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Catalytic Asymmetric Synthesis of Quaternary Carbons Bearing Two Aryl Substituents. Enantioselective Synthesis of 3-Alkyl-3-Aryl Oxindoles by Catalytic Asymmetric Intramolecular Heck Reactions

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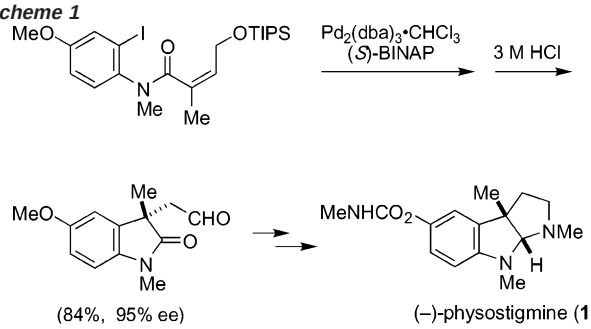
Abstract: A practical sequence involving three consecutive palladium(0)-catalyzed reactions has been developed for synthesizing 3-alkyl-3-aryloxindoles in high enantiopurity. The Heck cyclization precursors **10** and **11a**−**k** are generated in one step by chemoselective Stille cross-coupling of 2′-triflato-(*Z*)-2-stannyl-2-butenanilide **9** with aryl or heteroaryl iodides. The pivotal catalytic asymmetric Heck cyclization step of this sequence takes place in high yield and with high enantioselectivity (71−98% ee) with the Pd-BINAP catalyst derived from $Pd(OAc)_2$ to construct oxindoles containing a diaryl-substituted all-carbon quaternary carbon center. A wide variety of aryl and heteroaryl substituents, including ones of considerable steric bulk, can be introduced at C3 of oxindoles in this way (Table 4). The only limitations encountered to date are aryl substituents containing ortho nitro or basic amine functionalities and the bulky *N*-alkyl-7-oxindolyl group. Asymmetric Heck cyclization of butenalide **22** having an *o*-(*N*-acetyl-*N*-benzylamino)phenyl substituent at C2 provided a ∼1:1 mixture of amide atropisomers **23** and **24** in high yield and high enantioselectivity. These atropisomers are formed directly upon Heck cyclization of **22** at 80 °C, as they interconvert thermally to only a small extent at this temperature.

Introduction

As a result of extreme steric congestion, the construction of carbon atoms having four carbon ligands, all-carbon quaternary centers, is a formidable challenge for chemical synthesis. This challenge is magnified when the central carbon is stereogenic.[2] The most powerful extant method for enantioselective construction of stereogenic all-carbon quaternary centers is the catalytic asymmetric intramolecular Heck reaction, first reported in 1989.[3,4] A particular focus of our investigations in this area has been enantioselective synthesis of chiral 3,3-disubstituted oxindoles, as these heterocycles have numerous potential applications in the synthesis of alkaloids, drug candidates, and clinical pharmaceuticals.[5] In this context, we described some years ago efficient catalytic asymmetric syntheses of the Calabar alkaloids physostigmine (**1**) and physovenine, the former of which is used in the clinical practice of medicine (Scheme 1).[5a,d]

Scheme 1



Extension of this catalytic approach to asymmetric synthesis of oxindoles containing an aryl substituent at C3 could expedite enantioselective synthetic access to a broad range of indole alkaloids and congeners that contain one or more diaryl-

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(2) For reviews, see: (a) Christoffers, J.; Mann, A. *Angew. Chem., Int. Ed.* **2001**, *40*, 4591−4597. (b) Corey, E. J.; Guzman-Perez, A. *Angew. Chem., Int. Ed.* **1998**, *37*, 388−401.

(3) (a) Carpenter, N. E.; Kucera, D. J.; Overman, L. E. *J. Org. Chem.* **1989**, *54*, 5846−5848. (b) The indirect formation of stereogenic quaternary carbons by group selective asymmetric intramolecular Heck reactions was also first described in 1989, see: (b) Sato, Y.; Sodeoka, M.; Shibasaki, M. *J. Org. Chem.* **1989**, *54*, 4738−4739.

(4) For recent reviews of asymmetric Heck reactions, see: (a) Link, J. T. *Org. React.* **2002**, *60*, 157−534. (b) Shibasaki, M.; Vogl, E. M. *J. Organomet. Chem.* **1999**, 1−15. (c) Donde, Y.; Overman, L. E. In *Catalytic Asymmetric Synthesis*, 2nd ed.; Ojima, I., Ed.; Wiley: New York, 2000; Chapter 8G. (d) Shibasaki, M. In *Advances in Metal-Organic Chemistry*; Liebeskind, L. S., Ed.; JAI: Greenwich, 1996; pp 119−151. (d) Dounay, A. B.; Overman, L. E. *Chem. Rev.* **2003**, *103*, in press.

(5) (a) Ashimori, A.; Matsuura, T.; Overman, L. E.; Poon, D. J. *J. Org. Chem.* **1993**, *58*, 6949−6951. (b) Ashimori, A.; Bachand, B.; Overman, L. E.; Poon, D. J. *J. Am. Chem. Soc.* **1998**, *120*, 6477−6487. (c) Ashimori, A.; Bachand, B.; Calter, M. A.; Govek, S. P.; Overman, L. E.; Poon, D. J. *J. Am. Chem. Soc.* **1998**, *120*, 6488−6499. (d) Matsuura, T.; Overman, L. E.; Poon, D. J. *J. Am. Chem. Soc.* **1998**, *120*, 6500−6503. (e) Overman, L. E.; Poon D. J. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 518−521. (f) Overman, L. E.; Rosen, M. D. *Angew. Chem., Int. Ed.* **2000**, *39*, 4596−4599.

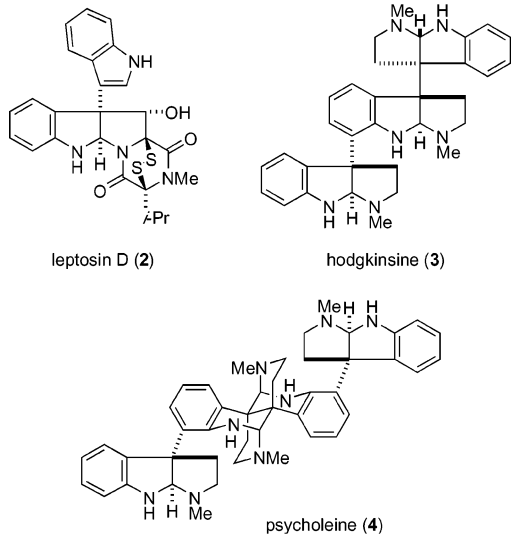
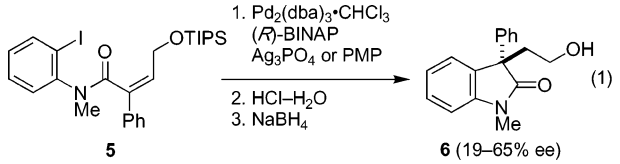


Figure 1. Representative indole alkaloids containing diaryl-substituted quaternary stereocenters.

substituted quaternary stereocenters. Representative bioactive indole alkaloids displaying this structural motif include the epidithiodiketopiperazine alkaloid leptosin D (**2**),[6] the polypyrrolidinoindoline alkaloid hodgkinsine (**3**),[7] and the dodecacyclic alkaloid psycholeine (**4**) (Figure 1).[7]

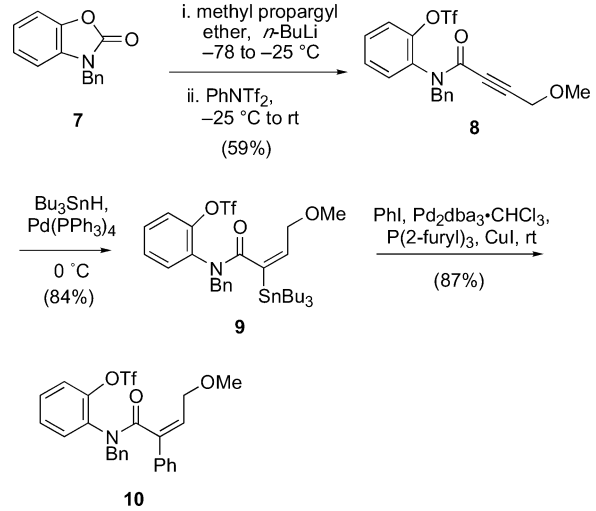
Our early investigations of the asymmetric intramolecular Heck reaction focused only briefly on synthesis of oxindoles having an aryl substituent at C3.[5b,c] Illustrative of these studies, cyclization of 2′-iodo-(*Z*)-2-phenyl-2-butenanilide **5** was studied under both cationic (Ag_3PO_4 as an additive) and neutral (1,2,2,6,6-pentamethylpiperidine, PMP, as an additive) Heck conditions using a catalyst system generated from Pd_2dba_3·$CHCl_3$ and (*R*)-BINAP[8] (eq 1). Only moderate to low enantioselection (65% ee under cationic conditions and 19% ee under neutral conditions) was realized in the assembly of oxindole **6**.[5c] The observation that the cationic variant of the Heck cyclization of **5** was superior[5b,c,9] encouraged us to investigate the cyclization of analogous aryl triflates. In this paper, we describe our development of an expeditious way to prepare 2′-triflato-(*Z*)-2-aryl-2-butenanilides and the optimization of the catalytic asymmetric Heck cyclization of these precursors to furnish 3-alkyl-3-aryl oxindoles of high enantiopurity.



Results

A. Synthesis of Heck Cyclization Precursors. Our investigations of the catalytic asymmetric construction of oxindoles bearing diaryl-substituted quaternary carbon stereocenters began with the development of a general route for assembling cyclization precursors. Initial efforts focused on preparing 2′-triflato-*N*-benzyl-(*Z*)-4-methoxy-2-phenyl-2-butenanilide (**10**) from 3-benzyl-3*H*-benzoxazol-2-one (**7**), the latter of which is available in one high-yielding step from commercially available 2-benzoxazolinone (Scheme 2).[10] Toward this end, lithiation of methyl propargyl ether with *n*-BuLi at −78 °C, followed by addition of benzoxazolinone **7** and subsequent quenching with *N*-phenyltriflimide, provided amide **8** in 59% yield. Regioselective palladium(0)-catalyzed hydrostannylation[11] of the triple bond of **8** delivered 2-stannyl-2-butenanilide **9**. Chemoselective Stille reaction of this intermediate and iodobenzene gave 2′-triflato-(*Z*)-2-phenyl-2-butenanilide **10** in high yield. Coupling to form **10** occurred optimally in *N*-methyl-2-pyrrolidone (NMP) in the presence of catalytic amounts of Pd_2dba_3·$CHCl_3$ and tri-2-furylphosphine[12a] and 1 equiv of CuI.[12b] This palladium(0)-catalyzed hydrostannylation−Stille cross-coupling sequence left the aryl triflate untouched and provided Heck cyclization precursor **10** in three steps and 43% overall yield from benzoxazolinone **7**. HPLC analysis established that the isomeric purity of **10** was >99%.[13]

Scheme 2



Stille cross-coupling of stannane **9** with various aromatic or heteroaromatic iodides provided a series of 2′-triflato-(*Z*)-2-aryl (or heteroaryl)-2-butenanilides (Table 1).[14] These chemoselective cross-coupling reactions were high yielding for all but one of

(6) Takahashi, C.; Numata, A.; Ito, Y.; Matsumura, E.; Araki, H.; Iwaki, H.; Kushida, K. *J. Chem. Soc., Perkin Trans. 1* **1994**, 1859−1864.
(7) For a recent review of polypyrrolidinoindoline alkaloids, see: Anthoni, U.; Christophersen, C.; Nielsen, P. H. *Alkaloids: Chemical and Biological Perspectives*; Pelletier, S. W., Ed.; Permagnon: New York, 1999; Vol. 13, pp 163−236.
(8) Takaya, H.; Mashima, K.; Koyano, K.; Yagi, M.; Kumobayashi, H.; Taketomi, T.; Akutagawa, S.; Noyori, R. *J. Org. Chem.* **1986**, *51*, 629−635.
(9) Similar results (73% ee under cationic conditions and 35% ee under neutral conditions) were seen with the corresponding *E* stereoisomer.[5b]
(10) Ucar, H.; Vanderpoorten, K.; Cacciaguerra, S.; Spampinato, S.; Stables, J. P.; Depovere, P.; Isa, M.; Masereel, B.; Delarge, J.; Poupaert, J. H. *J. Med. Chem.* **1998**, *41*, 1138−1145.
(11) (a) Zhang, H. X.; Guibé, F.; Balavoine, G. *J. Org. Chem.* **1990**, *55*, 1857−1867. (b) Cochran, J. C.; Bronk, B. S.; Terrence, K. M.; Phillips H. K. *Tetrahedron Lett.* **1990**, *31*, 6621−6624. (c) Betzer, J. F.; Delaloge, F.; Muller, B.; Pancrazi, A.; Prunet, J. *J. Org. Chem.* **1997**, *62*, 7768−7780.
(12) (a) Farina, V.; Krishnan, B. *J. Am. Chem. Soc.* **1991**, *113*, 9585−9595. (b) Liebeskind, L. S.; Fengl, R. W. *J. Org. Chem.* **1990**, *55*, 5359−5364. Farina, V.; Kapadia, S.; Krishnan, B.; Wang, C.; Liebeskind, L. S. *J. Org. Chem.* **1994**, *59*, 5905−5911. Han, X.; Stoltz, B. M.; Corey, E. J. *J. Am. Chem. Soc.* **1999**, *121*, 7600−7605.
(13) An Alltech Alltima SiO_2 5 μ column (98:2 *n*-hexane−2-propanol) provided baseline separation of **10** and its *E* stereoisomer.
(14) Iodides that are not available from commercial sources were prepared by literature procedures or are reported in the Supporting Information: (a) Table 1, entry 6: Olah, G. A.; Lin, H. C. *J. Am. Chem. Soc.* **1974**, *96*, 2892−2898. (b) Table 1, entry 8: Witulski, B.; Buschmann, N.; Bergsträsser, U. *Tetrahedron* **2000**, *56*, 8473−8480. (c) Table 1, entry 9: Kelly, T. A.; McNeil, D. W. *Tetrahedron Lett.* **1994**, *35*, 9003−9006. (d) Table 1, entry 10: Park, Y.; Lee, I.; Kim, Y. *J. Heterocycl. Chem.* **1994**, *31*, 1625−1630.

Table 1. Stille Coupling of 9 with Aryl Iodides

9 **11a–k**

entry	aryl iodide	product	yield, %
1	4-iodoanisole	**11a**	87
2	3-iodopyridine	**11b**	87
3	*N*-(4-iodophenyl)-acetamide	**11c**	87
4	1-iodonaphthalene	**11d**	86
5	1-iodo-2-nitrobenzene	**11e**	92
6	1-iodo-3-methyl-2- nitrobenzene	**11f**	90
7		**11g**	68
8		**11h**	51
9	*N*-Boc-2-iodoaniline	**11i**	87
10	*N*-benzyl-2-iodoaniline	**11j**	93
11		**11k**	75

the aryl and heteroaryl iodides surveyed. A variety of functionalities were tolerated, including nitro groups and basic amines (entries 5−6, 10). The efficiency of this carbon−carbon bond-forming reaction was also not sensitive to steric effects, as aryl iodides containing bulky ortho substituents (entries 7, 9−11) coupled in good to excellent yields (75−93%). The sole exception was the coupling of stannane **9** with *N*-(*tert*-butoxycarbonyl)-3-iodoindole[14c] (entry 8), which proceeded in only 51% yield. The isomeric purity of the 2′-triflato-*N*-methyl-(*Z*)-4-methoxy-2-aryl (or heteroaryl)-2-butenanilides prepared in this way was judged to be >95% based on ^{1}H NMR analysis and by analogy with the high stereospecificity observed in the preparation of triflate **10**.[15]

B. Optimization of the Heck Cyclization Conditions. We initially examined the catalytic asymmetric intramolecular Heck reaction of 2′-triflato-*N*-benzyl-(*Z*)-2-phenyl-4-methoxy-2-butenanilide (**10**).[16] These studies were carried out using various palladium precatalysts, chiral bidentate phosphine ligands, and 1,2,2,6,6-pentamethylpiperidine (PMP) as the acid scavenger

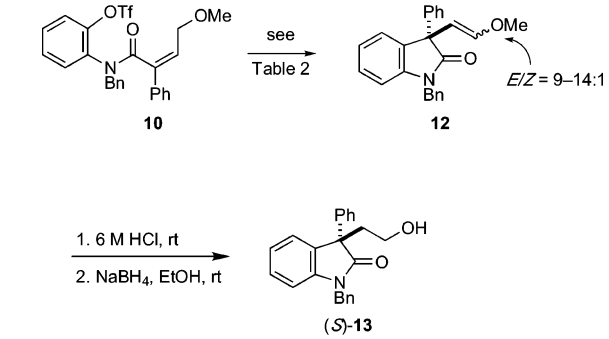
Table 2. Effect of the Precatalyst on Heck Cyclization of 10[a]

entry	precatalyst	solvent	yield **12**, %[b]	ee (*S*)-**13** %[c]
1	$Pd(OAc)_2$	THF	98	80
2	Pd_2dba_3·$CHCl_3$	THF	<5	nd[d]
3	$Pd(OAc)_2$	DMA	94	84
4	Pd_2dba_3·$CHCl_3$	DMA	23	82

[a] Conditions: 10 mol % $Pd(OAc)_2$/20 mol % (*R*)-BINAP or 5 mol % Pd_2dba_3·$CHCl_3$/11 mol % (*R*)-BINAP, 4.0 equiv of PMP, 80 °C, THF, or 100 °C, *N*,*N*-dimethylacetamide (DMA) for 4 h, substrate concentration = 0.1 M. [b] Yield of the mixture of enol ethers **12** (*E*/*Z* = 9−14:1). [c] Enantiomeric excess (±1% ee) of (*S*)-**13** was measured by HPLC using a Chiralcel OJ column. [d] Not determined.

(Scheme 3). Reactions were conducted at a substrate concentration of 0.1 M, employed catalyst loadings of 10 mol % of palladium, and were performed for a set time of 4 h. The enantioselectivity of the Heck cyclization step was determined by HPLC analysis using a chiral stationary phase[17] after converting the mixture of stereoisomeric oxindole enol ethers **12** to β-hydroxyethyl derivative (*S*)-**13**. Enantioselectivites determined in this way were reproducible within ±1% ee over multiple runs.

Scheme 3



Initial experiments employed either 5 mol % of Pd_2dba_3·$CHCl_3$ and 11 mol % of (*R*)-BINAP or 10 mol % $Pd(OAc)_2$ and 20 mol % of (*R*)-BINAP (Table 2). Both conditions generate 10 mol % of a Pd(0)-diphosphine complex.[18] To our surprise, the Pd_2dba_3·$CHCl_3$/(*R*)-BINAP catalyst system, previously reported by us to be optimal for the cyclization of 2′-iodo-(*Z*)-2-methyl-2-butenanilides,[5a,c] was kinetically sluggish for cyclization of **10** (entries 2 and 4). Use of $Pd(OAc)_2$ as the precatalyst led to substantially higher reaction rates (entries 1 and 3). For example, only a trace of product was observed when the intramolecular Heck reaction of **10** was conducted at 80 °C using the catalyst derived from Pd_2dba_3·$CHCl_3$, whereas complete conversion to **12** was achieved within 4 h with the catalyst generated from $Pd(OAc)_2$. Even at 100 °C, **10** was only partially converted to **12** using the Pd_2dba_3·$CHCl_3$/(*R*)-BINAP catalyst system (entry 4).

Upon identification of $Pd(OAc)_2$ as a suitable precatalyst for Heck cyclization of **10**, the use of alternative bidentate phosphine ligands was investigated (Table 3). In addition to (*R*)-BINAP (**14**), (*R*)-Tol-BINAP (**15**), (*S*,*S*)-DIOP (**16**), and (*S*,*S*)-

(15) These butenanilides exist in solution as two amide bond rotamers, in ratios ranging from 4:1 to >20:1 depending upon the 2 substituent. Geometric purity was evaluated by inspection of the methyl ether region (3−4 ppm) of ^{1}H NMR spectra; in all cases only two singlets were observed.

(16) Other propargyl ethers were surveyed including triisopropylsilyl (TIPS) and methoxymethyl ether (MOM) derivatives. The enantiopurity of (*S*)-**13** prepared from these precursors was 20−30% lower than that obtained from methyl ether congener **10**.

(17) A Daicel Chiralcel OJ column (7:3 hexane−*i*-PrOH) provided baseline resolution of enantiomers; chromatograms are provided in the Supporting Information.

(18) Two equivalents of (*R*)-BINAP per equivalent of $Pd(OAc)_2$ are required because 1 equiv of the diphosphine is consumed in the reduction of Pd(II) to Pd(0), see: (a) Amatore, C.; Jutand, A.; Thuilliez, A. *Organometallics* **2001**, *20*, 3241−3249. (b) Ozawa, F.; Kubo, A.; Hayashi, T. *Chem. Lett.* **1992**, 2177−2180.

Table 3. Asymmetric Heck Cyclization of 10 to Oxindole 12[a]

entry	ligand	solvent	yield, %[b]	ee, %[c]	abs conf
1	**14**	toluene	93	78	S
2	**14**	THF	98	80	S
3	**14**	MeCN	96	85	S
4	**14**	DMA	94	84	S
5	**15**	toluene	89	82	S
6	**15**	THF	92	84	S
7	**15**	MeCN	95	87	S
8	**15**	DMA	96	88	S
9	**16**	toluene	95	32	S
10	**16**	THF	97[d]	49	S
11	**16**	MeCN	95	19	S
12	**16**	DMA	92	48	S
13	**17**	toluene	95	24	R
14	**17**	THF	93[d]	31	R
15	**17**	MeCN	94	39	S
16	**17**	DMA	96	25	R

[a] Conditions: 20 mol % $Pd(OAc)_2$, 40 mol % diphosphine, 4.0 equiv of PMP, 0.1 M substrate, 80 °C (THF or MeCN) or 100 °C (toluene or *N*,*N*-dimethylacetamide, DMA) for 4 h, unless otherwise noted. [b] Isolated yield of enol ethers **12** (*E*/*Z* = 8−20:1). [c] Enantiomeric excess was determined by HPLC analysis of the *E* enol ether. [d] Reaction time was 22 h as a result of incomplete conversion at 4 h.

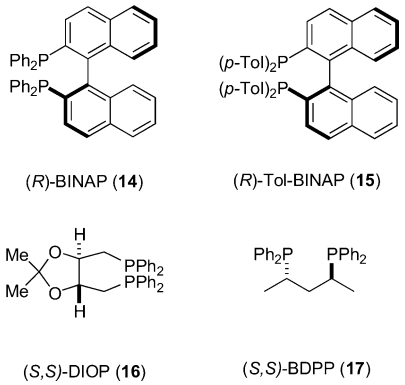


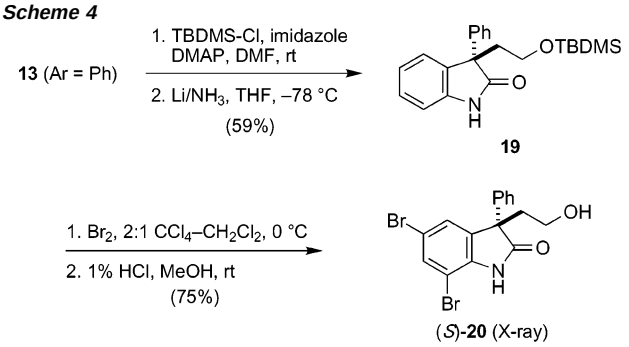
Figure 2. Chiral bisphosphine ligands.

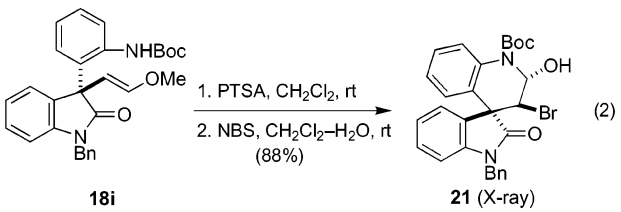
BDPP (**17**) were screened (Figure 2). The effect of changing solvent polarity on the enantioselectivity and chemical efficiency of the intramolecular Heck reaction of **10** was also examined. As summarized in Table 3, catalysts having a DIOP or BDPP ligand provided oxindole **12** in modest enantiopurity in each of the solvents surveyed (entries 9−16), whereas catalysts containing (*R*)-BINAP or (*R*)-Tol-BINAP furnished oxindole **12** in high enantiopurity (entries 1−8). In the case of the BINAP ligands, increasing solvent polarity led to slight increases in enantioselectivity.

C. Scope of the Heck Cyclization. The utility of this asymmetric intramolecular Heck reaction was investigated using aryl triflates **11a**−**j**, in which the steric and electronic nature of the aromatic or heteroaromatic 2 substituent varied considerably (Table 4). Heck cyclization of triflates **11a**−**i** to form 3-aryl (or heteroaryl)-3-alkyloxindoles **18a**−**i** proceeded cleanly and with high enantioselectivity. In most cases, complete conversion to the oxindole product was observed within 4 h at 80 °C using the catalyst derived from 10 mol of % $Pd(OAc)_2$ and 20 mol % of (*R*)-BINAP (entries 1, 3, 5, 7, and 9). In an effort to enhance the practicality of these transformations, the effect of decreasing catalyst loading on reaction efficiency was also examined. Lowering the catalyst loading to 5 mol % of $Pd(OAc)_2$ and 10 mol % of (*R*)-BINAP required an increase in the initial substrate concentration to 0.25 M to achieve complete conversion within 6 h (entries 2, 4, 6, 8, and 10). This lower catalyst loading had no appreciable effect on either the yield or the enantioselectivity of the cyclizations surveyed. In the few cases where Heck cyclizations were sluggish, longer reaction times (12−18 h) led to high conversions to oxindole products (entries 13 and 14). Substrates containing an *o*-nitrophenyl 2-substituent (entries 11 and 12) required extended reaction times and high catalyst loadings, 30−40 mol % of $Pd(OAc)_2$/60−80 mol % of (*R*)-BINAP, for complete consumption of starting material. In these cases, oxindole products **18e** and **18f** were isolated in only moderate yield, albeit with high enantiopurity.

The absolute configurations of oxindole products **12** and **18i**, formed using the catalyst derived from $Pd(OAc)_2$ and (*R*)-BINAP, were verified by X-ray crystallographic analysis of heavy atom derivatives **20** and **21**, respectively.[19] These derivatives were accessed as follows: Oxindole **12** (Ar = Ph) was converted to dibromooxindole (*S*)-**20** by the straightforward sequence summarized in Scheme 4, whereas oxindole **18i** (Ar = 2-$BocNHC_6H_4$) was converted to tetracyclic bromohydrin **21** by sequential reaction with *p*-toluenesulfonic acid (PTSA) and *N*-bromosuccinimide (NBS) in wet CH_2Cl_2 (eq 2). The absolute configuration of additional oxindoles prepared during these investigations was assigned by analogy with that established for **12**, **18i**, and related examples reported previously.[20] The absolute configuration observed in all cases is consistent with the model we previously advanced for absolute stereocontrol in intramolecular Heck cyclizations of (*Z*)-2-alkyl-2-butenanilides with Pd-BINAP.[5c]

Scheme 4



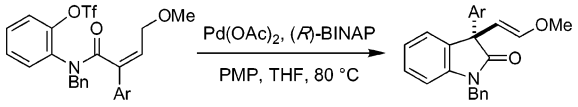


Heck cyclizations of substrates in which the 2 aryl substituent is an *o*-aminophenyl derivative (entries 15 and 16) proved to be quite sensitive to the nature of the protecting group on the aniline nitrogen. When this group was *tert*-butoxycarbonyl (Boc), the intramolecular Heck reaction proceeded efficiently

(19) Absolute configuration was assigned by analysis of the anomalous dispersion using the Rogers's η parameter, see: Flack, H. D. *Acta Crystallogr.* **1983**, *A39*, 876−881.

(20) The absolute configuration of three additional oxindoles formed by asymmetric Heck cyclizations of 2′-triflato-(*Z*)-2-aryl-2-butenanilides using Pd-BINAP has been verified, see: (a) Oestreich, M.; Dennison, P. R.; Kodanko, J. J.; Overman, L. E. *Angew. Chem., Int. Ed.* **2001**, *40*, 1439−1442. (b) Lebsack, A. L.; Link, J. T.; Overman, L. E.; Stearns, B. A. *J. Am. Chem. Soc.* **2002**, *124*, 9008−9009.

Table 4. Asymmetric Heck Cyclizations



10, 11a–j **12, 18a–j**

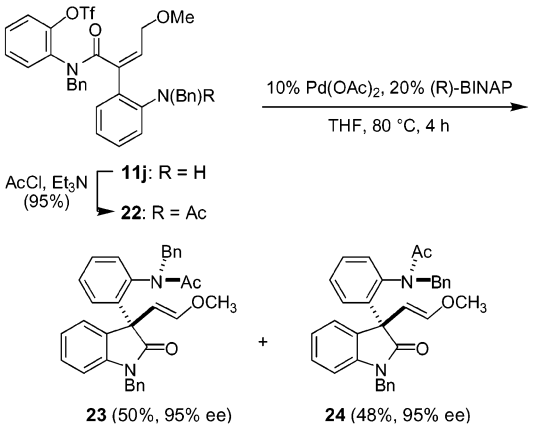
entry	Ar	$Pd(OAc)_2$, mol %	(*R*)-BINAP, mol %	[substrate], M	time, h	product	yield, %[a]	ee, %[b]
1	Ph	10	20	0.1	4	**12**	86	84
2		5	10	0.25	6	**12**	86	82
3	4-MeO-C_6H_4	10	20	0.1	4	**18a**	86	77[c]
4		5	10	0.25	6	**18a**	81	79[c]
5	3-pyridyl	10	20	0.1	4	**18b**	76	90[c]
6		5	10	0.25	6	**18b**	77	88[c]
7	4-$AcNHC_6H_4$	10	20	0.1	4	**18c**	92	72[c]
8		5	10	0.25	6	**18c**	91	71[c]
9	1-naphthyl	10	20	0.1	4	**18d**	95[d]	94[c]
10		5	10	0.25	6	**18d**	92[d]	92[c]
11	2-$NO_2C_6H_4$	30	60	0.1	5	**18e**	60	89[c,e]
12	2-NO_2-3-MeC_6H_3	40	80	0.1	5	**18f**	48	87[c,e]
13		10	20	0.1	18	**18g**	86	95[c]
14		10	20	0.1	12	**18h**	86	86[c,e]
15	2-$BocNHC_6H_4$	10	20	0.1	4	**18i**	91	98[e,f]
16	2-$BnNHC_6H_4$	10	20	0.1	4	**18j**	24	0

[a] Unless otherwise indicated, yield refers to the isolated yield of the *E* enol ether product; ^1H NMR analysis of crude cyclization product mixtures shows the *Z* enol ether to be a minor component (*E*/*Z* = 10−20:1). [b] Unless otherwise indicated, enantiomeric excess was determined by HPLC analysis of the primary alcohol derived from treatment of the cyclization product with 6 N HCl, then $NaBH_4$. [c] Absolute configuration was assigned in analogy with **12** and **18i**. [d] Isolated yield of mixture of *E*/*Z* isomers (∼10:1). [e] Enantiomeric excess was determined by HPLC analysis of *E* enol ether. [f] Enantiomeric excess of the *Z* enol ether product was 88%.

to furnish the corresponding oxindole in high enantiopurity (98% ee, Table 4, entry 15). In contrast, cyclization of triflate **11j** containing an *o*-(*N*-benzylamino)phenyl substituent at C2 (entry 16) proceeded in low yield and gave rise to racemic oxindole product **18j**. In this latter case, increasing the catalyst loading or reaction time had little effect on the yield or enantioselectivity of this reaction.

As the low yield and enantioselectivity observed in the Heck cyclization of *N*-benzylaniline substrate **11j** was atypical, acetamide derivative **22** was prepared and studied to probe the role of the basic nitrogen in undermining enantioselection in the catalytic asymmetric cyclization of **11j** (Scheme 5). Exposure of **22** to 10 mol % of $Pd(OAc)_2$ and 20 mol % of (*R*)-BINAP for 4 h at 80 °C provided an equimolar mixture of two products in high yield. Separation and characterization of these products led to their eventual identification as amide atropisomers **23** and **24**. The relative configuration of **23** was established by single-crystal X-ray analysis (Figure 3); enantiomeric purity of **23** and **24** was determined by HPLC analysis using a chiral stationary phase. Oxindole **24** is assigned as the atropisomer

Scheme 5



resulting from hindered rotation about the aryl carbon−nitrogen bond of the acetamide group based on the following observations: The ^{1}H NMR spectrum of **23** reveals a one-hydrogen doublet at δ 2.05 ppm, assignable to a benzylic hydrogen of the *N*-benzyl substituent. The large upfield shift of these methylene hydrogens is attributed to their shielding by the aromatic ring of the oxindole, a conclusion that is supported by the solid state structure of **23** (Figure 3). In contrast, the ^{1}H NMR spectrum of atropisomer **24** shows the *N*-benzyl methylene hydrogens at a fairly typical chemical shift, whereas the three-hydrogen singlet for the methyl group of the acetamide substituent is observed at δ 0.71 ppm. The upfield shift of ∼1 ppm for this group would be expected if **24** were the amide atropisomer of **23**, as the acetamide methyl group of the former would reside over the aromatic ring of the oxindole (see Figure 3).

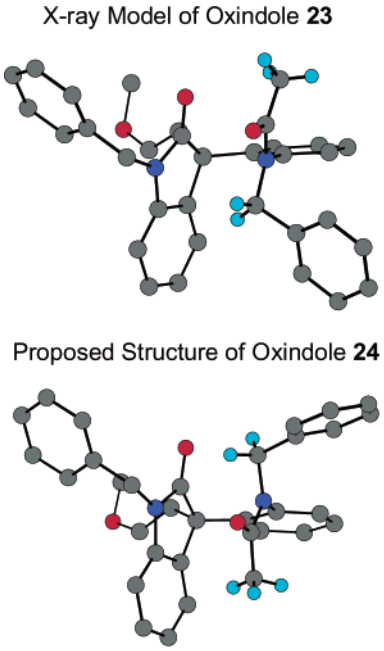


Figure 3. Chem 3D representations of the X-ray model of oxindole **23** and the proposed structure of **24**. For clarity, only the acetyl and benzylic hydrogens are shown.

Thermal interconversion of oxindoles **23** and **24** could be achieved conveniently at temperatures > 80 °C, consistent with these products being atropisomers (Table 5). This equilibration proceeded without erosion of enantiomeric purity (95% ee), thus

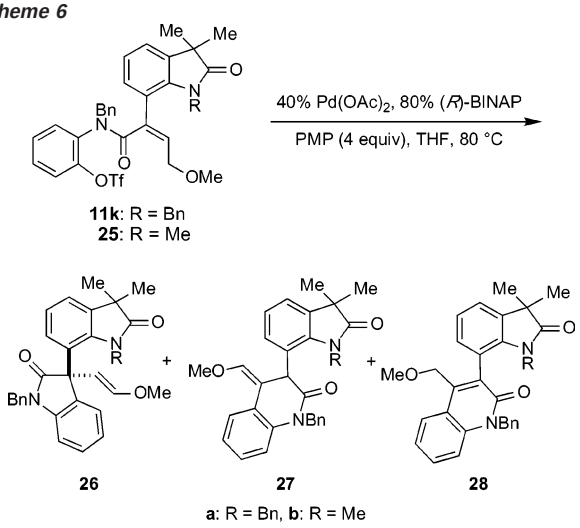
Table 5. Rate of Thermal Equilibration of 23

solvent	temp, °C	k, min^{-1}	$t_{1/2}$, min
THF	80	4×10^{-4}	900
toluene	80	4×10^{-4}	900
toluene	90	1.4×10^{-3}	240
toluene	100	1.00×10^{-2}	34.2
toluene	110	3.09×10^{-2}	11.1
toluene	120	6.73×10^{-2}	5.9

establishing that **23** and **24** have the same absolute configuration at their quaternary stereocenters. The barrier for conversion of **23** to **24** was measured in toluene to be 36.9 kcal/mol (E_a, $\Delta H^{\ddagger}$ = 36.3 kcal/mol) by Arrhenius analysis of the kinetic data in Table 5. In toluene, the equilibrium ratio of **23**:**24** was 1.0:1.6. Thermal conversion of atropisomer **23** to the 1.0:1.4 equilibrium mixture of **23**:**24** occurred in THF at 80 °C with a half-life of 15 h. As equilibration of **23** and **24** would be only ∼10% complete within 4 h at 80 °C (conditions of the Heck cyclization to generate these products), both of these atropisomers must be formed directly in the Heck cyclization of triflate **22**.

Although triflate **22** cyclized cleanly and with high enantioselectivity to form oxindoles **23** and **24**, strikingly different results were observed with the structurally related oxindole precursor **11k** (Scheme 6). In this case, a high catalyst loading (40 mol % of $Pd(OAc)_2$/80 mol % of (*R*)-BINAP) was required for complete consumption of triflate **11k** within 24 h at 80 °C. Cyclization of **11k** under these conditions delivered a complex mixture of products, in which quinolin-2-one **28a** was one component (∼20%). The presence of the exocyclic alkene isomer **27a** was suggested by the appearance of singlets at δ 6.56 and 5.41 ppm in the ^{1}H NMR of the crude product mixture.[21] When the mixture of products formed from the Heck cyclization of **11k** was treated with DBU in toluene at 110 °C, quinolin-2-one **28a** was isolated in 50% yield. The structure of **28a** was confirmed by single-crystal X-ray analysis.

Scheme 6



Quinolone **28a** could be formed from triflate **11k** either by direct 6-endo Heck cyclization or by a multistep sequence involving double-bond migration to form a β,γ-unsaturated anilide, 6-exo Heck cyclization of this intermediate to give exocyclic alkene product **27a**, and ultimately migration of the

(21) The exo-cyclic alkene **27a** could not be separated from other components of this complex mixture.

Table 6. Heck Cyclization of 25: Percent Conversion vs Time[a]

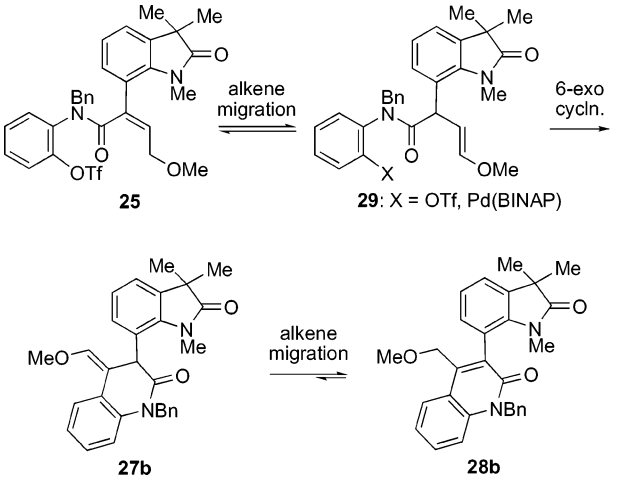
entry	time, min	**25**, %[b]	**26b**,%[b]	**27b**,%[b]	**28b**,%[b]	**27b**:**28b**
1	0	100	0	0	0	
2	15	68	0	0	0	
3	30	50	3	3	0	
4	45	42	7	6	0	
5	60	33	10	9	0	
6	75	22	12	11	2	5.5
7	90	12	16	13	3	4.3
8	105	6	21	17	5	3.4
9	150	0	28	22	8	2.8
10	180	0	30	23	9	2.6
11	240	0	38	30	16	1.9

[a] Conditions: 40 mol % $Pd(OAc)_2$/80 mol % (*R*)-BINAP, 4.0 equiv of PMP, *o*-tolualdehyde (internal standard, 1.14 equiv), 80 °C, d_8-THF, 6 h. [b] Percent conversion was measured by integration of diagnostic ^{1}H NMR signals (see Experimental Section for details) and was reproducible within ±1%.

double bond of this latter product to yield **28a**. Although direct 6-endo carbopalladation is documented in the literature for several biased substrates, 5-exo cyclization is preferred in the overwhelming majority of cases in which these two Heck cyclization pathways are possible.[4c,22]

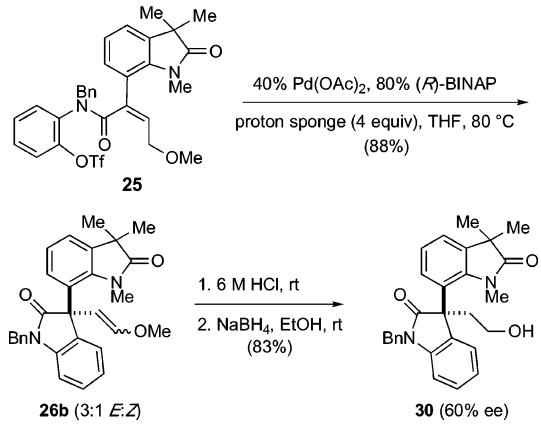
To probe the mechanism of quinolone formation, the Heck reaction of *N*-methyl congener **25** was examined in detail (Scheme 6).[23] Heck cyclization of triflate **25** using 40 mol % of $Pd(OAc)_2$ and 80 mol % of (*R*)-BINAP proceeded within 6 h to give the 5-exo product **26b** (38%) together with an inseparable 2:1 mixture of quinolones **27b** and **28b** (46%).[24] Monitoring the cyclization of triflate **25** by ^{1}H NMR spectroscopy revealed that oxindole **26b** and the exocyclic alkene isomer **27b** were formed more rapidly than quinolone **28b** (Table 6, entries 2−5). Furthermore, the ratio of **27b**:**28b** decreased with time (entries 6−11). The formation of **27b** prior to **28b** and the approach of the ratio of **27b**:**28b** toward equilibrium[25] during the reaction are consistent with quinolone **28b** being formed by the sequence outlined in Scheme 7.

Scheme 7



In principle, deconjugation of Heck cyclization substrate **25** to form **29** (Scheme 7) could be base-promoted or palladium-catalyzed. To pursue this issue, **25** was exposed to 4 equiv of PMP in d_8-THF at 80 °C for 22 h. Enol ether **29** was not detected by ^{1}H NMR analysis, suggesting that the isomerization of **25** to **29** is palladium-catalyzed. As 1,8-bis(dimethylamino)-naphthalene (Proton-Sponge) has been shown to minimize double-bond isomerizations caused by palladium(II) hydride species,[26] this base was substituted for PMP in the Heck cyclization of triflate **25**. Gratifyingly, the product of 5-exo cyclization, oxindole **26b**, was isolated in 88% yield, albeit in 60% ee, from this reaction (Scheme 8). Quinolinone product **27b** or **28b** was not detected by ^{1}H NMR analysis of the crude reaction mixture. Despite this success, these conditions failed to subvert quinolone formation in the cyclization of *N*-benzyl congener **11k**.

Scheme 8



Discussion

Synthesis of Heck Cyclization Precursors. The chemoselective Stille cross-coupling of aryl triflate stannane **9** with aromatic or heteroaromatic iodides provides an efficient, one-step route to diversely functionalized 2′-triflato-(*Z*)-2-aryl (or heteroaryl)-2-butenanilides.[27] The faster rate of oxidative addition of iodides than triflates to Pd(0) is undoubtedly the origin of the chemoselectivity observed in this reaction.[28] In addition to generating Heck precursors in high geometric purity, which is critical to realizing good enantiocontrol,[29] the mild conditions of the coupling approach reported here allow for the incorporation of a wide variety of functional groups in the aryl or heteroaryl fragment. For example, both basic amines (**11g** and **11j**) and acidic NH substituents (**11i**) were tolerated in the ortho position of the iodide coupling partner. Additionally, the efficiency of this Stille cross-coupling step was not adversely affected by neighboring substituents of considerable steric bulk (e.g., **11g** and **11k**).

Asymmetric Heck Cyclization. Heck cyclization of 2′-triflato-(*Z*)-2-phenyl-2-butenanilide **10** was significantly faster

(22) 6-Endo Heck cyclization has been observed when 5-exo cyclization would lead to a strained product, see: Dankwardt, J. W.; Flippin, L. A. *J. Org. Chem.* **1995**, *60*, 2312−2313.
(23) Whereas the ^{1}H NMR resonances of **11k** are not resolved at 80 °C, the ^{1}H NMR resonances of **25** are resolved, making **25** a more suitable substrate for this study.
(24) See Supporting Information for details of the structural assignments for **26b**, **27b**, and **28b**.
(25) The conversion of **27b** to **28b** was confirmed by exposing a 2:1 mixture of **27b**:**28b** to DBU at 80 °C in d_8-THF.; complete conversion to quinolone **28b** was observed within 1 h.
(26) Hii, K. K.; Claridge, T. D.; Brown, J. M. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 984−987.
(27) This rapid assembly of substrates for the catalytic asymmetric Heck synthesis of chiral 3-alkyl-3-aryloxindoles is a marked improvement to the route we employed previously to access 2-phenyl-(*Z*)-2-butenanilides.[5c]
(28) Alcazar-Roman, L. M.; Hartwig, J. F. *Organometallics* **2002**, *21*, 491−502, and references therein.
(29) Heck cyclizations of (*E*)- and (*Z*)-2′-iodo-2-phenyl-2-butenanilides under cationic conditions (Ag salts as the HI scavenger) lead to opposite absolute configurations at the newly formed quaternary carbon center.[5b,c]

when $Pd(OAc)_2$ rather than $Pd_2dba_3{\cdot}CHCl_3$ was used as the precatalyst. Studies by Amatore, Jutand, and co-workers have shown that the predominant species formed upon mixing $Pd_2dba_3{\cdot}CHCl_3$ and BINAP is a neutral Pd(BINAP)dba complex.[30] On the other hand, the anionic $Pd^0(dppp)OAc^-$ complex results from reaction of the bidentate phosphine dppp, 1,3-bis(diphenylphosphino)propane, with 0.5 equiv of $Pd(OAc)_2$.[18a] As oxidative addition of PhI to $Pd^0(PPh_3)_2(OAc)^-$ is 30 times faster than oxidative addition to the neutral complex $Pd^0(PPh_3)_2(DMF)$,[31] the rate increase observed in the cyclization of triflato anilide **10** with the $Pd(OAc)_2$-derived catalyst likely derives at least in part from the faster oxidative addition of the anionic $Pd^0(BINAP)OAc^-$ complex with this substrate.[32]

The Heck cyclizations summarized in Table 4 illustrate that the electronic and steric nature of the aryl or heteroaryl substituent at C2 of the 2′-triflato-(*Z*)-2-butenanilide cyclization substrate, not surprisingly, influences the enantioselectivity of the reaction. Several trends are apparent. The degree of enantioselection parallels electron density of the aromatic ring, with electron-rich substrates cyclizing in the lowest ee: **11c** ($4\text{-}NHAcC_6H_4$, 72% ee) < **11a** ($4\text{-}MeOC_6H_4$, 77% ee) < **10** (Ph, 83% ee) < **11b** (3-pyridyl, 89% ee). Heck precursors possessing large substituents at C2 cyclize in higher ee than the 2-phenyl substrate **10**. For example, naphthyl- and *N*-benzylindoline-substituted butenanilides **11d** and **11g** cyclize in 93% and 95% ee, respectively, as do substrates in which the aryl 2 substituent bears a bulky ortho substituent: **11e** ($2\text{-}NO_2C_6H_4$, 89% ee), **11i** ($2\text{-}BocNHC_6H_4$, 98%), and **22** (2-Ac-(Bn)NC_6H_4, 95%).

Plausible rationales of these observed trends in enantioselectivity can be advanced. To begin with, stereoinduction in the intramolecular Heck reaction of 2-butenanilides with Pd(BINAP) has been proposed to result from preferential migratory insertion of the more stable of the two possible diastereomeric Pd-olefin complexes.[5c] For the cases at hand, these are depicted in Figure 4. Large aromatic or heteroaromatic 2-substituents should further destabilize the disfavored olefin complex **B** through nonbonding interactions between the 2-substituent of the butenanilide and the *cis* pseudoaxial phenyl ring of BINAP. On the other hand, electron-deficient aryl or heteroaryl substituents could result in some shortening of the Pd−C bond lengths in these electron-deficient cationic olefin complexes,[33] which could augment the steric interactions that energetically differentiate complexes **A** and **B**.

The cyclization of substrate **11j**, having an *o*-(*N*-benzylamino)phenyl substituent at C2, provided racemic Heck product in low yield. All other substrates investigated in this survey cyclized to give oxindole products of high enantiopurity. The lack of enantioselectivity observed in the cyclization of **11j** is likely not an electronic effect, as other electron-rich, albeit more sterically encumbered substrates, such as **11h** (2-substituent = *N*-benzyl-7-indolinyl) cyclized to give oxindole products of high ee. A more likely explanation is that the aniline nitrogen of **11j** is ligated to palladium during the carbopalladation step. Such coordination would displace one of the phosphines from palladium and would be expected to significantly erode enantioselection.[4,5c,34]

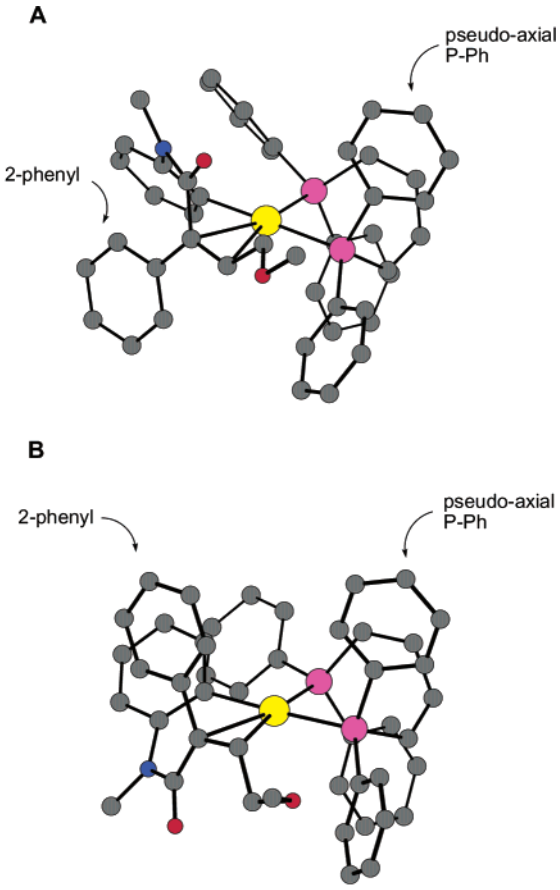
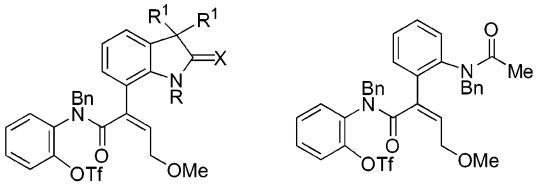


Figure 4. Models of the favored (A) and disfavored (B) diastereomeric cationic square planar complexes formed from Pd-(*R*)-BINAP and 2′-triflato-*N*-benzyl-(*Z*)-2-phenyl-2-butenanilide having the alkene π and aryl C−Pd σ bonds nearly coplanar. For clarity, the naphthalene rings of BINAP and the phenyl ring of the *N*-benzyl substituent are not shown.

Heck cyclization of acetamide **22** provided the isolable atropisomers **23** and **24** in excellent yield and high ee. The disparity in time periods required for Heck cyclization of **22** (4 h) and equilibration of **23** and **24** (>20 h) establishes that these atropisomers were generated from the cyclization of different rotamers about the aryl carbon−nitrogen bond of the acetamide group of **22**.[35]

One of the more notable attributes of the method reported here for forming 3-alkyl-3-aryl oxindoles is the efficiency of the cyclization even in cases where the aryl substituent projects considerable steric bulk in the vicinity of the newly formed, all-carbon quaternary stereocenter. Examples include the conversions of **11d** → **18d** (1-naphthyl), **11g** → **18g** (*N*-benzyl-7-indolinyl), **22** → **23** and **24** [*o*-(*N*-benzyl-*N*-acylamino)phenyl)], and **25** → **26b** (1,3,3-trimethyl-7-oxindolyl). The last example

(30) Pd(BINAP)dba and Pd(BINAP) have both been implicated as reactive species in oxidative addition reactions with iodobenzene, see: Amatore, C.; Broeker, G.; Jutand, A.; Khalil, F. *J. Am. Chem. Soc.* **1997**, *119*, 5176−5185.
(31) Amatore, C.; Jutand, A. *J. Organomet. Chem.* **1999**, *576*, 254−278.
(32) This rationale may be an oversimplification, as many steps are involved in the Heck reaction with each palladium catalyst system.
(33) Small effects on Pd−olefin bond lengths are seen in X-ray analyses of a series of para-substituted *trans*-β-nitrostyrene Pd(0) complexes, see: Stahl, S. S.; Thorman, J. L.; Siva, N.; Guzei, I. A.; Clark, R. W. *J. Am. Chem. Soc.* **2003**, *125*, 12−13.
(34) The coordination of amino substituents to palladium during Heck reactions has been suggested occasionally; for a recent example, see: Nilson, P.; Larhed, M.; Hallberg, A. *J. Am. Chem.* **2001**, *123*, 8217−8225.
(35) The *N*-benzylacetamide substituent is undoubtedly canted nearly perpendicular to the arene in both amide rotamers of **22**. This orientation is likely responsible for the observation that enantioselection is essentially the same in the cyclization of both amide rotamers.



11g: R = Bn; X = H,H; R^1 = H
11k: R = Bn, X = O; R^1 = Me
25: R = Me; X = O; R^1 = Me
31: R = H; X = O; R^1,R^1 = OCH_2CH_2O

22

Figure 5. Structurally related and sterically crowded intramolecular Heck substrates.

appears to push the limit of steric encumberance that can be tolerated, as a 40% catalyst loading was required to obtain useful cyclization rates at 80 °C. Under these conditions, deconjugation of the double bond of **25** was competitive with 5-exo Heck cyclization. Moreover, enantioselection in forming **26b** was poor (60% ee), with good yields requiring the use of 1,8-bis-(dimethylamino)naphthalene as the base (presumably by minimizing palladium-catalyzed deconjugation of **25**).[26] Finally, the limit of this method was defined in the cyclization of the *N*-benzyl congener **11k**, which did not provide useful amounts of oxindole product even when Proton Sponge was used as the base.

Although the asymmetric intramolecular Heck reactions of substrates **11g**, **22**, and **31**[20a] proceeded readily and with high enantioselectivity, cyclizations of related oxindole substrates **11k** and **25** were problematic (Figure 5). We believe this discrepancy in reactivity stems from the following: During the catalytic cycle of the Heck reaction of the *o*-triflato-(*Z*)-2-aryl-(or heteroaryl)-2-butenanilides described in this account, carbopalladation likely occurs by a conformation wherein the 2-aryl or 2-heteroaryl substituent and the alkene are nearly coplanar. If these two π systems were orthogonal, a severe steric interaction between the C2 aryl substituent and the aryl group of the anilide would develop in a 5-exo carbopalladation process (see Figure 6, model **A**). In the cases of oxindole substrates **11k** and **25**, having *N*-alkyl substituents, conformations in which the alkene and oxindole C2 substituents are coplanar would be destabilized by severe nonbonding interactions between the *N*-alkyl substituent of the oxindole and the acyl group of the buteneanilide fragment (model **B**).[36] This destabilizing interaction would be much less severe in similar coplanar conformations of substrates **11g** (C2 substituent = *N*-benzyl-7-indolyl), **22** (C2 substituent = *o*-(*N*-benzyl-*N*-acylamino)phenyl), or **31** (C2 substituent = 3-ethyl-enedioxy-7-oxindoyl), all of which undergo smooth 5-exo Heck cyclization. In the case of indoline **11g**, the *N*-benzyl substituent could be canted from the plane of the oxindole ring (model **C**), whereas with acetamide **22**, the *N*-benzyl and acetyl fragments could be perpendicular to the plane of the C2 arene.[37] The absence of a substituent on the oxindole nitrogen would also mitigate destabilizing interactions in a coplanar cyclization conformation analogous to **B**, thus rationalizing the facile, highly enantioselective 5-exo Heck cyclization of substrate **31**.[20a]

(36) The alkene and oxindole C2 substituent are perpendicular in the solid state conformation of **11k**.
(37) Such an orientation of the *N*-benzylacetamide group is observed in the X-ray structure of oxindole Heck product **23**; see Figure 3.

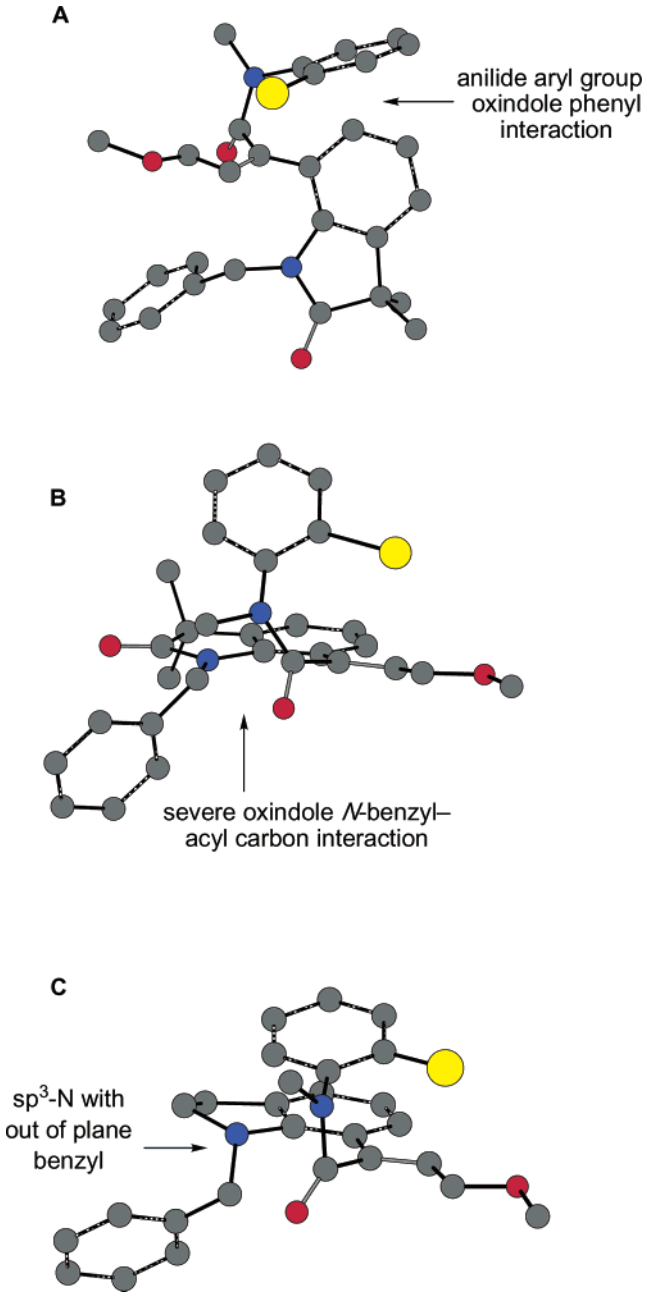


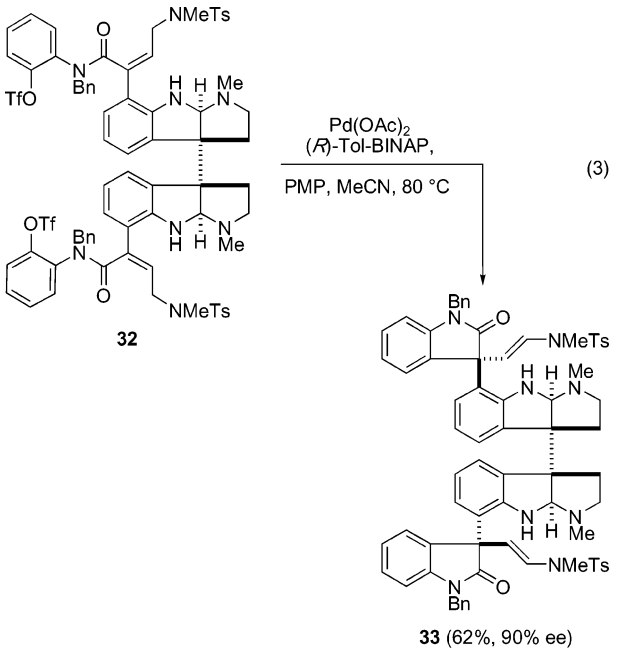
Figure 6. Chem 3-D models of conformations for 5-exo carbopalladation of Heck substrates **11k** (A and B) and **11g** (C). In A the alkene π bond and the oxindole C2 substituent are perpendicular, whereas in B and C these groups are coplanar. The palladium atom is displayed in yellow; for clarity, the phenyl ring of the acetanilide *N*-benzyl substituent has been removed.

Conclusions

A practical sequence involving three consecutive palladium-(0)-catalyzed reactions has been developed for synthesizing 3-alkyl-3-aryloxindoles in high enantiopurity. The 2′-triflato-(*Z*)-2-aryl-2-butenanilide Heck cyclization precursors are generated in one step from easily accessible (*Z*)-2-stannyl-2-butenanilide **9** and aryl or heteroaryl iodides. The pivotal catalytic asymmetric Heck cyclization step of this sequence takes place in high yield and with high enantioselectivity to forge the new diaryl-substituted all-carbon quaternary carbon center of the oxindole products. Of particular note is the wide variety of aryl and heteroaryl substituents, including ones of considerable steric bulk, that can be introduced into an oxindole in this

way. The only limitations encountered to date are aryl substituents containing ortho nitro or basic amine functionalities and the extremely bulky *N*-alkyl-7-oxindolyl group. In terms of both reaction rate and enantioselectivity, the Pd-BINAP catalyst derived from $Pd(OAc)_2$ is far superior to that formed from $Pd_2dba_3{\cdot}CHCl_3$.

This asymmetric synthesis of 3-aryl or 3-hetroaryl oxindoles should find particular use for the enantioselective synthesis of a range of indole alkaloids and congeners that contain one or more diaryl-substituted quaternary stereocenters. A compelling example of the utility of this chemistry is found in our recent asymmetric total syntheses of quadrigemine C and psycholeine (**4**).[20b] In the key step of these syntheses (**32** → **33**), two new oxindole rings, each having exceedingly bulky C-3 heteroaryl substituents, were formed in useful yield and high enantioselectivity (eq 3).



(3)

Experimental Section[38,39]

Trifluoromethanesulfonic Acid 2-(Benzyl-[4-methoxybut-2-ynoyl]-amino)phenyl Ester (8). A solution of methyl propargyl ether (3.00 g, 42.8 mmol) and THF (200 mL) was cooled to −78 °C and treated dropwise with a THF solution of *n*-BuLi (2.3 M, 20.5 mL, 47 mmol). After 1 h at −78 °C, 3-benzyl-3*H*-benzooxazol-2-one (**7**, 9.63 g, 42.8 mmol)[10] was added and the resulting solution was maintained at −25 °C. After 6 h, $PhNTf_2$ (22.5 g, 64.2 mmol) was added, and the resulting solution was allowed to warm to room temperature. After 15 min, the reaction mixture was combined with EtOAc (500 mL), and this solution was washed with brine (3 × 100 mL), dried (Na_2SO_4), filtered, and concentrated. The residue was purified by silica gel chromatography (1:9−3:7 EtOAc−hexanes) to give **8** (11.6 g, 59%) as a yellow oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.42−7.16 (m, 8H), 6.99 (dd, J = 8.0, 1.5 Hz, 1H), 5.60 (d, J = 14.5 Hz, 1H), 4.19 (d, J = 14.5 Hz, 1H), 4.00 (d, J = 16.9 Hz, 1H), 3.93 (d, J = 16.9 Hz, 1H), 2.95 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 153.4, 145.6, 135.8, 133.6, 132.6, 130.4, 129.1, 128.9, 128.7, 128.6, 128.0, 122.4, 88.9, 79.5, 59.6, 57.6, 51.5; IR (film) 1654 cm^{-1}; HRMS (CI) calcd for $C_{19}H_{17}F_3NO_5S$ $(M + H)^+$: 428.0779, found: 428.0782.

Trifluoromethanesulfonic Acid 2-(Benzyl-[2-tributylstannanyl-4-methoxy-but-2-enoyl]amino)phenyl Ester (9). A solution of amide **8** (600 mg, 1.40 mmol) and THF (15 mL) was deoxygenated by bubbling Ar through a submerged needle for 15 min. This solution was cooled to 0 °C, and $Pd(PPh_3)_4$ (80 mg, 0.070 mmol) was added. A solution of Bu_3SnH (0.38 mL, 1.4 mmol) and THF (2 mL) then was added by syringe over 40 min. The reaction was maintained at 0 °C under Ar for an additional 2 h, then concentrated without external heating. The residue was purified by silica gel chromatography (1:9−2:8 EtOAc−hexanes) to provide **9** (860 mg, 84%) as a clear oil: ^{1}H NMR and ^{13}C NMR are complex due to slow rotation of the amide group on the NMR time scale; copies of these spectra are included in the Supporting Information; IR (thin film) 1646, 1215 cm^{-1}. HRMS (ESMS, MeOH) calcd for $C_{31}H_{44}F_3NO_5SSnNa$ $(M + Na)^+$: 742.1817, found: 742.1839.

General Procedure for Stille Coupling: Preparation of Trifluoromethanesulfonic Acid 2-[Benzyl-(4-methoxy-2-phenylbut-2-enoyl)-amino]phenyl Ester (10). A stirred mixture of $Pd_2dba_3{\cdot}CHCl_3$ (6 mg, 0.006 mmol), P(2-furyl)$_3$ (12 mg, 0.051 mmol), and freshly distilled *N*-methylpyyrolidinone (NMP, 2 mL) was deoxygenated by bubbling Ar through a submerged needle for 1 h, during which time a bright yellow solution resulted. A deoxygenated solution of stannane **9** (200 mg, 0.28 mmol), iodobenzene (52 mg, 0.25 mmol), and NMP (5 mL) was then added via syringe. Copper(I) iodide (46 mg, 0.28 mmol) was then added, and the resulting mixture was flushed with a stream of Ar for 15 min and then maintained at room temperature for 24 h. After diluting the reaction with EtOAc (100 mL), the resulting solution was washed with 5% aqueous NH_4OH (3 × 10 mL) and brine (3 × 10 mL). The organic layer was dried (Na_2SO_4) and filtered, and the filtrate was concentrated. The residue was purified by flash chromatography (1:9−3:7 EtOAc−hexanes) to give **10** as a viscous, nearly colorless oil (110 mg, 87%): *E*/*Z* ratio = 0.9:99.1, HPLC (Alltech, Alltima SiO_2 5 μ, column temperature 23 °C, *n*-98:2 hexane−2-propanol, flow rate 1.0 mL·min^{-1}) 9.8 min (major *Z* stereoisomer), 11.5 min (minor *E* stereoisomer); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.34−7.29 (m, 5H), 7.19−6.99 (m, 5H), 6.83 (dd, J = 7.2, 1.2 Hz, 2H), 6.80 (dd, J = 7.6, 1.6 Hz, 1H), 6.25 (dd, J = 8.0, 1.2 Hz, 1H), 5.96 (d, J = 14.4 Hz, 1H), 5.81 (t, J = 6.4 Hz, 1H), 4.23 (d, J = 6.4 Hz, 2H), 3.95 (d, J = 14.4 Hz, 1H), 3.38 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.7, 145.4, 139.5, 136.8, 136.6, 133.4, 132.4, 131.5, 129.6, 129.3, 128.4, 128.2, 128.1, 127.8, 127.6, 125.6, 121.0, 118.2 (q, $^1J_{CF}$ = 255 Hz), 69.9, 58.3, 51.7; IR (film) 1660 cm^{-1}. Anal. Calcd for $C_{25}H_{22}F_3NO_5S$: C, 59.40; H, 4.39; N, 2.77. Found: C, 59.18; H, 4.44; N, 2.69.

General Procedure for Intramolecular Asymmetric Heck Cyclizations. Preparation of (*S*)-1-Benzyl-3-(2-methoxyvinyl)-3-phenyl-1,3-dihydroindol-2-one, (*S*)-12. A base-washed and oven-dried 10 mL sealable tube equipped with a magnetic stir bar was charged with **10** (98 mg, 0.19 mmol, 1.0 equiv), PMP (0.14 mL, 0.78 mmol, 4.0 equiv), and THF (0.8 mL). This solution was deoxygenated by bubbling Ar through a submerged needle for 20 min, and $Pd(OAc)_2$ (2.2 mg, 9.7 μmol, 5 mol %) and (*R*)-BINAP (12 mg, 19 μmol, 10 mol %) were then added. Deoxygenation and vigorous stirring were continued for 15 min, during which time a red solution resulted. The tube then was sealed and heated at 80 °C for 6 h. After cooling to room temperature, the solution was diluted with EtOAc (10 mL) and washed with $NaHCO_3$ (3 × 10 mL). The organic layer was dried (Na_2SO_4), filtered, and concentrated. The residue was purified by flash chromatography (9:1 hexanes−ethyl acetate) to give (*S*)-**12** as an amorphous, colorless solid (59 mg, 0.17 mmol, 86%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36−7.23 (m, 10H), 7.18 (dd, J = 7.6, 7.6 Hz, 1H), 7.12 (d, J = 7.2 Hz, 1H), 7.02 (dd, J = 7.2, 7.6 Hz, 1H), 6.78 (d, J = 8.0 Hz, 1H), 6.43 (d, J = 12.8 Hz, 1H), 5.36 (d, J = 12.8 Hz, 1H), 5.00 (d, J = 15.6 Hz, 1H),

(38) General experimental details have been described: Minor, K. P.; Overman, L. E. *J. Org. Chem.* **1997**, *62*, 6379−6387.

(39) Crystallographic data for the structures reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication nos. CCDC-200985 (**20**), CCDC-200986 (**28a**), CCDC-200987 (**23**), CCDC-200988 (**11k**), and CCDC-200989 (**21**). Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB21EZ, UK (fax: (+44)1223-336-033; e-mail deposit@ccdc.cam.ac.uk.).

4.95 (d, $J = 15.6$ Hz, 1H), 3.61 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 177.4, 149.8, 141.7, 140.8, 135.6, 132.2, 128.4, 128.3, 127.8, 127.3, 127.0, 126.9, 126.8, 124.9, 122.4, 109.3, 103.5, 56.1, 55.8, 43.4; IR (film) 2915, 1711, 1611 cm^{-1}; HRMS (CI) calcd for $C_{24}H_{21}NO_2$ $(M)^+$: 355.1572, found: 355.1573. Anal. Calcd for $C_{24}H_{21}NO_2$: C, 81.10; H, 5.96; N, 3.94. Found: C, 81.16; H, 6.03; N, 3.98.

General Procedure for Converting Heck Products to the Corrsponding 2-Hydroxyethyl Derivatives: Preparation of (*S*)-1-Benzyl-3-(2-hydroxyethyl]-3-phenyl-1,3,3a,7a-tetrahydroindole-2-one, (*S*)-13. A solution of oxindole enol ethers **12** (83 mg, 0.230 mmol), 6 M HCl (1 mL), and THF (2 mL) was maintained at room temperature for 1 h, then combined with saturated aqueous $NaHCO_3$ (25 mL) and extracted with EtOAc (3 × 10 mL). The organic extracts were dried, filtered, and concentrated. The crude residual aldehyde was suspended in EtOH (3 mL), and $NaBH_4$ (90 mg, 2.3 mmol) was added at room temperature. After 1 h at room temperature, the mixture was combined with 0.5 M NaOH (20 mL), and the aqueous layer was extracted with EtOAc (3 × 10 mL). The organic extracts were combined, dried, and filtered, and the filtrate was concentrated. The residue was purified by silica gel chromatography (Et_2O) to provide alcohol (*S*)-**13** (70 mg, 89%, 84% ee) as an amorphous, colorless solid: HPLC (Daicel Chiracel OJ column, column temperature 23 °C, 7:3 *n*-hexane−2-propanol, flow rate 1.0 mL·min^{-1}) 12.2 min (major enantiomer), 24.2 min (minor enantiomer); mp 97 °C (hexanes−Et_2O); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.16−7.38 (m, 12H), 7.04 (t, $J = 7.5$ Hz, 1H), 6.76 (d, $J = 7.9$ Hz, 1H), 4.92 (s, 2H), 3.45−3.53 (m, 2H), 2.81 (dt, $J = 13.9$, 7.0 Hz, 1H), 2.43 (dt, $J = 13.9$, 6.0 Hz, 1H), 1.85 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 179.2, 142.8, 140.1, 135.8, 132.0, 128.8, 128.7, 128.3, 127.3, 126.7, 122.8, 109.6, 59.5, 55.0, 44.1, 40.1; IR (film) 1695, 1610 cm^{-1}; LRMS (CI) *m*/*z* 343 $(M)^+$; HRMS (CI) calcd for $C_{23}H_{21}NO_2$: 343.1572, found: 343.1575.

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Supporting Information Available: Experimental procedures and characterization data for new compounds not described in the Experimental Section, HPLC traces used to determine enantiopurity, Arrhenius analysis for the atropisomerization of **23** to **24**, measurements of the equilibrium constant, and details of the experiments reported in Table 6. This material is available free of charge via the Internet at http://pubs.acs.org.

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