Catalytic Asymmetric Synthesis of Quaternary Carbon Centers. Exploratory Studies of Intramolecular Heck Reactions of (*Z*)-α,*β*-Unsaturated Anilides and Mechanistic Investigations of Asymmetric Heck Reactions Proceeding via Neutral Intermediates

Atsuyuki Ashimori,[1a] Benoit Bachand,[1b] Michael A. Calter,[1c] Steven P. Govek, Larry E. Overman,* and Daniel J. Poon[1d]

Contribution from the Department of Chemistry, 516 Physical Sciences 1, University of California, Irvine, California 92697-2025

Received March 9, 1998

Abstract: Intramolecular Heck reactions of seven (*Z*)-α,*β*-unsaturated 2-iodoanilides catalyzed by Pd−BINAP were surveyed using two reaction conditions: (1) silver-promoted cyclizations in the presence of 2 equiv of Ag_3PO_4 and (2) base-promoted cyclizations in the presence of 4 equiv of 1,2,2,6,6-pentamethylpiperidine (PMP). A comparison of these results with the outcome of the corresponding intramolecular Heck reactions of the *E* stereoisomers leads to the following conclusions: (1) (*E*)- and (*Z*)-α,*β*-unsaturated 2-iodoanilides give opposite enantiomers of the Heck product when Ag_3PO_4 is the HI acceptor (cationic pathway); the absolute configuration of the product is independent of alkene geometry when the HI acceptor is PMP (neutral pathway). (2) When the 2-substituent is Me or *prim*-alkyl, stereoinduction is optimal in PMP-promoted insertions of *Z* substrates which occur with ee's as high as 97%. (3) When the 2-substituent is large, stereoinduction is optimal in insertions of *E* substrates carried out in the presence of Ag_3PO_4. (4) Contributions from the *β*-alkene substituent are minor. The neutral Heck reaction manifold can be entered from triflate substrates by carrying out the cyclization in the presence of added halide salts. The ability to vary both the alkene geometry and the Heck reaction pathway allows chiral 3,3-disubstituted-2-oxindoles having a wide range of substituents at the quaternary carbon (Me, *prim*-alkyl, *tert*-alkyl, and aryl) to be prepared with useful levels of enantioselection (72−97% ee). A number of studies were carried out aimed at clarifying the mechanism of the neutral Heck reaction pathway. Key results are the following: (1) Chiral amplification studies show that the catalyst is monomeric Pd−BINAP. (2) Investigations of monophosphine analogues of BINAP, which were designed to mimic a partially dissociated BINAP chelate, support the conclusion that BINAP is chelated during the enantioselective step. (3) Enantioselectivity is insensitive to solvent polarity. From these data, we propose that the stereochemistry determining step of the neutral pathway occurs during the process in which iodide is displaced by the tethered alkene (Figure 2, **41** → **47** → **45**). In light of the variety of pentacoordinate intermediates that could be involved, it is premature to advance a model to rationalize stereoinduction in asymmetric Heck reactions proceeding by the neutral pathway. Nonetheless, the finding that the enantioselective step of asymmetric Heck reactions taking place by the neutral pathway involves five-coordinate intermediates significantly broadens the vista for design of asymmetric ligands for this and related reactions.

Introduction

The asymmetric intramolecular Heck reaction, first described in 1989,[2] has emerged as one of the most important methods for enantioselective synthesis of C−C bonds.[3] In the preceding paper, our initial systematic studies of asymmetric Heck cyclizations of *N*-alkyl-2′-iodoanilide derivatives of (*E*)-α,*β*-unsaturated acids were summarized.[4] These studies identified BINAP as a particularly efficacious ligand and showed that for many (*E*)-α,*β*-unsaturated 2-iodoanilide substrates either enantiomer of the Heck product could be formed with good enantioselectivity using a *single* enantiomer of a chiral diphosphine ligand (Figure 1). For halide substrates, this latter discovery led to the identification of two synthetically useful asymmetric Heck reaction manifolds: cyclization in the presence of a halide scavenger such as a silver salt (cationic pathway) or cyclization in the presence of a tertiary amine (neutral pathway).[3,5]

In this paper we describe our complementary investigations of asymmetric Heck cyclizations of (*Z*)-α,*β*-unsaturated 2-io-

(1) Current addresses: (a) The Green Cross Corporation, Research Division, 2-25-1, Shodai-Ohtani, Hirakata, Osaka 573-1153, Japan. (b) BioChem Therapeutique Inc., 275, Boul, Armand-Frappier, Laval, Quebec, H7V 4A7, Canada. (c) Chemistry Department, Virginia Polytechnic Institute and State University, 107 Davidson Hall, Blacksburg, Virginia 24061-0212. (d) Department of Chemistry, Colorado State University, Fort Collins, Colorado 80523-1872.

(2) (a) Sato, Y.; Sodeoka, M.; Shibasaki, M. *J. Org. Chem.* **1989**, *54*, 4738. (b) Carpenter, N. E.; Kucera, D. J.; Overman, L. E. *J. Org. Chem.* **1989**, *54*, 5846.

(3) For recent reviews, see: (a) Shibasaki, M. In *Advances in Metal-Organic Chemistry*; Liebeskind, L. S., Ed.; JAI: Greenwich, 1996; pp 119−151. (b) Shibasaki, M.; Boden, C. D. J.; Kojima, A. *Tetrahedron* **1997**, *53*, 7371.

(4) Ashimori, A.; Bachand, B.; Overman, L. E.; Poon, D. J. *J. Am. Chem. Soc.* **1998**, *120*, 6477−6487.

(5) For our initial report, see: Ashimori, A.; Overman, L. E. *J. Org. Chem.* **1992**, *57*, 4571.

S0002-7863(98)00787-2 CCC: $15.00
Published on Web 06/20/1998

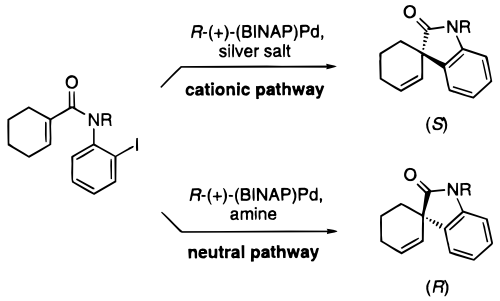
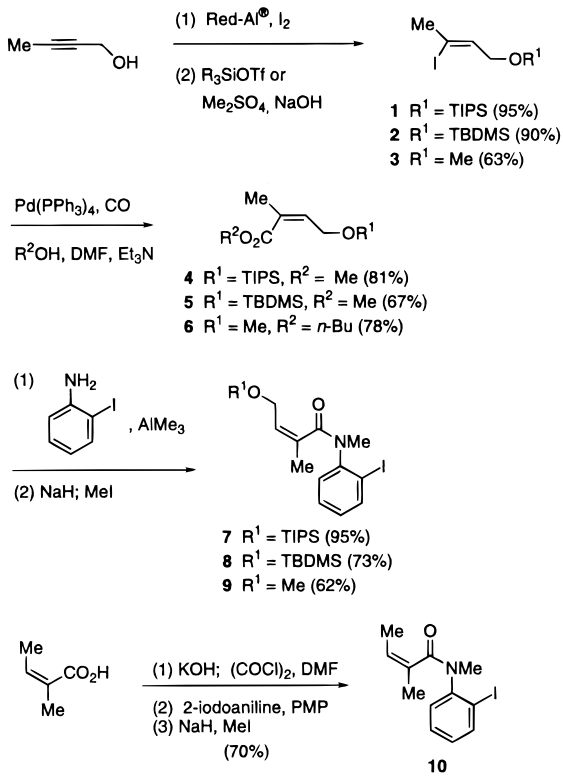


Figure 1.

Scheme 1

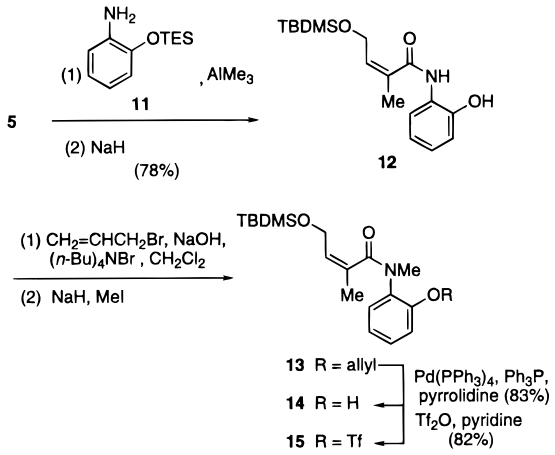


doanilides and related triflate substrates.[6] In many cases these cyclizations proceed with higher enantioselection than those of the corresponding *E* stereoisomers, with enantioselectivities as high as 97% being obtained in cyclizations conducted in the presence of amines. We report also that the neutral reaction manifold can be entered from triflate substrates if the Heck cyclization is carried out in the presence of halide additives and that both phosphorus atoms of BINAP and one halide are coordinated to palladium during the enantioselective step[7] of the neutral pathway.[8]

Results

A. Asymmetric Heck Cyclizations of (*Z*)-α,*β*-Unsaturated 2-Iodoanilides. Preparation of Cyclization Substrates. (*Z*)-4-Siloxy(or alkoxy)-2-butenanilides containing a 2-methyl group were prepared from 2-butyn-1-ol as summarized in Scheme 1. Reduction with Red-Al and quenching the resulting alane with I_2 afforded (*Z*)-3-iodo-2-butenol,[9] which was protected to provide **1**−**3**. Palladium mediated carbonylation of **1** and **2** in the presence of MeOH[10] furnished (*Z*)-α,*β*-unsaturated esters **4** and **5**. To reduce the volatility of the corresponding ester, iodide **3** was carbonylated in the presence of butanol to provide **6**. Condensation of these esters with 2-iodoaniline under Weinreb conditions[11] yielded the corresponding anilides, which were methylated to afford cyclization substrates **7**−**9**. The corresponding anilide **10** lacking the *γ*-siloxy group was prepared in short order from the acid chloride of angelic acid (Scheme 1).

Scheme 2



The 2-methyl-(*Z*)-2-butenanilide triflate **15** was prepared as outlined in Scheme 2. Condensation of α,*β*-unsaturated ester **5** with the dimethylaluminum derivative of triethylsilyl (TES)-protected 2-aminophenol (**11**), followed by exposure of this product to NaH in THF to affect cleavage of the TES group gave anilide **12** in 78% yield. The phenol was then protected as an allyl ether,[12] and the secondary amide was *N*-methylated to furnish anilide **13**. Cleavage of the allyl group[13] and exposure of the resulting phenolic anilide **14** to Tf_2O and pyridine gave triflate **15** in good overall yield. Our inability to selectively allylate the oxygen of *o*-aminophenol and the sensitivity of the triethylsilyl group to the *N*-methylation conditions necessitated this somewhat cumbersome protection strategy.

Preparation of the 2-phenyl-, 2-*tert*-butyl-, and 2-(2,2-dimethoxyethyl)-(*Z*)-2-butenanilides **20**−**22** began with reductive iodination of the corresponding propargylic alcohols (Scheme 3). Conversion of these products to the desired anilide products was simplified by the discovery that lithium reagents derived from these iodides could be directly condensed with 2-iodophenyl isocyanate (**19**).[14] Thus, reaction of vinyl iodides **16**−**18** with 2 equiv of *t*-BuLi at −78 °C in THF,[15] followed by trapping with **19** and subsequent methylation of the anilide nitrogen, furnished the respective (*Z*)-2-butenanilides **20**−**22** in 21−74% overall yield.

Scope of Asymmetric Heck Cyclizations. Intramolecular Heck reactions of seven (*Z*)-α,*β*-unsaturated 2-iodoanilide

(6) For a preliminary report, see: Ashimori, A.; Matsuura, T.; Overman, L. E.; Poon, D. J. *J. Org. Chem.* **1993**, *58*, 6949.

(7) The first irreversible enantiodifferentiating step would determine asymmetric induction, see: C. R. Landis, J. Halpern, *J. Am. Chem. Soc.* **1987**, *109*, 425.

(8) For a preliminary report, see: Overman, L. E.; Poon, D. J. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 518.

(9) (a) Corey, E. J.; Katzenellenbogen, J. A.; Posner, G. H. *J. Am. Chem. Soc*. **1967**, *89*, 4245. (b) Blanchette, M. A.; Malmas, M. S.; Nantz, M. H.; Roberts, J. C.; Somjai, P.; Whritenour, D. C.; Masamune, S.; Kageyama, M.; Tamura, T. *J. Org. Chem*. **1989**, *54*, 2817.

(10) Schoenberg, A.; Bartoletti, I.; Heck R. F. *J. Org. Chem.* **1974**, *39*, 3318.

(11) (a) Lipton, M. F.; Bisha, A.; Weinreb, S. M. *Org. Synth.* **1978**, *59*, 49. (b) Greenlee, W. J.; Hangauer, D. G. *Tetrahedron Lett.* **1983**, *24*, 4559.

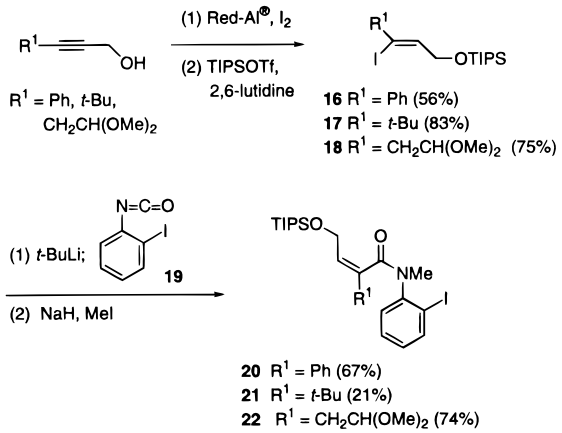
(12) McKillop, A.; Fiaud, J. C.; Hug, R. P. *Tetrahedron* **1974**, *30*, 1379.

(13) Deziel, R. *Tetrahedron Lett.* **1987**, *28*, 4371.

(14) Cizmarik, J.; Novosedlikova, D.; Racanska, E. *Pharmazie* **1990**, *45*, 64.

(15) Neumann, H.; Seebach, D. *Chem. Ber.* **1978**, *111*, 2785.

Scheme 3



substrates (Table 1 and Scheme 4) were surveyed using the two reaction conditions developed during our earlier investigations:[4] (1) silver-promoted cyclizations were conducted with 5 mol % $Pd_2(dba)_3 \cdot CHCl_3$ and 12 mol % (*R*)-BINAP in the presence of 2 equiv of Ag_3PO_4 at 100 °C in *N*,*N*-dimethylacetamide (DMA, 0.07−0.1 M), and (2) base-promoted cyclizations were carried out identically in the presence of 4 equiv of PMP (no Ag_3PO_4). Results of these investigations are summarized in Table 1. The enantiomeric purity of the oxindole products was determined by HPLC analysis using a chiral stationary phase; with the exception of oxindole aldehyde **28**, this assay was carried out on the derived oxindole alcohol.

Pd−BINAP catalyzed asymmetric Heck cyclizations of 2-methyl-4-siloxy (or methoxy)-(*Z*)-2-butenanilides **7**−**9** in the presence of either Ag_3PO_4 or 1,2,2,6,6-pentamethylpiperidine (PMP) furnished, after hydrolysis of the intermediate (*E*)- and (*Z*)-enol ethers **23**, (*R*)-oxindole aldehyde **25**. Enantioselectivity was highest (89−92% ee) when PMP was employed as the HI scavenger and varied little with the nature of the oxygen protecting group (entries 1−6). 2-Butenanilide **10** having no substituent on the 4-carbon cyclized to (*R*)-oxindole **24** in similar fashion with only slightly reduced enantioselectivity (entries 7 and 8). As was seen in the (*E*)-2-butenanilide series, dramatic changes in enantioselectivity resulted from variations in the α-substituent. Cyclization of the 2-Me and 2-(2,2-dimethoxyethyl)-2-butenanilides (**7** and **22**) in the presence of PMP proceeded with excellent enantioselectivities (entries 1 and 13); the opposite stereochemical descriptor for oxindole aldehyde **28** arises from a change in Cahn−Ingold−Prelog priority assignment. Attempted cyclization of **22** in the presence of Ag_3PO_4 resulted in decomposition. The 2-Ph substrate **20** cyclized with poor enantioselectivity (19% ee) in the presence of PMP but underwent intramolecular Heck insertion in 65% ee in the presence of Ag_3PO_4; an analogous trend was also observed in the (*E*)-2-butenanilide series.[4] Reaction of the 2-*t*-Bu analogue **21** under either cyclization condition gave the corresponding oxindole aldehyde **27** in low enantiomeric purity (entries 11 and 12).

Kinetic Resolution in the *β*-Hydride Elimination Step. Cyclizations of the 2-methyl-(*Z*)-2-buten-2′-iodoanilides were studied in greatest detail; in each case the aldehyde and stereoisomeric enol ethers generated in the initial Heck cyclization step were separated and individually converted to oxindole alcohol **29** for enantiomeric purity assessment. These analyses reveal that internal kinetic resolution in the *β*-hydride elimination step is operative.[16] For example, Pd−BINAP catalyzed cyclization of **7** in the presence of PMP afforded a 32:1 mixture of the (*E*)- and (*Z*)-enoxysilanes **23** (R^1 = Me, R^2 = OTIPS). Separation of these products by preparative TLC, hydrolysis to oxindole aldehyde **25**, and reduction provided alcohol **29** in 92% ee from the (*E*)-enoxysilane intermediate and 73% ee from the corresponding *Z* stereoisomer, corresponding to an overall ee of 90%. Asymmetric Heck cyclization of **7** in the presence of Ag_3PO_4 yielded a 4:1:3 mixture of (*E*),(*Z*)-enoxysilanes **23** (R^1 = Me, R^2 = OTIPS) and aldehyde **25**. Isolation of these components by flash and preparative thin-layer chromatography and conversion of each to oxindole alcohol **29** produced material of 87, 84, and 70% ee, respectively, corresponding to an overall ee of 80%. Similar results were observed in cyclizations of (*Z*)-2-butenanilides **8** and **9** and are discussed elsewhere.[17]

Assignment of Absolute Configuration. The absolute configuration of oxindole aldehyde **25** was secured by chemical correlation with (+)-esermethole (**34**), whose absolute configuration is well-established (Scheme 5).[18] (−)-Oxindole aldehyde **25**, produced from Pd−(*R*)-BINAP catalyzed cyclization of 2-methyl-(*Z*)-2-butenanilide **8** in the presence of PMP, was reductively aminated to yield dextrorotatory pyrroloindoline **32**. This intermediate was then converted to (+)-esermethole following the procedure of Fuji and co-workers.[19] The absolute configurations of oxindole aldehydes **27** and **28** were established by chemical correlation with **25** as documented in the preceding paper in this issue. The 3-vinyloxindole **24** was correlated with **29** by hydroboration-oxidation.[4] The absolute configuration of the α-phenyl oxindole aldehyde **26** was not established.

B. Mechanistic Investigations. Nature and Stability of the Catalyst. Evidence suggesting that monomeric Pd−BINAP was the active catalyst was secured through a chiral amplification study.[20] Asymmetric Heck cyclizations of the iodide **8** were performed under both PMP and Ag_3PO_4 conditions using BINAP of varying enantiopurities (Table 2). A linear relationship between enantioselection and BINAP enantiopurity was found with both HI scavengers.[21]

To ascertain whether enantioselectivity was affected by adventitious water, asymmetric Heck cyclizations of **8** were conducted in DMA containing varying concentrations of water. As is apparent in the data summarized in Table 3 (entries 1−5), addition of up to 5% (v/v) water had no detectable impact on enantioselectivity and only a minor effect on enoxysilane ratios and reaction rate. Measurable but minor erosion of yield and ee was observed when 10% water was added. Although the presence of 5% water had no effect, changing the solvent to THF increased enantioselectivity to 97% (entry 7).

Adventitious oxygen can oxidize phosphine ligands.[22] Oxidation of a chiral bidentate ligand such as BINAP could lead to ligand dissociation and loss of stereoinduction. An investigation into the integrity of Pd−BINAP at prolonged reaction times was undertaken. The catalyst, generated in situ by mixing $Pd_2(dba)_3 \cdot CHCl_3$ and (*R*)-BINAP in DMA, was preheated to 100 °C for varying lengths of time. Iodide **8** and PMP were then added, and the enantioselectivity of the reaction was determined (Table 4).

The experiments reported in entries 1−4 were conducted in a 10 mL recovery flask sealed with a rubber septum under a

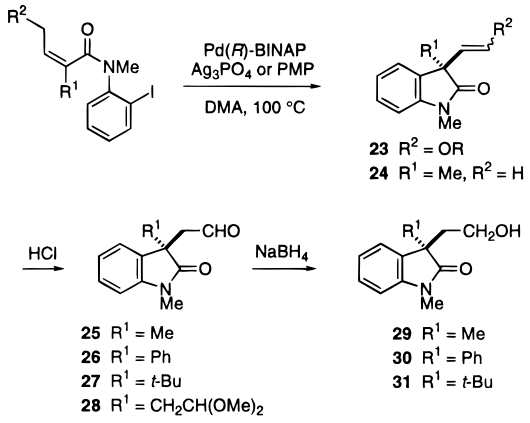
(16) Ozawa, F.; Kubo, A.; Matsumoto, Y.; Hayashi, T. *Organometallics* **1993**, *12*, 4188.
(17) Poon, D. J. Ph.D. Dissertation, University of California, Irvine, 1996.
(18) Takano, S.; Ogasawara, K. In *The Alkaloids*; Brossi, A., Ed.; Academic: New York, 1989; Vol. 36, pp 224−251.
(19) Node, M.; Itoh, A.; Masaki, Y.; Fuji, K. *Heterocycles* **1991**, *32*, 1705.
(20) Puchot, C.; Samuel, O.; Duñach, E.; Zhao, S.; Agami, C.; Kagan, H. B. *J. Am. Chem. Soc*. **1986**, *108*, 2353.
(21) Plots of these data are provided in the Supporting Information.
(22) Wilke, G.; Schott, H.; Hemibach, P. *Angew. Chem*. **1967**, *79*, 62.

Table 1. Cyclizations of 2′-Iodo-*N*-methyl-(*Z*)-2-substituted-2-butenanilides with Pd−(*R*)-BINAP[a]

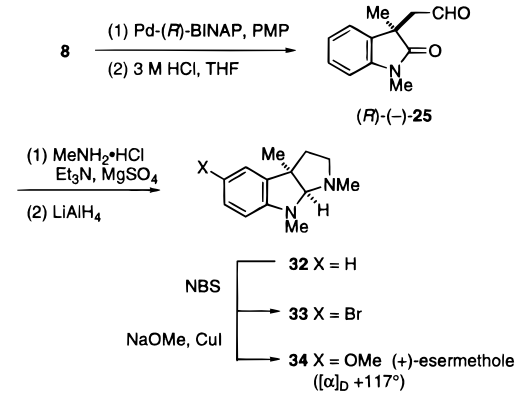
entry	substrate	R^1	R^2	additive	*E*:*Z*:aldehyde[b]	overall ee,[c] %	yield,[d] %
1	**7**	Me	OTIPS	PMP	32:1:0	90 (*R*)	87
2				Ag_3PO_4	4:1:3	80 (*R*)	73
3	**8**	Me	OTBDMS	PMP	24:1:0	92 (*R*)	80
4				Ag_3PO_4	1:0:1	78 (*R*)	53
5	**9**	Me	OMe	PMP	9:1:0	89 (*R*)	76
6				Ag_3PO_4	4:1:	80 (*R*)	72
7	**10**	Me	H	PMP		85 (*R*)	89
8				Ag_3PO_4		69 (*R*)	85
9	**20**	Ph	OTIPS	PMP	9:1:0	19[e]	nd[f]
10				Ag_3PO_4	12:1:9	65[e]	86
11	**21**	*t*-Bu	OTIPS	PMP	19:1:0	0	76
12				Ag_3PO4	6:1:0	33 (*S*)	55
13	**22**	$CH_2CH(OMe)_2$	OTIPS	PMP	49:1:0	91 (*S*)	93

[a] Conditions: 5 mol % $Pd_2(dba)_3$·$CHCl_3$, 12 mol % (*R*)-BINAP, 4 equiv of PMP or 2 of equiv Ag_3PO_4, DMA (0.07−0.1 M), 100 °C. [b] Ratios of (*E*)-enol ether:(*Z*)-enol ether:aldehyde were determined by capillary GC or by ^{1}H NMR analysis. [c] Determined by HPLC analysis of **28**−**31** using a Chiralcel OB-H, OD, or OJ column. [d] Combined yield of oxindole **28**−**31**. [e] The PMP- and Ag_3PO_4-promoted cyclizations produce the same enantiomers[d] of unknown absolute configuration. The major enantiomer elutes first on a Chiracel OJ column (85:15 hexane−propanol). [f] Not determined.

Scheme 4



Scheme 5



nitrogen atmosphere. Under these conditions, significant erosion of enantioselectivity was observed when the precatalysts were heated at 100 °C for 12 h prior to adding the substrate and PMP. This apparent loss of catalyst integrity could be avoided using more rigorous Schlenk techniques (entry 5). In this case, the catalyst was rigorously deoxygenated by the freeze−pump−thaw method and purged with argon. A DMA solution of iodide **8** and PMP was deoxygenated in the same way prior to being added to a preheated DMA solution of Pd−BINAP. Under these conditions, no erosion of enantioselectivity was observed when the catalyst was incubated for 18 h at 100 °C prior to adding **8** and PMP. As a result of these findings, Schlenk techniques were employed in all of our subsequent mechanistic studies (vide infra).

Table 2. Cyclization of Iodide **8** To Form Oxindole Alcohol **29** Using (*R*)-BINAP of Varying Enantiopurity[a]

ee of (*R*)-BINAP, %	PMP−promoted ee of **29**,[b] %	Ag_3PO_4-promoted ee of **29**,[b] %
25	23	21
50	44	43
75	69	60
>99	92	78

[a] Conditions: 5 mol % $Pd_2(dba)_3$·$CHCl_3$, 12 mol % (*R*)-BINAP, 4 of equiv PMP or 2 of equiv Ag_3PO_4, DMA (0.1 M); reactions employing PMP were conducted at 100 °C, those employing Ag_3PO_4 at 80 °C. All reactions proceeded to completion and produced (*R*)-**29**. [b] Determined by HPLC analysis of **29** using a CHIRALCEL OB-H column.

Table 3. Pd−(*R*)-BINAP-Catalyzed Cyclization of Iodide **8** To Ultimately Form Oxindole Alcohol **29** in DMA Containing Varying Amounts of Water and in THF[a]

entry	solvent	(*E*)/(*Z*) ratio[b]	yield,[c] %	ee,[d] %
1	DMA	22:1	73	91
2	0.1% H_2O−DMA (v/v)	22:1	76	92
3	0.5% H_2O−DMA (v/v)	23:1	*e*	91
4	1.0% H_2O−DMA (v/v)	22:1	*e*	90
5	5.0% H_2O−DMA (v/v)	28:1	75	90
6	10.0% H_2O−DMA (v/v)	28:1	68	87
7	THF	*e*	73	97

[a] Conditions: 5 mol % $Pd_2(dba)_3$·$CHCl_3$, 12 mol % (*R*)-BINAP, 4 equiv of PMP, DMA (0.1 M), 100 °C. All reactions proceeded to completion. [b] Enoxysilane stereoisomer ratios were determined by GLC analysis. [c] Overall yield alcohol **29**. [d] Enantiomeric excess (±2% ee) of (*R*)-**29** was measured by HPLC using a Chiralcel OB-H or AS column. [e] Not determined.

Effects of Added Salts on Asymmetric Heck Cyclizations of 2-Methyl-(*Z*)-2-butenanilide Iodide 8 and Triflate 15. There are many reports that added salts can enhance reactivity and selectivity of palladium mediated processes.[23,24] The effect of added halide salts on Pd−BINAP catalyzed cyclizations of iodide **8** carried out in the presence of PMP are summarized in Table 5. Addition of 1−2 equiv of hydrohalide salts of PMP had little effect on enantioselection (93 ± 2% ee); however,

(23) For a recent review, see: Jeffery, T. In *Advances in Metal Organic Chemistry*; Liebeskind, L. S., Ed.; JAI: Greenwich, 1996; Vol. 5, pp 153−260.

(24) Selected examples include: (a) Sonesson, C.; Larhead, M.; Nyqvist, C.; Hallberg, A. *J. Org. Chem.* **1996**, *61*, 4756. (b) Jeffery, T. *Tetrahedron* **1996**, *52*, 10113. (c) Amatore, A.; Jutand, A.; Suarez, A. *J. Am. Chem. Soc.* **1993**, *115*, 9531. (d) Merlic, C. A.; Semmelhack, M. F. *J. Organomet. Chem.* **1990**, *391*, C23. (e) Scott, W. J.; Stille, J. K. *J. Am. Chem. Soc.* **1986**, *108*, 3033.

Table 4. Cyclization of Iodide **8** To Ultimately Form Oxindole Alcohol **29** Using Pd−(*R*)-BINAP Preformed in Different Ways[a]

entry	catalyst formation time,[b] h	enoxysilane (*E*)/(*Z*)[c]	**29** ee,[d] %
1	1	23:1	89
2	3	23:1	91
3	6	20:1	90
4	12	4:1	54
5[e]	18	21:1	91

[a] Conditions: 5 mol % $Pd_2(dba)_3$·$CHCl_3$, 12 mol % (*R*)-BINAP, 4 equiv of PMP, DMA (0.1 M) at 100 °C. Reactions were conducted under nitrogen in recovery flasks sealed with a septa unless noted otherwise. All reactions proceeded to completion. [b] The precatalysts were heated for the specified time at 100 °C prior to adding **8** and PMP. [c] Enoxysilane ratios were determined by GLC analysis. [d] Enantiomeric excess (±2%) of (*R*)-**29** was measured by HPLC using a Chiralcel OB-H column. [e] Reaction was conducted in Schlenk equipment under Ar and degassed by the freeze−pump−thaw method (see text).

Table 5. Cyclization of Iodide **8** with Pd(*R*)-BINAP To Ultimately Form Oxindole **29** in the Presence of PMP and Added Salts[a]

entry	additive[b]	solvent	ee,[c] %	yield,[d] %
1	none	DMA	91	76
2	PMP·HI	DMA	91	62
3	PMP·HI[e]	DMA	92	39
4	PMP·HBr	DMA	95	45
5	PMP·HCl	DMA	94	75
6	AgOTf	DMA	43	*f*

[a] Conditions: 5 mol % $Pd_2(dba)_3$·$CHCl_3$, 12 mol % (*R*)-BINAP, 4 equiv of PMP, DMA (0.1 M), 100 °C. All reactions proceeded to completion. [b] One equiv with respect to substrate. [c] Enantiomeric excess (±2% ee) of (*R*)-**29** were measured by HPLC using a Chiralcel OB-H or AS column. [d] Overall yield of alcohol **29**. [e] Two equiv with respect to substrate. [f] Not determined.

the yield of oxindole alcohol **29** was somewhat reduced. As expected from the results summarized in Table 1, addition of AgOTf decreased enantioselection. The reduction was considerably greater with AgOTf (to 43% ee) than with Ag_3PO_4 (compare entry 6 of Table 5 with entry 4 of Table 1).

Asymmetric Heck cyclization of 2-butenanilide triflate **15** proceeded with an enantioselectivity of 45 ± 3% in DMA, within experimental error to the enantioselection realized in cyclization of iodide **8** in the presence of AgOTf (compare entry 6 of Tables 5 and entry 1 of Table 6). Within experimental uncertainty, enantioselectivity was unaffected by the addition of 5−10% water (Table 6, entries 2 and 3) or if THF was employed as the reaction solvent (entry 4). Addition of excess triflate also had no discernible effect (entry 1 vs 5). However, addition of alkylammonium halides to cyclizations of triflate **15** in DMA dramatically raised enantioselectivity to 90 ± 3% ee (Table 6, entries 1, 6−8). The high enantiomeric excesses obtained in these reactions are identical, within experimental uncertainty, to those realized in the cyclization of iodide **8** (Table 5). Qualitatively similar results were observed upon adding hydrohalic salts of PMP (entries 9−11). The marked effect of halide salts was not dependent on the polarity of the reaction solvent, since nearly identical enhancements upon addition of *n*-Bu_4NI were observed in DMA, DMA containing 5−10% water, and THF (entries 1 and 12−14).

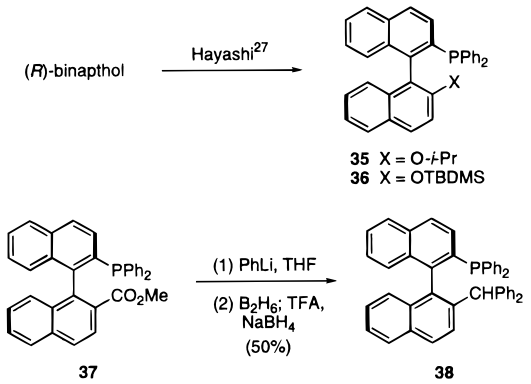
Studies with Chiral Monodentate Phosphine Ligands. Phosphine dissociation has been postulated to be the cause of the low stereoinduction often seen in asymmetric Heck reactions of aryl and vinyl halides conducted in the absence of halide scavengers.[3,16,25] To explore the possibility of phosphine dissociation in the PMP-promoted Heck reactions of α,β-unsaturated 2-iodoanilide substrates, we examined the cyclization of iodide **8** using monophosphine analogues of (*R*)-BINAP. Ligands **35** and **36**[26] were prepared as described by Hayashi,[26d] while **38** was synthesized from the known (*R*)-phosphine ester **37** (Scheme 6).[27] Condensation of **37** with excess PhLi followed by in situ protection of the phosphine moiety as a borane complex[28] and reduction of the triaryl carbinol with $NaBH_4$ and trifluoroacetic acid[29] furnished ligand **38** in 50% overall yield.

Table 6. Cyclization of Triflate **15** with Pd−(*R*)-BINAP To Ultimately Form Oxindole **29** in the Presence of PMP and Added Salts[a]

entry	additive[b]	solvent	ee,[c] %	yield,[d] %
1		DMA	43−48	72
2		5% H_2O−DMA	49	78
3		10% H_2O−DMA	47	72
4		THF	49	81
5	*n*-Bu_4NOTf	DMA	42	70[e]
6	*n*-Bu_4NI	DMA	90	62
7	*n*-Bu_4NBr	DMA	93	59
8	*n*-Bu_4NCl	DMA	93	52
9	PMP·HI[f]	DMA	91	40
10	PMP·HBr	DMA	92	62
11	PMP·HCl	DMA	88	60
12	*n*-Bu_4NI	5% H_2O−DMA	90	90
13	*n*-Bu_4NI	10% H_2O−DMA	88	91
14	*n*-Bu_4NI	THF	93	89

[a] Conditions: 5 mol % $Pd_2(dba)_3$·$CHCl_3$, 12 mol % (*R*)-BINAP, 4 equiv of PMP, DMA (0.1 M), 100 °C. All reactions proceeded to completion. [b] One equiv with respect to substrate. [c] Enantiomeric excess (±2% ee) of (*R*)-**29** was measured by HPLC using a Chiralcel OB-H or AS column. [d] Overall yield of alcohol **29**. [e] Overall yield of aldehyde **25**. [f] Reaction proceeded to 66%.

Scheme 6



Asymmetric Heck cyclizations of iodide **8** in the presence of 5% $Pd_2(dba)_3$·$CHCl_3$ and 11% (*R*)-monophosphines **35**, **36**, or **38** at 100 °C in DMA in the presence of 4 equiv of PMP provided (*S*)-oxindole alcohol **29** (the opposite enantiomer to that produced using (*R*)-BINAP in low ee (Table 7). Increasing the ratio of **36** to Pd did not significantly affect enantioselectivity (entries 3−6). A striking feature of the monophosphine-mediated cyclizations is their high reaction rate. Heck cyclization of **8** mediated by Pd(*R*)-BINAP requires 20−60 min at 100 °C to proceed to completion, while this reaction using mono-

(25) (a) Cabri, W.; Candiani, I. *Acc. Chem. Res.* **1995**, *28*, 2.
(26) (a) Uozumi, Y.; Tanahashi, A.; Lee, S. Y.; Hayashi, T. *J. Org. Chem.* **1993**, *58*, 1945. (b) Hayashi, T. *J. Synth. Org. Chem. Jpn.* **1994**, *52*, 900. (c) Uozumi, Y.; Hayashi, T. *J. Am. Chem. Soc.* **1991**, *113*, 9887.
(27) Uozumi, Y.; Suzuki, N.; Ogiwara, A.; Hayashi, T. *Tetrahedron* **1994**, *50*, 4293.
(28) (a) Frisch, M. A.; Heal, H. G.; Mackle, H.; Maden, I. O. *J. Chem. Soc.* **1965**, 899. (b) Gough, S. T. D.; Triplett, S. *J. Chem. Soc.* **1961**, 4264. (c) Bailey, W. J.; Buckler, S. A. *J. Am. Chem. Soc.* **1957**, *79*, 3567.
(29) Frisch, M. A.; Heal, H. G.; Mackle, H.; Maden, I. O. *J. Chem. Soc.* **1965**, 899.

Table 7. Cyclization of Iodide **8** To Ultimately Form Oxindole Alcohol **29** Using Palladium−Monophosphine Catalysts and Pd−(*R*)-BINAP

entry	ligand	ligand:Pd[b]	enoxysilane ratio (*E*:*Z*)[c]	ee of **29**,[d] %	config of **29**
1	**35**	1.1:1	1.4:1	27	*S*
2	**36**	1.1:1	1.2:1	23	*S*
3	**36**	1.6:1	1.4:1	21	*S*
4	**36**	2.1:1	1.5:1	21	*S*
5	**36**	2.9:1	1.5:1	24	*S*
6	**38**	1.2:1	1.3:1	19	*S*
7	BINAP	1.1:1	22:1	91	*R*

[a] Conditions: 5 mol % $Pd_2(dba)_3$·$CHCl_3$, 12 mol % ligand, 4 equiv of PMP, DMA (0.1 M), 100 °C. All ligands are of the *R* configuration and all reactions proceeded to completion. [b] Equiv. [c] Determined by GLC analysis. [d] Enantiomeric excess (±2% ee) of **29** was measured by HPLC using a Chiralcel OB-H or AS column.

phosphine **36** as ligand is complete in 10 min at ambient temperature. Reactions carried out at 54 °C for 5 min using 5 mol % $Pd_2(dba)_3$·$CHCl_3$ without added ligand or 5 mol % $Pd_2(dba)_3$·$CHCl_3$ in the presence of 11 mol % of BINAP or **36** give a rough estimate of relative rates. Under these conditions, the Pd−(*R*)-BINAP reaction did not proceed to a detectable extent, the $Pd_2(dba)_3$·$CHCl_3$ catalyzed reaction proceeded to ∼50% completion, and the Pd-**36** catalyzed reaction was complete in 5 min.

Discussion

Introductory Observations. The general outlines of the mechanism of the Heck reaction—oxidative addition, coordination of the alkene, insertion, and β-hydride elimination—have been appreciated since the 1970s and have been discussed in numerous reviews.[30] During the past few years, individual steps of the Heck reaction have been subjected to increasing scrutiny. The extensive investigations of Amatore, Jutand, and co-workers have shed much light on the nature of the active catalyst and its participation in the oxidative addition step.[31] Recently, for example, they demonstrated that the predominant species in mixtures of $Pd(dba)_2$ and BINAP is the monomeric Pd(dba)-BINAP complex which oxidatively adds to PhI to form (BINAP)Pd(Ph)I.[31d] Other recent studies have shown that $(Ph_3P)_2$(aryl)PdCl complexes do not readily undergo chloride dissociation in DMF,[32] whereas the corresponding triflate complexes are completely ionized.[32,33] That two different oxidative addition products can be formed has led to general acceptance of two reaction manifolds for Heck reactions: cationic and neutral.[3,25,30c−g,34] These are depicted schematically in Figure 2 for intramolecular insertion of an unsaturated aromatic substrate brought about by a (bisphosphine)Pd(0) catalyst.

First introduced independently by Cabri[34a] and Hayashi,[34b] the cationic reaction manifold has been uniformly invoked to describe asymmetric Heck reactions of unsaturated triflates or halides when carried out in the presence of Ag(I) or Tl(I) salts.[3] Triflate dissociation, or halide abstraction by Ag(I) or Tl(I) salts, vacates a coordination site on the Pd(II) complex, facilitating olefin complexation (Figure 2, **40** → **42** or **39** → **41** → **42**). A convincing demonstration of the stability of (bisphosphine)-(aryl)palladium(II) halide complexes such as **41** and their activation for migratory insertion by halide removal is provided by Brown's recent stoichiometric simulation studies.[35] As illustrated in Scheme 7, reaction of **48** with [1,1′-bis(diphenylphosphino)ferrocene]($^2\eta$-cyclooctatetraene)palladium gave the stable, crystallographically characterized adduct **49** having no direct interaction of the alkene and palladium. However, exposing this arylpalladium iodide complex to AgOTf at −78 °C resulted in immediate precipitation of AgI and rapid reaction (at −40 °C) to form ultimately **50**. Since both phosphines of a chiral bisphosphine ligand are readily accommodated during the migratory insertion step (**42** → **43**), the cationic mechanism provides a simple rationale for the higher enantioselectivity often seen in asymmetric Heck reactions of halides when carried out in the presence of Ag(I) or Tl(I) salts.

Heck reactions of aryl or vinyl halides with palladium catalysts having bidentate ligands in the absence of Ag(I) or Tl(I) salts are notorious for their sluggishness.[30] The intransigence of these reactions has been widely attributed to the reluctance of a chelating bisphosphine ligand to dissociate from (bisphosphine)(aryl)Pd(halide) complexes. In asymmetric Heck reactions, partial dissociation of a chiral bisphosphine ligand would result in a loss of ligand rigidity which could erode enantioselectivity.[3] In contrast to this conventional wisdom, we first reported in 1992 that Pd−BINAP catalyzed intramolecular Heck reactions of some aryl halide substrates take place at 80−100 °C with high enantioselectivity in solvents such as DMA *in the absence of halide scavengers*.[5] Current understanding of the neutral Heck reaction manifold is obviously incomplete, and this pathway warrants closer scrutiny, an issue we will return to shortly.

Synthetic Applications of Intramolecular Heck Cyclizations. The studies reported in this and the preceding paper[4] demonstrate that enantioenriched 3,3-disubstituted oxindoles, indolines, and dihydrobenzofurans can be prepared by Pd−BINAP-catalyzed intramolecular Heck reactions of *o*-iodoarenes tethered to (*E*)- or (*Z*)-trisubstituted alkenes. Enantioselectivities range from moderate to high (up to 97% ee). These investigations moreover convincingly demonstrate that synthetically useful enantioselectivities can be realized in intramolecular Heck insertions of iodide substrates proceeding by *either* the cationic (HI acceptor is Ag_3PO_4) or neutral (HI acceptor is PMP) pathways.[4]

Our investigations of experimental procedures for conducting asymmetric Heck reactions provided a useful caveat: To obtain optimum enantioselectivities in asymmetric Heck reactions that proceed slowly at elevated temperatures, the reaction should be conducted with rigorous exclusion of oxygen. We also demonstrated that when the reaction is carried out in a dipolar aprotic solvent such as DMA, small amounts of water (up to 5%) do not affect enantioselection.

(30) Selected reviews include: (a) Heck, R. F. *Org. React.* **1982**, *27*, 345. (b) Heck, R. F. In *Comprehensive Organic Synthesis*; Trost, B. M., Ed.; Pergamon: London, 1991; Vol. 4, pp 833−863. (c) Davies; G. D.; Hallberg, A. *Chem. Rev.* **1989**, *89*, 1433. (d) de Meijere, A.; Meyer, F. E. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 2379. (e) Gibson, S. E.; Middleton, R. J. *Contemp. Org. Synth.* **1996**, *3*, 447. (f) Bräse, S.; de Meijere, A. In *Metal-catalyzed Cross-coupling Reactions*; Diederick, F., Stang, P. J., Eds.; Wiley-VCH: Weinheim, 1998; Chapter 3. (g) Link, J. T.; Overman, L. E. In *Metal-catalyzed Cross-coupling Reactions*; Diederick, F., Stang, P. J., Eds.; Wiley-VCH: Weinheim, 1998; Chapter 6.

(31) (a) Amatore, C.; Azzabi, M.; Jutand, A. *J. Am. Chem. Soc.* **1991**, *113*, 8375. (b) Amatore, C.; Jutand, A.; M'Barki, M. A. *Organometallics* **1995**, *14*, 1818. (c) Amatore, C. Jutand, A.; Suarez, *J. Am. Chem. Soc.* **1993**, *115*, 9531. (d) Amatore, C.; Broeker, G.; Jutand, A.; Khalil, F. *J. Am. Chem. Soc.* **1997**, *119*, 5176.

(32) Jutand, A.; Mosleh, A. *Organometallics* **1995**, *14*, 1810.

(33) (a) Stang, P. J.; Kowalski, M. H.; Schiavilli, M. D.; Longford, D. *J. Am. Chem. Soc.* **1989**, *111*, 3347. (b) Stang, P. J.; Kowalski, M. H. *J. Am. Chem. Soc.* **1989**, *111*, 3356. (c) Hinkle, R. J.; Stang, P. J.; Kowalski, M. H. *J. Org. Chem.* **1990**, *55*, 5033. (d) Brown, J. M.; King, K. *Angew. Chem., Int. Ed. Eng.* **1996**, *35*, 657.

(34) Cabri, W.; Candiani, I.; DeBernardis, S.; Francalanci, F.; Penco, S. *J. Org. Chem.* **1991**, *56*, 5796.

(35) Brown, J. M.; Pérez-Torrente, J. J.; Alcock, N. W.; Clase, H. J. *Organometallics* **1995**, *14*, 207.

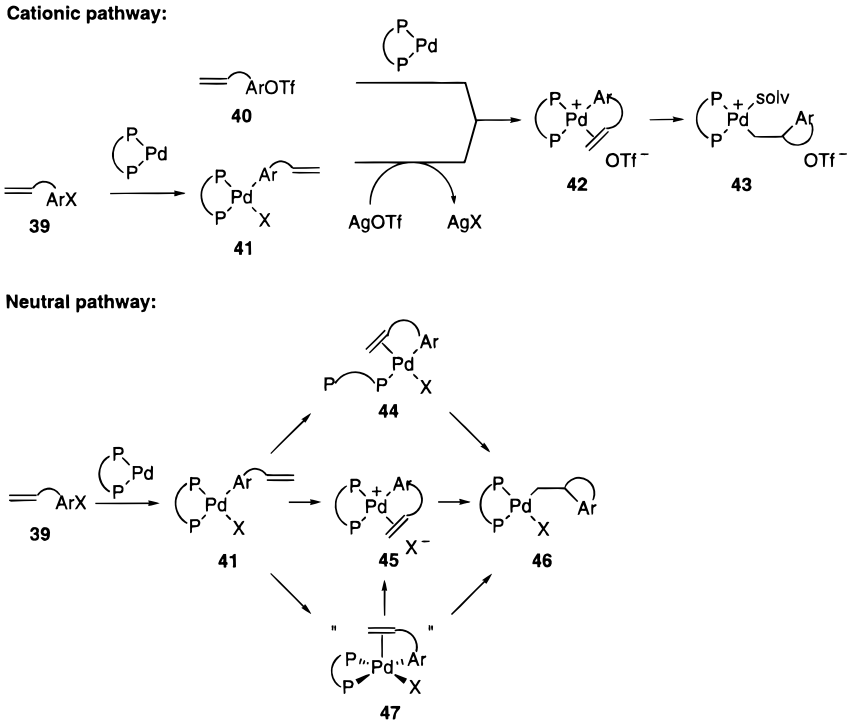
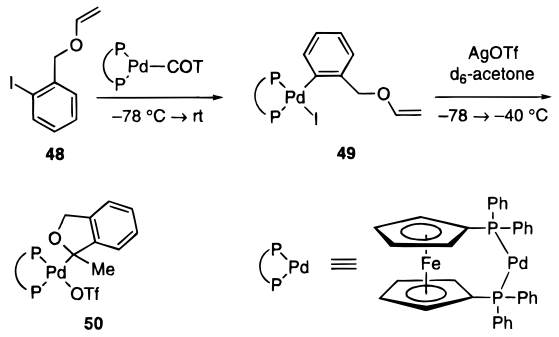


Figure 2. Cationic and neutral Heck reaction manifolds.

Scheme 7



While the cationic manifold of the Heck reaction can be entered from an aryl halide precursor in the presence of silver or thallium salts, the converse, accessing the neutral pathway from a triflate substrate, had not been explored in depth.[24b,36] The identical ee's obtained in PMP-promoted Heck cyclizations of (*Z*)-2-butenanilide triflate **10** in the presence of added iodide and (*Z*)-2-butenanilide iodide **8** alone demonstrate the feasibility of entering the neutral reaction manifold from triflate precursors. Since the iodide and triflate functional groups display quite different reactivity with many common reagents, the flexibility of being able to enter the cationic or neutral asymmetric Heck reaction manifolds from either precursor allows for important latitude in the preparation of cyclization substrates.

A comparison of the results presented in Table 1 for intramolecular Heck insertions of (*Z*)-α,*β*-unsaturated 2-iodoanilide substrates with the outcome of corresponding insertions of (*E*)-2-butenanilides[4] leads to the following conclusions: (1) (*E*)- and (*Z*)-α,*β*-unsaturated 2-iodoanilides give opposite enantiomers of the Heck product when Ag_3PO_4 is the HI acceptor, while the sense of stereoinduction is independent of alkene geometry when the HI acceptor is PMP. (2) When the 2-substituent is Me or *prim*-alkyl, stereoinduction is optimal in PMP-promoted insertions of *Z* substrates and take place with *ee's as high as 90*−*97%*. (3) When the 2-substituent is large, stereoinduction is optimal in insertions of *E* substrates carried out in the presence of Ag_3PO_4. (4) Contributions from the *β* alkene substituent are minor.

The ability to vary both the alkene geometry and the Heck reaction manifold allows chiral 3,3-disubstituted-2-oxindoles having a wide range of substituents at the quaternary carbon (Me, *prim*-alkyl, *tert*-alkyl, and aryl) to be prepared with ee's ranging from 72 to 97%. Enantioenriched oxindoles of this type are certain to be valuable intermediates for asymmetric synthesis of a variety of indole alkaloids. Our initial use of these intermediates to prepare both enantiomers of physostigmine and other Calabar alkaloids is detailed in the following paper.[37]

It has often been observed that stereoisomeric alkenes give opposite enantiomers in asymmetric Heck cyclizations proceeding by the cationic pathway.[3] The sense of stereoinduction observed in Pd−BINAP catalyzed cyclizations of the α,*β*-unsaturated 2-iodoanilides examined in this and the companion study[4] can be rationalized by the insertion proceeding preferentially[38,39] via the most stable cationic square planar alkene complex having an approximate coplanar orientation of the alkene *π* and aryl-C *σ* bonds.[40] Models of these complexes are shown in Figure 3 for intermediates resulting from the reaction of Pd−(*R*)-BINAP with iodide **10** and its *E* stereoisomer.[41,42] Two destabilizing interactions are discernible: (a) interaction between the *β*-methyl group of the alkene and the

(36) Maddaford, S. P.; Anderson, W. G.; Cristofoli, W. A.; Keay, B. A. *J. Am. Chem. Soc*. **1996**, *118*, 7108.

(37) Matsuura, T.; Overman, L. E.; Poon, D. *J. Am. Chem. Soc*. **1998**, *120*, 6500−6503.

(38) Thorn, D. L.; Hoffmann, R. *J. Am. Chem. Soc*. **1978**, *100*, 2079.

(39) Either formation or insertion of this intermediate could be the enantioselective step.

(40) Abelman, M. M.; Overman, L. E.; Tran, V. D. *J. Am. Chem. Soc.* **1990**, *112*, 6959.

(41) The models depicted in Figure 3 represent local minima and were built using the Tripos 5.7 force field in the molecular mechanics module of Spartan 2.0. The X-ray coordinates of $PdCl_2$[(R)-BINAP] served as the starting point.[42]

(42) Toshiro, K.; Ito, T.; Takaya, H.; Souchi, S.; Noyori, R. *Acta Crystallogr*. **1982** *B38*, 807.

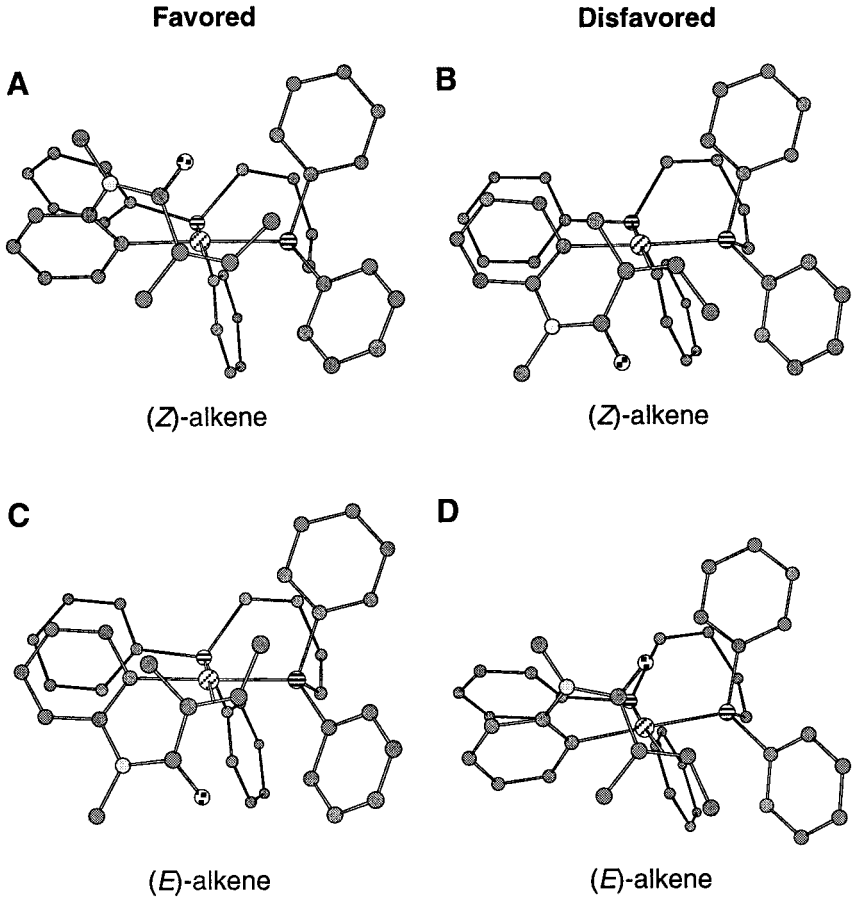


Figure 3. Models of cationic square planar complexes formed from Pd−(*R*)-BINAP and 2′-iodo-*N*-methyl-(*E*)- or -(*Z*)-2-methyl-2-butenanilide having the alkene π and aryl C−Pd σ bonds nearly coplanar. The naphthalene rings of BINAP have been removed for clarity.

proximal *pseudo*-equatorial phenyl group of BINAP[43] and (b) contact between the twisted aryl ring of the substrate and the other *pseudo*-equatorial phenyl group of BINAP. For the *Z* substrate, the closest contact between the β-methyl carbon and the nearest carbon of the *pseudo*-equatorial phenyl is 3.2 Å in complex **A** and 2.9 Å in diastereomeric complex **B**. Considering the aryl−phenyl interaction, the closest C−C contact is 3.2 Å in complex **A** and 2.8 Å in diastereomeric complex **B**. The situation is less clear with the *E* substrate, since destabilizing interactions with the β-methyl group are present in **D** and with the aryl group in **C**.[44] Preferential formation of (*S*)-oxindole products with substrates in the *E* series (via intermediate **C**) suggests that the former interaction is more severe. That higher enantioselectivity is typically observed in the *Z* series would be consistent with reinforcing destabilizing interactions in this series.

Enantioselective Step of the Neutral Pathway. As noted previously, details on how a (bisphosphine)(aryl)palladium halide complex undergoes migratory insertion in the absence of halide scavengers are virtually nonexistent. Since the results we initially obtained in 1992 were unexpected,[5] we decided to initially verify that monomeric Pd−BINAP was involved. We pursued this issue through chiral amplification studies[22] and found a linear relationship between the enantiopurity of the BINAP and enantioselectivity in insertions taking place by both the cationic and neutral pathways (Table 2). This relationship indicates that there is no detectable preequilibrium self-association of the catalyst prior to entry into the catalytic cycle, a result consistent with Amatore's recent findings.[31d,45,46]

Two possibilities for the enantioselective step can be easily dismissed. Our observation that added halide directs reactions of triflate substrates down the neutral pathway, undoubtedly by forming **41**,[24c] *provides strong evidence that oxidative addition is not reversible*. If it were, when the added halide was Cl^- or Br^-, the aryl bromide or aryl chloride analogue of **39** would have accumulated in experiments with triflate **15**. Oxidative addition, however, cannot be the enantioselective step,[47] since iodides give products of quite different enantiopurity when silver (or thallium) salts are present. An alternate scenario in which migratory insertion is reversible and enantioselectivity is dictated in the penultimate β-hydride elimination step can also be ruled out since it would be inconsistent with the dependence of enantioselection on the geometry of the alkene substrate.

Within the neutral manifold, C−C bond formation could occur through at least three pathways as depicted in Figure 2: (1) Insertion from a neutral four coordinate complex **44** resulting

(43) This interaction has been commented on in general terms by previous authors.[3]

(44) That the phenyl groups, particularly the *quasi* equatorial phenyl groups, of BINAP and related ligands play a critical role in enantiodiscrimination has been pointed out by many authors See, *inter alia*.: (a) Fryzuk, M. D.; Bosnich, B. *J. Am. Chem. Soc.* **1997**, *99*, 66262. (b) Pavlov, V. A.; Klabunovskii, E. I.; Struchkov, T.; Voloboev, A. A.; Yanovsky, A. I. *J. Mol. Catal.* **1988**, *44*, 217. (c) Kagan, H. B. *Compr. Organomet. Chem.* **1982**, *8*, 463. (d) Seebach, D.; Plattner, D. A.; Beck, A. K.; Wang, Y. M.; Hunziker, D. *Helv. Chem. Acta* **1992**, *75*, 2171.

(45) Buchwald has recently isolated and characterized Pd[(*R*)-BINAP](dba): Wolfe, J. P.; Wagaw, S.; Buchwald, S. L. *J. Am. Chem. Soc.* **1996**, *118*, 7215.

(46) Formation of μ-bridged dimers with the bridging ligand being dba or BINAP, although unlikely, is nonetheless conceivable.

(47) Oxidative addition could be the enantioselective step if the intermediates undergoing oxidative addition were the diastereomeric Pd−BINAP alkene complexes.

from partial BINAP dissociation. (2) Insertion via a cationic four coordinate complex **45** resulting from halide ionization. (3) Direct insertion of a neutral pentacoordinate complex represented in generic fashion by **47**. Enantioselection in the neutral pathway must occur during olefin coordination to form intermediates **44**, **45**, or **47** or in the migratory insertion of these species.

Most previous authors have assumed, or specifically suggested, that the neutral Heck reaction manifold proceeds by phosphine dissociation: the sequence **41** → **44** → **46**.[3,25,30] Our studies with monophosphine analogues of BINAP were designed to examine the validity of this supposition by mimicking a partially dissociated BINAP chelate. Should a bisphosphine be monocoordinated during the enantioselective step, enantioselectivities obtained with monodentate models of BINAP should be similar to those obtained with BINAP. Just the opposite was observed. Asymmetric Heck cyclization of iodide **8** with the monophosphine BINAP analogues **35**, **36**, and most importantly **38**, proceeded in low ee to produce the enantiomeric oxindole to that produced as the major isomer using BINAP. This result supports the conclusion that in the corresponding reactions of BINAP both phosphines are bound to Pd during the enantioselective step. The **41** → **44** → **46** sequence can be ruled out.

Substitution chemistry of square planar Pd(II) complexes is dominated by associative processes.[48,49] In the neutral Heck reaction manifold, associative olefin complexation would occur by initial axial coordination of the alkene, as depicted in **47**.[48,50] At this juncture, migratory insertion could proceed in two ways, via halide expulsion (**47** → **45** → **46**) or directly from a five coordinate species (**47** → **46**). That a pentacoordinate intermediate is conceivable gains some support from the number of pentacoordinate Pd(II) alkene complexes that have been recently isolated and characterized.[51]

Theoretical calculations of Thorn and Hoffmann predict that migratory insertion from five coordinate Pt(II) complexes will have higher activation barriers than from four coordinate complexes.[38] This prediction is supported by the kinetic investigation of Samsel and Norton[52] who established that insertion of a tethered alkyne into a $(Ph_3P)_2$(aryl)Pd(II) chloride complex proceeds by phosphine expulsion. In light of the literature precedence available at this time, direct insertion through a five coordinate Pd(II) intermediate appears unlikely.

Through the process of elimination, the neutral manifold is reduced to the sequence **41** → **47** → **45** → **46**. Stereoinduction must then reside either in the preferential formation of one diastereomer of complex **47** or **45** or in the **45** → **46** insertion step. If insertion were the enantioselective step in both the cationic and neutral pathways, cationic alkene complex **45** having a halide counterion would have to behave quite differently from the similar triflate complex **42**. Disparate behavior, however, would be impossible if complexes **42** and **45** were dissociated. The evidence to date supports just such a conclusion. First, conductivity measurements demonstrate that *trans*-Ar−Pd$(PPh_3)_2$OTf is fully dissociated in *N*,*N*-dimethylformamide (DMF)[32] strongly suggesting similar behavior for **42** in DMA.[53] Second, our experimental results provide no evidence for ion pairing in the neutral pathway. For example, enantioselectivity in the neutral pathway is *unchanged in going from dry DMA to DMA containing 5% water* (Table 3). An identical lack of solvent effect was seen when the neutral pathway was entered from a triflate precursor (Table 6). We suggest that the stereochemistry determining step of the neutral pathway occurs during the process where halide is displaced by the tethered alkene (**41** → **47** → **45**).[54] This proposal is consistent with the following experimental observations: (1) BINAP is coordinated in bidentate fashion during the enantioselective step. (2) Enantioselectivity is insensitive to solvent polarity. (3) Addition of iodide (or other halides) to Heck reactions of a triflate substrate leads to the same stereoinduction realized with the corresponding iodide precursor in the absence of additives.

While it can be deduced that enantioselection in asymmetric Heck reactions proceeding via the neutral pathway resides in the process of olefin substitution, it cannot at present be surmised which step of this undoubtedly complex pathway is stereoregulating. The sequence **41** → **47** → **45** as written in Figure 2 is a significant oversimplification of a much more complicated process. A number of distinct pentacoordinate intermediates undoubtedly intervene between **41** and **45**.[48,55] At a minimum, an initially formed square-pyramidal complex must evolve to a square-pyramidal isomer having X apical, the most plausible immediate precursor of **45**. In principle, the enantioselective step could be the formation or breakdown of any of these intermediates. A corollary to this conclusion is that it is vastly premature to advance a three-dimensional model to rationalize stereoinduction in asymmetric Heck reactions that proceed by the neutral pathway.

Conclusion

This and the companion studies in this issue[4,37] detail two useful extensions of intramolecular asymmetric Heck chemistry: (a) use of basic amines as the HI scavenger in reactions of iodide substrates and (b) use of halide additives to direct reactions of triflate substrates to the neutral pathway. For example for the first time we have shown that enantioselection in asymmetric Heck insertions of some triflates can be dramatically enhanced by the addition of halide salts. One now has the ability to vary three important reaction parameters: stereochemistry of the alkene, nature of the group undergoing oxidative addition, and the Heck reaction manifold (cationic or neutral). Tuning these variables will allow a wide variety of enantioenriched products to be prepared in high enantiopurity by intramolecular asymmetric Heck reactions. The studies described here illustrate this versatility through the synthesis of chiral 3,3-disubstituted-2-oxindoles having a wide range of substituents at the quaternary carbon—Me, *prim*-alkyl, *tert*-alkyl, and aryl—in useful levels of enantiocontrol (72−97%).

In 1992, we first reported that Pd−BINAP-catalyzed intramolecular Heck reactions of some aryl halide substrates take place

(48) For reviews, see: (a) Cross, R. J. *Adv. Inorg. Chem*. **1989**, *34*, 219. (b) Tobe, M. L. In *Comprehensive Coordination Chemistry*; Wilkinson, G., Gillard, R. D., McCleverty, J. A., Eds.; Pergamon: Oxford, 1987; Vol. 1, pp 281−329.

(49) In certain circumstances dissociative substitution is observed. For a review, see: Romero, R. *Comments Inorg. Chem.* **1990**, *11*, 21.

(50) The set of all five-coordinate intermediates is represented in Figure 2 by **47**.

(51) (a) Albano, V. G.; Castellari, C.; Cucciolito, M. E.; Panunzi, A.; Vitagliano, A. *Organometallics* **1990**, *9*, 1269. (b) Albano, V. G.; Natile, G.; Panunzi, A. *Coord. Chem. Rev.* **1994**, *133*, 67.

(52) Samsel, E. G.; Norton, J. R. *J. Am. Chem. Soc*. **1984**, *106*, 5505.

(53) Carlson, R.; Lundstedt, T.; Albano, C. *Acta Chem. Scand.* **1985**, *39*, 79.

(54) There is some precedent for olefin displacement of halide in (bisphosphine)(aryl) Pd(halide) complexes: Portnoy, M.; Ben-David, Y.; Rousso, I.; Milstein, D. *Organometallics* **1994**, *13*, 3465.

(55) Relevant issues are discussed in a recent study of the insertion of norbornene into palladium−carbon bonds of complexes having bidentate nitrogen ligands: Groen, J. H.; Delis, J. G. P.; van Leeuwen, P. W. N. M.; Vrieze, K. *Organometallics* **1997**, *16*, 68.

(56) General experimental details have been described.[4] Conventional silica gel flash chromatography is abbreviated as sgc.

at 80−100 °C with high enantioselectivity in the *absence of halide scavengers*.[5] We disclosed herein the first investigations of the mechanism of this poorly understood neutral Heck reaction manifold. Key results were the following: (1) Chiral amplification studies show that the catalyst is monomeric Pd−BINAP. (2) Investigations of monophosphine analogues of BINAP, which were designed to mimic a partially dissociated BINAP chelate, support the conclusion that BINAP is chelated during the enantioselective step. (3) Enantioselectivity is insensitive to solvent polarity. (4) Oxidative addition is irreversible. From these data, we suggest that the stereochemistry determining step of the neutral pathway occurs during the process in which iodide is displaced by the tethered alkene (Figure 2, **41** → **47** → **45**). In light of the variety of pentacoordinate intermediates that could be involved, it is premature to advance a model to rationalize stereoinduction in asymmetric Heck reactions proceeding by the neutral pathway. Nonetheless, the finding that asymmetric Heck reactions that take place by the neutral pathway involve five-coordinate intermediates broadens the vista for the design of asymmetric ligands for this and related reactions.

Despite these advances, many aspects of the neutral Heck reaction manifold remain poorly understood. For example, several authors have described Heck reactions of halide substrates that proceed by the neutral pathway with low ee.[3] Critical is learning what are the structural requirements for obtaining high enantioselectivity in the less-studied neutral pathway of intramolecular Heck reactions. Our current investigations are directed at this and related issues.

Experimental Section[56]

Methyl (*Z*)-4-(*tert*-Butyldimethylsiloxy)-2-methyl-2-butenoate (5). A solution of (*Z*)-3-iodo-2-buten-1-ol[9] (6.4 g, 32.5 mmol) and dry CH_2Cl_2 (100 mL) was treated dropwise sequentially with 2,6-lutidine (11 mL, 94 mmol) and *tert*-butyldimethylsilyl triflate (11 mL, 46 mmol) at −78 °C. The reaction was stirred at −78 °C for 3 h and poured into saturated aqueous NH_4Cl solution (80 mL). The layers were separated, and the aqueous layer was extracted with Et_2O (3 × 100 mL). The combined organic layers were washed with brine (100 mL), dried (Na_2SO_4), and filtered, and the filtrates were concentrated. Purification of the pale violet residue by sgc (49:1 hexanes−EtOAc) gave 8.06 g (77%) of **2** as a pale orange oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.68 (td, J = 3.8 Hz, 1.5, 1H), 4.17 (dd, J = 2.1, 1.5 Hz, 2H), 2.50 (d, J = 1.4 Hz, 3H), 0.91 (s, 9H), 0.08 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 135.3, 99.1, 68.5, 33.5, 25.9, 18.3, −5.1; IR (film) 2959, 2925, 2875, 2851, 1466, 1459, 1378 cm^{-1}.

A solution of *N*,*N*-diisopropylethylamine (10 mL, 57 mmol) and methanol (24 mL, 0.6 mmol) was purged with CO (3×) at room temperature. A solution of **2** (3.72 g, 11.9 mmol) and dry DMF (30 mL) was added, the resulting solution was purged again with CO (3×), and $Pd(PPh_3)_4$ (1.38 g, 1.2 mmol) was added in one portion followed by further purging with CO (3×). After 1 h, the reaction became a red homogeneous solution which was maintained overnight at room temperature, whereupon it became a thick yellow slurry. The reaction was treated with saturated aqueous $NaHCO_3$ (20 mL), the resulting solids were removed by filtration, the filtrate was extracted with hexanes (3 × 50 mL), and the organic layers were combined and concentrated. The residue was dissolved in THF (30 mL), and a 3:1 water−bleach solution (60 mL) was added. The reaction was maintained for 30 min and then extracted with hexanes (3 × 50 mL). The combined organic layers were washed with 1:1 brine−water solution (2 × 100 mL), dried ($MgSO_4$), filtered, and concentrated. Purification of the residue by sgc (12:1 hexanes−EtOAc) gave 1.94 g (67%) of **5** as a pale yellow oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.17−6.10 (m, 1H), 4.59 (app d, J = 17 Hz, 2H), 3.71 (s, 3H), 2.21 (s, 3H), 0.89 (s, 9H), 0.06 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 167.7, 146.4, 125.4, 62.1, 51.4, 25.9, 19.7, 18.3; IR (film) 2956, 2931, 2887, 1720, 1483, 1367, 1333, 1254, 1228, 1141, 1104 cm^{-1}.

2′-Iodo-*N*-methyl-(*Z*)-4-(*tert*-butyldimethylsiloxy)-2-methyl-2-butenanilide (8). Following a modification of the procedure of Weinreb,[11] Me_3Al (2.0 M in hexane, 2.9 mL, 5.8 mmol) was added dropwise to a solution of 2-iodoaniline (1.04 g, 4.74 mmol) and dry CH_2Cl_2 (9.5 mL) at 0 °C. Hydrogen evolution ensued, and the reaction was maintained at 0 °C for 10 min and then allowed to warm to room temperature. After 45 min, a solution of **5** (549 mg, 2.25 mmol) and dry CH_2Cl_2 (9 mL) was added dropwise, and the reaction was maintained at room temperature overnight. The reaction was quenched with 1 M Rochelle's salt solution (10 mL) at 0 °C, and the resulting mixture was stirred for 10 min at room temperature, poured into water (50 mL), and extracted with CH_2Cl_2 (3 × 50 mL). The combined organic layers were then washed with brine (150 mL), dried ($MgSO_4$), filtered, and concentrated. The residue was dissolved in THF (20 mL) and added dropwise to a stirring suspension of NaH (60% oil dispersion, 220 mg, 5.5 mmol) in THF (20 mL) at 0 °C. After 15 min, the reaction was allowed to warm to room temperature, and MeI (0.33 mL, 5.30 mmol) was added. The reaction was maintained overnight at room temperature and then poured into saturated aqueous $NaHCO_3$ solution (50 mL), and the resulting mixture was extracted with Et_2O (2 × 30 mL) and EtOAc (30 mL). The combined organic layers were washed with brine (100 mL), dried ($MgSO_4$), filtered, and concentrated. Purification of the residue by sgc (5:1 hexanes−EtOAc) afforded 738 mg (73%) of **8** as an orange oil. NMR analysis showed that this compound is a 2.4:1 mixture of amide rotamers. ^{1}H NMR (300 MHz, $CDCl_3$) major rotamer: δ 7.88 (app d, J = 7.4 Hz, 1H), 7.31 (m, 2H), 7.05−7.02 (m, 1H), 5.34 (m, 1H), 4.34−4.27 (m, 2H), 3.25 (s, 3H), 1.56 (s, 3H), 0.92 (s, 9H), 0.10 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) major rotamer: δ 170.1, 145.2, 140.0, 131.8, 130.5, 129.5, 129.2, 129.1, 98.3, 61.2, 36.5, 25.9, 20.1, −5.2; IR (film) 2952, 2927, 2855, 1649, 1578, 1470, 1381, 1360, 1252, 1102, 1058 cm^{-1}; MS (EI) *m*/*z* 445.0933 (M, 445.0934 calcd for $C_{18}H_{28}INO_2Si$). Anal. Calcd for $C_{18}H_{28}INO_2Si$: C 48.54; H 6.34; N 3.14. Found: C 48.57; H 6.34; N 3.20.

2′-Hydroxy-(*Z*)-4-(*tert*-butyldimethylsiloxy)-2-methyl-2-butenanilide (12). A solution of triethylsilyl chloride (2.4 mL, 14.3 mmol), 2-aminophenol (1.03 g, 9.44 mmol), imidazole (2.51 g, 36.87 mmol), and dry CH_2Cl_2 (9 mL) was stirred at room temperature for 3 h and poured into water (20 mL). The layers were separated, and the aqueous layer was extracted with Et_2O (20 mL). The organic extracts were combined, dried (Na_2SO_4), and concentrated. The resulting crude residue was purified by sgc (9:1 to 4:1 hexanes−EtOAc) to give 1.79 g (85%) of **11** as a brown oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.81 (m, 3 H), 6.61 (app td, J = 7.6, 1.8 Hz, 1H), 3.72 (s, 2H, N*H*), 1.01 (t, J = 8.0 Hz, 9H), 0.76 (q, J = 8.0 Hz, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 143.0, 138.1, 121.9, 118.4, 118.3, 118.2, 115.6, 6.8, 5.3; IR (CCl_4) 3478, 3388, 3032, 2960, 2877, 1742, 1613, 1592, 1503, 1414, 1277, 1218 cm^{-1}. Anal. Calcd for $C_{12}H_{21}NOSi$: C 64.52; H 9.48; N 6.27. Found: C 64.34; H 9.59; N 6.24.

A hexane solution of Me_3Al (2.0 M, 14 mL) was added dropwise to a cooled solution of **11** (6.67 g, 30 mmol) and dry toluene (30 mL) at 0 °C. The resulting dark green solution was maintained at 0 °C for 10 min and then allowed to warm to room temperature. After 45 min, a solution of methyl ester **5** (7.35 g, 30 mmol) and dry toluene (15 mL) was added dropwise. The reaction was maintained at room temperature for 4 h, warmed to 60 °C for 2 h, cooled to 0 °C, and quenched by slow addition of 1 M aqueous Rochelle's salt solution (100 mL). The resulting mixture was stirred overnight at room temperature and then poured into EtOAc (50 mL), and the layers were separated. The aqueous layer was extracted with Et_2O (100 mL), and the organic layers were combined, washed with brine (200 mL), dried ($MgSO_4$), filtered, and concentrated. A solution of this crude anilide and dry THF (10 mL) was cooled to 0 °C and added to a mixture of NaH (60% oil dispersion, 1.6 g, 42 mmol, prewashed with hexane) and THF (10 mL) at 0 °C, and the resulting mixture was stirred for 20 min and then allowed to warm to room temperature. After 3 h the reaction was quenched with ice and poured into saturated aqueous NH_4Cl solution (50 mL), and the layers were separated. The aqueous layer was extracted with EtOAc (50 mL), and Et_2O (50 mL) and the combined organic layers were washed with brine (100 mL), dried (Na_2SO_4), filtered, and concentrated. The resulting brown oil was purified by sgc (9:1 to 4:1 hexanes−EtOAc) to give 7.0 g (72% from **5**) of **12** as

an amber oil which solidified upon standing: mp 69−71 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.21 (br s, 1H), 9.09 (s, 1H), 7.14 (app td, J = 7.6, 1.3 Hz, 1H) 7.04 (dd, J = 7.6, 0.9 Hz, 1H), 6.96 (dd, J = 7.9, 1.2 Hz, 1H), 6.85 (app td, J = 7.9, 1.2 Hz, 1H), 6.10 (app td, J = 7.5, 1.2 Hz, 1H), 4.31 (d, J = 7.5 Hz, 2H), 2.06 (s, 3H), 0.90 (s, 9H), 0.12 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.0, 149.0, 134.4, 127.1, 125.8, 122.6, 120.3, 119.6, 59.6, 25.9, 20.5, 18.3, −5.0; IR (film) 3276, 2954, 2929, 2857, 1664, 1633, 1598, 1533, 1454, 1256, 1059 cm^{-1}. Anal. Calcd for $C_{17}H_{27}NO_3Si$: C 63.51; H 8.47; N, 4.36. Found: C 63.43; H 8.48; N 4.30.

2′-(Allyloxy)-*N*-methyl-(*Z*)-4-(*tert*-butyldimethylsiloxy)-2-methyl-2-butenanilide (13). Following the general method of McKillop,[12] a mixture of anilide **12** (1.42 g, 4.42 mmol), allyl bromide (0.9 mL, 10 mmol), tetrabutylammonium bromide (150 mg, 0.47 mmol), 1 M aqueous NaOH (6 mL), CH_2Cl_2 (20 mL), and water (14 mL) was wrapped with aluminum foil to prevent exposure to light and the resulting yellow-orange mixture was stirred vigorously for 12 h at room temperature. The reaction was allowed to stand, and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (2 × 20 mL), and the combined organic layers were washed with saturated aqueous citric acid solution (100 mL) and brine (100 mL), dried (Na_2SO_4), filtered, and concentrated.

A mixture of this crude residue (1.37 g, 3.79 mmol), NaH (60% oil dispersion, 250 mg, 6.2 mmol), and dry THF (16 mL) was stirred at 0 °C for 10 min and allowed to warm to room temperature over 3 h. Methyl iodide (0.7 mL, 1.6 g, 11 mmol) was then added in one portion, and the mixture was stirred overnight at room temperature. Workup as described for the preparation of **8** and purification by sgc (7:1 to 4:1 to 2:1 hexanes−Et_2O) gave 1.05 g (74%) of **13** as a golden oil; NMR analysis indicates that this compound is a 10:1 mixture of amide rotamers. ^{1}H NMR (500 MHz, $CDCl_3$) major rotamer: δ 7.24 (app td, J = 7.9, 1.6 Hz, 1H), 7.16 (dd, J = 7.6, 1.5 Hz, 1H), 6.88 (app t, J = 6.3 Hz, 1H), 6.86 (m, 1H), 6.02 (m, 2H), 5.43 (dd, J = 17.2, 1.3 Hz, 1H), 5.28 (dd, J = 10.4, 1.2 Hz, 1H), 4.56 (d, J = 1.0 Hz, 2H), 4.29−4.08 (m, 2H), 3.23 (s, 3H), 1.59 (s, 3 H), 0.9 (s, 9H), 0.09 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) major rotamer: δ 170.5, 152.9, 132.3, 131.6, 130.9, 129.4, 128.8, 128.1, 119.7, 116.7, 116.6, 67.8, 60.2, 34.7, 25.0, 19.3, −6.2; IR (film) 2954, 2928, 2856, 1643, 1596, 1501, 1453, 1423, 1348, 1275, 1255, 1096, 1060 cm^{-1}. Anal. Calcd for $C_{21}H_{33}NO_3Si$: C 66.44; H 8.64; N 3.87. Found: C 66.67; H 8.59; N 3.98.

2′-(Hydroxy)-*N*-methyl-(*Z*)-4-(*tert*-butyldimethylsiloxy)-2-methyl-2-butenanilide (14). Following a modification of the procedure of Deziel,[13] a mixture of anilide **13** (1.5 g, 4.1 mmol), $Pd(PPh_3)_4$ (140 mg, 0.12 mmol), Ph_3P (42 mg, 0.16 mmol), and dry MeCN (16 mL) was stirred at 0 °C for 5 min and a solution of pyrrolidine (1.4 mL, 17 mmol) and dry MeCN (16 mL) was added dropwise. The resulting mixture was stirred at 0 °C for 10 min and then at 40 °C for 2 h. After cooling to room temperature, the reaction was poured into a saturated aqueous citric acid solution (20 mL), and the layers were separated. The organic layer was washed with saturated aqueous citric acid solution (20 mL) and brine (20 mL), dried (Na_2SO_4), and concentrated. The resulting crude residue was purified by sgc (7:1 to 4:1 to 2:1 hexanes−EtOAc) to give 1.15 g (83%) of **14** as a viscous yellow oil; NMR analysis indicates that this compound is a 9:1 mixture of amide rotamers. ^{1}H NMR (300 MHz, $CDCl_3$) major rotamer: δ 8.20 (br s, 1 H), 7.21 (m, 1H), 7.08 (dd, J = 7.8, 1.6 Hz, 1H), 6.96 (dd, J = 8.2, 1.4 Hz, 1H), 6.87 (app td, J = 7.6, 1.4 Hz, 1H), 5.12 (m, 1H), 4.29 (m, 2H), 3.21 (s, 3H), 1.66 (d, J = 1.7 Hz, 1H), 0.95 (s, 9H), 0.19 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) major rotamer: δ 171.5, 152.1, 131.8, 129.3, 128.6, 127.9, 126.7, 119.2, 117.1, 61.1, 35.0, 25.1, 20.2, 17.7, −6.2; IR (film) 3172, 2886, 2857, 1741, 1620, 1588, 1513, 1461, 1392, 1291, 1256, 1094 cm^{-1}. Anal. Calcd for $C_{18}H_{29}NO_3Si$: C 64.44; H 8.71; N 4.17. Found: C 64.33; H 8.76; N 4.12.

2′-(Trifluoromethanesulfonyloxy)-*N*-methyl-(*Z*)-4-(*tert*-butyldimethylsiloxy)-2-methyl-2-butenanilide (15). A flame dried, 250 mL round-bottom flask was wrapped in aluminum foil and charged with phenol **14** (5.6 g, 17 mmol), pyridine (8 mL), and dry CH_2Cl_2 (65 mL). The resulting yellow solution was cooled to 0 °C, and freshly distilled triflic anhydride (5.0 mL, 29 mmol) was added dropwise (the reaction turned dark green). After 30 min, the reaction was allowed to warm to room temperature over 30 min, then recooled to 0 °C, and quenched with saturated aqueous citric acid solution (50 mL). The layers were separated, and the organic layer was dried ($MgSO_4$) and concentrated to afford a dark green residue which was purified by sgc (6:1 to 4:1, hexanes−EtOAc) to give 6.40 g (82%) of **15** as a yellow oil; NMR analysis of this compound showed it to be a 1.2:1 mixture of amide rotamers. Triflate **15** was stored in a refrigerator, since it slowly decomposed when stored at room temperature in the light. ^{1}H NMR (300 MHz, $CDCl_3$) major rotamer: δ 7.48−7.33 (m, 4H), 5.34 (app t, J = 6.0 Hz, 1H), 4.13 (app d, J = 6.1 Hz, 2H), 3.32 (s, 3H), 1.58 (s, 3H), 0.80 (s, 9H), 0.06 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) major rotamer: δ 169.9, 143.8, 135.0, 131.5, 131.3, 128.2, 128.0, 121.4, 60.0, 36.0, 25.0, 19.0, 17.3, −6.3; IR (film) 2955, 2930, 2858, 1657, 1605, 1582, 1423, 1249, 1140, 1082 cm^{-1}; MS (EI) m/z 468.1486 (MH, 468.1488 calcd for $C_{19}H_{29}NO_5F_3SSi$). Anal. Calcd for $C_{19}H_{28}NO_5F_3SSi$: C 48.81; H 6.04; N 3.00. Found: C 48.81; H 6.00; N 2.99.

2′-Iodo-*N*-methyl-(*Z*)-4-(triisopropylsiloxy)-2-phenyl-2-butenanilide (20). A pentane solution of *t*-BuLi (1.6 M, 24 mL, 39 mmol) was added to a solution of crude **16** (12 g of a 2:1 mixture of **16** and the corresponding TIPS-protected propargyl ether) and dry Et_2O (100 mL) at −78 °C. The reaction was maintained at −78 °C for 1 h, and then a solution of 2-iodophenylisocyanate (9.0 g, 40 mmol)[14] and Et_2O (45 mL) was added rapidly. The reaction was maintained at −78 °C for 10 min, allowed to warm to room temperature over 3 h, and then quenched with water (100 mL). The layers were separated, and the aqueous layer was extracted with EtOAc (2 × 100 mL). The combined organic layers were washed with brine (200 mL), dried ($MgSO_4$), and concentrated. The crude secondary amide was purified by sgc (19:1 hexanes−EtOAc) to give 8.8 g (86%, corrected for the purity of **16**) of an opaque oil.

A solution of the above product (1.92 g, 3.59 mmol) and dry THF (20 mL) was added to a stirring suspension of NaH (60%, 250 mg, 6.2 mmol) and THF (20 mL) over 30 min at 0 °C. The resulting suspension was stirred at 0 °C for 20 min, MeI (1.5 mL, 21 mmol) was added in one portion, and the cooling bath was removed. The reaction was stirred for an additional 2 h at room temperature and quenched with saturated aqueous NH_4Cl solution (25 mL). The layers were then separated, the aqueous layer was extracted with EtOAc (50 mL), and the combined organic layers were washed with brine (100 mL), dried ($MgSO_4$), and concentrated. Purification of the residue by sgc (19:1 hexanes−EtOAc) afforded 1.54 g (78%) of **20** as an amber oil; NMR analysis indicates that this compound is a 2.4:1 mixture of rotamers. ^{1}H NMR (300 MHz, $CDCl_3$) major rotamer: δ 7.59 (dd, J = 1.2, 8.9 Hz, 1H), 7.44−7.34 (m, 2H), 7.25−7.00 (m, 4H), 6.90 (dd, J = 1.3, 7.3, Hz, 1H), 6.85 (dd, J = 1.8, 10.4 Hz, 1H), 5.76 (t, J = 6.3 Hz, 1H), 4.61 (d, J = 6.3 Hz, 2H), 3.30 (s, 3H), 1.11 (m, 21H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 169.4, 145.5, 139.9, 137.4, 134.8, 131.3, 130.9, 129.3, 129.1, 128.7, 128.4, 126.8, 98.6, 62.0, 39.1, 18.4, 12.3; IR (film) 3477, 3056, 2939, 2859, 2714, 1639, 1574, 1465, 1370, 1247, 1072, 1014, 876 cm^{-1}. Anal. Calcd for $C_{26}H_{36}INO_2Si$: C 56.82; H 6.60; N 2.25. Found: C 56.59; H 6.53; N 2.51.

Heck Cyclizations. Cyclizations reported in Tables 1−4 were carried out using the standard conditions described in the preceding paper.[4] Experiments reported in Tables 5−7 were conducted using more rigorous Schlenk techniques. The following procedure is representative.

General Procedure for Pd−BINAP Catalyzed Cyclizations of Iodide 8 and Triflate 15 in the Presence of Additives. A base-washed and flame-dried 10 mL Schlenk flask was fitted with a three-way stopcock. The flask was charged with $Pd_2(dba)_3$·$CHCl_3$ (8.1 mg, 0.008 mmol) and (*R*)-BINAP (11.2 mg, 0.018 mmol) and purged under an Ar flow for 10 min. Dry DMA (0.8 mL) was added, and the resulting purple-brown suspension was stirred for 2 h to give a bright orange solution. A solution of triflate **15** (74.6 mg, 0.16 mmol), PMP (120 μL, 100 mg, 0.66 mmol), and dry DMA (0.4 mL) was added followed by tetrabutylammonium chloride monohydrate (53 mg, 0.18 mmol) and additional DMA (0.4 mL). The resulting suspension was stirred for 15 min, the resulting red-orange solution was frozen at −78 °C, and the apparatus was evacuated (0.1−0.2 mm), sealed, and allowed to warm to room temperature. This freeze−pump−thaw cycle was repeated four times. The reaction then was heated at 100 °C for 23 h

under an argon atmosphere. After cooling to room temperature, the reaction was quenched with saturated aqueous $NaHCO_3$ solution (5 mL) and diluted with water (10 mL) and EtOAc (10 mL). The layers were separated, and the aqueous layer was extracted with EtOAc (2 × 20 mL). The combined organic extracts were washed with brine (50 mL), dried (Na_2SO_4), filtered, and concentrated. The resulting dark brown residue was partially purified by sgc (19:1 to 4:1 hexanes−EtOAc) to give a bright yellow oil that was a mixture of enoxysilane stereoisomers contaminated with residual dba. Capillary GLC analysis indicated a 20:1 ratio of *E* to *Z* enoxysilane stereoisomers.[4]

This mixture was dissolved in THF (2 mL), 3 M HCl (2 mL) was added, and the reaction was maintained overnight at room temperature and then quenched with saturated $NaHCO_3$ aqueous solution (5 mL). The layers were separated, the aqueous layer was extracted with EtOAc (5 mL), and the combined organic layers were dried (Na_2SO_4), filtered, and concentrated. The resulting bright yellow oil was purified by sgc (4:1 to 2:1 hexanes−EtOAc) to give 21 mg (66%) of oxindole aldehyde **25**.

(*R*)-2-Diphenylmethane-2′-diphenylphosphino-1,1′-binaphthyl (38). A solution of phenyllithium (1.4 M in Et_2O−cyclohexane, 7.5 mL, 10 mmol) was added dropwise using a syringe pump to a cooled solution of ester **37**[27] (1.02 g, 2.05 mmol) and dry THF (10 mL) at 0 °C. The reaction was maintained at 0 °C for 20 min and then allowed to warm to room temperature. After 40 min, the reaction was poured into a mixture of ice and 1 M HCl (20 mL). The layers were separated, and the aqueous layer was extracted with Et_2O (15 mL) and EtOAc (15 mL). The organic layers were combined and washed with 1 M HCl (20 mL) and brine (20 mL). The dried ($MgSO_4$) organic layer was concentrated, and the resulting residue was adsorbed onto silica gel and chromatographed (19:1 to 9:1 cyclohexanes−Et_2O) to give 791 mg (62%) of the corresponding carbinol as a pale yellow solid.

Diborane was generated by the dropwise addition of $BF_3{\cdot}OEt_2$ (1.6 mL, 13 mmol) to a solution of $NaBH_4$ (0.35 g, 9.3 mmol) and dry diglyme. The resulting diborane gas was bubbled into a cooled solution of the carbinol (104 mg, 0.168 mmol) and dry CH_2Cl_2 (1 mL) at 0 °C, and the reaction was maintained at 0 °C for 1 h. The resulting colorless solution was added to a freshly prepared suspension of trifluoroacetic acid (1.8 mL, 24 mmol), $NaBH_4$ (0.30 g, 7.9 mmol), and dry CH_2Cl_2 (5 mL) at 0 °C. After 5 min at 0 °C, the reaction was quenched with water (10 mL) and poured into a mixture of ice and 1 M NaOH (20 mL). The layers were separated, the aqueous layer was extracted with Et_2O (10 mL), and the combined organic layers were washed with brine (20 mL), dried ($MgSO_4$), filtered, and concentrated. The crude residue was purified by sgc (hexanes to 19:1 hexanes−Et_2O) to give 81 mg (80%) of **36** as a colorless solid: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.92 (d, J = 8.6 Hz, 1H), 7.87 (d, J = 8.5 Hz, 1H), 7.80 (app t, J = 7.7 Hz, 2H), 7.47−7.44 (m, 2H), 7.31 (t, J = 7.4 Hz, 1H), 7.23 (app d, J = 7.8 Hz, 1H), 7.21−7.08 (m, 18 H), 6.82 (app t, J = 7.5 Hz, 1H), 6.74 (app t, J = 7.2 Hz, 1H), 6.67 (m, 3H), 6.60 (app d, J = 8.4 Hz, 1H), 5.41 (s, 1H); MS (CI) *m*/*z* 604.2345 (M, 604.2320 calcd for $C_{45}H_{33}P$).

(+)-Esermethole (34). Triethylamine (1.70 mL, 12.2 mmol) was added dropwise at room temperature to a stirring mixture of (*R*)-aldehyde **25** (249 mg, 1.23 mmol; 92% ee by Chiral HPLC analysis of derived primary alcohol), methylamine hydrochloride (827 mg, 12.2 mmol), $MgSO_4$ (900 mg), and THF (25 mL). After 17 h, $LiAlH_4$ (465 mg, 12.3 mmol) was added, and the resulting mixture was refluxed for 90 min. Excess $LiAlH_4$ was decomposed by dropwise addition of EtOAc (30 mL) followed by saturated aqueous $NaHCO_3$ (30 mL). The phases were separated, the aqueous layer was extracted with EtOAc (2 × 50 mL), and the combined organic extracts were washed with brine (80 mL), dried (Na_2SO_4), concentrated, and the residue was purified by sgc (99:1 to 20:1 $CHCl_3$−MeOH) to give 152 mg (61%) of pyrroloindoline **32**.

Following the procedure of Fuji and co-workers,[19] a solution of *N*-bromosuccinimide (100 mg, 0.56 mmol) and DMF (2 mL) was added to a solution of **32** (113 mg, 0.56 mmol) and DMF (2 mL) at room temperature. The reaction was stirred at room temperature for 27 h, poured into water (175 mL), and extracted with CH_2Cl_2 (30 mL, 5×). The combined organic extracts were washed with brine (80 mL), dried (Na_2SO_4), and concentrated, and the residue was purified by sgc (99:1 to 20:1 $CHCl_3$−MeOH) to give 137 mg (87%) of bromopyrroloindoline **33**.[19]

Chips of sodium metal (150 mg, 6.52 mmol) were cautiously added to methanol (1.5 mL) to generate NaOMe. A solution of bromopyrroloindoline **33** (165 mg, 0.59 mmol) and DMF (2 mL) was then added followed immediately by cuprous iodide (220 mg, 1.2 mmol), and the resulting mixture was heated at 120 °C for 15 h. After cooling to room temperature, the reaction mixture was filtered through Celite with DMF and concentrated. The concentrate was partitioned between CH_2Cl_2 (15 mL) and 2% NaOH (15 mL), and the aqueous layer was washed with CH_2Cl_2 (2 × 15 mL). The combined organic extracts were washed with brine (20 mL), dried (Na_2SO_4), and concentrated, and the residue was purified by sgc (99:1 to 20:1 $CHCl_3$−MeOH) to give 100 mg (74%) of (+)-esermethole (**34**): $[\alpha]_D^{25}$ +117°, $[\alpha]_{450}$ +284°, $[\alpha]_{435}$ +239°, $[\alpha]_{546}$ +139°, $[\alpha]_{577}$ +122° (*c* 0.14, benzene).

Acknowledgment. This research was supported NIH Grant GM-30859 and the Green Cross Corporation. Additional support from the National Science and Engineering Research Council of Canada through a Postdoctoral Fellowship to B.B., from the American Cancer Society through a Postdoctoral Fellowship to M.C., from the U.S. DOEd through a GAANN Predoctoral Fellowship to D.J.P., and from Merck, Pfizer, Roche Biosciences, and SmithKline Beecham and are gratefully acknowledged. NMR and mass spectra were determined at Irvine using instruments acquired with the assistance of NSF and NIH Shared Instrumentation Programs. We also wish to thank Professor T. Keith Hollis (UCR) for his insightful discussion.

Supporting Information Available: Experimental procedures and characterization data for new compounds not described in the Experimental Section (8 pages, print/PDF). See any current masthead page for ordering information and Web access instructions.

JA980787H