Intramolecular Enantioselective Palladium-Catalyzed Heck Arylation of Cyclic Enamides

Lena Ripa and Anders Hallberg*

Department of Organic Pharmaceutical Chemistry, Uppsala Biomedical Center, Uppsala University, Box 574, SE-751 23 Uppsala, Sweden

Received September 24, 1996[⊗]

Palladium-catalyzed intramolecular cyclization of *N*-formyl-6-[3-(2-iodophenyl)propyl]-1,2,3,4-tetrahydropyridine (**1a**) and *N*-formyl-6-[2-(2-iodophenyl)ethyl]-1,2,3,4-tetrahydropyridine (**1b**) in the presence of $AsPh_3$ resulted in formation of the spiro compounds *N*-formyl-3,3′,4,4′-tetrahydrospiro[naphthalene-1(2*H*),2′(1′*H*)-pyridine] (**2a**) and *N*-formyl-3′,4′-dihydrospiro[indan-1,2′(1′*H*)-pyridine] (**2b**), respectively, and in the presence of PPh_3 and TlOAc in the spiro compounds *N*-formyl-3,4,5′,6′-tetrahydrospiro[naphthalene-1(2*H*),2′(1′*H*)-pyridine] (**3a**) and *N*-formyl-5′,6′-dihydrospiro[indan-1,2′(1′*H*)-pyridine] (**3b**), respectively. Cyclization of *N*-formyl-6-(3-{2-[(trifluoromethanesulfonyl)-oxy]phenyl}propyl)-1,2,3,4-tetrahydropyridine (**7**) in presence of a chiral (phosphinoaryl)oxazoline ((*S*)-**8**) resulted in formation of (*R*)-**3a** and (*R*)-*N*-formyl-1′,3,4,6′-tetrahydrospiro[naphthalene-1(2*H*),2′(3′*H*)-pyridine] ((*R*)-**6a**) in high enantiomeric excesses, 87% and >99%, respectively, and in good yield. The oxazoline ligand (*S*)-**8** furnished higher enantiomeric excesses and improved regioselectivities than (*R*)-BINAP.

Introduction

The construction of tetrasubstituted carbon centers can be achieved by application of intramolecular Heck reactions.[1] A number of complex natural products have been prepared relying on this strategy.[2] The first examples of enantioselective intramolecular Heck reactions were reported by Shibasaki[3] and Overman.[4] Grigg used enamides as an olefinic counterpart in intramolecular arylation reactions, for the assembly of spiro compounds comprising a nitrogen atom in the new ring formed.[5] Attachment of a chiral auxiliary to the nitrogen atom prior to cyclization allowed highly diastereoselective reactions to occur.[6] We have previously conducted regiocontrolled intermolecular palladium-catalyzed arylations of cyclic enamides,[7] and Ozawa and Hayashi[8] have employed the combination of aryl triflates and (*R*)-BINAP to achieve high asymmetric inductions in asymmetric Heck reactions of cyclic enamides.

Herein we report an intramolecular palladium-catalyzed arylation of cyclic enamides which provides spiro compounds accommodating an α-phenylpiperidine fragment. Rigidified molecules with this fragment constitute scaffolds, which after appropriate functionalizations should provide valuable bioactive molecules useful in the search for new anticonvulsants.[9]

Results

Palladium-catalyzed intramolecular spirocyclization of **1a** and **1b** with triphenylarsine as ligand afforded **2a** and **2b** in 67% and 74% isolated yields, respectively (Scheme 1). Triphenylarsine[10] was more effective than other monodentate ligands tested[11] in promoting the concomitant migration of the double bond. Hydrogenation of **2a** and **2b** occurred smoothly to deliver **4a** and **4b**, with subsequent removal of the formyl group by methyllithium providing the secondary amines **5a** and **5b** in good yields.

Cyclizations in the presence of thallium acetate and triphenylphosphine allowed the double bond migration to be suppressed[5c] and produced less than 2% of the undesired double bond isomers, enabling isolation of **3a** and **3b** in 91% and 84% yields, respectively. Hydrogenation afforded **4a** and **4b**. Use of silver carbonate was equally effective in suppressing double bond isomerization[12] but produced lower yields. Attempts to prepare the other allylic double bond isomer by use of palladium

[⊗] Abstract published in *Advance ACS Abstracts,* January 15, 1997.

(1) For recent reviews see: (a) de Meijere, A.; Meyer, F. E. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 2379−2411. (b) Cabri, W.; Candiani, I. *Acc. Chem. Res.* **1995**, *28*, 2−7. (c) Ojima, I.; Tzamarioudaki, M.; Li, Z.; Donovan, R. J. *Chem. Rev.* **1996**, *96*, 635−662.

(2) See for example: (a) Laschat, S.; Narjes, F.; Overman, L. E. *Tetrahedron* **1994**, *50*, 347−358. (b) Overman, L. E. *Pure Appl. Chem.* **1994**, *66*, 1423−1430. (c) Negishi, E.-i.; Copéret, C.; Ma, S.; Liou, S.-Y.; Liu, F. *Chem. Rev.* **1996**, *96*, 365−393.

(3) Sato, Y.; Sodoeka, M.; Shibasaki, M. *J. Org. Chem.* **1989**, *54*, 4738−4739.

(4) Carpenter, N. E.; Kucera, D. J.; Overman, L. E. *J. Org. Chem.* **1989**, *54*, 5846−5848.

(5) (a) Grigg, R.; Sridharan, V.; Stevenson, P.; Sukirthalingam, S. *Tetrahedron* **1989**, *45*, 3557−3568. (b) Grigg, R.; Sridharan, V.; Stevenson, P.; Sukirthalingam, S.; Worakun, T. *Tetrahedron* **1990**, *46*, 4003−4018. (c) Grigg, R.; Loganathan, V.; Santhakumar, V.; Sridharan, V.; Teasdale, A. *Tetrahedron Lett.* **1991**, *32*, 687−690. Recently the regioselectivity of related intramolecular arylations of enamides to provide polycyclic systems has been studied in some detail. (d) Comins, D. L.; Baevsky, M. F.; Hong, H. *J. Am. Chem. Soc.* **1992**, *114*, 10971−10972. (e) Comins, D. L.; Joseph, S. P.; Zhang, Y.-m. *Tetrahedron Lett.* **1996**, *37*, 793−796. (f) Gibson, S. E., (née Thomas); Middleton, R. J. *J. Chem. Soc., Chem. Commun.* **1995**, 1743−1744. (g) Rigby, J. H.; Hughes, R. C.; Heeg, M. J. *J. Am. Chem. Soc.* **1995**, *117*, 7834−7835. (h) Rigby, J. H.; Mateo, M. E. *Tetrahedron* **1996**, *52*, 10569−10582. See also: (i) Iida, H.; Yuasa, Y.; Kibayashi, C. *J. Org. Chem.* **1980**, *45*, 2938−2942.

(6) Grigg, R.; Dorrity, M. J. R.; Malone, J. F.; Mongkolaussavaratana, T.; Amilaprasadh Norbert, W. D. J.; Sridharan, V. *Tetrahedron Lett.* **1990**, *31*, 3075−3076.

(7) Nilsson, K.; Hallberg, A. *J. Org. Chem.* **1990**, *55*, 2464−2470.

(8) (a) Hayashi, T.; Kubo, A.; Ozawa, F. *Pure Appl. Chem.* **1992**, *64*, 421−427. (b) Ozawa, F.; Hayashi, T. *J. Organomet. Chem.* **1992**, *428*, 267−277.

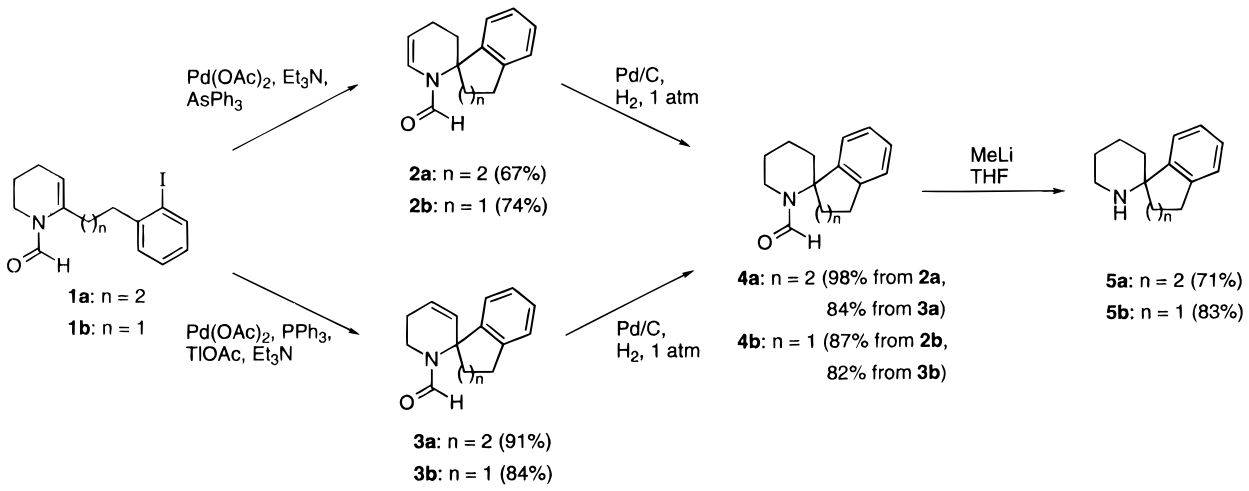
(9) (a) Bigge, C. F. *Biochem. Pharmacol.* **1993**, *45*, 1547−1561. (b) Ornstein, P. L.; Monn, J. A.; Schoepp, D. D. *Drug News Perspec.* **1994**, *7*, 5−12.

(10) For use of triphenylarsine in Heck reaction see: (a) Zhang, H.-C.; Daves, G. D., Jr. *J. Org. Chem.* **1992**, *57*, 4690−4696. (b) Zhang, H.-C.; Daves, G. D., Jr. *Organometallics* **1993**, *12*, 1499−1500. (c) Ripa, L.; Hallberg, A. *J. Org. Chem.* **1996**, *61*, 7147−7155.

(11) In the absence of phosphine or arsine ligands (see ref 10c) a slow reaction was encountered. Addition of triphenylphosphine, tri-*o*-tolylphosphine, or tri-2-furylphosphine gave mixtures of double bond isomers.

S0022-3263(96)01832-4 CCC: $14.00

Scheme 1



acetate, (*R*)-BINAP, and triethylamine[10c] gave as expected a mixture of isomers.

The rate of the 6-exo cyclizations of **1a** were slower than the 5-exo cyclization of **1b** and required more of the palladium catalyst for satisfactory conversion.[13]

The enantiomeric excesses achieved with (*R*)-BINAP[14] as ligand is summarized in Table 1. Cyclization of **1a** with a catalytic system prepared in situ from palladium acetate and (*R*)-BINAP, and in the presence of silver nitrate and triethylamine in acetonitrile at 80 °C, led to a mixture of **2a**, **3a** and the double bond isomer **6a** (entry 1).[15] The enamide (*R*)-**2a** (38% ee) and a mixture of (*S*)-**3a** (8% ee) and (*R*)-**6a** (35% ee) were isolated in 39% and 20% yields, respectively. Hydrogenation of the reaction mixture after subjecting **1a** to the cyclization conditions afforded (*R*)-**4a** in 52% total yield in an enantiomeric excess of 31%. Cyclization of **1b** under the conditions used for **1a** led to formation of (*R*)-**2b**,[16] as the major product, in low enantiomeric excess and in low yield (22%, 17% ee). Substitution of the silver nitrate for silver phosphate[17] and employing **1a** as starting material gave (*R*)-**2a** (42% ee) and the mixture of (*R*)-**3a** (13% ee) and (*R*)-**6a** (20% ee), and a similar result was obtained with calcium carbonate as base[18] (entries 2 and 3). Use of calcium carbonate and silver phosphate in more polar solvents improved the enantiomeric excess of (*R*)-**2a** [DMF 51% ee, dimethylacetamide (DMAA) 54% ee] but still mixtures of double bond isomers were observed (entries 4 and 5). Omitting calcium carbonate or triethylamine and using $Pd_2(dba)_3$ and (*R*)-BINAP as catalytic system[19] allowed isolation of a mixture of (*R*)-**3a** (38% ee) and (*R*)-**6a** (15% ee) in 59% yield together with (*R*)-**2a** (18% ee) in 15% yield (entry 6).

Intramolecular cyclization of the aryl triflate **7** at 60 °C with (*R*)-BINAP and triethylamine as base in acetonitrile led to the enamide (*R*)-**2a** (40% ee) and the mixture of (*S*)-**3a** (19% ee) and (*R*)-**6a** (20% ee) in low yields, 30% and 14%, respectively (entry 7). Reactions in DMF produced similar results (entry 8). With less polar solvents, a greater degree of asymmetric induction was encountered, although the reactions required considerably longer reaction times for completion. Thus, after reaction in THF, at 60 °C, (*R*)-**2a** was isolated in 30% yield and in an enantiomeric excess of 71% (entry 9). The mixture of (*S*)-**3a** and (*R*)-**6a** was isolated in 29% yield, and (*R*)-**6a** gave 68% ee, while (*S*)-**3a** gave only 13% ee. A lower reaction temperature, 40 °C, had a limited influence on the enantioselectivity and resulted in slow conversion (entry 10). The outcome of reactions in toluene was high enantiomeric excesses of (*R*)-**2a** (90% ee) and of (*R*)-**6a** (89% ee), but the enantiomeric purity of (*S*)-**3a** in this solvent was also low (8% ee) (entry 11). Additionally, a long reaction time, 168 h, was needed for full conversion. A comparison of entry 9 and entry 12 reveals that a similar product composition was attained when starting from $Pd_2(dba)_3$, but this reaction required higher temperature for a satisfactory conversion.[20] The low isolated yields encountered with the reactions using the aryl triflate **7** is, to a large extent, due to reduction prior to insertion, causing deoxygenation of **7**.[21] Inorganic bases,[22] which have been reported to circumvent

(12) The beneficial effect of silver additives in controlling double bond isomerization in the Heck reaction was first observed by Overman's group. (a) Abelman, M. M.; Oh, T.; Overman, L. E. *J. Org. Chem.* **1987**, *52*, 4130−4133. (b) Abelman, M. M.; Oveman, L. E. *J. Am. Chem. Soc.* **1988**, *110*, 2328−2329. For use of silver salts in controlling double bond isomerization in heterocycles see: (c) Larock, R. C.; Gong, W. H.; Baker, B. E. *Tetrahedron Lett.* **1989**, *30*, 2603−2606. (d) Larock, R. C.; Gong, W. H. *J. Org. Chem.* **1989**, *54*, 2047−2050. (e) Larock, R. C.; Gong, W. H. *J. Org. Chem.* **1990**, *55*, 407−408. (f) Sakamoto, T.; Kondo, Y.; Yamanaka, H. *Tetrahedron Lett.* **1992**, *33*, 6845−6848. (g) Nilsson, K.; Hallberg, A. *J. Org. Chem.* **1992**, *57*, 4015−4017. See also refs 7 and 10c.

(13) For a related example see ref 5a.

(14) BINAP = 2,2′-bis(diphenylphosphino)-1,1′-binaphthyl. Noyori, R.; Takaya, H. *Acc. Chem. Res.* **1990**, *23*, 345−350.

(15) Prolonged reaction times do not alter the product distribution.

(16) (*R*)-**2a** and (*R*)-**2b** carry the aryl ring on opposite side of the tetrahydropyridine ring. See ref 27.

(17) The counter anion of the silver salts has been reported to influence the chiral induction in asymmetric Heck reactions. (a) Sato, Y.; Sodoeke, M.; Shibasaki, M. *Chem. Lett.* **1990**, 1953−1954. (b) Nukui, S.; Sodeoka, M.; Shibasaki, M. *Tetrahedron Lett.* **1993**, *34*, 4965−4968. (c) Sato, Y.; Nukui, S.; Sodeoka, M.; Shibasaki, M. *Tetrahedron* **1994**, *50*, 371−382.

(18) A combination of silver phosphate and calcium carbonate was used by Shibasaki to obtain high enantiomeric excess, see ref 17a.

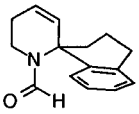
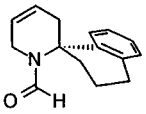
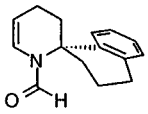
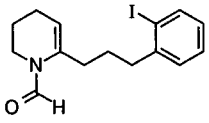
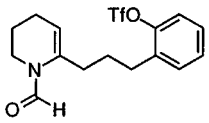
(19) (a) Ashimori, A.; Overman, L. E. *J. Org. Chem.* **1992**, *57*, 4571−4572. Applying Overman's conditions omitting silver additives and with 1,2,2,6,6-pentamethylpiperidine as base rendered racemic products. (b) Ashimori, A.; Matsuura, T.; Overman, L. E.; Poon, D. J. *J. Org. Chem.* **1993**, *58*, 6949−6951.

(20) Ozawa and Hayashi found that the kinetic resolution process was promoted by acetate ions displacing the olefin from the π-complex. Ozawa, F.; Kubo, A.; Matsumoto, Y.; Hayashi, T.; Nishioka, E.; Yanagi, K.; Moriguchi, K.-i. *Organometallics* **1993**, *12*, 4188−4196.

(21) Employing sterically hindered amine bases (1,2,2,6,6-pentamethylpiperidine and diisopropylethylamine) reduced the formation of the undesired reduction product but furnished lower yields and moderate asymmetric induction of **2a** (ee < 40%).

(22) The bases tested were KOAc, NaOAc, TlOAc, $NaHCO_3$, and K_2CO_3.

Table 1. Enantiomeric Excesses in Intramolecular Palladium-Catalyzed Arylation of 1a and 7 with (*R*)-BINAP as Ligand

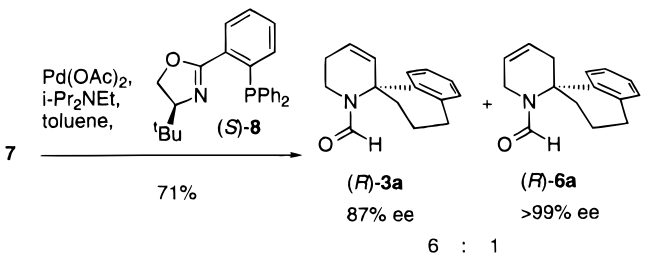
entry	substrate	conditions[a]	 **3a** % ee[b]	 (*R*)-**6a** % ee[b]	**3a** / **6a**[c] (% yield)[d]	 (*R*)-**2a** % ee[b]	**2a** % yield[d]
1	 **1a**	$Pd(OAc)_2$, Et_3N, $AgNO_3$, CH_3CN, 80 °C, 144 h	8 (*S*)	35	1 / 2.4 (20)	38	39
2		$Pd(OAc)_2$, Et_3N, Ag_3PO_4, CH_3CN, 80 °C, 23 h	13 (*R*)	20	2.6 / 1 (25)	42	21
3		$Pd(OAc)_2$, $CaCO_3$, Ag_3PO_4, CH_3CN, 80 °C, 37 h	22 (*R*)	19	9 / 1 (20)	42	20
4		$Pd(OAc)_2$, $CaCO_3$, Ag_3PO_4, DMF, 80 °C, 23 h	22 (*R*)	32	2.3 / 1 (26)	51	33
5		$Pd(OAc)_2$, $CaCO_3$, Ag_3PO_4, DMAA[e], 80 °C, 23 h	27 (*R*)	30	2.6 / 1 (29)	54	28
6		$Pd_2(dba)_3$, Ag_3PO_4, DMAA[e], 80 °C[f], 74 h	38 (*R*)	15	19 / 1 (59)	18	15
7	 **7**	$Pd(OAc)_2$, Et_3N, CH_3CN, 60 °C, 27 h	19 (*S*)	20	1 / 2.4 (14)	40	30
8		$Pd(OAc)_2$, Et_3N, DMF, 60 °C, 23 h	21 (*S*)	32	1 / 1.3 (9)	48	26
9		$Pd(OAc)_2$, Et_3N, THF, 60 °C, 48 h	13 (*S*)	68	1 / 1.8 (29)	71	30
10		$Pd(OAc)_2$, Et_3N, THF, 40 °C, 144 h	21 (*S*)	73	1 / 2 (28)	69	31
11		$Pd(OAc)_2$, Et_3N, Toluene, 60 °C, 168 h	8 (*R*)	89	1 / 2.2 (36)	90	8
12		$Pd_2(dba)_3$, Et_3N, THF, 80 °C, 48 h	8 (*S*)	66	1 / 2.6 (25)	67	34

[a] The reactions were conducted under argon atmosphere in sealed heavy-walled Pyrex tubes. [b] The enantiomeric excess was determined by GLC analysis on a chiral capillary column. See ref 29. [c] The isomer ratio was determined by GLC and double bond isomers were assumed to have the same response factors. [d] Isolated yields (not optimized) by column chromatography. [e] DMAA = dimethylacetamide. [f] See ref 19.

this problem,[23] had a deleterious effect on the reaction rate, although the competing reduction was eliminated. At higher reaction temperatures (80−120 °C) the catalytic system decomposed before satisfactory conversion was achieved.

Recently Pfaltz[24] reported the successful use of the chiral (phosphinoaryl)oxazoline (*S*)-**8**[25] (Scheme 2) as ligand in the Heck arylation of 2,3-dihydrofuran with phenyl triflate at 60 °C in THF. (*R*)-2-Phenyl-2,5-dihydrofuran was produced in an enantiomeric excess of

Scheme 2



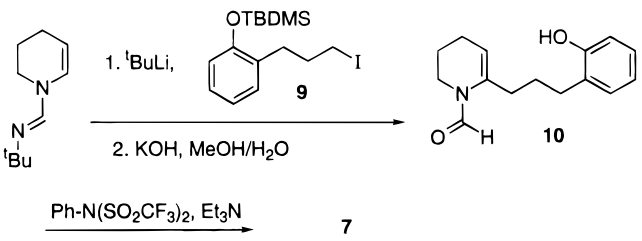
97%, and the double bond isomer 2-phenyl-2,3-dihydrofuran was not detected.[24a] Applying Pfaltz's reaction conditions to the triflate **7** resulted in a slow reaction, furnishing only minute amounts of product after 48 h. However, after raising the temperature to 110 °C, isolation of a 2:1 mixture of (*R*)-**3a** (86% ee) and (*R*)-**6a** (>99% ee) was allowed. A higher regioselectivity was obtained with a more nonpolar solvent (toluene), which afforded 71% yield of a 6:1 mixture of (*R*)-**3a** (87% ee) and (*R*)-**6a** (>99% ee) after 48 h (Scheme 2).[26]

(23) Cabri, W.; Candiani, I.; DeBernardinis, S.; Francalanci, F.; Penco, S.; Santi, R. *J. Org. Chem.* **1991**, *56*, 5796−5800. See also ref 2a.

(24) (a) Loiseleur, O.; Meier, P.; Pfaltz, A. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 200−202. See also: (b) Pfaltz, A. *Acta Chem. Scand.* **1996**, *50*, 189−194.

(25) The systematic name of (*S*)-**8** is (−)-(*S*)-4-*tert*-butyl-2-[2-(diphenylphosphino)phenyl]-4,5-dihydrooxazole. (a) Koch, G.; Lloyd-Jones, G. C.; Loiseleur, O.; Pfaltz, A.; Prétôt, R.; Schaffner, S.; Schnider, P.; von Matt, P. *Recl. Trav. Chim. Pays-Bas* **1995**, *114*, 206−210. (b) Peer, M.; de Jong, J. C.; Kiefer, M.; Langer, T.; Rieck, H.; Schell, H.; Sennhenn, P.; Sprintz, J.; Steinhagen, H.; Wiese, B.; Helmchen, G. *Tetrahedron* **1996**, *52*, 7547−7583.

Scheme 3

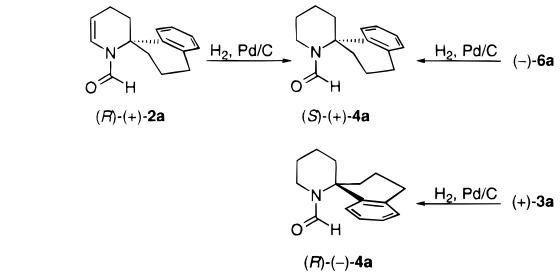


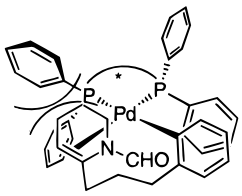
The absolute configurations of **2a** and **2b** were assigned based on empirical force-field calculations (MM2-91) and by analyses of the circular dichroism spectra.[27] Isolation of the pure enantiomers of **3a** and **6a** was achieved by HPLC, using a chiral stationary phase.[28] Compounds (+)-**3a** and (−)-**6a** were, after reduction to **4a** and subsequent comparison on a chiral GLC-column[29] with a sample of (*S*)-**4a**, assigned to be the (*S*)-**3a** and (*R*)-**6a** enantiomers, respectively.[30]

Starting Materials. Compounds **1a** and **1b** were prepared from the corresponding enamidines[10c] by hydrolysis in 77% and 80% yield, respectively. In an analogous reaction sequence the *N*-(*N′-tert*-butylformimidoyl)-1,2,3,4-tetrahydropyridine[31] was alkylated with **9** to give **10** after subsequent hydrolysis of the enamidine function, and **10** was converted thereafter to the triflate **7** as outlined in Scheme 3.

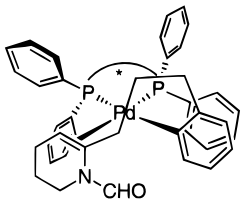
Discussion

For the preparation of compounds **2a** and **2b**, triphenylarsine was employed to enhance the reaction rate. Triphenylarsine, with the characteristic feature of stabilizing Pd(0) while binding less strongly to Pd(II),[32] is less prone than phosphine ligands to compete with the olefin for the coordination sites of the hydrido−palladium π-complexes, thus facilitating the double bond migration.





11_S



11_R

Figure 1. π-Complexes $\mathbf{11}_S$ and $\mathbf{11}_R$. The binaphthylene group in the (*R*)-BINAP ligand is omitted for clarity. See ref 34.

Asymmetric Arylations with (*R*)-BINAP as Ligand. The results reported by Ozawa and Hayashi, where phenyl triflate was employed in asymmetric intermolecular arylations of 1-(alkoxycarbonyl)-2,3-dihydropyrroles, afforded (*R*)-1-(alkoxycarbonyl)-2-phenyl-2,3-dihydropyrroles in 64−73% ee, as the major products.[8b] The regioisomers 1-(alkoxycarbonyl)-2-phenyl-2,5-dihydropyrroles had the opposite, (*S*), configuration and were produced with lower enantiomeric excesses.[8b] The mechanism proposed by the authors involves a catalytic kinetic resolution process.[33] The related intramolecular spirocyclizations of **7** reported here provided **2a** and **3a** with a preference for enantiomers with the same absolute configuration as obtained by Ozawa and Hayashi, in their intermolecular arylations, (*R*) and (*S*), respectively. The third regioisomer **6a** was produced with a preference for the (*R*) configuration. We believe that the enantiomeric excesses of the three products, formed either from the triflate **7** or from the iodide **1a** in combination with silver salts, can be accounted for by involvement of a kinetic resolution process similar to that suggested by Ozawa and Hayashi in the intermolecular reaction.

The oxidative addition is followed by a selection of enantiofaces, generating two π-complexes, $\mathbf{11}_S$ and $\mathbf{11}_R$, the former being more sterically crowded (Figure 1). After insertion and β-hydrogen elimination, hydrido−palladium π-complexes are formed (Scheme 4). One of the phenyl groups of (*R*)-BINAP in the π-complex $\mathbf{12}_R$ suffers from a considerable steric repulsion from the phenyl group of the rigid spirosystem according to a molecular model analysis.[34] Rotation of the palladium−olefin bond, a prerequisite for the double bond migration, releases the steric strain and consecutive readdition and β-hydrogen elimination provides the (*R*) enantiomers **2a** and **6a**. In contrast, the rotation of the olefin−palladium bond in $\mathbf{12}_S$ is disfavored due to steric reasons. Decomplexation of $\mathbf{12}_S$ dominates and delivers the (*S*) enantiomer of **3a**.

Asymmetric Arylations with (*S*)-8 as Ligand. With the (phosphinoaryl)oxazoline ligand (*S*)-**8** two oxidative addition complexes are conceivable. The thermodynamically most stable complex is likely to have the soft aryl group trans to the harder nitrogen, and the soft phosphine, with a large trans effect,[35] trans to the leaving

(26) Using (*S*)-**8** as ligand in cyclization reactions starting from aryl iodide **1a** in DMAA with silver phosphate resulted in racemic **3a** as the major product.

(27) Ripa, L.; Hallberg, A.; Sandström, J. Manuscript in preparation.

(28) Compounds **3a** and **6a** were resolved on columns packed with swollen microcrystalline triacetylcellulose (TAC), packed and provided by Dr Roland Isaksson, Department of Analytical Pharmaceutical Chemistry, Box 574, Uppsala University, BMC, SE-751 23 Uppsala, Sweden, see: Isaksson, R.; Erlandsson, P.; Hansson, L.; Holmberg, A.; Berner, S. *J. Chromatogr.* **1990**, *498*, 257−280.

(29) Analytical separations of the enantiomers were achieved by gas chromatography, on a chiral capillary column (10 m × 0.32 mm) with H_2 as carrier gas and a flame ionization detector. Compounds **2a**, **3a**, **4a**, and **6a** were separated on a column coated with 50% heptakis(6-*O*-*tert*-butyldimethylsilyl-2,3-di-*O*-methyl)-β-cyclodextrin in OV 1701 and compound **2b** on a column coated with 20% octakis(2,6-di-*O*-methyl-3-*O*-pentyl)-γ-cyclodextrin in OV 1701, prepared and developed by Prof. W. A. König, Institut für Organische Chemie, Universität Hamburg, D-201 46 Hamburg, Germany.

(30)

(31) Meyers, A. I.; Edwards, P. D.; Bailey, T. R.; Jagdmann, G. E. J. *J. Org. Chem.* **1985**, *50*, 1019−1026.

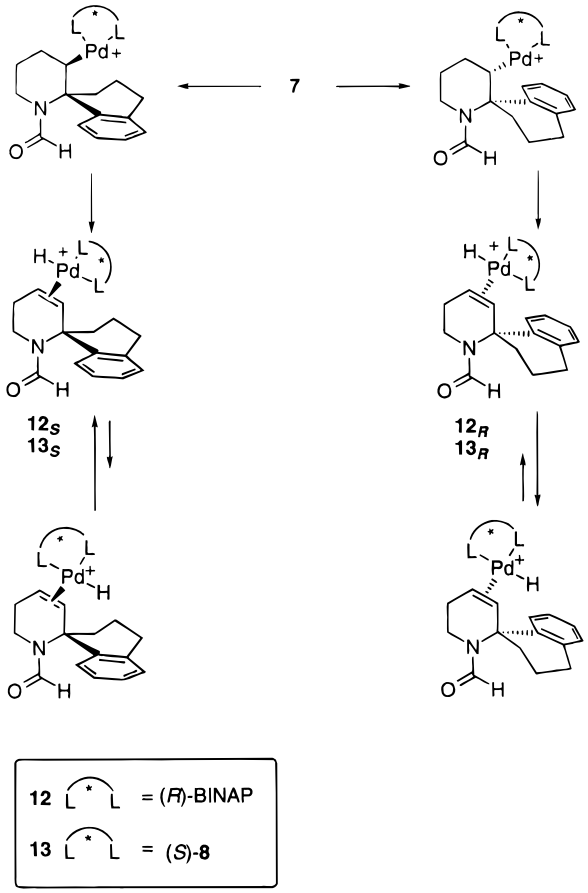
(32) Farina, V.; Krishnan, B. *J. Am. Chem. Soc.* **1991**, *113*, 9585−9595.

(33) For the related intermolecular arylation of 2,3-dihydrofuran, see: (a) Ozawa, F.; Kubo, A.; Hayashi, T. *J. Am. Chem. Soc.* **1991**, *113*, 1417−1419. (b) Ozawa, F.; Kubo, A.; Hayashi, T. *Tetrahedron Lett.* **1992**, *33*, 1485−1488. See also ref 19.

(34) The molecular model analyses were based on the X-ray structure of $PdCl_2$[(*R*)-BINAP], see ref 20.

(35) Togni, A.; Venanzi, L. M. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 497−526.

Scheme 4



triflate.[36] Olefin coordination to the fourth coordination site enables formation of four diastereomeric π-complexes (Figure 2). Complexes of the type **14**, with the aryl groups trans to the nitrogen, are less prone to migratory insertion than complexes such as **15**, and isomerization of **14** to **15** may occur before insertion takes place.[37] Examination of molecular models[38] of complexes **14** and **15** suggests that both the complexes giving the spiro product with *R* configuration ($\mathbf{14_R}$ and $\mathbf{15_R}$) are the sterically least hindered. The higher enantiomeric excess for (*R*)-**6a** (>99%) as compared to (*R*)-**3a** 87% can be interpreted by assuming involvement of a kinetic resolution process as discussed previously (Scheme 4). The rotation of the palladium in complex $\mathbf{13_S}$ should be strongly disfavored due to steric interactions between (*S*)-**3a** and both the *tert*-butyl group and one of the phenyl groups in the ligand.

Conclusion

We have demonstrated that intramolecular cyclization of enamides with aryl iodides provides an entry to rigid α-phenyl piperidines with the double bond restored for further manipulations. These spiro compounds were isolated in fair to good yields. Triphenylarsine was a suitable ligand for the promotion of double bond migration while thallium acetate efficiently retarded the double bond migration process. With (*R*)-BINAP, addition of silver additives, or alternatively employment of a phenyl triflate, leads to moderate to high enantioselectivities, although the yields are low. Employment of (phosphinoaryl)oxazoline (*S*)-**8** as ligand rendered good isolated yield of spiro compounds as well as high enantiomeric excesses.

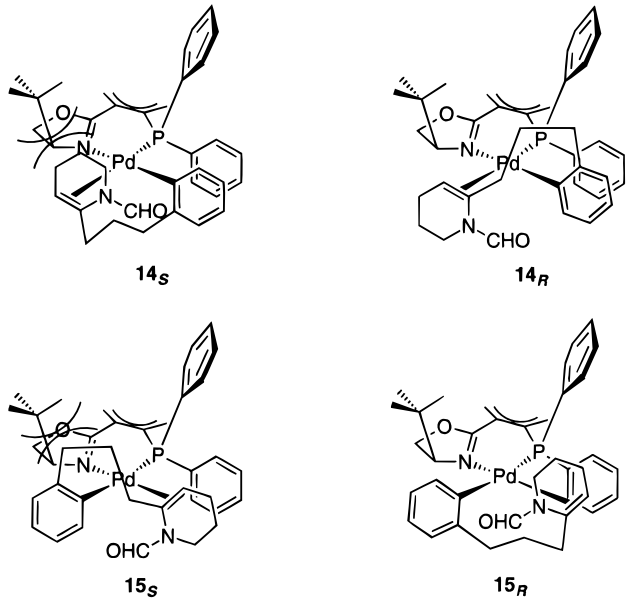


Figure 2. Diastereomeric π-complexes $\mathbf{14_S}$, $\mathbf{14_R}$, $\mathbf{15_S}$, and $\mathbf{15_R}$. See ref 38.

Experimental Section

General Methods. ^{1}H and ^{13}C NMR spectra were recorded at 270 and 67.8 MHz, respectively. Spectra were recorded at ambient temperature with $CDCl_3$ as solvent and tetramethylsilane as internal standard. The ^{1}H NMR spectra of the *N*-formyl compounds show (with the exeption of compounds **4a**, **4b**, and **6a**) the existence of two rotamers in an approximately 96:4 ratio. Shift values are given only for the major isomer. Peak assignments of the spiro compounds were made by ^{13}C−^{13}C and ^{1}H−^{13}C correlation experiments. Coupling constants are given as absolute values. Low-resolution electron-impact MS spectra were measured at an ionization potential of 70 eV. The mass detector was interfaced with a gas chromatograph, equipped with a HP-1 (25 m × 0.20 mm) column. Isomers were assumed to have the same response factors. Infrared spectra were recorded on a FTIR spectrophotometer as solutions in $CDCl_3$ unless otherwise noted. Elemental analyses were performed by Mikro Kemi AB, Uppsala, Sweden, or by Analytische Laboratorium, Prof. Dr. H. Malissa and G. Reuter GmbH, Gummersbach, Germany. The high resolution MS analysis was performed by Einar Nilsson, Instrumentstationen, Kemicentrum, Lund. Melting points were determined in open capillary tubes in a melting point microscope and are uncorrected. All palladium-catalyzed cyclization reactions were carried out in heavy-walled Pyrex tubes, sealed with a screw cap fitted with a Teflon gasket. Thin layer chromatography (TLC) was carried out on aluminum sheets precoated with silica gel 60 F_{254} (0.2 mm, E. Merck). Column chromatography was performed on silica using kiselgel 60 (0.032−0.063 mm, E. Merck, or 0.015−0.040 mm (fine), E. Merck). Preparative HPLC was performed on a Dynamax 60-A 21.4 × 250 mm, 8-μm silica column. A dynamax UV-1 UV detector (254 nm) and a Gilson 305 piston pump (1% EtOH in isohexane at a flow rate of 13 mL/min) were used.

(36) For a discussion of hard and soft acids and bases coordinating to soft Pd(II), see: (a) Davies, J. A.; Hartley, F. R. *Chem. Rev.* **1981**, *81*, 79−90. See also: (b) Clark, G. R.; Palenik, G. J. *Inorg. Chem.* **1970**, *9*, 2754−2760. (c) Dekker, G. P. C. M.; Buijs, A.; Elsevier, C. J.; Vrieze, K.; van Leeuwen, P. W. N. M.; Smeets, W. J. J.; Spek, A. L.; Wang, Y. F.; Stam, C. H. *Organometallics* **1992**, *11*, 1937−1948.

(37) van Leeuwen, P. W. N. M.; Roobeek, C. F.; van der Heijden, H. *J. Am. Chem. Soc.* **1994**, *116*, 12117−12118. See also ref 36c.

(38) The molecular model analyses were based on the X-ray structure of a π-allyl palladium complex with a similar ligand published previously. Sprinz, J.; Kiefer, M.; Helmchen, G.; Reggelin, M.; Hutter, G.; Walter, O.; Zsolnai, L. *Tetrahedron Lett.* **1994**, *35*, 1523−1526.

Materials. Triethylamine was distilled from potassium hydroxide, and THF and diethyl ether were distilled from sodium/benzophenone prior to use. Acetonitrile (CH_3CN) was stored over activated 3 Å molecular sieves and degassed with argon before use. Triphenylphosphine (PPh_3) (Merck) was recrystallized from 95% ethanol. $Pd(OAc)_2$ (Merck), $Pd(dba)_2$ (Lancaster), $Pd_2(dba)_3$ (Aldrich), triphenylarsine ($AsPh_3$) (Acros Chimica), and (*R*)-(+)-2,2′-bis(diphenylphosphino)-1,1′-binaphthyl ((*R*)-BINAP) (Aldrich) were used as supplied. The ligand (*S*)-**8** was prepared according to the procedure reported by Pfaltz,[25a] and the spectroscopic data was consistent with data reported.[25b] Compound **9** was prepared according to a synthetic strategy described elsewhere[39] from 2-allylphenol (Acros Chimica). *N*-(*N*′-*tert*-Butylformimidoyl)-6-[2-(2-iodophenyl)-ethyl]-1,2,3,4-tetrahydropyridine and *N*-(*N*′-*tert*-butylformimidoyl)-6-[3-(2-iodophenyl)propyl]-1,2,3,4-tetrahydropyridine were prepared as described elsewhere[10c] from *N*-(*N*′-*tert*-butylformimidoyl)-1,2,3,4-tetrahydropyridine.[31] All other reagents were obtained from commercial sources and used as received.

***N*-Formyl-6-[3-(2-iodophenyl)propyl]-1,2,3,4-tetrahydropyridine (1a).** A solution of *N*-(*N*′-*tert*-butylformimidoyl)-6-[3-(2-iodophenyl)propyl]-1,2,3,4-tetrahydropyridine[10c] (89 mg, 0.22 mmol) and KOH (85 mg, 1.5 mmol) in MeOH (1.8 mL) and water (0.7 mL) was heated at 55 °C under argon until TLC indicated complete consumption of the formamidine. Upon cooling, the solvent was removed under reduced pressure, and the residue was dissolved in CH_2Cl_2 (3 mL). The organic layer was washed with saturated aqueous $NaHCO_3$ (3 × 1 mL) and brine (2 mL), dried (K_2CO_3), and concentrated. Purification by column chromatography (SiO_2, pentane/EtOAc 4:1, R_f 0.33) gave **1a** (60 mg, 77%). ^{1}H NMR δ 8.53 (s, 1H), 7.81 (dd, 1H), 7.31−7.14 (m, 2H), 6.89 (app dt, 1H), 4.94 (t, J = 3.9 Hz, 1H), 3.67 (app t, 2H), 2.73 (app t, 2H), 2.45 (app t, 2H), 2.13−2.07 (m, 2H), 1.85−1.63 (m, 4H); ^{13}C NMR δ 159.0, 139.5, 144.0, 135.5, 129.3, 128.4, 127.9, 108.8, 100.5, 40.1, 39.4, 32.0, 27.8, 22.5, 21.5; IR ($CDCl_3$) 1647 cm^{-1}; MS [IP 70 eV; *m*/*z* (% rel int)] 355 (M^+, 32), 228 (9), 125 (67), 97 (100). Anal. Calcd for $C_{15}H_{18}INO$: C, 50.72; H, 5.11; N, 3.94. Found: C, 50.8; H, 5.2; N, 3.9.

***N*-Formyl-6-[2-(2-iodophenyl)ethyl]-1,2,3,4-tetrahydropyridine (1b).** Compound **1b** was synthesized from *N*-(*N*′-*tert*-butylformimidoyl)-6-[2-(2-iodophenyl)ethyl]-1,2,3,4-tetrahydropyridine[10c] (3.5 g, 8.8 mmol) as described above for the synthesis of **1a**. Purification by column chromatography (SiO_2, pentane/EtOAc 3:1, R_f 0.41) gave **1b** (2.4 g, 80%). ^{1}H NMR δ 8.70 (s, 1H), 7.82 (dd, 1H), 7.28 (app dt, 1H), 7.16 (dd, 1H), 6.91 (app dt, 1H), 4.90 (t, J = 3.9 Hz, 1H), 3.70−3.66 (m, 2H), 2.92 (app t, 2H), 2.63 (app t, 2H), 2.07−2.04 (m, 2H), 1.82−1.68 (m, 2H); ^{13}C NMR δ 159.0, 143.1, 134.9, 139.4, 129.4, 128.3, 128.1, 109.4, 100.0, 39.4, 38.9, 32.9, 22.4, 21.3; IR ($CDCl_3$) 1648 cm^{-1}; MS [IP 70 eV; *m*/*z* (% rel int)] 341 (M^+, 2), 340 (3), 214 (100), 186 (83), 141 (48). Anal. Calcd for $C_{14}H_{16}$-INO: C, 49.29, H, 4.73, N, 4.10. Found: C, 49.5; H, 5.1; N, 4.1.

3-{2-[(*tert*-Butyldimethylsilyl)oxy]phenyl}-1-iodopropane (9).[39] 2-Allylphenol (13.4 g, 0.10 mol) was mixed with *tert*-butyldimethylsilyl chloride (16.6 g, 0.11 mol), triethylamine (15.2 g, 0.15 mol), and 4-(dimethylamino)pyridine (1.2 g, 0.01 mol) in CH_2Cl_2 (300 mL) and stirred at room temperature until TLC indicated complete consumption of the alcohol. The reaction mixture was washed consecutively with brine (140 mL), water (140 mL), and brine (140 mL) and was thereafter dried ($MgSO_4$) and concentrated. Purification by column chromatography (SiO_2, pentane, R_f 0.64) gave **allyl-2-[(*tert*-butyldimethylsilyl)oxy]benzene** (22.4 g, 90%). ^{1}H NMR δ 7.17−7.04 (m, 2H), 6.89 (app dt, 1H), 6.79 (dd, 1H), 6.03−5.93 (m, 1H), 5.08−5.05 (m, 1H), 5.04−5.00 (m, 1H), 3.37 (d, J = 6.6 Hz, 2H), 1.01 (s, 9H), 0.24 (s, 6H); ^{13}C NMR δ 153.3, 137.0, 130.7, 130.1, 127.0, 121.1, 118.4, 115.4, 34.4, 25.8, 18.2, −4.1; MS [IP 70 eV; *m*/*z* (% rel int)] 248 (M^+, 3), 191 (100), 163 (55). Anal. Calcd for $C_{15}H_{24}OSi$: C, 72.52; H, 9.74. Found: C, 72.4; H, 9.6. To a solution of the protected 2-allylphenol (7.0 g, 28 mmol) in THF (50 mL) was added dropwise BH_3·THF (28 mL, 28 mmol, 1 M in THF) at 0 °C, and the resulting mixture was stirred at room temperature for 2 h. The reaction mixture was quenched with water (12 mL) followed by 10% aqueous NaOH (12 mL) and 30% aqueous H_2O_2 (7 mL) at 0 °C and thereafter stirred for additional 3 h at 0 °C, acidified with 5% HCl to pH 4, and extracted with diethyl ether (2 × 100 mL). The organic layers were washed with saturated aqueous $NaHCO_3$ (50 mL) and brine (50 mL), dried (Na_2SO_4), and concentrated to yield 7.64 g of the crude alcohol. To a solution of the alcohol in benzene (100 mL) at 0 °C were added imidazole (4.8 g, 70 mmol), PPh_3 (16.8 g, 64 mmol), and I_2 (14.2 g, 56 mmol), and the reaction mixture was stirred for 1.5 h at room temperature. An 10% aqueous $Na_2S_2O_3$ solution (130 mL) was added, and the mixture was extracted with EtOAc (2 × 70 mL), dried (Na_2SO_4), and concentrated. Purification by column chromatography (SiO_2, pentane, R_f 0.33) gave **6** (6.6 g, 62%). ^{1}H NMR δ 7.15 (app dt, 1H), 7.08 (dd, 1H), 6.89 (app dt, 1H), 8.80 (dd, 1H), 3.19 (t, J = 6.9 Hz, 2H), 2.70 (app t, 2H), 2.17−2.09 (m, 2H), 1.03 (s, 9H), 0.25 (s, 6H); ^{13}C NMR δ 153.5, 130.9, 130.3, 127.2, 121.0, 118.4, 33.4, 31.5, 25.8, 18.2, 6.7, −4.1; MS [IP 70 eV; *m*/*z* (% rel int)] 376 (M^+, 1), 319 (77), 191 (100). Anal. Calcd for $C_{15}H_{25}IOSi$: C, 47.87; H, 6.70. Found: C, 47.9; H, 6.6.

***N*-Formyl-6-[3-(2-hydroxyphenyl)propyl]-1,2,3,4-tetrahydropyridine (10).** To a solution of *N*-(*N*′-*tert*-butylformimidoyl)-1,2,3,4-tetrahydropyridine[31] (1.7 g, 10 mmol) in diethyl ether/THF 4:1 (20 mL) was slowly added *t*-BuLi (9.3 mL, 13 mmol, 1.4 M in hexane) at −78 °C. The yellow solution was stirred at −20 °C until a white solid had precipitated (2 h). The reaction mixture was cooled to −78 °C, after which compound **9** (5.6 g, 15 mmol) was added and the reaction mixture was stirred at −20 °C overnight. The reaction mixture was poured into saturated NH_4Cl (100 mL) and extracted with diethyl ether (3 × 50 mL). The combined ether layers were washed with brine (40 mL), dried over K_2CO_3/Na_2-SO_4 1:1, and concentrated to a yellow oil. The crude product (5.8 g) was dissolved in MeOH (70 mL), KOH (3.9 g, 70 mmol) in water (30 mL) was added, and the mixture was heated at 60 °C for 2 h. Upon cooling, the solvent was removed under reduced pressure, and the residue was dissolved in CH_2Cl_2 (200 mL). The organic layer was washed with saturated aqueous $NaHCO_3$ (3 × 50 mL) and brine (50 mL), dried ($NaHCO_3$), and concentrated. Purification by column chromatography (SiO_2, pentane/EtOAc 1:1, R_f 0.45) gave **10** (1.4 g, 5.6 mmol, 56%) as a white solid, mp 97−98 °C. ^{1}H NMR δ 8.47 (s, 1H), 7.09−7.04 (m, 2H), 6.85−6.76 (m, 2H), 6.45 (broad s, 1H), 4.94 (t, J = 3.8 Hz, 1H), 3.68−3.63 (m, 2H), 2.66 (t, J = 7.4 Hz, 2H), 2.40 (t, J = 7.4 Hz, 2H), 2.09−2.05 (m, 2H), 1.90−1.72 (m, 4H); ^{13}C NMR δ 159.7, 154.1, 136.0, 130.3, 127.7, 127.3, 120.3, 115.3, 109.0, 39.6, 32.2, 29.9, 27.3, 22.5, 21.5; IR ($CDCl_3$) 3599, 3300−3150, 1615 cm^{-1}; MS [IP 70 eV; *m*/*z* (% rel int)] 245 (M^+, 20), 227 (21), 138 (76), 97 (100). Anal. Calcd for $C_{15}H_{19}NO_2$: C, 73.44; H, 7.81; N, 5.71. Found: C, 73.6; H, 7.9; N, 5.8.

***N*-Formyl-6-(3-{2-[(trifluoromethanesulfonyl)oxy]-phenyl}propyl)-1,2,3,4-tetrahydropyridine (7).** Compound **10** (0.96 g, 3.9 mmol) was mixed with *N*-phenylbis-(trifluoromethane)sulfonimide (2.8 g, 7.8 mmol) and triethylamine (0.6 mL, 3.4 mmol) in CH_2Cl_2 (40 mL). The solution was stirred at 20 °C for 48 h, diluted with CH_2Cl_2 (50 mL), washed with 10% aqueous K_2CO_3 (3 × 40 mL), dried (Na_2-SO_4), and concentrated. Purification by column chromatography (SiO_2, pentane/EtOAc 3:1, R_f 0.23) gave **7** (1.3 g, 87%). ^{1}H NMR δ 8.49 (s, 1H), 7.37−7.22 (m, 4H), 4.93 (t, J = 3.8 Hz, 1H), 3.68−3.64 (m, 2H), 2.74 (app t, 2H), 2.43 (t, J = 7.3 Hz, 2H), 2.10−2.05 (m, 2H), 1.91−1.73 (m, 4H); ^{13}C NMR δ 158.9, 147.9, 135.1, 134.2, 130.9, 128.5, 128.1, 121.4, 118.5 (q), 109.3, 39.4, 32.0, 29.2, 27.2, 22.5, 21.4; IR ($CDCl_3$) 1673, 1642 cm^{-1}; MS [IP 70 eV; *m*/*z* (% rel int)] 377 (M^+, 18), 216 (5), 125 (47), 97 (100). Anal. Calcd for $C_{16}H_{18}F_3NO_4S \cdot {}^1/_2H_2O$: C, 49.74; H, 4.96; N, 3.63. Found: C, 49.9; H, 4.9; N, 3.7.

***N*-Formyl-3,3′,4,4′-tetrahydrospiro[naphthalene-1(2*H*),2′(1′*H*)-pyridine] (2a).** $Pd(OAc)_2$ (7.2 mg, 0.032 mmol) and $AsPh_3$ (39.2 mg, 0.13 mmol) were mixed in CH_3CN (20 mL) under a stream of argon. Triethylamine (80 mg, 0.8 mmol) and **1a** (142 mg, 0.40 mmol) were added to the mixture. The reaction mixture was stirred and heated at 80 °C for 120

(39) Takemoto, T.; Sodeoka, M.; Sasai, H.; Shibasaki, M. *J. Am. Chem. Soc.* **1993**, *115*, 8477−8478.

h. After cooling, the mixture was poured out on saturated aqueous $NaHCO_3$ (60 mL) and extracted with EtOAc (3 × 40 mL), and the combined organic layers were washed with brine (2 × 40 mL), dried (K_2CO_3), and concentrated. The crude product was purified by column chromatography (SiO_2 (fine), pentane/EtOAc 4:1, R_f 0.37) to yield **2a** (61 mg, 67%) as a white solid, mp 74−75 °C. ^{1}H NMR δ 7.80 (s, 1H, C*H*O), 7.33−7.09 (m, 5H, Ar-H and H-6′), 5.29−5.22 (m, 1H, H-5′), 2.92−2.75 (m, 2H, H-4), 2.31−1.70 (m, 8H, H-2, H-3, H-3′ and H-4′); ^{13}C NMR δ 161.0 (*C*HO), 138.0, 137.7 (C-9, C-10), 129.5, 127.6, 127.3, 127.0, 121.8 (C-5, C-6, C-7, C-8 and C-6′), 108.6 (C-5′), 57.4 (C-1), 30.0 (C-4), 36.0, 33.3, 19.8, 18.3 (C-2, C-3, C-3′ and C-4′); IR ($CDCl_3$) 1660 cm^{-1}; MS [IP 70 eV; *m*/*z* (% rel int)] 227 (M^+, 78), 198 (6), 129 (100). Anal. Calcd for $C_{15}H_{17}NO$: C, 79.26; H, 7.54; N, 6.16. Found: C, 79.2; H, 7.5; N, 6.2.

***N*-Formyl-3′,4′-dihydrospiro[indan-1,2′(1′*H*)-pyridine] (2b).** **2b** was prepared from **1b** (171 mg, 0.50 mmol), $Pd(OAc)_2$ (5.6 mg, 0.025 mmol), $AsPh_3$ (31 mg, 0.10 mmol), and triethylamine (101 mg, 1.0 mmol) in CH_3CN (25 mL) as described above for the preparation of **2a** from **1a** (80 °C, 64 h). Purification by column chromatography (SiO_2 (fine), pentane/EtOAc 4:1, R_f 0.37) gave **2b** (79 mg, 74%) as a white solid, mp 65−66 °C. ^{1}H NMR δ 7.65 (s, 1H, C*H*O), 7.35−7.14 (m, 5H, Ar-H and H-6′), 5.32−5.25 (m, 1H, H-5′), 3.10−2.88 (m, 2H, H-3), 2.42−2.10 (m, 5H, H-2, H-3′ and H-4′), 1.85−1.76 (m, 1H, H-4′); ^{13}C NMR δ 159.5 (*C*HO), 143.9, 143.0 (C-8 and C-9), 128.9, 127.5, 125.2, 123.5, 121.9 (C-4, C-5, C-6, C-7 and C-6′), 109.5 (C-5′), 67.2 (C-1), 37.8 (C-2), 33.4 (C-3′), 29.1 (C-3), 20.1 (C-4′); IR ($CDCl_3$) 1655 cm^{-1}; MS [IP 70 eV; *m*/*z* (% rel int)] 213 (M^+, 33), 168 (100), 129 (67). Anal. Calcd for $C_{14}H_{15}NO$: C, 78.84; H, 7.09; N, 6.56. Found: C, 78.9; H, 6.9; N, 6.4.

***N*-Formyl-3,4,5′,6′-tetrahydrospiro[naphthalene-1(2*H*),2′(1′*H*)-pyridine] (3a).** $Pd(OAc)_2$ (3.6 mg, 0.016 mmol), PPh_3 (16.8 mg, 0.064 mmol), and TlOAc (58 mg, 0.22 mmol) were mixed in CH_3CN (10 mL) under a stream of argon. Triethylamine (40 mg, 0.4 mmol) and **1a** (71 mg, 0.2 mmol) were added to the mixture. The reaction mixture was stirred and heated at 80 °C for 50 h. After cooling, the black mixture was poured out on saturated aqueous $NaHCO_3$ (60 mL) and extracted with EtOAc (3 × 40 mL), and the combined organic layers were washed with brine (2 × 40 mL), dried (K_2CO_3), and concentrated. The crude product was purified by column chromatography (SiO_2 (fine), pentane/EtOAc 2:1, R_f 0.26) to yield **3a** (41 mg, 91%) as a white solid, mp 111−112 °C. ^{1}H NMR δ 7.66 (s, 1H, C*H*O), 7.23−7.07 (m, 4H, Ar-H), 6.01−5.95 (m, 1H, H-4), 5.55 (ddd, J = 10.1, 2.7 and 1.1 Hz, 1H, H-3′), 4.62 (app dd, 1H, H-6′), 2.97−2.72 (m, 3H, H-4 and H-6′), 2.46−2.32 (m, 1H, H-5′), 2.20−2.04 (m, 2H, H-2 and H-5′), 1.90−1.64 (m, 3H, H-2 and H-3); ^{13}C NMR δ 163.3 (*C*HO), 138.0, 135.7 (C-9 and C-10), 134.4 (C-3′), 129.3, 128.8, 127.9, 126.8 (C-5, C-6, C-7 and C-8), 124.3 (C-4′), 58.9 (C-1), 34.3 (C-2), 33.9 (C-6′), 29.3 (C-4), 24.7 (C-3′), 17.9 (C-3); IR ($CDCl_3$) 1637 cm^{-1}; MS [IP 70 eV; *m*/*z* (% rel int)] 227 (M^+, 63), 198 (48), 170 (100). Anal. Calcd for $C_{15}H_{17}NO$: C, 79.26; H, 7.54; N, 6.16. Found: C, 79.1; H, 7.4; N, 6.0.

***N*-Formyl-5′,6′-dihydrospiro[indan-1,2′(1′*H*)-pyridine] (3b).** Compound **3b** was prepared from **1b** (171 mg, 0.50 mmol), $Pd(OAc)_2$ (5.6 mg, 0.025 mmol), PPh_3 (26 mg, 0.10 mmol), TlOAc (145 mg, 0.55 mmol), and triethylamine (101 mg, 1.0 mmol) in CH_3CN (25 mL) as described above for the preparation of **3a** from **1a** (80 °C, 19 h). Purification by column chromatography (SiO_2 (fine), pentane/EtOAc 3:1, R_f 0.25) gave **3b** (90 mg, 84%) as a white solid, mp 96−98 °C. ^{1}H NMR δ 7.56 (s, 1H, C*H*O), 7.29−7.14 (m, 4H, Ar-H), 6.02−5.97 (m, 1H, H-4′), 5.58 (ddd, J = 10.0, 2.7 and 1.2 Hz, 1H, H-3′), 4.58 (dd, J = 10.3 and 5.2 Hz, 1H, H-6′), 3.05−2.89 (m, 3H, H-3 and H-6′), 2.44−2.27 (m, 1H, H-5′), 2.30 (app t, 2H, H-2), 2.22−2.11 (m, 1H, H-5′); ^{13}C NMR δ 161.3 (*C*HO), 144.4, 142.6 (C-8 and C-9), 132.1 (C-3′), 128.9, 127.4, 125.2, 125.0, 124.7 (C-4, C-5, C-6, C-7 and C-4′), 68.4 (C-1), 39.3 (C-2), 35.4 (C-6′), 29.6 (C-3), 24.5 (C-3′); IR ($CDCl_3$) 1647 cm^{-1}; MS [IP 70 eV; *m*/*z* (% rel int)] 213 (M^+, 61), 184 (36), 168 (100). Anal. Calcd for $C_{14}H_{15}NO$: C, 78.84; H, 7.09; N, 6.56. Found: C, 79.1; H, 7.3; N, 6.5.

***N*-Formyl-1′,3,4,6′-tetrahydrospiro[naphthalene-1(2*H*),2′(3′*H*)-pyridine] (6a).** Compound **6a** was prepared from **1a** (533 mg, 1.5 mmol), $Pd(OAc)_2$ (16.8 mg, 3.0 mmol), TFP (69 mg 0.30 mmol), and triethylamine (304 mg, 3.0 mmol) in CH_3CN (45 mL) as described above for the peparation of **2a** from **1a** (80 °C, 14 h). Purification by column chromatography (SiO_2, pentan/EtOAc 4:1 to 2:1) gave **2a** (104 mg, 31%) and a mixture of **3a** and **6a** (166 mg, 49%). The mixture of **3a** (t_R 139 min) and **6a** (t_R 131 min) was further purified on preperative HPLC to yield **6a** (36 mg, 11%), mp 96−98 °C. ^{1}H NMR δ 7.72 (d, J = 1.1 Hz, 1H, C*H*O), 7.42−7.37 (m, 1H, Ar-H), 7.25−7.14 (m, 3H, Ar-H), 5.93−5.80 (m, AB spectra, 2H, H-4′ and H-5′), 4.56−4.47 (m, 1H, H-6′), 3.63−3.54 (m, 1H, H-6′), 3.00−2.93 (m, 1H, H-3′), 2.84−2.80 (m, 2H, H-4), 2.26−2.16 (m, 2H, H-2 and H-3′), 1.85−1.52 (m, 3H, H-2 and H-3); ^{13}C NMR δ 163.7 (*C*HO), 138.6, 136.5 (C-9 and C-10), 129.8, 128.2, 127.8, 126.7 (C-5, C-6, C-7 and C-8), 123.5, 122.4 (C-4′ and C-5′), 57.1 (C-1), 39.8 (C-6′), 38.6 (C-3′), 33.4 (C-2), 30.1 (C-4), 18.4 (C-3); IR ($CDCl_3$) 1632 cm^{-1}; MS [IP 70 eV; *m*/*z* (% rel int)] 227 (M^+, 80), 198 (47), 182 (100), 167 (57), 145 (49), 128 (83). HRMS (EI) *m*/*z* calcd for $C_{15}H_{17}NO$ 227.1310, found 227.1314.

***N*-Formyl-3,4-dihydrospiro[naphthalene-1(2*H*),2′-piperidine] (4a).** Compound **2a** (21 mg, 0.09 mmol) and 10% Pd/C (10 mg, 0.009 mmol) were mixed in absolute ethanol (2 mL) under H_2 (1 atm) for 16 h. The mixture was filtered through Celite and concentrated to yield **4a** (21 mg, 98%) as a white solid, mp 90−91 °C. Compound **4a** (17 mg, 84%) was prepared in the same way from compound **3a** (20 mg, 0.09 mmol). ^{1}H NMR δ 7.70 (s, 1H, C*H*O), 7.45−7.42 (m, 1H, Ar-H), 7.39−7.05 (m, 3H, Ar-H), 4.42 (ddd, J = 13.9, 4.6 and 2.3 Hz, 1H, H-6′), 3.75−2.70 (m, 3H, H-4 and H-6′), 2.32−2.06 (m, 1H, H-2), 2.05−2.00 (m, 1H) and 1.96−1.51 (m, 8H) (H-2, H-3, H-3′, H-4′ and H-5′); ^{13}C NMR δ 164.1 (*C*HO), 138.2, 138.0 (C-9 and C-10), 129.6, 127.9, 127.4, 126.6 (C-5, C-6, C-7 and C-8), 58.5 (C-1), 36.8 (C-6′), 32.1 (C-2), 30.0 (C-4), 39.2, 24.8, 20.1, 18.4 (C-3, C-3′, C-4′ and C-5′); IR ($CDCl_3$) 1641 cm^{-1}; MS [IP 70 eV; *m*/*z* (% rel int)] 229 (M^+, 82), 200 (72), 128 (100). Anal. Calcd for $C_{15}H_{19}NO$: C, 78.57; H, 8.35; N, 6.11. Found: C, 78.38; H, 8.19; N, 6.19.

***N*-Formylspiro[indan-1,2′-piperidine] (4b).** Compound **4b** was prepared from **2b** (55 mg, 0.26 mmol), as described above for the preparation of **4a** from **2a** to yield (48 mg, 87%) as a white solid, mp 105−106 °C. Compound **4b** (57 mg, 82%) was prepared in the same way from compound **3b** (68 mg, 0.32 mmol).^{1}H NMR δ 7.63 (s, 1H, C*H*O), 7.33−7.23 (m, 4H, Ar-H), 4.58−4.49 (m, 1H, H-6′), 3.00−2.74 (m, 3H, H-3 and H-6′), 2.41−2.32 (m, 1H, H-2), 2.20−1.52 (m, 7H, H-2, H-3′, H-4′ and H-5′); ^{13}C NMR δ 161.7 (*C*HO), 144.0, 142.8 (C-8 and C-9), 128.8, 127.0, 125.4, 124.4 (C-4, C-5, C-6 and C-7), 68.8 (C-1), 38.0 (C-6′), 36.0 (C-2), 30.0 (C-3), 37.7, 24.9, 21.3 (C-3′, C-4′ and C-5′); IR ($CDCl_3$) 1646 cm^{-1}; MS [IP 70 eV; *m*/*z* (% rel int)] 215 (M^+, 34), 186 (50), 170 (65), 158 (43), 144 (56), 130 (83), 128 (78), 115 (100). Anal. Calcd for $C_{14}H_{17}NO$: C, 78.11; H, 7.96; N, 6.50. Found: C, 78.0; H, 7.7; N, 6.4.

3,4-Dihydrospiro[naphthalene-1(2*H*),2′-piperidine] (5a). Compound **4a** (17 mg, 0.074 mmol) was dissolved in dry THF (0.5 mL), and MeLi (0.12 mL, 0.18 mmol) was added slowly at 0 °C. The reaction mixture was kept at 0 °C for additional 45 min after which water (1 mL) was added. The reaction mixture was acidified by adding 3 N HCl and washed with diethyl ether (3 × 0.5 mL). The aqueous layer was made alkaline with 10% aqueous K_2CO_3 and extracted with diethyl ether (4 × 1 mL). The combined organic layers were dried (K_2CO_3) and concentrated to yield **5a** (11 mg, 71%) as a white solid, mp 49−50 °C. Spectroscopic data was consistent with data described elsewhere.[10c]

Spiro[indan-1,2′-piperidine] (5b). Compound **5b** was prepared from **4b** (22 mg, 0.1 mmol), as described above for the preparation of **5a** from **4a**, to yield **5b** (16 mg, 83%). Spectroscopic data was consistent with data described elsewhere.[10c]

General Procedure for Asymmetric Cyclization. Cyclization of 1a. $Pd(OAc)_2$ (0.1 equiv), (*R*)-BINAP (0.2 equiv), and $AgNO_3$ (1.0 equiv) were mixed in well degassed solvent (5 mL) under a stream of argon. Triethylamine (2.0 equiv) and **1a** (0.10 mmol) were added to the mixture. The reaction

mixture was stirred and heated at 60−80 °C for 24−168 h until GLC indicated complete consumption of **1a**. After cooling, the mixture was poured out on saturated aqueous $NaHCO_3$ (10 mL) and extracted with EtOAc (3 × 5 mL), and the combined organic layers were washed with brine (2 × 5 mL), dried (K_2CO_3), and concentrated. The crude product was purified by column chromatography (SiO_2, pentane/EtOAc 4:1−2:1) to yield **2a** and a mixture of **3a** and **6a**. The enantiomeric excesses was determined by enantioselective GLC.[29]

Cyclization of 7. $Pd(OAc)_2$ (0.1 equiv) and (*R*)-BINAP (0.2 equiv) were mixed in well degassed solvent (5 mL) under a stream of argon. Triethylamine (2.0 equiv) and **7** (0.10 mmol) were added to the mixture. The reaction mixture was stirred and heated to 60−80 °C for 24−168 h until GLC indicated complete consumption of **7**. Workup and purification as described for the cyclization of **1a**.

Determination of Absolute Configurations of Compounds 2a, 2b, 3a, and 6a. General. The absolute configurations of compounds **2a** and **2b** were assigned based on empirical force-field calculations (MM2-91) and by analyses of the circular dichroism spectra and are descibed elsewhere.[27]

Compounds **3a** and **6a** were resolved on two TAC[28] columns (600 × 10 mm i.d.) in series at a flow rate of 1.0 mL min^{-1}. A 1.1 mL loop was employed to introduce the samples. Detection was carried out at 254 nm with a variable wavelength detector. The mobile phase consisted of ethanol/water 96:4 and was degassed with He prior to use. The collected fractions of each enantiomer were concentrated, dissolved in 7 mL of diethyl ether, dried (K_2CO_3), and concentrated.

Chromatogaphic Enantiomer Separation of 3a. Racemic **3a** (60 mg) was dissolved in degassed ethanol/water (96:4, 3.5 mL) and filtered. Four injections were made. The first eluted band, (+)-**3a**, was found to be optically pure, but the second eluted band, (−)-**3a**, was reinjected. The fractions were optically pure according to GLC.[29] (+)-**3a**, $[\alpha]^{23}_D$ +10.1 (*c* 0.74, absolute ethanol), (−)-**3a**, $[\alpha]^{23}_D$ −10.9 (*c* 0.68, absolute ethanol).

Chromatogaphic Enantiomer Separation of 6a. Racemic **6a** (15 mg) was dissolved in degassed ethanol/water (96:4, 0.9 mL) and filtered. One injection was made. The first eluted band, (+)-**6a**, was not pure (95% according to GLC), but the second eluted band, (−)-**6a**, was found to be optically pure.[29] (+)-**6a**, $[\alpha]^{23}_D$ +18.8 (*c* 0.67, absolute ethanol), (−)-**6a**, $[\alpha]^{23}_D$ −28.5 (*c* 0.60, absolute ethanol).

Correlation of 3a and 6a with (*R*)-2a by Hydrogenation to 4a. Compound (*R*)-**2a**[27] (6.0 mg, 0.026 mmol) and 10% Pd/C (2.8 mg, 0.0022 mmol) were mixed in absolute ethanol (0.5 mL) under H_2 (1 atm) for 15 h. The mixture was filtered through Celite and concentrated to yield (*S*)-**4a** (6.0 mg, 99%).

Compound (+)-**3a** was hydrogenated in the same way to yield (*R*)-**4a**, $[\alpha]^{23}_D$ −24.1 (*c* 0.65, absolute ethanol) and compound (−)-**6a** to yield (*S*)-**4a**, $[\alpha]^{23}_D$ +24.2 (*c* 0.43, absolute ethanol). The absolute configurations were determined by comparison of the products on a chiral GLC-column.[29]

Acknowledgment. The authors are grateful to the Swedish Natural Science Research Council for financial support.

JO961832B