Palladium-Catalyzed, Asymmetric Hetero- and Carboannulation of Allenes Using Functionally-Substituted Aryl and Vinylic Iodides

John M. Zenner and Richard C. Larock*

Department of Chemistry, Iowa State University, Ames, Iowa 50011

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Aryl and vinylic iodides with a nucleophilic substituent in the ortho or allylic position, respectively, react with 1,2-dienes in the presence of a palladium catalyst and a chiral bisoxazoline ligand to afford five- and six-membered ring heterocycles and carbocycles in good yields and 46−88% enantiomeric excess. The generality of this process has been demonstrated by the use of nucleophilic substituents as varied as tosylamides, alcohols, phenols, carboxylic acids, and stabilized carbanions.

Introduction

Biologically active molecules, which are chiral, often exhibit significant variance in biological activity between enantiomers.[1] For this reason, the development of asymmetric synthetic methodologies has been of prime importance to organic chemists. The enantioselective, palladium-catalyzed allylic substitution reaction has been shown to be a useful means of forming new chiral carbon−carbon,[2] carbon−nitrogen,[3] carbon−oxygen,[4] and carbon−sulfur bonds.[5] Most work in this area has focused on intermolecular nucleophilic substitution of the symmetrical 1,3-diphenyl-π-allylpalladium system and the development of improved chiral ligands for use in this process.[6] Relatively little work has been done on more complicated unsymmetrical systems.[7]

Asymmetric induction in intramolecular π-allylpalladium displacements has received far less attention with only three examples of this type of process appearing in the literature.[8] Tsuji reported in 1982 an asymmetric cyclization of methyl (*E*)-3-oxo-9-phenoxy-7-nonenoate in the presence of a chiral diphosphine ligand to give the cyclized product in up to 48% ee.[8a] Genet and Grisoni synthesized an ergot alkaloid synthon in up to 70% ee using a palladium-chiraphos catalyst,[8b] and Shibasaki et al. have recently reported the synthesis of a *cis*-decalin derivative in up to 83% ee via an asymmetric π-allylpalladium displacement.[8c]

We have recently reported the regioselective, palladium-catalyzed hetero- and carboannulation of allenes using functionally substituted aryl[9] and vinylic halides.[10] The nature of the π-allylpalladium intermediates involved encouraged us to examine asymmetric versions of these annulation processes. Preliminary results of this work have been published in the form of a communication.[11] We now report, in greater detail, the results of our investigation.

Results and Discussion

The reaction of *N*-tosyl-2-iodoaniline with 1,2-undecadiene was chosen as a model system to optimize conditions for asymmetric induction. We have previously reported that using as reaction conditions 5 mol % $Pd(OAc)_2$, 5 mol % PPh_3, 3 molar equiv of Na_2CO_3, and 1 equiv of *n*-Bu_4NCl (TBAC) in DMF at 100 °C for 1 day, the desired product was obtained in 85% yield (eq 1).[9] Initial attempts at asymmetric induction utilized these same conditions, but replaced PPh_3 with (R)-BINAP.

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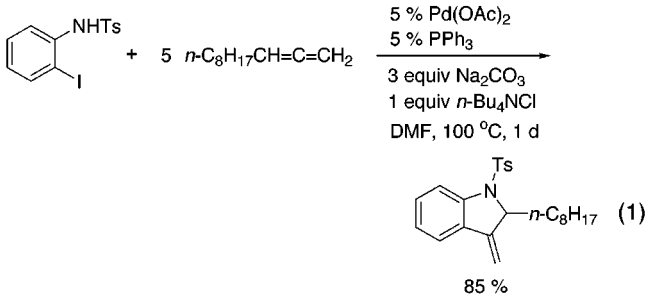
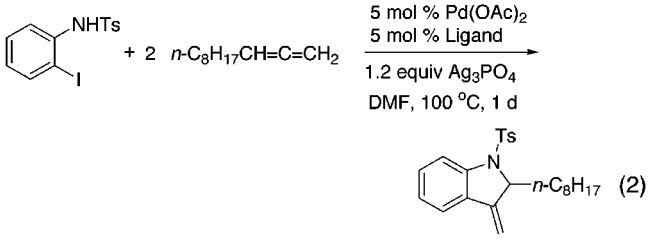


Under these conditions, the product was obtained in 87% yield, but only 5% ee (Table 1, entry 1). Removal of TBAC from the system did not lead to improved enantioselectivity (Table 1, entry 2).

Recent reports by Shibasaki et al. have demonstrated that in the presence of silver salts, significantly enhanced levels of asymmetric induction can be achieved in chiral ligand mediated Heck-type reactions of aryl or vinylic halides.[12] It is thought that in the presence of Ag^+, I^- is precipitated as AgI, allowing stronger coordination of the chiral ligand to palladium.[12a] For this reason, reaction conditions were altered to include a silver base. Replacement of Na_2CO_3 with a silver salt led to enhanced levels of enantioselectivity (Table 1, entries 3 and 4), although the overall yield was reduced significantly. We hypothesized that a redox reaction between Pd(0) and Ag(I) could account for the lower yields and the observed mirror on the reaction vial. Since only 1 equiv of Ag^+ is theoretically needed, the amount of Ag_3PO_4 was reduced to 0.4 molar equiv (1.2 ion equiv), and under these conditions the product was obtained in 65% yield and a slightly higher 30% ee (Table 1, entry 5). Variation of the reaction temperature had a pronounced effect on the enantioselectivity (Table 1, entries 5−7). Raising or lowering the reaction temperature 20 °C caused a reduction in ee, to the extent of affording an essentially racemic product at 80 °C. Solvent effects were also very important both in terms of chemical yield and ee with the original solvent DMF giving the best results (Table 1, entries 8−12). There was no significant effect on enantioselectivity when $Pd(OAc)_2$ was replaced by either $Pd(dba)_2$ or $PdCl_2$ in this system.

The final variable examined was the chiral ligand itself. A variety of chiral ligands were purchased by or donated to the research group and used in the reaction of *N*-tosyl-2-iodoaniline and 1,2-undecadiene (eq 2). The



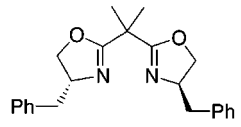
results are summarized in Table 2.

The following observations have been made with regard to ligand structure. Those ligands which when coordinated to Pd form a six-membered ring lead to products of higher ee than those which form a five-membered ring, and more electron-rich ligands tend to give higher asymmetric induction. Best results were obtained using the bisoxazoline ligands developed by Pfaltz and others (Table 2, entries 14−21),[6b−d,19,20] particularly compound **1**. Further optimization using **1** afforded the desired product in 94% yield and 82% ee (Table 3, entry 1). Only after most of our work had been completed using ligand **1** did we find that in the presence of chiral ligand **2**,[20] these same reaction conditions give the desired product in 84% yield and an even higher enantiomeric excess of 88%. However, subsequent results have suggested that **2** does not generally give higher levels of asymmetric induction than chiral ligand **1**. The reactions of *N*-tosyl-2-iodoaniline with the internal allenes 4,5-nonadiene and 1,2-cyclotridecadiene using ligand **1** also gave the desired products in high yield and showed no change in the level of enantioselectivity (Table 3, entries 2 and 3).

Table 1. Optimization of Conditions for the Enantioselective Reaction of *N*-Tosyl-2-iodoaniline and 1,2-Undecadiene (eq 1)[a]

	base					
entry	type	mol/ArI	solvent	temp (°C)	yield (%)	ee (%)
1[b]	Na_2CO_3	3.0	DMF	100	87	5
2	Na_2CO_3	3.0	DMF	100	78	4
3	Ag_2CO_3	1.0	DMF	100	36	25
4	Ag_3PO_4	1.0	DMF	100	36	25
5	Ag_3PO_4	0.4	DMF	100	65	30
6	Ag_3PO_4	0.4	DMF	120	44	16
7[c]	Ag_3PO_4	0.4	DMF	80	63	0
8	Ag_3PO_4	0.4	DMA	100	63	0
9	Ag_3PO_4	0.4	THF	100	56	13
10	Ag_3PO_4	0.4	DMSO	100	71	7
11	Ag_3PO_4	0.4	toluene	100	15	20
12	Ag_3PO_4	0.4	CH_3CN	100	23	10

[a] $Pd(OAc)_2$ (5 mol %) and of BINAP (5 mol %) were used as the catalyst. [b] TBAC (1 equiv) was used in this reaction. [c] Similar results were obtained using DiPAMP and MeO−BIPHEP as chiral ligands.



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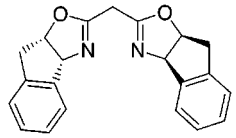

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Extension of this process to other nucleophilic substrates has been achieved, although, in general, not to

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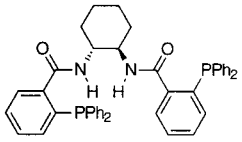
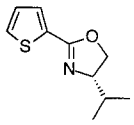
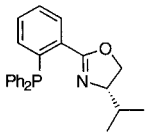
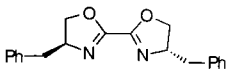
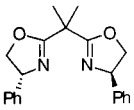
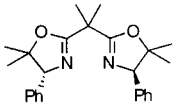
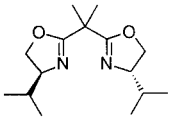
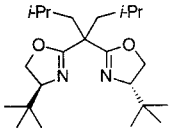
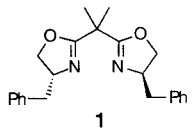
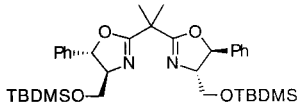
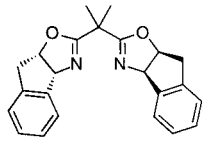
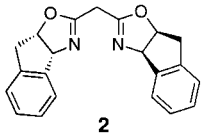
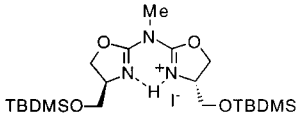
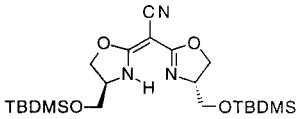
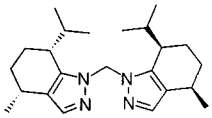
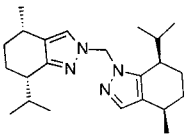
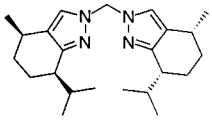
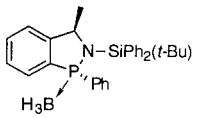
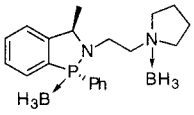
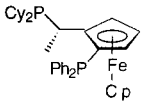
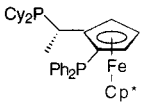
Table 2. Comparison of the Asymmetric Induction of Various Chiral Ligands in the Reaction of *N*-Tosyl-2-iodoaniline and 1,2-Undecadiene (eq 2)[a]

entry	chiral ligand	ref	% yield	% ee
1	BINAP	-	65	30
2	DIPAMP	6a	32	23
3	BIPHEMP	13	65	26
4	MeO-BIPHEP	13	63	53
5	DUPHOS	14	40	3
6	Chiraphos	-	58	0
7	Sparteine	-	73	3
8	MeO-MOP	15	85	31
9	Pybox	16	79	18
10		2f	84	27
11		6g	92	1
12		2e	52	50
13		6b	53	14
14		6f	79	39
15		17	80	50
16		6f	88	67
17		18	96	24
18	 **1**	6e,f	79	75
19		19	87	78
20		20	98	77
21	 **2**	20	90	86
22		6e	88	~0
23		6e	0	-
24		6i	76	20
25		6i	88	29
26		6i	74	17
27		6j	76	<5
28		6j	62	<5
29		6k	40	7
30		6k	29	<5

[a] All reactions were run in the presence of 5 mol % of $Pd(OAc)_2$, 5 mol % of the chiral ligand, and 1.2 ion equiv of Ag_3PO_4 in DMF at 100 °C for 1 day.

the level of success attained in the model system. For all substrates, the highest enantiomeric excesses have been obtained using 1 equiv of the aryl or vinylic iodide, 2 equiv of the allene, and 1.2 equiv of Ag_3PO_4 in DMF using a Pd/**1** catalyst, at a temperature low enough to achieve asymmetric induction, while still allowing the reaction to go to completion in a reasonable time (Table 3). While in general a catalyst system comprising 5 mol % $Pd(OAc)_2$ and 10 mol % **1** affords the desired products in both high yield and high enantiomeric excess (Table 3; catalysts A and B), limited optimization of the catalyst system for each aryl or vinylic halide led to the following observations. For some substrates, increasing the chiral ligand **1**/Pd catalyst ratio from 1:1 to 2:1 led to no improvement

Table 3. Palladium-Catalyzed, Asymmetric Annulation of Allenes Using Chiral Bisoxazoline Ligand 1[a]

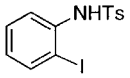
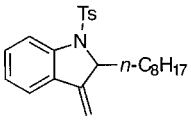
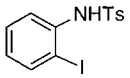
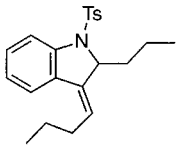
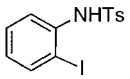
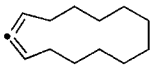
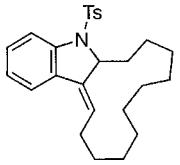
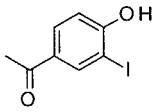
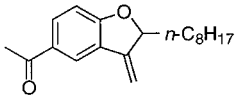
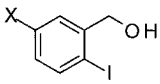
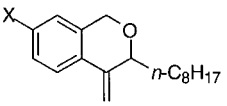
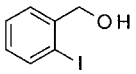
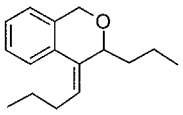
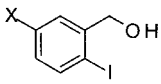
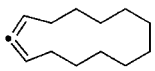
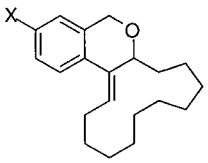
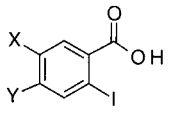
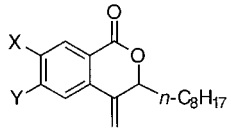
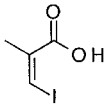
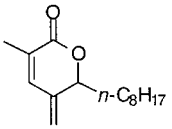
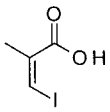
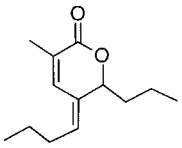
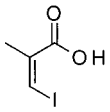
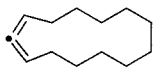
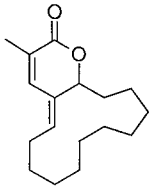
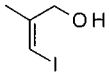
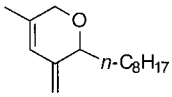
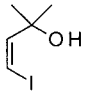
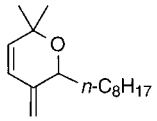
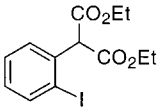
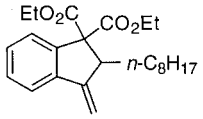
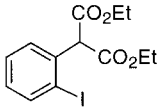
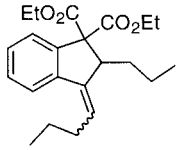
entry	organic iodide	allene	catalyst[b]	temp. (°C)	time (d)	product	% isolated yield	% ee	$[\alpha]_D$
1		n-$C_8H_{17}CH{=}C{=}CH_2$	A	90	1		94	82	-19.4°
2		n-$C_3H_7CH{=}C{=}CH$-n-C_3H_7	A	90	1		95	80	-32.5°
3			A	90	1		95	81	-37.0°
4		n-$C_8H_{17}CH{=}C{=}CH_2$	B	100	2		95	52	-61.2°
		n-$C_8H_{17}CH{=}C{=}CH_2$							
5			A	80	4	X = H	72	73	-15.6°
6			A	80	4	X = Me	56	67	-17.1°
7			A	80	4	X = Br	64	67	-8.7°
8		n-$C_3H_7CH{=}C{=}CH$-n-C_3H_7	A	80	3		73	55	-71.6°
									
9			A	80	3	X = H	29	77	-148.9°
10			A	80	3	X = Br	33	-[c]	-118.0°
		n-$C_8H_{17}CH{=}C{=}CH_2$							
11			C	40	3	X = Y = H	50	67	-79.5°
12			C	40	6	X = Me, Y = H	69	63	-70.7°
13			C	40	6	X = Y = MeO	78	71	-52.6°
14			C	40	6	X = Br, Y = H	67	48	-47.1°
15		n-$C_8H_{17}CH{=}C{=}CH_2$	D	40	3		41	80	-93.5°

Table 3 (Continued)

entry	organic iodide	allene	catalyst[b]	temp. (°C)	time (d)	product	% isolated yield	% ee	$[\alpha]_D$
16		*n*-C_3H_7CH=C=CH-*n*-C_3H_7	D	40	5		59	46	-97.5°
17			D	40	3		52	61	-202.6°
18		*n*-C_8H_{17}CH=C=CH_2	A	80	4		70	79	-11.5°
19			B	40	15		21	88	undet.
20		*n*-C_8H_{17}CH=C=CH_2	B	80	4		62	-[d]	+46.0°
21		*n*-C_8H_{17}CH=C=CH_2	E	90	3		67	75	+48.8°
22		*n*-C_3H_7CH=C=CH-*n*-C_3H_7	E	75	3		79 (*Z*:*E* = 7:1)	47	+28.0°

[a] All reactions were run in the presence of 1.2 silver ion equiv of Ag_3PO_4 in DMF (1.0 mL/0.50 mmol of organic iodide). [b] Catalyst A: 5 mol % of $Pd(OAc)_2$, 10 mol % of ligand **1**. Catalyst B: 5 mol % of $Pd(OAc)_2$, 5 mol % of ligand **1**. Catalyst C: 5 mol % of $Pd(dba)_2$, 5 mol % of ligand **1**. Catalyst D: 5 mol % of $Pd(dba)_2$, 10 mol % of ligand **1**. Catalyst E: 10 mol % of $Pd(dba)_2$, 10 mol % of ligand **1**. [c] Recrystallized product appeared to be >95% ee ($[\alpha]_D = -211.0°$). [d] The ee of this product has not been determined, since the ee could not be obtained using Eu(hfc)$_3$.

in asymmetric induction (Table 3; catalysts B, C, and E). In addition, annulations of allenes using carboxylic acids or carbanions gave slightly higher ee's using $Pd(dba)_2$ as the catalyst (Table 3; catalysts C, D, and E). Annulations using malonate nucleophiles required 10 mol % of both the Pd catalyst and the chiral ligand to increase product yields to acceptable levels (Table 3; catalyst E).

Aryl and vinylic iodides containing oxygen nucleophiles have been used to form six-membered ring heterocycles in fair to excellent ee values. The reaction of 2-iodo-4-acetylphenol and 1,2-undecadiene afforded the desired benzofuran derivative in excellent yield, but only 52% ee (Table 3, entry 4). Experimental conditions for asymmetric induction were not optimized for this system. 2-Iodobenzyl alcohol reacts with 1,2-undecadiene to give the desired product in 72% yield and 73% ee (Table 3, entry 5). Substitution in the 5-position of 2-iodobenzyl alcohol had little effect on the enantioselectivity (Table 3, entries 6 and 7).

In general, for all functionalized aryl iodides, except *N*-tosyl-2-iodoaniline, internal allenes gave lower levels of enantioselectivity than terminal allenes. For example, the reaction of 2-iodobenzyl alcohol with 4,5-nonadiene gave the annulation product in 73% yield, but only 55% ee (Table 3, entry 8). Since chiral ligand **2** had performed better than **1** in the annulation of 1,2-undecadiene using *N*-tosyl-2-iodoaniline, it was tried in the reaction of 2-iodobenzyl alcohol with 4,5-nonadiene. However, in this case the reaction was much slower, lower yielding and afforded the product in the same 55% ee. While the same aryl iodide reacted with 1,2-cyclotridecadiene to afford the desired product in 77% ee, the yield was only 29% (Table 3, entry 9).

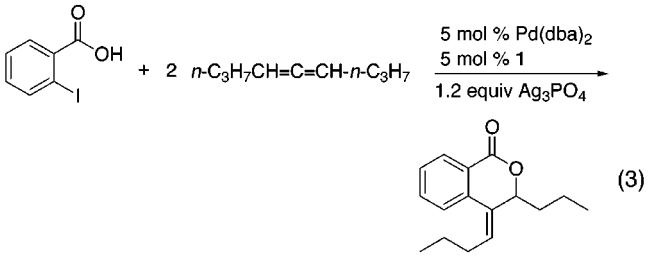
The reaction of 2-iodobenzoic acid with the terminal allene 1,2-undecadiene gave good selectivity, but in this system substituents on the aromatic ring of the substrate did cause significant variation in the ee (Table 3, entries 11−14).

The reaction of 2-iodobenzoic acid and 4,5-nonadiene gave the desired product in only low yield, although the ee remained reasonably high (Table 4, entry 1) (eq 3). Due to the low overall yield, further optimization of this reaction was attempted (Table 4). Solvent effects were found to be most crucial, both in terms of product yield and ee. Unfortunately, those solvents which facilitate product formation seem to do so at the expense of enantioselectivity.

Table 4. Effect of Solvent on Product Yield and Enantioselectivity in the Reaction of 2-Iodobenzoic Acid and 4,5-Nonadiene (eq 3)[a]

entry	solvent	temp (°C)	time (d)	yield (%) (E/Z ratio)[b]	ee (%)
1	DMF	40	3	16	69
2	CH_2Cl_2	40	2	61 (6:1)	35
3	CH_2Cl_2	rt	1	40 (6:1)	45
4	$ClCH_2CH_2Cl$	40	2	81 (7:1)	30
5	$CHCl_3$	40	3	84 (8:1)	36
6	THF	40	3	87	44
7	THF	rt	5	87	39
8	DMF/THF (1:1)	40	17	39	48
9	Toluene	40	3	71 (6:1)	30
10	Tetramethylurea	40	3	30	43
11	DMSO	40	3	0	
12	CH_3CN	40	3	65	23
13	CH_3NO_2	40	3	45 (4:1)	38

[a] All reactions were run in the presence of 5 mol % of $Pd(OAc)_2$, 5 mol % of ligand **1**, and 1.2 ion equiv of Ag_3PO_4. [b] If no *E*/*Z* ratio is specified, only the *E* isomer was obtained.



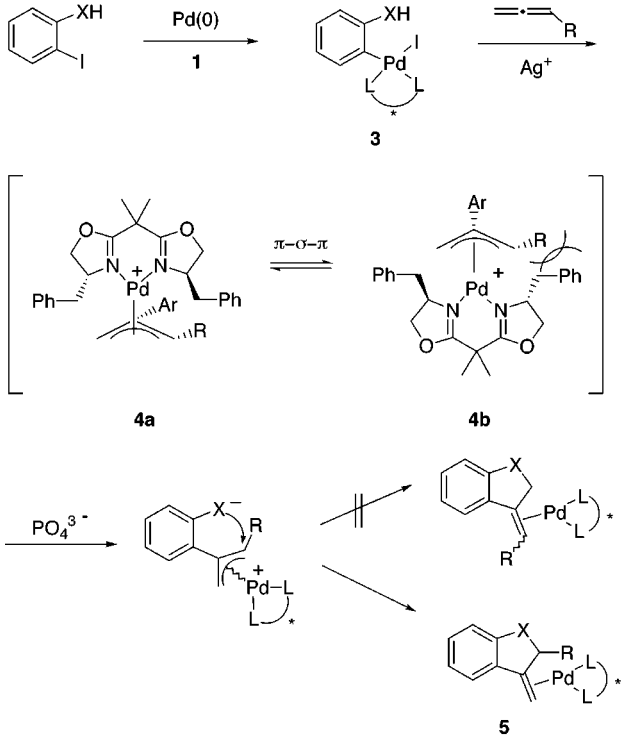
(3)

The formation of six-membered ring heterocycles using vinylic iodides bearing alcohol or carboxylic acid functionality in the allylic position followed the same trends found with the aryl analogues (Table 3, entries 15−20). Entries 18 and 19 (Table 3) demonstrate a quite significant temperature effect in the reaction of (*Z*)-3-iodo-2-methyl-2-propen-1-ol and 1,2-undecadiene. This reaction at 40 °C afforded a product in 88% ee; higher than we had observed in any other annulation process. Unfortunately, at this lower temperature, the reaction was very sluggish and even after a reaction time of 15 days the product was isolated in only a 21% yield.

Carboannulation has also been carried out enantioselectively using this methodology. Using as the substrate diethyl 2-iodophenylmalonate, it again was found that terminal allenes led to products of higher optical purity than internal symmetrical allenes (Table 3, entries 21 and 22).

The mechanism of this reaction has been outlined in our earlier publication and is reproduced in Scheme 1.[11] The first step is undoubtedly reduction of Pd(II) to Pd(0), followed by oxidative addition of the organic halide. The addition of aryl or vinylic palladium compounds to allenes is known to produce π-allylpalladium compounds, which readily undergo intramolecular nucleophilic substitution.[9,10,21] In the presence of Ag^+, the iodide is removed as AgI, allowing the formation of a 16 electron, positively charged Pd intermediate to which the bidentate chiral ligand is coordinated.[12] This system then resembles those investigated by Bosnich in which interconversion

Scheme 1



between diastereomers is accomplished via a $\pi-\sigma-\pi$ process.[7] This interconversion is known to occur rapidly in terminal π-allylpalladium species, and this is no doubt of paramount importance to eventual enantiodiscrimination.[7b] Bosnich's work has suggested that the major π-allylpalladium intermediate gives rise to the major enantiomer observed. In light of this, we speculate that steric interactions between the benzyl groups of chiral ligand **1** and the terminal alkyl substituent of the π-allylpalladium intermediate lead to a preference for one diastereomer **4a** over the other, which goes on to form the major observed enantiomer. Therefore, enantioselectivity is achieved due to minimization of steric interactions. Assuming backside nucleophilic displacement of **4a**, this mechanistic model predicts an (*S*) absolute configuration for the observed product. An X-ray crystal structure determination of 7-bromo-3,4-dihydro-4-methylene-3-*n*-octyl-1*H*-2-benzopyran (Table 3, entry 7) has confirmed the predicted (*S*) absolute configuration.

In the case of internal allenes, if the π-allyl system maintains a syn-syn conformation, a symmetrical π-allylpalladium species is generated in which steric interactions cannot be minimized (Scheme 2). This system would then resemble a 1,3-disubstituted π-allylpalladium intermediate for which factors leading to enantioselectivity in the intermolecular nucleophilic attack have been well described elsewhere.[19,22] Those studies conclude that nucleophilic attack occurs at the end of the π-allyl system

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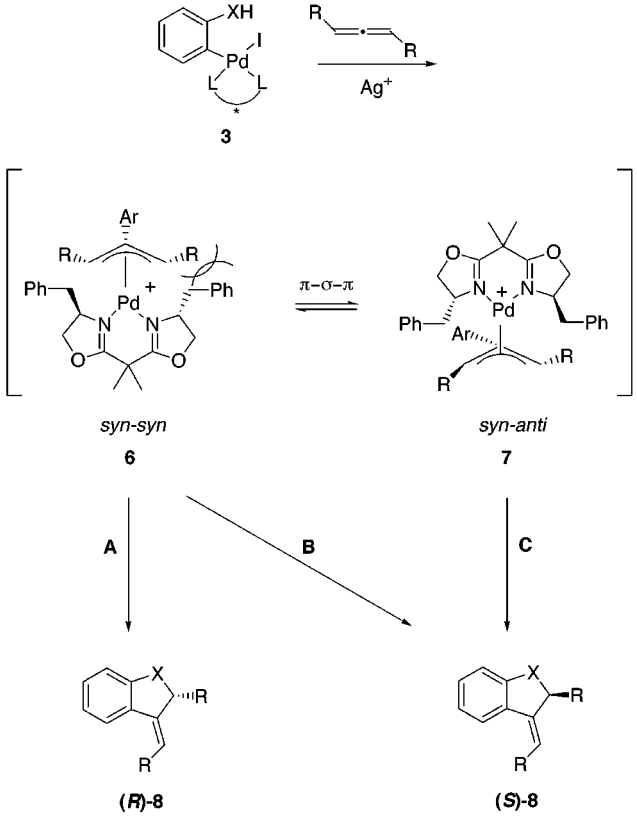
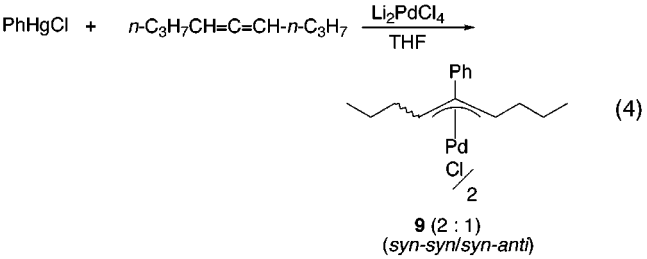
Scheme 2

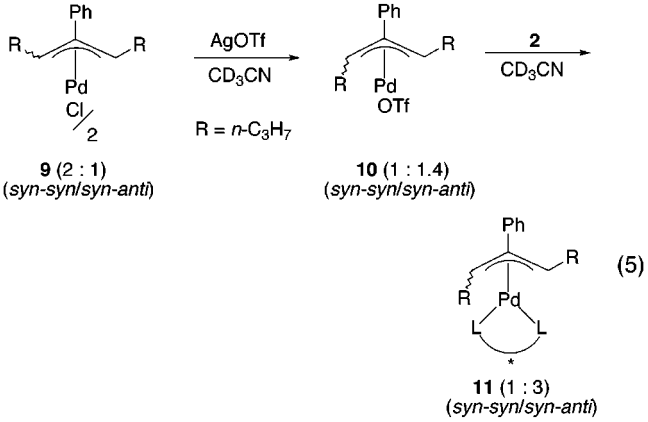


at which there exists steric interactions between the π-allyl substituent and the substituent on the oxazoline ring.[19] As the π-bound Pd(0)-alkene primary product is formed, this strain is alleviated (Scheme 2, path A). The above-described mechanism of asymmetric induction would predict an (*R*) absolute configuration for the products of internal allene annulation. However, the optical rotations of the products we have obtained from internal allenes, as well as the ^{1}H NMR splitting patterns in the presence of a chiral lanthanide shift reagent, appear more consistent with the (*S*) configuration observed for products arising from the annulation of terminal allenes. A determination of the X-ray crystal structure of (*E*)-3-bromo-5,6a,7,8,9,10,11,12,13,14,15,16-dodecahydrobenzo[*d*]cyclotrideca[*b*]pyran (Table 3, entry 10) has shown the absolute configuration is in fact (*S*). Therefore, we hypothesize that, in the case of a 1,2,3-trisubstituted π-allylpalladium system, the steric bulk of the substituent in the 2-position may lead to an equilibrium which favors the syn-anti (**7**) over the syn-syn (**6**) configuration (Scheme 2).[23]

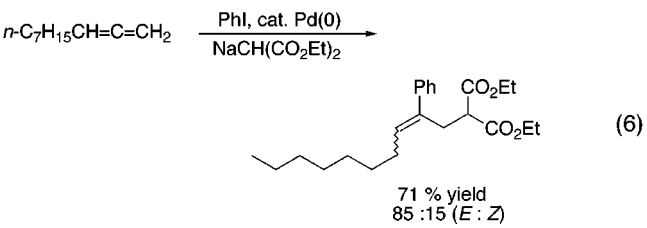
To confirm this suspicion, we synthesized and isolated di-μ-chlorodi(η^3-5-phenylnon-4-enyl)dipalladium(II) as a mixture of oil and crystals.[24] Proton and ^{13}C NMR analysis of the viscous oil component showed a 1:1 mixture of syn-syn and syn-anti isomers, while the crystals were essentially pure syn-syn isomer. A solution of syn-syn isomer in chloroform equilibrated over time, or at elevated temperature, to a 1:1 mixture of syn-syn and syn-anti isomers (eq 4).



We hypothesize that coordination of the bisoxazoline chiral ligand may further shift this equilibrium toward the syn-anti isomer since this stereoisomer is relatively free of steric interactions between the benzyl substituents of the bound ligand and the substituents on the π-allyl system (**7**). To examine this possibility, we formed the (η^3-5-phenylnon-4-enyl)palladium(II)−**2** complex (**11**) in CD_3CN. Initial attempts to form this complex by stirring di-μ-chlorodi(η^3-5-phenylnon-4-enyl)dipalladium(II) and **2** in CD_3CN at 80 °C gave no evidence of coordination. Therefore, di-μ-chlorodi(η^3-5-phenylnon-4-enyl)dipalladium(II) (**9**) was first stirred with AgOTf, precipitating AgCl and leading to the formation of (η^3-5-phenylnon-4-enyl)palladium(II) triflate (**10**). This species was then stirred with ligand **2** in CD_3CN at 80 °C (eq 5). Analysis



of the resulting complex **11** by ^{1}H NMR spectroscopy verified that in the ligand-bound π-allylpalladium species this equilibrium is further shifted, favoring the syn-anti over the syn-syn isomer in a ratio of 3:1. This same experiment using ligand **1** resulted in a 3.8:1 mixture of syn-anti and syn-syn isomers. These results have precedent in the work of Goré and co-workers, who reported an 85:15 (*E*/*Z*) ratio of products from the intermolecular displacement of a 1-*n*-heptyl-2-phenyl-π-allylpalladium intermediate by sodium diethylmalonate (eq 6).[21a]



Again, if as suggested by Bosnich[7] and others,[4c] the major π-allylpalladium intermediate present in solution gives rise to the major enantiomer observed, backside nucleophilic attack must occur preferentially at the anti terminus of the π-allyl system in order to give the

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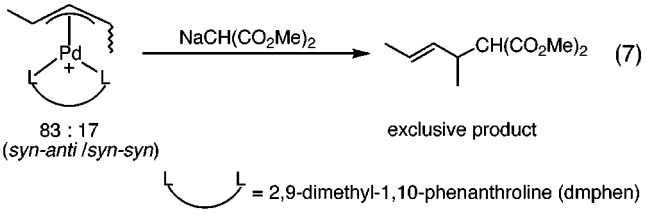
observed product of (*S*) absolute configuration at the stereogenic center and (*E*) configuration about the double bond (Scheme 2, path C). The higher reactivity of the anti-substituted carbon, required by this mechanistic path, has precedent in work by Åkermark (eq 7).[23c]



(7)

Di-μ-chlorodi(η^3-5-(2′-hydroxymethylphenyl)non-4-enyl-)dipalladium(II) has been prepared by the reaction of 2-(chloromercurio)benzyl alcohol, 4,5-nonadiene, and Li_2-$PdCl_4$,[24] but this π-allylpalladium compound rapidly decomposed at room temperature. Therefore, we were unable to attempt to correlate the ratio of syn-syn and syn-anti isomers to the ee of the annulation product (*E*)-4-*n*-butylidene-3,4-dihydro-3-*n*-propyl-1*H*-2-benzopyran. Alternatively, nucleophilic attack at the end of the π-allyl system, which is relatively free of steric interactions in the syn-syn isomer (Scheme 2, path B), also leads to the observed (*S*) enantiomer. We have as yet been unable to determine the precise mechanism at work in these systems.

The regioselectivity of this annulation process is generally quite high, often better than that observed under our previously reported conditions using PPh_3 as the ligand.[9,10] The reaction of aryl or vinylic iodides and 1,2-undecadiene forms five- or six-membered ring products by nucleophilic attack exclusively at the more substituted end of the π-allylpalladium intermediate (Table 3; entries 1, 4−7, 11−15, and 18−21). The regioselectivity of attack at the more sterically congested π-allyl terminus may be explained on the basis of two electronic factors: (1) the net positive charge on the π-allylpalladium species being more localized at the alkyl-substituted terminus[25] and (2) the observation that electron-rich palladium(0)-ligand complexes favor coordination to the more electron-deficient, less-substituted double bond of the observed product.[7,26] For these reasons, the transition state leading to the observed product may be favored.

Conclusion

The palladium-catalyzed, asymmetric hetero- and carboannulation of allenes using functionally substituted aryl and vinylic iodides has been achieved in moderate to high levels of enantiomeric excess. The generality of this process has been demonstrated by the use of a wide variety of aryl and vinylic iodides, internal nucleophiles and allenes. This generality, combined with the procedural ease with which these reactions are carried out, make this an attractive route to enantiomerically enriched hetero- and carbocycles. The results of this study include the highest ee's reported for a palladium-catalyzed, intramolecular, allylic substitution reaction.

Experimental Section

General. All ^1H and ^{13}C NMR spectra were recorded at 300 and 75.5 MHz, respectively. Thin-layer chromatography was performed using commercially prepared 60-mesh silica gel plates (Whatman K6F), and visualization was effected with short wavelength UV light (254 nm) or basic $KMnO_4$ solution [3 g of $KMnO_4$ + 20 g of K_2CO_3 + 5 mL of NaOH (5%) + 300 mL of H_2O]. All melting points are uncorrected.

Reagents. All reagents were used directly as obtained commercially unless otherwise noted. All palladium reagents were donated by Johnson Matthey Inc. and Kawaken Fine Chemicals Co., Ltd. 2-Iodoaniline, 2-iodobenzyl alcohol, 2-iodobenzoic acid, 2-iodobenzyl chloride, propargyl alcohol, *p*-toluenesulfonyl chloride, diethyl malonate, 1-decene, 4-octene, cyclododecene, bromoform, MeLi, Et_3N, PCC, and $Eu(hfc)_3$ were purchased from Aldrich Chemical Co., Inc. 5-Bromo-2-iodobenzoic acid, 2-iodo-5-methylbenzoic acid, and 2-iodo-4,5-dimethoxybenzoic acid were obtained from Trans World Chemicals, Inc.

Allenes. 1,2-Undecadiene, 4,5-nonadiene, and 1,2-cyclotridecadiene were prepared by treating the corresponding 1,1-dibromocyclopropanes with methyllithium according to a literature procedure.[27] The appropriate 1,1-dibromocyclopropanes were prepared from the corresponding alkenes using a literature procedure.[28]

***N*-Tosyl-2-iodoaniline.** Tosylation of 2-iodoaniline (25 mmol) was carried out by treating 2-iodoaniline with tosyl chloride (25 mmol) in pyridine (8 mL) and heating for 3 h at 80 °C.[29] The product was purified by recrystallization from ethanol, followed by washing several times with hexanes: ^1H NMR ($CDCl_3$) δ 2.4 (s, 3 H), 6.95 (ddd, 1 H, J = 7.5, 7.5, 1.5 Hz), 7.34 (d, 2 H, J = 7.8 Hz), 7.37 (ddd, 1 H, J = 8.1, 7.5, 1.5 Hz), 7.47 (dd, 1 H, J = 8.1, 1.5 Hz), 7.65 (d, 2 H, J = 8.1 Hz), 7.79 (dd, 1 H, J = 8.1, 1.5 Hz), 8.0 (bs, 1 H); ^{13}C NMR ($CDCl_3$) δ 21.6, 122.4, 126.8, 127.4, 129.4, 129.6, 135.8, 137.4, 139.1, 144.2 (one sp^2 signal missing due to overlap); IR ($CHCl_3$) 3300, 1285, 1233 cm^{-1}. Anal. Calcd for $C_{13}H_{12}INO_2S$: C, 41.82: H, 3.22. Found: C, 41.77; H, 3.47.

4-Hydroxy-3-iodoacetophenone. Prepared using a modification of a procedure by Schreiber and Stevenson.[30] To a solution of 4-hydroxyacetophenone (37.6 mmol) in concentrated ammonium hydroxide (250 mL) was added with rapid stirring to a solution of potassium iodide (185 mL, 30.7 g) and iodine (37.90 mmol) in water (76 mL). After overnight stirring at room-temperature, the mixture was filtered through Celite. The filtrate was acidified to pH 1. The heterogeneous solution was cooled to 5 °C and filtered. The solid collected was dissolved in ether and treated with activated carbon. Filtration, concentration, and purification by column chromatography afforded 4-hydroxy-3-iodoacetophenone in 56% yield. After recrystallization from MeOH/H_2O (2:1) the product was obtained in 49% yield: mp 153−155 °C (mp 154−156 °C); ^1H NMR ($CDCl_3$) δ 2.55 (s, 3 H), 5.91 (s, 1 H), 7.02 (d, 1 H, J = 8.4 Hz), 7.87 (dd, 1 H, J = 8.3, 2.0 Hz), 8.30 (d, 1 H, J = 2.1 Hz).

5-Bromo-2-iodobenzyl Alcohol. Prepared in 55% yield by borane reduction of the corresponding benzoic acid following a literature procedure:[31] ^1H NMR ($CDCl_3$) δ 2.25 (bs, 1 H), 4.62 (s, 2 H), 7.13 (dd, 1 H, J = 8.1, 2.1 Hz), 7.61 (d, 1 H, J = 2.1 Hz), 7.64 (d, 1 H, J = 8.1 Hz); ^{13}C NMR ($CDCl_3$) δ 68.7, 94.6, 123.0, 131.1, 132.2, 140.3, 144.6; IR ($CHCl_3$) 3250 cm^{-1}.

2-Iodo-5-methylbenzyl Alcohol. Prepared in 83% yield by borane reduction of the corresponding benzoic acid following a literature procedure:[31] ^1H NMR ($CDCl_3$) δ 2.02 (bs, 1 H), 2.26 (s, 3 H), 4.58 (s, 2 H), 6.76 (dd, 1 H, J = 8.1, 1.5 Hz), 7.21 (d, 1 H, J = 1.5 Hz), 7.61 (d, 1 H, J = 8.1 Hz); ^{13}C NMR ($CDCl_3$) δ 21.0, 69.1, 93.3, 129.3, 130.2, 138.5, 138.8, 142.2; IR ($CHCl_3$) 3230 cm^{-1}.

Diethyl 2-Iodophenylmalonate. Prepared by treatment of ethyl 2-iodophenylacetate with NaH and diethyl carbonate

(25) (a) He, Y. M.S. Thesis, Iowa State University, 1992. (b) Berrios-Peña, N. G. Ph.D. Dissertation, Iowa State University, 1989.

(26) Hartley, F. R. *Chem. Rev.* **1969**, *69*, 799−844.

(27) Landor, P. D. *The Chemistry of Allenes*; Academic Press: New York, 1982; Vol. 3, p 867.

(28) Skattebol, L. *Acta Chem. Scand.* **1963**, *17*, 1683−1693.

(29) Modified from a procedure by Ratcliffe (Ratcliffe, J. *J. Chem. Soc.* **1951**, 1140−1141).

(30) Schreiber F. G.; Stevenson, R. *J. Chem. Soc., Perkin Trans. 1* **1977**, 90−92

(31) Yoon, N. M.; Pak, C. S.; Brown, H. C.; Krishnamurthy, S.; Stocky, T. P. *J. Org. Chem.* **1973**, *38*, 2786−2792.

according to a literature procedure:[32] ^{1}H NMR ($CDCl_3$) δ 1.28 (t, 6 H, J = 7.2 Hz), 4.25 (dq, 4 H, J = 7.2, 1.5 Hz), 5.12 (s, 1 H), 7.01 (dt, 1 H, J = 7.8, 1.5 Hz), 7.37 (dq, 1 H, J = 7.8, 1.2 Hz), 7.47 (dd, 1 H, J = 7.8, 1.5 Hz), 7.87 (dd, 1 H, J = 7.8, 1.5 Hz); ^{13}C NMR ($CDCl_3$) δ 14.0, 29.4, 62.0, 101.6, 128.5, 129.6, 129.7, 136.4, 139.6, 167.7; IR (neat) 1736, 1217, 1175 cm^{-1}; HRMS for $C_{13}H_{15}IO_4$ calcd 362.0015, found 362.0013.

(***Z***)**-3-Iodo-2-methylpropen-1-ol.** Prepared in 42% yield from propargyl alcohol by treating with MeMgI and CuI in THF/Et_2O and subsequent addition of I_2 according to a literature procedure:[33] ^{1}H NMR ($CDCl_3$) δ 1.80 (t, 1 H, J = 6.3 Hz), 1.98 (s, 3 H), 4.24 (d, 2 H, J = 6.3 Hz), 5.98 (s, 1 H); ^{13}C NMR ($CDCl_3$) δ 21.5, 67.6, 74.7, 145.8; IR (neat) 3354, 1134 cm^{-1}.

(***Z***)**-3-Iodo-2-methylpropenoic Acid.** Prepared from (*Z*)-3-iodo-methylpropen-1-ol by first oxidizing with PCC to give (*Z*)-3-iodo-2-methylpropenal. This compound was not characterized due to its rapid decomposition. (*Z*)-3-Iodo-2-methylpropenal was immediately converted to the acid by $NaClO_2$/H_2O_2-mediated oxidation according to a literature procedure:[34] ^{1}H NMR ($CDCl_3$) δ 2.11 (s, 3 H), 7.10 (s, 1 H), 11.3 (bs, 1 H); ^{13}C NMR ($CDCl_3$) δ 22.46, 86.67, 137.6, 172.0; IR ($CHCl_3$) 2980, 1693 cm^{-1}.

(***Z***)**-1-Iodo-3-methyl-1-buten-3-ol.** To a three-neck round-bottom flask with condenser was added 14.74 mmol of 1 M MeMgBr in ether. (*Z*)-Ethyl 3-iodopropenoate in 5 mL of ether was then slowly added dropwise. The resultant solution warmed to reflux and then turned orange. This solution was heated at reflux for an additional 60 min. After quenching with water, the aqueous mixture was extracted with ether (3 × 25 mL). The combined organic phase was dried over $MgSO_4$, concentrated, and purified via flash column chromatography (9:1 hexanes/EtOAc) to afford (*Z*)-1-iodo-3-methyl-1-buten-3-ol: ^{1}H NMR ($CDCl_3$) δ 1.41 (s, 6 H), 2.40 (s, 1 H), 6.21 (d, J = 8.4 Hz, 1 H), 6.64 (d, J = 8.4 Hz, 1 H); ^{13}C NMR ($CDCl_3$) δ 29.47, 72.27, 75.83, 146.43.

General Procedure for the Enantioselective, Palladium-Catalyzed Annulation of Allenes. To a 1-dram vial were added the palladium reagent (0.019 mmol), the appropriate organic iodide (0.375 mmol), Ag_3PO_4 (0.150 mmol), the appropriate allene (0.750 mmol), and 0.75 mL of a DMF/chiral ligand stock solution containing the desired amount of bisoxazoline ligand **1** (0.019 or 0.038 mmol). The vial is then flushed with N_2, capped with a screw cap containing a Teflon liner, and placed in an oil bath at the desired temperature for the specified period of time (see Table 3). The vial was then removed from the oil bath, and the reaction mixture was columned directly on silica gel using hexanes/EtOAc as eluents. Determination of the enantiomeric excess of the products was accomplished using the chiral NMR shift reagent Eu(hfc)$_3$. Optical rotations were determined at 20 °C using a Jasco DIP-370 digital polarimeter.

Spectral Data. *N*-Tosyl-2,3-dihydro-3-methylene-2-*n*-octylindole (Table 3, entry 1). Obtained as a pale yellow oil in 94% yield from the reaction of *N*-tosyl-2-iodoaniline and 1,2-undecadiene after purification by column chromatography using 10:1 hexanes/EtOAc: $[\alpha]_D = -19.4°$ (c = 0.040, dichloroethane) [82% ee, based on integration of two aromatic peaks corresponding to H-7 and Ts in the presence of Eu(hfc)$_3$]; ^{1}H NMR ($CDCl_3$) δ 0.86 (t, 3 H, J = 6.9 Hz), 1.1−1.5 (m, 12 H), 1.70−1.85 (m, 1 H), 1.95−2.15 (m, 1 H), 2.32 (s, 3 H), 4.55−4.67 (m, 1 H), 4.85 (d, 1 H, J = 2.0 Hz), 5.34 (d, 1 H, J = 2.0 Hz), 7.03 (ddd, 1 H, J = 7.5, 7.5, 0.6 Hz), 7.13 (d, 2 H, J = 8.1 Hz), 7.27 (t, 1 H, J = 7.8 Hz), 7.29 (d, 1 H, J = 7.8 Hz), 7.53 (d, 2 H, J = 8.1 Hz), 7.74, (d, 1 H, J = 7.8 Hz); ^{13}C NMR ($CDCl_3$) δ 14.1, 21.5, 22.6, 22.8, 29.6, 29.4, 29.6, 31.8, 37.2, 66.6, 102.6, 116.9, 120.7, 124.3, 127.1, 129.4, 129.8, 130.3, 134.4, 143.8, 143.9, 145.1; HRMS for $C_{24}H_{31}NO_2S$ calcd 397.2075, found 397.2069. Anal. Calcd for $C_{24}H_{31}NO_2S$: C, 72.51; H, 7.86. Found: C, 70.70; H, 7.80.

(*E*)-*N*-Tosyl-3-*n*-butylidene-2,3-dihydro-2-*n*-propylindole (Table 3, entry 2). Obtained as a clear, colorless oil in 95% yield from the reaction of *N*-tosyl-2-iodoaniline and 4,5-nonadiene after purification by column chromatography using 10:1 hexanes/EtOAc: $[\alpha]_D = -32.5°$ (c = 0.045, dichloroethane) [80% ee, based on integration of two aromatic peaks corresponding to H-7 and Ts in the presence of Eu(hfc)$_3$]; ^{1}H NMR ($CDCl_3$) δ 0.84 (t, 3 H, J = 7.5 Hz), 0.89 (t, 3 H, J = 7.5 Hz), 1.31−1.45 (m, 4 H), 1.60−1.74 (m, 1 H), 1.78−1.92 (m, 1 H), 2.21−2.27 (m, 2 H), 2.30 (s, 3 H) 4.53 (td, 1 H, J = 5.4, 1.5 Hz), 5.28 (td, 1 H, J = 7.4, 1.5 Hz), 7.04 (td, 1 H, J = 7.7, 0.9 Hz), 7.10 (d, 2 H, J = 8.4 Hz), 7.22 (td, 1 H, J = 7.5, 0.9 Hz), 7.38 (d, 1 H, J = 7.5 Hz), 7.47 (d, 2 H, J = 8.4 Hz), 7.72 (d, 1 H, J = 8.1 Hz); ^{13}C NMR ($CDCl_3$) δ 13.6, 14.0, 16.8, 21.4, 22.6, 30.0, 40.2, 67.4, 117.6, 124.5, 127.0, 128.5, 129.3, 130.9, 134.6, 143.5, 144.2 (three sp^2 signals missing due to overlap); IR (neat) 3060, 3030, 2950, 2920, 2860, 1592, 1490, 1450, 1353, 1168 cm^{-1}; HRMS for $C_{22}H_{27}NO_2S$ calcd 369.1763, found 369.1766. Anal. Calcd for $C_{22}H_{27}NO_2S$: C, 71.51; H, 7.37. Found: C, 70.02; H, 7.40.

(*E*)-*N*-Tosyl-5a,6,7,8,9,10,11,12,13,14,15-undecahydrocyclotridec[*b*]indole (Table 3, entry 3). Obtained as a white solid in 95% yield from the reaction of *N*-tosyl-2-iodoaniline and 1,2-cyclotridecadiene after purification by column chromatography using 10:1 hexanes/EtOAc: mp 147−149 °C; $[\alpha]_D = -37.0°$ [81% ee, based on integration of two aromatic peaks corresponding to H-7 and Ts in the presence of Eu(hfc)$_3$]; ^{1}H NMR ($CDCl_3$) δ 1.0−1.35 (m, 16 H), 1.63−1.77 (m, 2 H), 2.08−2.23 (m, 1 H), 2.27 (s, 3 H), 2.52−2.68 (m, 1 H), 4.63 (m, 1 H), 5.37 (dd, 1 H, J = 10.4, 5.1 Hz), 6.99 (t, 1 H, J = 8.0 Hz), 7.10 (d, 2 H, J = 8.1 Hz), 7.19 (t, 1 H, J = 8.0 Hz), 7.51 (d, 1 H, J = 8.0 Hz), 7.56 (d, 2 H, J = 8.1 Hz), 7.76 (d, 1 H, J = 8.0 Hz); ^{13}C NMR ($CDCl_3$) δ 18.5, 21.4, 24.2, 24.9, 25.2, 25.4, 26.4, 27.1, 27.8, 28.3, 36.9, 66.9, 115.9, 123.8, 123.9, 124.8, 126.9, 128.7, 129.4, 130.3, 134.6, 136.0, 143.6, 144.7; IR (neat) 1356, 1184 cm^{-1}; HRMS for $C_{26}H_{33}NO_2S$ calcd 423.2232, found 423.2232. Anal. Calcd for $C_{26}H_{33}NO_2S$: C, 73.72; H, 7.85. Found: C, 73.72; H, 7.85.

5-Acetyl-2,3-dihydro-3-methylene-2-*n*-octylbenzofuran (Table 3, entry 4). Obtained as a pale yellow oil in 95% yield from the reaction of 2-iodo-4-acetylphenol and 1,2-undecadiene after purification by column chromatography using 10:1 hexanes/EtOAc: $[\alpha]_D = -61.2°$ (c = 0.30, $CHCl_3$) [52% ee, chiral HPLC]; ^{1}H NMR ($CDCl_3$) δ 0.87 (t, 3 H, J = 6.0 Hz), 1.20−1.60 (m, 12 H), 1.70−1.90 (m, 2 H), 2.57 (s, 3 H), 4.98 (d, 1 H, J = 3.0 Hz), 5.25 (m, 1 H), 5.54 (d, 1 H, J = 3.0 Hz), 6.84 (d, 1 H, J = 9.0 Hz), 7.86 (dd, 1 H, J = 9.0, 2.1 Hz), 8.01 (d, 1 H, J = 2.1 Hz); ^{13}C NMR ($CDCl_3$) δ 14.0, 22.6, 24.3, 26.3, 29.2, 29.3, 29.4, 31.8, 36.1, 87.4, 101.6, 110.0, 121.6, 126.4, 130.5, 132.0, 146.0, 166.0, 196.4; HRMS for $C_{19}H_{26}O_2$ calcd 286.1933, found 286.1929. This compound slowly decomposes and thus was not submitted for elemental analysis.

3,4-Dihydro-4-methylene-3-*n*-octyl-1*H*-2-benzopyran (Table 3, entry 5). Obtained as a clear, colorless oil in 72% yield from the reaction of 2-iodobenzyl alcohol and 1,2-undecadiene after purification by column chromatography using 30:1 hexanes/EtOAc: $[\alpha]_D = -15.6°$ (c = 0.30, dichloroethane) [73% ee, based on integration of the vinylic hydrogens in the presence of Eu(hfc)$_3$]; ^{1}H NMR ($CDCl_3$) δ 0.88 (t, 3 H, J = 7.0 Hz), 1.20−1.40 (m, 12 H), 1.70−1.80 (m, 2 H), 4.27 (dd, 1 H, J = 7.2, 6.6 Hz), 4.71 (d, 1 H, J = 15.3 Hz), 4.82 (d, 1 H, J = 15.3 Hz), 5.02 (s, 1 H), 5.59 (s, 1 H), 6.98−7.03 (m, 1 H), 7.18−7.24 (m, 2 H), 7.61−7.65 (m, 1 H); ^{13}C NMR ($CDCl_3$) δ 14.1, 22.7, 25.6, 29.3, 29.5, 29.6, 31.9, 65.7, 77.2, 106.9, 123.9, 124.3, 126.8, 127.6, 131.6, 134.4, 142.0 (one sp^3 carbon missing due to overlap); IR (neat) 1103 cm^{-1}; HRMS for $C_{18}H_{26}O$ calcd 258.1984, found 258.1980.

3,4-Dihydro-7-methyl-4-methylene-3-*n*-octyl-1*H*-2-benzopyran (Table 3, entry 6). Obtained as a clear, colorless oil in 56% yield from the reaction of 2-iodo-5-methylbenzyl alcohol and 1,2-undecadiene after purification by column chromatography using 30:1 hexanes/EtOAc: $[\alpha]_D = -17.1°$ (c = 0.026, EtOAc) [67% ee, based on integration of the vinylic

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hydrogens in the presence of Eu(hfc)$_3$]; ^{1}H NMR ($CDCl_3$) δ 0.87 (t, 3 H, J = 6.9 Hz), 1.20−1.60 (m, 12 H), 1.70−1.80 (m, 2 H), 2.32 (s, 3 H), 4.25 (dd, 1 H, J = 7.5, 6.3 Hz), 4.64 (d, 1 H, J = 15.0 Hz), 4.72 (d, 1 H, J = 15.0 Hz), 4.97 (d, 1 H, J = 1.2 Hz), 5.54 (s, 1 H), 6.83 (s, 1 H), 7.03 (d, 1 H, J = 8.4 Hz), 7.53 (d, 1 H, J = 7.8 Hz); ^{13}C NMR ($CDCl_3$) δ 14.6, 21.7, 23.2, 26.1, 29.8, 30.1, 30.1, 32.4, 33.0, 66.1, 77.8, 106.3, 124.3, 125.2, 128.3, 129.3, 134.8, 138.0, 142.4; IR (neat) 1106 cm^{-1}; HRMS for $C_{19}H_{28}O$ calcd 272.2140, found 272.2138.

7-Bromo-3,4-dihydro-4-methylene-3-*n*-octyl-1*H*-2-benzopyran (Table 3, entry 7). Obtained as a clear, colorless oil in 64% yield from the reaction of 5-bromo-2-iodobenzyl alcohol and 1,2-undecadiene after purification by column chromatography using 30:1 hexanes/EtOAc: $[\alpha]_D$ = −8.7° (c = 0.034, EtOAc) [67% ee, based on integration of the vinylic hydrogens in the presence of Eu(hfc)$_3$]; ^{1}H NMR ($CDCl_3$) δ 0.88 (t, 3 H, J = 6.9 Hz), 1.22−1.59 (m, 12 H), 1.69−1.78 (m, 2 H), 4.25 (t, 1 H, J = 6.6 Hz), 4.60 (d, 1 H, J = 15.3 Hz), 4.68 (d, 1 H, J = 15.3 Hz), 5.05 (s, 1 H), 5.58 (s, 1 H), 7.17 (d, 1 H, J = 1.2 Hz), 7.32 (dd, 1 H, J = 8.4, 1.8 Hz), 7.48 (d, 1 H, J = 8.4 Hz); ^{13}C NMR ($CDCl_3$) δ 14.2, 22.7, 25.5, 29.3, 29.6, 31.9, 32.5, 65.2, 77.2, 107.5, 121.6, 125.7, 127.3, 130.1, 130.7, 136.4, 141.2 (one sp^3 carbon missing due to overlap); IR (neat) 1111 cm^{-1}; HRMS for $C_{18}H_{25}BrO$ calcd 336.1089, found 336.1091.

***(E)*-4-*n*-Butylidene-3,4-dihydro-3-*n*-propyl-1*H*-2-benzopyran (Table 3, entry 8).** Obtained as a clear, colorless oil in 73% yield from the reaction of 2-iodobenzyl alcohol and 4,5-nonadiene after purification by column chromatography using 30:1 hexanes/EtOAc: $[\alpha]_D$ = −71.6° (c = 0.030, dichloroethane) [55% ee, based on integration of the vinylic hydrogen in the presence of Eu(hfc)$_3$]; ^{1}H NMR ($CDCl_3$) δ 0.90 (t, 3 H, J = 7.8 Hz), 0.95 (t, 3 H, J = 7.8 Hz), 1.30−1.65 (m, 6 H), 2.36 (dq, 2 H, J = 7.5, 2.1 Hz), 4.28 (dd, 1 H, J = 6.9, 5.7 Hz), 4.64 (d, 1 H, J = 14.7 Hz), 4.70 (d, 1 H, J = 14.7 Hz), 5.51 (t, 1 H, J = 6.9 Hz), 7.06 (dd, 1 H, J = 6.9, 1.5 Hz), 7.18−7.28 (m, 2 H), 7.41 (dd, 1 H, J = 6.9, 1.5 Hz); ^{13}C NMR ($CDCl_3$) δ 14.0, 14.1, 19.0, 23.5, 31.0, 36.3, 65.4, 79.4, 124.2, 126.3, 126.8, 127.9, 128.1, 132.6, 133.7, 136.3; IR (neat) 1082 cm^{-1}; HRMS for $C_{16}H_{22}O$ calcd 230.1671, found 230.1672.

***(E)*-5,6a,7,8,9,10,11,12,13,14,15,16-Dodecahydrobenzo[*d*]cyclotridec[*b*]pyran (Table 3, entry 9).** Obtained as a clear, colorless oil in 29% yield along with a trace of an unknown impurity from the reaction of 2-iodobenzyl alcohol and 1,2-cyclotridecadiene after purification using 30:1 hexanes/EtOAc: $[\alpha]_D$ = −148.9° (c = 0.017, dichloroethane) [77% ee, based on integration of the vinylic hydrogen in the presence of Eu(hfc)$_3$]; ^{1}H NMR ($CDCl_3$) δ 1.20−1.60 (m, 16 H), 1.62−1.75 (m, 2 H), 2.10−2.25 (m, 1 H), 2.55−2.70 (m, 1 H), 4.38 (dd, 1 H, J = 8.7, 3.6 Hz), 4.60 (d, 1 H, J = 14.1 Hz), 4.68 (d, 1 H, J = 14.1 Hz), 5.64 (dd, 1 H, J = 11.1, 5.1 Hz), 7.09 (d, 1 H, J = 6.3 Hz), 7.19−7.30 (m, 2 H), 7.53 (d, 1 H, J = 7.2 Hz); ^{13}C NMR ($CDCl_3$) δ 22.4, 24.6, 24.8, 25.3, 26.0, 26.1, 27.3, 27.8, 28.7, 33.1, 66.1, 80.1, 124.5, 126.6, 126.7, 127.2, 129.4, 132.6, 133.1, 136.8; IR (neat) 1081 cm^{-1}; HRMS for $C_{20}H_{28}O$ calcd 284.2140, found 284.2138.

***(S)*-(*E*)-3-Bromo-5,6a,7,8,9,10,11,12,13,14,15,16-dodecahydrobenzo[*d*]cyclotridec[*b*]pyran (Table 3, entry 10).** Obtained as a pale yellow oil in 33% yield along with a trace of an unknown impurity from the reaction of 5-bromo-2-iodobenzyl alcohol and 1,2-cyclotridecadiene after purification using 30:1 hexanes/EtOAc: $[\alpha]_D$ = −118.0° (c = 0.021, $CDCl_3$). This oil was crystallized from hexane to give white needles: $[\alpha]_D$ = − 211.0° (c = 0.008, $CDCl_3$) [>95% ee, no resolution of the vinylic hydrogen was observed in the presence of Eu(hfc)$_3$]; ^{1}H NMR δ 1.2−1.6 (m, 16 H), 1.62−1.80 (m, 2 H), 2.12−2.25 (m, 1 H), 2.48−2.62 (m, 1 H), 4.35 (dd, 1 H, J = 8.4, 3.3 Hz), 4.56 (d, 1 H, J = 14.7 Hz), 4.64 (d, 1 H, J = 14.7 Hz), (5.64 (ddd, 1 H, J = 10.8, 5.1, 0.3 Hz), 7.26 (s, 1 H), 7.39 (d, 2 H, J = 1.2 Hz); ^{13}C NMR ($CDCl_3$) δ 22.2, 24.6, 24.8, 25.3, 25.9, 26.1, 27.2, 27.8, 28.6, 32.9, 65.5, 80.0, 120.6, 127.6, 128.9, 129.8, 130.1, 131.6, 132.3, 138.9; IR ($CHCl_3$) 2932, 1478, 1465 cm^{-1}; HRMS for $C_{20}H_{27}O^{79}Br$ calcd 362.1245, found 362.1245; $C_{20}H_{27}O^{81}Br$ calcd 364.1226, found 364.1223.

4-Methylene-3-*n*-octyl-1-isochromanone (Table 3, entry 11). Obtained as a clear, colorless oil in 50% yield from the reaction of 2-iodobenzoic acid and 1,2-undecadiene after purification by column chromatography using 10:1 hexanes/EtOAc: $[\alpha]_D$ = −79.5° (c = 0.068, dichloroethane) [67% ee, based on integration of aromatic H-8 in the presence of Eu(hfc)$_3$]; ^{1}H NMR ($CDCl_3$) δ 0.86 (t, 3 H, J = 6.9 Hz), 1.20−1.55 (m, 12 H), 1.60−1.75 (m, 1 H), 1.80−2.00 (m, 1 H), 5.00 (t, 1 H, J = 7.2 Hz), 5.33 (s, 1 H), 5.71 (s, 1 H), 7.42−7.48 (dq, 1 H, J = 8.1, 2.4 Hz), 7.57−7.61 (m, 2 H), 8.11 (d, 1 H, J = 7.8 Hz); ^{13}C NMR ($CDCl_3$) δ 14.0, 22.5, 25.2, 29.1, 29.3, 31.7, 34.6, 81.9, 113.3, 123.5, 123.8, 129.0, 129.9, 133.9, 136.2, 138.6, 164.1 (one sp^3 signal missing due to overlap); IR ($CHCl_3$) 1720, 1114 cm^{-1}; HRMS for $C_{18}H_{24}O_2$ calcd 272.1776, found, 272.1771.

7-Methyl-4-methylene-3-*n*-octyl-1-isochromanone (Table 3, entry 12). Obtained as a clear, colorless oil in 69% yield from the reaction of 2-iodo-5-methylbenzoic acid and 1,2-undecadiene after purification by column chromatography using 10:1 hexanes/EtOAc: $[\alpha]_D$ = −70.7° (c = 0.033, dichloroethane) [63% ee, based on integration of aromatic H-8 in the presence of Eu(hfc)$_3$]; ^{1}H NMR ($CDCl_3$) δ 0.87 (t, 3 H, J = 6.6 Hz), 1.20−1.55 (m, 12 H), 1.66 (m, 1 H), 1.92 (m, 1 H), 2.43 (s, 3 H), 4.99 (t, 1 H, J = 6.9 Hz), 5.28 (s, 1 H), 5.66 (s, 1 H), 7.42 (dd, 1 H, J = 8.1, 0.9 Hz), 7.49 (d, 1 H, J = 8.1 Hz), 7.94 (s, 1 H); ^{13}C NMR ($CDCl_3$) δ 14.1, 21.2, 22.6, 25.3, 29.2, 29.3, 29.4, 31.8, 34.8, 82.1, 112.4, 123.3, 123.8, 130.2, 133.6, 134.9, 138.6, 139.3, 164.5; IR ($CHCl_3$) 1715, 1183 cm^{-1}; HRMS for $C_{19}H_{26}O_2$ calcd 286.1933, found 286.1939.

6,7-Dimethoxy-4-methylene-3-*n*-octyl-1-isochromanone (Table 3, entry 13). Obtained as a clear, colorless oil in 78% yield from the reaction of 2-iodo-4,5-dimethoxybenzoic acid and 1,2-undecadiene after purification by column chromatography using 10:1 hexanes/EtOAc: $[\alpha]_D$ = −52.6° (c = 0.027, dichloroethane) [71% ee, based on integration of the vinylic hydrogens in the presence of Eu(hfc)$_3$]; ^{1}H NMR ($CDCl_3$) δ 0.87 (t, 3 H, J = 6.9 Hz), 1.20−1.55 (m, 12 H), 1.60−1.75 (m, 1 H), 1.85−1.95 (m, 1 H), 3.95 (s, 3 H), 4.00 (s, 3 H), 4.98 (t, 1 H, J = 6.9 Hz)), 5.25 (s, 1 H), 5.59 (s, 1 H), 6.97 (s, 1 H), 7.55 (s, 1 H); ^{13}C NMR ($CDCl_3$) δ 14.1, 22.7, 25.4, 29.2, 29.4, 31.9, 35.0, 56.2, 56.3, 82.2, 105.3, 111.2, 111.6, 116.4, 130.7, 138.8, 150.0, 154.0, 164.3 (one sp^3 signal missing due to overlap); IR (neat) 1714, 1653, 1140, 1061 cm^{-1}; HRMS for $C_{20}H_{28}O_4$ calcd 332.1988, found 332.1997.

7-Bromo-4-methylene-3-*n*-octyl-1-isochromanone (Table 3, entry 14). Obtained as a clear, colorless oil in 67% yield from the reaction of 5-bromo-2-iodobenzoic acid and 1,2-undecadiene after purification by column chromatography using 10:1 hexanes/EtOAc: $[\alpha]_D$ = −47.1° (c = 0.024, dichoroethane) [48% ee, based on integration of aromatic H-8 in the presence of Eu(hfc)$_3$]; ^{1}H NMR ($CDCl_3$) δ 0.87 (t, 3 H, J = 6.9 Hz), 1.15−1.45 (m, 12 H), 1.60−1.70 (m, 1 H), 1.80−1.95 (m, 1 H), 5.00 (t, 1 H, J = 6.9 Hz), 5.37 (s, 1 H), 5.72 (s, 1 H), 7.46 (d, 1 H, J = 8.4 Hz), 7.72 (dd, 1 H, J = 8.4, 2.1 Hz), 8.25 (d, 1 H, J = 2.1 Hz); ^{13}C NMR ($CDCl_3$) δ 14.1, 22.6, 25.3, 29.1, 29.3, 31.8, 34.7, 82.0, 114.1, 123.1, 125.1, 125.7, 132.8, 135.0, 137.0, 137.8, 162.9 (one sp^3 signal missing due to overlap); IR ($CHCl_3$) 1710, 1150 cm^{-1}; HRMS for $C_{18}H_{23}BrO_2$ calcd 350.0881, found 350.0890.

5,6-Dihydro-3-methyl-5-methylene-6-*n*-octyl-2*H*-pyran-2-one (Table 3, entry 15). Obtained as a clear, colorless oil in 41% yield from the reaction of (*Z*)-3-iodo-2-methyl-2-propenoic acid and 1,2-undecadiene after purification using 10:1 hexanes/EtOAc: $[\alpha]_D$ = −93.5° (c = 0.014, dichloroethane) [80% ee, based on integration of the methyl hydrogens in the presence of Eu(hfc)$_3$]; ^{1}H NMR ($CDCl_3$) δ 0.88 (t, 3 H, J = 6.6 Hz), 1.22−1.55 (m, 12 H), 1.66−1.79 (m, 1 H), 1.80−1.93 (m, 1 H), 1.99 (s, 3 H), 4.99 (dd, 1 H, J = 8.1, 5.7 Hz), 5.13 (s, 1 H), 5.22 (s, 1 H), 6.77 (s, 1 H); ^{13}C NMR ($CDCl_3$) δ 14.1, 17.1, 22.7, 24.8, 29.3, 29.5, 31.9, 36.1, 80.8, 115.9, 127.2, 138.7, 139.5, 164.7 (one sp^3 carbon missing due to overlap); IR (neat) 1716, 1110 cm^{-1}; HRMS for $C_{15}H_{24}O_2$ calcd 236.1776, found 236.1770.

***(E)*-5-*n*-Butylidene-5,6-dihydro-3-methyl-6-*n*-propyl-2*H*-pyran-2-one (Table 3, entry 16).** Obtained as a clear, colorless oil in 59% yield (96:4 *E*/*Z*) from the reaction of (*Z*)-3-iodo-2-methyl-2-propenoic acid and 4,5-nonadiene after purification using 10:1 hexanes/EtOAc: $[\alpha]_D$ = −97.5° (c = 0.027, dichloroethane) [46% ee, based on integration of the allylic

methyl hydrogens in the presence of Eu(hfc)$_3$]; ^{1}H NMR ($CDCl_3$) δ 0.93 (t, 3 H, J = 6.9 Hz), 0.94 (t, 3 H, J = 7.2 Hz), 1.30−1.52 (m, 4 H), 1.58−1.72 (m, 1 H), 1.78−1.90 (m, 1 H), 2.00 (s, 3 H), 2.19 (qt, 2 H, J = 14.7, 7.5 Hz), 4.84 (t, 1 H, J = 6.9 Hz), 5.55 (t, 1 H, J = 7.8 Hz), 7.03 (s, 1 H); ^{13}C NMR ($CDCl_3$) δ 13.7, 13.9, 17.5, 18.4, 22.6, 29.4, 38.1, 81.9, 126.1, 130.4, 132.3, 133.7, 165.3; IR (neat) 1714, 1105 cm^{-1}; HRMS for $C_{13}H_{20}O_2$ calcd 208.1463, found 208.1467.

(*E*)-6,7,8,9,10,11,12,13,14,15,15a-Undecahydro-3-methylcyclotridec[*b*]pyran-2-one (Table 3, entry 17). Obtained as a clear, colorless oil in 52% yield (98:2 *E*/*Z*) from the reaction of (*Z*)-3-iodo-2-methyl-2-propenoic acid and 1,2-cyclotridecadiene after purification using 10:1 hexanes/EtOAc: $[\alpha]_D$ = −202.6° (*c* = 0.022, dichloroethane) [61% ee, based on integration of the methyl hydrogens in the presence of Eu(hfc)$_3$]; ^{1}H NMR ($CDCl_3$) δ 1.18−1.66 (m, 16 H), 1.80 (qt, 2 H, J = 13.2, 6.3 Hz), 2.01 (s, 3 H), 2.07−2.22 (m, 1 H), 2.28−2.42 (m, 1 H), 4.91 (t, 1 H, J = 5.1 Hz), 5.56 (dd, 1 H, J = 11.1, 6.0 Hz), 7.02 (s, 1 H); ^{13}C NMR ($CDCl_3$) δ 17.6, 21.4, 24.7, 24.8, 26.2, 26.4, 26.6, 28.0, 35.5, 82.4, 126.2, 130.0, 133.3, 133.6, 165.1 (two sp^3 carbons missing due to overlap); IR (neat) 1714, 1125 cm^{-1}; HRMS for $C_{17}H_{26}O_2$ calcd 262.1933, found 262.1932.

5,6-Dihydro-3-methyl-5-methylene-6-*n*-octyl-2*H*-pyran (Table 3, entry 18). Obtained as a clear, colorless oil in 70% yield from the reaction of (*Z*)-3-iodo-2-methyl-2-propen-1-ol and 1,2-undecadiene after purification using 30:1 hexanes/EtOAc: $[\alpha]_D$ = −11.5° (*c* = 0.031, dichloroethane) [79% ee, based on integration of the allylic methyl hydrogens in the presence of Eu(hfc)$_3$]; ^{1}H NMR ($CDCl_3$) δ 0.88 (t, 3 H, J = 6.9 Hz), 1.15−1.45 (m, 12 H), 1.45−1.55 (m, 1 H), 1.65−1.75 (m, 1 H), 1.71 (s, 3 H), 3.95−4.15 (m, 3 H), 4.72 (s, 1 H), 4.73 (s, 1 H), 5.97 (s, 1 H); ^{13}C NMR ($CDCl_3$) δ 14.3, 18.8, 22.7, 25.6, 29.4, 29.7, 29.7, 32.0, 32.1, 66.4, 75.4, 107.3, 122.4, 136.1, 142.9; IR ($CHCl_3$) 1653, 1616, 1102 cm^{-1}; HRMS for $C_{13}H_{22}O$ calcd 194.1471, found 194.1468.

5,6-Dihydro-2,2-dimethyl-5-methylene-6-*n*-octyl-2*H*-pyran (Table 3, entry 20). Obtained as a clear, colorless oil in 62% yield from the reaction of (*Z*)-4-iodo-2-methyl-3-buten-2-ol and 1,2-undecadiene after purification using 30:1 hexanes/EtOAc: $[\alpha]_D$ = +46.0° (*c* = 0.036, $CHCl_3$) (ee undetermined); ^{1}H NMR ($CDCl_3$) δ 0.88 (t, 3 H, J = 7.2 Hz), 1.20−1.45 (m, 18 H), 1.50−1.70 (m, 1 H), 1.75−1.90 (m, 1 H), 4.22 (m, 1 H), 4.83 (d, 2 H, J = 9.6 Hz), 5.69 (d, 1 H, J = 9.9 Hz), 6.07 (d, 1 H, J = 9.9 Hz); ^{13}C NMR ($CDCl_3$) δ 14.2, 22.7, 24.6, 25.4, 29.4, 29.6, 29.7, 29.7, 31.9, 32.0, 69.6, 72.3, 108.7, 125.5, 136.6, 143.0; IR (neat) 1177, 1089 cm^{-1}; HRMS for $C_{16}H_{28}O$ calcd 236.2140, found 236.2139.

Diethyl 3-Methylene-2-*n*-octyl-1,1-indanedicarboxylate (Table 3, entry 21). Obtained as a pale yellow oil in 67% yield from the reaction of diethyl 2-iodophenylmalonate and 1,2-undecadiene after purification using 10:1 hexanes/EtOAc: $[\alpha]_D$ = 48.8° (*c* = 0.29, dichloroethane) [75% ee, based on integration of the vinylic hydrogens in the presence of Eu(hfc)$_3$]; ^{1}H NMR ($CDCl_3$) δ 0.87 (t, 3 H, J = 6.9 Hz), 1.22 (t, 3 H, J = 7.2 Hz), 1.29 (t, 3 H, J = 6.9 Hz), 1.21−1.52 (m, 14 H), 3.62−3.72 (m, 1 H), 4.02−4.34 (m, 4 H), 5.11 (d, 1 H, J = 1.2 Hz), 5.52 (d, 1 H, J = 1.8 Hz), 7.25−7.33 (m, 2 H), 7.45−7.48 (m, 1 H), 7.59−7.63 (m, 1 H); ^{13}C NMR ($CDCl_3$) δ 14.0, 14.2, 14.2, 22.7, 27.1, 29.3, 29.5, 29.7, 30.4, 31.9, 50.8, 61.3, 61.7, 68.1, 105.0, 120.8, 127.4, 128.5, 128.8, 140.3, 140.8, 149.8, 169.3, 169.6; IR (neat) 1734, 1615, 1190 cm^{-1}; HRMS for $C_{24}H_{34}O_4$ calcd 386.2457, found 386.2448.

Diethyl 3-*n*-Butylidene-2-*n*-propyl-1,1-indanedicarboxylate (Table 3, entry 22). Obtained as a pale yellow oil in 79% yield (7:1 *Z*/*E*) from the reaction of diethyl 2-iodophenylmalonate and 4,5-nonadiene after purification using 10:1 hexanes/EtOAc: $[\alpha]_D$ = 28.0° (*c* = 0.037, dichloroethane) [47% ee, based on integration of the vinylic hydrogen in the presence of Eu(hfc)$_3$]; (*Z* isomer) ^{1}H NMR ($CDCl_3$) δ 0.86 (t, 3 H, J = 6.9 Hz), 0.98 (t, 3 H, J = 7.2 Hz), 1.19 (t, 3 H, J = 7.2 Hz), 1.29 (t, 3 H, J = 6.9 Hz), 1.15−1.50 (m, 4 H), 1.55 (qt, 2 H, J = 14.7, 7.2 Hz), 2.36−2.47 (m, 2 H), 3.54 (dd, 1 H, J = 8.4, 4.8 Hz), 4.0−4.4 (m, 4 H), 5.59 (t, 1 H, J = 7.5 Hz), 7.21−7.33 (m, 2 H), 7.51 (d, 1 H, J = 7.2 Hz), 7.63 (dd, 1 H, J = 6.9, 1.8 Hz); (*E* isomer) ^{1}H NMR ($CDCl_3$) δ 0.79 (t, 3 H, J = 6.9 Hz), 1.00 (t, 3 H, J = 7.2 Hz), 1.16 (t, 3 H, J = 7.2 Hz), 1.31 (t, 3 H, J = 6.9 Hz), 1.15−1.50 (m, 4 H), 1.51 (m, 2 H), 2.15−2.35 (m, 2 H), 3.92 (m, 1 H), 4.0−4.4 (m, 4 H), 5.93 (t, 1 H, J = 7.5 Hz), 7.21−7.33 (m, 2 H), 7.37 (dd, 1 H, J = 6.6, 2.1 Hz), 7.59 (dd, 1 H, J = 7.2, 1.5 Hz). This product mixture was not further characterized.

Di-μ-chloro-di(η^3-5-phenylnon-4-enyl)dipalladium(II) (9). Obtained as a 1:1 mixture of the syn-syn and syn-anti isomers from the reaction of 4,5-nonadiene, Li_2PdCl_4 and PhHgCl in CH_3CN according to a literature procedure:[22] (syn-syn) ^{1}H NMR ($CDCl_3$) δ 0.78 (t, 6 H, J = 6.9 Hz), 1.20−1.40 (m, 4 H), 1.40−1.58 (m, 4 H), 3.73 (m, 2 H), 7.36−7.43 (m, 3 H), 7.63−7.65 (m, 2 H); ^{13}C NMR ($CDCl_3$) δ 13.9, 22.0, 31.5, 81.7, 127.4, 127.8, 128.3, 130.0, 133.6; (syn-anti) ^{1}H NMR ($CDCl_3$) δ 0.78 (t, 3 H, J = 6.9 Hz), 0.99 (t, 3 H, J = 7.2 Hz), 1.20−1.40 (m, 2 H), 1.40−1.58 (m, 2 H), 1.58−1.70 (m, 2 H), 1.80−1.92 (m, 2 H), 3.73 (m, 2 H), 7.36−7.43 (m, 3 H), 7.63−7.65 (m, 2 H).

(η^3-5-Phenyl-non-4-enyl)palladium(II) trifluoromethanesulfonate (10). Di-μ-chlorodi(η^3-5-phenyl-non-4-enyl)dipalladium(II) and AgOTf were stirred at 80 °C in CD_3CN for 0.25 h. The starting π-allylpalladium chloride dimer was a 1:1 ratio of syn-anti to syn-syn isomers. A white precipitate of AgCl was observed immediately upon mixing. ^{1}H NMR spectral analysis of an aliquot of the resulting solution indicated it was a 1.4:1 mixture of syn-anti and syn-syn isomers based on integration of the methyl peaks. For the two stereoisomers all three *syn*-methyl groups are found at 0.78 ppm, while the *anti*-methyl group is found at 1.02 ppm. Spectral data for the product mixture: ^{1}H NMR (CD_3CN) δ ^{1}H NMR ($CDCl_3$) δ 0.78 (t, 9 H, J = 6.9 Hz), 1.02 (t, 3 H, J = 7.2 Hz), 1.27−1.54 (m, 12 H), 1.55−1.70 (m, 2 H), 1.80−1.90 (m, 2 H), 3.99 (m, 2 H), 7.44−7.49 (m, 5 H).

(η^3-5-Phenylnon-4-enyl)palladium(II) trifluoromethanesulfonate−Ligand 2 (11). (η^3-5-Phenylnon-4-enyl)palladium(II) trifluoromethanesulfonate and **2** were stirred in CD_3CN at 80 °C for 16 h. The mixture was cooled to room temperature and an aliquot removed and analyzed by ^{1}H NMR spectroscopy. Determination of the ratio of syn-anti and syn-syn isomers was based upon integration of the methyl peaks. See the Supporting Information for a ^{1}H NMR spectrum of this complex.

(η^3-5-Phenylnon-4-enyl)palladium(II) trifluoromethanesulfonate−Ligand 1. This complex was formed as described for the preparation of (η^3-5-phenylnon-4-enyl)palladium−**2**. The ^{1}H NMR spectral data were recorded at 65 °C to eliminate peak broadening. See the Supporting Information for a ^{1}H NMR spectrum of this complex.

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Supporting Information Available: NMR spectral data (^{1}H and ^{13}C) of all key intermediates and new annulation products. This material is available free of charge via the Internet at http://pubs.acs.org.

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