Catalytic Asymmetric Synthesis of Quaternary Carbon Centers. Exploratory Investigations of Intramolecular Heck Reactions of (*E*)-α,*β*-Unsaturated 2-Haloanilides and Analogues To Form Enantioenriched Spirocyclic Products

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Received March 9, 1998

Abstract: The effect of chiral diphosphine structure, method of catalyst generation, reaction solvent, and HI scavenger on the formation of enantioenriched 3,3-disubstituted 2-oxindole **5** from asymmetric Heck cyclization of **4** was studied (eq 1). Depending upon whether the HI scavenger was a silver salt or a basic tertiary amine, either enantiomer of **5** could be formed with good selectivity using the same enantiomer of BINAP. Using Pd−BINAP as catalyst, a variety of enantioenriched 3,3-disubstituted oxindoles, indolines, and dihydrobenzofurans was prepared from (*E*)-α,*β*-unsaturated 2-haloaniline substrates (Table 5). With but one exception, cyclizations conducted in the presence of Ag_3PO_4 or 1,2,2,6,6-pentamethylpiperidine (PMP) afforded opposite enantiomers of the spirocyclic product. Which HI acceptor results in highest enantioselection is substrate dependent. These studies demonstrate, for the first time, that asymmetric Heck reactions of halide substrates can proceed with useful levels of enantioselectivity in the absence of silver or thallium salts.

Introduction

Although first reported more than 25 years ago,[2] it is only within the past decade that the enormous potential of the Heck reaction in organic synthesis has been revealed.[3] When employed intramolecularly, Heck reactions succeed in many contexts,[3c] including insertions into trisubstituted and even tetrasubstituted double bonds.[4] The ability of intramolecular Heck reactions to reliably fashion carbon−carbon bonds in polyfunctional molecules has led to wide application of this reaction at the strategy level for the synthesis of complex natural products.[5]

One of the most important developments in this area is the increasing success being realized in effecting catalytic asymmetric Heck reactions using enantiopure ligands.[6] Undoubtedly due to early reports that chelating diphosphines were unsuitable ligands for bimolecular Heck reactions,[7] asymmetric Heck reactions were first described only in 1989.[8,9] Although only modest enantiocontrol was described in the initial disclosures from Shibasaki's and our laboratories, rapid progress in this area has been made; many asymmetric Heck reactions proceeding with enantioselectivities of >90% have now been described.[6]

Since our first disclosure of the exceptional facility with which fully substituted carbon centers can be constructed by intramolecular Heck reactions, our investigations in this area have centered on Heck cyclizations that form quaternary carbons.[4b,10] In 1989, we reported the first example of directly creating a quaternary center by an asymmetric Heck cyclization, in this case asymmetric bis-cyclization of a trienyl triflate.[9] We report herein details of our subsequent investigations of asymmetric Heck cyclizations of alkenyl aryl halides to prepare enantioenriched heterocycles. A variety of heterocycles are produced with moderate to high levels of enantiomeric purity. Moreover, these investigations led to the unanticipated discovery that depending upon how HI is scavenged, either enantiomer of the spirocyclic product could be formed with good selectivity using the same enantiomer of a chiral diphosphine ligand (Figure 1). These studies demonstrated, for the first time, that asymmetric Heck reactions not proceeding via cationic intermediates (vide infra) can occur with high (>90%) enantioselectivity.[11] In two accompanying papers, we further elaborate the scope of these

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S0002-7863(98)00786-0 CCC: $15.00
Published on Web 06/20/1998

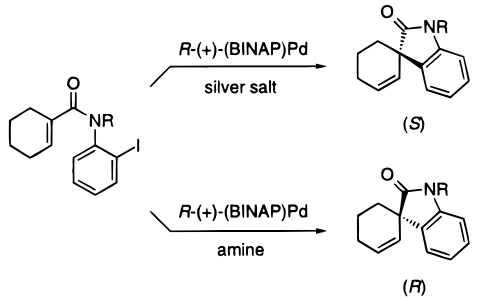
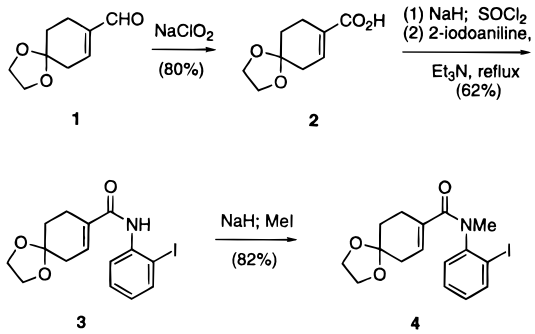


Figure 1.

Scheme 1



reactions,[12,13] report initial mechanistic investigations,[12,14] and illustrate the utility of "neutral" asymmetric Heck reactions for asymmetric synthesis of 3a-substituted pyrroloindolines, including pharmacologically important Calabar alkaloids.[15]

Results and Discussion

Initial Exploratory Studies. To avoid potentially complicating double bond isomerization of the Heck product, 2-iodo-*N*-(1,4-dioxaspiro[4.5]dec-7-en-8-ylcarbonyl)-*N*-methylaniline (**4**) was chosen for our initial studies. This anilide was readily synthesized on multigram scales as summarized in Scheme 1. Aldehyde **1**[16] was first converted to carboxylic acid **2** by Lindgren oxidation[17] and then coupled, via the acid chloride derivative, with 2-iodoaniline to give **3**. Finally, deprotonation of anilide **3** with NaH followed by reaction with excess MeI in refluxing THF provided **4** in 41% overall yield from **1**.

As did other early workers in this field,[8,18] we initially assumed that iodide would have to be scavenged to achieve good selectivity in Heck cyclizations of **4** carried out in the presence of enantiopure diphosphine ligands (eq 1). This presumption followed from the expectation that the migratory insertion step **6** → **7** would proceed from a four-coordinate intermediate, which would accommodate a bidentate ligand only if iodide was removed from the palladium coordination sphere (Scheme 2). Our inaugural experiments were guided by recent

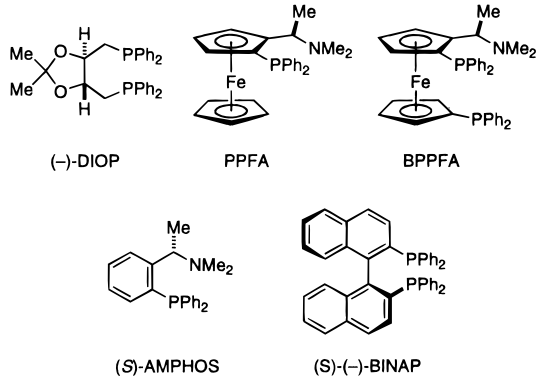


Figure 2.

Scheme 2

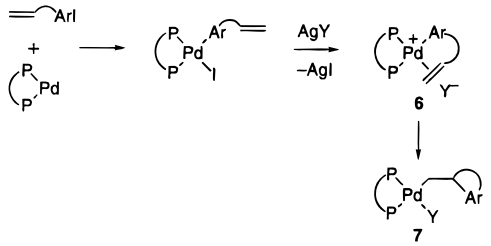
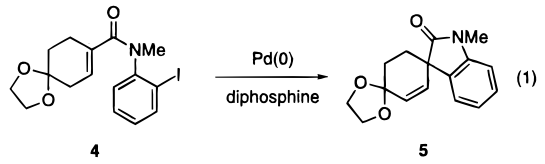


Table 1. Asymmetric Heck Cyclization of **4** to Spirooxindole **5**[a]

ligand	solvent	time, h	yield, %	abs config	ee, %
(−)-DIOP	toluene	8	76		rac[b]
(−)-DIOP	MeCN	22	58[c]	*S*	9
(+)-DIOP	NMP	6	91		rac[b]
PPFA	toluene	4	87	*S*	26
PPFA	NMP	8	81	*S*	23
BPPFA	NMP	24	39[c]	*R*	26
AMPHOS	toluene	24	45[c]	*S*	5
AMPHOS	NMP	25	34[c]		
(*S*)-(−)-BINAP	toluene	23	47[c]	*R*	20
(*S*)-(−)-BINAP	THF	12	79	*R*	38
(*S*)-(−)-BINAP	MeCN	28	33[c]	*R*	20
(*S*)-(−)-BINAP	NMP	23	70	*R*	51

[a] Conditions: 10 mol % $Pd(OAc)_2$, 10 mol % bisphosphine, 2 equiv of Ag_3PO_4, 0.1 M substrate, 80 °C. [b] Racemic. [c] Anilide **4** was not fully consumed.

disclosures from the Shibasaki group that Ag_3PO_4 was the optimal halide scavenger for asymmetric Heck cyclizations that formed tertiary centers.[19] Results obtained from our initial study of the cyclization of iodide **4** to form 3-spiro-2-oxindole **5** using $Pd(OAc)_2$, commercially available enantiopure chiral disphos-



phines (Figure 2), and excess Ag_3PO_4 are presented in Table 1. Enantiomeric purity was determined by integrating the *N*-methyl signals of **5** in ^1H NMR spectra ($CDCl_3$) measured in the presence of tris[3-(trifluoromethylhydroxymethylene)-(+)-camphorato]ytterbium(III), Yb(tfc)$_3$.

The rate of cyclization of **4** varied considerably with ligand structure: DIOP∼PPFA>BINAP>AMPHOS. With all ligands, Heck cyclizations in MeCN were particularly slow. As is apparent in Table 1, BINAP was the most promising ligand.

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Table 2. Forming (*S*)-Spirooxindole **5** Using Pd(*R*)-BINAP Generated from Tris(dibenzylideneacetone)dipalladium(0)[a]

entry	solvent	temp, °C	time, h	yield,[b] %	ee,[b] %
1	NMP	80	26	86	70
2[c]	NMP	80	26	78−80	68−69
3[c]	DMPU	80	26	68−70	49−53
4[d]	THF	80	26	84	22
5	MeCN	80	26	42	63
6	DMA	80	26	81	71
7	DMF	80	26	69	70
8	DMSO	80	26	67	42
9	DMA	60	88	78	71
10	DMA	110	4	86	67
11[e]	DMA	80	4	90	65

[a] $Pd_2(dba)_3$ (5 mol %) was treated with (*R*)-BINAP (11 mol %) in the presence of Ag_3PO_4 (2 equiv) at room temperature for 40 min (unless noted otherwise) before the addition of **4**. The reaction was then maintained at 80 °C. [b] A range is reported for reactions run in duplicate. [c] Same as *a* with a pretreatment time of 20 min. [d] Same as *a* with a pretreatment time of 90 min. [e] Same as *a* with 10 mol % $Pd_2(dba)_3$ and 22 mol % (*R*)-BINAP.

Table 3. Effect of Silver and Thallium Salts on Asymmetric Heck Cyclization of **4** with Pd(*R*)-BINAP to Form (*S*)-**5**[a]

entry	silver salt	conversion,[b] %	yield, %	ee, %
1	Ag_3PO_4	100	86	70
2	Ag_2CO_3	100	83	68
3	Ag_2O	100	79	64
4	AgOAc	62	38	22
5	AgOBz	14	4	11
6	AgO_2CCF_3	7	4	0
7	$AgNO_3$	6	4	0
8	AgOTf	73	*c*	
9	$AgBF_4$	70	*c*	
10[d]	Tl_2CO_3	100	86	48
11	none	19	6	68[e]

[a] A mixture of 5 mol % $Pd_2(dba)_3$, 11 mol % (*R*)-BINAP, and 2 equiv of a silver salt was stirred in NMP under Ar at room temperature for 40 min prior to adding **4**. The reaction was then maintained at 80 °C for 26 h. [b] By capillary GC analysis. [c] Loss of **4** was determined by capillary GC analysis, but no **5** was detected by TLC analysis. [d] The solvent was DMA and reaction time was 2.5 h. [e] The absolute configuration of the predominant enantiomer was *R*.

Enantioselectivities realized in cyclizations of **4** in the presence of (*S*)-(−)-BINAP were solvent dependent, with the highest ee's being realized in *N*-methylpyrrolidine (NMP).

Since incomplete ligation of Pd(0) with BINAP would result in an achiral metal species being present (and potentially catalyzing the formation of racemic **5**), we next examined in situ generation of Pd(BINAP) from other palladium precatalysts. Using Cl_2Pd−BINAP as the precatalyst, enantioselectivities realized in the **4** → **5** conversion were not reproducible, while ee's were no higher if bis(acetonitrile)palladium(II)chloride $[PdCl_2(MeCN)_2]$[20] was employed as the precatalyst. However, higher enantioselectivities were obtained using tris(dibenzylideneacetone)dipalladium(0) $[Pd_2(dba)_3]$,[21] which is known to rapidly exchange dibenzylideneacetone ligands with phosphines. The results summarized in Table 2 were obtained when the catalyst was generated by stirring $Pd_2(dba)_3$ (5 mol %) under an Ar atmosphere with (*R*)-BINAP (11 mol %) in the presence of 2 equiv of Ag_3PO_4 in various solvents at room temperature for 20−90 min prior to adding a solution of **4**. Enantioselection was again found to be quite solvent dependent, with the polar solvents NMP, *N*,*N*-dimethylacetamide (DMA), and DMF giving (*S*)-**5** in highest ee (68∼71%). Doubling the catalyst generation time in NMP (entries 1 and 2) had no effect on enantioselectivity. Enantioselectivity was also not changed, within experimental error, when the cyclization temperature was varied from 60 to 110 °C in DMA (entries 6, 9, and 10). Doubling the catalyst loading also had little effect on ee; however, as expected cyclization was faster (entry 11). At this stage, $Pd_2(dba)_3$ was chosen as the optimal palladium source, and NMP and DMA were selected as solvents for further studies.

The effect of varying the silver salt in Heck cyclizations of **4** with Pd(*R*)-BINAP, generated in situ from $Pd_2(dba)_3$, was studied next. Cyclizations carried out at 80 °C for 26 h in the presence of 2 equiv of Ag_2CO_3, Ag_2O, or Ag_3PO_4 provided (*S*)-**5** in high yield and 64−70% ee (Table 3, entries 1−3). Qualitatively similar results were observed in the presence of Tl_2CO_3 (entry 10). Cyclizations of **4** were much slower in the presence of silver carboxylate salts (AgOAc, AgOBz, and AgO_2CCF_3) and took place with low or no asymmetric induction (entries 4−6). With silver salts of even less basic anions ($AgNO_3$, AgOTf, and $AgBF_4$) virtually no spirooxindole **5** was formed, although anilide **4** was slowly consumed to provide a complex mixture of products in the presence of AgOTf and $AgBF_4$. Most revealing was the observation that **4** cyclized, albeit inefficiently, in the absence of silver salts to produce (*R*)-**5** in a remarkable 68% ee (entry 11). We assumed that the low yield of **5** realized in cyclizations of **4** carried out in the absence of a silver salt, or in the presence of silver salts with weakly basic or nonbasic counterions, reflected the inability to regenerate a competent Pd(0) catalyst from "HPdI". Nonetheless, it was particularly provocative that *the opposite enantiomer of 5 was formed in good ee when no HI scavenger was present.*

To further pursue the effect of additives on enantioselection, Heck reactions of **4** with Pd(*R*)-BINAP were carried out in the presence of other bases that would not specifically scavenge iodide. As summarized in Table 4, cyclizations in NMP in the presence of 2 equiv of Na_3PO_4, $(n\text{-}Bu)_4NH_2PO_4$, K_2CO_3, or $KHCO_3$ took place within 2−26 h in high yield, although little enantioselection was realized (entries 4−7). Cyclizations in the presence of 2 equiv of $CaHPO_4$ or Na_2HPO_4 occurred slowly at 80 °C in NMP producing the *R* enantiomer of **5** in 65−68% ee (entries 1 and 2). With this latter base, raising the reaction temperature to 110 °C in DMA resulted in some decrease in enantioselection (entry 3).

The best combination of rate and enantioselectivity was realized with tertiary amine bases. Although cyclizations of **4** in the presence of 5−15 equiv of Et_3N and 10 mol % Pd(*R*)-BINAP were slow, the rate was approximately doubled by use of the more basic tertiary amine, 1,2,2,6,6-pentamethylpiperidine (PMP) (entries 8−10). Doubling the catalyst loading to 20 mol % provided (*R*)-**5** in 65% yield and 66% ee, although the reaction time was still not practical (entry 11). However, when the reaction temperature was raised to 110 °C, Heck cyclization was complete in 8 h, and (*R*)-**5** was isolated in 71% yield without significant diminution of enantiomeric purity (entry 12). Two other strongly basic amines, 1,8-bis(dimethylamino)-naphthalene (PS)[22] and 1,1,2,3,3-pentaisopropylguanidine (PIG),[23] were screened and also afforded (*R*)-**5** in good yield within hours at 110 °C, although enantioselection was slightly lower than that obtained in the presence of PMP (entries 12−14).

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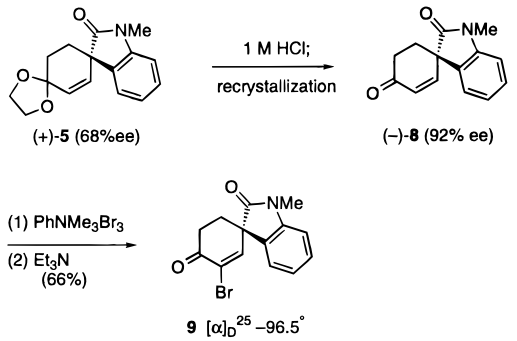
Table 4. Effect of Inorganic and Organic Bases on Asymmetric Heck Cyclizations of **4** with Pd(*R*)-BINAP To Form (*R*)-**5**[a]

							oxindole(*R*)-**5**	
entry	additive[b]	solvent	$Pd_2(dba)_3$, %	(*R*)-BINAP, %	time, h	conv[c]	yield, %	ee, %
1	$CaHPO_4$	NMP	5	11	26	14	8	68
2	Na_2HPO_4	NMP	5	11	26	34	12	65
3[d]	Na_2HPO_4	DMA	10	22	9	53	32	51
4	Na_3PO_4	NMP	5	11	26	100	77	7
5	TBAP[e]	NMP	5	11	26	100	76	25
6	K_2CO_3	NMP	5	11	3	100	85	8[f]
7	$KHCO_3$	NMP	5	11	1.7	100	86	4[f]
8	Et_3N	NMP	5	11	26	16	8	65
9	Et_3N[g]	NMP	5	11	192	62	37	48
10	PMP[h]	NMP	5	11	26	30	22	57
11	PMP[h]	DMA	10	22	138	84	65	66
12[d]	PMP[h]	DMA	10	22	8	100	71	63
13[d]	PS[i]	DMA	10	22	11	100	70	46
14[d]	PIG[j]	DMA	10	22	4	100	76	56

[a] The catalyst was generated as detailed in Table 3 prior to adding **4**. The final concentration of **4** was 0.1 M, and reactions were conducted at 80 °C unless noted otherwise. [b] Unless indicated otherwise, 2 equiv of inorganic bases and 5 equiv of organic bases were employed. [c] By capillary GLC analysis. [d] Reaction temperature was 110 °C. [e] $(n\text{-}Bu)_4NH_2PO_4$. [f] The *S* enantiomer predominates. [g] 15 equiv. [h] PMP = 1,2,2,6,6-pentamethylpiperidine. [i] PS = 1,8-bis(dimethylamino)naphthalene. [j] PIG = 1,1,2,3,3-pentaisopropylguanidine.

Scheme 3



Although enantiomeric purity of a sample allylic acetal (+)-**5** (68% ee, obtained from (*R*)-BINAP cyclization in the presence of Ag_2CO_3) could not be enhanced by recrystallization, the corresponding enone **8** was enriched to 92% ee by recrystallization from Et_2O (Scheme 3). To prepare a derivative suitable for determining absolute configuration by single-crystal X-ray analysis, **8** was brominated by reaction with trimethylphenylammonium tribromide in THF, and the product was dehydrobrominated by exposure to Et_3N to give levorotatory α-bromo enone **9** in good yield. This product provided single crystals that were suitable for determining absolute configuration by X-ray diffraction.[24]

Scope of Asymmetric Heck Cyclizations of (*E*)-α,*β*-Unsaturated 2-Haloaniline Derivatives. A. Preparation of Cyclization Substrates. The scope of asymmetric Heck cyclizations using Pd−BINAP was surveyed with the series of (*E*)-α,*β*-unsaturated 2-haloaniline derivatives depicted in Figure 3. Anilides **10** and **11** were obtained from secondary amide **3** by alkylation of the sodium salt with BnBr or SEM-Cl, while *tert*-butoxycarbonyl derivative **12** was obtained by coupling of **3** with di-*tert*-butyl dicarbonate in the presence of Et_3N and 4-(dimethylamino)pyridine (DMAP) (Scheme 4). The synthesis of the bromo analogues of anilides **14**, **16**, and **17** has been described,[4] and the iodide derivatives were prepared in similar fashion. Anilides **13** and **20** were prepared from 2-iodoaniline

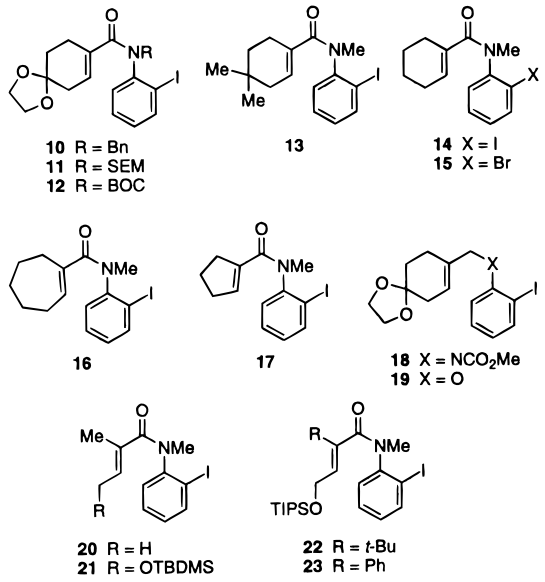


Figure 3.

and the corresponding α,*β*-unsaturated acid; details are provided in Supporting Information. The allylic carbamate **18** and allylic ether **19** were obtained from allylic chloride **24** and 2-iodoaniline or 2-iodophenol in straightforward fashion as summarized in Scheme 4.

The synthesis of α-methyl (*E*)-butenanilide **21** is summarized in Scheme 5. The Wittig reagent derived from methyl 2-bromopropionate (**26**) was condensed with glyoxylic acid monohydrate in MeCN to give (*E*)-acid **27** with high stereoselectively (>98%).[25] Reduction of this carboxylic acid with BH_3·THF[26] followed by TBDMS protection provided **29** in 58% overall yield from **27**. Condensation of **29** with the reagent prepared from 2-iodoaniline and Me_3Al[27] gave the corresponding anilide, which, again without purification, was methylated to provide **21**.

The corresponding α-*tert*-butyl (*E*)-buteneanilide **22** was prepared in related fashion (Scheme 6). Reductive iodination[28] of 4,4-dimethylpent-2-yn-1-ol (**30**),[29] which is available from

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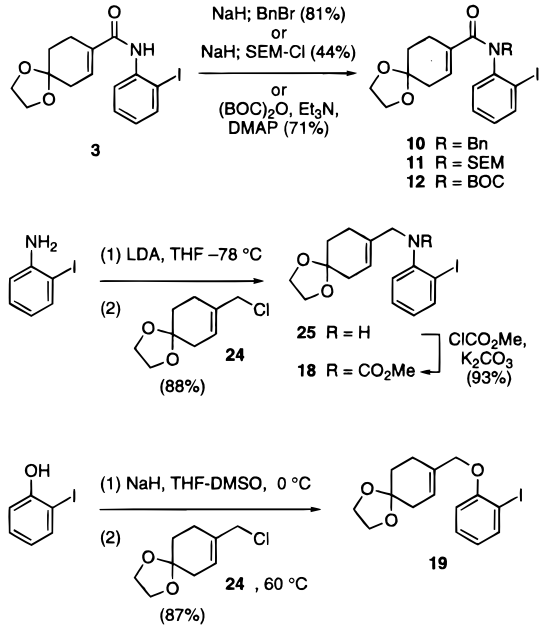
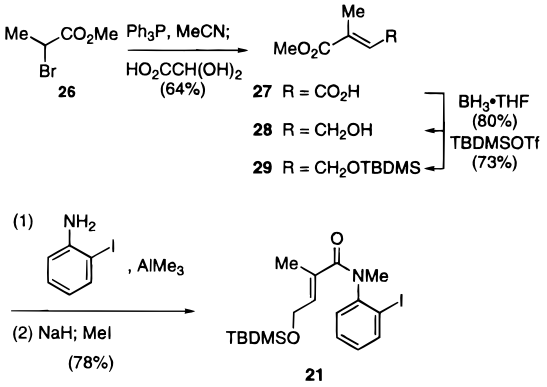
Scheme 4



Scheme 5



the hydroxymethylation of 3,3-dimethylbutyne,[30] followed by protection of the resulting alcohol as a TIPS ether afforded **31** in 74% yield. Carboxylation of iodide **31** by sequential treatment with *tert*-butyllithium and CO_2 afforded (*Z*)-carboxylic acid **32**, which was converted to the corresponding methyl ester **33** by reaction with MeI and DBU.[31] Condensation of **33** with the trimethylaluminum derivative of 2-iodoaniline[27] provided a single amide product **34** in 32% yield. That the alkene had completely isomerized, presumably by conjugate addition−elimination, to the more stable *E* configuration was apparent by comparison of **34** with the corresponding *Z* isomer, which had been prepared in a stereochemically unambiguous fashion.[12] *N*-Methylation of **34** then provided tertiary amide **22** in high yield.

The synthesis of α-phenyl (*E*)-buteneanilide **23** began with stannylation of readily available ester **35** to give an 8:1 mixture of vinylstannane **36** and a regioisomer (Scheme 7). Iodination of this mixture and removal of the minor isomer by chromatography provided iodide **37** in 75% yield, as described for the *tert*-butyldimethylsilyl analogue.[32] Palladium(0) catalyzed cross-coupling of **37** with the phenylzinc chloride, generated in situ by transmetalation of phenylmagnesium bromide with $ZnCl_2$, afforded **38**. Aminolysis of this ester following the Weinreb procedure[27] provided (*E*)-amide **39**, which was contaminated with ~8% of the corresponding *Z* isomer. Removal of the minor stereoisomer by column chromatography and subsequent *N*-methylation then furnished **23**.

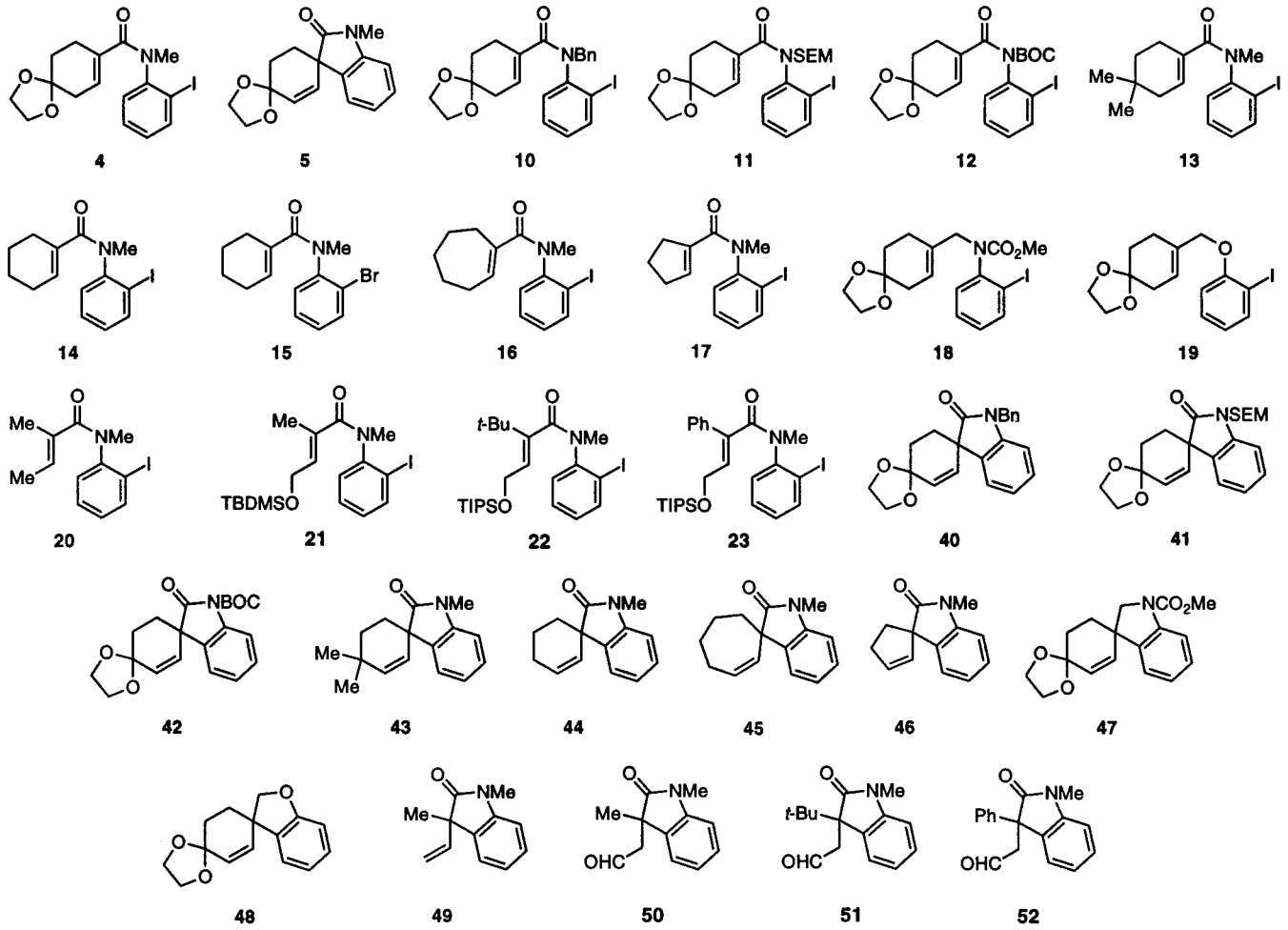
B. Scope of Asymmetric Heck Cyclizations. The scope of asymmetric Heck cyclizations of (*E*)-α,*β*-unsaturated 2-haloaniline derivatives was surveyed using two reaction conditions: (1) silver-promoted cyclizations were conducted with 5 mol % $Pd_2(dba)_3$ and 11 mol % (*R*)-BINAP in the presence of 2 equiv of Ag_3PO_4 in DMA or NMP at 60−80 °C, and (2) amine-promoted cyclizations employed 10 mol % $Pd_2(dba)_3$ and 22 mol % (*R*)-BINAP with 5 equiv of PMP in the same solvents at 100−120 °C. The results of these investigations are summarized in Table 5. Enantiomer ratios were determined either by ^{1}H NMR analysis of the spirocyclic products in the presence of chiral shift reagents or by HPLC analysis using a chiral stationary phase. In four cases (entries 4, 13, 15, 23, and 24), enantiomeric purity was determined by both methods; agreement between the two methods was ±2−5%. Absolute configuration is specified when it was rigorously established (vide infra); in other cases the sign of rotation at the sodium D line is reported. Yields of spirooxindole products were typically good (60−95%). *With all anilide substrates except* ***22****, Ag_3PO_4- and PMP-promoted cyclizations occurred with opposite enantioselection.*

The nature of the nitrogen protecting group had some effect (entries 1−10), particularly in the case of the *N*-BOC derivative **12**. Heck cyclization of this latter substrate in the presence of Ag_3PO_4 occurred slowly and took place with lower enantioselection, while attempted cyclizations of **12** in the presence of PMP at 100 °C resulted in cleavage of the BOC group. That the acetal substituent at the homoallylic carbon had little effect was apparent in the nearly identical stereoselection observed in cyclizations of **4** and **13** (entries 1−3, 11 and 12).

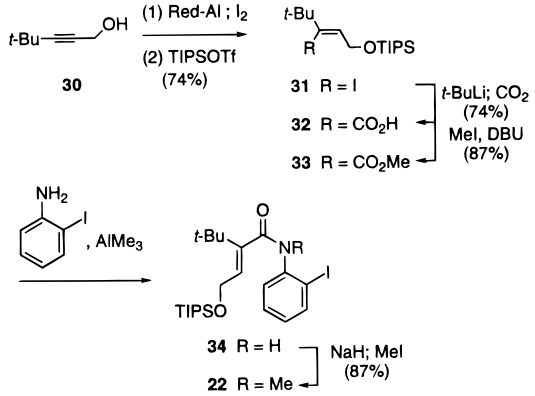
Cyclizations of unsubstituted five-, six-, and seven-membered cycloalkenyl analogues **14**, **16**, and **17** provided the known[4] oxindoles **44**−**46**, accompanied with varying amounts of double bond regioisomers (see Table 5). The excellent enantioselectivity (up to 95% ee) observed in forming (*R*)-**44** is undoubtedly due to preferential double bond migration of the initially generated palladium hydride complex of the minor *S* enantiomer. Enantiomeric enrichment by this type of kinetic resolution was first seen by Hayashi and co-workers in a bimolecular Heck reaction.[18] Consistent with this explanation, the enantiomeric excess of the $\Delta^{3,4}$ isomer **53**, which was isolated in 44% yield from the cyclization summarized in entry 15, was only 31% (the *R* enantiomer predominated). The enantiomeric purity of (*R*)-**53** (obtained by PMP-promoted cyclization) was determined by oxidation with CrO_3·(pyridine)$_2$ to afford enone (*R*)-**8** in low yield (eq 2).[33] The PMP-promoted Heck cyclization of the corresponding cyclohexenyl aryl bromide **15** occurred at a convenient rate only at 120 °C and provided (*R*)-**44** in low ee. Cyclizations of cycloheptenyl anilide **16** and cyclopentenyl anilide **17** occurred with no meaningful stereoinduction in the presence of Ag_3PO_4, whereas the corresponding PMP-promoted cyclizations provided **45** in 88% ee and **46** in 56% ee. We presume that enantioselection in forming **45** is also enhanced by subsequent kinetic resolution, since the $\Delta^{3,4}$ and $\Delta^{4,5}$ isomers of **45** were obtained in 40% and 4% yields, respectively.

(29) MacInnes, I.; Walton, J. C. *J. Chem. Soc., Perkin Trans. 2* **1987**, 1077.
(30) Collier, W. L.; Macomber, R. S. *J. Org. Chem.* **1973**, *38*, 1367.
(31) Koji, A.; Ono, N.; Saito, T.; Tanaka, K.; Yamada, T. *Bull. Chem. Soc. Jpn.* **1978**, 51, 2401.
(32) Rossi, R.; Carpita, A.; Cossi, P. *Tetrahedron* **1992**, *48*, 8801.
(33) Dauben, W. G.; Lorber, M.; Fullerton, D. S. *J. Org. Chem.* **1969**, *34*, 3587.

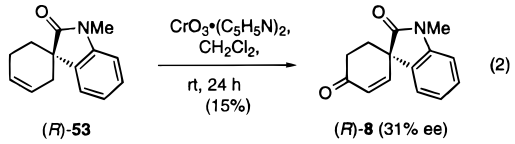
Chart 1



Scheme 6

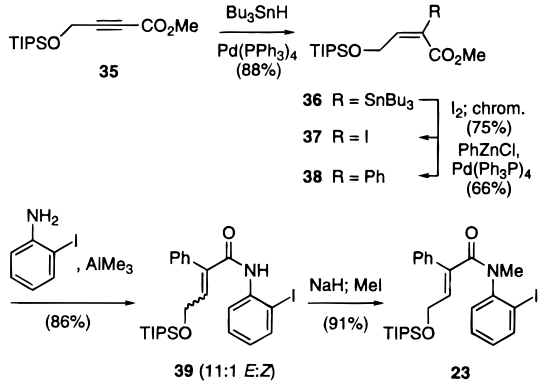


However, in this case we did not establish that these isomers were enriched in the *S* enantiomer.



Allylic carbamate **18** and allylic ether **19** underwent Heck cyclizations to give the corresponding spirocyclic products **47** and **48** in moderate ee in the presence of Ag_3PO_4. However, nearly racemic products were obtained in the presence of PMP (Table 5, entries 21−24).

Scheme 7



That the factors controlling enantioselection are varied and subtle is seen in cyclizations of acyclic (*E*)-acrylolyl 2-iodoanilides **20**−**23**. For example, changing the β-substituent from Me to $CH_2OTBDMS$ results in a decrease in enantioselectivity of the Ag_3PO_4-promoted Heck cyclization but an increase in enantioselection in the corresponding PMP-promoted reaction. More dramatic are the changes occasioned by changing the α-substituent (entries 27−32). Although low enantioselection is seen in cyclizations conducted with both Ag_3PO_4 and PMP, when this group is methyl (entries 27 and 28), the *t*-Bu substrate **22** provides (*R*)-**51** in 72% ee in the presence of Ag_3PO_4 (entry 29). In contrast, phenyl analogue **23** cyclizes with poor enantioselectivity in the presence of PMP and provides the opposite enantiomer **52** in 73% ee in the presence of Ag_3PO_4

Table 5. Scope of Asymmetric Heck Cyclizations of (*E*)-α,β-Unsaturated 2-Haloanilides with Pd(*R*)-BINAP

			reaction conditions				Heck product	
	convn[m]	HX scavenger	solvent	time, h	temp, °C	yield, %	ee, %	abs config[a]
1	**4** → **5**	Ag_3PO_4	DMA	26	80	81	71[c]	*S*
2		Ag_3PO_4	NMP	26	80	86	70[c]	*S*
3		PMP	DMA	8	110	71	66[c]	*R*
4		Ag_3PO_4	DMA	11	80	91	41−51[c,d]	*S*
5	**10** → **40**	Ag_3PO_4	NMP	13	80	91	50[c]	*S*
6		PMP	DMA	4.5	100	66	66[c]	*R*
7		Ag_3PO_4	DMA	52	80	76	65[c]	*S*
8	**11** → **41**	Ag_3PO_4	NMP	29	80	78	58[c]	*S*
9		PMP	DMA	6.5	100	68	75[c]	*R*
10	**12** → **42**	Ag_3PO_4	DMA	72	80	65	42[c,e]	*S*
11	**13** → **43**	Ag_3PO_4	DMA	3.5	80	99	72[c]	+
12		PMP	DMA	1	100	89	71[c]	−
13		Ag_3PO_4	DMA	25	60	74[f]	79−81[c,d]	*S*
14	**14** → **44**	Ag_3PO_4	NMP	25	60	70[g]	80[c]	*S*
15		PMP	DMA	1.5	100	45[h]	89−95[c,d]	*R*
16	**15** → **44**	PMP	DMA	9	120	51[i]	32[c]	*R*
17	**16** → **45**	Ag_3PO_4	DMA	7.5	80	62[j]	0	*b*
18		PMP	DMA	1.5	100	50[k]	88[c]	*b*
19	**17** → **46**	Ag_3PO_4	DMA	23	60	81	7[c]	*b*
20		PMP	DMA	1.3	100	96	56[c]	
21	**18** → **47**	Ag_3PO_4	NMP	24	60	90	64[c]	+
22		PMP	DMA	7	100	51	8[c]	−
23	**19** → **48**	Ag_3PO_4	NMP	24	60	91	49−55[c,d]	+
24		PMP	DMA	6	100	66	0−7[c,d]	−
25	**20** → **49**	Ag_3PO_4	DMA	27	80	88	59[c]	*S*
26		PMP	DMA	1.3	100	91	25[c]	*R*
27	**21** → **50**	Ag_3PO_4	DMA	2	80	80	45[d]	*S*
28		PMP	DMA	1	100	85	38[d]	*R*
29	**22** → **51**	Ag_3PO_4	DMA	4	120	41	72[d]	*R*
30		PMP	DMA	2	120	90	27[d]	*R*
31	**23** → **52**	Ag_3PO_4	DMA	2.5	80	93	73[d]	*l*
32		PMP	DMA	14	100	74	35[d]	*l*

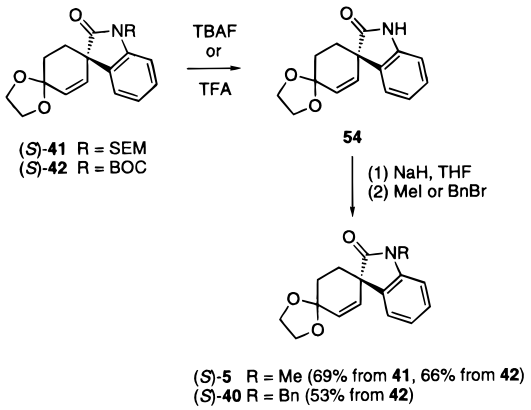
[a] For compounds for which absolute configuration are not determined, sign of optical rotation is shown instead. [b] Not determined. [c] Determined by ^{1}H NMR analysis in the presence of Eu(tfc)$_3$, Eu(hfc)$_3$ or Yb(tfc)$_3$. [d] Determined by HPLC analysis using a Chiralcel OD, OJ or OB−H column. [e] Determined by analysis of the 1-unsubstituted oxindole prepared by treatment of **42** with TFA. [f] The $\Delta^{3,4}$ isomer was formed also (8% yield). [g] The $\Delta^{3,4}$ isomer was formed also (14% yield). [h] The $\Delta^{3,4}$ isomer was formed also (44% yield). [i] The $\Delta^{3,4}$ isomer was formed also (36% yield). [j] The $\Delta^{3,4}$ and $\Delta^{4,5}$ isomers were formed also (13% and 17% yields, respectively). [k] The $\Delta^{3,4}$ and $\Delta^{4,5}$ isomers were formed also (40% and 4% yields, respectively). [l] The PMP- and Ag_3PO_4-promoted cyclizations produced opposite enantiomers[d] of unknown absolute configuration. The major enantiomer formed in the PMP-promoted reaction elutes first on a Chiracel OJ column (85:15 hexane-2-propanol). [m] Structures are shown in Chart 1.

(entries 31 and 32). The cyclization of **22** → **51** is also notable in that it is the only Heck cyclization of an (*E*)-α,β-unsaturated anilide that affords the same enantiomer in the presence of PMP and Ag_3PO_4.

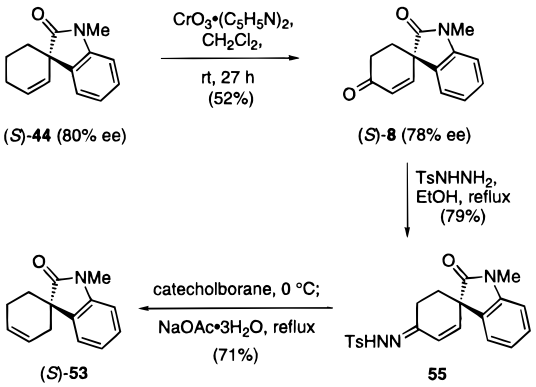
The absolute configurations of spirooxindole acetals **40**−**42** were established by the straightforward chemical correlations summarized in Scheme 8. The absolute configuration of **44** was determined by allylic oxidation[33] to give, in the case of the product formed in the presence of Ag_3PO_4, (*S*)-**8** in 52% yield (Scheme 9). This intermediate was also employed to confirm the configuration assigned to **53**. Thus, conversion of (*S*)-**8** to the corresponding tosylhydrazone **55**, followed by reduction with catecholborane,[34] provided an authentic sample of (*S*)-**53**.

The absolute configuration of **50** was assigned by conversion to physostigmine derivative (+)-esermethole,[12] while the configuration of **49** was assigned by straightforward chemical

Scheme 8



Scheme 9



correlation with **50**. The absolute configuration of *t*-Bu congener **51** was established by chemical correlation with (*S*)-**56**[12] (Scheme 10). First, the absolute configuration of (*S*)-**56** was secured by decarbonylation using Wilkinson's catalyst,[35] followed by hydrolysis of the resulting acetal, to provide (*S*)-(+)-**50** in 27% overall yield. The preparation of *tert*-butyl derivative **61** from **56** was considerably more involved. Alkylation of the *N*-cyclohexylimine derivative of (*S*)-**56** by sequential treatment with LDA, MeI, and hot aqueous NH_4Cl gave monomethylated aldehyde **57**. Unfortunately, the monomethylated imine intermediate could not be deprotonated with LDA, lithium diethylamide, or lithium pyrrolidide in THF (with or without DMPU) precluding direct dimethylation of the imine intermediate. Nevertheless, **57** could be methylated under phase transfer conditions[36] to provide a 2:1 mixture of **58** and enol ether **59** in 50% combined yield. However, all attempts to reductively deoxygenate aldehyde **58** to provide the corresponding *tert*-butyl derivative failed.[37] The desired conversion of **58** → **61** was finally accomplished in an indirect fashion. Aldehyde **58** was first homologated to **60** by reaction with methoxymethyltriphenylphosphorane[38] followed by hydrolysis. Aldehyde **60** was then decarbonylated using Wilkinson's catalyst to afford acetal **61** in low yield. Hydrolysis of this intermediate provided (*S*)-**51**. Since only a small amount of (*S*)-**51** (∼1 mg) was obtained from this multistep correlation, comparison of the corresponding alcohol derivative **62** with this derivative of the

(34) Kabalka, G. W.; Hutchins, R.; Natale, N. R.; Yang, D. T. C.; Broach, V. *Organic Syntheses*; Wiley: New York, 1988; Collect. Vol. VI, p 293.

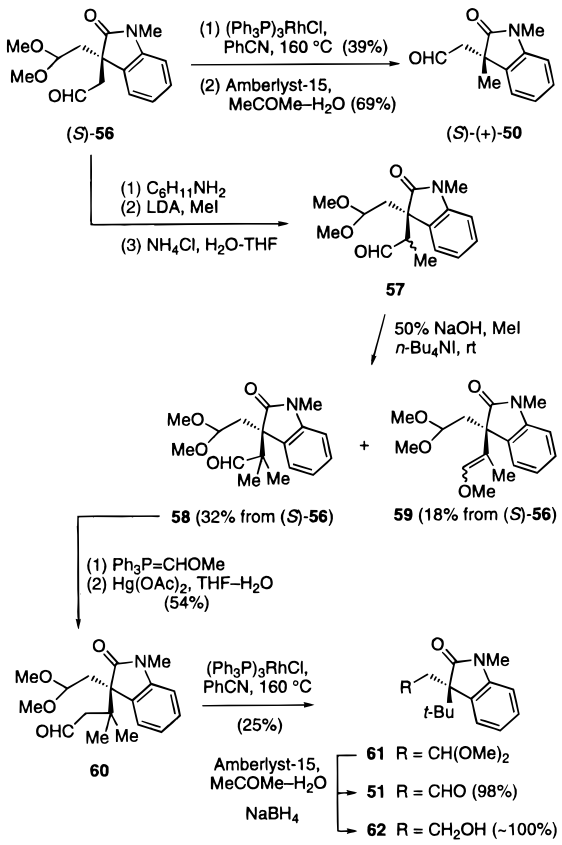
(35) Ohno, K.; Tsuji. J. *Synthesis* **1969**, 157.

(36) Brannock, K. C.; Dietl, H. K. *Tetrahedron Lett.* **1973**, 1273.

(37) Barton deoxygenation of the xanthate derivative and Wolf−Kishner reduction of the tosylhydrazone derivative failed. Attempts to prepare the tosylate or iodide derivative of the corresponding primary alcohol, as a prelude to reduction, were also unsuccessful.

(38) Claremon, D. A.; Magolda, R. L.; Nicolaou, K. C. *J. Am. Chem. Soc.* **1980**, *102*, 2, 1404.

Scheme 10



product produced from Heck cyclization of **22** was utilized to establish absolute configuration.

Discussion

A variety of 3,3-disubstituted 2-oxindoles can be prepared in moderate enantiomeric purity (typically 55−75% ee) by cyclization of *N*-alkyl-2-iodoanilide derivatives of (*E*)-α,*β*-unsaturated acids. At the time these results were first reported,[11] they represented the highest enantioselectivities obtained in asymmetric Heck reactions that directly form chiral quaternary carbon centers. In cases where the major enantiomer can be enriched, either by in situ kinetic resolution (e.g., oxindoles **44** and **45**) or recrystallization (e.g., oxindole **8**), asymmetric Heck cyclizations using Pd−BINAP provide convenient access to 3,3-disubstituted 2-oxindoles of high (>90%) enatiomeric purity.

The exploratory investigations reported here reveal the important role the HX scavenger plays in determining both rate and enantioselection in asymmetric Heck cyclizations. A moderately strong proton base must be present to obtain useful catalytic rates. This requirement is seen in Heck cyclizations conducted in the presence of silver salts, where salts having weakly basic counterions (e.g., OTf^-, NO_3^-, BF_4^-) do not effectively promote Heck cyclization. This trend of higher reaction rate in the presence of more basic proton acceptors is also seen in Heck cyclizations carried out in the presence of inorganic or tertiary amine bases (Table 4). Both observations suggest that the turnover-limiting step is regeneration of an active Pd(0) catalyst from a hydridopalladium(II) halide intermediate.

Certainly the most provocative result of these investigations is the unprecedented observation that either enantiomer of a Heck product can be obtained using the same enantiomer of a chiral ligand. In all cases but one, Heck cyclizations of (*E*)-α,*β*-unsaturated 2-iodoanilides using Pd(*R*)-BINAP produce the *S* enantiomer of the oxindole when the HI acceptor is Ag_3PO_4 and the *R* enantiomer when 1,2,2,6,6-pentamethylpiperidine (PMP) is the HI scavenger (see Figure 1).

Which HI acceptor is optimal for achieving highest enantioselection is substrate dependent. For example, allylic carbamate **18** and allylic ether **19** cyclized with moderate enantioselection in the presence of Ag_3PO_4, yet provided racemic products in the presence of PMP. On the other hand, with anilide substrates **14**, **16**, and **17** enantioselectivities were higher in the presence of PMP than Ag_3PO_4. With (*Z*)-α,*β*-unsaturated 2-iodoanilide substrates, whose asymmetric Heck cyclizations are reported in the accompanying paper, enantioselection in Pd−BINAP catalyzed cyclizations is much higher in the presence of PMP. Although the origin of these trends is only partially understood at this time, the ability to carry out asymmetric Heck cyclizations in two distinct ways provides additional opportunities for reaction optimization.

The high enantioselectivities realized in asymmetric Heck cyclizations carried out in the absence of halide scavengers dispels the notion that a halide counterion cannot be present for high enantioselection in asymmetric Heck reactions using chiral diphosphine catalysts to be achieved. Investigations aimed at further defining this novel halide-containing (neutral) asymmetric Heck reaction manifold are presented in the following paper.[12]

Conclusion

Enantioenriched 3,3-disubstituted oxindoles, indolines, and dihydrobenzofurans can be prepared by Pd−BINAP-catalyzed intramolecular Heck reactions of *o*-iodoarenes tethered to (*E*)-trisubstituted alkenes. Enantioselectivities are typically moderate (55−75% ee); however, in cases where the major enantiomer can be enriched by in situ kinetic resolution (e.g., oxindoles **44** and **45**) or recrystallization (e.g., oxindole **8**), asymmetric Heck cyclizations provide convenient access to heterocycles of high (>90%) enantiomeric purity.

These investigations led to the unprecedented discovery that depending upon how HX is scavenged, either enantiomer of the Heck product can be formed with good selectivity using a *single* enantiomer of a chiral diphosphine ligand (Figure 1). Moreover, these studies demonstrate that the presence of a halide scavenger is not obligatory for realizing high enantioselection in (diphosphine)palladium-catalyzed asymmetric Heck insertions of some halide substrates.

The two accompanying papers report (a) intramolecular Heck reactions of related substrates containing (*Z*)-trisubstituted alkenes, which in the absence of halide scavengers proceed with high enantioselectivity,[12,13] (b) our initial mechanistic investigations of this unusual "neutral" asymmetric Heck pathway,[12,14] and (c) one illustration of the utility of "neutral" asymmetric Heck reactions for natural products construction.[15]

Experimental Section[39]

1,4-Dioxaspiro[4.5]dec-7-ene-8-carboxylic Acid (2). A solution of $NaClO_2$ (10.1 g, 89.3 mmol), NaH_2PO_4 (7.0 g, 58 mmol), and H_2O (70 mL) was added dropwise at room temperature to a solution of

(39) Chromatography was carried out on silica gel as described by Still and co-workers[40] and is abbreviated as sgc. Tetrahydrofuran was purified by distillation from sodium and benzophenone and *N*,*N*-dimethylacetamide (DMA) was purified by distillation from CaH_2 at 20 mm. $Pd_2(dba)_3$ and BINAP were purchased from Aldrich Chemical Co. High-resolution mass spectra were measured on a MicroMass Analytical 7070E spectrometer (EI or CI-isobutane); uncertainty (s) in mass measurements is 1.0 millimass unit (molecular weight < 400) or 1.5 millimass units (molecular weight 400−1000). Other general experimental details have been described: Deng, W.; Overman, L. E. *J. Am. Chem. Soc.* **1994**, *116*, 11241.

aldehyde **1**[16] (12.0 g, 71.4 mmol), *t*-BuOH (355 mL), and 2,3-dimethyl-2-butene (85 mL).[17] The mixture was stirred at room temperature for 24 h and then concentrated. The resulting aqueous solution was basified to pH 10 with 6 M NaOH, diluted with H_2O (470 mL), and then washed with hexanes (2 × 350 mL). The aqueous solution was acidified to pH 3 with 6 M HCl and then extracted with Et_2O (5 × 250 mL). The extract was washed with brine (250 mL), dried ($MgSO_4$), and concentrated. The residue was recrystallized from hexanes−EtOAc to give 10.6 g (81%) of **2** as colorless scales: mp 105−105.5 °C; ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.00 (m, 1H), 3.99 (s, 4H), 2.6−2.4 (m, 4H), 1.80 (t, J = 6.4 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.1, 139.1, 129.3, 107.1, 64.5, 36.3, 30.6, 23.1; IR (CCl_4) 2956, 2883, 1692, 1650 cm^{-1}; MS (EI) *m*/*z* 184.0718 (184.0736 calcd for $C_9H_{12}O_4$). Anal. Calcd for $C_9H_{12}O_4$: C, 58.69; H, 6.55. Found: C, 58.79; H, 6.61.

2-Iodo-*N*-(1,4-dioxaspiro[4.5]dec-7-en-8-ylcarbonyl)-*N*-methylaniline (4). A solution of **2** (10.1 g, 54.6 mmol) and THF (72 mL) was added dropwise to a suspension of NaH (60%, 2.41 g, 60.3 mmol) and THF (90 mL) with ice bath cooling. The resulting mixture was stirred at room temperature for 2 h and recooled in an ice bath, and then $SOCl_2$ (4.38 mL, 60.1 mmol) was added dropwise over 6 min. After having been stirred at room temperature for 2.5 h a solution of 2-iodoaniline (11.9 g, 54.3 mmol), Et_3N (7.92 mL, 56.8 mmol), and THF (54 mL) was added dropwise at room temperature. The resulting mixture was heated at reflux for 5 h, allowed to cool to room temperature, diluted with Et_2O (750 mL), and then washed successively with 250 mL of H_2O, saturated aqueous $NaHCO_3$, and brine. After drying ($MgSO_4$), the organic layer was concentrated, and the residue was purified by sgc (3:2 hexanes−EtOAc) to give 13.1 g (62%) of **3** as a yellow oil: ^{1}H NMR (250 MHz, $CDCl_3$) δ 8.33 (dd, J = 8.3, 1.5 Hz, 1H), 7.84 (d, 1H, J = 0.7 Hz), 7.77 (dd, J = 7.9, 1.4 Hz, 1H), 7.34 (td, J = 7.9, 1.4 Hz, 1H), 6.83 (td, J = 7.7, 1.5 Hz, 1H), 6.76 (m, 1H), 4.02 (s, 4H), 2.68 (m, 2H), 2.50 (m, 2H), 1.89 (t, J = 6.5 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.3, 138.7, 138.2, 133.1, 132.4, 129.2, 125.7, 121.6, 107.0, 89.9, 64.5, 36.0, 30.7, 23.8; IR (CCl_4) 3398, 1689, 1645 cm^{-1}; MS (EI) *m*/*z* 385.0166 (385.0176 calcd for $C_{15}H_{16}INO_3$).

A solution of **3** (12.9 g, 33.4 mmol) and THF (55 mL) was added dropwise at 0 °C to a stirring suspension of NaH (60%, 2.01 g, 50.3 mmol) and THF (35 mL). The resulting mixture was stirred at 0 °C for 40 min, and then MeI (5.20 mL, 84.0 mmol) was added. The reaction mixture was then heated at reflux for 75 min, allowed to cool to room temperature, diluted with Et_2O (750 mL), and washed successively with 100 mL of H_2O, saturated aqueous $NaHCO_3$, and brine. After drying ($MgSO_4$), the organic layer was concentrated, and the residue was purified by sgc (3:2 hexanes−EtOAc) to give 10.9 g (82%) of **4** as pale yellow crystals: mp 109−110 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.87 (dd, J = 7.9, 1.3 Hz, 1H), 7.35 (td, J = 7.7, 1.4 Hz, 1H), 7.15 (d, J = 7.5 Hz, 1H), 6.99 (td, J = 7.7, 1.4 Hz, 1H), 5.9−5.7 (br m, 1H), 3.86 (s, 4H), 3.23 (s, 3H), 2.6−1.9 (br m, 4H), 1.8−1.4 (br m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.3, 147.0, 140.0, 133.5, 129.7, 129.3, 129.1, 128.9, 106.9, 98.9, 64.2, 37.1, 35.5, 30.7, 25.3; IR (CCl_4) 1662, 1640 cm^{-1}; MS (EI) *m*/*z* 399.0320 (399.0332 calcd for $C_{16}H_{18}INO_3$). Anal. Calcd for $C_{16}H_{18}NO_3$: C, 48.14; H, 4.54; N, 3.51. Found: C, 48.22; H, 4.51; N, 3.45.

Typical Procedure for Asymmetric Heck Cyclization Using $Pd_2(dba)_3$, (*R*)-BINAP and Ag_3PO_4 in DMA. Preparation of (*S*)-(+)-1′,2′-Dihydro-1′-methyl-2′-oxospiro[1,4-dioxaspiro[4.5]dec-6-ene-8,3′-3′*H*-indole] [(*S*)-5]. Under an Ar atmosphere, a mixture of $Pd_2(dba)_3$ (11.5 mg, 0.0126 mmol), (*R*)-BINAP (16.8 mg, 0.0270 mmol), Ag_3PO_4 (210 mg, 0.501 mmol), and DMA (1 mL) was stirred at room temperature for 40 min, and then a solution of **4** (100 mg, 0.251 mmol) and DMA (1.5 mL) was added. After stirring at 80 °C for 26 h, the mixture was diluted with Et_2O (20 mL) and washed with saturated aqueous $NaHCO_3$ (7 mL). The aqueous layer was further extracted with Et_2O (2 × 10 mL), and the combined organic extracts were washed with brine (7 mL) and dried ($MgSO_4$). Concentration followed by sgc (1:1 EtOAc−hexanes) gave 54.4 mg (80%) of (*S*)-(+)-**5** (71% ee) as a colorless solid, $[\alpha]^{25}_D$ +3.8° (*c* 0.54, MeOH). Recrystallization from toluene-hexanes gave (*S*)-(+)-**5** as off-white crystals: mp (racemate) 124−126 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.29 (td, J = 7.7, 1.2 Hz, 1H), 7.25 (d, J = 7.6 Hz, 1H), 7.05 (td, J = 7.5, 0.9 Hz, 1H), 6.84 (d, J = 7.8 Hz, 1H), 5.96 (d, J = 10.0 Hz, 1H), 5.49 (d, J = 10.0 Hz, 1H), 4.14−3.95 (m, 4H), 2.44 (ddd, J = 13.7, 10.1, 3.5 Hz, 1H), 2.22 (dddd, J = 13.0, 9.0, 3.6, 0.5 Hz, 1H), 2.10−1.95 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 178.0, 143.1, 132.8, 131.1, 129.9, 128.3, 123.8, 122.6, 108.0, 104.3, 64.7, 64.6, 49.2, 30.6, 29.7, 26.4; IR (CCl_4) 1719, 1613 cm^{-1}; MS (EI) *m*/*z* 271.1194 (271.1208 calcd for $C_{16}H_{17}NO_3$). Anal. Calcd for $C_{16}H_{17}NO_3$: C, 70.83; H, 6.32; N, 5.16. Found: C, 70.71; H, 6.35; N, 5.13.

Determination of Enantiomeric Excess of 5 by ^{1}H NMR Using Yb(tfc)$_3$. $Yb(tfc)_3$ was stored and weighed in a glovebox, and the $CDCl_3$ was stored over 4 Å molecular sieves and K_2CO_3. Oxindole **5** was dissolved in $CDCl_3$ (5−6 mg in 0.5 mL). A solution of $Yb(tfc)_3$ (10 mg/mL) and $CDCl_3$ was added dropwise (10−14 drops) to the NMR tube and the *N*-methyl singlet at 3.21 ppm split into two singlets (3.6−3.8 ppm) which could be integrated. Addition of too much $Yb(tfc)_3$ caused the *N*-methyl signals to overlap with signals of the ethylene ketal.

Typical Procedure for Asymmetric Heck Cyclization Using $Pd_2(dba)_3$, (*R*)-BINAP and PMP in DMA. Preparation of (*R*)-(−)-1′,2′-Dihydro-1′-methyl-2′-oxospiro[1,4-dioxaspiro[4.5]dec-6-ene-8,3′-3′*H*-indole] [(*R*)-5]. A mixture of $Pd_2(dba)_3$ (23.2 mg, 0.0253 mmol), (*R*)-BINAP (33.9 mg, 0.0544 mmol), and DMA (1 mL) was stirred at room temperature for 40 min, and then a solution of **4** (100 mg, 0.251 mmol), PMP (0.23 mL, 1.27 mmol), and DMA (1.5 mL) was added. After having been stirred at 110 °C for 8 h, the resulting mixture was worked up as decribed for the cyclization using Ag_3PO_4 and purified by sgc to give 48.1 mg (71%) of (*R*)-(−)-**5** (63% ee) as a colorless solid, $[\alpha]^{25}_D$ −2.1° (*c* 0.74, MeOH).

(*S*)-(−)-1′,2′-Dihydro-1′-methyl-2′-oxo-4-oxospiro[cyclohex-2-ene-1,3′-3′*H*-indole] [(*S*)-(−)-8]. To a solution of (+)-**5** (68% ee, 552 mg, 2.07 mmol) and THF (20 mL) at 0 °C, 1 M HCl (20 mL) was added, and the resulting solution was allowed to warm to room temperature over 40 min and then was poured into 30% aqueous K_2CO_3 (30 mL). This mixture was extracted with CH_2Cl_2 (60 mL, 2 × 45 mL), and the extract was washed with brine (30 mL) and dried ($MgSO_4$). Concentration followed by sgc (1:1 EtOAc−hexanes) gave 462 mg (∼100%) of (*S*)-(−)-**8** as a pale yellow solid, 60% ee: $[\alpha]^{25}_D$ −31.8° (*c* 0.51, MeOH); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.37 (t, J = 7.7 Hz, 1H), 7.21 (d, J = 7.3 Hz, 1H), 7.11 (t, J = 7.8 Hz, 1H), 6.92 (d, J = 7.8 Hz, 1H), 6.48 (d, J = 10.0 Hz, 1H), 6.27 (d, J = 10.0 Hz, 1H), 3.26 (s, 3H), 3.13 (ddd, J = 17.3, 9.8, 5.3 Hz, 1H), 2.63 (ddd, J = 17.3, 7.1, 5.1 Hz, 1H), 2.42 (ddd, J = 13.2, 6.5, 6.5 Hz, 1H), 2.29 (ddd, J = 14.0, 9.5, 4.7 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 197.9, 176.2, 146.2, 143.1, 131.4, 131.2, 129.1, 123.6, 123.0, 108.6, 49.6, 33.1, 32.0, 26.6; IR ($CHCl_3$) 1711, 1678, 1612 cm^{-1}; MS (EI) *m*/*z* 227.0943 (227.0946 calcd for $C_{14}H_{13}NO_2$). Anal. Calcd for $C_{14}H_{13}NO_2$: C, 73.99; H, 5.77; N, 6.16. Found: C, 74.06; H, 5.80; N, 6.14.

Recrystallization of a 360 mg sample from Et_2O three times afforded 67 mg of (*S*)-(−)-**8** as colorless crystals which were 92% ee.

(*S*)-(−)-1′,2′-Dihydro-1′-methyl-2′-oxo-3-bromo-4-oxospiro[cyclohex-2-ene-1,3′-3′*H*-indole] [(*S*)-(−)-9]. A solution of $PhNMe_3Br_3$ (107 mg, 0.285 mmol) and THF (0.8 mL) was added dropwise to a solution of (*S*)-(−)-**8** (92% ee, 58.9 mg, 0.259 mmol) and THF (0.8 mL) at −10 °C. The resulting mixture was stirred at −10 °C for 1.5 h, at 0 °C for 5 h, and at room temperature for 1.5 h and then recooled to 0 °C, and Et_3N (0.054 mL, 0.39 mmol) was added. After stirring at room temperature for 75 min, the reaction mixture was diluted with Et_2O (20 mL) and then washed with H_2O (7 mL). The aqueous layer was back-extracted with Et_2O (2 × 10 mL), and the combined extracts were washed with 7 mL of saturated aqueous $NaHCO_3$ and brine. After drying ($MgSO_4$), the organic layer was concentrated, and the residue was purified by sgc (3:2 hexanes−EtOAc) to give 51.4 mg (65%) of (*S*)-(−)-**9** as a colorless solid. Recrystallization from acetone−hexanes gave colorless single crystals, which were suitable for X-ray crystallographic analysis: mp 176−177 °C; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.38 (t, J = 7.7 Hz, 1H), 7.24 (d, J = 7.4 Hz, 1H), 7.13 (t, J = 7.5 Hz, 1H), 6.93 (s, 1H), 6.92 (d, J = 7.8 Hz, 1H), 3.37 (ddd, J = 16.6, 9.6, 7.0 Hz, 1H), 3.26 (s, 3H), 2.79 (dt, J = 17.2 Hz, 5.5 Hz, 1H), 2.46−2.34 (m, 2H); ^{13}C NMR (CDCl3, 125 MHz) δ 190.0, 174.7, 146.6, 142.9, 130.3, 129.5, 126.8, 123.7, 123.3, 108.8, 52.2, 33.4, 32.0, 26.7;

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IR ($CHCl_3$) 1712, 1614, 1601 cm^{-1}; MS (CI) *m/z* 308.0093 (308.0109 calcd for $C_{14}H_{13}{}^{81}BrNO_2$), 307.0056 (307.0030, calcd for $C_{14}H_{12}{}^{81}BrNO_2$). Anal. Calcd for $C_{14}H_{12}BrNO_2$: C, 54.92; H, 3.94; N, 4.57. Found: C, 54.79; H, 4.00; N, 4.52.

(*S*)-(−)- and (*R*)-(+)-1′-Benzyl-1′,2′-dihydro-2′-oxospiro[1,4-dioxaspiro[4.5]dec-6-ene-8,3′-3′*H*-indole] [(*S*)-(−)- and (*R*)-(+)-40]: a slightly yellow oil; ^1H NMR (300 MHz, $CDCl_3$) δ 7.4−7.2 (m, 6H), 7.17 (t, J = 7.7 Hz, 1H), 7.01 (t, J = 7.5 Hz, 1H), 6.72 (d, J = 7.8 Hz, 1H), 6.00 (d, J = 9.9 Hz, 1H), 5.55 (d, J = 9.9 Hz, 1H), 4.95 and 4.87 (ABq, J = 15.7 Hz, 2H), 4.2−4.0 (m, 4H), 2.50 (ddd, J = 13.5, 10.0, 3.3 Hz, 1H), 2.28 (ddd, J = 13.4, 9.2, 3.8 Hz, 1H), 2.4−2.0 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 178.1, 142.1, 135.8, 132.9, 131.4, 129.9, 128.8, 128.3, 127.6, 127.2, 123.9, 122.6, 109.1, 104.4, 64.8, 64.7, 49.2, 43.7, 30.8, 29.8; IR ($CHCl_3$) 1709, 1612 cm^{-1}; MS (EI) *m/z* 347.1529 (347.1521 calcd for $C_{22}H_{21}NO_3$).

Table 5, entry 5: (*S*)-(−)-**40**, 50% ee, $[\alpha]^{25}_D$ −1.9° (*c* 0.50, MeOH); entry 6 (*R*)-(+)-**40** 66% ee, $[\alpha]^{25}_D$ +9.6° (*c* 0.71, $CHCl_3$).

(*S*)-(−)- and (*R*)-(+)-1′,2′-Dihydro-2′-oxo-1′-(2-trimethylsilylethoxymethyl)spiro[1,4-dioxaspiro[4.5]dec-6-ene-8,3′-3′*H*-indole] [(*S*)-(−)- and (*R*)-(+)-41]: off-white crystals; mp (racemate) 108−109 °C (toluene-hexanes); ^1H NMR (500 MHz, C_6D_6) δ 7.11 (d, J = 7.3 Hz, 1H), 7.00 (td, J = 8.2, 0.9 Hz, 1H), 6.88 (d, J = 7.8 Hz, 1H), 6.78 (t, J = 7.3 Hz, 1H), 5.95 (d, J = 9.9 Hz, 1H), 5.40 (d, J = 9.9 Hz, 1H), 4.98 and 4.92 (ABq, J = 11.0 Hz, 2H), 3.6−3.45 (m, 6H), 2.66 (ddd, J = 13.8, 10.4, 3.3 Hz, 1H), 2.33 (ddd, J = 13.6, 9.3, 3.8 Hz, 1H), 2.11−2.0 (m, 2H), 0.86 (app qt, J = 14.1, 7.6 Hz, 2H), −0.10 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 178.4, 141.5, 132.5, 131.4, 129.8, 128.4, 123.8, 123.1, 109.7, 104.3, 69.5, 64.8, 64.7, 49.5, 31.0, 29.7, 17.8, −1.5; IR ($CHCl_3$) 1719, 1613 cm^{-1}; MS (EI) *m/z* 387.1852 (387.1866 calcd for $C_{21}H_{29}NO_4Si$).

Table 5, entry 7: (*S*)-(−)-**41**, 65% ee, $[\alpha]^{25}_D$ −5.0° (*c* 0.61, MeOH); entry 9: (*R*)-(+)-**4**, 68% ee, $[\alpha]^{25}_D$ +5.9° (*c* 0.68, MeOH).

(*S*)-(−)-1′-(*tert*-Butoxycarbonyl)-1′,2′-dihydro-2′-oxospiro[1,4-dioxaspiro[4.5]dec-6-ene-8,3′-3′*H*-indole] [(*S*)-(−)-42]: colorless crystals; mp (racemate) 147−147.5 °C (toluene−hexanes); ^1H NMR (300 MHz, $CDCl_3$) δ 7.85 (d, J = 8.2 Hz, 1H), 7.31 (td, J = 7.8, 1.4 Hz, 1H), 7.24 (dd, J = 7.5, 1.4 Hz, 1H), 7.15 (td, J = 7.4, 0.9 Hz, 1H), 5.98 (d, J = 9.9 Hz, 1H), 5.54 (d, J = 10.0 Hz, 1H), 4.1−3.95 (m, 4H), 2.45 (ddd, J = 13.5, 10.2, 3.4 Hz, 1H), 2.24 (dddd, J = 13.5, 7.5, 3.4, 0.6 Hz, 1H), 2.07 (ddd, J = 13.7, 10.5, 3.4 Hz, 1H), 1.98 (dddd, J = 13.3, 7.5, 3.4, 0.5 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 176.1, 149.3, 138.9, 131.9, 131.8, 129.4, 128.5, 124.6, 123.7, 115.0, 104.1, 84.5, 64.9, 64.6, 49.4, 31.8, 29.4, 28.1; IR (*CH*Cl3) 1660, 1626 cm^{-1}; MS (EI) m/z 357.1560 (357.1576 calcd for C20H23NO5). Anal. Calcd for C20H23NO5: C, 67.21; H, 6.49; N, 3.92. Found: C, 67.14; H, 6.52; N, 3.94.

Table 5, entry 10: 42% ee, $[\alpha]^{25}_D$ −11.8° (*c* 0.60, MeOH).

(−)- and (+)-1′,2′-Dihydro-1′-methyl-2′-oxo-4,4-dimethylspiro-[cyclohex-2-ene-1,3′-3′*H*-indole] (43): a colorless solid; ^1H NMR ($CDCl_3$, 500 MHz) δ 7.27 (t, J = 7.8 Hz, 1H), 7.19 (d, J = 7.4 Hz, 1H), 7.04 (t, J = 7.5 Hz, 1H), 6.83 (d, J = 7.7 Hz, 1H), 5.85 (d, J = 9.9 Hz, 1H), 5.15 (d, J = 9.8 Hz, 1H), 3.21 (s, 3H,), 2.07 (ddd, J = 13.5, 9.5, 3.9 Hz, 1H), 1.98 (dddd, J = 12.9, 9.3, 4.4, 1.6 Hz, 1H), 1.78−1.66 (m, 2H), 1.16 (s, 3H), 1.15 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 179.6, 143.0, 141.7, 134.5, 127.9, 123.7, 122.4, 122.3, 107.8, 49.5, 32.8, 31.0, 29.9, 29.5, 29.2, 26.3; IR ($CHCl_3$) 1701, 1612 cm^{-1}; MS (EI) *m/z* 241.1463 (241.1467 calcd for $C_{16}H_{19}NO$). Anal. Calcd for $C_{16}H_{19}NO$: C, 79.63; H, 7.94; N, 5.80. Found: C, 79.47; H, 7.92; N, 5.80.

Table 5, entry 11: 72% ee, $[\alpha]^{25}_D$ +18.0° (*c* 0.61, MeOH); entry 12: 71% ee, $[\alpha]^{25}_D$ −17.9° (*c* 0.66, MeOH).

1′,2′-Dihydro-1′-methyl-2′-oxospiro[cyclohept-2-ene-1,3′-3′*H*-indole] (45) and Its $\Delta^{3,4}$ and $\Delta^{4,5}$ Isomers. Anilide **16** (88.5 mg, 0.249 mmol) was cyclized with Pd−(*R*)-BINAP in the presence of PMP as described for the formation of (−)-**5** to give after repeated sgc (4:1 hexanes−EtOAc, four times; 5:1 hexanes−EtOAc, once) 30.3 mg (54%) of a 93:7 mixture of **45** (88% ee) and its $\Delta^{4,5}$ isomer as a colorless oil and 22.6 mg (40%) of the corresponding $\Delta^{3,4}$ isomer also as a colorless oil: **45** ^1H NMR (500 MHz, $CDCl_3$) δ 7.28 (t, J = 7.5 Hz, 1H), 7.28−7.25 (m, 1H), 7.05 (t, J = 7.6 Hz, 1H), 6.83 (d, J = 7.7 Hz, 1H), 6.03 (dt, J = 11.7, 5.8 Hz, 1H), 5.30 (d, J = 11.7 Hz, 1H), 3.20 (s, 3H), 2.62−2.50 (m, 1H), 2.40−2.30 (m, 1H), 2.16−2.06 (m, 1H), 2.06−1.96 (m, 1H), 1.95−1.75 (m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 179.6, 142.6, 135.5, 131.0, 129.4, 127.7, 123.9, 122.3, 107.9, 55.3, 36.1, 34.6, 28.2, 26.2, 24.6; IR ($CHCl_3$) 1701, 1612 cm^{-1}; MS (CI) *m/z* 227.1297 (227.1310 calcd for $C_{15}H_{17}NO$). $\Delta^{3,4}$ isomer: ^1H NMR (500 MHz, $CDCl_3$) δ 7.57 (d, J = 7.4 Hz, 1H), 7.28 (td, J = 7.7, 1.1 Hz, 1H), 7.01 (t, J = 7.4 Hz, 1H), 6.86 (d, J = 7.7 Hz, 1H), 6.10 (m, 1H), 5.69 (m, 1H), 3.21 (s, 3H), 2.85 (ddd, J = 14.6, 3.0, 1.8 Hz), 2.45−2.33 (m, 2H), 2.19 (ddd, J = 13.4, 12.1, 1.7 Hz), 2.01 (ddd, J = 14.5, 8.4, 0.9 Hz, 1H), 1.87−1.70 (m, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 180.8, 142.9, 134.3, 133.7, 127.5, 125.6, 121.6, 107.8, 47.9, 38.6, 33.8, 28.8, 26.2, 21.0; IR ($CHCl_3$) 1697, 1612 cm^{-1}; MS (CI) *m/z* 228.1357 (228.1388 calcd for $C_{15}H_{18}NO$).

(+)- and (−)-1′,2′-Dihydro-1′-(methoxycarbonyl)spiro[1,4-dioxaspiro[4.5]dec-6-ene-8,3′-3′*H*-indole] [(+)- and (−)-47]: a colorless solid; mp (racemate) 135.5−136 °C (toluene−hexanes); ^1H NMR (500 MHz, $CDCl_3$) δ 7.87 (br s, 1H), 7.23 (t, J = 7.4 Hz, 1H), 7.13 (d, J = 7.4 Hz, 1H), 6.99 (t, J = 7.7 Hz, 1H), 5.80 (d, J = 9.9 Hz, 1H), 5.78 (d, J = 10.1 Hz), 4.10−3.95 (m, 5H), 3.83 (br s, 3H), 3.76 (d, J = 11.2 Hz, 1H), 2.40−1.80 (m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 153.5, 141.4, 136.9, 135.6, 129.1, 128.3, 123.8, 122.8, 114.9, 104.6, 64.6, 64.5, 58.9, 52.5, 44.6, 34.1, 30.5; IR ($CHCl_3$) 1702, 1600 cm^{-1}; MS (EI) *m/z* 301.1310 (301.1314 calcd for $C_{17}H_{19}NO_4$). Anal. Calcd for $C_{17}H_{19}NO_4$: C, 67.76; H, 6.36; N, 4.65. Found: C, 67.78; H, 6.40; N, 4.64.

Table 5, entry 21: (+)-**47** 64% ee, $[\alpha]^{25}_D$ +17.0° (*c* 0.64, MeOH); entry 22: (−)-**49**, 8% ee, $[\alpha]^{25}_D$ −0.5° (*c* 0.56, MeOH).

Spiro[1,4-dioxaspiro[4.5]dec-6-ene-8,3′(2*H*)-benzofuran]: a colorless oil; ^1H NMR (500 MHz, $CDCl_3$) δ 7.16 (td, J = 7.6, 1.4 Hz, 1H), 7.14 (d, J = 7.4 Hz, 1H), 6.88 (t, J = 7.4 Hz, 1H), 6.82 (d, J = 8.0 Hz, 1H), 5.84 (d, J = 9.9 Hz, 1H), 5.78 (d, J = 10.0 Hz, 1H), 4.42 and 4.25 (ABq, J = 8.9 Hz, 2H), 4.10−3.97 (m, 4H), 2.07−1.96 (m, 3H), 1.90−1.81 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 159.4, 135.1, 133.5, 129.3, 128.7, 123.9, 120.7, 109.9, 104.7, 81.0, 64.6, 47.1, 33.2, 30.7; IR (film) 1650, 1608 cm^{-1}; MS (CI) *m/z* 245.1175 (245.1178 calcd for $C_{15}H_{17}O_3$).

Table 5, entry 23: (+)-**48**, 55% ee, $[\alpha]^{25}_D$ +59.7° (*c* 0.96, MeOH).

(−)- and (+)-3-Ethenyl-1,2-dihydro-1,3-dimethyl-2-oxo-3*H*-indole [(−)- and (+)-49]: a pale yellow oil; ^1H NMR (500 MHz, $CDCl_3$) δ 7.30 (t, J = 7.7 Hz, 1H), 7.19 (d, J = 7.2 Hz, 1H), 7.09 (t, J = 7.4 Hz, 1H), 6.87.(d, J = 7.8 Hz, 1H), 5.95 (dd, J = 17.2, 10.4 Hz, 1H), 5.14 (d, J = 9.2 Hz, 1H), 5.13 (d, J = 16.7 Hz, 1H), 3.21 (s, 3H), 1.49 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 178.6, 143.0, 138.1, 132.6, 128.0, 123.8, 122.4, 115.1, 108.2, 51.1, 26.3, 22.4; IR (film) 1717, 1702, 1635, 1612 cm^{-1}; MS (EI) *m/z* 187.0991 (187.0997 calcd for $C_{12}H_{13}NO$).

Table 5, entry 25: (−)-**49**, 59% ee, $[\alpha]^{25}_D$ −32.1° (*c* 0.79, MeOH); entry 26: (+)-**49**, 25% ee, $[\alpha]^{25}_D$ +15.2° (c 0.79, MeOH).

(*R*)- and (*S*)-1,2-Dihydro-1,3-dimethyl-2-oxo-3-(2-oxoethyl)-3*H*-indole [(*R*)-and (*S*)-50]: a pale yellow oil; ^1H NMR (300 MHz, $CDCl_3$) δ 9.52 (t, J = 1.5 Hz, 1H), 7.28 (td, J = 7.7, 1.2 Hz, 1H), 7.18 (dd, J = 7.5, 0.7 Hz, 1H), 7.05 (td, J = 7.6, 0.8 Hz, 1H), 6.88 (d, J = 7.8 Hz, 1H), 3.26 (s, 3H), 2.99, 2.94 (app qd, J = 17.2, 1.6 Hz, 2H), 1.42 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 198.7, 179.5, 143.1, 132.7, 128.3, 122.6, 122.4, 108.3, 50.5, 44.9, 26.4, 23.9; IR (film) 1716, 1702, 1635, 1615 cm^{-1}; MS (CI) *m/z* 204.1014 (204.1024 calcd for $C_{12}H_{14}NO_2$).

Table 5, entry 27: 45% ee; entry 28: 38% ee.

(*R*)-3-(1,1-Dimethylethyl)-1,2-dihydro-1-methyl-2-oxo-3-(2-oxoethyl)-3*H*-indole (51): a beige semisolid; ^1H NMR (300 MHz, $CDCl_3$) δ 9.19 (d, J = 2.6 Hz, 1H), 7.26 (td, J = 7.7, 1.0 Hz, 1H), 7.12 (dd, J = 7.5, 0.8 Hz, 1H), 6.98 (td, J = 7.5, 1.1 Hz, 1H), 6.90 (dd, J = 7.7, 0.8 Hz, 1H), 3.23 (s, 3H), 3.19 (d, J = 17.0 Hz, 1H), 3.03 (dd, J = 17.0, 2.6 Hz, 1H), 0.97 (s, 9H); ^{13}C NMR (75 Mz, $CDCl_3$) 199.1, 178.4, 144.4, 129.8, 128.1, 124.5, 121.6, 107.6, 53.9, 45.2, 36.3, 25.9, 24.9; IR (neat, melted) 1728, 1708, 1611 cm^{-1}. Anal. Calcd for $C_{15}H_{19}NO_2$: C, 73.44; N, 5.71; H, 7.81. Found: C, 73.21; N, 5.69; H, 7.78.

Table 5, entry 29: 72% ee (determined by HPLC analysis of the corresponding primary alcohol on a Chiralcel OD column, 9:1 hexane-2-propanol); $[\alpha]^{24}_D$ −9.0° (*c* 0.75, benzene).

(*R*)- and (*S*)-1,2-Dihydro-1-methyl-2-oxo-3-(2-oxoethyl)-3-phenyl-3*H*-indole (52): a colorless semisolid; ^1H NMR (300 MHz, $CDCl_3$) δ

9.53 (s, 1H), 7.34−7.23 (m, 7H), 7.10 (app t $J = 7.5$ Hz, 1H), 6.93 (d, $J = 7.8$ Hz, H), 3.41 and 3.40 (ABq, $J = 2.5$ Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 198.6, 177.7, 144.0, 138.7, 131.0, 128.9, 127.8, 126.6, 124.6, 122.9, 108.7, 52.6, 50.7, 26.7. Anal. Calcd for $C_{17}H_{15}NO_2$: C 76.95; H 5.70; N 5.28. Found: C 76.75; H 5.76; N 5.25.

Table 5, entry 31: 73% ee (determined by HPLC analysis of the corresponding primary alcohol on a Chiralcel OJ column); Table 5, entry 32: 35% ee of the other enantiomer.

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., the U.S. DOEd through a GAANN Predoctoral Fellowship to D.J.P., and from Merck, Pfizer, Roche Biosciences, and SmithKline Beecham is gratefully acknowledged. NMR and mass spectra were determined at Irvine using instruments acquired with the assistance of NSF and NIH Shared Instrumentation Programs.

Supporting Information Available: Experimental procedures and characterization data for new compounds not described in the Experimental Section (20 pages, print/PDF). See any current masthead page for ordering and Web access instructions.

JA980786P