINAPAs	THF	60	36	86	61
3[a]	(*R*)-BINAP	toluene	60	14	78	87
4[a]	(*R*)-BINAPAs	toluene	60	14	89	86
5[b]	(*R*)-BINAP	toluene	40	46	74	89
6[b]	(*R*)-BINAPAs	toluene	40	46	91	88
7[b]	(*R*)-BINAP	1,2-dichloroethane	60	12	73	82
8[b]	(*R*)-BINAPAs	1,2-dichloroethane	60	12	88	81
9[b]	(*R*)-BINAP	1,2-dichloroethane	40	48	76	88
10[b]	(*R*)-BINAPAs	1,2-dichloroethane	40	48	95	81

a: 5 mol % $Pd_2(dba)_3$, 20 mol % ligand
b:10 mol % $Pd_2(dba)_3$, 30 mol % ligand

reaction of **7** was carried out using $Pd_2(dba)_3$ (5 mol %), (*R*)-BINAPAs (20 mol %) and K_2CO_3 (5 molar equiv) in toluene (60 °C, 14 h), **8** in 86% ee was formed in 89% yield. On the other hand, the reaction using (*R*)-BINAP under identical reaction conditions resulted in the formation of **8** in 87% ee and in 78% yield. A much greater disparity between the reactivities of BINAPAs and BINAP was obtained by carrying out the asymmetric Heck reaction at lower temperature as shown in Table 1 (run 5 and 6). Moreover, BINAPAs also gave a better result than BINAP when 1,2-dichloroethane was used as a solvent. (Table 1, run 7 and 8).

After realizing that BINAPAs was a more effective chiral ligand than BINAP, enhancing the reaction rate in the intramolecular asymmetric Heck reaction of the aryl triflate **7**, we next examined the applicability to an intermolecular asymmetric Heck reaction of aryl triflates. An intermolecular asymmetric Heck reaction of the aryl triflate **9** with 2,3-dihydrofuran (**10**) was reported by Hayashi, Ozawa and coworkers,[13] in which (*R*)-**11** (72%, 67% ee) and (*S*)-**12** (4%, 50% ee) were obtained on treatment with palladium(II) acetate (5 mol %), (*R*)-BINAP (10 mol %) and *N*,*N*-diisopropylethylamine (3 molar equiv) in benzene at 40 °C for 36 h. This transformation was carried out using (*R*)-BINAPAs under otherwise identical reaction conditions, resulting in the formation of (*R*)-**11** (28%, 82% ee) and (*R*)-**12** (48%, 45% ee). It is quite noteworthy that the product ratio was dramatically changed, indicating that the dissociation of the BINAPAs-Pd^+-H complex from a resulting olefinic double bond occurs more readily than that of the BINAP-Pd^+-H complex. This is the reason why (*R*)-2-phenyl-2,5-dihydrofuran (**12**) was formed as a major product. Pfaltz's chiral ligand **13** has also been shown to furnish **12** as a major product.[14] Thus, an asymmetric Heck reaction of aryl triflate **9**, 2,3-dihydrofuran (**10**) and **13** was also carried out under identical reaction conditions. The results are summarized in Table 2.

Table 2. Intermolecular Asymmetric Heck Reaction Using BINAPAs, BINAP, and Phosphinooxazoline ligand



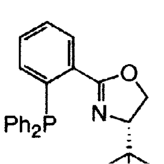
run	chiral ligand	time(h)	yield(%)[b]		ee(%)[c]		
			11	**12**	(*R*)-**11**	(*S*)-**12**	(*R*)-**12**
1	(*R*)-BINAP	36	72	4	67	50	
2	(*R*)-BINAPAs	36	29	48	82		45
3[d]	ligand **13**	36		14			95

Initial condition: **9** / **10** / base / $Pd(OAc)_2$ / chiral ligand =1 / 5 / 3 / 0.05 / 0.1

[a] Base; *N*,*N*-diisopropylethylamine [b] Isolated yield by silica gel column chromatography.

[c] Determined by ^1H NMR analysis using an optically active shift reagent $Eu(hfc)_3$.

[d] $Pd_2(dba)_3$ was used.



13

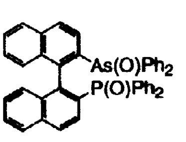
In conclusion, we have succeeded in synthesizing BINAPAs (**2**) for the first time and in evaluating BINAPAs (**2**) as a chiral ligand in an asymmetric Heck reaction of aryl triflates, demonstrating that **2** is a more effective chiral ligand than BINAP. As mentioned in the introductory remarks, we already found that BINAs is a more effective chiral ligand than BINAP in an intramolecular asymmetric Heck reaction of alkenyl iodides.[3] Thus, two chiral ligands, BINAs and BINAPAs, have been shown to have superior reactivity to BINAP in an asymmetric Heck reaction. Further studies are currently under investigation.

Acknowledgment.

We thank the Kyorin Pharmaceutical, Co., LTD. for the toxicity examinations of BINAs, BINAP, and triphenylarsine.

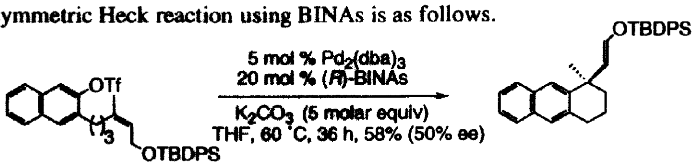
References and Notes

1. (a) Shibasaki, M.; Boden, C. D. J.; Kojima, A. *Tetrahedron* **1997**, 53, 7371. (b) Shibasaki, M.; Sodeoka, M. *J. Synth. Org. Chem. Jpn.* **1994**, 52, 956. (c) Ashimori, A.; Matsuura, T.; Overman, L. E.; Poon, D. J. *J. Org. Chem.* **1993**, 58, 6969. (d) Ozawa, F.; Kubo, A.; Matsumoto, Y.; Hayashi, T.; Nishioka, E.; Yanagi, K.; Moriguchi, K. *Organometallics* **1993**, 12, 4188. (e) Sakamoto, T.; Kondo, Y.; Yamanaka, H. *Tetrahedron Lett.* **1992**, 33, 6845. (f) Tietze, L. F.; Schimpf, R. *Angew. Chem. Int. Ed. Engl.* **1994**, 33, 1089. (g) Sakuraba, S.; Awano, K.; Achiwa, K. *Synlett* **1994**, 291. (h) Moinet, C.; Fiaud, J.-C. *Tetrahedron Lett.* **1995**, 36, 2051.
2. (a) Noyori, R.; Takaya, H. *Acc. Chem. Res.* **1990**, 23, 345. (b) Takaya, T.; Mashima, K.; Koyano, K.; Yagi, M.; Kumobayashi, H.; Taketomi, T.; Akutagawa, S.; Noyori, R. *J. Org. Chem.* **1986**, 51, 629, and references cited therein.
3. Kojima, A.; Boden, C. D. J.; Shibasaki, M. *Tetrahedron Lett.* **1997**, 38, 3459.
4. BINAs, triphenylarsine, BINAP toxicity data: oral; rat; 30 mg/kg; no toxic effect noted; [Kyorin Pharma. Co., LTD.]
5. Mann, F. G.; Pragnell, M. J. *J. Am. Chem. Soc.* **1965**, 4120.
6. Cai, D.; Payack, J. F.; Bender, D. R.; Bender, D. R.; Hughes, D. L.; Verhoeven, T. R.; Reider, P. J. *J. Org. Chem.* **1994**, 59, 7180.
7. Uozumi, Y.; Tanahashi, A.; Lee, S. Y.; Hayashi, T. *J. Org. Chem.* **1993**, 58, 1945.
8. Gilheany, D. G.; Mitchell, C. M. *The Chemistry of Organophosphorus Compounds*; Hartley, F. R., Ed.; John Wiley and Sons: Chichester, 1990; Vol. 1, p151 and references cited therein.
9. (*R*)-BINAPAs (2), mp 230-232 °C; IR (KBr) 3045, 1581, 1480, 1432 cm^{-1}; ^{1}H-NMR (500 MHz, $CDCl_3$): 6.85-6.96(m,4H), 7.03-7.20(m, 20H), 7.32-7.37(m, 2H), 7.44(d, J = 8.54, 1H), 7.44(m, 1H), 7.82(d, J = 8.24, 1H), 7.84(d, J = 8.02, 1H), 7.85(d, J = 7.94, 1H), 7.91(d, J = 8.54, 1H); ^{31}P-NMR -12.32 (s); ^{13}C-NMR (125.65 MHz, $CDCl_3$): 125.8, 126.0, 126.2, 126.6, 127.2, 127.4, 127.7, 127.8, 128.0, 128.1, 128.2, 128.3, 128.4, 130.4, 130.7, 133.0, 133.1, 133.2, 133.3, 133.4, 133.8, 134.0, 134.1, 135.5, 135.6, 137.4, 137.5, 139.0, 140.2, 140.3, 144.0, 145.4, 145.7. Anal. calcd for $C_{44}H_{32}PAs$, C; 79.28, H; 4.84. Found, C; 79.01, H; 4.87. Mass (FAB): 667(M^++1).



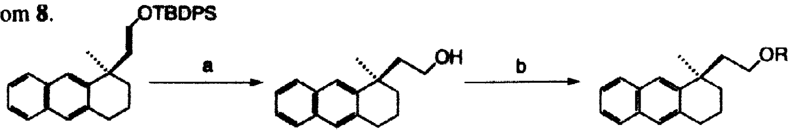
i

10. Kojima, A.; Takemoto, T.; Sodeoka, M.; Shibasaki, M. *J. Org. Chem.* **1996**, 61, 4876.
11. An intramolecular asymmetric Heck reaction using BINAs is as follows.



7 **8**

12. The enantiomeric excess of **8** was determined by DAICEL CHIRALCEL OD (hexane: 2-propanol, 9:1) using **iii** readily derived from **8**.



8 **ii** **iii** R= COC_6H_4*p*-NO_2

Reaction conditions:(a) (1) *n*-Bu_4NF (2 equiv), AcOH (3 molar equiv), THF, 0 °C to rt (2) $NaBH_4$ (5 molar equiv), MeOH, 0 °C to rt (2 steps, 90%);(b) 4-nitrobenzoyl chloride (1.1 equiv), Et_3N, 4-(dimethylamino)pyridine, CH_2Cl_2 , 0 °C to rt (95%)

13. (a) Ozawa, F.; Kubo, A.; Hayashi, T. *J. Am. Chem. Soc.* **1991**, 113, 1417. (b) Ozawa, F.; Hayashi, T. *J. Organomet. Chem.* **1992**, 428, 267. (c) Ozawa, F.; Kubo, A.; Hayashi, T. *Tetrahedron Lett.* **1992**, 33, 1485. (d) Hayashi, T.; Kubo, A.; Ozawa, F. *Pure Appl. Chem.* **1992**, 64, 421. (e) Ozawa, F.; Kubo, A.; Hayashi, T. *Chem. Lett.* **1992**, 2177.
14. Loiseleur, O.; Meier, P.; Pfaltz, A. *Angew. Chem. Int. Ed. Engl.* **1996**, 35, 200. The use of THF as a solvent is reported to give much higher chemical yields.