Regiochemical Control and Suppression of Double Bond Isomerization in the Heck Arylation of 1-(Methoxycarbonyl)-2,5-dihydropyrrole

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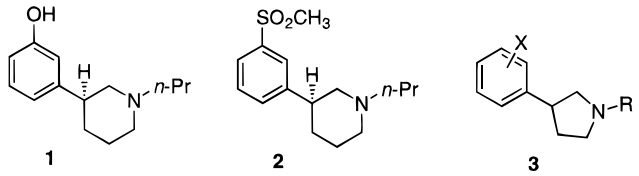
Arylation of 1-(methoxycarbonyl)-2,5-dihydropyrrole under standard Heck reaction conditions produces a mixture of compounds. The olefin undergoes two types of palladium-catalyzed reactions: (a) arylation to provide C-3 arylated derivatives and (b) competing double bond isomerization. Addition of silver carbonate and thallium acetate fully suppressed the isomerization, and good yields of C-3 substituted compounds were achieved after arylation with aryl halides. With regard to aryl triflates as arylating agents, addition of lithium chloride was necessary to promote the Heck reaction. This additive excluded the use of silver and thallium salts, but high regioselectivity and good yields could be obtained by employing tri-2-furylphosphine as ligand. Arylation was rendered both regioselective and enantioselective (58% ee) with 1-naphthyl triflate as substrate utilizing a (*R*)-BINAP/thallium acetate combination. The C-3 arylated enamides were converted further into the corresponding 3-arylpyrrolidines.

Introduction

Regioselective palladium-catalyzed C-2 arylation of cyclic five- and six-membered enol ethers[1,2] or of enamides[3] with aryl halides or triflates can be achieved in good yields. In addition, cyclic five-membered allylic compounds such as sulfolene can undergo facile arylation[4] and Larock has reported relatively recently that 2,5-dihydrofuran reacts smoothly under mild reaction conditions producing the C-3 arylated 2,3-dihydrofuran in high yield.[5] A low degree of regioselectivity is observed in the arylation of six-membered, cyclic *N*-acylallylamines, possessing two nonequivalent vinylic positions, while a highly regioselective Pd−N chelate-controlled vinylic substitution of the corresponding cyclic *N*-alkylallylamines occurs.[6] The latter reaction[6] was applied to the synthesis of the partial dopamine D_2-agonist, preclamol (**1**),[7a,b] currently undergoing clinical trials.[7c] The arylpiperidine **2** was recently reported as a preferential DA (dopamine) autoreceptor antagonist, with an interesting pharmacological profile.[8] To expand the SAR (structure−activity relationship), access to a short and convergent procedure was needed for the preparation of related C-3 substituted pyrrolidines **3**, as potential DA receptor antagonists.

Chart 1



1 **2** **3**

We herein report a regioselective palladium-catalyzed arylation reaction of *N*-substituted 2,5-dihydropyrroles **4a**,**b**, that provides 3-aryl(heteroaryl)-2,3-dihydropyrroles **5a**−**j**, key intermediates in this synthesis of 3-aryl(heteroaryl)pyrrolidines **3a**−**j**.

Results

The initial Heck arylation experiments[9] were conducted using iodobenzene as arylating agent. Arylation of 1-(methoxycarbonyl)-2,5-dihydropyrrole (**4a**) with iodobenzene under the following reaction conditions: a catalytic amount of palladium acetate, dppp (1,3-bis-[diphenylphosphino]propane) as phosphine ligand, and *N*,*N*-diisopropylethylamine as base in DMF at 100 °C, resulted in a reaction mixture comprised of 1-(methoxycarbonyl)-3-phenyl-2,3-dihydropyrrole (**5a**), 1-(methoxycarbonyl)-2-phenyl-2,3-dihydropyrrole (**6a**), and 1-(meth-

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(3) (a) Nilsson, K.; Hallberg, A. *J. Org. Chem.* **1990**, *55*, 2464. (b) Ozawa, F.; Hayashi, T. *J. Organomet. Chem.* **1992**, *428*, 267. (c) Hillers, S.; Sartori, S.; Reiser, O. *J. Am. Chem. Soc.* **1996**, *118*, 2087.

(4) Harrington, P. J.; DiFiore, K. A. *Tetrahedron Lett.* **1987**, *28*, 495.

(5) Larock, R. C.; Baker, B. E. *Tetrahedron Lett.* **1988**, *29*, 905.

(6) Nilsson, K.; Hallberg, A. *J. Org. Chem.* **1992**, *57*, 4015.

(7) (a) Hacksell, U.; Arvidsson, L.-E.; Svensson, U.; Nilsson, L. G.; Sanchez, D.; Wikström, H.; Lindberg, P.; Hjorth, S.; Carlsson, A. *J. Med. Chem.* **1981**, *24*, 1475. (b) Hjorth, S.; Carlsson, A.; Clark, D.; Svensson, K.; Wikström, H.; Sanchez, D.; Lindberg, P.; Hacksell, U.; Arvidsson, L.-E.; Johansson, A.; Nilsson, J. L. G. *Psychopharmacology* **1983**, *81*, 89. (c) Tamminga, C. A.; Cascella, N. G.; Lahti, R. A.; Lindberg, M.; Carlsson, A. *J. Neural Transm. [GenSect]* **1992**, *88*, 165.

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(9) For reviews on the Heck reaction see; (a) Heck, R. F. *Org React.* **1982**, *27*, 345. (b) Trost, B. M.; Verhoeven, T. R. *Comprehensive Organometallic Chemistry*; Wilkinson, G., Stone, F. G. A., Abel, E. W., Eds.; Pergamon Press: Oxford, 1982; Vol. 8, pp 854. (c) Heck, R. F. *Palladium Reagents in Organic Synthesis*; Academic Press; London, 1985; pp 276. (d) Heck, R. F. *Comprehensive Organic Synthesis*; Trost, B. M., Flemming, I., Eds.; Pergamon Press: Oxford 1991; Vol. 4, pp 833. (e) de Meijere, A.; Meyer, F. E. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 2379. (f) Cabri, W.; Candiani, I. *Acc. Chem. Res.* **1995**, *28*, 2. (g) For Heck arylation of heteroatom-substituted double bonds see Tsuji, J. *Palladium Reagents and Catalysts: Innovations in Organic Chemistry*; John Wiley & Sons: Chichester, 1995; pp 125−163. (h) Daves, G. D., Jr.; Hallberg, A. *Chem. Rev.* **1989**, *89*, 1433.

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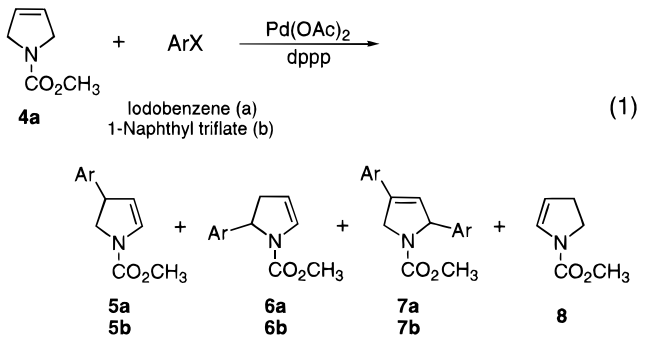
oxycarbonyl)-2,4-diphenyl-2,5-dihydropyrrole (**7a**) as the major products, all formed in yields higher than 10% (eq 1). In addition, a considerable amount of **4a** had isomerized to the enamide **8**.[10] This isomerization continued even after complete consumption of the aryl halide. The compounds **5**−**8** were also the major components, together with the deoxygenated naphthalene, when 1-naphthyl triflate was employed under similar reaction conditions. The naphthyl derivatives **5b** and **6b** were formed in equal amounts (eq 1) We observed that separation of



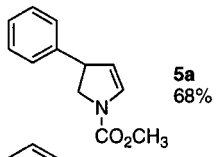
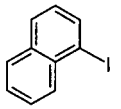
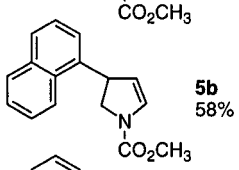
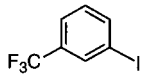
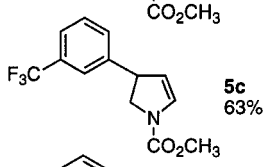
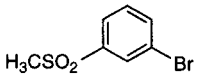
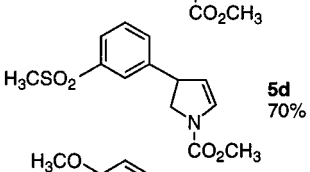
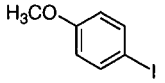
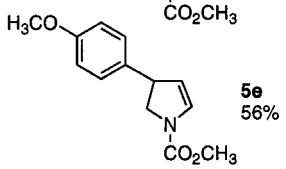
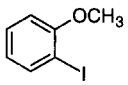
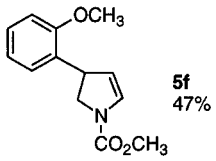
(1)

the two regioisomers **5** and **6**, or separation of their saturated counterparts, was not facile by standard chromatographic procedures, and it was therefore essential for our preparative purposes to have access to methods providing a high **5**/**6** ratio.

The olefin **4a** undergoes two types of palladium-catalyzed reactions: (a) arylation to provide **5** and (b) double bond isomerization. These processes are competitive and subsequent arylation of the isomerized double bond furnishes the undesired compound **6**. Thus, our primary objective was the suppression of the isomerization process and secondly, were this to prove unrealizable, to find conditions disfavoring arylation of the isomerization product **8** relative to the 2,5-dihydropyrrole **4a**.

Iodobenzene as Arylating Agent. The beneficial effect of silver additives in controlling double bond migration in intramolecular Heck-reactions was first observed by Overman's group.[11a,b] Although we realized that the isomerization in our system precedes the arylation, we assumed that a similar type of catalytic species could be involved in both reactions. We therefore decided to examine the effect of silver additives on the undesired conversion of the allylamide to the enamide. Addition of 0.7 equiv of silver carbonate[12] to reactions using iodobenzene (1.0 equiv) as arylating agent and P(*o*-tol)$_3$[13] as ligand suppressed the formation of **6a** completely.

Table 1. Palladium-Catalyzed Regioselective Reaction of 4a with Aryl Halides

aryl halide	time (h)	isolated yield (%)[a] of **5**
	4	 **5a** 68%
	4	 **5b** 58%
	8	 **5c** 63%
	9	 **5d** 70%
	22	 **5e** 56%
	20	 **5f** 47%

Reactions were run under an argon atmosphere. Reactions utilized ArX (3 mmol), *i*-Pr$_2$NEt (4 eq.), **4a** (10 eq.), Ag_2CO_3 (0.7 eq.), Pd(OAc)$_2$ (0.05 eq.), P(*o*-tol)$_3$ (0.11 eq.) and DMF (8 ml) at 100 °C. The **5**/**6** ratio were >99/1 according to GC/MS. [a] >95% purity by GC/MS.

Furthermore, we did not observe isomerization of the olefin **4a** to the enamide **8** under these reaction conditions. To minimize the undesired diarylation, the main cause of the moderate yields of **5**, an excess of the olefin was required (an olefin/iodobenzene ratio of 10/1 was sufficient). These conditions gave less than 10−20% of **7**, depending on the arylating substrate used, and **7** could be separated easily from **5** by chromatography. A 56% yield of **7a** was isolated after employing an olefin/iodobenzene ratio of 1/2, reflecting the importance of conducting the reaction with an excess of olefin.

1-Naphthyl Triflate as Arylating Agent. Employing PPh$_3$ or P(*o*-tol)$_3$ instead of the bidentate ligand dppp led only to small amounts of product with 1-naphthyl triflate remaining. Addition of lithium chloride was required to promote the reaction.[14,15] This additive also strongly suppressed the undesired reduction of the naphthyl triflate,[16] but the unsatisfactory isomer ratio, derived from the olefin isomerization, remained as an obstacle.

(10) We recently reported that **8** was conveniently prepared from **4a** under Heck reaction conditions omitting aryl halide. Sonesson, C.; Hallberg, A. *Tetrahedron Lett.* **1995**, *36*, 4505.

(11) (a) Abelman, M. M.; Oh, T.; Overman, L. E. *J. Org. Chem.* **1987**, *52*, 4130. (b) Abelman, M. M.; Overman, L. E. *J. Am. Chem. Soc.* **1988**, *110*, 2328. For recent applications of silver additives in intramolecular Heck reactions see: (c) Ahimori, A.; Overman, L. E. *J. Org. Chem.* **1992**, *57*, 4571. (d) Larock, R. C. *Pure Appl. Chem.* **1990**, *62*, 653. (e) Sato, Y.; Watanabe, S.; Shibasaki, M. *Tetrahedron Lett.* **1992**, *33*, 2589. (f) Sato, Y.; Honda, T.; Shibasaki, M. *Tetrahedron Lett.* **1992**, *33*, 2593. (g) Nukui, S.; Sodeoka, M.; Shibasaki, M. *Tetrahedron Lett.* **1993**, *34*, 4965. (h) Sakamoto, T.; Kondo, Y.; Uchiyama, M.; Yamanaka, H. *J. Chem. Soc., Perkin Trans. 1* **1993**, 1941. (i) Jin, Z.; Fuchs, P. L. *Tetrahedron Lett.* **1993**, *34*, 5205. (j) Tietze, L. F.; Schimpf, R. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 1089. (k) Steinig, A. G.; Bräse, S.; de Meijere, A. 8th IUPAC Symposium on Organo-Metallic Chemistry directed towards Organic Synthesis, Santa Barbara, 1995, Abstr. No. 241.

(12) A 0.7 equiv amount of silver carbonate was the minimum amount needed to fully suppress the formation of **6a**.

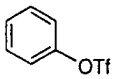
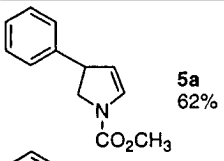
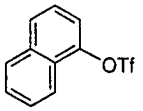
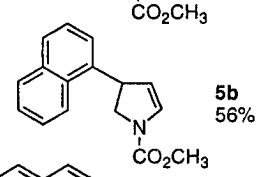
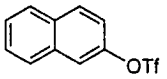
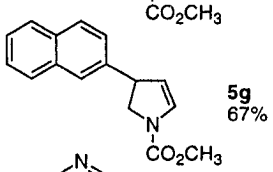
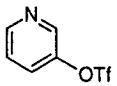
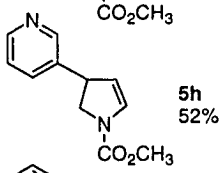
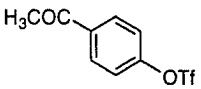
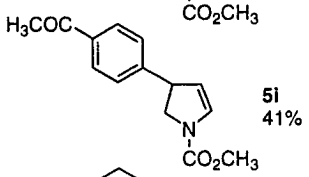
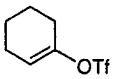
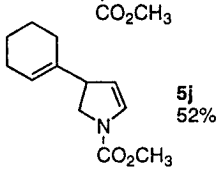
(13) In a screening of ligands we found that the monodentate ligands, and in particular P(*o*-tol)$_3$, were superior to the bidentate ligands with regard to regioselectivity and yield.

(14) (a) Echavarren, A. M. and Stille, J. K. *J. Am. Chem. Soc.* **1987**, *109*, 5478. (b) Amatore, C.; Azzabi, M.; Jutand, A. *J. Am. Chem. Soc.* **1991**, *113*, 8375. (c) Amatore, C.; Jutand, A.; Suarez, A. *J. Am. Chem. Soc.* **1993**, *115*, 9531. (d) Jutand, A.; Mosleh, A. *Organometallics* **1995**, *14*, 1810. (e) Larhed, M.; Andersson, C.-M.; Hallberg, A. *Tetrahedron* **1994**, *50*, 285. (f) Farina, V.; Krishnan, B.; Marshall, D. R.; Roth, G. P. *J. Org. Chem.* **1993**, *58*, 5434.

(15) No conversion of the aryl triflate occurred with dppp in presence of chloride, as expected from recent findings. See refs 16 and 35d.

(16) Cabri, W.; Candiani, I.; DeBernardinis, S.; Francalanci, F.; Penco, S.; Santi, R. *J. Org. Chem.* **1991**, *56*, 5796.

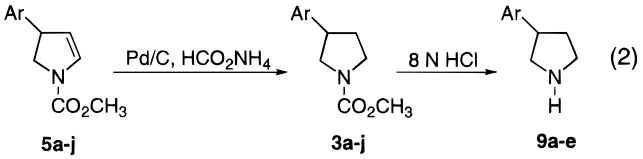
Table 2. Palladium-Catalyzed Regioselective Reaction of 4a with Aryl- or Vinyl Triflates

aryl/vinyl triflate	time (h)	isolated yield (%)[a] of **5**
	4	 **5a** 62%
	4	 **5b** 56%
	4	 **5g** 67%
	10	 **5h** 52%
	18	 **5i** 41%
	3	 **5j** 52%

Reactions were run under an argon atmosphere. Reactions utilized ArOTf or VinylOTf, (3 mmol), *i*-Pr$_2$NEt (4 eq.), **4a** (10 eq.), LiCl (3 eq.), Pd(OAc)$_2$ (0.05 eq.), TFP (0.11 eq.) and DMF (8 ml) at 100 °C. The **5**/**6** ratio were >96/4 according to GC/MS. [a] >95% purity by GC/MS.

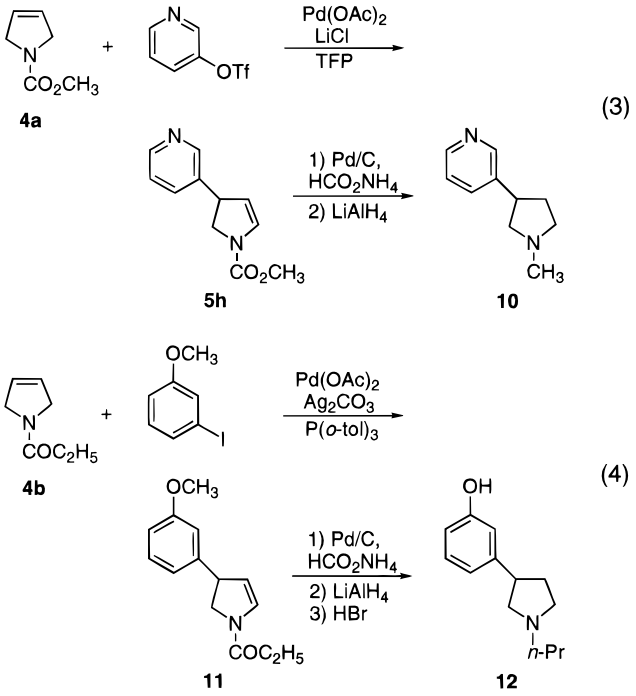
The chloride addition precluded the use of silver and thallium ions, but by employing the weakly palladium(II)-coordinating TFP (tri[2-furyl]phosphine)[17] as ligand, a satisfactory **5b**/**6b** ratio (98/2) was achieved.

To prove the generality of the Ag/P(*o*-tol)$_3$ conditions with organohalides and the chloride/TFP procedure with organotriflates, we selected eleven different arylating reagents and one vinyl triflate. The preparative results are summarized in Table 1 and Table 2. Fair isolated yields of coupled products were obtained with both electron-rich and electron-poor organopalladium precursors, including the pyridyl triflate. The arylated cyclic enamides **5a**−**j** tended to decompose slowly upon isolation, and full characterization, including elemental analyses, were therefore conducted after the subsequent hydrogenation reaction. The hydrogenated products **3a**−**j** were converted to the secondary amines **9a**−**e** by hydrolysis (eq 2).



5a-j **3a-j** **9a-e** (2)

We have applied the arylation−hydrogenation procedure to the preparation of isonicotine, **10** (eq 3), recently reported to be a good ligand for nicotine receptors *in vitro*,[18] and to the preparation of the partial dopamine agonist USDA 19, **12**[7a] (eq 4).



Asymmetric Reactions. In 1989, Shibasaki[19] and Overman[20] independently reported the first examples of an intramolecular asymmetric Heck reaction. The first example of an intermolecular asymmetric Heck reaction was reported in 1991 by Hayashi,[2a] who performed C-2 arylations of 2,3-dihydrofuran[2a,b] and *N*-substituted 2,3-dihydropyrroles[3b] with aryl triflates in high enantiomeric excess. The enantioselectivity was even better with alkenyl triflates,[21] while no or only a low ee was experienced with iodoarenes.[2a−c,3a,22] The potential use of 3-aryl substituted cyclic enamides as precursors for **3** encouraged us to briefly study asymmetric arylation of **4a**. It is important to emphasize that this olefin contains two vinylic carbon atoms interrelated by a C_2-axis. We are only aware of one example of chiral induction of analogous olefins, namely in the arylation of 4,7-dihydro-1,3-dioxepin and some of its analogs (which furnished up to 75% ee).[23]

We focussed on 1-naphthyl triflate as arylating agent, since the *N*-propyl substituted **9b** had exhibited interesting pharmacological properties in an initial receptor binding study.[24] The reactions were performed with a

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

(18) (a) Dukat, N.; Damaj, M. I.; Glassco, W.; Dumas, D.; May, E. L.; Martin, B. R. *Med. Chem. Res.* **1994**, *4*, 131. (b) *Ber. Dtsch. Chem. Ges. B* **1938**, *71*, 1276.

(19) (a) Sato, Y.; Sodeoka, M.; Shibasaki, M. *J. Org. Chem.* **1989**, *54*, 4738. (b) Ohrai, K.; Kondo, K.; Sodeoka, M.; Shibasaki, M. *J. Am. Chem. Soc.* **1994**, *116*, 11737. (c) Kondo, K.; Sodeoka, M.; Shibasaki, M. *J. Org. Chem.* **1995**, *60*, 4322.

(20) (a) Carpenter, N. E.; Kucera, D. J.; Overman, L. E. *J. Org. Chem.* **1989**, *54*, 5846. (b) Ashimori, A.; Matsuura, T.; Overman, L. E.; Poon, D. J. *J. Org. Chem.* **1993**, *58*, 6949.

(21) Ozawa, F.; Kobatake, Y.; Hayashi, T. *Tetrahedron Lett.* **1993**, *34*, 2505.

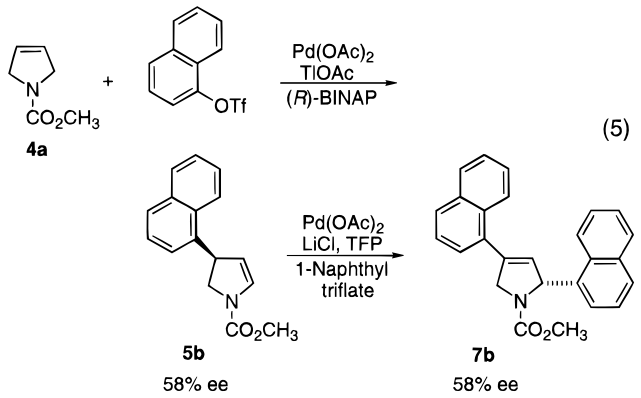
(22) Asymmetric arylation of the cyclic vinyl ether 4*H*-1,3-dioxin with (*R*)-BINAP as ligand has been achieved in 43% ee utilizing iodobenzene/silver carbonate. Sakamoto, T.; Kondo, Y.; Yamanaka, H. *Tetrahedron Lett.* **1992**, *33*, 6845.

(23) Koga, Y.; Sodeoka, M.; Shibasaki, M. *Tetrahedron Lett.* **1994**, *35*, 1227.

(24) Sonesson, C.; Wikström, H.; Smith, M. W.; Svensson, K.; Carlsson, A.; Waters, N. *Bioorg. Med. Chem. Lett.*, to be submitted.

catalyst generated *in situ* from $Pd(OAc)_2$ and (*R*)-BINAP[25] as cocatalyst, since it is known that the active Pd(0) catalyst is generated under similar conditions.[2b,19b,26] Our initial experiments revealed that DMF as solvent was superior to the less polar benzene[27] and toluene with *N*,*N*-diisopropylethylamine as the base. Although chiral induction was achieved with (*R*)-BINAP, the use of this bidentate ligand: as was the case with dppp (eq 1), was accompanied by a low **5b**/**6b** ratio. We found that the presence of acetate, weakly coordinating to Pd(II),[19b,28] was beneficial both for the **5b**/**6b** ratio[29] and for the enantiomeric enrichment, while the addition of LiCl ruined the chiral induction.[30] Even a catalytic amount of acetate tended to exhibit a positive effect on the product distribution and substitution of $Pd(OAc)_2$ for $Pd(0)_2(dba)_3-CHCl_3$[20b,31] or Pd(II)acac as precatalysts furnished a mixture of almost equal amounts of **5b** and **6b**. The addition of 0.5−2.0 mol equiv of acetic acid, generating ammonium acetate in the system, provided a **5b**/**6b** selectivity of 95/5[32,33] and an enantiomeric excess of 50−60%.[34]

However, for efficient synthesis of **9b** in enantiomeric excess, a **5b**/**6b** ratio higher than 95/5 was desired. Addition of thallium acetate[35] fulfilled this requirement. In fact, it was found that the presence of 1.0 equiv of thallium acetate, replacing acetic acid, allowed the synthesis of isomerically pure **5b** (**5b**/**6b** > 99/1) in 58% ee and 34% isolated yield (eq 5). Unfortunately, substantial chiral induction was realized only in the case of 1-naphthyl triflate, despite several attempts with both



phenyl triflate and 2-naphthyl triflate. Equally disappointing results were encountered with 1-iodonaphthalene after the addition of silver carbonate or thallium acetate, which was expected to provide a similar cationic π-complex as suggested in aryl triflate reactions.[9e,f,36] The relatively low yield in the asymmetric arylation of **4a** is probably mainly attributable to an inefficient coordination−insertion step[9f,30] and not to a slow oxidative addition of 1-naphthyl triflate, which proved to be an efficient process as deduced by the large amounts of naphthalene formed.[16,37]

In addition, enantiomerically enriched **5b** was allowed to react with 2 equiv of 1-naphthyl triflate, employing similar conditions used for the racemic reactions in Table 2 (eq 5). A complete chirality transfer (100%) was encountered, and **7b** was isolated in 48% yield (58% ee).

Discussion

Reactions with Neutral Arylpalladium Halide Species. Although we have made no detailed studies which permit the evaluation of the reaction mechanism for the formation of **5**−**8**, we suggest the catalytic cycle in Scheme 1. Initial reduction of palladium(II) to the active zero-valent state is facile under the conditions used with the olefin, amine, or phosphine acting as reducing agent.[38] With regard to the isomerization[39] of **4a** to **8** we observed, under Heck reaction conditions omitting iodobenzene, that $Pd(OAc)_2$ was active as a catalyst. However, omission of the phosphine and the amine (both capable of reducing palladium(II) from the reaction mixture) afforded a completely inactive isomerization catalyst. It has been demonstrated that Pd/C catalyzes the transformation of *N*-acyl-1,2,5,6-tetrahydropyridines to enamides.[40] Pd/C in the absence of phosphine/amine exhibits isomerization capacity also in our catalytic system.

(25) 2,2′-Bis(diphenylphosphino)-1,1′-binaphthyl. See. Noyori, R.; Takaya, H. *Acc. Chem. Res.* **1990**, *23*, 345.

(26) Ozawa, F.; Kubo, A.; Hayashi, T. *Chem. Lett.* **1992**, 2177.

(27) DMF was also found to be superior to benzene in the asymmetric arylation of 4*H*-1,3-dioxin. See ref 22.

(28) The acetate ion is considered to possess an intermediately strong dissociating ability to Pd(II), with respect to the easily dissociated triflate ion and the more strongly complexed halide ions. See refs 16 and 35d.

(29) (a) Suppression of double bond migration by acetate addition in Heck reactions has been reported. See, Laschat, S.; Narjes, F.; Overman, L. E. *Tetrahedron* **1994**, *50*, 347. See also ref 2b and 5. (b) It is also noteworthy that the chemoselectivity was improved (**5b**/**6b** = 99/1, 32% yield) utilizing the racemic combination $Pd(OAc)_2$/DPPP/KOAc (2.0 equiv).

(30) PhPdCl complexes of dippb (1,4-bis[diisopropylphosphino]-butane), a nonasymmetric bidentate ligand with a four-carbon tether (same as BINAP), is found to exist in both the η^1 coordination mode and in the chelating mode. Portnoy, M.; Ben-David, Y.; Rousso, I.; Milstein, D. *Organometallics* **1994**, *13*, 3465.

(31) (a) Sato, Y.; Nukui, S.; Sodeoka, M.; Shibasaki, M. *Tetrahedron* **1994**, *50*, 371. (b) Tsuda, T.; Kiyoi, T.; Saegusa, T. *J. Org. Chem.* **1990**, *55*, 3388.

(32) To examine the effect of acetate concentration three competitive experiments with equal concentration (5.0 equiv) of **4a** and **8** were performed in DMF. 1-Naphthyl triflate (1.0 equiv) was used as arylating agent, and *i*-Pr_2NEt (4.0 equiv) and three different catalytic systems, $Pd(0)_2(dba)_3-CHCl_3$/(*R*)-BINAP, $Pd(OAc)_2$/(*R*)-BINAP, and $Pd(OAc)_2$/(*R*)-BINAP/HOAc (1.0 equiv) were employed. All three reactions at 80 °C afforded after 18 h an almost identical 11/89 mixture of **5b** and **6b**, demonstrating the higher reactivity of **8** irrespective of the acetate concentration. This result corroborate the proposal that the increased **5b**/**6b** ratio in the asymmetric arylation is due to acetate-mediated suppression of isomerization.

(33) Regrettably, the acetate/P(*o*-tol)$_3$ combination was found to be inferior to silver carbonate/P(*o*-tol)$_3$ in controlling the regioselectivity with aryl halides.

(34) A high (*R*)-BINAP/Pd ratio (2.2/1) was needed for enantiomeric induction, which might be due to the consumption of BINAP in the reduction of Pd(II). See ref 26. Prereduction of $Pd(OAc)_2$ with cyclohexene in the presence of base and BINAP did not improve the ee. See ref 31a.

(35) Thallium(I) salts have been introduced and proved to be very useful in Pd-catalyzed reactions. (a) Grigg, R.; Loganathan, V.; Sukirthalingam, S.; Sridharan, V. *Tetrahedron Lett.* **1990**, 31, 6573. (b) Grigg, R.; Loganathan, V.; Santhakumar, V.; Sridharan, V.; Teasdale, A. *Tetrahedron Lett.* **1991**, 32, 687. (c) Carfagna, C.; Musco, A.; Sallese, G.; Santi, R. and Fiorani, T. *J. Org. Chem.* **1991**, 56, 261. (d) Cabri, W.; Candiani, I.; Bedeschi, A.; Penco, S.; Santi, R. *J. Org. Chem.* **1992**, *57*, 1481.

(36) In solution the triflate anion is not coordinated to palladium(II). See ref 14d and Decker, G. P. C. M.; Elsevier, C. J.; Vrieze, K.; van Leeuwen, P. W. N. M. *Organometallics* **1992**, *11*, 1598.

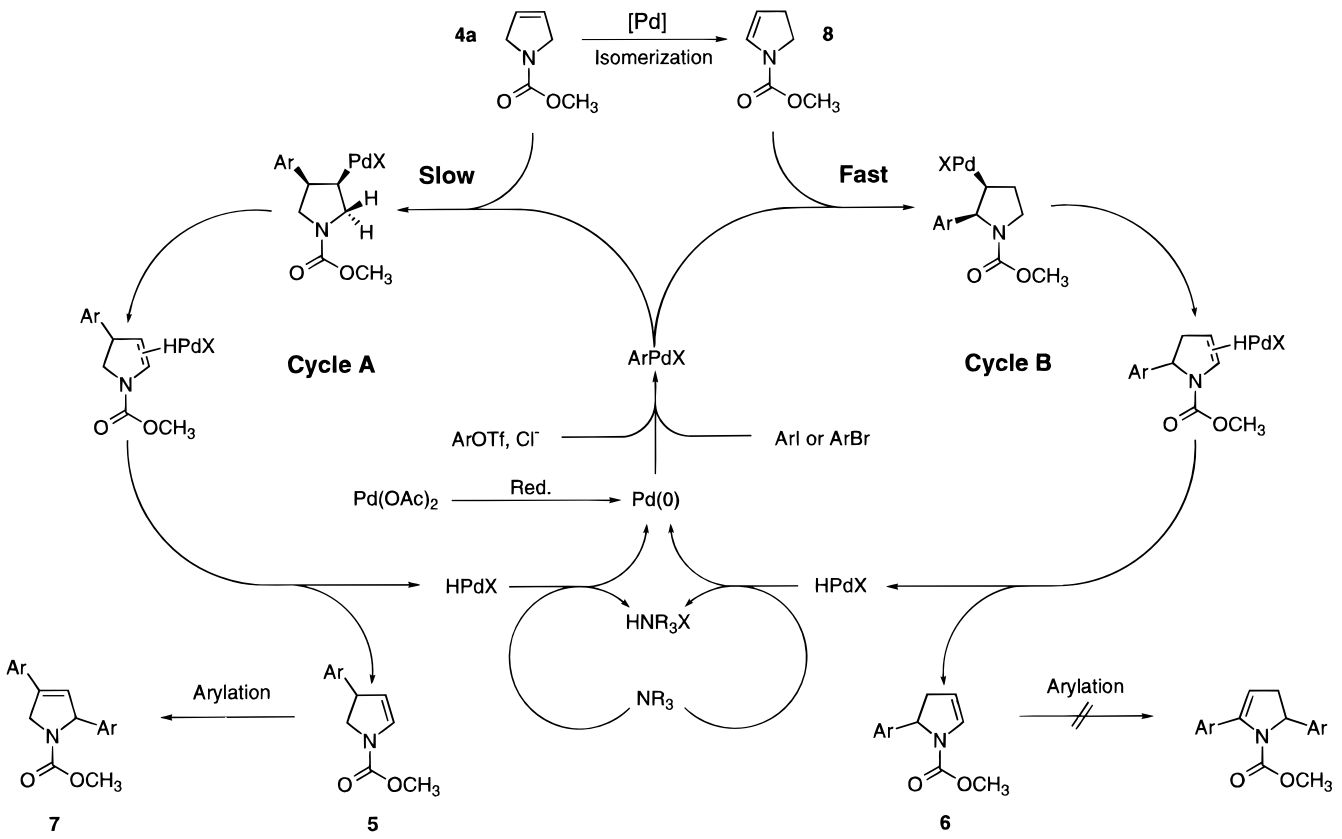
(37) Saá, J. M.; Dopico, M.; Martorell, G.; García-Raso, A. *J. Org. Chem.* **1990**, *55*, 991.

(38) For olefin as reducing agent see: (a) Trost, B. M.; Murphy, D. J. *Organometallics* **1985**, *4*, 1143. For amine as reducing agent see: (b) McCrindle, R.; Ferguson, G.; Arsenault, G.; McAlees, A. J. *J. Chem. Soc., Chem. Commun.* **1983**, 571. For phosphine as reducing agent see; (c) Amatore, C.; Jutand, A.; M'Barki, M. A. *Organometallics* **1992**, *11*, 3009. (d) Amatore, C.; Carré, E.; Jutand, A.; M'Barki, M. A. *Organometallics* **1995**, *14*, 1818. (e) Mandai, T.; Matsumoto, T.; Tsuji, J. *Tetrahedron Lett.* **1993**, 34, 2513. See also ref 26.

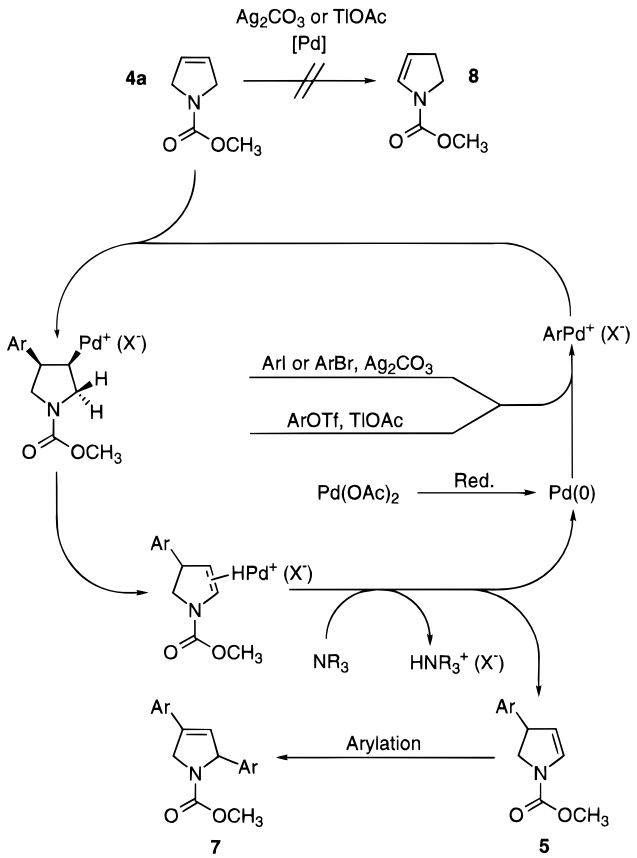
(39) (a) Parshall, G. W.; Ittel, S. D. *Homogeneous Catalysis*; John Wiley & Sons Inc: New York, 1992; p 8. (b) For Pd(II)-catalyzed olefin isomerization see: Sen, A.; Lai, T.-W. *Inorg. Chem.* **1984**, *23*, 3257. (c) For isomerization of *N*-allylamides catalyzed by other transition metal complexes see: Stille, J. K.; Becker, Y. *J. Org. Chem.* **1980**, *45*, 2139.

(40) (a) Wanner, K. Th.; Kärtner, A. *Heterocycles* **1987**, *26*, 917. (b) Wanner, K. Th.; Kärtner, A. *Arch. Pharm. (Weinheim)* **1987**, *320*, 1050.

Scheme 1



Scheme 2



Reaction of the aryl halide or triflate with an anionic acetate−palladium(0)−phosphine complex[38c] or a stabilized chloropalladium(0)−phosphine compound,[14b,41] results in an oxidative addition complex.[42] In the next step a neutral π-complex is formed, and the olefin **4a** inserts into the Pd−aryl bond, eventually providing **5** (cycle A). The isomerization product **8** competes favorably with **4a** for the arylpalladium halide species, leading to the formation of the regioisomer **6** (cycle B). Surprisingly, only the enamide **5** seemed prone to further arylation, and we were only able to detect traces of product derived from a second arylation of **6**. This result, probably of steric origin, is unexpected considering the elegant approach to *trans*-2,5-diaryltetrahydrofurans, based on diarylation of 2,3-dihydrofuran, reported by Larock[43] and Hayashi.[44]

Reactions with Cationic Aryl Palladium Species. A likely mechanism for the Heck reaction performed in the presence of silver carbonate (aryl halides) or thallium acetate (asymmetric arylation of 1-naphthyl triflate) is presented in Scheme 2. In this catalytic cycle, halide abstraction by silver carbonate or dissociation of the labile triflate or acetate ligand generates cationic palladium intermediates. An explanation for the complete suppression of the isomerization process (providing a **5**/**6** ratio higher than 99/1) after addition of 0.7 equiv of silver carbonate to reactions of aryl halides is not obvious. Double bond migration in the arylation of certain cyclic[11] and acyclic[45] alkenes is also suppressed by silver additives.[46] We have conducted one experiment where iodo-

(41) Negishi, E.; Takahashi, T.; Akiyoshi, K. *J. Chem. Soc., Chem. Commun.* **1986**, 1338.

(42) Recently, Hartwig *et al.* have reported that oxidative addition of aryl halides to $Pd[P(o\text{-tol})_3]_2$ in benzene results in dimeric products $\{Pd[P(o\text{-tol})_3](Ar)(X)\}_2$. See: (a) Paul, F.; Hartwig, J. F. *J. Am. Chem. Soc.* **1995**, *117*, 5373. (b) Paul, F.; Patt, J.; Hartwig, J. F. *Organometallics* **1995**, *14*, 3030.

(43) Larock, R. C.; Gong, W. H. *J. Org. Chem.* **1990**, *55*, 407.

(44) Ozawa, F.; Kubo, A.; Hayashi, T. *Tetrahedron Lett.* **1992**, *33*, 1485.

(45) (a) Jeffery, T. *Tetrahedron Lett.* **1991**, *32*, 2121. (b) Jeffery, T. *Tetrahedron Lett.* **1993**, *34*, 1133.

benzene was not initially included in the reaction mixture, but was added after 20 h. Arylation occurred, proving that the active palladium catalyst formed in this Pd(0)/Ag(I) system is able to undergo oxidative addition to the aryl halide, but not capable of acting as an isomerization catalyst. We observed that silver triflate[47] did not suppress the double bond isomerization, and arylation of **4a** with iodobenzene yielded the C-2 arylated derivative **6a** as the major product. Silver nitrate exhibited only a weak suppressive effect on the isomerization rate.[48] Addition of thallium acetate to a reaction mixture with iodobenzene in the presence of dppp provided an almost identical product pattern to that found after silver carbonate addition, and the olefin isomerization was fully suppressed.

Effect of Ligands in Reactions with Neutral Arylpalladium Halide Species. The regioselectivity in the reaction with iodobenzene (in the absence of metal additives) was affected by the choice of phosphine ligand. While the use of the bidentate ligand dppp resulted in a low 3-aryl/2-aryl ratio (80/20), a much higher selectivity and increased yields were achieved with the monodentate ligands PPh_3 (92/8) and P(*o*-tol)$_3$ (95/5). We considered three factors that might explain the inferior selectivity with dppp: (a) a dppp-induced rate enhancement of the olefin isomerization, or (b) a lower rate of arylation of the allylic amide **4a** with dppp, or (c) a higher preference for the enamide **8** as substrate with dppp as ligand. An experiment employing **4a** and omitting iodobenzene showed that both monodentate ligands in comparison to dppp were similarly effective in promoting the double bond isomerization. However, the arylation reactions with monodentate ligands were considerably faster (especially with poor palladium(II) ligands[17,49] such as TFP, $AsPh_3$, and P(*o*-tol)$_3$) than reactions where bidentate ligands (dppe, dppp, and dppb) were employed. This suggests that olefin coordination occurs by phosphine rather than halide displacement from the oxidative addition complex,[9e,f] both with mono- and bidentate ligands. The **5**/**6** ratio appears to be an inverse function of the coordinating ability of the phosphine ligand.[49] Competitive experiments with iodobenzene and an excess of an equal amount of the two olefins **4a** and **8** revealed that the enamide **8** was the preferred substrate,[50] but also that the substrate selectivity was slightly influenced by the choice of ligand. While use of P(*o*-tol)$_3$ gave a 2-aryl/3-aryl ratio of 80/20, the corresponding ratio when employing dppp was 88/12. 1-Naphthyl iodide showed even higher preference for the enamide **8** as substrate, especially pronounced with dppp as ligand. Thus, we conclude that the low regioselectivity obtained with the strongly palladium-coordinated dppp is due to a slow arylation of **4a** and a faster arylation of the more reactive enamide **8**. The fact that TFP/Cl^- was preferable in the reactions of aryl triflates indicates that the phosphine ligand displacement is important also in this case.

Conclusion

In summary, we have developed three different sets of reaction conditions which allow fully controlled regioselectivity and high yields of C-3 arylated 2,3-dihydropyrroles: (1) the use of the silver carbonate/P(*o*-tol)$_3$ combination with aryl halides, (2) the lithium chloride/TFP procedure with aryl triflates, and finally, (3) the thallium acetate/BINAP system in the asymmetric arylation reaction.

The arylated cyclic enamides isolated can in principle undergo further regiocontrolled functionalizations both in the α-positions and β-positions to the nitrogen atom.[40b,51] Subsequent hydrogenation of the arylated enamides offers an alternative route to 3-arylpyrrolidines, and this competes favorably with other existing methods.[52]

Experimental Section

General. ^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$ at 300 MHz and 75.4 MHz, respectively, or at 270 MHz and 67.8 MHz, respectively. In addition, the ^{1}H NMR spectra for compounds **5f**, **7a**, and **11** were recorded at 500 MHz and the ^{1}H-NMR spectra for compound **7b** was recorded at 400 MHz. ^{13}C-NMR spectra for compound **4b** were recorded at 125.6 MHz. Resolution enhancements were performed with the routine software installed in the machine (**7a** and **7b**). Chemical shifts were reported as δ values (ppm) relative to an internal standard (tetramethylsilane). The ^{1}H and ^{13}C NMR spectra for the enamides and amides show, when recorded in $CDCl_3$ at rt, the existence of two rotamers in an approximately 1/1 ratio, except compound **11** which displays a 1/3 ratio. The spectra for the secondary amines were recorded as the HCl salts, except compound **9a** which was recorded as the free base. Low resolution mass spectra were recorded on a instrument operating at an ionization potential of 70 eV. The mass detector was interfaced with a gas chromatograph equipped with a fused silica column (11 m × 0.22 mm) coated with cross linked SE-54 (film thickness 0.3 μm, He gas, flow ~40 cm/s). The column temperature was 70−300 °C (initial time 2 min, gradient 20 °C/min). 1-(Methoxycarbonyl)pyrrolines **4a** and **8** and aryl-substituted isomers **5** and **6**, respectively, were assumed to have the same GC/MS response factor. Samples for chiral GLC-analysis were taken up in CH_2Cl_2 and washed with water before being subjected to small scale flash chromatography. Separation of the enantiomers (**5a**, **5b**, **5g**) was achieved with a gas chromatograph, equipped with a capillary column (20 m × 0.32 mm), coated with 50% heptakis(6-*O*-*tert*-butyldimethylsilyl-2,3-di-*O*-methyl)-β-cyclodextrin in OV 1701[53] and connected to a flame ionization detector. The column temperature was 145−165 °C and H_2 was used as the carrier gas at a flow rate of ~60 cm/s. Peak areas were determined by means of an HP 3396 Series 2 integrator. The ee of **7b** was determined by HPLC analysis: DAICEL CHIRALCEL OD, hexane/2-propanol/diethylamine (90/10/0.1), 0.5 mL/min, UV monitor (254 nm). The absolute configurations of **5b** and

(46) (a) Karabelas, K.; Hallberg, A. *Tetrahedron Lett.* **1985**, *26*, 3131. (b) Karabelas, K.; Westerlund, C.; Hallberg, A. *J. Org. Chem.* **1985**, *50*, 3896. (c) Karabelas, K.; Hallberg, A. *J. Org. Chem.* **1986**, *51*, 5286. (d) Karabelas, K.; Hallberg, A. *J. Org. Chem.* **1989**, *54*, 1773. (e) For a positive effect of $AgBF_4$ in olefin insertion. into the palladium−aryl bond, see; Kawataka, F.; Shimizu, I.; Yamamoto, A. *Bull. Chem. Soc. Jpn.* **1995**, *68*, 654.

(47) AgOTf was also found by Overman's group to be less efficient in the suppression of alkene isomerization, see ref 11a.

(48) Shibasaki *et al.* have suggested that the interaction between Pd(II) and counterions such as $AgCO_3$− is weak. In contrast, the interactions between non silver containing monovalent counterions is expected to be stronger. See ref 31a.

(49) (a) Reaction with a Pt(II)-complex and P(*o*-tol)$_3$ or $AsPh_3$ results in a low displacement energy. Manzer, L. M.; Tolman, C. A. *J. Am. Chem. Soc.* **1975**, *97*, 1955. (b) A palladacycle acting as an efficient catalyst was recently prepared from Pd(OAc)$_2$ and P(*o*-tol)$_3$. Herrmann, W. A.; Brossmer, C.; Öfele, K.; Reisinger, C. P.; Priermeier, T.; Beller, M.; Fischer, H. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 1844.

(50) Irrespective if the reaction follows a neutral or cationic pathway, olefin **8** is more reactive than **4a**. For a more general discussion, see ref 9f.

(51) (a) Amino, Y.; Nishi, S.; Izawa, K. *Bull. Chem. Soc. Jpn.* **1991**, *64*, 620. (b) Wistrand, L. G. *Janssen Chim. Acta*, **1986**, *4*, 34 and references cited therein.

(52) (a) Ebenöther, A.; Hasspacher, K. Swiss Patent 526,536, 1972. *Chem. Abstr.* **1972**, *77*, 164454s. (b) Bettoni, G.; Cellucci, C.; Tortorella, V. *J. Heterocycl. Chem.* **1976**, *13*, 1053. (c) Tseng, C. C.; Terashima, S.; Yamada, S. I. *Chem. Pharm. Bull.* **1977**, *25*, 166. (d) Laborde, E. *Tetrahedron Lett.* **1992**, *33*, 6607. (e) Meyers, A. I.; Snyder, L. *J. Org. Chem.* **1993**, *58*, 36. (f) Adkins, H.; Coonradt, H. *J. Am. Chem. Soc.* **1941**, *63*, 1563.

(53) Prepared and developed by Prof. W. A. König, Institut für Organische Chemie, Universität Hamburg, D-20146 Hamburg (Germany).

7b are unknown. Elemental analyses were performed by Mikro Kemi AB, Uppsala, Sweden. High resolution mass spectrometry was performed by Dr. Hasse Karlsson, MS Lab, Dept. of Medicinal Chemistry, Göteborg University, Sweden (EI^+). Melting points were determined with a melting point microscope and are uncorrected. Silica gel 60 (0.040−0.063 mm, E. Merck, no. 9385) was used for flash chromatography. The coupling reactions were run under argon, in flasks equipped with reflux condensers. Asymmetric coupling reactions were performed under nitrogen in heavy-walled and thin-necked Pyrex tubes, sealed with a Teflon-brand stopcock.

Materials. Palladium(II) acetate was obtained from Sigma Chemical Co. and was recrystallized from benzene.[2b] *N*,*N*-Diisopropylethylamine was distilled from potassium hydroxide prior to use. DMF was stored over activated 4 Å molecular sieves and was degassed with argon before use. Tris(dibenzylideneacetone)dipalladium(0)−chloroform adduct ($Pd[0]_2[dba]_3$−$CHCl_3$), tri-*o*-tolylphosphine ($P(o\text{-}tol)_3$), 1,3-bis(diphenylphosphino)propane (DPPP), 1,2-bis(diphenylphosphino)ethane (DPPE), 1,4-bis(diphenylphosphino)butane (DPPB), (*R*)-BINAP, and (*S*)-BINAP were obtained from Aldrich Co. and used as supplied. Palladium(II) acetylacetonate (Pd[II]acac), 10% Pd/C, and triphenylarsine ($AsPh_3$) were bought from Acros Chimica. Triphenylphosphine (PPh_3) was obtained from Merck, and tri(2-furyl)phosphine (TFP) from Lancaster Synthesis. 3-Pyrroline was obtained from Aldrich and contained 20−35% pyrrolidine according to GC/MS. Different concentrations of the methoxycarbonyl-substituted pyrrolidine were not found to influence the outcome of the Heck reactions. 1-Bromo-3-methanesulfonylbenzene and the enamide **8** were prepared as described elsewhere.[10,54] Aryl triflates were prepared from the corresponding phenols by a standard procedure using triethylamine as base.[37] The cyclohexenyltriflate was prepared according to ref. 55. All other reagents obtained from commercial sources were used as received. Compounds **4a**,[56] **6a**,[3b] **10**,[18] **11**,[57] 1-[3-(3-methoxyphenyl)pyrrolidin-1-yl]propan-1-one,[7a] 3-(3-methoxyphenyl)-1-propylpyrrolidine,[7a] and **12**[7a] are known compounds.

1-(Methoxycarbonyl)-2,5-dihydropyrrole (4a).[56] To a 2 L round bottom flask was added 3-pyrroline (25.0 g, 65% pure, 236 mmol of 3-pyrroline), powdered potassium carbonate (97.5 g, 707 mmol), and methylene chloride (800 mL). The mixture was stirred at 0 °C. Methyl chloroformate (30.8 mL, 398 mmol) dissolved in methylene chloride (300 mL) was added dropwise over a period of 30 min. The reaction mixture was allowed to reach rt. After an additional 60 min at rt the reaction mixture was filtered through a pad of Celite and was washed with two portions of 10% Na_2CO_3, dried ($MgSO_4$), filtered, and concentrated by evaporation. Distillation (50−55 °C, 0.1 torr) of the residual liquid afforded 34.5 g (76%) as a colorless oil containing 34% of the corresponding pyrrolidine (GC/MS): MS *m*/*z* (relative intensity, 70 eV) 127 (70, M^+), 112 (100), 68 (38), 67 (49), 59 (38); ^1H NMR ($CDCl_3$, 300 MHz) δ 3.62 and 3.74 (rotamers, s, 3H), 4.05−4.20 (m, 4H), 5.69−5.81 (m, 2H); ^{13}C NMR ($CDCl_3$, 75.4 MHz) δ 52.2, 52.7 and 53.2 (rotamers, 2 × CH_2), 124.8 (2 × CH), 158.6.

1-(Ethylcarbonyl)-2,5-dihydropyrrole (4b). A solution of 3-pyrroline (25.0 g, 65% pure, 236 mmol of 3-pyrroline) and triethylamine (40.2 g, 362 mmol) in methylene chloride (100 mL) was cooled to 0 °C an atmosphere of argon. Then propionyl chloride (40.4 g, 398 mmol) dissolved in methylene chloride (50 mL) was added dropwise over a period of 30 min. The reaction mixture was allowed to reach rt. After an additional 120 min at rt the reaction mixture was washed with two portions of 10% Na_2CO_3 and two portions of 10% HCl, dried ($MgSO_4$), filtered, and concentrated by evaporation. The residue was further purified by silica gel flash-chromatography (EtOAc) to yield pure **4b** as a colorless oil (20.6 g, 70%): MS *m*/*z* (relative intensity, 70 eV) 125 (40, M^+), 69 (54), 68 (100), 57 (28), 53 (5); ^1H NMR ($CDCl_3$, 300 MHz) δ 1.25 (t, J = 7.6 Hz, 3H), 2.35 (m, 2H), 4.35 (bs, 4H), 5.85−6.00 (m, 2H); ^{13}C NMR ($CDCl_3$, 125.6 MHz) δ 8.6, 27.3, 52.6 and 53.0 (rotamers, 2 × CH_2), 124.7 and 126.2 (rotamers, 2 × CH), 171.9. High resolution mass spectrum calcd for $C_7H_{11}NO$ (M^+) 125.08398, found 125.0840.

Preparative Palladium-Catalyzed Reactions. General Procedure for Aryl Halides (Table 1). To a stirred solution of 30 mmol **4a** (or **8** for the formation of **6a** and **6b**) in DMF (10 mL) under an argon atmosphere at rt were sequentially added *i*-Pr_2NEt (1.55 g, 12.0 mmol), Ag_2CO_3 (0.580 g, 2.10 mmol), aryl halide (3.00 mmol), $P(o\text{-}tol)_3$ (0.100 g, 0.329 mmol), and $Pd(OAc)_2$ (0.034 g, 0.151 mmol). GC/MS analysis of the reaction mixture was periodically performed on small samples taken up in diethyl ether and washed with a small quantity of brine. The reaction was stirred and heated at 100 °C for 4−22 h and then cooled to rt, quenched with 10% Na_2CO_3 (40 mL) and extracted several times with diethyl ether. The combined organic phases were dried ($MgSO_4$) and filtered, and the solvent was removed under reduced pressure. The excess of **4a** (or **8**) was removed by bulb-to-bulb distillation conducted with a Büchi Kugelrohr (∼0.1 torr, oven temperature ∼50 °C). The residue was further purified by flash chromatography in an appropriate solvent.

1-(Methoxycarbonyl)-3-phenyl-2,3-dihydropyrrole (5a). Colorless oil, 0.41 g (68%); eluent hexane/diethyl ether (2/1, v/v): MS *m*/*z* (relative intensity, 70 eV) 203 (M^+, 100), 144 (79), 128 (83), 115 (44), 104 (78); ^1H NMR ($CDCl_3$, 300 MHz) δ 3.68 (m, 4H, OCH_3 + NC*H*H), 4.11 (m, 2H, NC*H*H + ArCH), 5.08 and 5.12 (rotamers, m, 1H, NCH=C*H*), 6.61 and 6.75 (rotamers, m, 1H, NC*H*=CH), 7.05−7.35 (m, 5H, Ar); ^{13}C NMR ($CDCl_3$, 75.4 MHz) δ 47.1 and 48.3 (rotamers), 52.7, 53.9, 112.2 and 112.5 (rotamers), 127.0, 127.2 (2 × CH), 128.7 (2 × CH), 129.5 and 130.4 (rotamers), 143.8, 152.3 and 153.4 (rotamers). High resolution mass spectrum calcd for $C_{12}H_{13}NO_2$ (M^+) 203.0946, found: 203.0937.

1-(Methoxycarbonyl)-2,4-diphenyl-2,5-dihydropyrrole (7a). A second fraction from the chromatographic separation of **5a** was obtained (0.10 g, 12%) and was found to be the diphenylated compound (**7a**): MS *m*/*z* (relative intensity, 70 eV) 279 (M^+, 78), 264 (70), 220 (50), 202 (100), 115 (81); ^1H NMR ($CDCl_3$, 500 MHz) δ 3.60 and 3.72 (rotamers, s, 3H, OCH_3), 4.76−4.81 and 4.82−4.87 (rotamers, ddd, J = 15 Hz, 4 Hz, 2 Hz, 1H, NC*H*H), 4.81−4.86 and 4.90−4.94 (rotamers, app dt, J = 15 Hz, 2 Hz, 1H, NC*H*H), 5.72 and 5.81 (rotamers, ddd, J = 4 Hz, 2 Hz, 2 Hz, 1H, PhCH), 6.20 and 6.25 (rotamers, app. q, J = 2 Hz, 1H, CH=C), 7.20−7.46 (m, 10 H, Ar); ^{13}C NMR ($CDCl_3$, 75.4 MHz) δ 52.5, 53.9 and 54.5 (rotamers), 68.7 and 69.2 (rotamers), 124.5−128.7 (10 × CH (Ar) + 1 × C=C), 132.8, 136.3 and 136.6 (rotamers), 141.1 and 141.7 (rotamers), 155.0 and 155.5 (rotamers). High resolution mass spectrum calcd for $C_{18}H_{17}NO_2$ (M^+) 279.1258, found: 279.1287.

1-(Methoxycarbonyl)-3-(1-naphthyl)-2,3-dihydropyrrole (5b). Light yellow oil, 0.44 g (58%); eluent hexane/diethyl ether (2/1, v/v): MS *m*/*z* (relative intensity, 70 eV) 253 (M^+, 100), 238 (35), 178 (46), 166 (34), 165 (89); ^1H NMR ($CDCl_3$, 300 MHz) δ 3.60−3.81 (m, 4H, OCH_3 + NC*H*H), 4.39 (dd, J = 11.7 Hz, 1H, NC*H*H), 4.9 (br m, 1H, ArCH), 5.3 (br m, 1H, NCH=C*H*), 6.79 and 6.94 (rotamers, br m, 1H, NC*H*=CH), 7.34−7.60 (m, 4H, Ar), 7.75 (d, J = 8.8 Hz, 1H, Ar), 7.9 (d, J = 8.7 Hz, 1H, Ar), 8.0 (d, J = 7.8 Hz, 1H, Ar); ^{13}C NMR ($CDCl_3$, 75.4 MHz) δ 42.9 and 44.0 (rotamers), 52.6 and 52.7 (rotamers), 53.3 and 53.4 (rotamers), 110.8 and 111.1 (rotamers), 123.2−129.0 (7 × CH (Ar)), 129.1 and 130.2 (rotamers), 131.3, 134.0, 139.6, 152.4 and 153.5 (rotamers). High resolution mass spectrum calcd for $C_{16}H_{15}NO_2$ (M^+) 253.1103, found: 253.1099.

Preparative Palladium-Catalyzed Reactions. General Procedure for Aryl Triflates (Table 2). To a stirred solution of 30 mmol of **4a** in DMF (10 mL) under an argon atmosphere at rt were sequentially added *i*-Pr_2NEt (1.55 g, 12.0 mmol), LiCl (0.38 g, 9.0 mmol), triflate (3.00 mmol), TFP (0.077 g, 0.332 mmol), and $Pd(OAc)_2$ (0.034 g, 0.151 mmol). GC/MS analysis of the reaction mixture was periodically performed on small samples taken up in diethyl ether and washed with a small quantity of brine. The reaction was stirred and heated at 100 °C for 4−18 h. After the completion

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the reaction mixture was allowed to cool and was purified as described in Preparative Palladium-Catalyzed Reactions. General Procedure for Aryl Halides.

General Method for Catalytic Hydrogenation. 1-(Methoxycarbonyl)-3-phenylpyrrolidine (3a). The synthesis of the parent **3a** is typical. Compound **5a** (0.40 g, 1.97 mmol) was dissolved in methanol (25 mL). Solid ammonium formate (0.25 g, 3.94 mmol) and Pd/C (30 mg 10%) were added. The resulting mixture was heated to reflux under a nitrogen atmosphere for 4 h and then filtered through a pad of Celite. The solvent was evaporated *in vacuo*, and the residue was redissolved in 10% Na_2CO_3 (15 mL). The aqueous phase was extracted several times with methylene chloride, and the combined organic phases were dried ($MgSO_4$), filtered and evaporated to dryness. The crude product was purified by flash chromatography (hexane/diethyl ether (9/1, v/v), affording **3a** (0.36 g, 89%) as a colorless oil: MS *m/z* (relative intensity, 70 eV) 205 (M^+, 37), 190 (46), 130 (29), 117 (46), 101 (100); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.92−2.08 (m, 1H), 2.24−2.35 (m, 1H), 3.30−3.95 (m, 8H), 7.21−7.38 (m, 5H); ^{13}C NMR ($CDCl_3$, 75.4 MHz) δ 32.4 and 33.3 (rotamers), 43.2 and 44.2 (rotamers), 45.7 and 46.2 (rotamers), 52.1 and 52.3 (rotamers), 52.4, 126.8, 127.0 (2 × CH), 128.6 (2 × CH), 141.2, 155.5. Anal. Calcd. for $C_{12}H_{15}NO_2$: C, 70.2; H, 7.4; N, 6.8. Found: C, 70.0; H, 7.2; N, 6.7.

General Procedure for Preparation of Secondary Amines. The carbamate (**3a**−**d** and **3g**) was dissolved in 5 mL of methanol or ethanol. To the solution was added 8 N HCl (15 mL). The mixture was refluxed and after one or two days, the conversion was complete (monitored by GLC). The reaction mixture was evaporated to dryness and the excess of HCl and water was distilled azeotropically with 99.5% ethanol. The remaining salt was recrystallized from an appropriate solvent.

3-Phenylpyrrolidine (9a). Prepared from compound **3a** (0.35 g, 1.71 mmol) using ethanol as cosolvent and refluxed for two days. The resulting HCl salt was basified with 10% Na_2CO_3 (10 mL) and extracted several times with methylene chloride. The combined organic phases were dried ($MgSO_4$), filtered, and evaporated to dryness. The free amine was converted to the fumarate salt and recrystallized from ethanol/isopropyl ether (0.35 g 78%); mp 139−141 °C (fumarate); MS *m/z* (relative intensity, 70 eV) 147 (M^+, 100), 117 (59), 115 (38), 91 (37), 51 (35); ^{1}H NMR (free base, $CDCl_3$, 300 MHz) δ 2.1 (m, 1H), 2.45 (m, 1H), 3.25 (m, 1H), 3.4−3.9 (m, 4H), 4.7 (br s, 1H, NH), 7.2−7.4 (m, 5H); ^{13}C NMR ($CDCl_3$, 75.4 MHz) δ 32.4, 43.6, 45.2, 50.6, 127.1 (2 × CH), 127.6 (2 × CH), 129, 138.3. Anal. Calcd for $C_{14}H_{17}NO_4 \cdot 0.1H_2O$: C, 63.4; H, 6.5; N, 5.3. Found: C, 63.8; H, 6.8; N, 5.2.

3-(3-Methoxyphenyl)-1-propylpyrrolidine.[7a] A solution of 1-[3-(3-methoxyphenyl)pyrrolidin-1-yl]propan-1-one (0.35 g, 1.50 mmol) in dry diethyl ether (30 mL) was cooled to 0 °C. Solid $LiAlH_4$ (0.20 g, 5.3 mmol) was then added in small portions. The reaction mixture was then allowed to reach rt and refluxed for 2 h. The reaction was then quenched by the addition of 0.2 mL of water, 0.2 mL 15% sodium hydroxide solution, and 0.6 mL of water. The resulting mixture was filtered through a Celite pad in a F sintered glass suction filter, the Celite pad was washed with diethyl ether, and the combined organic phases were dried ($MgSO_4$) and evaporated to dryness. The residue was purified by chromatography on silica column with methylene chloride/methanol (19/1, v/v) as eluent. The solvents from the collected fractions containing pure reduced product were evaporated yielding 0.30 g (92%) as an oil. MS *m/z* (relative intensity, 70 eV) 219 (M^+, 10), 191 (19), 190 (100), 84 (23), 57 (12); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.9 (t, 3H), 1.55 (sext, 2H), 1.9 (m, 1H), 2.2−2.7 (m, 5H), 2.85 (q, 1H), 3.1 (t, 1H), 3.4 (q, 1H), 3.8 (s, 3H), 6.75 (dd, J = 8.2 Hz, 2.0 Hz, 1H), 6.87 (m, 2H), 7.2 (t, J = 7.8 Hz, 1H).

3-(1-Propylpyrrolidin-3-yl)phenol (12, USDA 19).[7a] 3-(3-Methoxyphenyl)-1-propylpyrrolidine (0.30 g, 1.29 mmol) was converted to the corresponding hydrochloride salt and then dissolved in 48% hydrobromic acid (15 mL). The solution was stirred at 120 °C for 3 h under an atmosphere of argon. After completion, the solvent was removed and azeotropically distilled with absolute ethanol *in vacuo* followed by recrystallization from methanol/ether affording pure **12**·HBr (0.34 g, 87%): mp 124−128 °C (lit.[7a] 128−129 °C); free base MS *m/z* (relative intensity, 70 eV) 205 (M^+, 10), 177 (18), 176 (100), 147 (12), 84 (21); ^{1}H NMR (CD_3OD, HBr salt, 300 MHz) δ 1.1 (t, 3H), 1.85 (m, 2H), 2.1−2.35 (m, 1H), 2.5 (m, 1H), 3.1−4.0 (m, 7H), 6.75 (dd, J = 8.0 Hz, 1.8 Hz, 1H), 6.82−6.87 (m, 2H), 7.2 (t, J = 7.9 Hz, 1H).

Asymmetric Synthesis of 5b. A mixture of $Pd(OAc)_2$ (0.0225 g, 0.100 mmol) and (*R*)-BINAP (0.137 g, 0.220 mmol) were dissolved in DMF (5 mL) under a stream of nitrogen. To the solution were added in the following order: *i*-Pr_2NEt (0.52 g, 4.00 mmol), 1-naphthyl triflate (0.276 g, 1.00 mmol), **4a** (10 mmol), and TlOAc (0.263 g, 1.00 mmol). The reaction mixture was heated to 60 °C in an oil bath for 16 h. GC/MS analysis of the reaction mixture was periodically performed on small samples taken up in methylene chloride and washed with a small quantity of brine. An unexpected finding, according to GC/MS, was the presence of PPh_3 in the reaction mixture.[14e,58] The product **5b** was purified as described in Preparative Palladium-Catalyzed Reactions. General Procedure for Aryl Halides. Yellow oil, 0.087 g (34%), 58% ee: $[\alpha]^{20}_D = +80°$ (c = 1.0, $CHCl_3$).

Synthesis of Enantiomerically Enriched 1-(Methoxycarbonyl)-2,4-di(1-naphthyl)-2,5-dihydropyrrole (7b). A solution consisting of $Pd(OAc)_2$ (0.00185 g, 0.0082 mmol) and TFP (0.00422 g, 0.0182 mmol) in 0.5 mL of DMF was stirred for 5 min under a nitrogen atmosphere. Each of the remaining reactants were added together with 0.5 mL of DMF under nitrogen in the following order: LiCl (0.021 g, 0.49 mmol), 1-naphthyl triflate (0.091 g, 0.330 mmol), *i*-Pr_2NEt (0.085 g, 0.658 mmol), and **5b** (0.042 g, 0.166 mmol). The flask was closed, and the content was stirred for 20 h at 100 °C. The product was purified according to Preparative Palladium-Catalyzed Reactions. General Procedure for Aryl Halides. Yellow oil, 0.030 g (48%); eluent diethyl ether/pentane (1/3, v/v): MS *m/z* (relative intensity, 70 eV) 379 (M^+, 100), 364 (25), 320 (33), 252 (34), 165 (30); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 3.55 and 3.74 (rotamers, s, 3H, OCH_3), 4.85−5.12 (m, 2H, NCH_2), 6.18 and 6.20 (rotamers, m, 1H, CH=C), 6.64 and 6.71 (rotamers, m, 1H, ArCH), 7.38−7.60 (m, 8H, Ar), 7.75−7.93 (m, 4H, Ar), 8.05 (t, J = 7 Hz, 1H, Ar), 8.22 (dd, J = 21 Hz, 8 Hz, 1H, Ar); ^{13}C NMR ($CDCl_3$, 67.8 MHz) δ 52.8, 57.3, and 57.8 (rotamers), 66.0 and 66.7 (rotamers), 122.5−137.9 (22 × CH), 155.3 and 155.8 (rotamers). High resolution mass spectrum calcd for $C_{26}H_{21}NO_2$ (M^+) 379.1572, found: 379.1565. 58% ee: $[\alpha]^{20}_D = -48°$ (c = 1.1, $CHCl_3$).

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Supporting Information Available: Experimental details and characterization data for compounds **3b**−**j**, **5c**−**j**, **6b**, **9b**−**e**, **10**, **11**, and 1-[3-(3-methoxyphenyl)pyrrolidin-1-yl]propan-1-one and ^{1}H and/or ^{13}C-NMR spectra for **4b**, **5a**−**5j**, **7a**−**b**, and **11** (34 pages). This material is contained in 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.

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(58) This might be a result of the migration of phenyl groups of BINAP from phosphorus to Pd. Similar phenomena have been observed in nonasymmetric Heck coupling reactions. See: (a) Herrmann, W. A.; Brossmer, C.; Öfele, K.; Beller, M.; Fischer, H. J. *Organomet. Chem.* **1995**, *491*, C1−C4. (b) Kelkar, A. A.; Hanaoka, T.; Kubota, Y.; Sugi, Y. *J. Mol. Cat.* **1994**, *88*, L113. Exchange of metal- and phosphine-bound aryls has also been observed in Pd-catalyzed Stille and Suzuki coupling reactions. (c) Morita, D. K.; Stille, J. K.; Norton, J. R. *J. Am. Chem. Soc.* **1995**, *117*, 8576 and references cited therein.