J. Org. Chem. 1992, 57, 4571-4572

Catalytic Asymmetric Synthesis of Quarternary Carbon Centers. Palladium-Catalyzed Formation of Either Enantiomer of Spirooxindoles and Related Spirocyclics Using a Single Enantiomer of a Chiral Diphosphine Ligand

Atsuyuki Ashimori[1] and Larry E. Overman*

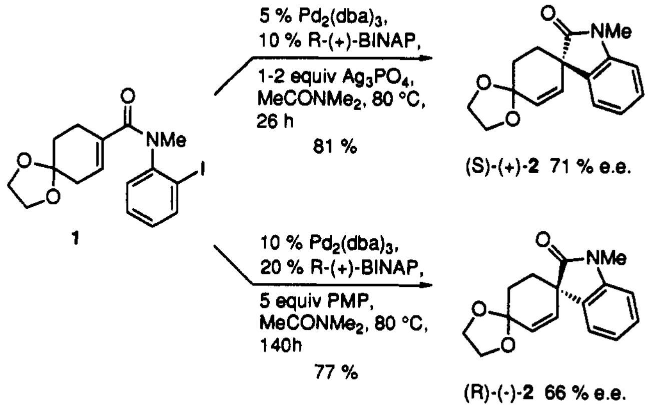
Department of Chemistry, University of California, Irvine, California 92717

Received June 18, 1992

Summary: The asymmetric synthesis of eight spirooxindoles and related spirocyclics from the corresponding aryl iodide by palladium catalyzed cyclizations in the presence of the diphosphine ligand (R)-(+)-BINAP is reported.

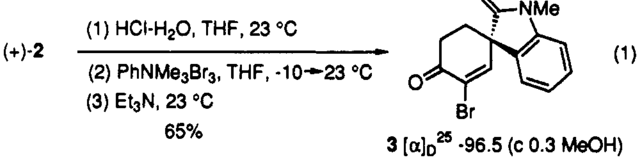
Catalytic asymmetric synthesis using transition-metal complexes is emerging as one of the most powerful methods for the enantioselective preparation of organic compounds.[2] In spite of the significant progress recorded in this area, few excellent methods yet exist for asymmetric carbon–carbon bond formation.[2] Particularly underdeveloped is the asymmetric synthesis of quaternary carbon centers using chiral metal complexes.[2,3] Heck-type arylations and alkenylations of alkenes are a promising class of asymmetric C–C bond-forming reactions.[4–6] Enantioselectivities of ≥80% were reported recently by Shibasaki[4b,d] and Ozawa and Hayashi[4c] for Heck reactions that directly form tertiary carbon centers. In 1989 we reported the first example of creating a quaternary carbon center through an asymmetric Heck reaction, although the enantioselectivity was modest.[5] In this paper, we report that a variety of spirocyclic compounds can be prepared with useful levels of enantioselection by asymmetric Heck cyclizations. We also report the unexpected observation that either enantiomer of the chiral product can often be formed with good selectivity using a *single* enantiomer of a chiral diphosphine ligand.

Scheme I



The synthesis of 3,3-spirooxindole 2 from the acryloyl 2′-iodoanilide 1 was chosen for our initial studies (Scheme I).[7] These investigations examined a variety of chiral phosphine ligands[8] and palladium catalyst precursors and solvents and employed 1–2 equiv of a silver salt[9] to favor a catalytic cycle proceeding via cationic palladium(II) intermediates.[4b,c]

Enantioselectivities were highest, and most reproducible, with a catalyst prepared in polar solvents from (*R*)-BINAP,[10] tris(dibenzylideneacetone)dipalladium, and either Ag_2CO_3, Ag_2O, or Ag_3PO_4. Under optimum conditions, (*S*)-(+)-2 was obtained in 71% enantiomeric excess and a chemical yield of 81% (Scheme I).[11] The absolute configuration of (+)-2 was determined by hydrolysis to the corresponding enone, which could be purified to an ee of 92% by recrystallization and subsequent bromination to afford 3 (eq 1). The α-bromoenone 3 was suitable for X-ray crystallographic analysis.[12]



Cyclization of 1 was much slower in the presence of silver salts of less basic anions (AgO_2CCF_3, AgOAc, $AgNO_3$) and took place with virtually no asymmetric induction. Replacement of the silver salt with K_2CO_3 or Na_3PO_4 resulted in a rapid cyclization, which occurred also with little face selectivity. Remarkably, cyclizations carried out without any added HI scavenger, or in the presence of tertiary amines, proceeded with good enantioselectivity to form the *R* enantiomer of 2. Reactions conducted in the presence of the basic tertiary amine 1,2,2,6,6-pentamethylpiperidine (PMP) occurred slowly at 80 °C and afforded (*R*)-(−)-2 in

---

[1] On leave from the Green Cross Corporation, Osaka, Japan.

[2] For recent reviews, see: (a) Noyori, R.; Takaya, H. *Acc. Chem. Res.* **1990**, *23*, 345. (b) Noyori, R. *Science* **1990**, *248*, 1194. (c) Ojima, I.; Clos, N.; Bastos, C. *Tetrahedron* **1989**, *45*, 6901. (d) Blystone, S. L. *Chem. Rev.* **1989**, *89*, 1663. (e) Brunner, H. *Top. Stereochem.* **1988**, *18*, 129.

[3] Examples include: Brunner, H.; Hammer, B. *Angew. Chem., Int. Ed. Engl.* **1984**, *23*, 312. Hayashi, T.; Kanehira, K.; Hagihara, T.; Kumada, M. *J. Org. Chem.* **1988**, *53*, 113. Ito, Y.; Sawamura, M.; Shirakawa, E.; Hayashizaki, K.; Hayashi, T. *Tetrahedron Lett.* **1988**, *29*, 235.

[4] Formation of trisubstituted carbon centers: (a) Sato, Y.; Sodeoka, M.; Shibasaki, M. *J. Org. Chem.* **1989**, *54*, 4738. (b) Sato, Y.; Sodeoka, M.; Shibasaki, M. *Chem. Lett.* **1990**, 1953. (c) Ozawa, F.; Kubo, A.; Hayashi, T. *J. Am. Chem. Soc.* **1991**, *113*, 1417. (d) Kagechika, K.; Shibasaki, M. *J. Org. Chem.* **1991**, *56*, 4093. (e) Suzuki, T.; Uozumi, Y.; Shibasaki, M. *J. Chem. Soc., Chem. Commun.* **1991**, 1593. (f) Brunner, H.; Kramler, K. *Synthesis* **1991**, 1121. (g) Sato, Y.; Watanabe, S.; Shibasaki, M. *Tetrahedron Lett.* **1992**, *33*, 2589. (h) Sato, Y.; Honda, T.; Shibasaki, M. *Tetrahedron Lett.* **1992**, *33*, 2593.

[5] Formation of quaternary carbon centers: Carpenter, N. E.; Kucera, D. J.; Overman, L. E. *J. Org. Chem.* **1989**, *54*, 5846.

[6] Formation of a quaternary carbon center under the combined influence of a chiral auxiliary and a chiral catalyst: Grigg, R.; Dorrity, M. J. R.; Malone, J. F.; Mongkolaussavaratana, T.; Amilaprasadh Norbert, W. D. J.; Sridharan, V. *Tetrahedron Lett.* **1990**, *31*, 3075.

[7] Abelman, M. M.; Oh, T.; Overman, L. E. *J. Org. Chem.* **1987**, *52*, 4130.

[8] DIOP, PPFA, AMPHOS, and BPPFA were all much inferior to BINAP. A compilation of ligand acronyms can be found in ref 2e.

[9] For initial reports of the beneficial use of silver salts in Heck cyclizations, see: Karabelas, K.; Westerlund, C.; Hallberg, A. *J. Org. Chem.* **1985**, *50*, 3896 and ref 7.

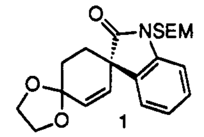
[10] (*R*)-2,2′-Bis(diphenylphosphino)-1,1′-binaphthyl: Takaya, H.; Mashima, K.; Koyano, K.; Yagi, M.; Kumobayashi, H.; Taketomi, T.; Akutagawa, S.; Noyori, R. *J. Org. Chem.* **1986**, *51*, 629.

[11] Enantiomer ratios reported in this paper were determined by ^{1}H-NMR analysis at 500 MHz in the presence of the chiral shift reagents Yb(tfc)$_3$, Eu(hfc)$_3$, or Eu(tfc)$_3$.

[12] (a) Absolute configuration was assigned by the method of Rogers: Rogers, D. *Acta Crystallogr.* **1981**, *A37*, 734. (b) The authors have deposited atomic coordinates for this structure with the Cambridge Crystallographic Data Centre. The coordinates can be obtained, on request, from the Director, Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB2 1EZ, UK.

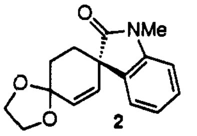
0022-3263/92/1957-4571$03.00/0

Table I. Asymmetric Synthesis of Either Spirocyclic Enantiomer from the Corresponding Aryl Iodide Using (*R*)-(+)-BINAP[a]



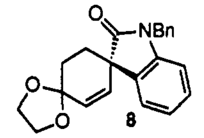
1

Ag - 76%, (S) 65 % e.e.
R$_3$N - 74%, (R) 75 % e.e.



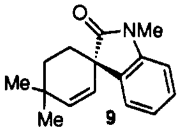
2

Ag - 81%, (S) 71 % e.e.
R$_3$N - 77%, (R) 66 % e.e.



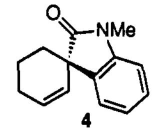
8

Ag - 91%, (S) 41-50 % e.e.[e]
R$_3$N - 66%, (R) 66 % e.e.[e]



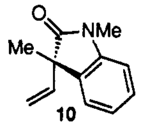
9

Ag - 99%, (+) 72 % e.e.
R$_3$N - 89%, (-) 71 % e.e.



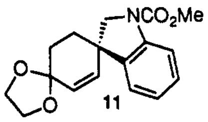
4

Ag - 74%, (S) 79-81 % e.e.[b,e]
R$_3$N - 45%, (R) 89-95 % e.e.[c,e]



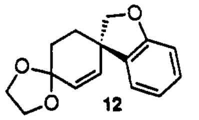
10

Ag - 88%, (-) 63 % e.e.
R$_3$N - 91%, (+) 25 % e.e.



11

Ag - 90%, (+) 64 % e.e.[d]
R$_3$N - 68%, (-) 8 % e.e.



12

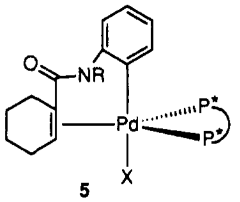
Ag - 91%, (+) 49-55 % e.e.[d,e]
R$_3$N - 66%, (-) 0-7 % e.e.[e]

[a] Reaction conditions: **Ag**–5% Pd$_2$(dba)$_3$, 10% (*R*)-(+)-BINAP, 2 equiv of Ag$_3$PO$_4$, *N*,*N*-dimethylacetamide, 60–80 °C; **R$_3$N**–10% Pd$_2$(dba)$_3$, 20% (*R*)-(+)-BINAP, 5 equiv of 1,2,2,6,6-pentamethylpiperidine, *N*,*N*-dimethylacetamide, 80–100 °C. [b] The $\Delta^{3,4}$ isomer was formed also (8% yield). [c] The $\Delta^{3,4}$ isomer was formed also (44% yield). [d] The solvent was *N*-methyl-2-pyrrolidinone. [e] Enantiomeric purity determined by both ^{1}H NMR[11] and HPLC (CHIRALCEL OD, 9:1 hexane/isopropanol) analysis.

77% yield and 66% ee (Scheme I).[13]

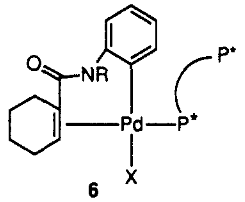
Table I summarizes our preliminary investigations of the scope of this method for the synthesis of optically active spirooxindoles and related spirocyclics (2, 4, 7–12).[14] Yields were typically good, and in all cases the silver- and amine-promoted cyclizations took place with opposite senses of enantioselection. The last two entries in Table I suggest that the scope of the silver-promoted asymmetric cyclization may be broader than the complementary reaction in the presence of amine bases. The excellent enantioselectivities observed for forming 4 likely arise from kinetic resolution in the double-bond migration step, since the cyclohexenyl oxindole 4 was accompanied by varying amounts of the $\Delta^{3,4}$ double-bond regioisomer (Table I).[15] A related scenario leading to enhanced enantioselection in a bimolecular Heck reaction was recently described by Ozawa and Hayashi.[4c]

The enantioselectivities reported here are the highest obtained to date in palladium-catalyzed alkene insertions that form quaternary carbon centers. In cases where the major isomer can be further enriched by crystallization or chromatography, this method provides useful access to spirocyclic products of high enantiomeric purity. The unprecedented observation that either enantiomer of the Heck product can be formed using a single enantiomer of the BINAP ligand has several implications. Foremost, the selectivities observed in cyclizations of acryloyl 2′-iodoanilides accomplished in the presence of tertiary amine bases demonstrate, contrary to recent suggestions,[4b,c] that useful enantioselectivities in asymmetric Heck reactions can be realized in the presence of a halide counter ion. The insertion step of the base-promoted asymmetric reactions most likely proceeds via the pentacoordinate intermediate 5 or a four-coordinate intermediate such as 6 in which the BINAP ligand coordinates through a single phosphorus atom.[17]



5

or



6

Investigations aimed at further optimizing this promising approach for the asymmetric synthesis of quaternary carbon centers are underway.

Acknowledgment. Support of this investigation by PHS Grant GM-30859 and the Green Cross Corporation is gratefully acknowledged. We particularly wish to thank Dr. Joseph Ziller, Director, UCI X-Ray Crystallography Laboratory, for the crystallographic analysis of 3 and Dr. David L. Coffen, Hoffmann-LaRoche, Inc., for a sample of (*R*)-BINAP.

Supplementary Material Available: Representative experimental procedures for the Ag- and R$_3$N-promoted cyclizations and full details of the conversion of (+)-2 → 3 (3 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

---

(13) A detailed study of the effect of HX scavengers on the rate and stereoselection of Heck reactions is underway.

(14) Products in Table I whose configuration was established by direct chemical correlation with 3 are indicated by *R* and *S* descriptors. Products whose assignment of absolute configuration is based solely on analogy are indicated without stereochemical descriptors.

(15) Consistent with this interpretation, the (*R*)-$\Delta^{3,4}$ isomer produced in the PMP-promoted cyclization (44% yield) had a reduced enantiomeric purity of 31%. The $\Delta^{3,4}$ isomer of 4 was correlated with the enone derived from (*R*)-(−)-2 by oxidation with CrO$_3$·2 pyridine.[16]

(16) Dauben, W. G.; Lorber, M.; Fullerton, D. S. *J. Org. Chem.* **1969**, *34*, 3587.

(17) Of these two possibilities, a four-coordinate mechanism would have the strongest experiment precedent, see: Samsel, E. G.; Norton, J. R. *J. Am. Chem. Soc.* **1984**, *106*, 5505.